Catalytic Cascades Creating Novel Architecture for Medicinal Chemistry

Elghareeb Elshahat Elghareeb Elboray

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The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

The section entitled "Pd(0) catalysed 5-component cascade synthesis of complex Z,Z-bisallylamines using ammonium tartrate" (pg 87-92) is based on a jointly authored publication with Sunisa Akkarasamiyo and Nutthawat Chuanopparat entitled "Stereoselective Pd(0) Catalysed Five Component Cascade Synthesis of Complex Z,Z-Bisallylamines" published in *Chem. Commun*. **2013**, 49, 2007-2009. My contribution was to demonstrate the feasibility of the new chemistry and initiate the synthetic work. This paper reports eleven new compounds directly attributed to myself and only these are described in the thesis. The other authors work contributed fifteen and six new compounds for Sunisa and Nutthawat, respectively.

The work in the paper entitled "Exploiting adamantane as a versatile organic tecton: multicomponent catalytic cascade reactions" published in *Chem. Commun*. **2012**, 48, 11504-11506 was all my own work and is located on pages 52-55 and 100-105 in the thesis.

Finally, the thesis section entitled "1,3-dipolar cycloaddition approach to pyrimidinylpyrrolidines" (pg 109-114) is based on a jointly authored publication with Mohammed A. B. Sarker entitled: "X=Y-ZH compounds as potential 1,3-dipoles. Part 65: atom economic cascade synthesis of highly functionalized pyrimidinylpyrrolidines" published in *Tetrahedron* **2011**, 67, 5700-5710. This paper reports 12 new compounds directly attributed to myself and only these are described in the thesis. The other author's work contributed 15 new compounds for Mohammed A. B. Sarker.

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Dedicated to My Family

Abstract

The thesis comprises five chapters. Chapter one, the introduction, starts with a brief discussion of the more famous Pd catalysed reactions and their relevance to Pd as a catalyst in allene chemistry. The main part of the introduction reviews the recent work in Pd catalysed allene chemistry (formation of C-C, C-O and C-N bonds) and its importance in both synthetic and natural product syntheses.

The second chapter "results and discussion" discusses the author own work including the selection of a broad series of novel substrates chosen to enable a wide range of multicomponent cascades to be designed. These cascades enable the combination of 3, 4, 5, 7 and 9 substrates in a regio and stereoselective manner delivering novel products that enabled exploration of "biochemical space". In all cases 1-4 *Z*-double bonds are created stereoselectively. These strategies are applied to the novel synthesis of potentially bioactive heterocycles including those derived from reactions of the rigid adamantyl tecton involving formation of eight new bonds.

The third chapter "results and discussion" summarises preliminary work on 1,3-dipolar cycloaddition generating pyrimidinylpyrrolidine.

The fourth chapter contains the experimental details of all new compounds.

Table of Contents

Acknowledgements ..... **iii**

Abstract ..... **v**

Table of Contents ..... **vi**

Abbreviations ..... **ix**

Chapter 1 (Introduction): Palladium Catalysed Allene Chemistry **2**

1.1 Fundamental Palladium Chemistry 2

1.2 Pd catalysed allene chemistry. 5

1.2.1 C−C Bond Formation. 6

1.2.2 C−C Bond formation via carbocyclisation. 13

1.2.3 C−N Bond Formation. 18

1.2.4 C−O Bond Formation. 23

1.2.5 Pd catalysed allene chemistry via C-H activation. 29

1.2.6 Allene scaffolds and natural product synthesis. 32

1.3 Conclusion. 37

Chapter 2 (Results and Discussion): Palladium (0) catalysed allene cascade reactions **39**

2.1 Introduction 39

2.1.1 Potentially biologically active building blocks. 39

2.2 Palladium (0) catalysed allene cascade reactions. 45

2.2.1 Background 45

2.2.2 Pd(0) catalysed three component cascades. 47

2.2.2.1 Synthesis of an *N*-allenylpurine 195 using theobromine 155. 47

2.2.2.2 *rac*-Methionine methyl ester as nucleophile. 48

2.2.2.3 γ-Carboline 187 as a nucleophile. 49

2.2.2.4 Maraviroc amine 188 as a nucleophile. 50

2.2.2.5 Mafenide 174 as a nucleophile. 52

2.2.2.6 Amantadine (1-aminoadamantane) 180 as a nucleophile. 52

2.2.2.7 Miscellaneous primary/secondary amines as nucleophiles. 55

2.2.2.8 Design and preparation of potential histone deacetylase (HDAC) inhibitors *via* three component cascade chemistry. 59

2.2.3 Pd(0) catalysed multi-component cascades. 64

2.2.3.1 Introduction. 64

2.2.3.1.1 Mechanism of multivalent ligand interactions. 64

2.2.3.1.2 Some examples of biologically active multivalent compounds. 65

2.2.3.2 Pd(0) catalysed five component cascades using splayed allenes. 69

2.2.3.2.1 Synthesis and incorporation of N^1,N^3-diallenyluracil 234 into cascade reactions. 70

2.2.3.2.2 Screening more complex splayed bisallenes in 5-component processes. 74

2.2.3.2.4 Incorporation of splayed bisallenes 239a-e in 5-component cascades. 75

2.2.3.3 Pd(0) Catalysed formation of macrocycles *via* bisallenes *vs* bisamines: preliminary studies. 78

2.2.3.4 Pd(0) catalysed five component cascades using di-amines (piperazine and homopiperazine). 83

2.2.3.5 Catalytic reactions of ammonia surrogates. 87

2.2.3.5.1 Pd(0) catalysed 5-component cascade synthesis of complex Z,Z-bisallylamines using ammonium tartrate. 87

2.2.3.5.2 Pd(0) catalysed synthesis of isoquinolinone and isoquinoline using ammonium tartrate. 92

2.2.3.6 Pd catalysed seven component cascades. 96

2.2.3.6.1 Design and preparation of a novel splayed trisallene 257. 96

2.2.3.6.2 Incorporation of the splayed trisallene 257 in 7-component cascade reactions. 97

2.2.3.7 1,3,5,7-tetrakis-(4-iodophenyl)adamantane as a splayed tetra-aryl iodide. 100

2.3 Conclusion. 106

Chapter 3 (Results and Discussion): 1,3-dipolar cycloaddition approach to pyrimidinylpyrrolidines 109

Conclusion 114

Experimental 116

References 224

Appendices 250

Abbreviations

AcO	acetate
AcOH	acetic acid
Ar	aryl
B_2pin_2	bis(pinacolato)diboron
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	1,4-benzoquinone
Bu	butyl
COSY	correlation spectroscopy
Cy	cyclohexyl
DCM	dichloromethane
di-Zn(II)	di(2-picolyl)amine-Zn(II) complex
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
Equiv	equivalent
Et	ethyl
Et_3N	triethyl amine
Fmoc	9-fluorenylmethyloxycarbonyl
Gly-AlaOMe	glycyl-(*S*)-alanine methyl ester
HAT	histone acetyl transferase
HDAC	histone deacetylase
HDLP	HDAC like protein
HMBC	heteronuclear multiple bond coherence spectroscopy
HMQC	heteronuclear multiple quantum correlation spectroscopy
HRMS	high resolution mass spectrometry
L	ligand
m.p.	melting point
Me	methyl

ML	multivalent ligand
MW	microwave
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect spectroscopy (1D)
Nu	nucleophile
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
Ph	phenyl
PMP	*p*-methoxyphenyl
PPI	protein-protein interaction
Pr	propyl
Py	pyridyl
rt	room temperature
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
TfO	triflate or trifluoromethanesulfonate
TFP	tri-(2-furyl)phosphine
THF	tetrahydrofuran
TMS	trimethylsilyl
TPS	*tert*-butyldiphenylsilyl
Ts	tosyl or (4-toluenesulfonyl)

Chapter 1

Introduction

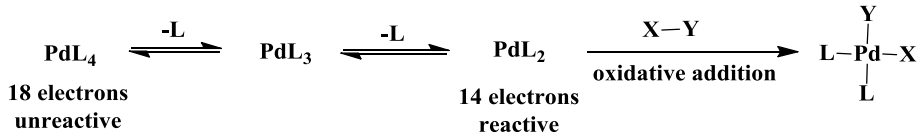
Palladium Catalysed Allene Chemistry

Chapter 1 (Introduction): Palladium Catalysed Allene Chemistry

Firstly, I briefly discuss important aspects of palladium chemistry relevant to allene chemistry including reactions used to form C-C and C-heteroatom bonds. Next, I review palladium catalysed allene chemistry and its application to generate carbo/heterocyclic skeletons and natural products. I will highlight the latest publications in each area. Ligands are omitted in the mechanisms for clarity.

1.1 Fundamental Palladium Chemistry

Palladium (0) is a $4d^{10}$ transition metal. It coordinates with four ligands, each donating two electrons to achieve a square planar eighteen electron configuration, i.e. tetrakis(triphenylphosphine)palladium(0). Also, Pd forms stable complexes with a sixteen electron configuration in certain cases, i.e. bis(acetonitrile)dichloropalladium(II). These complexes dissociate in solution and produce more reactive unsaturated coordination complexes with a fourteen electron configuration which interact with substrates (Scheme 1).

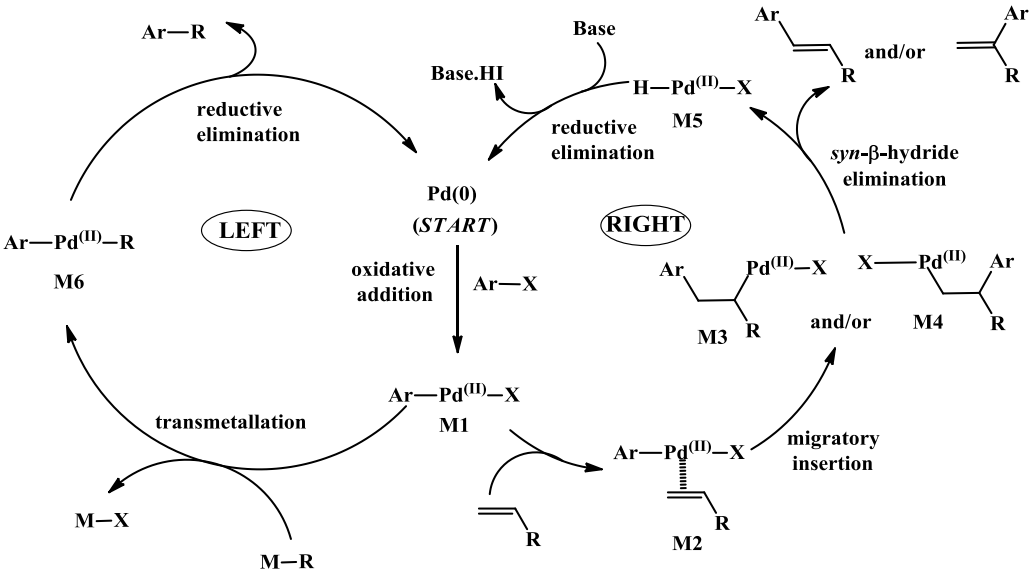


Scheme 1. Equilibrium between 18- and 14-electron species.

Pd complexes are widely employed to create new carbon-carbon bonds which are difficult to achieve by traditional methods. These cross-coupling reactions involve an electrophile (vinyllic/aryl/heteroaryl halide, triflate, phosphate, tosylate, mesylate or diazonium salt) reacting with a nucleophile (alkenes, organometallics, etc.) catalysed by a Pd catalyst and play important and diverse roles in synthetic, medicinal and agro-chemistry.[1] For example a widely used coupling reaction of an electrophile with an alkene (nucleophile) under palladium catalysed conditions, known as the Mizoroki-Heck reaction, delivers substituted alkenes and has found a multitude of applications.[1,2] The reaction mechanism involves four main steps (Scheme 2, right): (1) Pd(0) inserts in the Ar-X bond giving ArPd(II)X (**M1**), (2)

alkene coordination with Pd(II) complex **M2** and migratory insertion into the Pd-Ar bond affords **M3** or **M4**, (3) *syn*-β-hydride elimination then delivers the product followed by (4) base initiated reductive elimination of Pd(0) from **M5**.

A variety of organometallic compounds (nucleophiles) of Mg (Kumada),[1,3] Cu (Sonogashira),[1,4] Zn (Negishi),[1,5] Sn (Stille-Migita),[1,6] B (Suzuki-Miyaura),[1,7] Si (Hiyama)[1,8] couple with various electrophiles under Pd catalysis affording a diverse range of novel C-C bonds (Scheme 2, left). The organometallic cross-coupling mechanism starts with oxidative addition to generate the Pd(II) species **M1** followed by concomitant migration of the nucleophile from the metal to the Pd(II) complex with the halide (**X**) moves in the opposite direction in a transmetallation step (rate determining step) to give intermediate **M6** which undergoes reductive elimination to give the product and regenerates Pd(0). These reactions can be regio-, stereo-, and enantio-selective processes and involve inter- and intra-molecular coupling.[1j,2a,9]



Scheme 2. Catalytic cycle of Heck (right) and organometallic (left) cross-coupling reactions.

In the past, cross-coupling processes were used to furnish C−C bonds between C_{sp2}−C_{sp2}, C_{sp2}−C_{sp} and C_{sp}−C_{sp} partners. During the last two decades, enormous efforts have been expended to modify reaction conditions, catalysts and substrates.[1e-h,1o,p,6b,c,10] Also, palladium catalysed C−H activation is a relatively recent but powerful tool from the economic and waste reduction point of view. This process does not require specially activated functional groups in the reactants and allows functionalisation of aliphatic and aromatic compounds.[11] In general, the driving

force in C−H functionalisation is the existence of directing group on the substrate which coordinates with the catalyst and facilitates regioselective C-H activation. All of these processes extend cross-coupling to involve C_{sp3}-C_{sp3}, C_{sp3}-C_{sp2} and C_{sp3}-C_{sp} coupling.

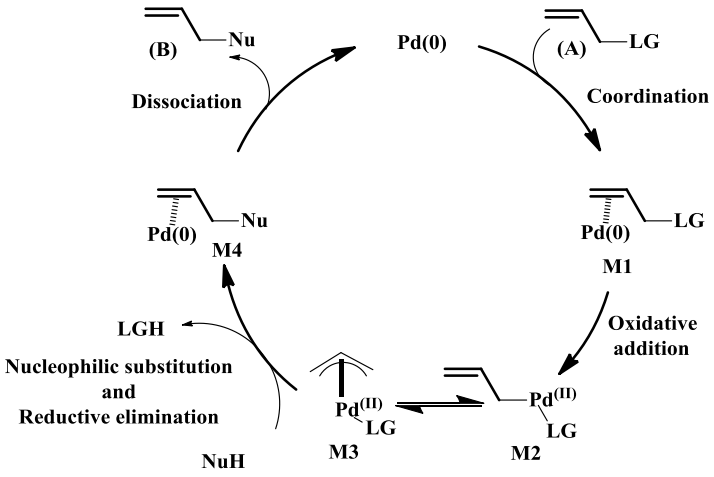
Pd catalysis has also been extensively used to create carbon-heteroatom bond formation.[1o,10i,11g,12] Buchwald and Hartwig developed Pd catalysed C−N bond formation by coupling aryl halides and amine nucleophiles in the presence of base.[8c,d.10i,11h,13]

Other important examples include Pd catalysed carbonylation of aromatic electrophiles in the presence of a range of nucleophiles which furnish a broad range of products, i.e. aldehydes, ketones, amides, carboxylic acids, esters and anhydrides.[14] For example, Fukuyama modified Negishi coupling employing thioesters as electrophiles, instead of aryl halides, and organo-zinc compounds generating ketones with no need for CO pressure.[15] Carboxylation of organometallics and alkenes using CO_2 gas in the presence of transition metals (Pd, Rh, Cu, Ni, Au) furnish carboxylic acid derivatives.[16] In the same vein, palladium catalysed cyanation of aryl halides generates benzonitriles.[17]

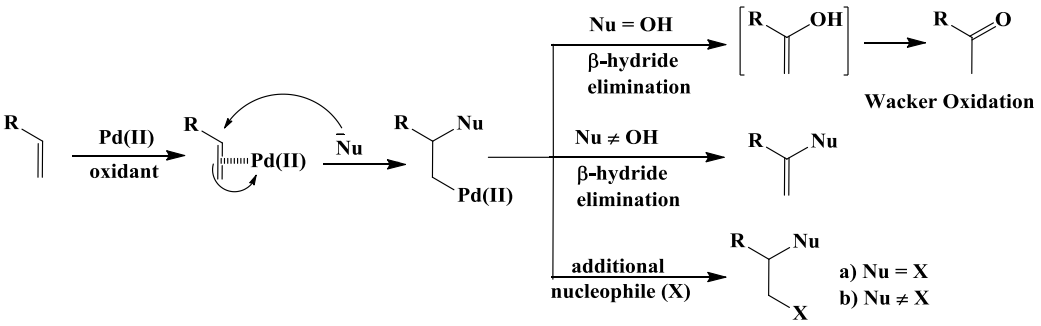
Transition metals catalysed nucleophilic substitution of allylic electrophiles is known as Tsuji-Trost reaction (Scheme 3).[18] The initial reaction used allylic esters and carbonates. This was extended to include benzylic esters/carbonates, vinyl epoxides and allylic halides, alcohols, carboxylic acids, phosphates, phenoxides, sulfones, carbamates, nitrates, etc.[18] Recently, C-H functionalisation of unactivated allylic compounds has attracted considerable attention. This reaction provides a way to install C-C and C-heteroatom bonds regio-, stereo- and enantio-selectively using a broad range of nucleophiles. Additionally, organometallics can participate as nucleophiles. The mechanism (Scheme 3) starts with coordination of Pd(0) with the allyl double bond **M1** followed by oxidative addition to give the η^1-σ-complex **M2** which equilibrates with the η^3-π-allyl Pd(II) complex **M3**. Nucleophilic attack on **M3** followed by reductive elimination and dissociation of Pd(0) affords the product (**B**).

The Wacker company invented the first catalytic organopalladium reaction applied on an industrial scale. It comprises a Pd(II) catalysed process for oxidation of ethylene to acetaldehyde in the presence of water and oxidants (oxygen and $CuCl_2$)

which reoxidise the generated Pd(0) to the active Pd(II) species. Wacker oxidation has been extended to include terminal substituted alkenes which affords the corresponding ketones. The Pd(II)-alkene π-complex activates the alkene to nucleophilic attack. The process is applicable to inter- and intra-nucleophilic addition in a regio-, stereo- and enantio-selective manner.[19]



Scheme 3. General mechanism of Tsuji-Trost reaction.



Scheme 4. Activation of alkene with Pd(II) toward nucleophilic substitution.

1.2 Pd catalysed allene chemistry.

Allenes are 1,2-dienes, e.g. propadiene (Fig. 1), with a central sp hybridized carbon linked to two sp^2 hybridized carbons. The two adjacent π-bonds are perpendicular to one another and have linear geometry.

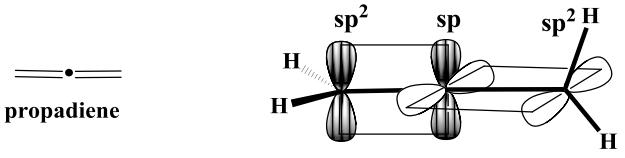


Figure 1. The chemical formula and orbital structure of propadiene.

Initially, allenes were considered to be difficult to synthesise and highly unstable which deterred work on their synthesis and applications. Allene chemistry has grown very rapidly during the last decade providing allenes with many different substituents[20] fueling their application to a wide range of allene reactions, e.g. addition, free radical, cycloaddition, cyclisation, etc.[21,22] Transition metal catalysed allene reactions provide a wide range of novel processes dependent on the metal.[23,24] In the same vein, the successful preparation of chiral allenes permits transfer of chirality to the products enabling natural product synthesis and the syntheses of biologically active compounds.[25] Allene chemistry provides powerful methods for the regio- and stereoselective C-C and C-heteroatom bond construction in an enantio-selective fashion through both inter- and intra-molecular reactions.[26]

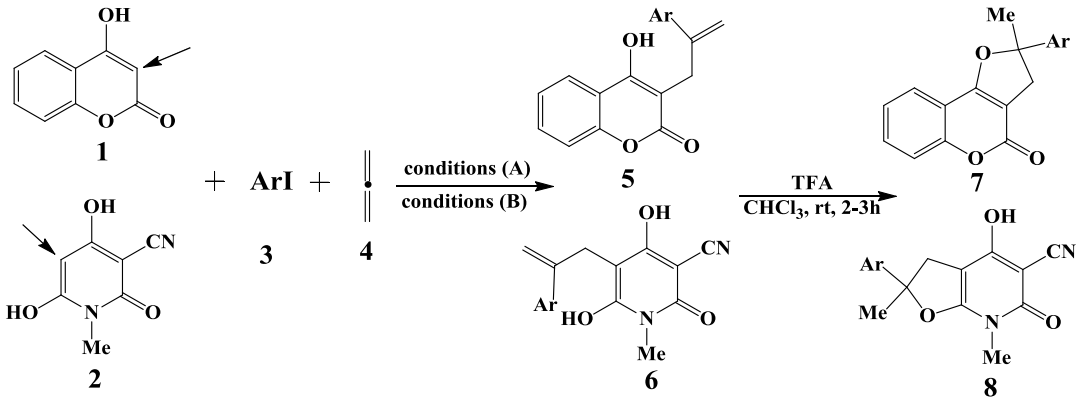
To the author's knowledge, a review[27a] and a book[27b] published in 2000 and 2004, respectively, are the only publications that have discussed Pd catalysed allene reactions in depth. Other reviews have treated this topic in general with other topics.[23f, 27c-f] The focus of this review is on allene reactions catalysed by palladium complexes which furnish C-C and C-heteroatom bonds in an inter/intra-molecular manner together with examples of their application to biologically active carbo-/heterocyclic backbones.

1.2.1 C−C Bond Formation.

Allenes coordinate to Pd generating π-allyl electrophilic intermediates which can be trapped by carbo-nucleophiles.[28] This methodology affords a versatile way of forming inter- and intra-molecular C-C bonds which are often difficult to achieve by traditional methods.

For example, Grigg's group utilised *C*-pronucleophiles, especially heterocyclic scaffolds having an enolic system, in Pd catalysed allene reactions.[29a-d] Thus, compounds **1** or **2** react with allene **4** (1 atm) and aryl iodides **3a** (electron rich/neutral) in three component cascade processes to furnish *C*-allylated intermediates **5** or **6**, respectively (Scheme 5). These were not isolated but converted to the dihydrofurocoumarines **7** (53-70%) or dihydrofuro[2,3-b]pyridinones **8** (35-55%), respectively, under acidic work up. However, incorporation of electron poor aryl iodides **3b** in these cascades suppressed the cyclisation process. In the presence

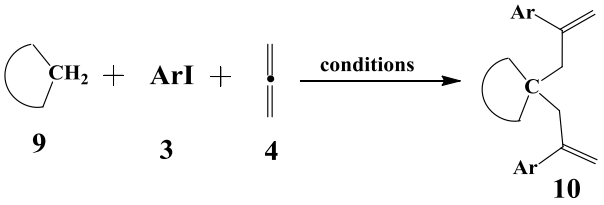
of acid and in the case of **1** monoallylation products **5** were obtained in 65-97% yield.[29a]



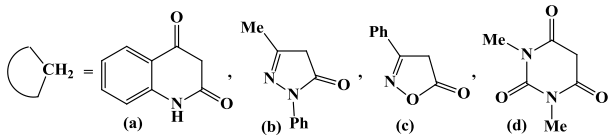
Conditions (A) $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2 equiv.), MeCN, 80 °C, 20 h.
Conditions (B) Pd_2dba_3 (2.5 mol%), TFP (10 mol%), K_2CO_3 (2 equiv.), DMF, 80 °C, 20 h.
(a) Ar^1 = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-thienyl, *N*,*N*-dimethyluracil-5-yl
(b) Ar^2 = 3,5-$(F_3C)_2C_3H_3$, 3,4-$Cl_2C_6H_3$, 3-Cl-4-FC_6H_3, 3-pyridyl, 2-chloro-5-pyridyl

Scheme 5. 3-Component cascade generating fused heterocyclic products. Arrows denote the active sites.

Heterocyclic pronucleophiles with activated methylene groups **9a-d** reacted with propadiene **4** (1 atm) and a range of ArI **3** (2.1-2.4 equiv.), both e-rich and e-poor, in five component cascades to give *C*,*C*-diallylation products **10** (Scheme 6).[29a,b]



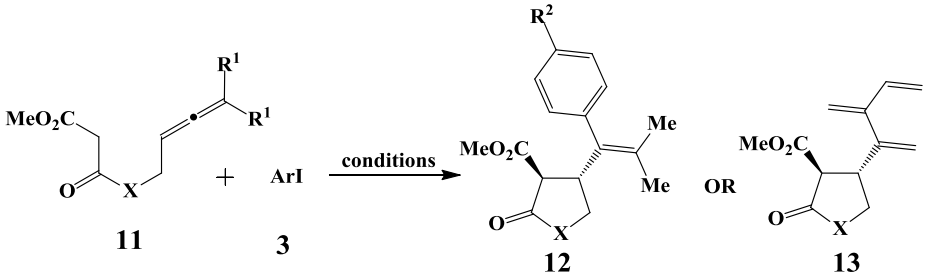
Conditions (A) Pd_2dba_3 (2.5 mol%), TFP (10 mol%), K_2CO_3 (2 equiv.), DMF, 80 °C, 20 h, 41-75% yield
Conditions (B) $Pd(OAc)_2$ (10 mol%), TFP (20 mol%), Cs_2CO_3 (2 equiv.), toluene, 130 °C, 24 h, 53-78% yield
Conditions (C) $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2 equiv.), MeCN, 80 °C, 20 h, 89-95% yield
Ar = Ph, 4-$MeOC_6H_4$, 4-$MeOCOC_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 3-Cl-4-FC_6H_3, 3,4-$Cl_2C_6H_3$, 4-BrC_6H_4, 2-thienyl, 3-pyridyl



Scheme 6. Five component *C*,*C*-diallylation cascades of active methylene heterocycles.

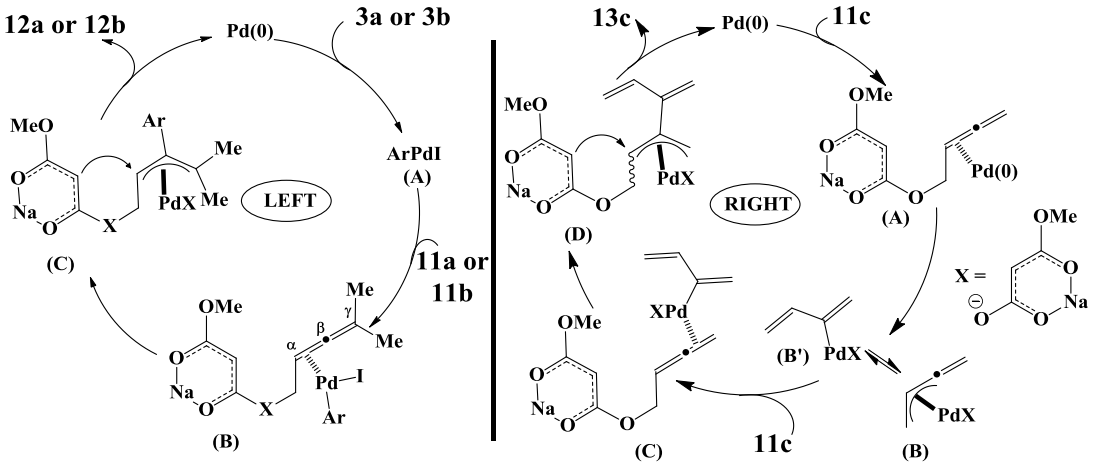
Allenyl malonamide **11a** was found to couple with a broad range of aryl iodides **3a** under phosphine free conditions (i) (*n*-BuLi was used to reduce Pd(II) and DMSO acted as both solvent and ligand) to generate, regio- and stereo-selectively, 4-(α-styryl)-γ-lactams **12a** in 61-88% yield (Scheme 7).[30] The mechanism involves oxidative addition of aryl iodide **3a** to Pd(0) followed by allene coordination

(intermediate (**B**)) and insertion to give π-allyl complex (**C**) which is intramolecularly attacked by the active methylene nucleophile at the α-position to deliver γ-lactam **12a** with regeneration of the active catalyst (Scheme 8, left).



Conditions: (i) $PdCl_2(MeCN)_2$(10 mol%), *n*-BuLi (20 mol%), NaH (1.2 equiv.), *n*-BuN_4Br (20 mol%), DMSO, 55 °C, 2.5 h
(ii) $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), NaH (1.2 equiv.), 15-crown-5 (1.2 equiv.), THF, 55 °C, 60 h
(iii) $Pd(OAc)_2$ (5 mol%), P(*t*-Bu) (30 mol%), NaH (1.2 equiv.), DMF, 18 h, rt
(a) X = NBn, R^1 = Me, Ar = 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-$AcOC_6H_4$, 4-BrC_6H_4, 3-thienyl, 3-pyridyl
(b) X = O, R^1 = Me, Ar = 4-$NO_2C_6H_4$
(c) X = O, R^1 = H, Ar = Ph

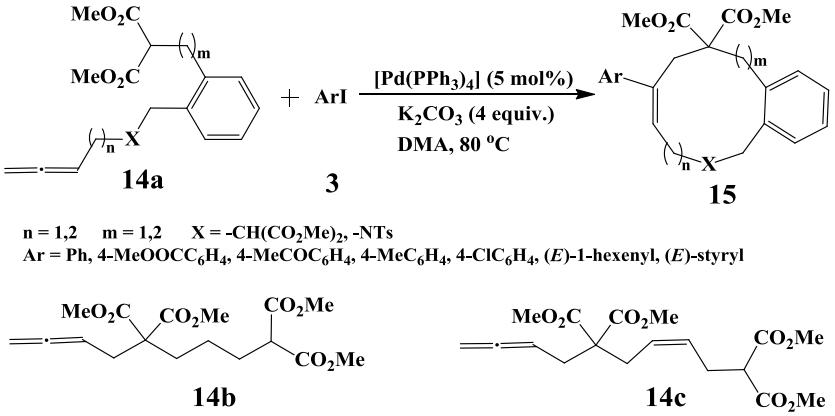
Scheme 7. Allenes as γ-lactam or γ-lactone precursors.



Scheme 8. Proposed mechanism for formation of **12a** and **12b** (left) or **13c** (right).

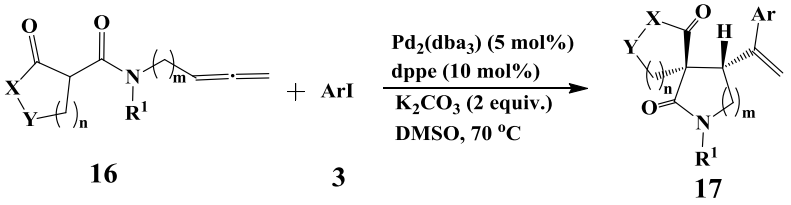
In the same vein, *O*-α-allenyl ester **11b** reacted with the electron poor aryl iodide **3b** under two different catalytic conditions (i) or (ii) (Scheme 7) to form only 4-(4-styryl)-γ-lactones **12b** in 49-53% yield.[31] The reaction of **11c** in the presence or absence of an electron neutral aryl iodide **3c** under conditions (iii) gave 3,4-*trans*-γ-lactone **13c** in 45% yield. A plausible strategy for the formation of **13c** (Scheme 8, right) proceeds *via* the Pd(0) π-complex (**A**). Oxidative addition affords η^3-π-allyl complex (**B**) (this step is faster than the oxidative addition in the presence of ArI) which is in equilibrium with η^1-σ-complex (**B′**). A second molecule of **11c** coordinates with (**B′**) then migratory inserts to afford η^3-π-allyl complex (**D**) which is attacked by the activated methylene group to form **13c** with regeneration of Pd(0).

Larger ring systems can be accessed with appropriate methylene tethered allenes **14a**. Aryl iodides **3** under Pd(0) catalysed conditions furnish 60-91% yields of 10-, 11- and 12-membered rings **15** in a regio- and stereoselective fashion (Scheme 9)[32] whilst allenes **14b** and **14c** react under the same conditions to give 9- and 10-membered carbocycles in 70 and 89% yield, respectively.



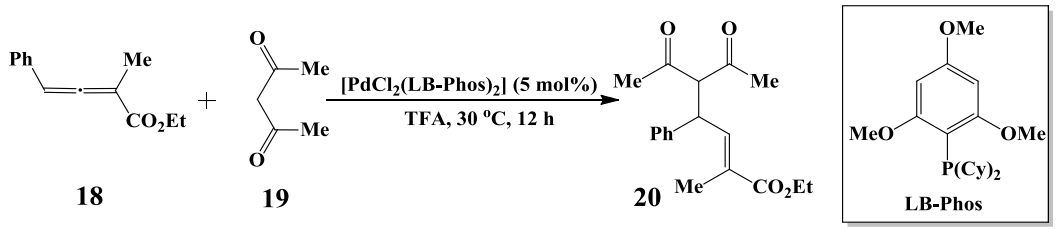
Scheme 9. Macrocycle formation *via* allene tethered *C*-nucleophiles.

Dixon and Li prepared spirocyclic lactams **17**, in 30-86 % yield, with diastereomeric ratios ranging from 3:1 to 47:1, *via* Pd catalysed reaction of tethered allene **16** with a broad range of aryl iodides **3** (Scheme 10).[33] The process is applicable to a variety of spirocyclic products.

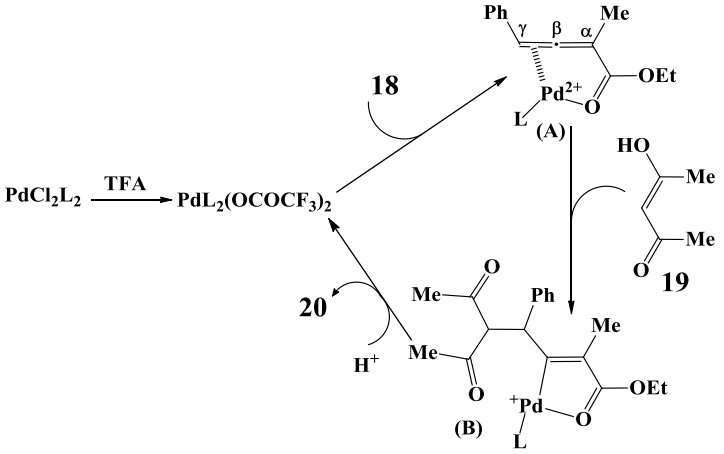


Scheme 10. Arylative carbocyclisation of allenes linked *C*-pronucleophiles.

Ma's group used acyclic 1,3-diketone **19** for the regio- and stereo-selective hydroalkylation of allene **18** in the presence of [($PdCl_2$(LB-Phos)$_2$]/TFA. The sole product was *E*-**20** (63%, Scheme 11).[34] The reaction starts with formation of complex (**A**) by coordination of Pd(II) to allene **18** followed by nucleophilic addition at the allene γ-position to give intermediate (**B**) (Scheme 12). Protonation of (**B**) gives exclusively *E*-**20** and recycles the Pd catalyst.

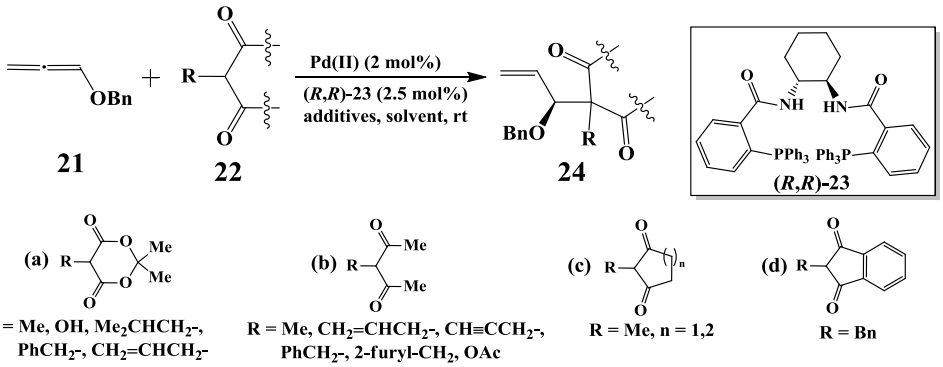


Scheme 11. Hydroalkylation of allene **18** with 1,3-diketone **19**.



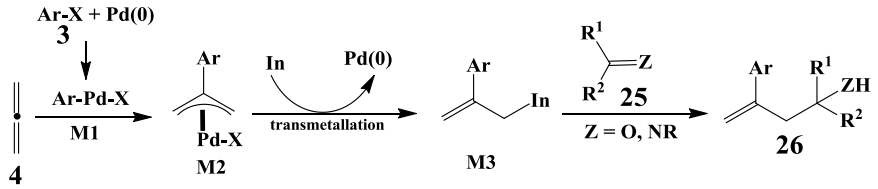
Scheme 12. Plausible mechanism for hydroalkylation of **18** with **19**.

Asymmetric addition of 1,3-diketones **22** to benzyloxyallene **21** was investigated by Trost's group using their chiral ligand **23**.[35a,b] The reactivity and enantioselectivity depends on the pH of the reaction mixture. Meldrum's acid **22a** reacted under acidic conditions (TFA, 1 mol%) to give **24a** (61-90%) with 82-99% ee (Scheme 13). The reaction of acyclic **22b** or cyclic-diketones **22c,d** occurs in buffer (benzoic acid/TEA, 2:1) or neutral medium (no additives), respectively, to furnish 67-97% yield and 77-99% ee of **24b-d**.[35b]



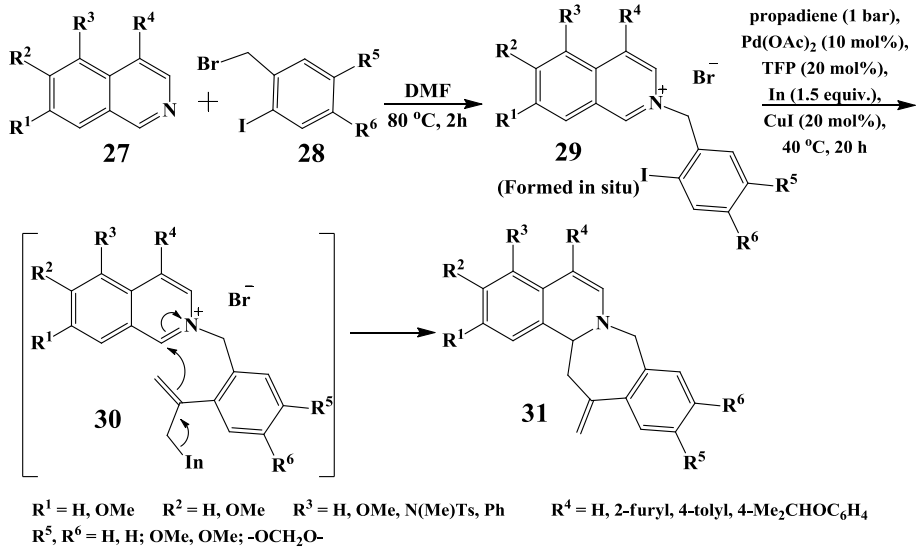
Scheme 13. Asymmetric hydroalkylation of allene **21** with activated *C*-nucleophiles **22**.

A versatile bimetallic Pd/In catalytic system was developed by Grigg *et al* for the construction of **26** (*sec*/*tert*-homoallyl alcohols,[36] β-amino acids,[37] enantioselective non-proteinogenic α-amino acids,[38] *N*-substituted pyrrolidines[39] and *N*-substituted piperidines[39]) *via* inter/intra-molecular reaction of aldehydes, ketones or imines **25** with allene **4** and aryl halides **3** (Scheme 14). The general Scheme involves the oxidative addition of Pd(0) to an aryl halide **3** followed by allene **4** coordination to ArPdX (**M1**) and migratory insertion into the Ar-Pd bond to give the electrophilic π-allyl Pd(II) species **M2** (Scheme 14). Reductive transmetallation of **M2** with indium reverses the electronic nature of the allyl species, affords the nucleophilic η^1-allylindium complex **M3** and regenerates Pd(0). Allylation of the electrophilic carbon centre of the aldehyde/ketone or imine **25** with **M3** delivers the desired product **26**.



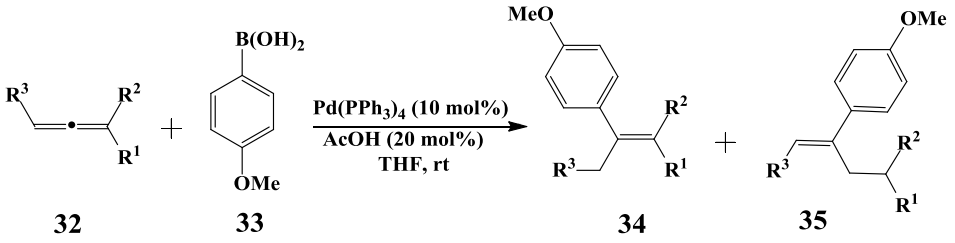
Scheme 14. Pd/In catalysed allylation of aldehydes, ketones and imines.

Thus, annulation of isoquinolines **27** to benzazepines **31** proceedes *via* sequential one pot reaction of **27** with 2-iodobenzyl bromide **28** to generate iminium salt **29** (Scheme 15).[40] Propadiene (1 bar) is then charged into the flask containing the Pd/In catalytic system generating **30** which undergoes regiospecific cyclisation to tetracycles **31** in 49-84% yield.



Scheme 15. Pd/In catalysed synthesis of homoprotoberberine analogues.

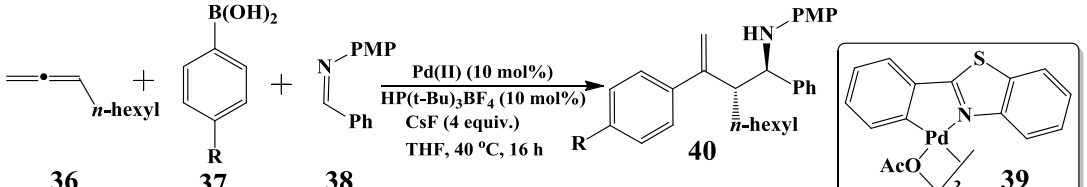
The reaction of substituted allene **32** with boronic acid **33** under Pd catalysed conditions ($Pd(PPh_3)_4$, AcOH, THF, rt) afforded *tri*- and *tetra*-substituted alkenes **34** and **35** (Scheme 16).[41] The regio- and stereo-selectivity ratios depend on the substituents on the allene **32**. Thus, reaction of **32a** with boronic acid **33** was >97:3 regioselective for **34** and **35** and 91:9 stereoselective for *trans*-**34**:*cis*-**34**. When less substituted allene **32b** was used, a 100% regio- and stereo-selectivity of *trans*-**34** was observed, while 1,3-disubstituted allene **32c** gave poor regioselectivity (64:36, *trans*-**34**:*trans*-**35**) but excellent stereoselectivity (only *trans*-isomers observed).



(a) $R^1 = CH_2CH(CO_2Me)_2$; R^2 = Bn; R^3 = H; 81% total yield; 34:35 (>97:3); *trans*-34:*cis*-34 (91:9)
(b) $R^1 = CH_2CH(CN)CO_2Me$; R^2 = H; R^3 = H;73% yield of 34; 34:35 (100:0); *trans*-34:*cis*-34 (100:0)
(c) $R^1 = CH_2CH(CO_2Me)_2$; R^2 = H; $R^3 = n\text{-}C_6H_{13}$; 90% total yield; *trans*-34 (64%); *trans*-35 (36%)

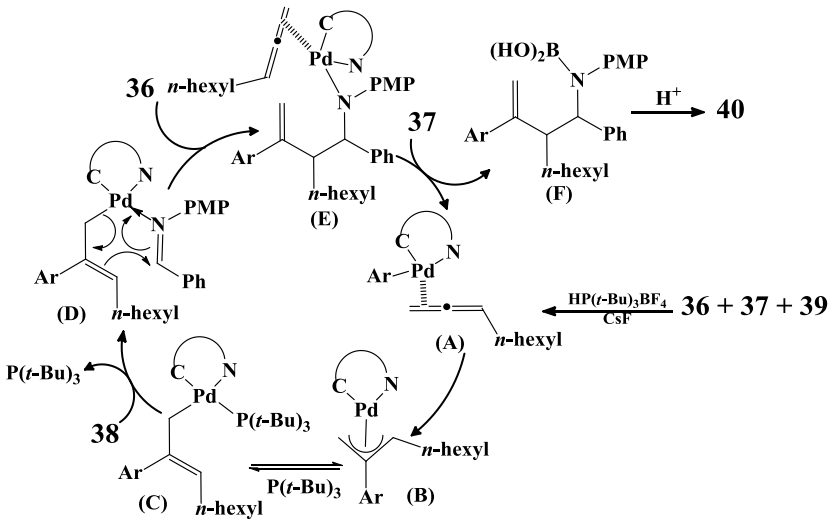
Scheme 16. Allene controlled regio- and stereo-selectivity.

Malinakova studied the cascade reaction of allene **36** with boronic acid **37** and imine **38** with two different Pd(II) complexes.[42] Palladacycle **39** (condition (i)) was more effective than $Pd(OAc)_2$ (conditions (ii)) (Scheme 17). Phosphine ligand ($HP(t\text{-}Bu)_3BF_4$) was necessary for conditions (i) (R = CO_2Me, 6 % yield in absence of ligand). A catalytic cycle (Scheme 18) was suggested. The ligand assisted in the splitting of Pd(II) dimer **39**. The resultant Pd(II) species transmetallated with boron **37** and coordinated with the allene **36** giving η^3-/η^1-complexes (**B** and **C**, respectively). Imine **38** displaces the phosphine ligand in (**C**) to give η^1-complex (**D**) which undergoes allyl transfer to afford intermediate (**E**). Transmetallation finally releases homoallyl amine **40** *via* intermediate (**F**) and regenerates intermediate (**A**).[42a]



	R =	CO_2Me,	OMe,	COMe,	CN,	F,	Cl,	Me
Pd-dimer 39 (conditions (i)): yield (%) =		76	64	77	54	37	56	58
$Pd(OAc)_2$ (conditions (ii)): yield (%) =		61	48	43	30	29	54	56

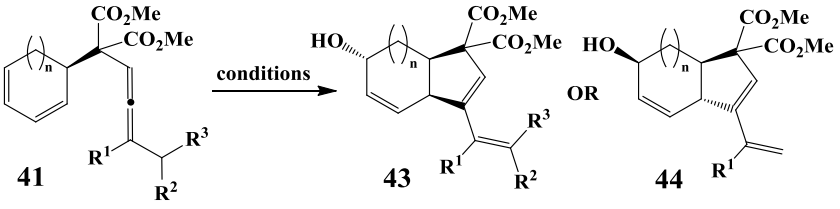
Scheme 17. Three component cascades delivering homoallyl amines.



Scheme 18. Plausible palladacycle/phosphine mechanism.

1.2.2 C−C Bond formation via carbocyclisation.

Pd catalysed carbocyclisation of allene tethered cyclic 1,3-dienes in the presence of different nucleophiles furnishes fused carbocyclic skeletons.[43] Thus, *trans*-1,4-carbohydroxylation of terminally symmetrical substituted allene linked conjugated diene **41a** under aerobic/non-aerobic conditions (i) and (ii) in aqueous THF gave a 41-90% yield of *cis*-fused products **43a** (Scheme 19).[44a,b] However, allene substituted cycloheptadiene **41b** afforded the *trans*-fused product **44b** in 90-94% yield whilst non-symmetrical substituted allene **41c** provided a mixture of isomers with *E*-**43c** as the major product.



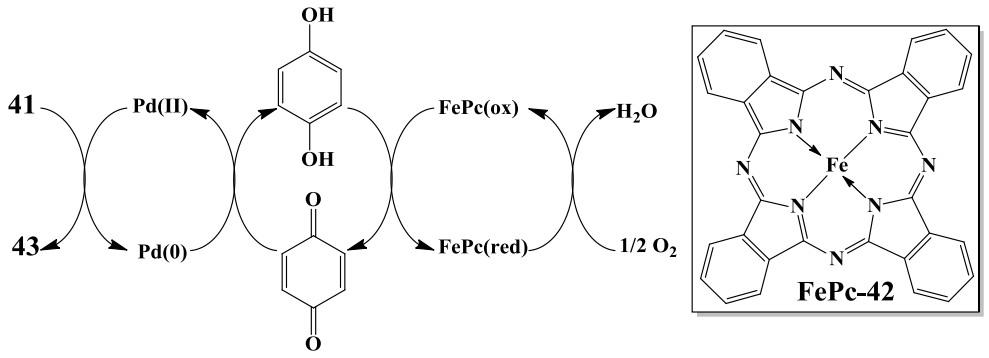
conditions (i) $Pd(TFA)_2$ (1-5 mol%), BQ (2 equiv.), H_2O/THF (4:1), rt
(ii) $Pd(TFA)_2$ (1-5 mol%), BQ (5-20 mol%), FePc-42 (1-5 mol%), O_2 atmosphere, H_2O/THF (4:1), rt

a) R^1, R^2 = Me, H; -$(CH_2)_4$- R^3 = H n = 1, 3
b) R^1, R^2 = Me, H R^3 = H n = 2
c) R^1, R^2 = Me, Me; Me, H, R^3 = Me, Pr n = 1, 3

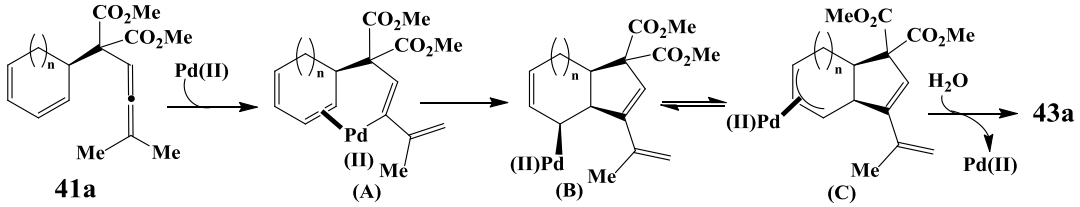
Scheme 19. *trans*-Carbohydroxylation of allene tethered conjugated dienes.

Bäckvall simulated biological processes in aerobic conditions by using a catalytic system comprising benzoquinone (BQ) and iron phthalocyanine (FePc) **42** to oxidize Pd(0) to Pd(II) and reduce O_2 to H_2O through two interlocked redox cycles (Scheme 20).[44a,45] The catalytic cycle of the previous reaction is illustrated in Scheme 21. The

allenyl and alkenyl double bonds in **41a** coordinate with Pd(II) followed by the nucleophilic allenyl central carbon atom attacking the electrophilic Pd(II) complex which furnishes intermediate (**A**). Rearrangement affords σ-complex (**B**) which is in equilibrium with the η^3-complex (**C**). Subsequent *exo*-water attack gives the product **43a**.

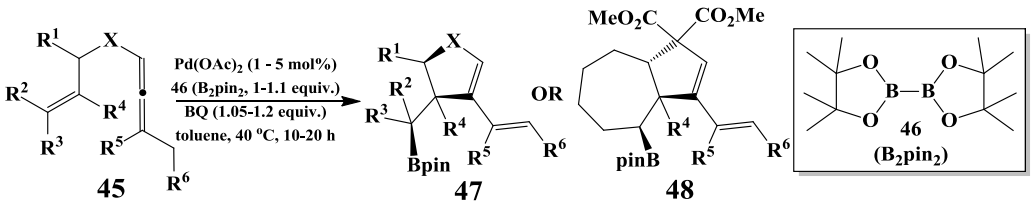


Scheme 20. Aerobic oxidation of Pd(0) to Pd(II).



Scheme 21. Sequential carbocyclisation and nucleophilic addition of water to **41a**.

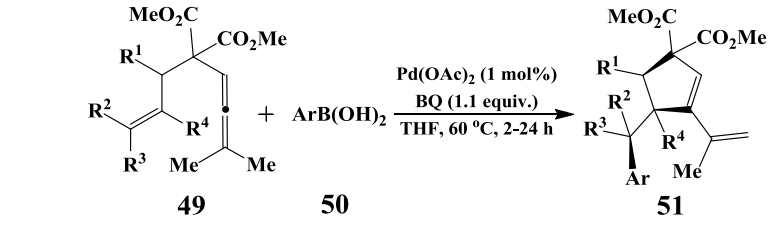
$Pd(OAc)_2$ was found to catalyse the *cis*-addition of carbon and boron derivatives to acyclic, cyclic and aza-enallenes. Thus, **45a-c** with bis(pinacolato)diboron (B_2pin_2) **46** gave carbocyclic, fused bicyclic and heterocyclic products **47a-c**, respectively, in 58-89% yield (Scheme 22).[46] However, allene substituted cycloheptene **45b** (R^1, R^2 = -$(CH_2)_4$-) gave *trans*-5,7-fused bicyclic **48** (63% yield) *via cis*-addition of carbon and boron to the cyclic double bond.



(a) X = -$C(CO_2Me)_2$ R^1, R^2, R^3, R^4 = H, H, H, H; H, H, Me, H; H, H, H, Me; H, H, Ph, H R^5, R^6 = Me, H; -$(CH_2)_4$-
(b) X = -$C(CO_2Me)_2$ R^1, R^2 = -$(CH_2)_3$-; -$(CH_2)_2$-; -$(CH_2)_5$- R^3 = R^4 = H R^5, R^6 = Me, H
(c) X = -NTs R^1, R^2, R^3, R^4 = H, H, H, H; H, H, Ph, H R^5, R^6 = Me, H

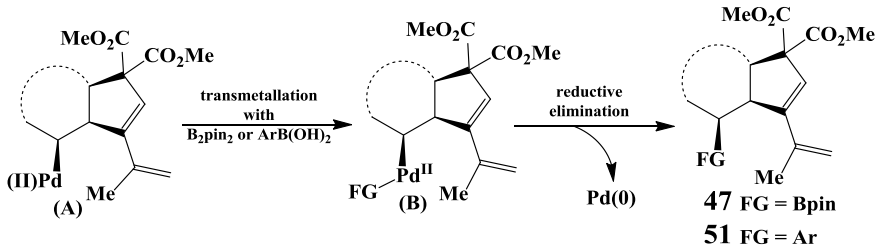
Scheme 22. Oxidative carbocyclisation/borylation of enallenes **45**.

Analogously, aryl boronic acid **50** was used in Pd(II) catalysed carbocyclisation/arylation of acyclic and cyclic enallenes **49** to construct mono- and dicarbocyclic skeletons **51** in 55-95% yield (Scheme 23).[47] Both carbocyclisation and arylation processes were selective for the *cis*-isomer.



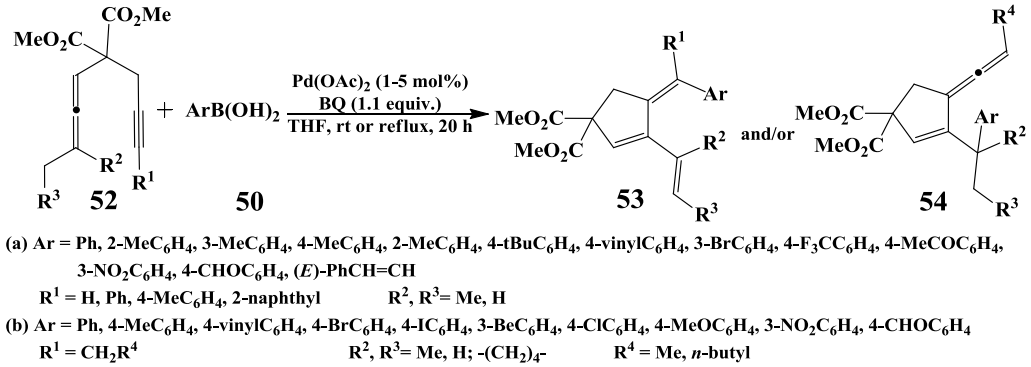
Scheme 23. Oxidative carbocyclisation/arylation of enallene **49.**

As previously mentioned in Scheme 21, the mechanism for **47** or **51** begins with $Pd(OAc)_2$ coordination of the alkene and allene double bonds which allows the middle allenyl carbon to attack Pd(II) followed by intramolecular *cis*-carbocyclisation generating intermediate (**A**) (Scheme 24). Sequential transmetallation of (**A**) with B_2pin_2 **46** or $ArB(OH)_2$ **50** gives Pd(II) complex (**B**). Reductive elimination of Pd(0) gives **47** or **51**, respectively. The catalytic cycle is completed *via* reoxidation of Pd(0) to Pd(II) with BQ.



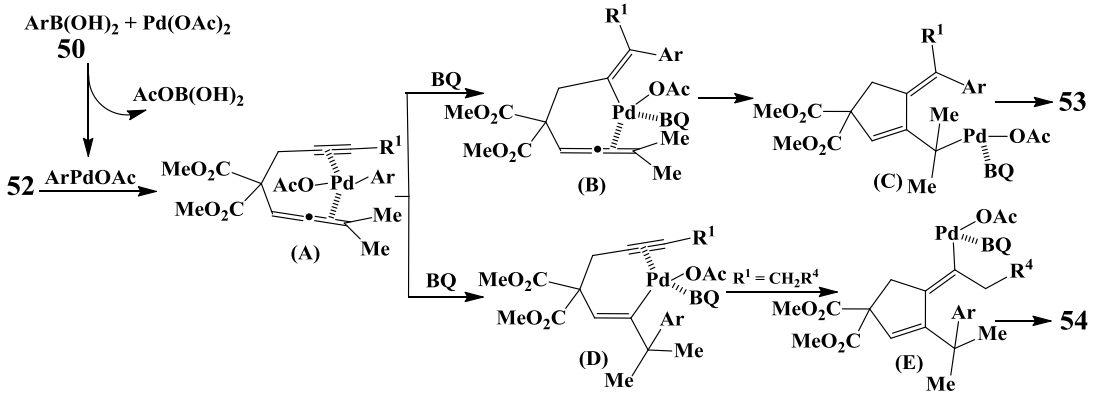
Scheme 24. Mechanism of oxidative cyclisation/borylation or arylation of enallene **45** or **49**.

A related process involving allenyne **52a** with arylboronic acid **50a** under the same conditions ($Pd(OAc)_2$, BQ, THF, rt, 20h) affords cross-conjugated trienes **53a** in 50-81% yield (Scheme 25).[48] However, allenyne **52b** (R^1 = Et, *n*-pentyl) under the same conditions gave mixtures of **54b** and **53b** ranging from 65:10% to 85:<2% yield, respectively.



Scheme 25. Oxidative carbocyclisation/arylation of allenyne **52**.

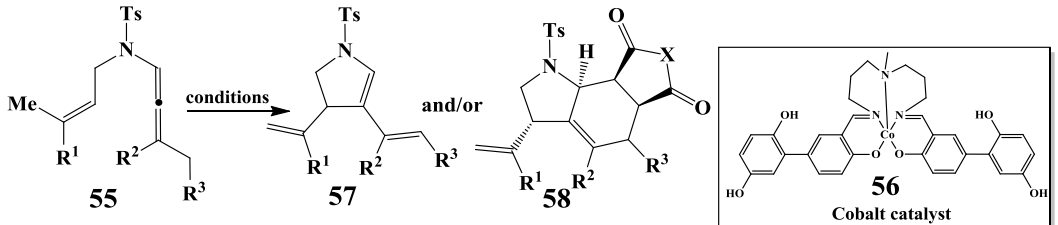
Formation of **53** fits a Scheme 24 mechanism but **54** does not fit the same catalytic cycle. The authors directed their attention towards initial transmetallation (Scheme 26) between the arylboronic acid **50** and palladium acetate giving ArPdOAc. The latter coordinates with the alkyne and allene **52** to furnish complex (**A**) followed by insertion to give vinyl palladium(II) intermediate (**B**). The terminal allene double bond inserts into the preformed Pd-C_{vinyl} bond to afford (**C**) which undergoes β-hydride elimination to give **53**. Compound **54** arises from the same intermediate (**A**) through sequential insertion of allene into the Pd-Ar bond to give (**D**) followed by insertion of the alkyne group into the preformed Pd-C_{vinyl} bond to afford (**E**) which undergoes β-hydride elimination to produce **54**. Regeneration of the complex involves loss of AcOH from HPdOAc generating Pd(0) which is oxidised by BQ to regenerate Pd(II).



Scheme 26. A possible mechanism for the formation of **53** and **54** from a common intermediate (**A**). BQ participates as a ligand and an oxidising agent.

Oxidative carbocyclisation of enallenes under both aerobic and non-aerobic conditions have been developed.[45,49] Aza-enallenes **55a** cyclised under conditions (i) and gave 71-84% yield of pyrrolines **57a** with small amounts of **58a** (X = CH=CH).

The latter resulted from [4+2] cycloaddition of 1,4-benzoquinone (BQ) to **57a** (Scheme 27).[50] Using BQ (2.1 equiv.) resulted in exclusive formation of *endo*-**58a** (R^1 = H, R^2 = Me, R^3 = H) in 95% yield. Applying aerobic conditions (ii) to Pd catalysed oxidative carbocyclisation of aza-enallenes **55b** gave only **57b** in 86-94% yield. Compound **55c** undergoes an oxidative carbocyclisation/Diels-Alder cascade in the presence of maleimide (as dipolarophile) under conditions (ii) to give a 91% yield of the fused tricyclic *endo*-adduct **58c** (X = NH). The catalytic cycle providing **57** is similar to Scheme 24 except the transmetallation step is replaced by a β-hydride elimination. Bäckvall and his co-workers enhanced the performance of the previous aerobic oxidation (Scheme 20) and engineered a new biomimetic hybrid cobalt catalyst **56** *via* covalently linking the 1,4-hydroquinone with Co(salmdpt) (salmdptH_2 = bis[3-(salicylideneimino)propyl]methylamine). Catalyst **56** combines the two redox cycles in Scheme 20 into one cycle and facilitates electron transfer between Pd(0) and the oxidant O_2.[49a,b, 50]

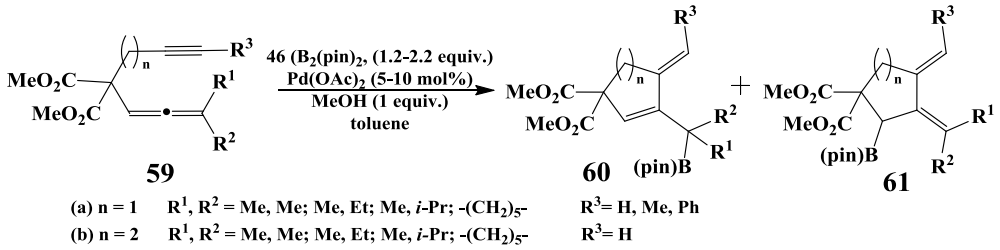


Conditions: (i) $Pd(OAc)_2$ (2 mol%), BQ (1.05 equiv.), THF, 50 °C, 4 h.
(ii) $Pd(OAc)_2$ (5 mol%), Co catalyst (5 mol%), O_2 (1 atm.), THF, 50 °C, 6 h.
(a) R^1 = H, Me R^2, R^3 = Me, Me; H, H; -$(CH_2)_4$- X = CH=CH
(b) R^1 = H, Me R^2, R^3 = Me, H; -$(CH_2)_4$-
(c) R^1 = R^3 = H R^2 = Me X = NH

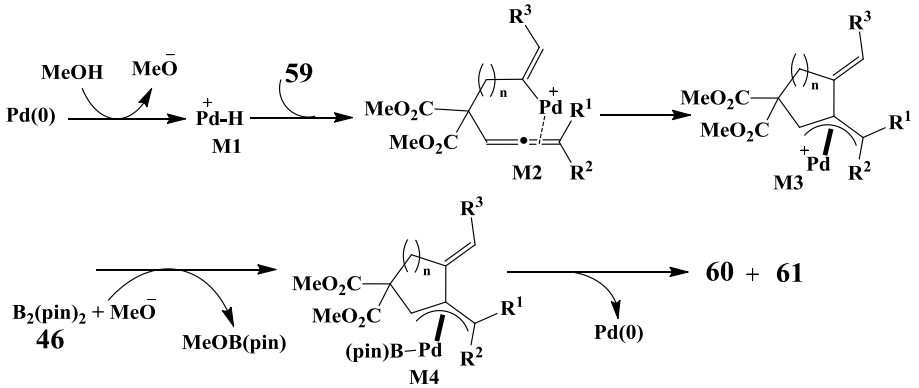
Scheme 27. Carbocyclisation of enallene **55** under aerobic and non-aerobic conditions.

Palladium catalysed carbocyclisation/borylation of allenyne **59a** (n = 1) in the presence of B_2pin_2 **46** gave a 36-82% yield of allylboronates **60a** and **61a** with ratios ranging from 67:33 to 100:0, respectively (Scheme 28).[51] Allenyne **59b** (n = 2) reacted under the same conditions to give the six-member allylboronates **60b** and **61b** (33-97%) with isomeric ratios of 23:77 to 100:0, respectively. The yield and the isomeric ratio are sensitive to the alkyne substituents (R^3 = Me, Ph) and the bulky groups (R^1, R^2 = Me, ^{i}Pr) on the terminal allenyl carbon. A possible mechanism is given in Scheme 29. Oxidative addition of MeOH to Pd(0) generates Pd-hydride species **M1** which hydropalladates the alkyne moiety in **59** forming vinyl-palladium intermediate **M2**. The allenyl group inserts into the Pd-vinyl carbon bond and

affords π-allyl complex **M3**. Transmetallation between **M3** and $B_2(pin)_2$ **46** gives **M4**. Reductive elimination of Pd(0) releases the products **60** and **61**.



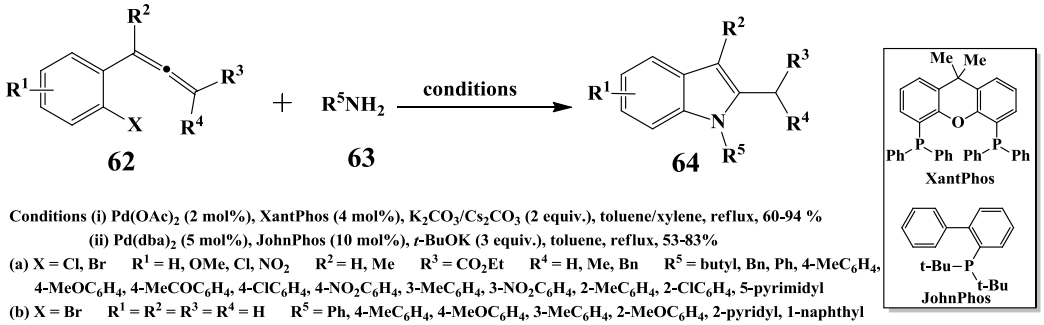
Scheme 28. Pd catalysed carbocyclisation/borylation of allenyne **59**.



Scheme 29. Proposed mechanism for the formation of **60** and **61**.

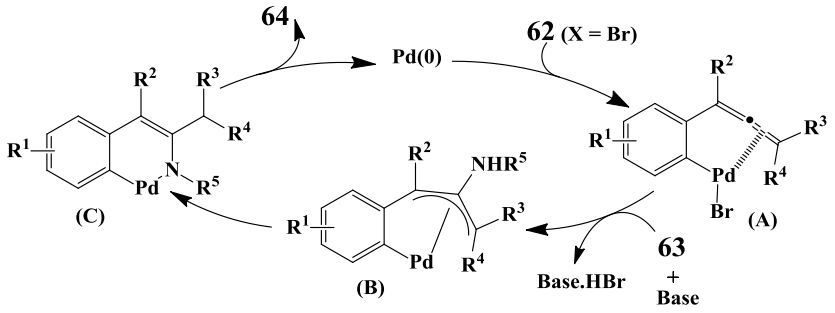
1.2.3 C−N Bond Formation.

The Pd catalysed nucleophilic addition of amines to allenes generates a C-N bond and provides a versatile and robust method for incorporating amines into acyclic and cyclic frameworks *via* both inter- and intramolecular reactions.[28a-c,52] A new synthesis of multisubstituted indoles was achieved with Pd(II)/XantPhos catalyst by reacting terminal substituted *ortho*-haloarylallenes **62a** with primary amines **63a** under conditions (i) to afford 60-94% of **64a** (Scheme 30).[53]



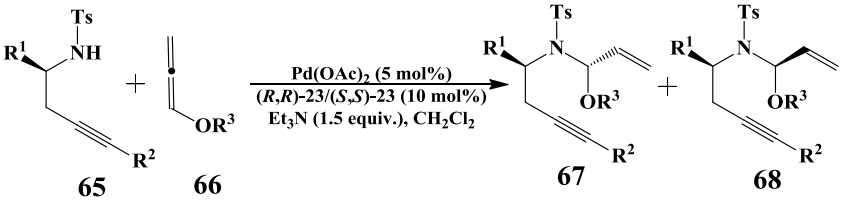
Scheme 30. Synthesis of indoles **64** *via* Pd catalysed *ortho*-haloarylallene/amine cascades.

However, terminal unsubstituted *ortho*-bromoallenes **62b** required modified (Pd(0)/JohnPhos) conditions (ii) to give indoles **64b** in 53-83% yield. A possible mechanism is shown in Scheme 31.

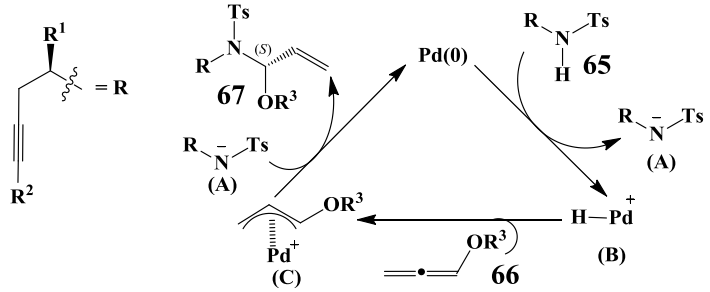


Scheme 31. Synthesis of substituted indoles through Pd catalysed allene reactions.

Homopropargyl amines **65** add to alkoxyallenes **66** (70 equiv.) using $Pd(OAc)_2$ in the presence of chiral ligand (*R*,*R*)-**23** (Scheme 13, page 10) to afford the *N*,*O*-acetals **67** and **68** in 96-99% yield with a diastereomeric ratio ranging from 14:1 to >25:1, respectively (Scheme 32).[54] The incorporation of (*S*,*S*)-**23** reversed the diastereoselectivity of **67** and **68** (ratio 1:13 to 1:25) with the same yield. A possible mechanism is depicted in Scheme 33. The reaction is initiated by oxidative addition of Pd(0) into N-H bond followed by hydropalladation of allene **66** to give π-allyl complex (**C**). Nucleophilic attack of anion (**A**) on (**C**) followed by reductive regeneration of Pd(0) afforded (*S*)-*N*,*O*-acetal **67** using chiral ligand (*R*,*R*)-**23**.

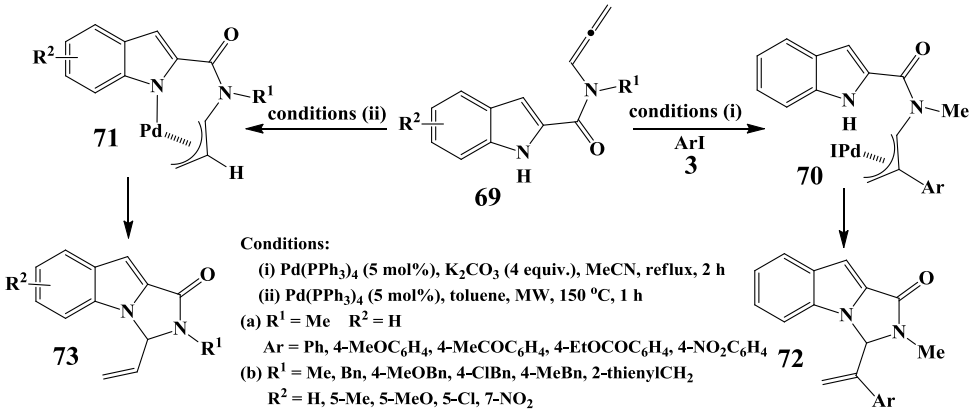


Scheme 32. Hydroamination of alkoxyallenes **66**.



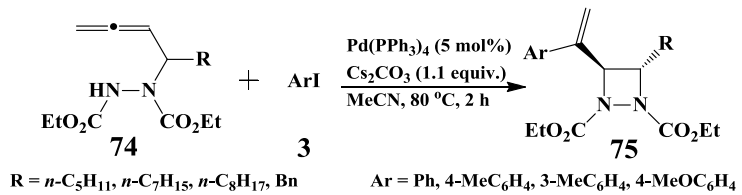
Scheme 33. Plausible hydroamination mechanism for the formation of **67**.

Broggini et al used allenamides as versatile scaffolds for creating 5- and 6-membered heterocycles.[55a-c] Thus, allenamide **69a** reacted with aryl iodides **3** and Pd(0) under thermal conditions (i) to generate the carbopalladation intermediate **70** which cyclised at the indolyl nitrogen to give tricyclic products **72** in 68-88% yield (Scheme 34). Subjecting **69b** to microwave conditions(ii), in the absence of ArI, afforded **73** (67-89%) *via* hydropalladation intermediate **71**.[55d]



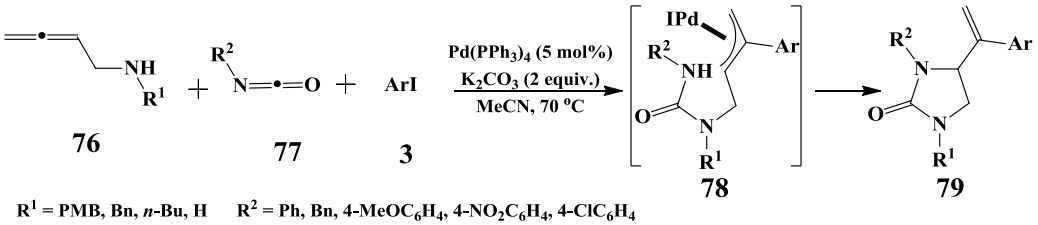
Scheme 34. Carboamination and hydroamination of allenamide **69**.

Ma and co-workers prepared allene tethered *N*-nucleophiles and coupled them with aryl halides using Pd conditions to generate an intermediate π-allyl which cyclised to give *N*-heterocycles.[56a-d] Thus, *trans*-1,2-diazetidines **75** (62-77%) were obtained from the reaction of allenyl hydrazines **74** with aryl iodides **3** (Scheme 35). Optically active allenes (*S*)-**74** (R = *n*-C_5H_{11}, *n*-C_7H_{15}) reacted with aryl iodides **3** (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$) under the same conditions to give 68-75% yield and 98.5-99.4% ee of (*S*,*S*)-**75**.[56e] The paper gives no explanation for the preference for formation of the 4-membered ring rather than the alternative 5- or 6-membered rings.



Scheme 35. Synthesis of *trans*-1,2-diazetidines **75**.

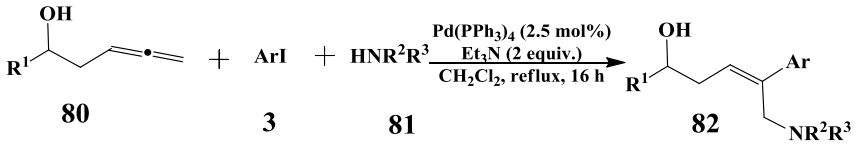
In the same vein, the Pd catalysed cascade reaction of allenyl amine **76** with isocyanate **77** and aryl iodide **3** afforded, *via* **78**, a 54-96% yield of imidazolidinones **79** (Scheme 36).[57]



R^1 = PMB, Bn, *n*-Bu, H R^2 = Ph, Bn, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4
Ar = Ph, 4-$MeOCOC_6H_4$, 4-$MeCOC_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-PhC_6H_4, 4-CNC_6H_4, 4-(4-BrC_6H_4)C_6H_4, 4-^{i}-PrC_6H_4, 3,5-$Me_2C_6H_3$, 3,4-$Me_2C_6H_3$, 3-thienyl, (*E*)-$C_6H_{13}CH$=CH, (*E*)-MeOCOCH=CH, 4-$NH_2C_6H_4$

Scheme 36. Pd Catalysed three component synthesis of imidazolidinones.

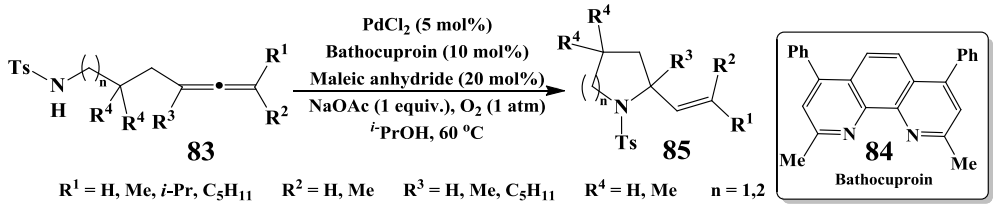
Homoallenol **80** undergoes Pd(0) catalysed reaction with aryl iodide **3** and amine **81** to give (*Z*)-1,5-amino alcohols **82** regio- and stereo-selectively in 54-90% yield (Scheme 37).[58] This process is applicable to both racemic and chiral (*R* and *S*) alcohol **80**. In the latter case, the chirality of the starting allene **80** was retained in the product (95-97% ee) with no involvement of the hydroxyl group.



R^1 = 4-$MeOC_6H_4$, 4-ClC_6H_4, $PhCH_2CH_2$ R^2 = Bn, *n*-Bu R^3 = H, *n*-Bu, Bn
Ar = Ph, 4-MeC_6H_4, 3-BrC_6H_4, 2-naphthyl

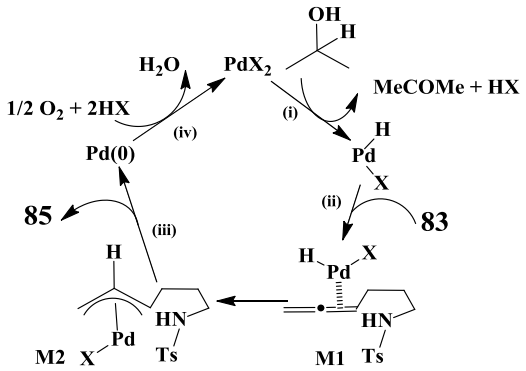
Scheme 37. Cascade synthesis of 1,5-amino alcohols.

Pyrrolidine and piperidine heterocycles **85** were synthesised in 41-85% yield from *N*-(allenyl)tosylamide **83** *via* a Pd(II) catalysed regio- and *trans*-selective hydroamination process in the presence of bathocuproin ligand **84**, an oxygen atmosphere and isopropanol (Scheme 38).[59] The proposed reaction sequence (Scheme 39) involves: (i) oxidation of isopropanol to acetone with generation of a Pd(II) hydride species, (ii) allene **83** coordination to the metal (intermediate **M1)** and insertion into the Pd-H bond to deliver π-allyl intermediate **M2**, (iii) intramolecular nucleophilic addition at the inner π-allyl-carbon gives the product **85** and reductively releases Pd(0), (iv) oxidation of Pd(0) by the oxygen atmosphere regenerates Pd(II).



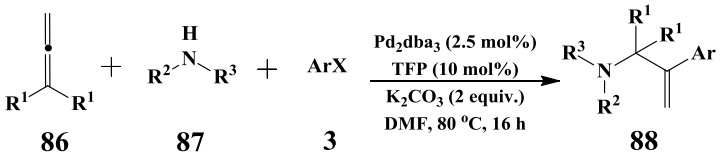
R^1 = H, Me, *i*-Pr, C_5H_{11} R^2 = H, Me R^3 = H, Me, C_5H_{11} R^4 = H, Me n = 1,2

Scheme 38. Synthesis of 5- and 6-membered nitrogen heterocycles.



Scheme 39. Pd(II) catalysed hydroamination.

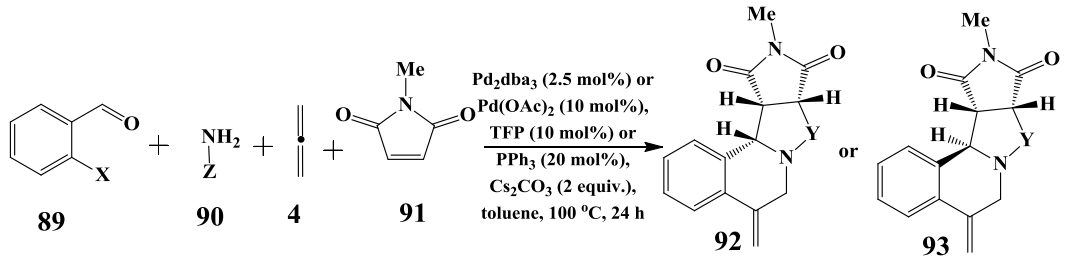
The Pd(0) catalysed reaction of allene **86** with protected hydroxylamine/formamide **87** and an aryl halide/triflate **3** afforded allylamines **88** in 67-97% yield (Scheme 40).[60] In the case of 1,1-dimethylpropadiene **86** (R^1 = Me), the nucleophile attacks the substituted end of π-allyl intermediate regioselectively and produces **88** as the sole product.



R^1 = H, Me R^2 = OBn, OBoc R^3 = H, Boc, CHO X = I, Br, OTf
Ar = Ph, 2-MeOC6H4, 4-MeCOC6H4, 4-MeOCOC6H4, 4-NO2C6H4, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-$MeCOC_6H_4$, 4-PhC_6H_4, 3-$MeOCOC_6H_4$, 2-thienyl, 2-pyridyl, 5-pyridyl, 1,3-dimethyluracil-5-yl

Scheme 40. Synthesis of multisubstituted allyl amines.

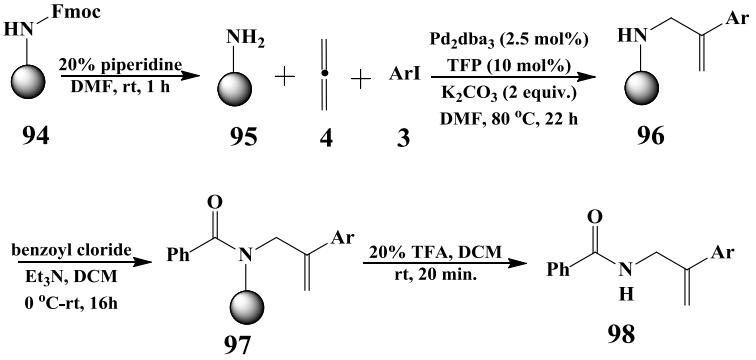
Grigg et al reported a sequential Pd catalysed allylation of *N*-nucleophiles tethered alkene in the presence of aryl halides and propadiene followed by Ru catalysed ring closing metathesis to give a broad range of five and six membered *N*-heterocycles.[61a,b] Rewardingly, combination of [3+2]cycloadditions with Pd catalysed allenylation strategies enabled the construction of triazolo- and tetrazolo-tetrahydroisoquinolines and isoquinolines in a one pot reaction.[61c] In the same vein, they reacted *ortho*-haloaryl aldehyde **89** with an α-amino acid ester or hydrazine or hydroxylamine **90** together with propadiene **4** and *N*-methylmaleimide **91** in the presence of a Pd(0) catalyst in four component cascade processes to form tetracyclic products **92** or **93** (Scheme 41). α-Amino acid ester **89a** gave exclusively *endo*-**92a** (54-69%) whilst hydrazine **90b** and hydroxylamine **90c** afforded *exo*-**93b** (53-72%) and *exo*-**93c** (62%), respectively.[61d]



(a) X = I, Br Z = CH(R)CO_2Me Y = C(R)CO_2Me R = Me, Ph, Bn, $MeSCH_2CH_2$, $MeOCOCH_2$
(b) X = I, Br Z = NHR Y = NR R = 2,5-$F_2C_6H_3$, 2-FC_6H_4, 2-$CF_3C_6H_4$, 3,4-$Cl_2C_6H_3$, 3-Cl-4-FC_6H_3, 2,4-$Cl_2C_6H_3$, CH_2CF_3
(c) X = I Z = OH Y = O

Scheme 41. Four component cascades.

Interestingly, the Grigg group developed sequential 1,3-dipolar cycloaddition/Pictet-Spengler/Pd catalysed allenylation reactions using solid phase technology.[62a] Furthermore, polymer supported allene and amines were involved in Pd catalysed four and three component cascades, respectively.[62b,c] In the latter case the resin, containing a protected primary amino group (Rink Amide MBHA) **94**, was sequentially deprotected then used as a nucleophile **95** together with propadiene **4** and aryl iodides **3** in three component Pd(0) catalysed process to give resin supported substituted allylamines **96** which were acylated with benzoyl chloride and finally removed from the resin to give high purity (96 - >99%) products **98** in 55-97% overall yield (Scheme 42).[62c]



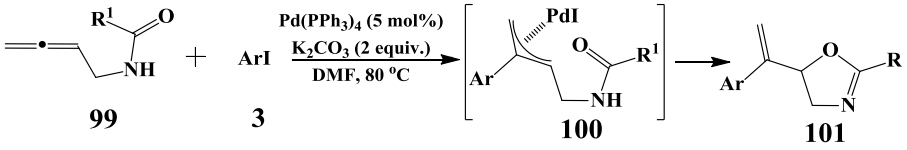
Ar = 3-$NO_2C_6H_4$, 3,4-$Cl_2C_6H_3$, 3-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 4-$EtOCOC_6H_4$, 4-$MeOCOC_6H_4$, 6-chloropyridyl, 1-naphthyl

Scheme 42. Solid phase cascades.

1.2.4 C−O Bond Formation.

The hydroxyl group is a well known nucleophile and allene tethered hydroxyl groups (e.g. alcohols, phenols, acids, enols) are used to attack both π-allyl species and activated allene double bonds intramolecularly affording broad range of oxygenated heterocycles.[63] Thus, *N*-(buta-2,3-dienyl)amide **99** couples with aryl iodide **3** to form

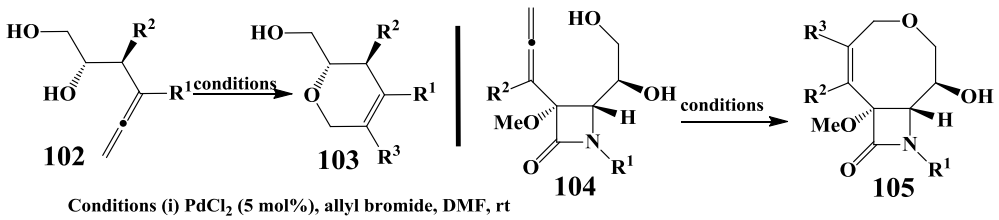
π-allyl intermediate **100** *in situ* which undergoes intramolecular *O*-cyclisation to form oxazoline derivatives **101 (**52-94%) (Scheme 43).[64]



R = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeOCOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, *n*-Bu, Bn, 2-furyl
Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-EtOCOC$_6$H$_4$, 4-MeCOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-CNC$_6$H$_4$, 4-PhC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-FC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-thienyl, *N*-tosyl-3-indolyl, (*E*)-PhCH=CH, (*E*)*n*-BuCH=CH

Scheme 43. Heterocyclisation of *N*-allenylamide.

Allene tethered hydroxyl groups at the α-δ positions provide access to 5-8 membered oxygen heterocycles through Pd(II) catalysed intramolecular oxycyclisation.[65a-i] For example, β,γ-allendiol **102a** reacts with allyl bromide in the presence of $PdCl_2$ in DMF at rt (conditions (i)) to give dihydropyrans **103a** in 65-78% yield (Scheme 44) whilst allene **102b** reacts under different conditions (conditions (ii)) to furnish oxybromination products **103b** in 51-53% yield. These reactions involve chemo- and regio-specific attack of β-OH groups at the terminal allene carbon atom. In contrast, γ,δ-allendiol **104c**,**d** reacts under both conditions (i and ii) to form 8-membered oxycycles **105c**,**d** in 58-73 and 44-52% yield, respectively. In the latter cases, the δ-OH group reacts chemoselectively and adds regioselectively to the terminal allenic carbon.[65c]

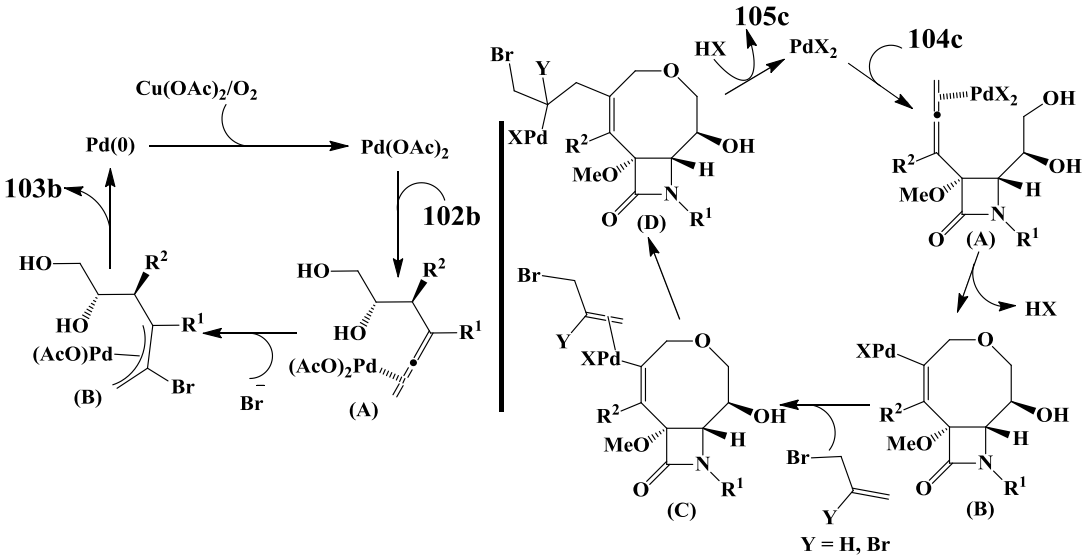


Conditions (i) $PdCl_2$ (5 mol%), allyl bromide, DMF, rt
(ii) $Pd(OAc)_2$ (7 mol%), LiBr, $Cu(OAc)_2$, O_2, K_2CO_3, MeCN, rt
(a) R^1 = Me, Ph R^2 = OCOPMP R^3 = CH$_2$CH=CH$_2$
(b) R^1 = Me R^2 = OCOPMP, OTPS R^3 = Br
(c) R^1 = PMP, Bn R^2 = Me, Et, Ph, CH$_2$OBn R^3 = CH$_2$CH=CH$_2$, CH$_2$C(Br)=CH$_2$
(d) R^1 = PMP, Bn R^2 = Me, Et R^3 = Br

Scheme 44. Chemo- and regioselectivity formation of **103** and **105**. (PMP = 4-methoxyphenyl, TPS = *tert*-butyldiphenylsilyl).

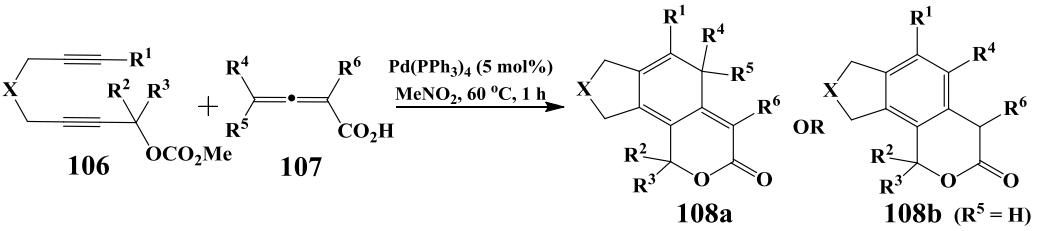
A possible catalytic cycle for oxybromination of allene **102b** to give bromodihydropyran **103b** is shown on the left hand side of Scheme 45. Chelation of the metal to the allene double bond gives the intermediate (**A**) which is attacked by bromide anion giving π-allyl palladium (II) complex (**B**). Chemospecific addition of the secondary β-OH group to the terminal carbon atom on the π-allyl gives the

product **103b**. Pd(II) is regenerated from Pd(0) *via* $Cu(OAc)_2/O_2$ oxidation. The formation of the 8-membered product **105c** (Scheme 45, right) proceeds *via* allene-palladium complex (**A**) which undergoes chemoselective intramolecular addition of the primary δ-OH group to the terminal allene carbon atom giving intermediate (**B**). Allyl bromide coordinates with the metal complex (**B**) to give (**C**) followed by migratory insertion to afford σ-complex (**D**) which under acidic conditions gives the product **105c** *via* β-bromide elimination.



Scheme 45. Possible mechanisms for the formation of **103b** (left) and **105c** (right).

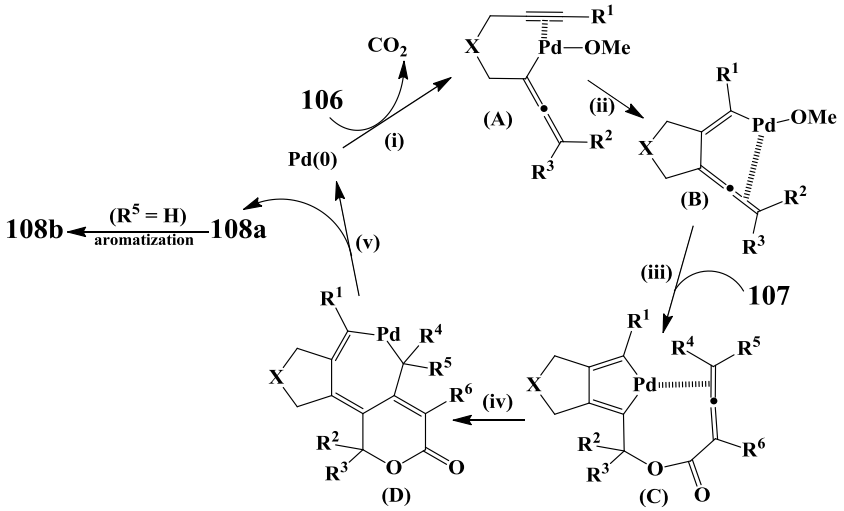
An interesting cascade process which generates tricyclic N/O-heterocycles has been reported (Scheme 46).[66] The cascade combins the 2,7-diynylic carbonate **106a** with the 2,3-allenoic acid **107a** in the presence of $Pd(PPh_3)_4$ in nitromethane and generates tricyclic products **108a (**54-87%) whereas allenoic acid **106b** gives aromatized products **108b** in 59-69% yield. The proposed mechanism (Scheme 47) involves, (i) oxidative addition of Pd(0) to propargylic carbonate **106** (Pd complex promotes the decarboxylation) generating complex (**A**), (ii) the terminal alkyne group coordinates to Pd(II) and inserts to give alkenyl-palladium methoxide (**B**), (iii) coordination of Pd(II) to the allenyl double bond facilitates intermolecular addition of the allenoic anion **107** to the terminal allene carbon which produces palladabicycle (**C**), (iv) intramolecular carbopalladation of the electron rich allenyl terminal double bond generates palladacycle (**D**), (v) reductive elimination of Pd(0) from (**D**) affords the tricyclic product **108a** which aromatizes when R^5 = H to produce **108b**.



(a) X = NTs, O, $(EtOCO)_2C$; R^1 = H, allyl, *n*-Bu; R^2, R^3 = H, H; Me, Me; $-(CH_2)_4-$; H, Ph; H, *n*-Pr; R^4, R^5 = Me, Me; Et, Ph; Me, 4-BrC_6H_4; $-(CH_2)_5-$; R^6 = Me, allyl

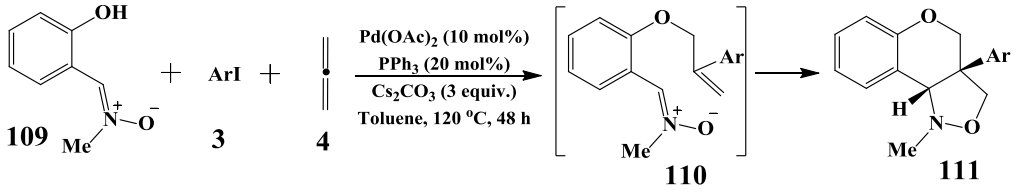
(b) X = NTs; R^1 = H; R^2, R^3 = Me, Me; R^4, R^5 = 1-naphthyl, H; 4-BrC_6H_4, H; R^6 = Pr

Scheme 46. Pd(0) catalysed formation of fused tricyclic skeletons.



Scheme 47. Possible mechanism for the formation of **108a** and **108b**.

Grigg's group developed a palladium catalysed cascade reaction of propadiene **4** with aryl iodide **3** and the phenol *ortho*-tethered nitrone **109** which generates the dipolarophile linked nitrone intermediate **110** *in situ* and subsequently undergoes intramolecular [3+2]cycloaddition to give tricyclic isoxazolidines **111** in 50-77% yield (Scheme 48).[67]

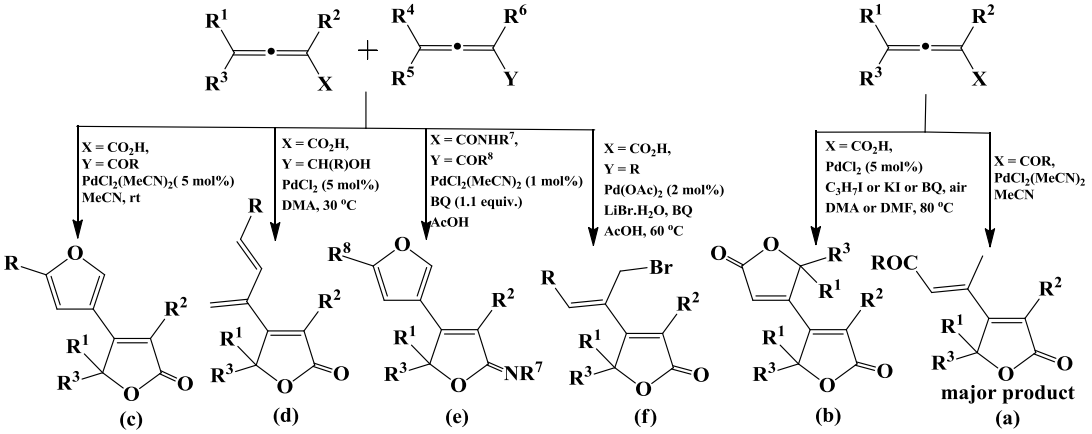


Ar = Ph, 3,5-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 3,4-$(OCH_2CH_2O)C_6H_3$, 2-thienyl, 3-pyridyl

Scheme 48. Palladium catalysed allene cascade with in situ dipolarophile generation/cycloaddition.

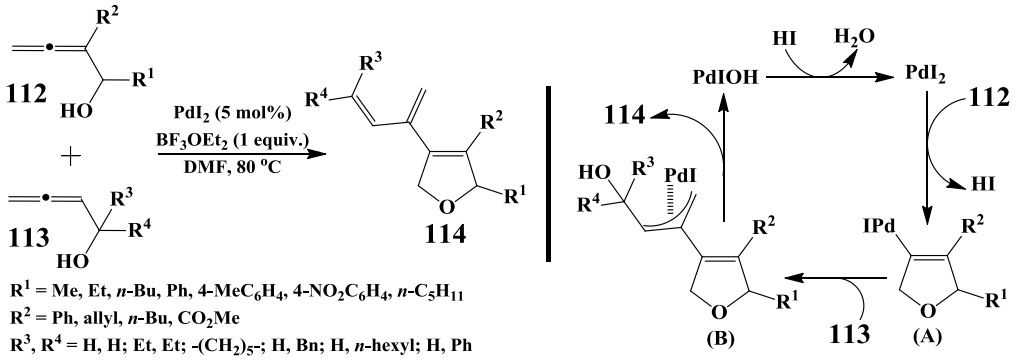
Ma and others have reported homodimeric-cyclisation of 1,2-allenyl ketones[68a,b] and 2,3-allenoic acids[68c,d] (Scheme 49, a and b), and heterodimeric cyclisation of 2,3-allenoic acids or 2,3-allenamides with 1,2-allenyl ketones[69a-c] (c, e) or 2,3-allenols[69d]

(d) or unfunctionalized allenes[69e] (f) as a versatile method for constructing new scaffolds employing Pd(II) catalysts.



Scheme 49. Pd(II) catalysed homo- (right) and heterodimeric cyclisation (left) of allenes.

In related work, Alcaide and Almendros heterocoupled 2,3-allenols with protected 2,3-allenols to furnish 2,5-dihydrofurans **114**.[70a] In this strategy, the unprotected 2,3-allenol supplies the 2,5-dihydrofuran moiety and the protected 2,3-allenol supplies the buta-1,3-diene fragment regioselectively at the 4-position of the dihydrofuran. Subsequently, Ma et al reported homodimeric coupling-cyclisation of 2,3-allenols giving the same backbone **114**.[70b] Interestingly, two different 2,3-allenols **112** and **113** couple to give dihydrofurans **114** in 38-81% yield (Scheme 50, left).[70c]

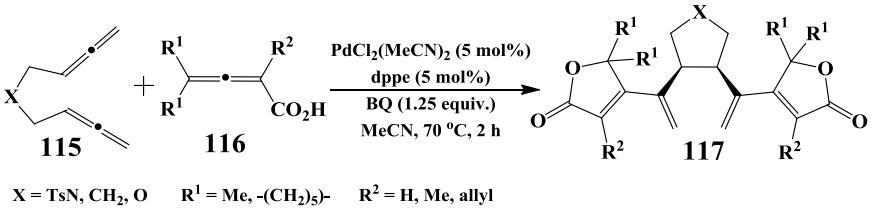


Scheme 50. Coupling-cyclisation reaction of two different α-allenols (left) and the proposed mechanism (right).

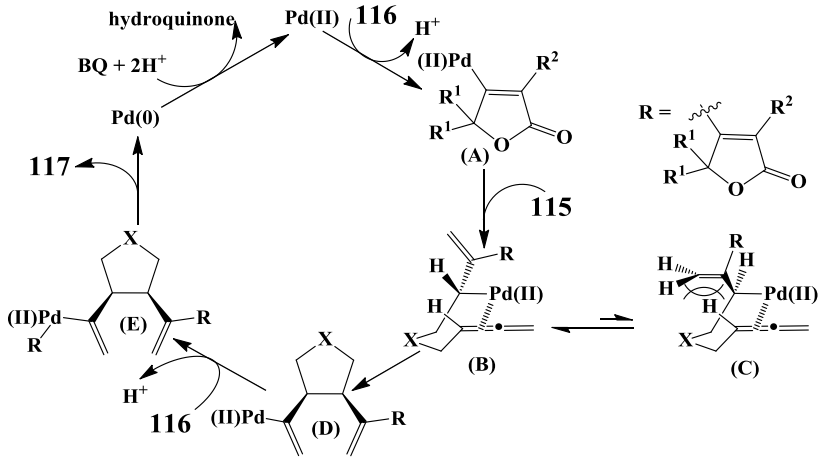
In this case the first 2,3-allenol **112**, which has a substituent at the 2-position, prefers to form a dihydrofuran moiety whereas the second 2,3-allenol **113**, which has no substituent at the 2-position, generates a 1,3-butadiene fragment at the 4-position of the preformed dihydrofuran species.[70c] A general mechanism for this strategy is depicted on the right hand side of Scheme 50. Pd(II) coordinates with the 2,3-allenol

112 terminal double bond and activates intramolecular OH addition to afford intermediate (**A**) which carbopalladates **113** to give the π-allyl complex (**B**). The latter undergoes β-hydroxide elimination to give the product **114** and PdIOH. The preformed HI converts PdIOH into the active PdI_2 to complete the catalytic cycle.

In 2010, Ma and his co-workers reported a process which creates 3-rings from 1,5-bisallenes **115** and 2,3-allenoic acids **116** and afforded *cis*-products **117** in 52-81% yield (Scheme 51).[71] A possible mechanism (Scheme 52) involves initial Pd(II) mediated cyclisation of allene **116** to afford oxypalladation intermediate (**A**). Carbopalladation of one allenyl group in **115** with (**A**) generates η^1-complexes (**B**) and (**C**). The latter complex (**C**) suffers from steric congestion which directs the equilibrium toward the stable intermediate (**B**). Intramolecular *cis*-carbopalladation of the second allenyl group gives σ-complex (**D**). A second molecule of **116** coordinates to complex (**D**) and promotes intramolecular cyclisation to give intermediate (**E**). The latter undergoes reductive elimination of Pd(0) and released the tricyclic product **117**. Oxidation of Pd(0) by benzoquinone in the presence of acid regenerates the active Pd(II) catalyst.



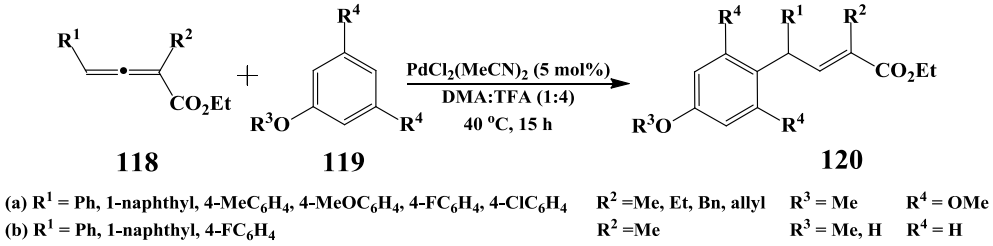
Scheme 51. Pd(II) catalysed tricyclisation of **115** with **116**.



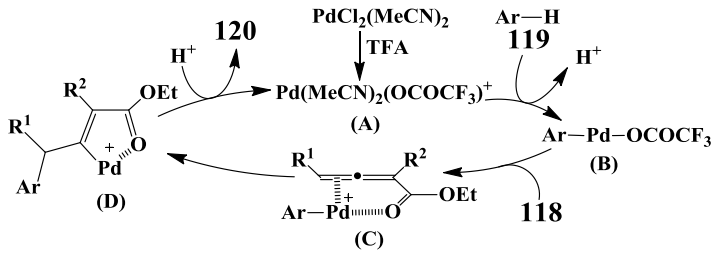
Scheme 52. A rational catalytic cycle for the formation of **117**.

1.2.5 Pd catalysed allene chemistry via C-H activation.

Palladium catalysed C-H functionalisation has attracted strong interest, from economic and green chemistry points of view, due to not requiring palladium activating scaffolds such as halogens, etc. Currently, few examples of Pd catalysed C-H functionalisation of arenes involving allenes are known. A typical example is the hydroarylation of 2,3-allenoates **118a,b** *via* Pd(II) catalysed C-H activation of 1,3,5-trimethoxybenzene **119a** or anisole **119b** (R^3, R^4 = Me, H) or phenol **119b** (R^3 = R^4 = H) to afford 4,4-diarylbut-2(*E*)-enoate **120** (37-70%) in a regio- and stereo-selective manner (Scheme 53).[72] A possible catalytic cycle (Scheme 54) is as follows: (i) $PdCl_2(MeCN)_2$ in the presence of TFA gives $Pd(MeCN)_2(OCOCF_3)_2$ (**A**), (ii) electrophilic palladation of Ar-H **119** gives aryl-palladium complex (**B**), (iii) chelation of **118** by the double bond and the carbonyl group gives intermediate (**C**) which undergoes migratory insertion regioselectively to give carbopalladation intermediate (**D**) in which Pd chelating C=O group and supporting *E*-isomer, (iv) protonation of (**D**) releases the product **120** and the Pd(II) species (**A**).



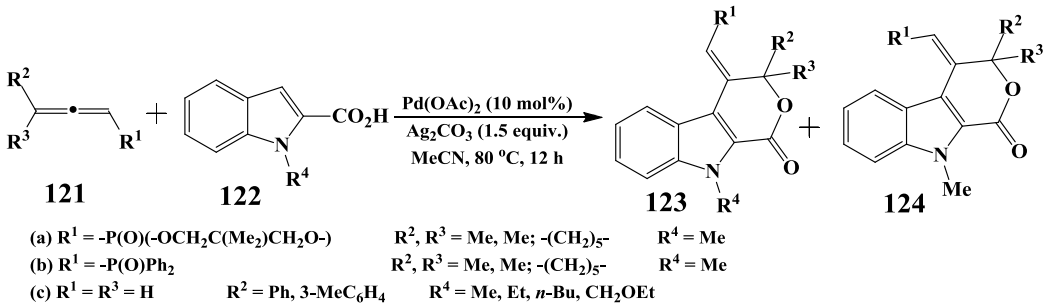
Scheme 53. Pd catalysed C-H functionalisation of **119** with **118**.



Scheme 54. Proposed mechanism for hydroarylation of **118**.

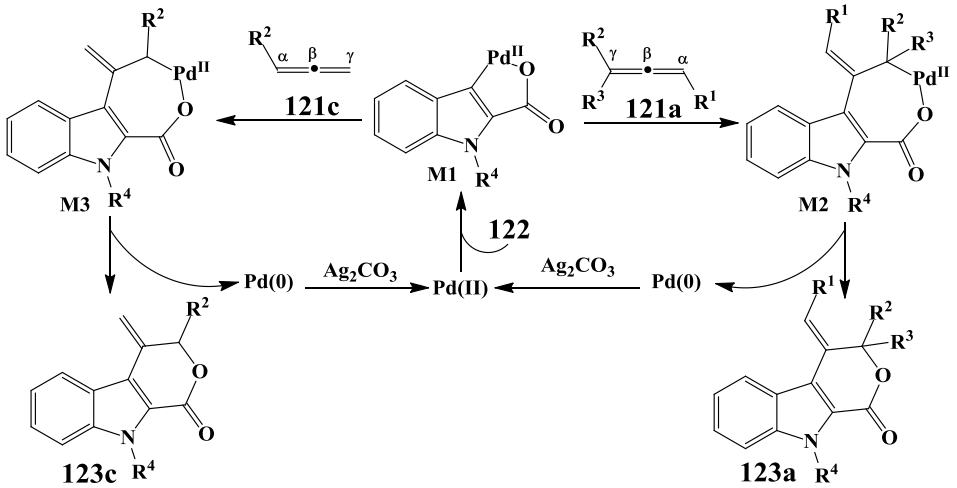
A further example is the reaction of allenylphosphonate **121a** with 1-methylindol-2-carboxylic acid **122a** *via* $Pd(OAc)_2$ catalysed C-H activation to give the *Z*-indolopyranone **123a** (65-68%) as the sole product whereas allenylphosphine oxide **121b** gives a 7:3 mixture of *Z*/*E* isomers **123b** and **124b** in 54-65% yield, respectively, (Scheme 55).[73] On the other hand, arylallene **121c** reacts

regioselectively with *N*-substituted indole-2-carboxylic acid **122c** under the same conditions to give the indolopyranones **123c (**43-68%).



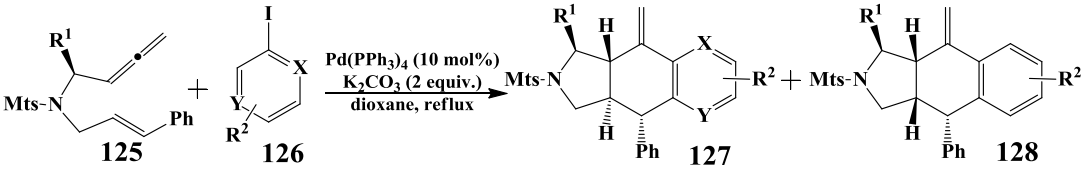
Scheme 55. Synthesis of indolopyranones **123** and **124**.

A mechanism for the formation of **123a** and **123c** is proposed in Scheme 56: (i) the acetate ligand on Pd(II) is displaced by the indole carboxylate ligand **122** which enhances intramolecular C-H activation of the indole 3-position and cyclisation to the palladacycle **M1**, (ii) allenes **121a** and **121c** coordinate with the Pd(II) complex **M1** and the external β,γ-C=C group in **121a** or the internal α,β-C=C group in **121c** undergo migratory insertion to **M2** or **M3**, respectively, (iii) reductive elimination of Pd(0), which is oxidized by Ag_2CO_3 and regenerates the Pd(II) complex, gives the products **123a** or **123c**, respectively.



Scheme 56. Proposed mechanistic route to pyranoindoles **123a** and **123c**.

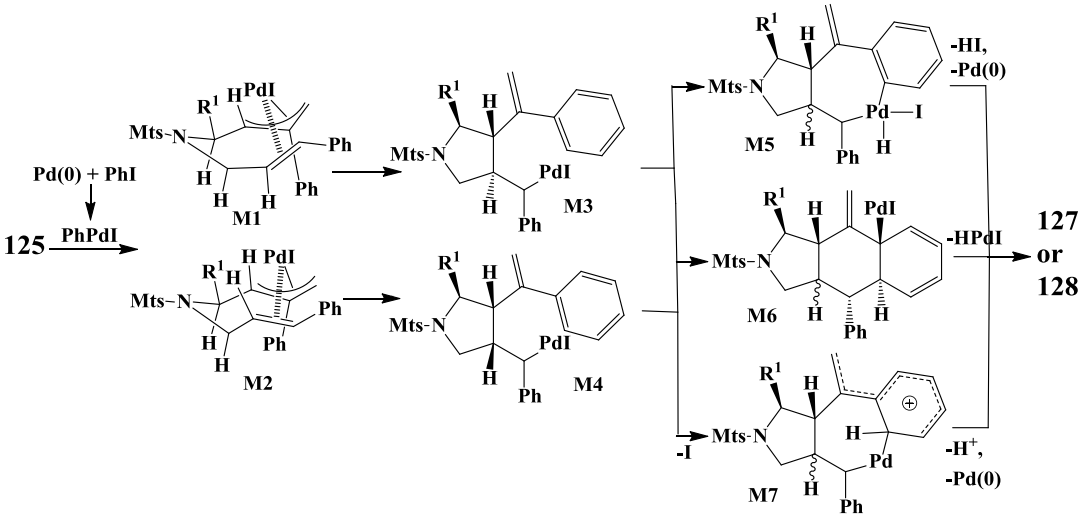
N-Cinnamylaminoallene **125a** reacts with aryl iodide **126a** in the presence of $Pd(PPh_3)_4$ and K_2CO_3 to furnish tricyclic products **127a** and **128a** in 21-41% and 2-36% yield, respectively (Scheme 57)[74] whereas 2-iodopyridine and 2-iodopyrazine under the same conditions afford **127b** as the sole product in 49-62% yield.



(a) X = Y = CH $R^1 = CHMe_2, CH_2CHMe_2, CH_2Ph, CMe_3, CH(Me)CH_2Me$ R^2 = H, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$
(b) X, Y = N, CH; N, N $R^1 = CHMe_2$ R^2 = H

Scheme 57. Production of fused tricyclic skeletons *via* C-H functionalisation. (Mts = 2,4,6-trimethylphenylsulfonyl)

A possible mechanism for the formation of **127** and **128** (Scheme 58) involves: (i) π-allyl Pd(II) intermediates **M1** and **M2** formed from sequential oxidative addition of Pd(0) to Ar-I, allene **128** coordination with ArPdI and insertion into Ar-Pd bond, (ii) intramolecular carbopalladation of the linked alkene group results in **M3** and **M4**, respectively, (iii) aromatic C-H activation followed by reductive elimination affords products **127** and **128**, respectively, and regenerated Pd(0). Activation of the C-H group could proceed in three possible ways. The first involves intramolecular oxidative addition of Pd(II) into the aromatic C-H bond forming Pd(IV) intermediate **M5**. The second is carbopalladation of the phenyl group to afford **M6** followed by an unusual *anti-β*-hydride elimination (supported by rearomatisation) or stereomutation of the allyl Pd(II) species through η^3-η^1-η^3 mechanism to deliver the acceptable *syn-β*-hydride elimination. The third is electrophilic addition of Pd(II) onto the aromatic group generating the cationic intermediate **M7**.

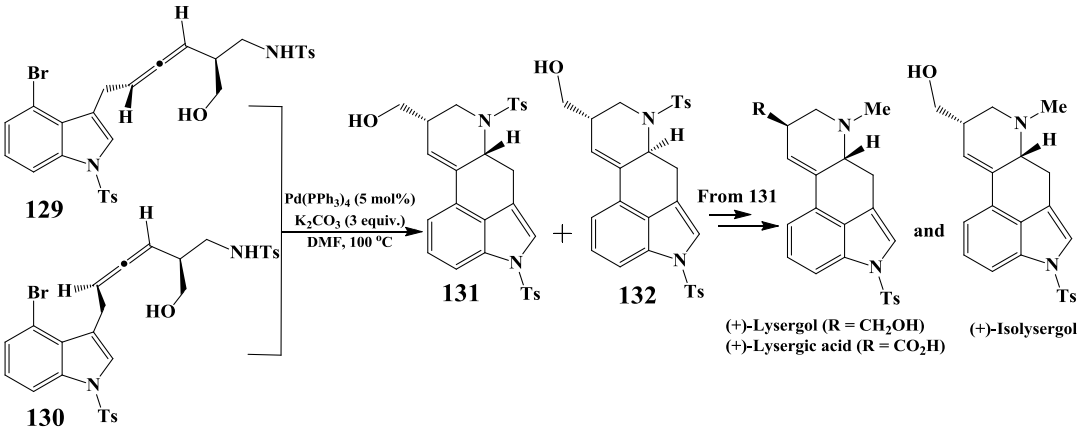


Scheme 58. Possible mechanisms for formation of **127** and **128**.

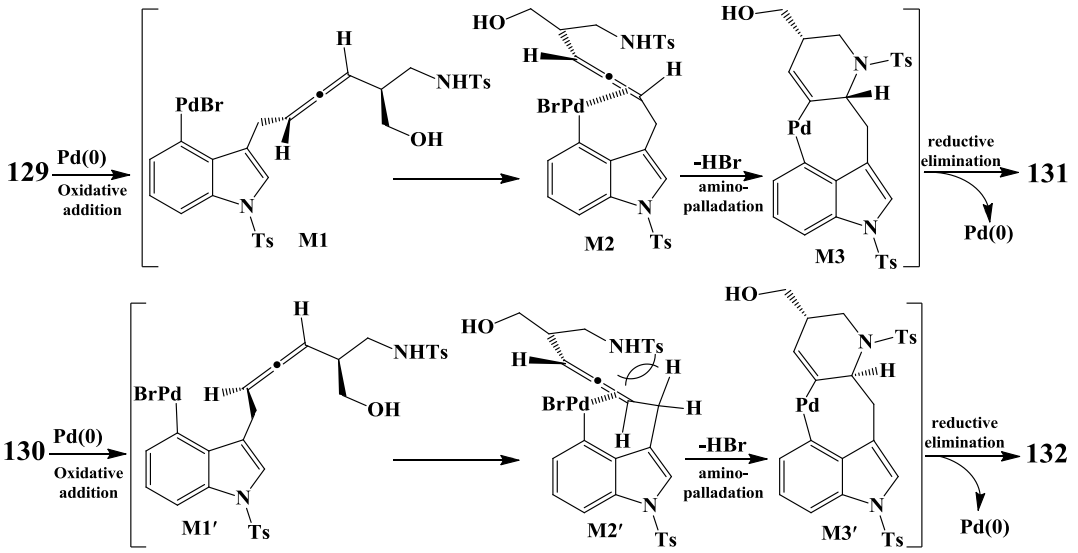
1.2.6 Allene scaffolds and natural product synthesis.

There are significant number of allenic natural products many of which have interesting biological activities.[25b,c,75] Derivatisation of bioactive compounds (e.g. steroids, amino acids, nucleoside analogues) with allenyl groups potentially offer access to modified biologically and pharmaceutically active products.[26] Moreover, chiral allenes have the ability to transfer chirality to new stereogenic centres in such products and thus permit construction of C-C and C-heteroatom bonds in a regio- and stereoselective manner. These features also encourage incorporation of allenes in asymmetric syntheses of biologically interesting skeletons and natural products.[25a,26] Some examples of the latter are given below.

Ergot alkaloids are a class of compounds produced by the fungus *Claviceps purpurea* and they have hallucinogenic, psychotropic, analgesic and uterus and intestine-stimulating properties.[76a,e,f] They find use as dopamine and serotonin receptors agonists, antimigraine, induce uterine muscle contraction and facilitate the transport of the antibiotics across cell membranes.[76a-c,e,f] These natural products are used in a broad range of drugs, e.g. cafergot, ergometrine, nicergoline, pergolide, cabergoline,....etc.[76d,e] Ergot alkaloids (lysergol, isolysergol and lysergic acid) have been synthesized by Fujii and Ohno *via* Pd(0) mediated intramolecular cyclisation of an allene tethered 4-bromoindolyl group from one end and an amino group from the other.[77a-c] Thus, $Pd(PPh_3)_4$ induced intramolecular carboamination of allene **129** (dr = 94:6) to give a 92:8 diastereomeric mixture of **131** and **132** in 76% yield (Scheme 59).[77a] The opposite diastereomer **130** (dr = 94:6) reacted under the same conditions to afford a 31:69 mixture of **131** and **132** in 43% yield. A rational carboamination mechanism is proposed in Scheme 60. Oxidative addition of **129** to Pd(0) affords intermediate **M1**. Intramolecular coordination between the allenyl group and the Pd(II) (intermediate **M2**) activates regioselective aminopalladation of the allenyl double bond and delivers palladacycle **M3** which undergoes a reductive elimination sequence to provide the major isomer **131**. Following the same sequence, **130** gave the opposite isomer **132** through intermediates **M1′**, **M2′** and **M3′**. The low yield in the case of **130** is ascribed to steric congestion between the NTs and methylene protons in the intermediate **M2′** which suppress the aminopalladation step.



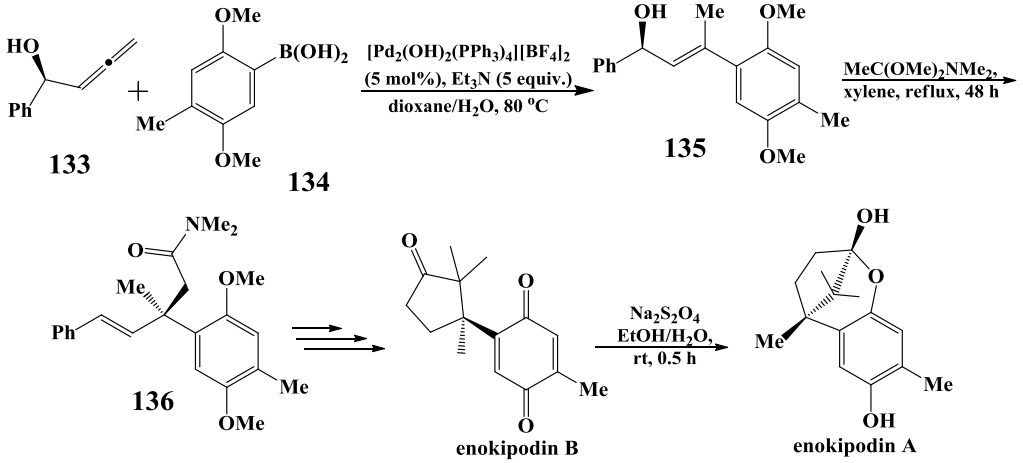
Scheme 59. Pd(0) catalysed synthesis of ergot alkaloids.



Scheme 60. Suggested aminopalladation mechanism for the synthesis **131** and **132**.

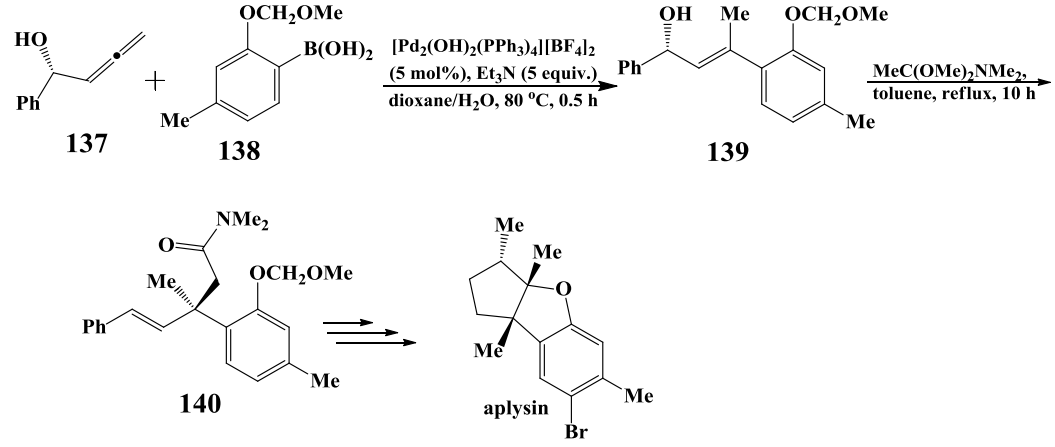
Enokipodins A and B are natural products isolated from the cultural broth of the edible mushroom *Flammulina velutipes*. They exhibit antimicrobial activity against the fungus *Cladosporium herbarum* and against both the gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis.*[78a-c] Aplysin is also a natural product isolated from the sea hare *Aplysia kurodai*, opisthobranchs and the red sea alga *Laurencia*. The latter is responsible for the natural occurrence of aplysin because the sea hare *Aplysia* and opisthobranchs feed on *Laurencia* and exhibit antifeedant properties to protect themselves from predators.[78d-f] Yoshida and co-workers based their synthesis of these natural products on a previous palladium catalysed regiospecific addition of an arylboronic acid to an allenol.[79a] Chiral allenol **133** coupled with arylboronic acid **134** in the presence of $[Pd_2(OH)_2(PPh_3)_4][BF_4]_2$ and

Et_3N in dioxane/H_2O (20:1) at 80 °C to afford *E*-allyl alcohol **135** (68%) (Scheme 61).[79b] Eschenmoser-Claisen rearrangement of alcohol **135** afforded the key intermediate **136** in 80% yield and 91% ee. A further five steps afforded enokipodin B which, when treated with $Na_2S_2O_4$, delivered enokipodin A. A reasonable catalytic sequence involves transmetallation between $PdL_n(OH)_2$ and $ArB(OH)_2$ **134** to give $ArPdL_n(OH)$. Allene **133** coordinates with $ArPdL_n(OH)$ then the terminal allene double bond inserts between Ar-Pd and generates an allyl palladium intermediate which hydrolyses to give **135** and regenerated $PdL_n(OH)_2$.[79c]



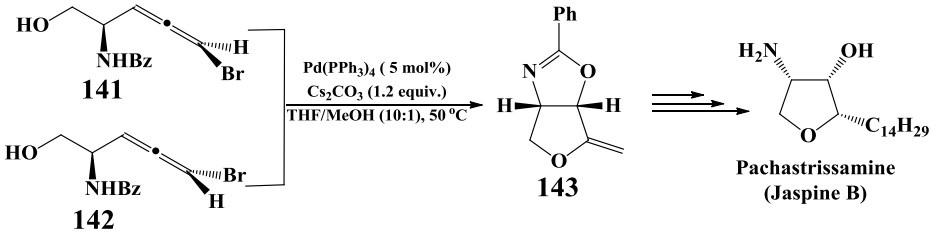
Scheme 61. Synthesis of enokipodins A and B.

A similar formal total synthesis of aplysin is depicted in Scheme 62.[79d] The reverse enantiomer **137** coupled with **138** and produced *E*-allyl alcohol **139** (74% yield, 95% ee). Claisen-type rearrangement of **139** gave the building block **140** (84% yield, 95% ee) which was subjected to further steps to finally deliver aplysin.

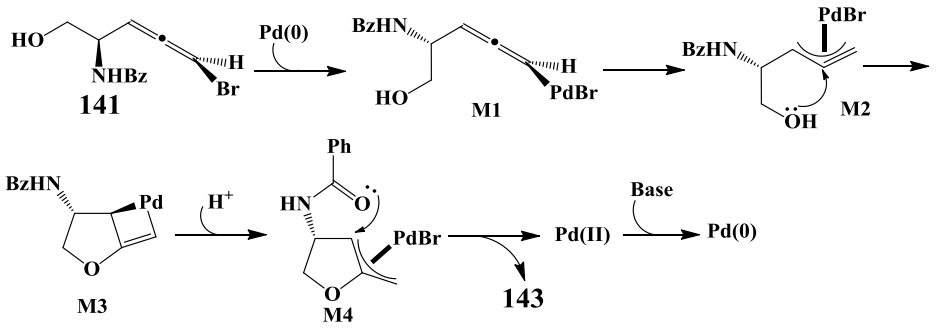


Scheme 62. Outline enantioselective synthesis of aplysin.

Bromoallenes tethered (*N*, *O*, *C*)-nucleophiles and bromoallenes linked with two nucleophiles separated by a linker have been developed by Ohno and Tanaka to furnish heterocyclic and fused bicyclic products, respectively.[80a-d] Furthermore, Ohno and Fujii designed propargyl chloride/carbonate and bromoallene scaffolds carrying a branched alkyl group with two nucleophiles as key starting materials for their synthesis of pachastrissamine (jaspine B).[80e,f] Pachastrissamine, isolated from two marine sponge *Pachastrissa* sp. and *Jaspis* sp., showed inhibition of melanoma cell growth and cytotoxicity (IC_{50} 0.01 μg/mL) against P388, A549, HT29 and MEL28 cell lines.[81] Pd(0) catalysed double cyclisation of bromoallene **141** or **142** gave the bicyclic tetrahydrofuran **143** (89 and 88%, respectively) which was converted to pachastrissamine in 5-steps (Scheme 63).[80e] The mechanism for the generation of the pachastrissamine precursor **143** is illustrated in Scheme 64: (i) oxidative addition of bromoallene **141** to Pd(0) produces η^1-allenyl palladium intermediate **M1** which is in equilibrium with η^3-propargyl palladium complex **M2**; (ii) intramolecular OH attack at the central carbon atom of the propargyl species **M2** furnishes palladacycle **M3**; (iii) protonation of **M3** generates π-allyl palladium complex **M4**; (iv) a second intramolecular amidic addition to the internal carbon of π-allyl **M4** releases the product **143** and Pd(II) which regenerated Pd(0) in the presence of base.

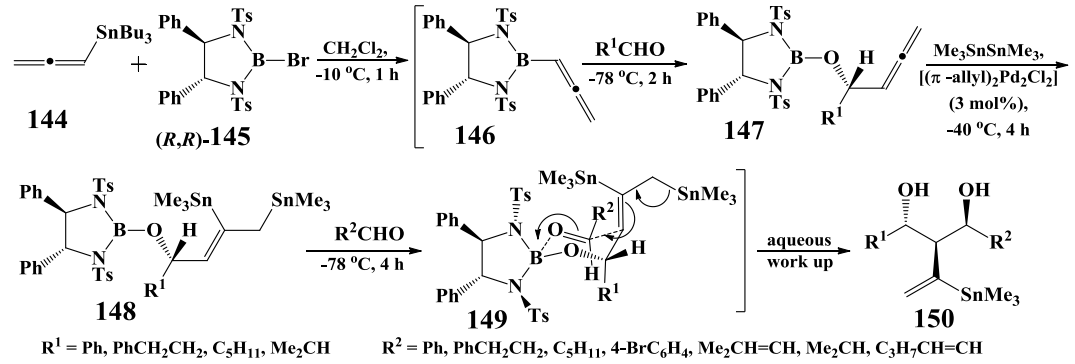


Scheme 63. Bromoallenes **141** and **142** gave the same pachastrissamine scaffold **143.**

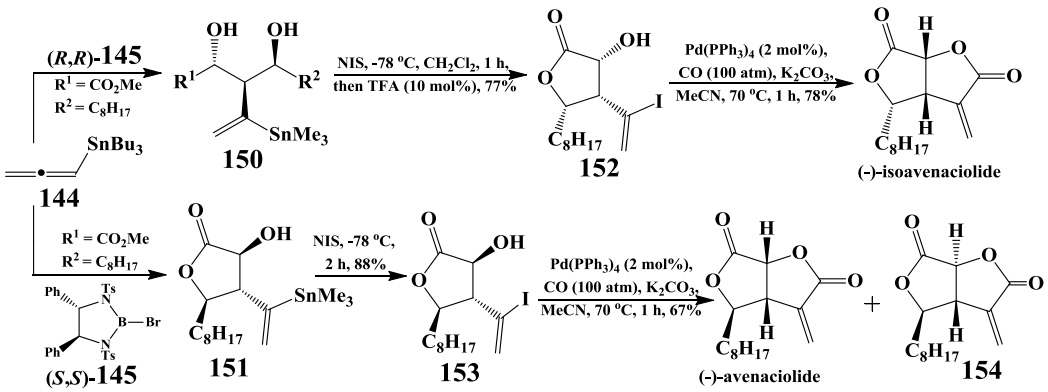


Scheme 64. Suggest mechanism generating key scaffold **143**.

Natural products (−)-isoavenaciolide and (−)-avenaciolide were isolated from the fermentation broth of *Aspergillus* and *Penicillium* species. The first has antibacterial and antifungal activity and inhibits the glutamate transporter in rat liver mitochondria whereas the second inhibits vaccinia H1-related (VAR) phosphatise activity.[82] Yu's group have reported their synthesis *via* stannyl allene **144** (Scheme 65).[83] Thus, sequential one pot cross-coupling between **144** and (*R*,*R*)-**145** produced boronylallene **146**. Addition of R^1CHO allowed an enantioselective allylic transfer to occur (boron group controlled the chirality and activated the aldehyde) affording **147**. Distannylation of allene **147** with $Me_3SnSnMe_3$ in the presence of [(π-allyl)$_2$Pd$_2$Cl$_2$] gave **148**. Addition of a second aldehyde (R^2CHO) achieved a second enantioselective allylic transfer *via* intermediate **149**. Aqueous work up gave a 63-81% yield of 2-(1-stannylvinyl)-1,3-diols **150** with three continuous stereogenic centres. This strategy was used to prepare (−)-isoavenaciolide in three steps (Scheme 66). (−)-Avenaciolide was synthesized using the same protocol but starting with (*S*,*S*)-bromoborane **145** which gave **151** which was reacted with *N*-iodosuccinimide (NIS) to give **153**. Carbonylation and epimerisation of **153** in the presence of Pd(PPh$_3$)$_4$, CO (100 atm) and K_2CO_3 in MeCN at 70 °C afforded (−)-avenaciolide together with **154** in 95:5 ratio, respectively.



Scheme 65. Sequential enantioselective allylic transfer.



Scheme 66. Synthesis of (−)-avenaciolide and (−)-isoavenaciolide.

1.3 Conclusion.

Discovering new methods for constructing C-C bonds are challenging targets. Palladium catalysed processes have proved fertile ground for this with Heck, Negishi and Suzuki leading the way. Their pioneering work led to the award of the shared Noble prize in 2010 due to the importance of these reactions in synthetic and industrial chemistry. I discussed in brief the general features of some palladium mediated reactions and their versatility in building C-C and C-heteroatom bonds. The review then focused on palladium catalysed allene chemistry as a potential method for constructing C-C and C-heteroatom bonds through inter- and intramolecular reactions. In particular, the versatility and uniqueness of the propadiene moiety of allenes as key building blocks in the synthesis of carbo- and heterocycles. Also, under the reaction conditions, the chirality of the starting materials can be transferred to the products as emphasised by the application of palladium catalysed allene chemistry in natural product synthesis.

Chapter 2

Results and Discussion

Palladium (0) catalysed allene cascade reactions

Chapter 2 (Results and Discussion): Palladium (0) catalysed allene cascade reactions

2.1 Introduction

As demonstrated in the introduction, allenes are versatile building blocks capable of a broad range of reactions. These features make allenes attractive starting materials and the chemistry of allenes is growing rapidly. My interest lies in palladium catalysed allene cascade reactions and their applications. This has involved creating di-, tri and tetra-trigger building blocks and their application in five, seven and nine component cascades, respectively. These complex cascades "open the door" to the synthesis of multivalent ligands which have numerous applications. I discuss in brief both the biological importance of the starting materials and the general features of our cascade chemistry in which 3-, 5-, 7- and 9-component cascades are discussed sequentially.

2.1.1 Potentially biologically active building blocks.

In this brief introduction, I highlight the broad biological importance of the building blocks which are used in my Pd(0) catalysed cascade chemistry. These are invariably heterocycles with two or more heteroatoms. Methylxanthines, (theobromine **155**, caffeine **156**, and theophylline **157**), have a range of bioactivities (Chart 1). They stimulate heart rate, force of contraction and cause cardiac arrhythmias at high concentrations.[84] In the CNS they increase alertness, stimulate the respiratory centre, and are used for treatment of infantile apnea.[85a-c] In high doses they can lead to convulsions that are resistant to anticonvulsants.[85a] They also induce acid and pepsin secretions in the GI tract and act as competitive nonselective phosphodiesterase inhibitors which raise intracellular cyclic adenosine monophosphate levels, activate protein kinase A, inhibit tumour necrosis factor TNF-alpha and leukotriene synthesis, and reduce inflammation and innate immunity.[86a-d] They are also nonselective adenosine receptor antagonists which inhibit sleep-inducing adenosine.[87]

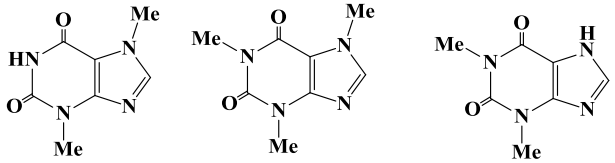


Chart 1. Methylxanthine group.

Tetrahydro-γ-carbolines have a broad spectrum of biological activity (i.e. antihistamine, serotonin inhibition, antidepressant, anti-inflammatory, neuroleptic activity, etc.).[88a-d] Dimebon **158** (Chart 2) is an old antihistamine drug which has recently shown inhibition of brain cell death in preclinical studies of Alzheimer and Huntington diseases as well as different types of schizophrenia, making it a potential treatment of these and other neurodegenerative diseases.[88c,d,89] Mebhydrolin **159** is an antihistamine drug used for relief of allergic symptoms caused by histamine release. Puig *et al.*,[90] recently used mebhydrolin as a scaffold and introduced a quinoline substituent on the benzyl group and added a carboxyl group to piperidine moiety to form a potent and selective cystinyl leukotriene (cys LT1) antagonist **160** for treating asthma. Bridoux and his co-workers introduced *N*-aroyl-tetrahydro-γ-carbolines **161** as dual 5-lipoxygenase (5-LOX)/cyclooxygenase (COX) inhibitors for treating the proliferation of malignant prostate cancer.[91]

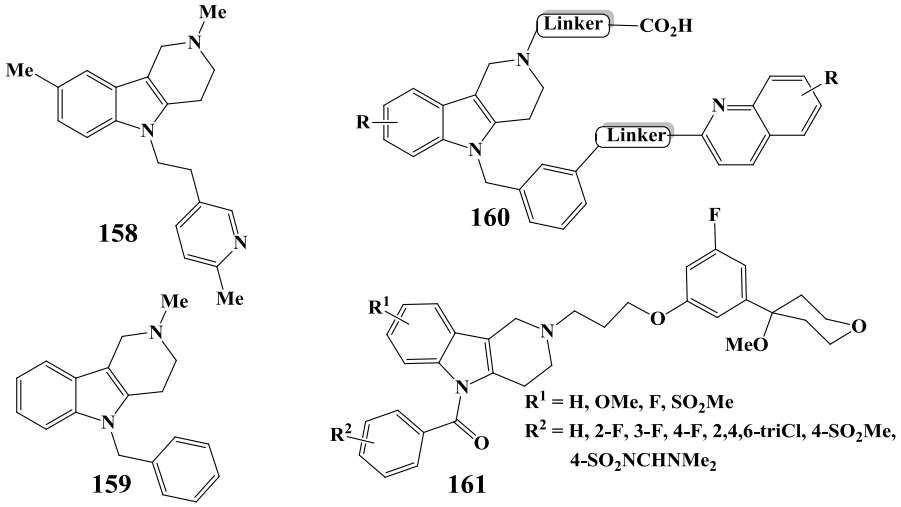


Chart 2. Broad biological application of tetrahydro-γ-carbolines.

The carboline nucleus appears to block central dopamine receptors and tetrahydro-**162**, **163** and hexahydro-γ-carboline derivatives **164**, **165** (Chart 3) were found to

have potential antipsychotic activity.[92] γ-Carbolines have affinity for serotonin (5-HT_{2A} and 5-HT_{5A}) receptors e.g. **166** shows high affinity for 5-HT_{5A} receptors.[93]

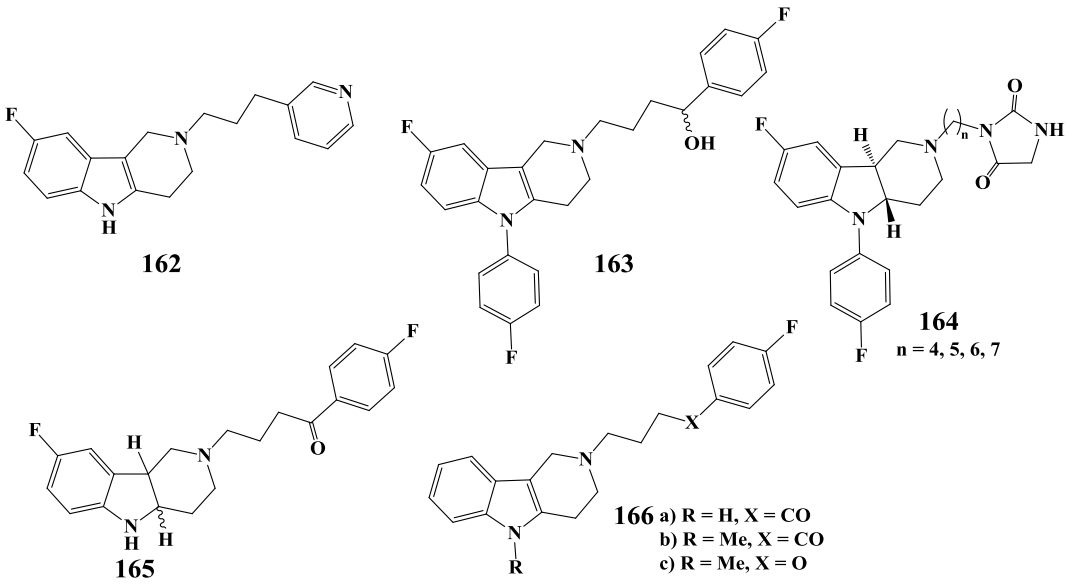


Chart 3. Some bioactive tetra/hexa-hydro-γ-carbolines.

An estimated 39.4 million people are infected with human immunodeficiency virus (HIV). Approximately 5 million new cases are diagnosed each year and there are 6 deaths from the disease per minute.[94a] The virus binds to chemokine receptor 5 (CCR-5) and targets white blood cells. It is incorporated into the cell's DNA where it mutates easily, adapts rapidly[94] and develops drug resistance.[95] Maraviroc (UK-427,857) **167** (Chart 4) is a CCR-5 antagonist, and is used in the treatment of HIV. It is potentially capable of blocking viral entry into human immune system cells, resulting in slowing progression of the disease.[94, 96]

Cocaine is one of the most powerfully addictive drugs known. Cocaine abuse puts a great burden on public health and safety and plays an important role in the rapid spread of AIDS and drug-resistant tuberculosis. It is also a factor in drug-related violent and nonviolent crimes.[97a] Cocaine binds to the dopamine transporter (DAT) and inhibits dopamine (DA) uptake thus elevating the concentration of dopamine in the synapse.[97b] Hence DAT is a target for drugs to treat cocaine abuse. The strategy is to develop compounds with high-affinity for, and slow-dissociation from DAT. Compounds **GBR 12935, 12909, 12783** (Chart 4)[97] were among the first compounds showing high-affinity for, and selective inhibition of, DA reuptake. Replacing the piperazine moiety in **GBR 12935** with homopiperazine gives **LR 1111** with similar binding affinity to **GBR 12935** for DAT but with a greater than 4000 fold inhibition

selectivity of DA uptake. Replacing the piperazine fragment in **GBR's** with a bridged piperazine or bridged homopiperazine **168** gives the same binding but with higher affinity and selectivity for DA uptake inhibition. Modification of the phenylpropyl tail of compound **GBR 12909** by incorporation of an OH group causes increased binding affinity and selectivity at the DAT binding site.

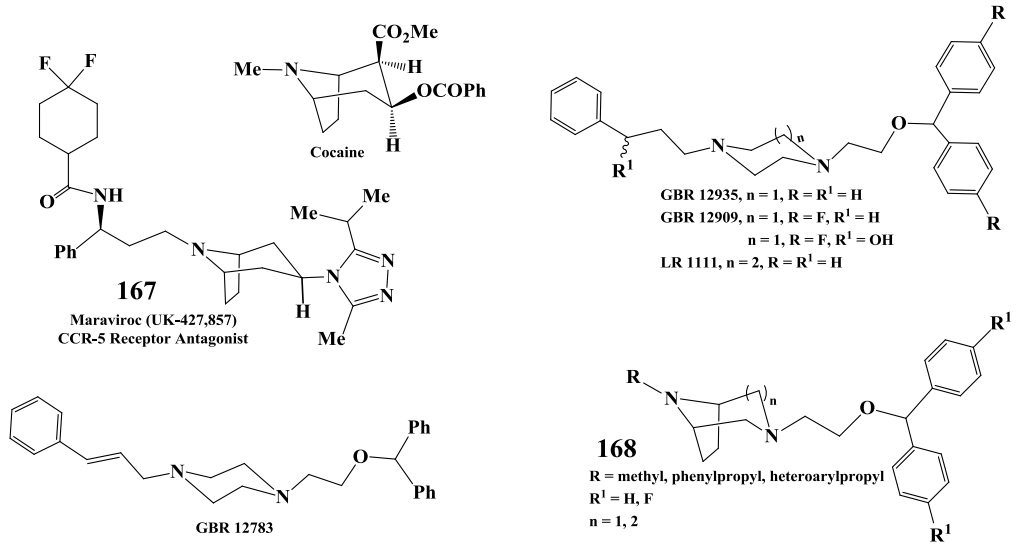


Chart 4. Selected biologically active cyclic and bridged cyclic amines.

Aromatic and heterocyclic sulphonamides (e.g. **169-174**, Chart 5) are carbonic anhydrase inhibitors[98] and also find application in treatment of glaucoma,[99] epilepsy,[100a] gastro-duodenal ulcers,[100b] osteoporosis,[100b] acute mountain sickness,[100c] and other neurological abnormal states.[99d,101] Aromatic sulphonamides also find application as diuretics[102a] and antimicrobial[102b] agents. Particular effort has been directed to screen aromatic and heterocyclic sulphonamides as isozyme-selective carbonic anhydrase inhibitors.[103]

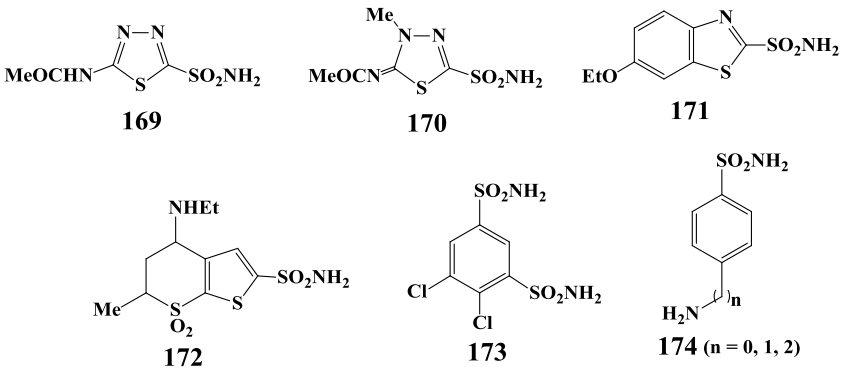


Chart 5. Selected biologically active sulphonamides.

The adamantane nucleus differs substantially from benzene in structure and physical properties.[104] It has great polarizability, occupies a larger volume of space and permits selective exploration of the space allowing drug discovery to benefit from controllable electrostatic steric and ionic interactions between adamantane and receptors/enzymes.[104b] These properties allow the absorption, distribution, metabolism and excretion properties of chemical candidates to be varied, e.g. the passage of 1-adamantylcarboxamide **175** and dopamantine **176** (Chart 6) through the blood brain barrier is attributed to the adamantyl moiety.[105] Kitagawa used an adamantane moiety, with high lipophilicity and low toxicity, as a carrier to deliver poorly absorbed drugs to the central nervous system across the blood brain barrier.[106]

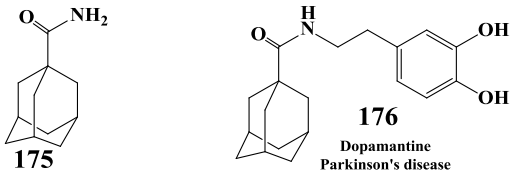


Chart 6. Adamantyl group enhancing blood brain barrier penetration.

The size and shape of the adamantyl group can be used to promote hydrophobic interactions, e.g. tetrahydrocannabinol **177** binds equally to two cannabinoid receptors: CB1 (found in CNS) and CB2 (found in the immune system), (Chart 7). Replacing the C-3 pentyl group in **177** with a 1-adamantyl group, as in **178**, promoted affinity and selectivity for the CB1 receptor whereas replacing C-3 pentyl group with a 2-adamantyl group, as in **179**, promoted affinity for the CB2 receptor.[107]

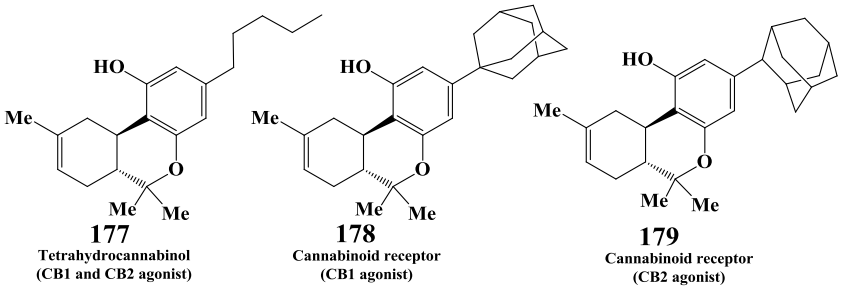


Chart 7. Derivatisation position of adamantyl group controlled the selectivity.

Adamantyl moieties perturb the influenza virus ion channels by disrupting the transmembrane flux through two mechanisms.[104b] The first mechanism “cork in the bottle” (adamantane derivatives in the ion channel cavity) disrupts the

transmembrane proton flux. The second mechanism “membrane side” involves adamantane derivatives that do not bind in the channel cavity but bind between the membrane and the proton channel. Adamantane derivatives have been developed to treat a broad spectrum of diseases (Chart 8).

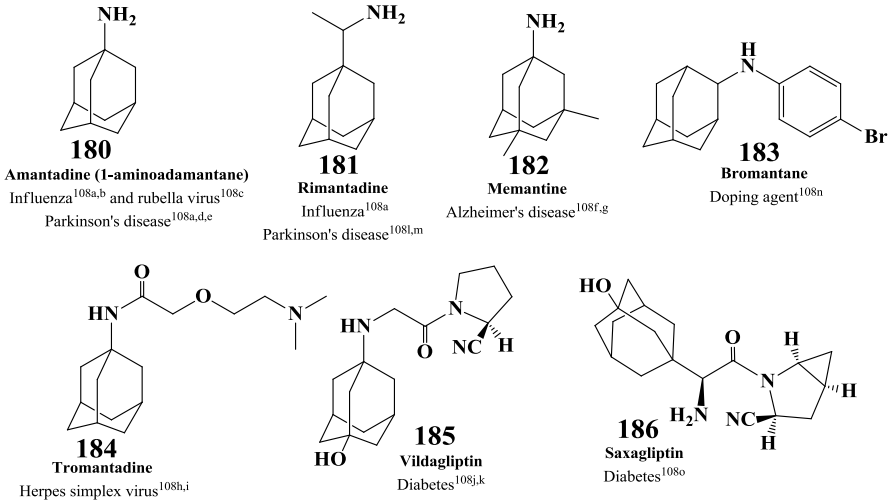


Chart 8. Selected examples of adamantane biological activity.

There are several ways to achieve potential bioactive lead compounds.[109a,b] One way is to use a known drug or compounds with the desired activity as a key intermediate for preparing novel lead compounds. The advantages are that the biological target is well known and the binding affinity to that target is maximised beside the other properties. Privileged structures are a class of frameworks capable of binding to several biological targets with high affinity.[109c,d] These structures provide a way for medicinal chemists to build a library of compounds based on one core scaffold and screen it against different biological targets. Thus, theobromine **155**, tetrahydro-γ-carboline **187**, 1-aminoadamantane **180**, maraviroc amine **188**, piperazine **189a**, homopiperazine **189b** and mafenide **174** (Chart 9) all have the ability to hit a range of biological targets and could be considered as privileged structures. Based on this principle, I incorporated such compounds into Pd(0) mediated allene cascade reactions in order to discover new lead compounds.

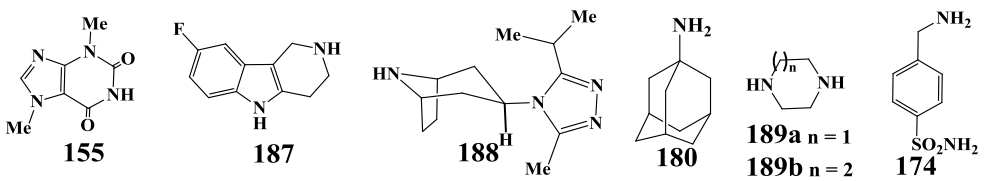
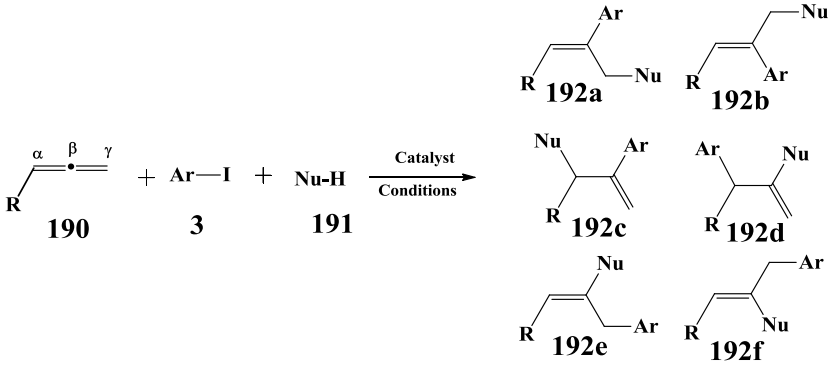


Chart 9. Some biologically active privileged scaffolds.

2.2 Palladium (0) catalysed allene cascade reactions.

2.2.1 Background

The Pd(0) catalysed reactions of an allene **190** with aryl halides **3** and nucleophiles **191** is well established (Scheme 67). There are notionally six possible products **192a-f** depending on regio/stereo-chemistry of addition of the aryl and nucleophile groups to the allene double bonds. In practice the process is normally regio- and stereo-selective.

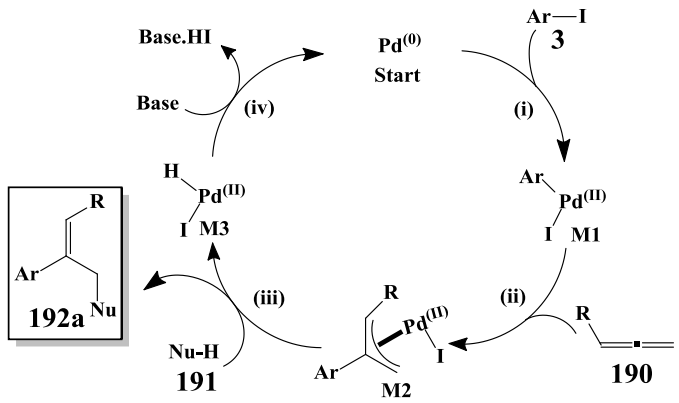


Scheme 67. Possible outcome from the reaction of allene with aryl iodide and nucleophile

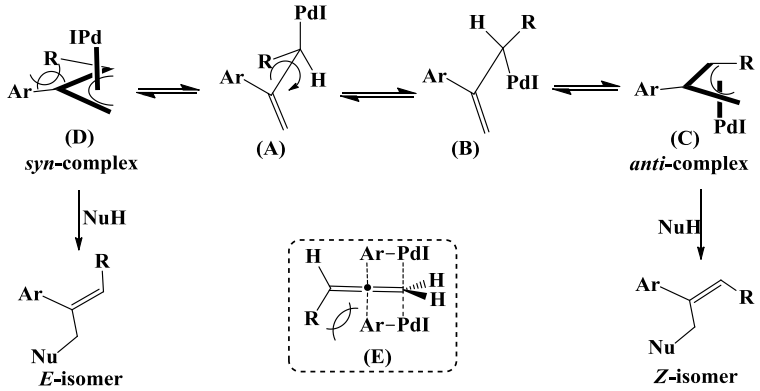
My task was to design novel Pd mediated mono- and poly-allene cascade reactions with aryl halides and nucleophiles. Simple mono-allene cascades generate trisubstituted olefins **192a** in a regio- and stereo-selective manner (Scheme 67). Typical conditions employ Pd_2dba_3 (tris(dibenzylideneacetone)dipalladium(0)), TFP (tri-(2-furyl)phosphine), K_2CO_3, MeCN and 80 °C. The mechanism (Scheme 68)[110] involves four steps. The first step is an oxidative addition of Pd(0) to the aryl/heteroaryl iodide **3** to form **M1**. The second step involves coordination of allene **190** to **M1** and insertion (Ar group adds regioselectively to the allene central carbon atom) creating a π-allyl complex **M2**. The third step involves nucleophilic attack of **191** on the π-allyl complex **M2** to produce tri-substituted alkene **192a** stereoselectively and a Pd(II) hydride species **M3**. The final step involves reductive elimination of Pd(II) in the presence of a base to generate Pd(0).

There are two possible *E*/*Z* stereoisomers in the case of monosubstituted allenes due to the possible interconversion between the intermediate *syn*- and *anti*-π-allyl complexes (**C** and **D**) through σ-complexes (**A** and **B**) (Scheme 69).[110] Nucleophilic attack at the least hindered site on the *syn*-complex (**D**) results in the formation of

the *E*-isomer, whilst nucleophilic attack at the least hindered site on the *anti*-complex (**C**) leads to the *Z*-isomer. Under our conditions, the *Z*-isomer is normally formed stereoselectively reflecting the steric interaction between the R-group and the aryl/heteroaryl group in the *syn*-π-allyl complex (**D**). 1,2-Disubstituted π-allyl complexes are normally completely regioselective for the *Z*-isomer. According to Glorius,[111] we can rationalise the selectivity of the process by considering intermediate (**E**). The carbopalladation of the terminal allene double bond from the top will deliver the favourable *Z*-isomer, whereas carbopalladation from the bottom (sterically congested intermediate) will lead to the disfavoured *E*-isomer.



Scheme 68. A rational mechanism for the Pd(0) catalysed 3-component cascade.



Scheme 69. A plausible *E*/*Z*-stereoselective mechanism.

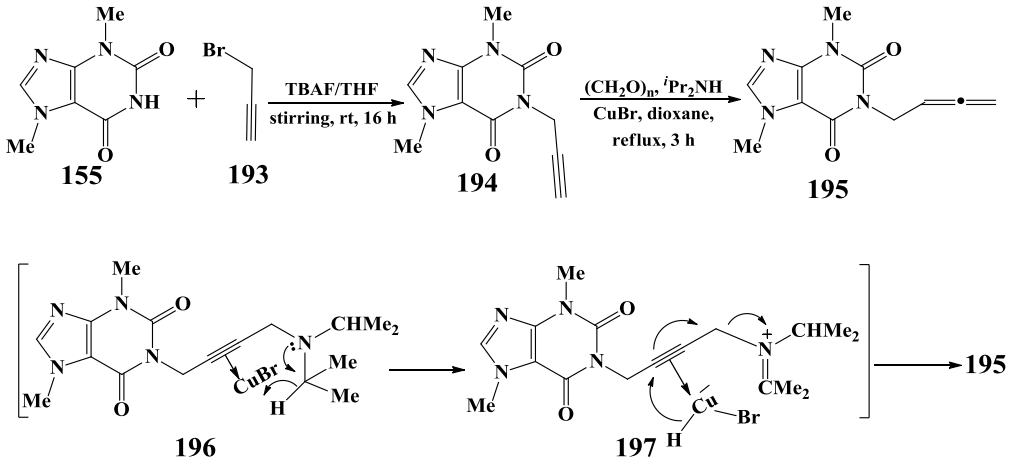
The general thrust of my work can be highlighted in the following points: (i) involve privileged compounds (e.g. theobromine **155**, γ-carboline **187**, maraviroc amine **188**, 1-aminoadamantane **180**, mafenide **174**, etc) in Pd catalysed allene cascades in order to discover novel, potentially bioactive, lead compounds, (ii) design multi-trigger scaffolds and incorporate them into novel cascade reactions in order to increase cascade complexity and provide more varied and efficient probes of the biological space.

2.2.2 Pd(0) catalysed three component cascades.

The first target of this work was to develop three component cascades of monosubstituted allenes with various ary/heteroaryl iodides and potentially bioactive *N*-nucleophiles in the presence of a palladium catalyst to furnish, stereoselectively, *Z*-trisubstituted olefins carrying pharmacophore moieties. All of these compounds would have one or more privileged groups.

2.2.2.1 Synthesis of an *N*-allenylpurine 195 using theobromine 155.

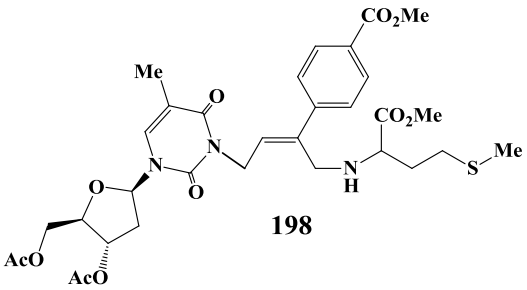
A previous worker in Grigg's group had used theobromine **155** to prepare 1-buta-2,3-dienyl-3,7-dimethyl-3,7-dihydro-purine-2,6-dione **195** in two steps.[112] The first step involved the *N*-alkylation of theobromine **155** with propargyl bromide **193** in the presence of TBAF (tetra-*n*-butylammonium fluoride) and THF to afford an 80% yield of **194** (Scheme 70).[113] In the second step, **194** was converted into the corresponding allene **195** *via* the Crabbé reaction (Scheme 70).[114] The Crabbé reaction is a homologation of **194** involving paraformaldehyde (2.5 equiv.) and diisopropylamine (2.0 equiv.) catalysed by CuBr (0.5 equiv.) in refluxing dioxane which afforded allene **195** (62%). The reaction proceeds *via* an intermediate Mannich base **196**, and is postulated involve π-complexed CuBr first accepting a hydride ion and then transferring it to the acetylenic carbon atom.[115] Ma's group[116] modified the Crabbé conditions by replacing diisopropylamine and CuBr by dicyclohexylamine (1.8 equiv.) and CuI (0.5 equiv.). I applied the Ma conditions to the alkyne **194** and obtained, after reflux for 3 h, an 83% yield of **195**.



Scheme 70. Formation of *N*-allenyl purine **195** *via* the proposed Crabbé mechanism.

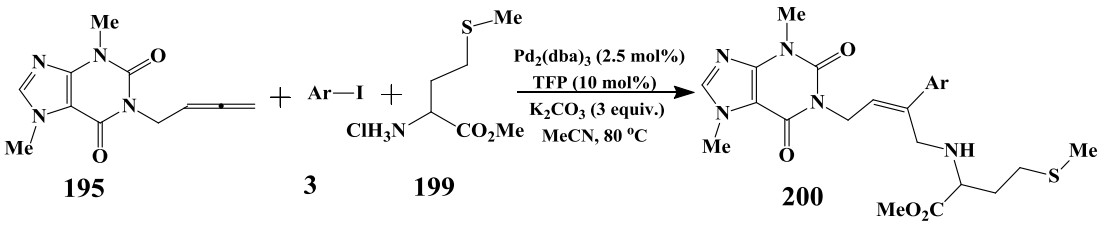
2.2.2.2 *rac*-Methionine methyl ester as nucleophile.

Previously, a member of the Grigg group synthesized compound **198**,[117] using a Pd(0) catalysed 3-component cascade reaction, as a potential antimalarial compound.

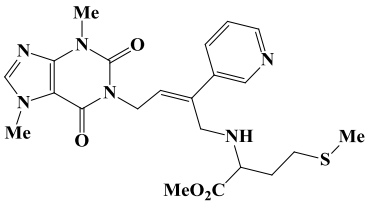


198

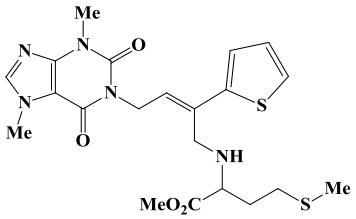
This result prompted me to synthesise further related compounds (Scheme 71) and introduce myself to allene cascade chemistry. Thus, reacting a mixture of allene **195**, aryl/heteroaryl iodide **3** and *rac*-methionine methyl ester hydrochloride **199** at 80 °C in MeCN containing $Pd_2(dba)_3$, TFP and K_2CO_3 afforded the *Z*-isomers **200** (72-85%). The reaction went only once at the methionine amino group and there was no indication of further functionalisation of the product NH-group under the reaction conditions.



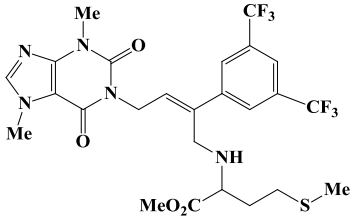
195 **3** **199** **200**



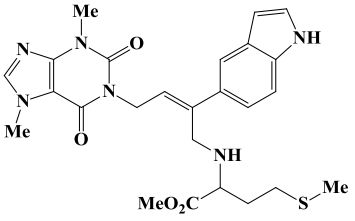
200a (82%)



200b (75%)



200c (85%)



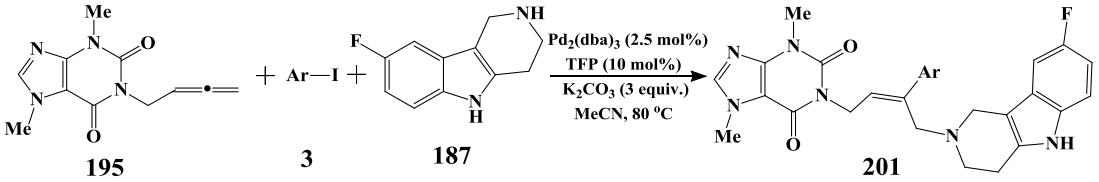
200d (72%)

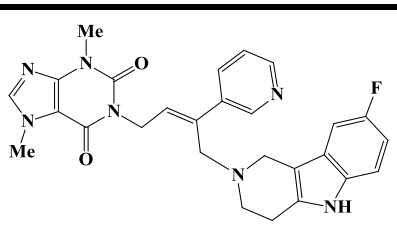
Reaction carried out at 80 °C in MeCN (5 mL) for 10-18 h and employed *N*-allenylpurine **195** (0.5 mmol), ArI **3** (0.6 mmol), *rac*-methionine methyl ester hydrochloride **199** (0.75 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.).

Scheme 71. Three component cascade using *rac*-methionine **199** as nucleophile.

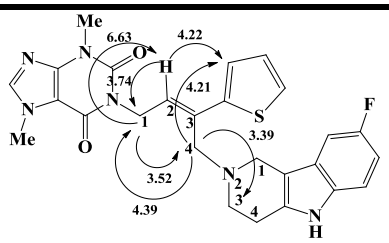
2.2.2.3 γ-Carboline 187 as a nucleophile.

The excellent selectivity and productivity results achieved from the incorporation of *rac*-methionine methyl ester hydrochloride **199** as a nucleophile encouraged use of γ-carboline (8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole) **187** as a nucleophile in 3-component cascade reactions (Scheme 72). The 3-component cascade proceeded smoothly to give *Z*-isomers **201** stereoselectively in 60-92% yield. It is worth mentioning that the cascade products precipitated from the hot reaction solution, so the reaction was self indicating and there was no need for sophisticated purification.

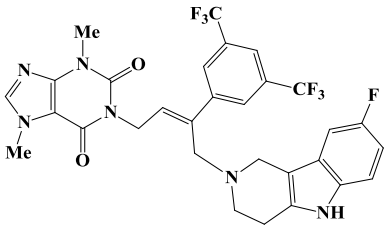




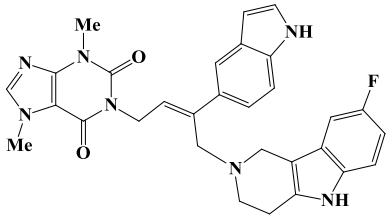
201a (92%)



201b (71%)



201c (60%)



201d (78%)

Reaction carried out at 80 ºC in MeCN (5 mL) for 2-3 h and employed *N*-allenylpurine **195** (0.5 mmol), ArI **3** (0.6 mmol), γ-carboline **187** (0.6 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.)

Scheme 72. Cascade products of **195** with γ-carboline **187** as nucleophile.

The ^{1}H-NMR spectrum of **201c** (Fig. 2) confirmed the formation of only one stereoisomer. The *Z*-configuration of **201a-201d** was assigned on the basis of NOE studies on **201b** (Scheme 72). Irradiation of 2-H (δ 6.13) caused 3.74% enhancement of 1-CH_2 and 4.22% enhancement of thienyl 3-H but no enhancement of 4-CH_2 protons. However, irradiation of 1-CH_2 (δ 4.92) resulted in 6.63% enhancement of 2-H and 3.52% enhancement of 4-CH_2 protons but no enhancement of thienyl

protons was observed. Irradiation of 4-CH_2 (δ 3.84) caused 4.21% enhancement of thienyl 3-H, 4.39% enhancement of 1-CH_2 and 3.39% enhancement of tetrahydropyridoindolyl 3-CH_2 protons but no enhancement of the 2-H proton.

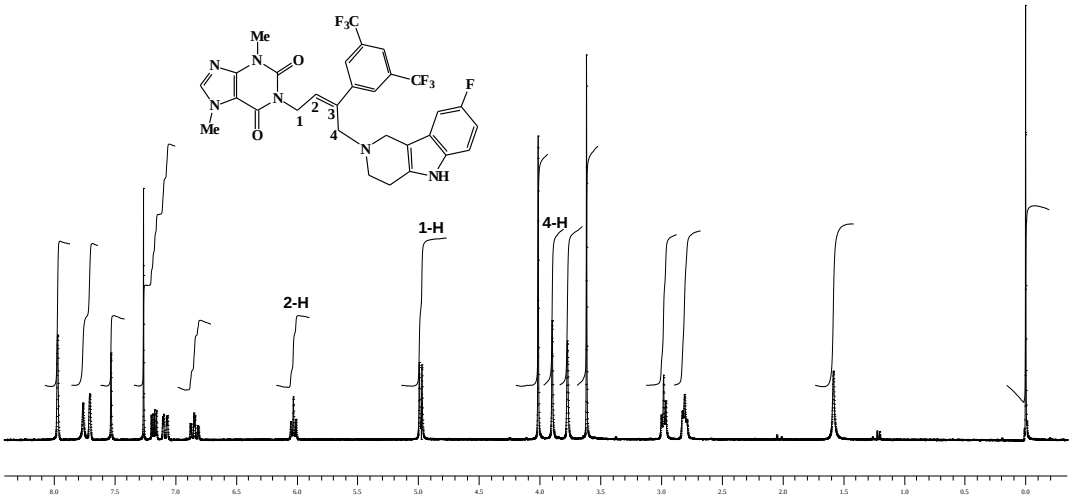


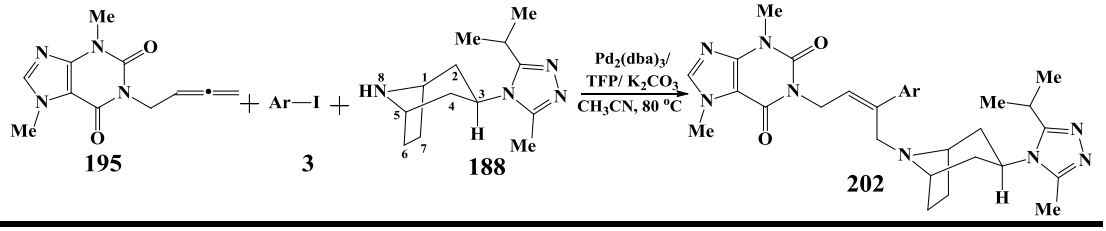
Figure 2. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **201c**.

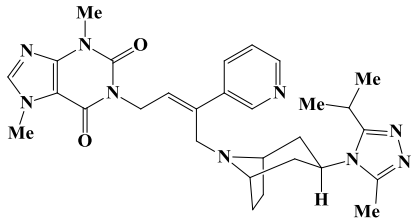
2.2.2.4 Maraviroc amine 188 as a nucleophile.

Maraviroc amine (3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane) **188** potentially brings two biological benefits to the Pd cascade chemistry. Firstly, it contains a major fragment of maraviroc **167** (an HIV drug marketed by Pfizer), so our products might be active against HIV. Secondly, **188** has the tropane moiety found in cocaine and might bind to the dopamine transporter (DAT) and block dopamine uptake. Heating a mixture of **195**, aryl/ heteroaryl iodide **3**, and **188** with $Pd_2(dba)_3$, TFP, and K_2CO_3 in MeCN at 80 °C gave the *Z*-product **202** together with *E*-isomer in 72-92% yield and in a ratio ranging from 93:7 to 88:12 (Scheme 73). The formation of some *E*-isomer despite the expected high NH-nucleophlicity of **188** (conjugate acid pK_a = 10.7)[118] compared with **199** and **187** (conjugate acid pK_a = 7.1 and 9.8, respectively)[118] suggested some steric congestion occurred in the transition state. Framework molecular models of **188** showed that the bicycle hydrogen atoms hindered the nucleophilic attack of the amino-group at the favourable *anti*-π-allyl complex (see Scheme 69) allowing the *syn*-π-allyl complex to compete thus forming some *E*-isomer.

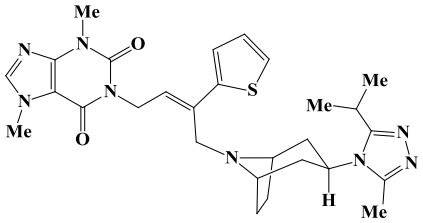
Z-Stereochemistry was assigned to the major isomer of **202c** from NOE experimental data (Table 1). Thus, irradiation of 1-H (δ 4.89) caused a 5.92% enhancement of 2-H and irradiation of 2-H (δ 6.00) resulted in a 3.26 and 1.95%

enhancement of 1-H and the *o*-phenyl protons, respectively. Irradiation of 4-H (δ 3.69) caused 4.35% enhancement of 1-H, 7.13% enhancement of *o*-phenyl protons and 5.66 and 3.97% enhancement of azabicyclooctyl protons (δ 3.46 and 2.30). The stereochemistry of the rest of cascade products was assigned based on this result (Scheme 73).

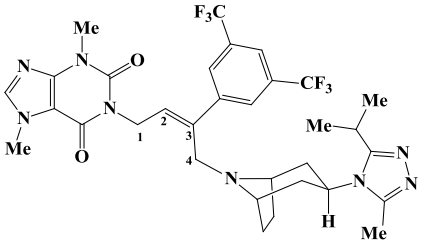




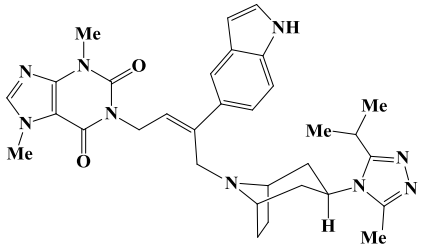
202a (Z:E 93:7, 92%)



202b (Z:E 90:10, 88%)



202c (Z:E 90:10, 86%)



202d (Z:E 88:12, 72%)

Reaction carried out at 80 ºC in MeCN (5 mL) for 8-26 h and employed **195** (0.5 mmol), ArI **3** (0.6 mmol), **188** (0.6 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.)

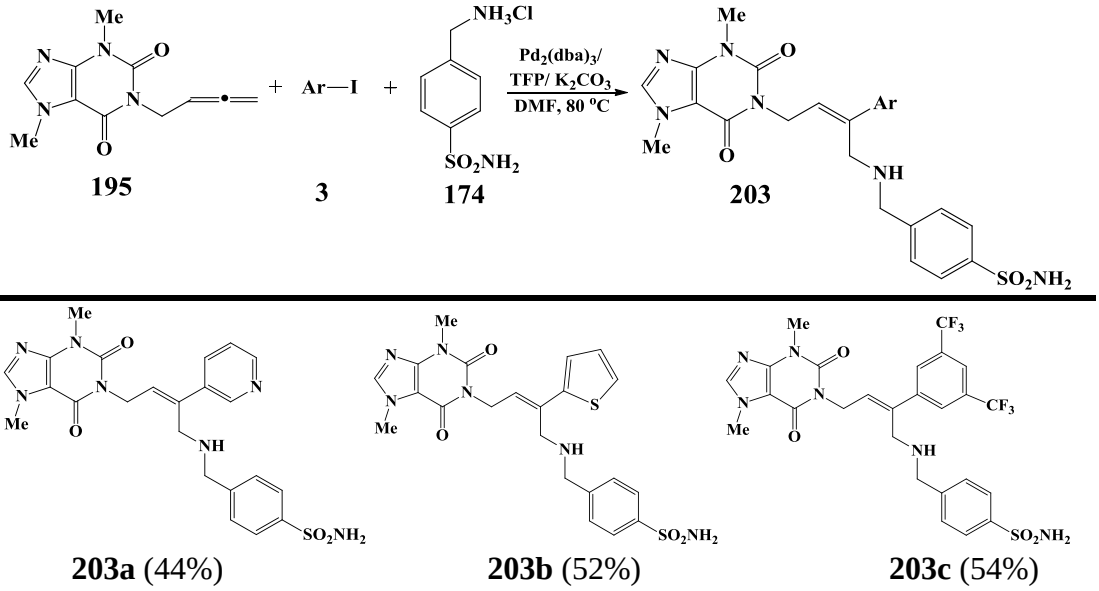
Scheme 73. 3-Component cascades of maraviroc amine as a nucleophile.

Table 1. NOE experimental data for *Z*-**202c**.

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Ph	Azabicyclooctyl-H
1-H		5.92	-	-	-
2-H	3.26		-	1.95	-
4-H	4.35	-		7.13	5.66 (δ 3.46), 3.97 (δ 2.30)

2.2.2.5 Mafenide 174 as a nucleophile.

Mafenide ((2-aminomethyl)benzensulfonamide), is a well known ointment used to treat severe burns.[119] It is also a carbonic anhydrase inhibitor and is bacteriostatic against gram positive and gram negative organisms.[119] Thus, the potential therapeutic benefits of sulphonamides prompted the evaluation of mafenide hydrochloride **174** as a nucleophile in three component cascade chemistry with *N*-allenylpurine **195** and aryl/heteroary iodide **3** at 80 °C in DMF in presence of $Pd_2(dba)_3$, TFP and K_2CO_3. The reaction occurred stereoselectively to afford cascade compounds *Z*-**203** (Scheme 74) in which the aliphatic amine, and not the sulphonamide, participated as a nucleophile. The reaction, in acetonitrile, was significantly slower (7 h) and the proton n.m.r of the crude mixture showed a mixture of isomers. This is attributed to the low solubility of mafenide hydrochloride in MeCN allowing both the sulphonamide NH_2-group and the *syn*-π-allyl complex (see Scheme 69) to participate in the reaction.



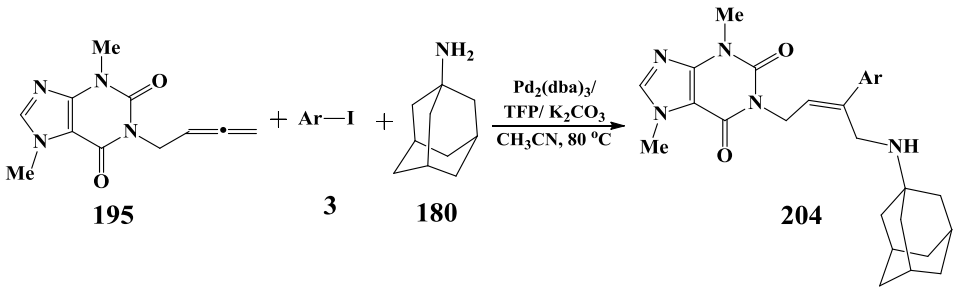
Reaction carried out at 80 ºC in DMF (2 mL) for 2-3 h and employed *N*-allenylpurine **195** (0.5 mmol), ArI **3** (0.6 mmol), (2-aminomethyl)benzensulfonamide HCl **174** (0.6 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.).

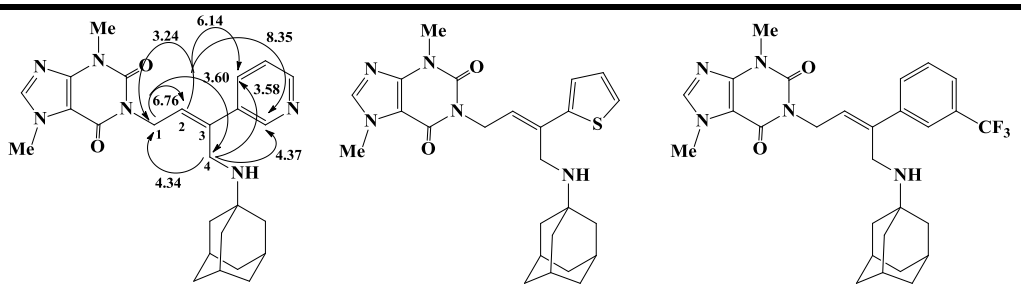
Scheme 74. 3-Component cascade with mafenide as nucleophile.

2.2.2.6 Amantadine (1-aminoadamantane) 180 as a nucleophile.

Amantadine **180** is a drug which has potential applications in drug design and discovery.[120] It was therefore used as a nucleophile in the cascade chemistry to create "privileged" adamantyl backbone products. Thus, 1-aminoadamantane **180** was incorporated in three component cascades by reacting with purine allene **195** and

aryl iodides **3** under Pd(0) catalysed conditions to give the *Z*-products **204** stereoselectively in 69-78% yield (Scheme 75).





204a (78%) **204b** (69%) **204c** (91%)

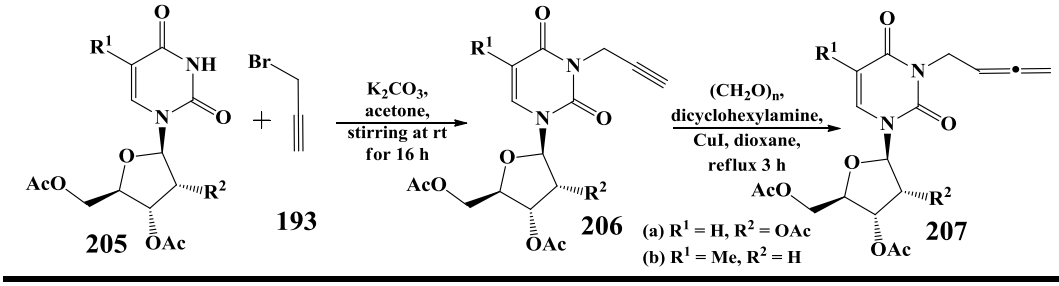
Reaction carried out at 80 ºC in MeCN (5 mL) for 2-5 h and employed *N*-allenylpurine **195** (0.5 mmol), ArI **3** (0.6 mmol), 1-aminoadamantane **180** (0.6 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.)

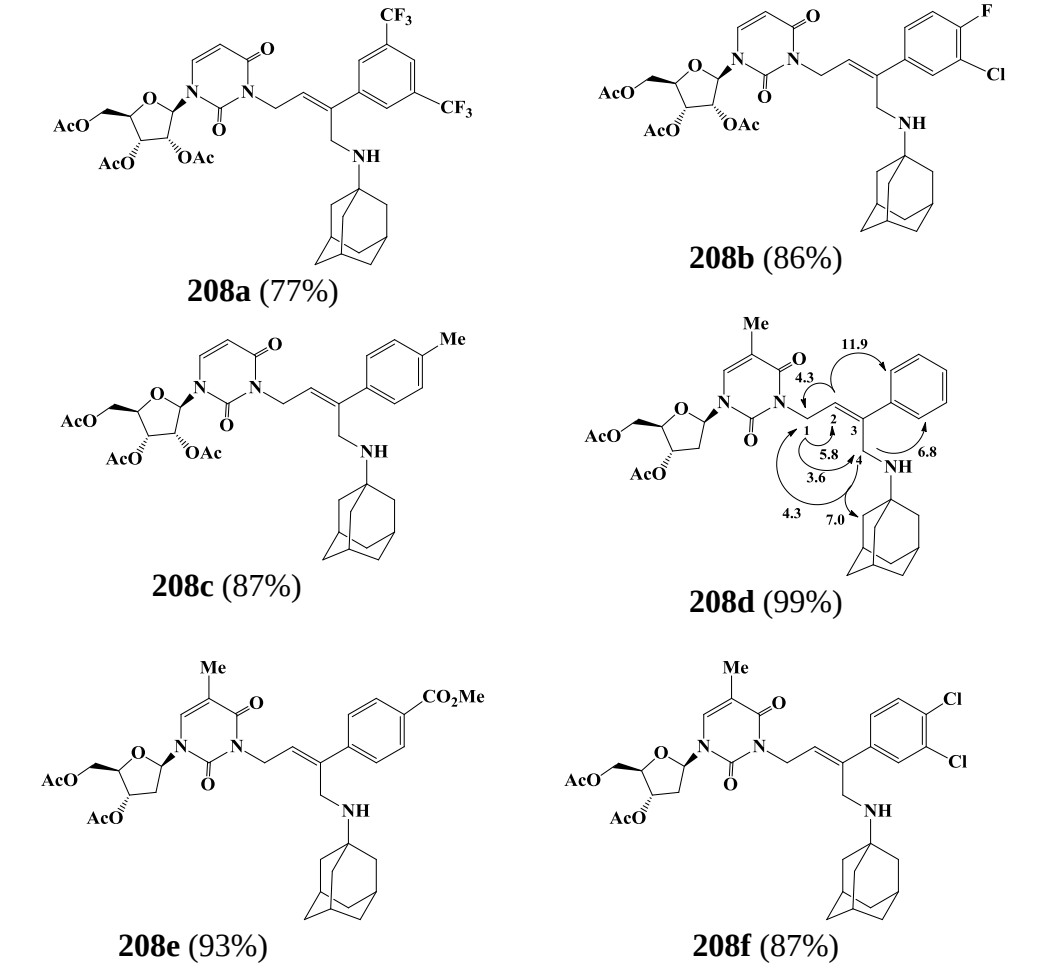
Scheme 75. Three component cascade products of 1-aminoadamantane **180**.

The *Z*-stereochemistry of **204a-c** was assigned on the basis of NOE studies on **204a** (Scheme 75). Irradiation of 2-H (δ 5.90) caused 3.24% enhancement of 1-CH_2 and 8.35 and 6.14% enhancement of pyridyl 2-H (δ 8.77) and pyridyl 4-H (δ 7.86), respectively, but no enhancement of the 4-CH_2 protons. However, irradiation of 1-CH_2 (δ 4.90) resulted in 6.76% enhancement of 2-H and 3.60% enhancement of 4-CH_2 protons but no enhancement of the pyridyl protons was observed. Irradiation of 4-CH_2 (δ 3.82) gave 4.34, 4.37, 3.58 % enhancements of 1-CH_2, pyridyl 2-H (δ 8.77) and pyridyl 4-H (δ 7.86) protons, respectively, but no enhancement of the 2-H proton was observed.

The potentially broad biological applications of the adamantyl core and the successful incorporation of amantadine **180** as a nucleophile in three component cascades (Scheme 75) prompted replacing the *N*-allenyl purine **195** with uridine and thymidine allenes **207a,b** (Scheme 76). Propargylation of 2',3',5'-tri-*O*-acetyluridine **205a** or 3',5'-di-*O*-acetylthymidine **205b** with propargyl bromide **193** in the presence of K_2CO_3 in acetone afforded *N*-propargyl derivatives **206a** and **206b**, respectively.[117,121] Compounds **206a,b** were subjected to the modified Crabbé

conditions[116] ($(CH_2O)_n$, dicyclohexylamine, CuI). The corresponding allenes **207a,b** were obtained in 80% and 75% yield, respectively. With allenes **207a,b** in hand, incorporation of amantadine **180** with a broad range of electron neutral, rich and deficient aryl iodides furnished products **208a-f** each of which contain two bioactive fragments (Scheme 76). The reactions occurred smoothly and in excellent yields to give single products (see Fig. 3).





Reaction carried out at 80 ºC in MeCN for 2-5 h and employed substituted allene **207** (1 equiv.), aryl iodide (1.2 equiv.), 1-aminoadamantane **180** (1.2 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.)

Scheme 76. Synthesis of uridine and thymidine allenes **207a,b** and their incorporation in 3-component cascade reactions with amantadine **180**.

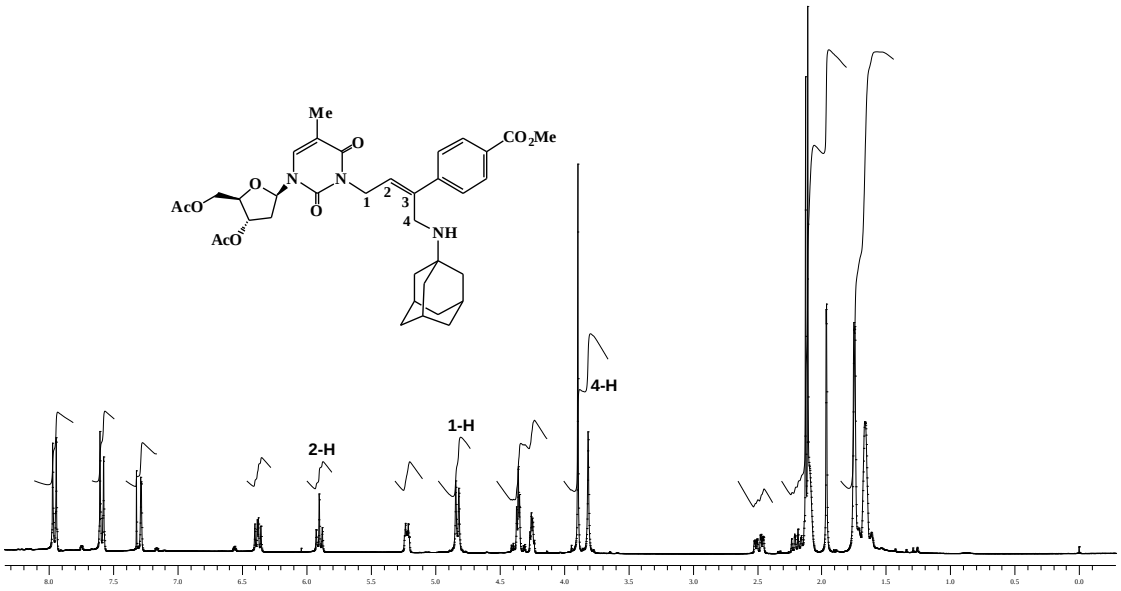


Figure 3. ^{1}H-NMR ($CDCl_3$, 300MHz) of **208e**.

The reaction of 1-aminoadamantane (1 equiv.) **180** with thymidine allene **207b** (2 equiv.) and iodobenzene (2.4 equiv.) under the same conditions but heating at 80 °C for 34h was tried in an attempt to force the remaining adamantyl NH group in **208d** to react again in a 5-component cascade. However, only **208d** was formed with no indication of further functionalisation of the remaining NH-group in **208d**. The *Z*-stereochemistry of **204a-c** and **208a-f** was assigned on the basis of NOE studies (see experimental). NOE data for **208d** indicated the *Z*-configuration (Scheme 76). Irradiation of 2-H (δ 5.82) caused 4.3% enhancement of 1-CH_2 and 11.9% enhancement of phenyl 2-H but no enhancement of 4-CH_2 protons. However, irradiation of 1-CH_2 (δ 4.82) resulted in 5.8% enhancement of 2-H and 3.6% enhancement of 4-CH_2 protons but no enhancement for phenyl protons was observed. Irradiation of 4-CH_2 (δ 3.83) caused 6.8, 4.3 and 7.0 % enhancements of phenyl 2-H, 1-CH_2 and adamantyl-CH_2 protons, respectively, but no enhancement of 2-H proton was observed.

2.2.2.7 Miscellaneous primary/secondary amines as nucleophiles.

The successful incorporation of *rac*-methionine methyl ester hydrochloride as a representative amino acid nucleophile (Scheme 71) encouraged expanding the scope of the cascade to incorporate glycyl-(*S*)-alanine methyl ester hydrochloride (Gly-AlaOMe) **209** as a representative peptide nucleophile to study the effect of the reaction conditions on the peptide bond and the chirality of the starting material. The

three component Pd(0) catalysed reaction of purine allene **195**, an aryl iodide and Gly-AlaOMe **209** afforded *Z*-double bond products **215a-c** stereoselectively in 76-85% yield (Chart 10). Furthermore, the chirality of **209** transferred cleanly to the products and there was no effect on the peptide bond. NOE data for **215c** established the formation of the *Z*-product (Chart 10). Irradiation of 3-H (δ 5.94) caused 3.20 and 11.64% enhancements of 4-H and phenyl-H protons, respectively, but no enhancement of 1-H_A/1-H_B protons was observed. Irradiation of 4-H_A/4-H_B (δ 4.94) resulted in 5.73, 4.40 and 1.60% enhancements of 3-H, 1-H_A and 1-H_B, respectively, but no enhancement of the phenyl protons whilst irradiation of 1-H_A (δ 4.00) caused a 2.92% enhancement of 4-H and 13.19% enhancement of 1-H_B protons but no enhancement of 3-H proton. Irradiation of 1-H_B (δ 3.83) caused a 4.68% enhancement of 4-H, 5.85% enhancement of 1-H_A and 6.20% enhancement of phenyl-H protons but no enhancement of 3-H proton. Accordingly, Z-stereochemistry was assigned to **215a,b** based on these data.

(*S*)-Serine methyl ester hydrochloride **210** was also studied as a nucleophile to probe the reactivity of the NH_2 group versus the OH group as nucleophiles. Note that the Grigg group has shown that phenols and activated methylenes are active cascade nucleophiles (see the introduction). The reaction went only at the NH_2 group with no sign of reaction of the OH group (compound **216**, Chart 10). ^{1}H-^{1}H COSY nmr experiments provided good evidence for the incorporation of the NH_2 as the nucleophile (Fig. 4) as judged by the strong correlation between OH (δ 6.67) and 7-CH_2 at (δ 4.20). Also, good interaction between NH (δ 2.91) and both 6-CH (δ 3.83) and 4-CH_2 (δ 4.27 and 4.07, H_A and H_B) were observed.

Further cascades using bioactive privileged structures, a metal chelator and fluorophors were successfully achieved. Thus, *N*-deacetylcolchicine **211** was incorporated, after deprotecting the amino group in colchicine,[122] as a nucleophile in the 3-component cascade reactions with allene **195** and aryl iodides. This delivered the novel colchicine derivatives **217a,b** in 94 and 85% yield (Chart 10). The ^{1}H-NMR of compound **217b** confirmed the formation of *Z*-isomer (Fig. 5) and showed the hybrid combination of the zinc binding HDAC benzamide moiety with bioactive deacetylcolchicine group was viable. 1-Aminomethylnaphthalene **212** and 1-aminomethylpyrene **213** are well known fluorophors[123] and we incorporated them as nucleophiles into our cascades. They reacted with purine allene **195** and 3-

iodopyridine under Pd(0) catalysed conditions to furnish the *Z*-products **218** and **219** in 86 and 89% yield, respectively, (Chart 10).

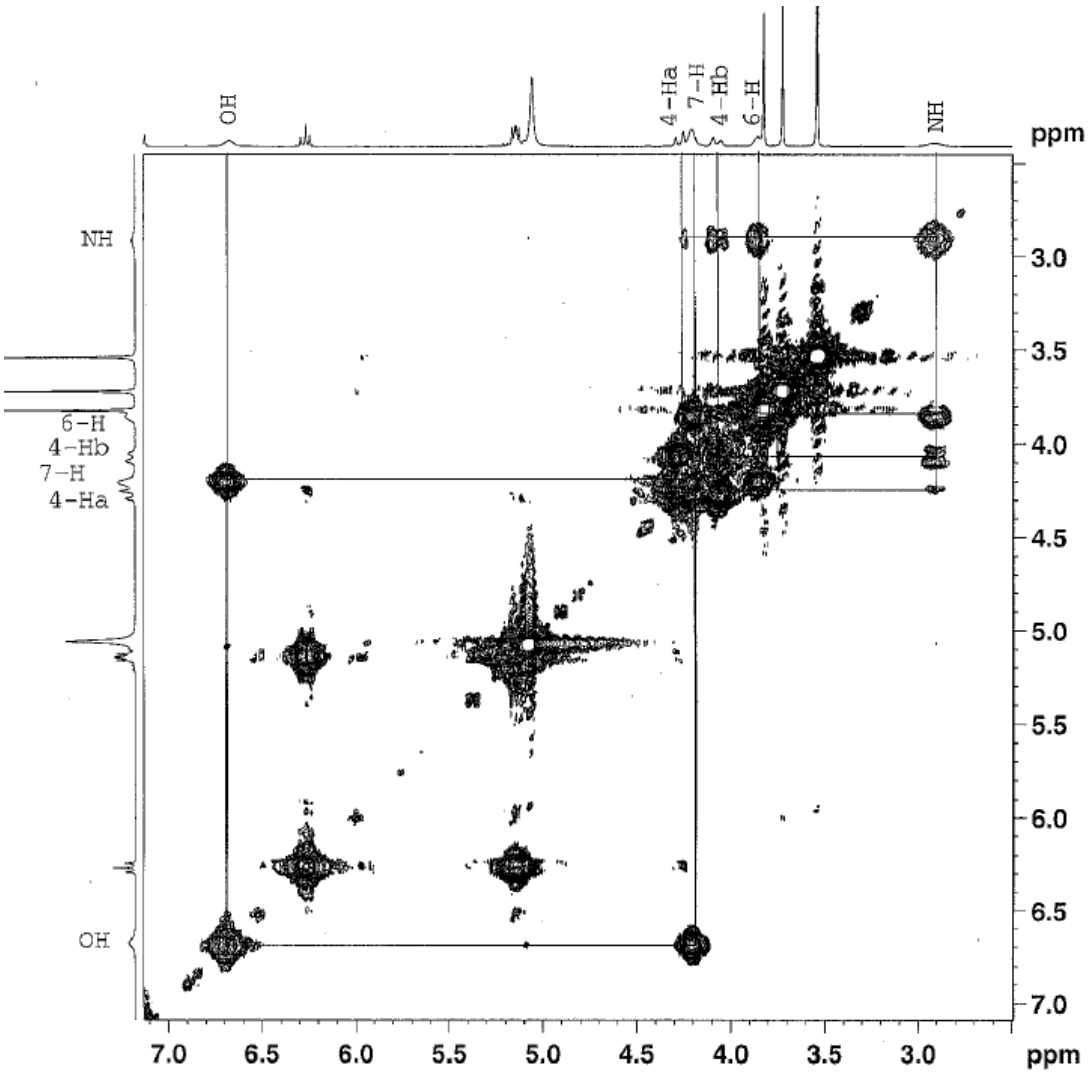


Figure 4. ^{1}H-^{1}H COSY nmr (300 MHz, pyridine-d_5) of **216**.

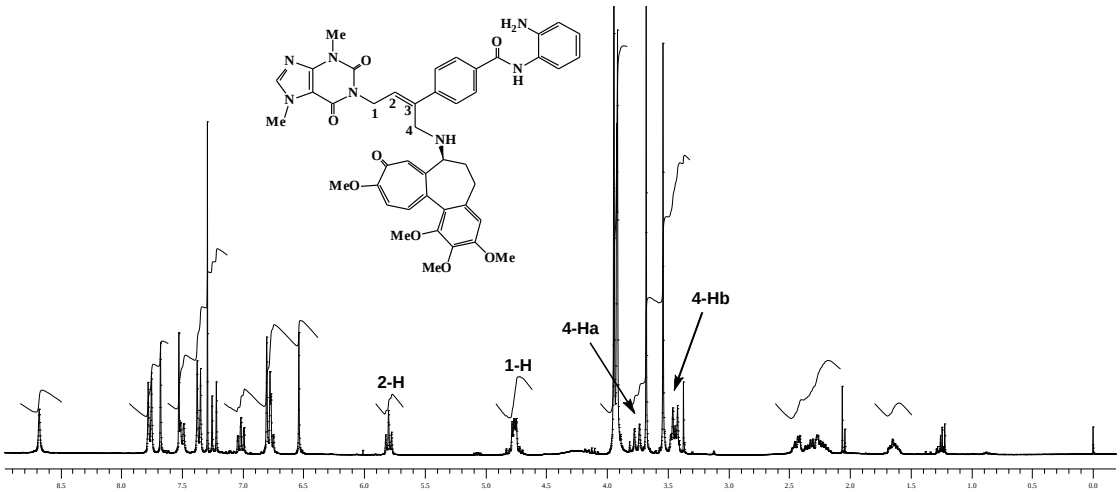
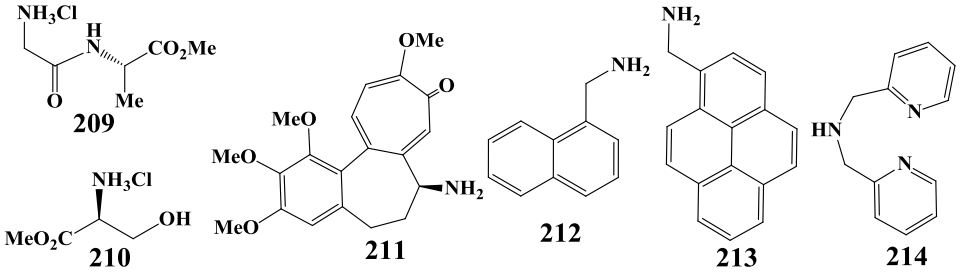
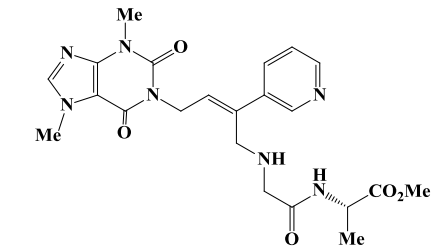


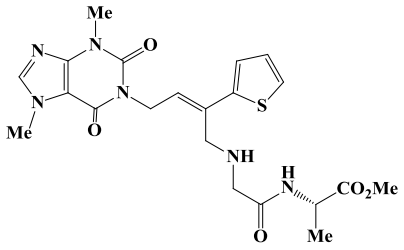
Figure 5. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **217b**.



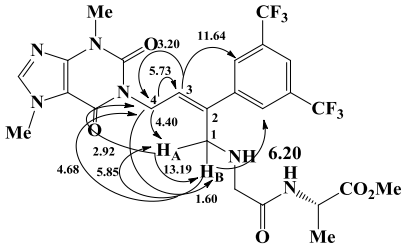
209 **210** **211** **212** **213** **214**



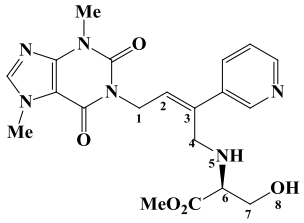
215a (85%)



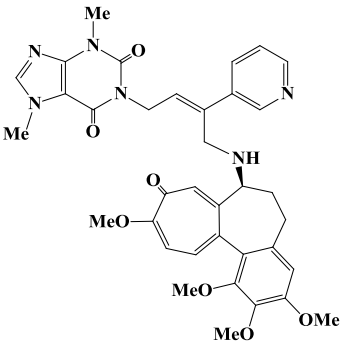
215b (76%)



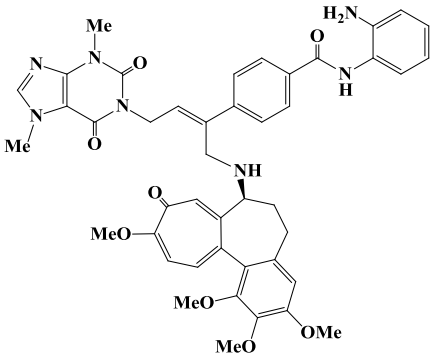
215c (76%)



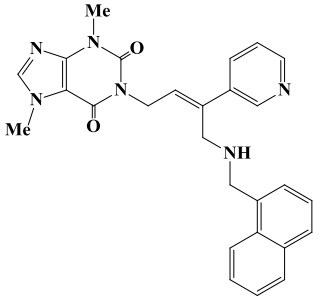
216 (70%)



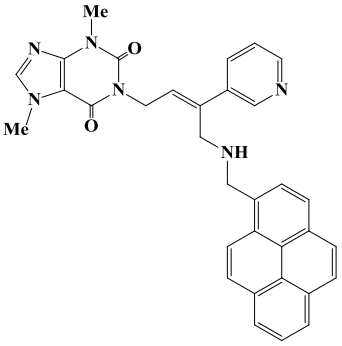
217a (94%)



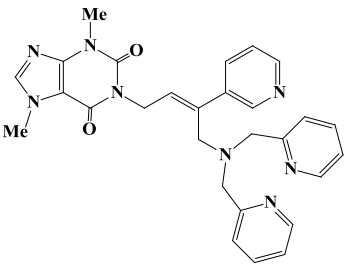
217b (85%)



218 (86%)



219 (89%)



220 (91%)*

Reaction carried out at 80 ºC in MeCN for 3-8 h and employed purine allene **195** (1 equiv.), aryl iodide (1.2 equiv.), nucleophile (1.0-1.2 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.). *In case of **220**, the reaction was carried out at 80 ºC in MeCN for 7 h and employed purine allene (2 equiv.), aryl iodide (2 equiv.), nucleophile (1 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.)

Chart 10. 3-Component cascade products.

The metal chelator[124] (di-(2-picolyl)amine) **214** (1 equiv.) was employed as a nucleophile in a Pd cascade reaction with purine allene **195** (2 equiv.) and 3-iodopyridine (2 equiv.) to afford 91% yield of *Z*-product **220** (Chart 10) showing that metal chelation of the catalyst was not a problem. This reaction ratio was used because when di-(2-picolyl)amine **214** (1.2 equiv.) was used with **195** (1 equiv.) and 3-iodopyridine (1.2 equiv.) the isolated product was extensively contaminated by the excess of **214**.

2.2.2.8 Design and preparation of potential histone deacetylase (HDAC) inhibitors *via* three component cascade chemistry.

Histones are primary protein components of chromatin used to compact the DNA in the cell nucleus through the interaction between the histones positive charged "tails", due to basic lysine and arginine residues, and the DNA negatively charged phosphate groups. The living cell controls the coiling and uncoiling of DNA around histones *via* the acetylation and deacetylation of lysine and this regulates gene transcription (Fig. 6). The coiling state is achieved by the assistance of HDAC enzymes which remove the acetyl groups from the lysine tails causing condensation of the DNA-histones resulting in gene transcription repression. The opposite, uncoiling, process is accomplished by histone acetyltransferases (HAT's) which acetylate the basic lysine tails of histones which destroys the charge interactions and opens up the DNA coil allowing gene transcription expression.

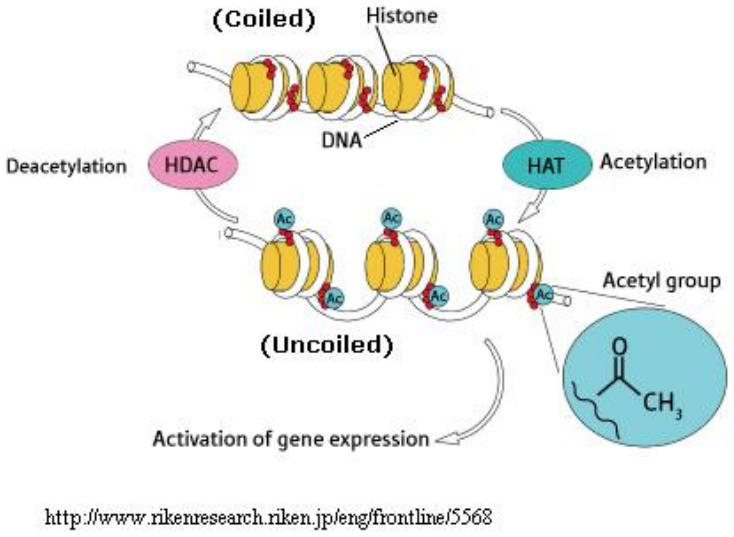


Figure 6. Coiling and uncoiling of DNA around histones.

The HDAC active site consists of a sock-shaped pocket with a zinc ion in the heel region bound to two His-Asp residues.[125a] An X-ray crystal structure of HDAC like

protein (HDLP), from *Aquifex aeolicus*, indicate a 11 Å tubelike "leg" channel with a 14 Å long internal "foot" or "toe" cavity near to the zinc ion (Fig. 7).[125b]

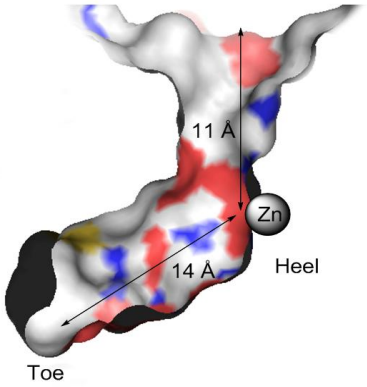


Figure 7. X-ray crystal structures of HDAC like protein.[125b]

HDAC inhibitors are used to suppress the histone deacetylation process, encourage relaxation of chromatin and facilitate gene transcription-expression. Major efforts are being directed to use this epigenetic mechanism to treat various cancers,[126] neurological diseases,[124,127] psychiatric diseases,[127a,128] malaria,[129] etc. (Chart 11).

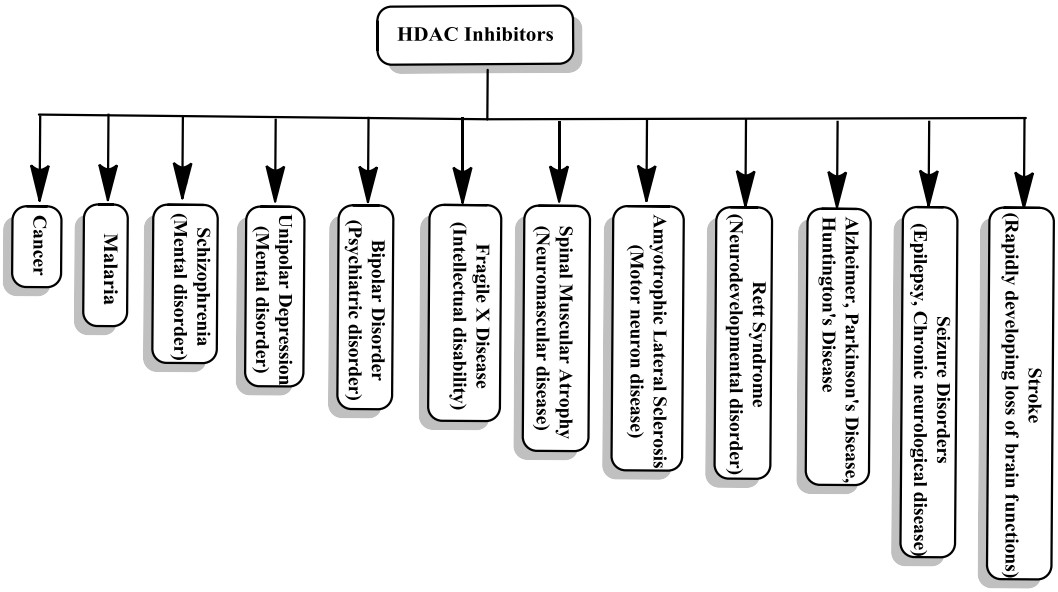


Chart 11. Some current areas of HDAC inhibitor activity.

The general structural features of HDAC inhibitors can be divided into three sections (Chart 12). The head, zinc binding, group is the first part which coordinates with the zinc active site. The second part is a hydrophobic linker of between four to six carbon atoms in length. The final part is a surface recognition cap to interact with the HDAC surface. There are many variations of HDAC inhibitors and Chart 13 lists the

four currently most popular groups: hydroxamic acids, short-chain fatty acids, cyclic peptides and benzamides. Our group have extensive experience in the preparation of potential benzamide HDAC inhibitors.[130] Our current lead compound is HDAC3 selective with 16 nM activity (Chart 13, **MI-192**[130b]).

Chart 12. General structure features of HDAC inhibitors.

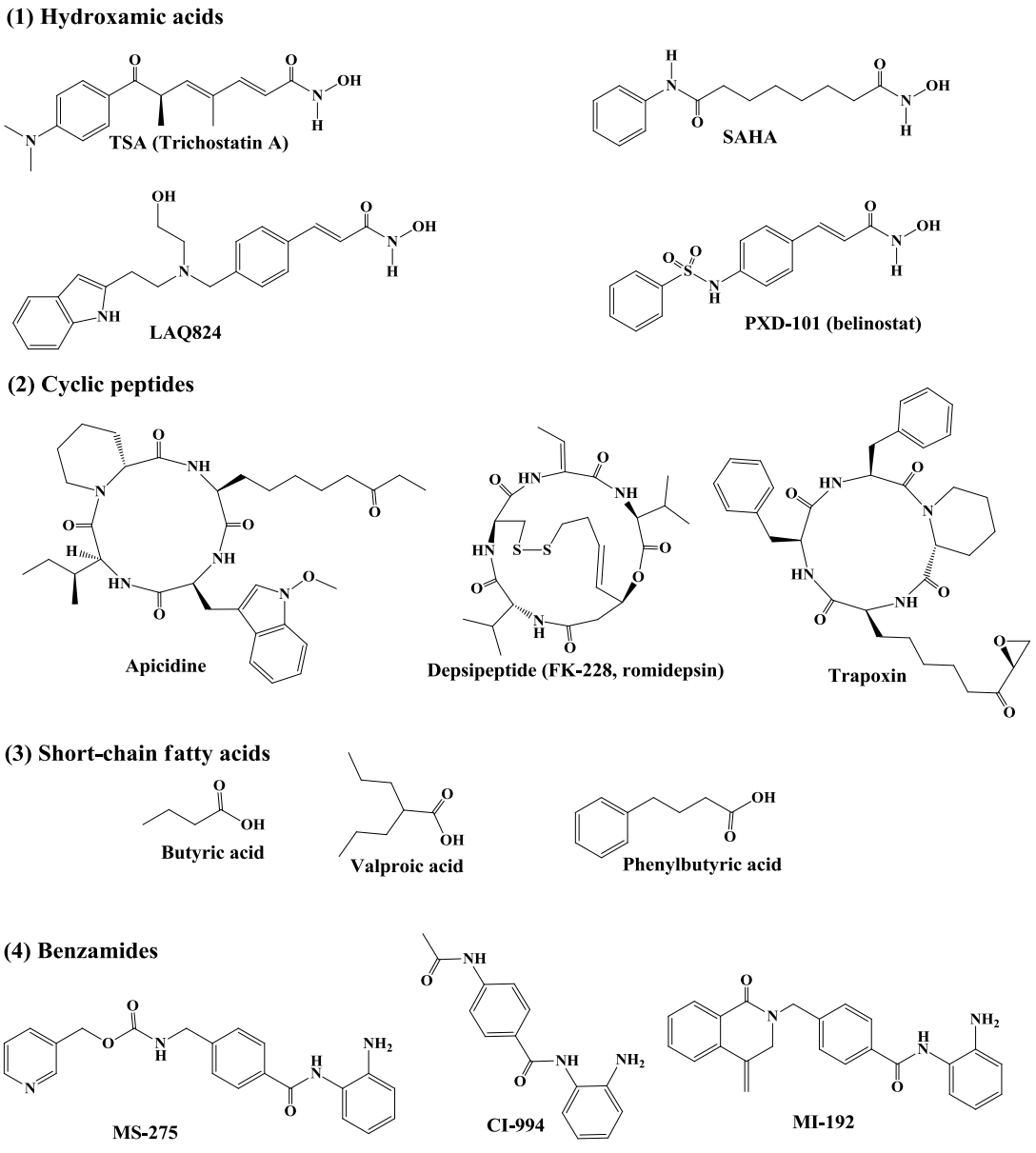
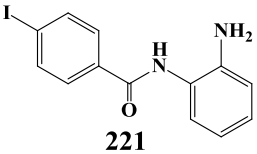
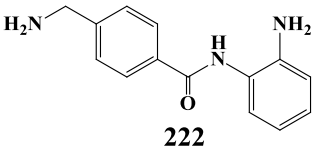


Chart 13. Classes of HDAC inhibitors.

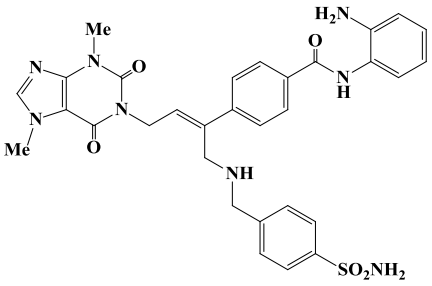
The author has studied some further Pd cascade processes to supplement this work (Chart 14). This involved the Pd(0) catalysed reaction of *N*-(2-aminophenyl)-4-iodobenzamide **221**[130c] (aryl iodide) with purine allene **195** and nucleophiles which gave the *Z*-products **223a-d** stereoselectively in 67-83% yield. Also, 4-(aminomethyl)-*N*-(2-aminophenyl)-benzamide **222**[130b] was reacted as a nucleophile with 3-iodopyridine to give **223e** (60%).



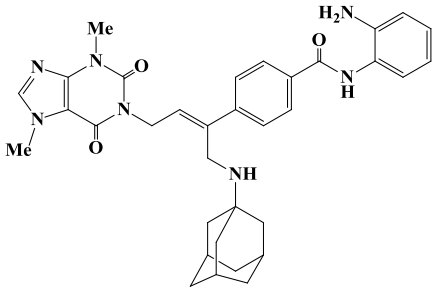
221



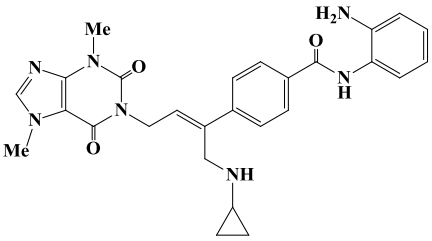
222



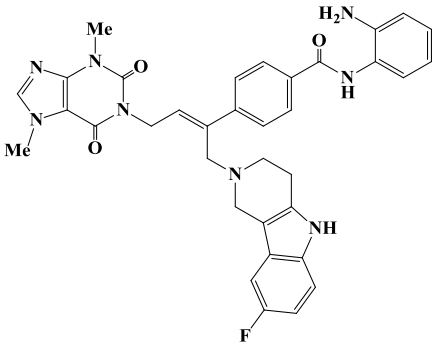
223a (67%)*



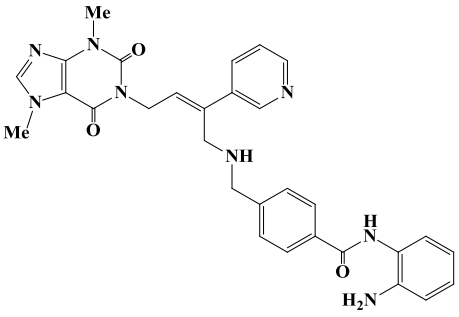
223b (83%)



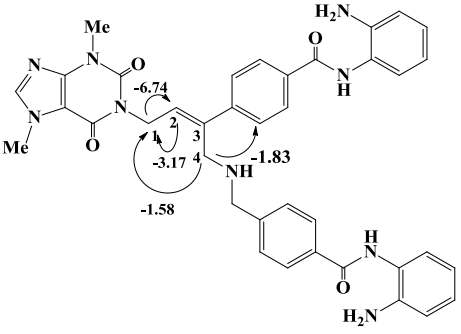
223c (76%)



223d (82%)



223e (60%)



223f (51%)

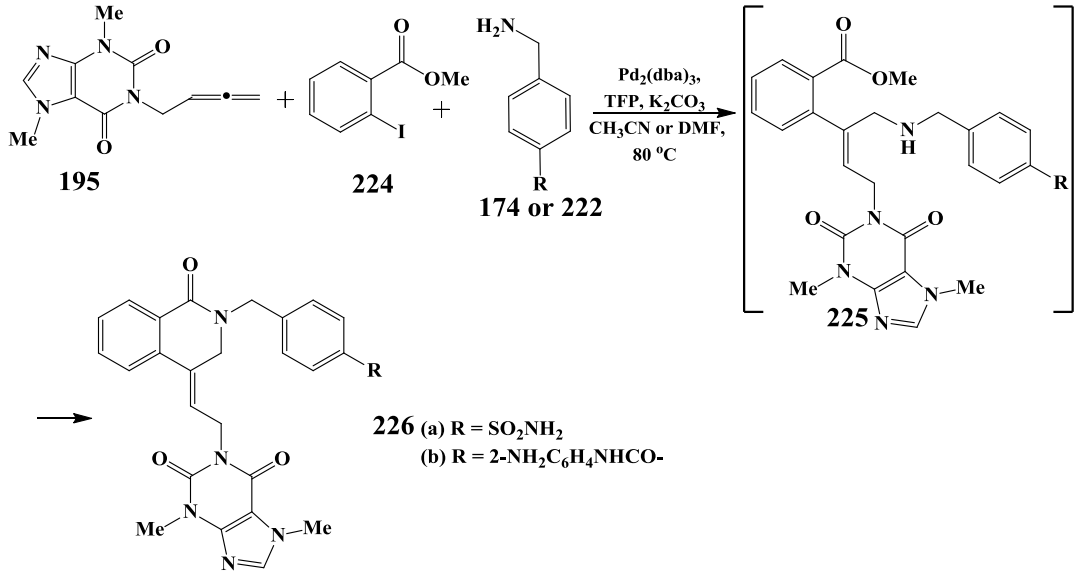
Reaction carried out at 80 ºC in MeCN (7 mL) and employed purine allene **195** (1.00 mmol), aryl iodide (1.20 mmol), nucleophile (1.20-1.50 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3equiv.). *Reaction carried out in DMF (4 mL).

Chart 14. Potential HDAC inhibitors.

Furthermore, **223f** with two zinc binding domains was prepared (51%) by reaction of **221** (aryl iodide) with **222** (nucleophile) and purine allene **195**. Interestingly, the reaction went chemoselectively and there is no indication of incorporation of aniline-NH_2 or amide-NH or sulphonamide-NH_2 groups into the cascades.

The *Z*-stereochemistry of **223a-f** was assigned on the basis of NOE studies on **223f** (Chart 14). Irradiation of 2-H (δ 5.91) caused -3.17% enhancement of 1-CH_2 but no enhancement of 4-CH_2 protons. However, irradiation of 1-CH_2 (δ 4.74) resulted in -6.74% enhancement of 2-H but no enhancement of 3-phenyl protons was observed. Irradiation of 4-CH_2 (δ 3.75) caused -1.83% enhancement of 3-phenyl-H and -1.58% enhancement of 1-CH_2 but no enhancement of 2-H proton was observed. The negative NOE data is attributed to the shape and molecular weight of the molecule rather than to the viscosity of the solvent which could also prevent mobility of the molecule in solution.[131]

A further two potential **MI192** analogues were prepared in order to extend the library of the compounds and study the effect of substituents on the exocyclic methylene double bond and also the effect of sulphonamide as zinc binding head group instead of the benzamide group. Thus, the reaction of purine allene **195** with methyl 2-iodobenzoate **224** and mafenide **174** or benzamide **222** under palladium catalysed conditions afforded **226a** and **226b** in 54% and 56% yield, respectively *via* the intermediate **225** (Scheme 77). NOE data of **226b** confirmed the *Z*-configuration of the exocyclic double bond (see experimental).



Scheme 77. Synthesis of **MI192** analogues.

2.2.3 Pd(0) catalysed multi-component cascades.

2.2.3.1 Introduction.

Protein-substrate recognition is crucial in drug design and recognition of the target protein can be achieved by several strategies. A common method is to design and synthesize compounds that target well defined cavities inside a protein to disrupt the normal protein-ligand interactions. An alternative strategy involves targeting a unique area on the protein surface and designing molecules to bind to it and disrupt protein-ligand and protein-protein interactions (PPIs).[132a-f] PPIs are important processes in cellular functions.[132g,133a] For example, the loss of essential PPIs or the formation and/or stabilization of PPIs at an inopportune time or location can cause cervical cancer, leukemia, bacterial infections and neurodegenerative diseases.[133] Non-obligate (short lived) and permanent interactions are two types of PPIs that depend on the stability and mechanism of their formation.[131b] The common forces governing PPIs are steric, hydrophobic/hydrophilic, electrostatic, Van der Waals interactions and hydrogen bonding. The complementarity of these forces are responsible for the life time, stability and specificity of the PPI and decide which partner is associated.[131a-d] The recognition surfaces range from 550 - >4400 $Å^2$ and are not necessarily flat and are covered with pockets, clefts and dentations.[131d-f,134a] Inhibitors of PPIs are not required to cover all the protein interface but they need to recognise some amino acids on the protein surface.[134] There are two targets, "hot spots" and "allosteric" sites, on the protein surface available to the inhibitors.[131e,f,134a] The hot spots are located as patches of amino acids on the protein surface and are responsible for the main interactions and stability of the interaction between the protein and its partner. Designing molecules having the ability to bind to protein hot spots and preventing normal protein partner association results in disruption of the protein function.[135] Allosteric sites are small groups of amino acids located away from the protein-protein interface where binding of inhibitors result in disruption of protein conformation and change of protein interfaces, resulting in inhibition of PPIs.[136]

2.2.3.1.1 Mechanism of multivalent ligand interactions.

Multivalent ligands (MLs) have multiple copies of receptor recognition elements and work as inhibitors or effectors in living cells. Multivalent inhibitors prevent receptor-ligand binding whereas multivalent effectors induce cellular response. The

mechanism of MLs interaction determines the particular purpose and potency of these ligands.[137]

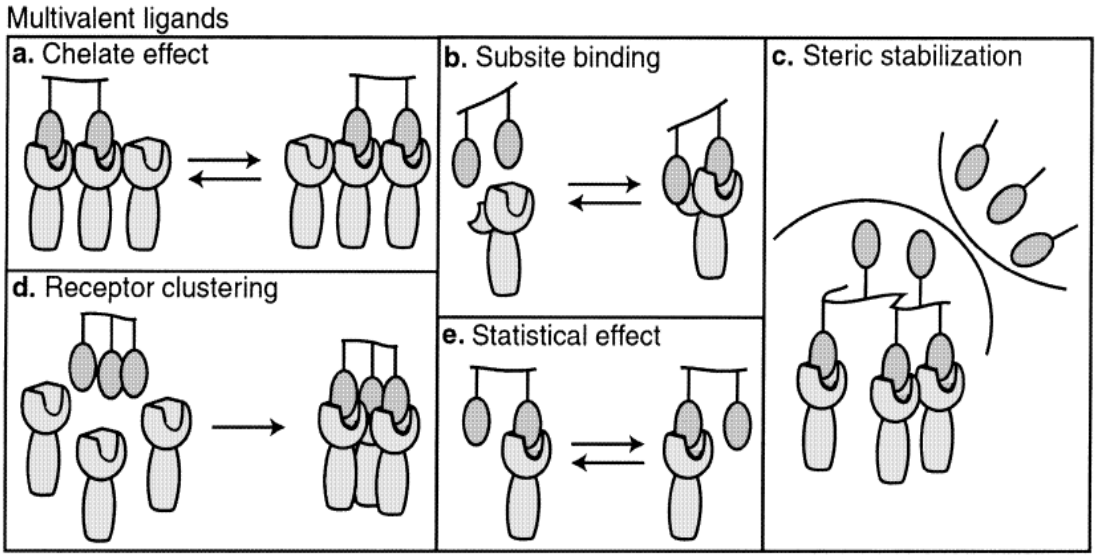


Figure 8.[137a] Mechanisms of MLs interactions.

There are different mechanisms for the binding of MLs with receptors (Fig. 8): (a) **Chelate effect:** MLs bind oligomeric receptors, chelate multiple recognition sites, decrease off-rate and increase interaction affinity. The rotational and translational entropy "fees" are paid only once by the first interaction between one of the MLs recognition groups and the receptor and successive binding of the recognition groups with the receptors is enhanced. (b) **Subsite binding:** some proteins contain both a primary binding site and an additional sub-binding site and MLs chelate these binding sites. (c) **Steric stabilisation:** the size of MLs prevents addition interactions between the receptors and other recognition groups. (d) **Receptor clustering:** the binding of MLs can change proximity and orientation of a group of receptors and enhance receptor clustering. (e) **Statistical effect:** high local concentration of binding elements on MLs increases statistical rebinding affinity.

2.2.3.1.2 Some examples of biologically active multivalent compounds.

Cytochrome *c* interacts with other proteins (e.g. cytochrome *c* oxidase, cytochrome c peroxidase, Apaf1) and activates mitochondrial electron transfer and cell death or apoptosis. The critical recognition region on cytochrome c exterior surface includes an array of lysine and arginine residues which surround a heme core in the middle of a hydrophobic patch. The exterior surface of cytochrome c partner proteins consist of

a hydrophobic area surrounded by various aspartic and glutamic residues which recognize cytochrome c surface active sites. Hamilton and his co-workers[138] used cytochrome c-partner protein interaction features and designed artificial partners **227a-j** (Fig. 9) through the incorporation of tetraphenylporphyrin as a hydrophobic core terminated with acidic (anionic) groups to match the hydrophobic and cationic residues on the cytochrome c surface thus disrupting the cytochrome c-partner interaction. They extended the hydrophobic diameter from 15.5 Å, tetraphenylporphyrin, to 24.0 Å, tetrabiphenylporphyrin and increased the number of carboxylic acid groups to 16 and used flexible binding groups. These modifications resulted in sub-nanomolar affinity to cytochrome c. The selectivity of **227j** for other proteins, cytochrome c_{551} and ferredoxin, was 270 and 25000 fold, respectively, weaker than for cytochrome c. These results indicated that the size of hydrophobic core and the number of negative charges are important for strong binding and selectivity.

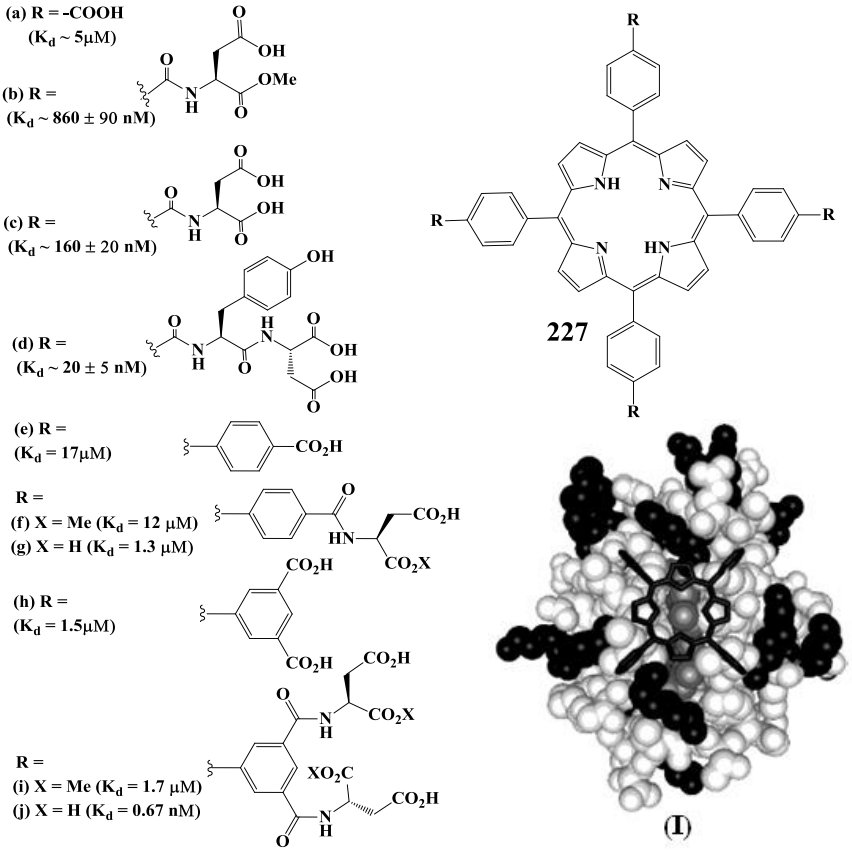


Figure 9. Substituted phenylporphyrin inhibitors. (I) Tetraphenylporphyrin coloured black cylindrical bonds drawn in the centre of X-ray crystal structure of horse heart cytochrome c. The heme group is coloured gray, lysine and arginine residues are coloured black and other residues coloured white.[138a]

Potassium channels consist of four identical protein subunits associated to form homo-tetrameric complexes around central ion pores. Ion channels blockers target only the central pores.[139] Recently, hot spots, glutamate or aspartate, were explored on the surface of the voltage-gated potassium channel K_v1x family. Thus, cationic tetraphenylporphyrin derivatives **228a-g** (Fig. 10) were developed by Trauner et al. These fourfold symmetrical multivalent molecules mimic, and interact with, homotetrameric anionic subunits on the channel surface (Fig. 10, I) with nanomolar affinities.[140]

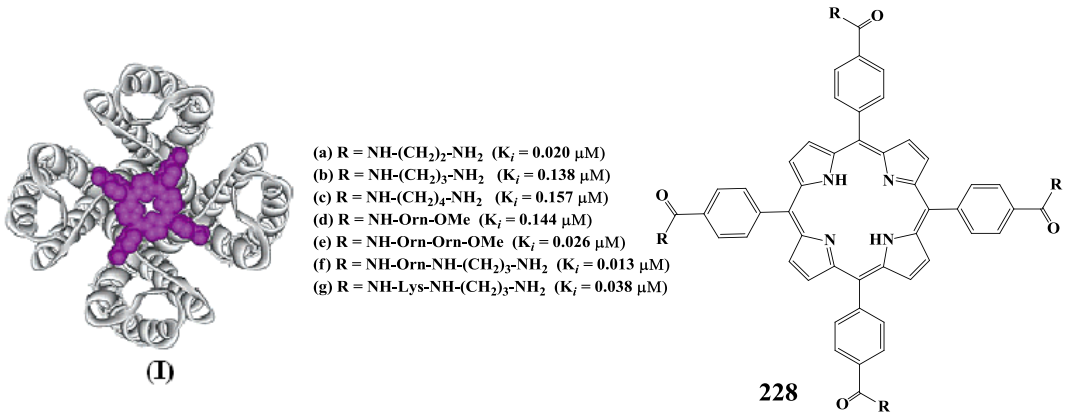


Figure 10. Tetraphenylporphyrin derivatives **228a-g**. (I) X-ray crystal structure of KcsA ion channel with tetraphenylporphyrin **228** (R = OH) coloured magenta.[140]

Strong metal-ligand interactions strategy was employed by Mallik and his group to recognise histidine residues on the surface of carbonic anhydrase protein (Chart 15). Good recognition was achieved by tris-Cu^{+2} complex **229** which was distance matched with tri-histidine residues on the enzyme surface. Other metal complexes afforded weak binding affinity due to low valency or distance not matched with the distance between histidine residues (Chart 15).[141]

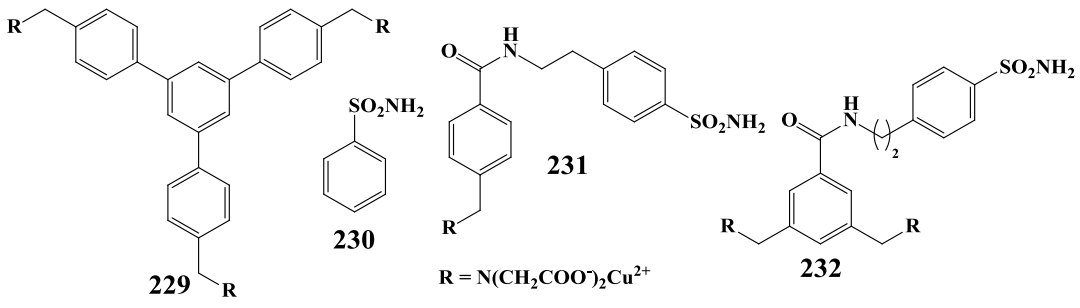


Chart 15. Carbonic anhydrase inhibitors.

Also, they modified the poor carbonic anhydrase inhibitor **230** to good inhibitors **231** and **232** (Chart 15) by attaching an enzyme surface recognition group. In this case, the sulphonamide group binds the enzyme active site Zn^{2+} and Cu^{2+} complexes of the recognition groups bind the enzyme surface histidine residues.[142]

Hamachi and his co-workers explored the first steps in the recognition of protein surface and the regulation of PPIs.[143] Their studies cover the recognition and fluorescence chemosensing of histidine and phosphorylated amino acid residues on the protein surface using metal-ligand interactions.[144] These interactions work efficiently in aqueous medium and they are much stronger than H-bonding and electrostatic interactions. They used Pd(en), palladium(II) ethylene diamine dinitrate complex, which has the ability to selectively recognise and stabilize the α-helix conformation of peptides having two histidine residues located at *i* and *i* + (3 or 4) through the coordination between Pd(en) and two histidine units (Fig. 11a). [145a]

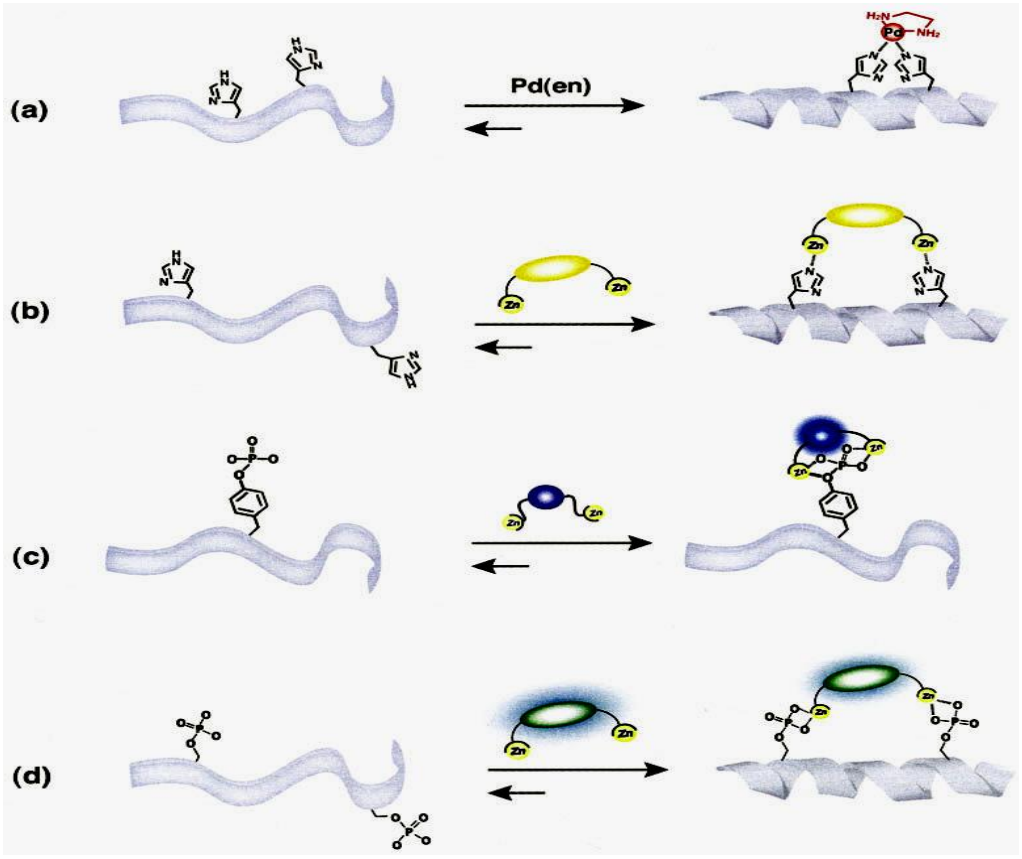


Figure 11.[143] Metal complexes used to recognise histidine and phosphorylated residues on peptide surfaces.

Complexes contain two di(2-picolyl)amine-Zn(II) recognition groups (di-Zn(II)) are used to recognise peptides having two histidine residues located at specific positions

and induce conformation of coiling α-helix (Fig 11b).[145b] The same authors designed di-Zn(II) complexes as novel fluorescent chemosensors to associate phosphorylated tyrosine peptides in aqueous solution (Fig. 11c).[145c] The chelation between two Zn(II) sites and phosphate group enhanced the fluorescence and binding affinity significantly. Di-Zn(II) complexes selectively recognise phosphate anion but no recognition was detected with sulfonate, nitrate, acetate and chloride ions. Fluorescent di-Zn(II) complexes are used to recognise diphosphorylated peptides through a two point intrapeptide cross linking strategy (Fig. 11d) and considerably stabilised α-helix conformation and afforded good binding affinity especially when the distance between the two phosphorylated serine units fits with the distance between two Zn(II) centers.[145d]

Hamachi collaborated with Tamamura and tested dipicolylamine-Zn(II) complexes as lower molecular weight nonpeptide chemokine receptor CXCR4 antagonists.[146] They found that di-Zn(II) complexes are stronger inhibitors than mono-Zn(II) complexes and the angle between the divalent complexes affected on the inhibition.

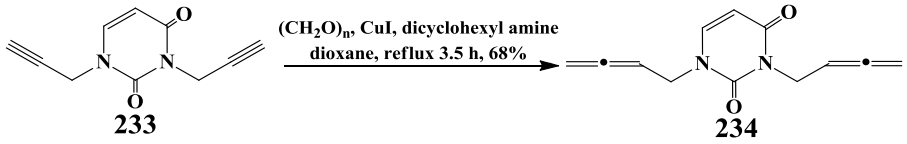
2.2.3.2 Pd(0) catalysed five component cascades using splayed allenes.

All of the previous three component products which carry one recognition group are designed to target a well defined protein active site. This is the old and the predominant strategy in the drug design and discovery. There is also a newer strategy in drug discovery which targets hot spots or allosteric groups on the protein surfaces and disrupts protein-ligand and protein-protein interactions. In the latter case you need a multivalent ligand which has two or more recognition groups to associate with the hot spots or the allosteric groups on the protein surface. Increasing the multivalence order, in another word increasing the number of recognition groups in the ligand, can lead to increasing the selectivity and binding affinity to the protein surface. Also, the complementarity between the ligand and the protein surface is very important.

My next goal was to direct our cascade processes to synthesize multivalent compounds. There are three ways to achieve multivalent compounds in our cascades, i.e. using multivalent allenes, aryl iodides or nucleophiles. Thus, I prepared and involved splayed bisallenes and piperazine/homopiperazine as bis-scaffolds targeted at constructing compounds bearing two identical recognition groups.

2.2.3.2.1 Synthesis and incorporation of N^1,N^3-diallenyluracil 234 into cascade reactions.

Uracil shows broad biological activity[147] and in order to increase the diversity and complexity of cascade products, we synthesised N^1,N^3-diallenyluracil **234** as a building block for Pd cascade chemistry. Compound **234** was synthesized from reaction of N^1,N^3-dipropargyluracil **233**[148a] with dicyclohexylamine (3.6 equiv.), paraformaldehyde (5 equiv.) and CuI (1 equiv.) in dioxane under reflux for 3h to give **234** in 68% yield (Scheme 78).



Scheme 78. Preparation of bisallene **234**.

With bisallene **234** in hand, I started incorporating it into five component cascade reactions. I was delighted to find that the reaction of **234** with aryl/heteroaryl iodides **3** (2.4 equiv.) and γ-carboline **187** (2.4 equiv.) under the optimum cascade conditions ($Pd_2(dba)_3$, TFP, K_2CO_3, MeCN, 80 °C) produced the desired Z,Z-adducts **235a-d** cleanly in 55-96% yield (Chart 16), e.g. the ^{1}H-NMR of **235a** (Fig. 12) showed only one stereoisomer. The stereochemistry of the *Z,Z*-products **235a-d** were assigned on the basis of NOE studies on **235c** (Chart 16). Irradiation of 2-H (δ 6.06) caused 8.87% enhancement of *o*-phenyl protons whilst irradiation of 1-CH_2 (δ 4.71) resulted in a 1.38% enhancement of 2-H and a 1.97% enhancement of the pyrimidinyl 6-H (δ 7.25) but no enhancement of the *o*-phenyl protons was observed. Irradiation of 4-CH_2 (δ 3.77) caused 1.40% enhancement of 1-CH_2, 5.88% enhancement of *o*-phenyl-H and 1.45% enhancement of tetrahydropyridoindolyl 3-CH_2 (δ 2.91) protons but no enhancement of 2-H proton was observed. Furthermore, irradiation of 1′-H (δ 4.87) caused a 1.74% enhancement of 4′-H and irradiation of 2′-H (δ 5.98) resulted in 1.34 and 7.73% enhancements of 1′-H and the *o*-phenyl protons, respectively. Irradiation of 4′-H (δ 3.83) caused 1.86% enhancement of 1′-H, 3.71% enhancement of *o*-phenyl protons and 1.59% enhancement of tetrahydropyridoindolyl 3′-CH_2 (δ 2.91).

Similarly, maraviroc amine **188** (2.4 equiv.) was involved in five component processes by reaction with N^1,N^3-diallenyluracil **234** (1 equiv.) and aryl iodides **3**

(2.4 equiv.) in the presence of $Pd_2(dba)_3$, TFP and K_2CO_3 in MeCN at 80 °C. In each case a 5-component *Z,Z*-product **235e-g** was obtained in 74-85% yield together with a second 5-component isomer in ratio's ranging from 90:10 to 84:16 (Chart 16). Comparing this result with the corresponding 3-component cascade (Scheme 73), the isomer ratio in both the 5-component and 3-component cascades are very similar.

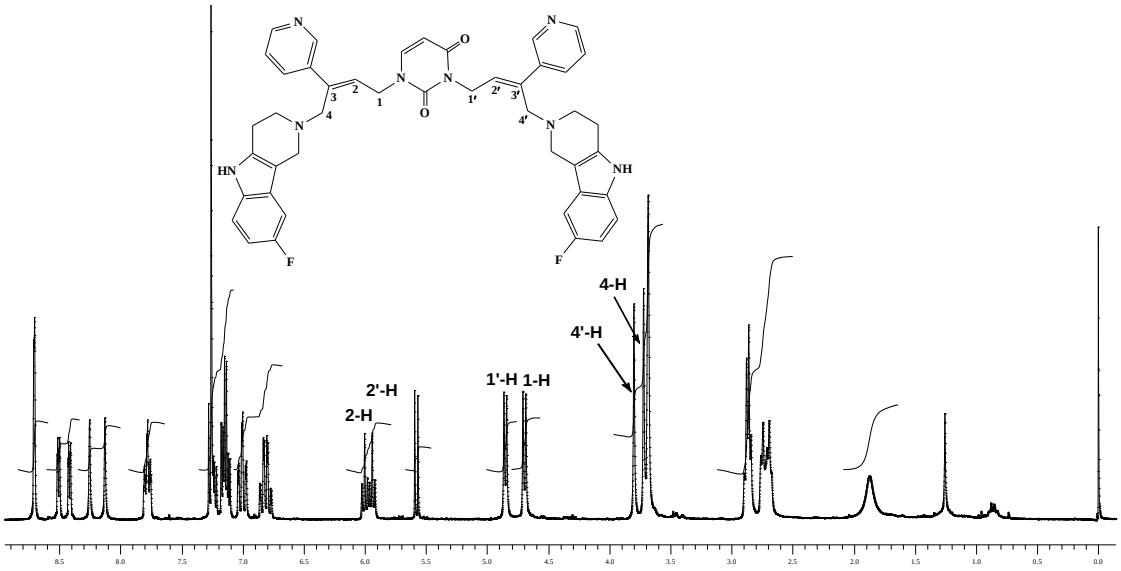
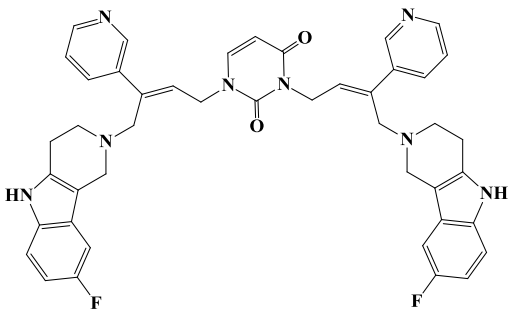
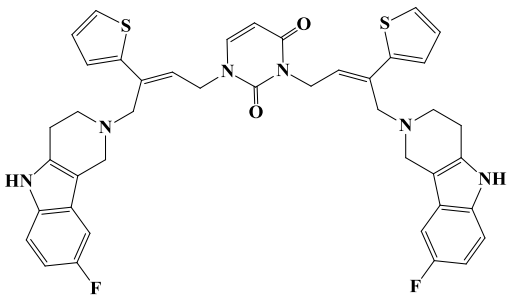


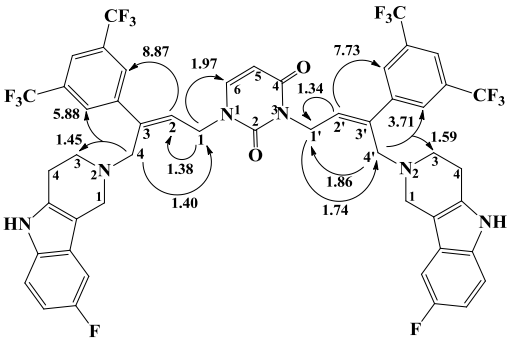
Figure 12. ^{1}H-NMR ($CDCl_3$, 300MHz) of **235a**.



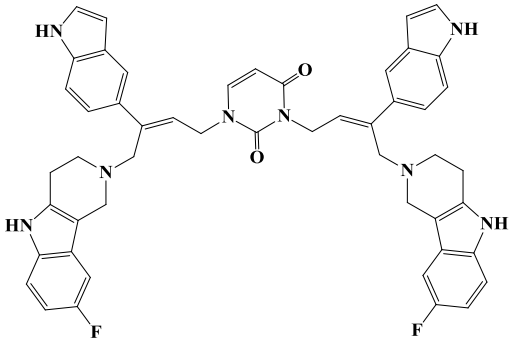
235a (96%)



235b (79%)

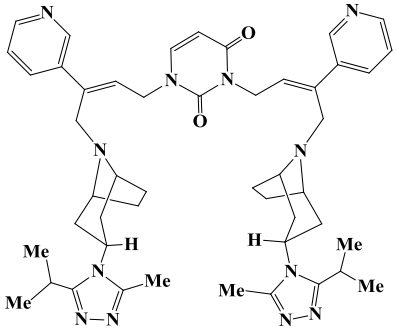


235c (55%)

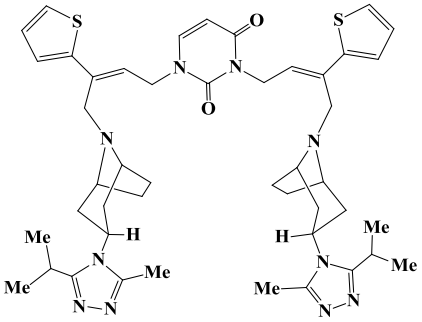


235d (58%)

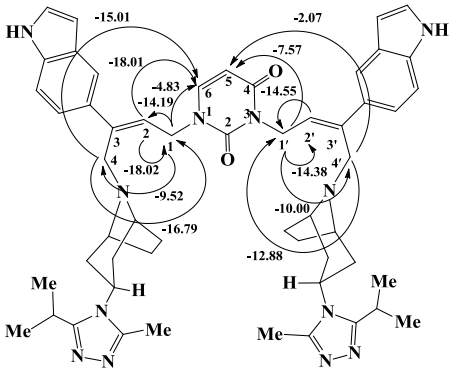
(continued)



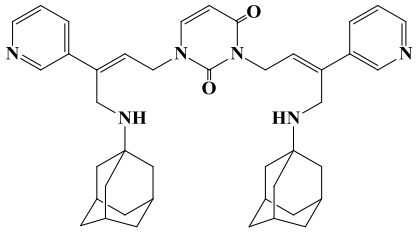
235e (76%, 90:10)



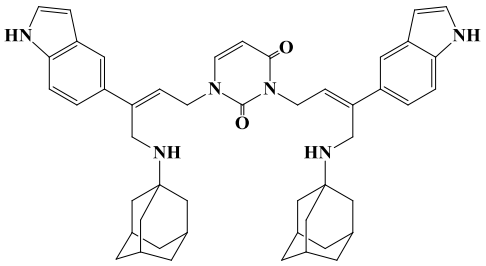
235f (85%. 84:16)



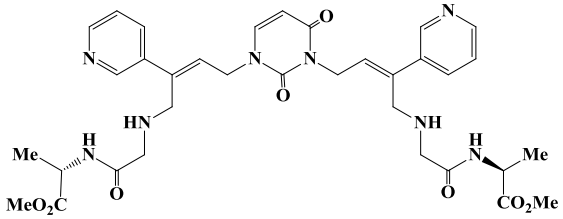
235g (74%, 88:12)



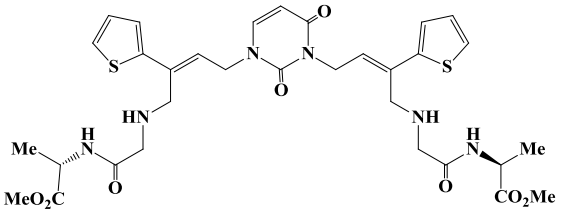
235h (83%)



235i (70%)



235j (70%)



235k (67%)

Reaction carried out at 80 ºC in MeCN (3-5 mL) and employed N^1,N^3-diallenyl uracil **234** (0.25 mmol), ArI (0.6 mmol), nucleophile (0.6 mmol), $Pd_2(dba)_3$ (5 mol%), TFP (20 mol%), and K_2CO_3 (6 equiv.).

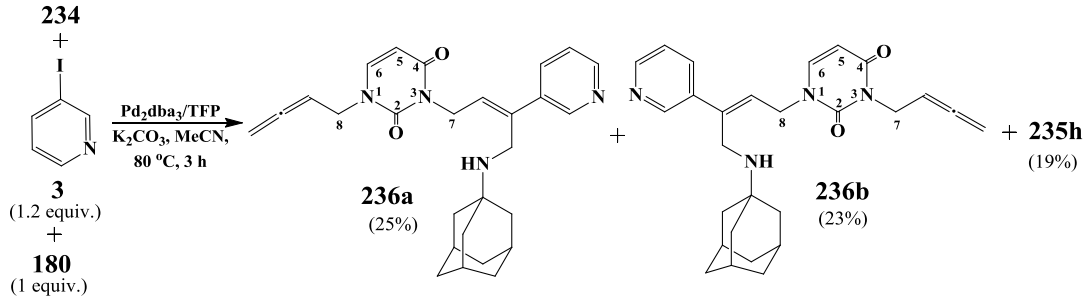
Chart 16. 5-Component cascades with N^1,N^3-diallenyluracil **234**.

Analogously, the *Z,Z*-stereochemistry of **235g** was assigned based on NOE data which showed negative enhancements[131] (Chart 16). Irradiation of 1-H (δ 4.90) caused -14.19, -9.52 and -4.83% enhancements of 2-H, 4-H and pyrimidinyl 6-H protons, respectively. Irradiation of 2-H (δ 5.87) resulted in a -18.02% enhancement

of 1-H and -18.01% enhancement of pyrimidinyl 6-H. Irradiation of 4-H (δ 3.71) caused -16.79 and -15.01% enhancements of 1-H and pyrimidinyl 6-H, respectively whilst irradiation of 2′-H (δ 5.81) caused -14.55% enhancement 1′-H proton. Irradiation of 1′-H (δ 4.70) resulted in -14.38, -10.00 and -7.57% enhancements of 2′-H, 4′-H and pyrimidinyl 5-H, respectively whilst irradiation of 4′-H (δ 3.62) caused -12.88% enhancement of 1′-H.

Moreover, the reaction of the splayed bisallene **234** (1 equiv.) with aryl iodide **3** (2.4 equiv.) and 1-aminoadamantane **180** or Gly-AlaOMe **209** (2.4 equiv.) in a five component reaction gave the desired products **235h-k** *Z,Z*-stereoselectively in 67-83% yield (Chart 16) with no indication of other isomers.

Reactions involving the splayed allene **234** contain two different environments for the allene moiety and the potential for chemoselectivity was briefly explored. Thus, the reaction of bisallene **234** (1 equiv.) with 3-iodopyridine (1.2 equiv.) and 1-aminoadamantane **180** (1 equiv.) was studied. Three products **236a**, **236b** and **235h** were obtained in 25, 23 and 19% yield, respectively, together with unreacted bisallene **234**. Based on this result, the reactivity of two allenyl moieties in **234** are essentially equal, i.e. the reaction went at both ends with no chemoselectivity. Furthermore, the different spacial orientation of the unreacted allenyl groups in **236a** and **236b** leaves them free from conjestion facilitating the formation of **235h**. The structure of **236a** and **236b** were assigned based on the NMR experiments and HRMS spectra. An HMBC experiment on **236a** showed correlations between the 8-CH_2 protons and both 6-C and 2-C=O carbons, while the 7-CH_2 protons correlated with 2-C=O and 4-C=O carbons. Analogously, the HMBC results of **236b** confirmed the relation between the 8-CH_2 protons and both 6-CH and 2-C=O carbons, whereas the 7-CH_2 protons showed correlations with 2-C=O and 4-C=O carbons.



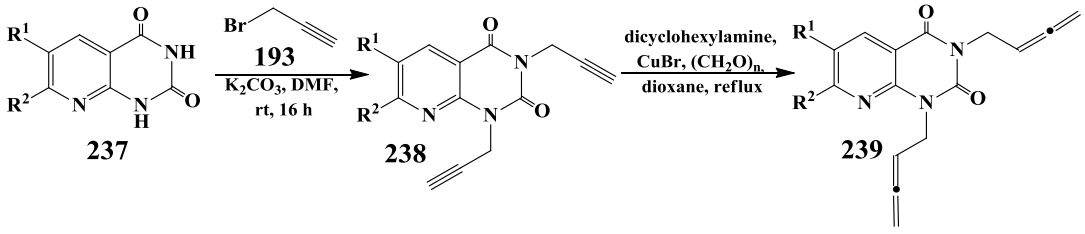
Scheme 79. Observed lack of cascade chemoselectivity of **234**.

2.2.3.2.2 Screening more complex splayed bisallenes in 5-component processes.

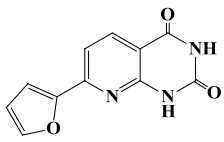
The success in designing and incorporating of N^1,N^3-diallenyluracil **234** into five component cascade processes generating two *Z*-double bonds and four new C-C and C-N bonds encouraged the attachment of two similar privileged fragments which might serve as targets for protein surfaces and/or disrupt protein-protein interaction. AstraZeneca[148b] provided five pyridopyrimidine compounds which looked promising substrates and these compounds gave us the opportunity to generalise the five component cascade using bisallene scaffolds and to probe any buttressing effects of the adjacent pyridine *N*-atom on the reaction.

2.2.3.2.3 Synthesis of splayed bisallenes.

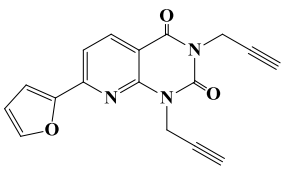
The preparation of the bisallenes involves two steps (Scheme 80). The first involved propargylation of pyridopyrimidine **237**[148b] with propargyl bromide and K_2CO_3 in DMF at room temperature to give dialkyne derivatives **238** in 69-96% yield. The second homologation step used the modified Crabbé method[116] to afford the splayed bisallenes **239** in 42-68% yield (Scheme 80). It is worth noting that compounds **238d** and **239d** are yellow coloured and emit bright yellow fluorescence under UV light. Hence, compound **239d** could be used as fluorophor and as divalent precursor to generate biologically active divalent fluorophors.



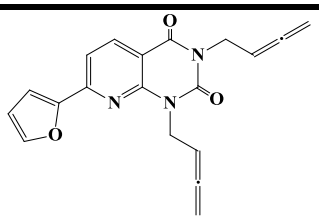
237 **238** **239**



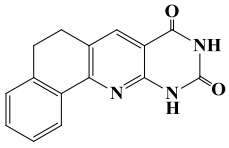
237a



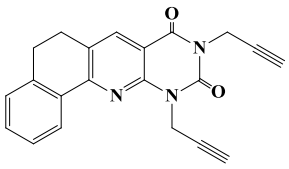
238a (71%)



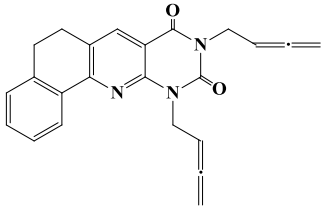
239a (59%)



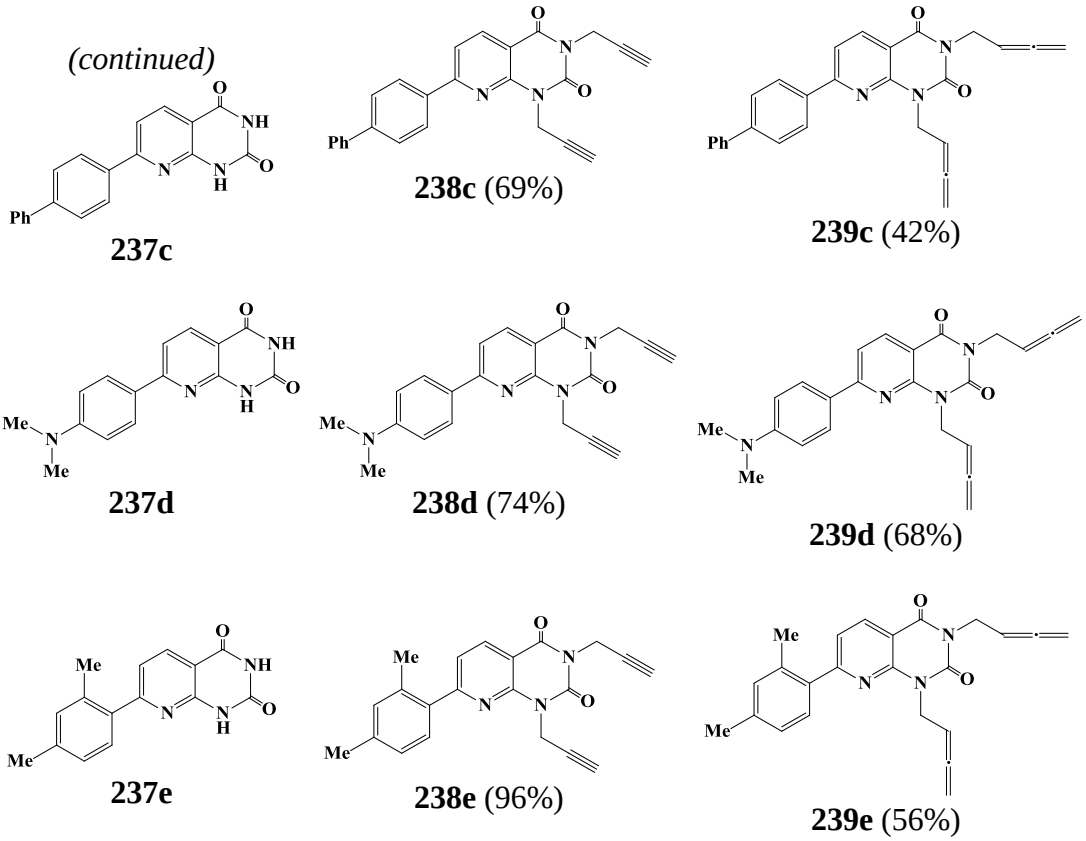
237b



238b (89%)



239b (60%)

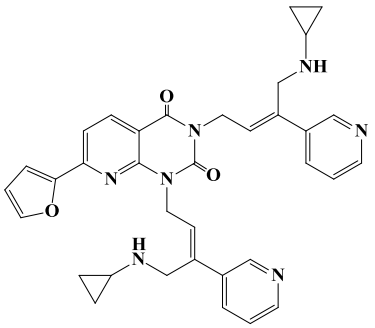


Synthesis of dialkynes **238a-e**: a mixture of pyridopyrimidine **237a-e** (1 equiv.), propargyl bromide (80% in toluene, 4 equiv.) and K_2CO_3 (6 equiv.) in DMF was stirred at rt for 16 h.
Synthesis of bisallenes **239a-e**: a mixture of dialkyne **238a-e** (1 equiv.), $(CH_2O)_n$ (5 equiv.), dicyclohexylamine (4 equiv.) and CuI (1 equiv.) in dioxane was refluxed for 40 min to 2.5 h.

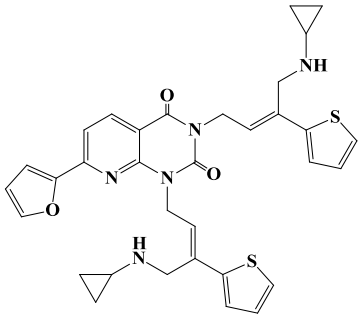
Scheme 80. Propargylation and homologation sequence to prepare bisallenes **239**.

2.2.3.2.4 Incorporation of splayed bisallenes 239a-e in 5-component cascades.

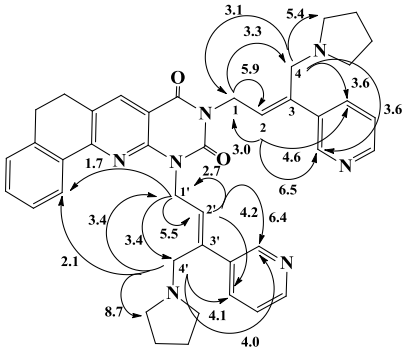
Molecularly diverse bisallenes enables Pd cascade chemistry to develop new architecture with two recognition divalent groups directed into two areas of biological space. Bisallenes **239a-e** (1 equiv.) were used successfully with aryl iodides (2.4 equiv.) and nucleophiles (2.4 equiv.) in a 5-component protocol in the presence of a Pd catalyst to generate the molecular diverse and complex materials **240a-n** in a stereoselective manner (Chart 17). A wide range of aryl iodides and amine nucleophiles were involved in this chemistry. Compounds **240h-j** are yellow to deep yellow colour and emit bright yellow fluorescence under UV light. Hence, they can be modified and used in biological systems as dual fluorophors and divalent ligands. ^{1}H-NMR spectra of selected compounds **240c** and **240l** (Fig. 13 and 14) showed only one product was formed. Extensive NOE studies on five selected cascade products based on bisallene scaffolds were used to assign the stereochemistry of the product double bonds.



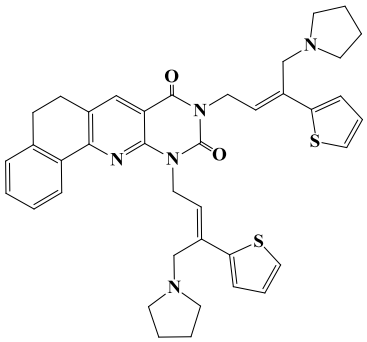
240a (63%)



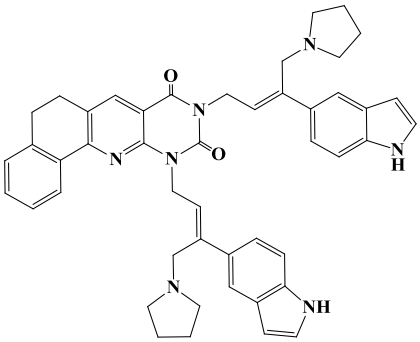
240b (55%)



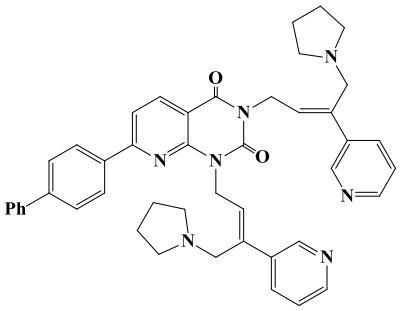
240c (78%)



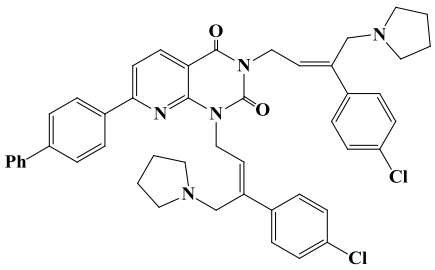
240d (53%)



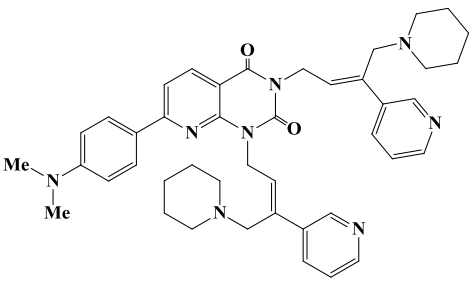
240e (65%)



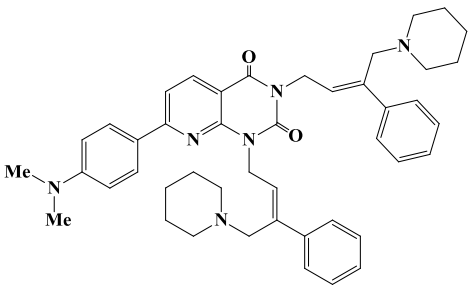
240f (71%)



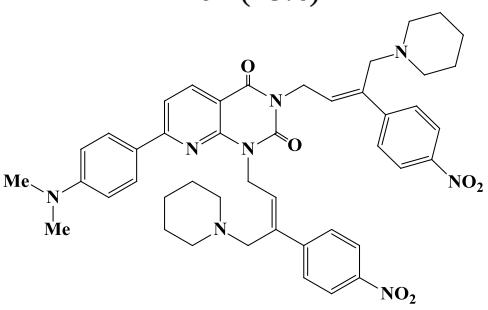
240g (86%)



240h (78%)

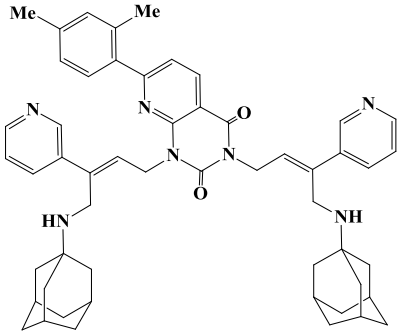


240i (79%)

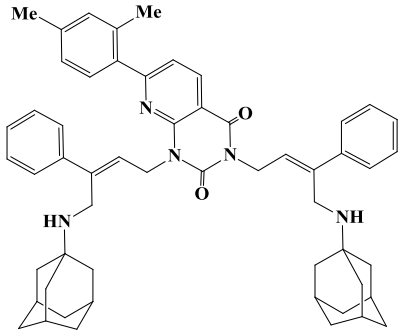


240j (80%)

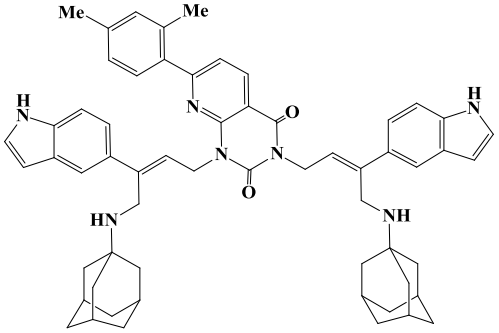
(continued)



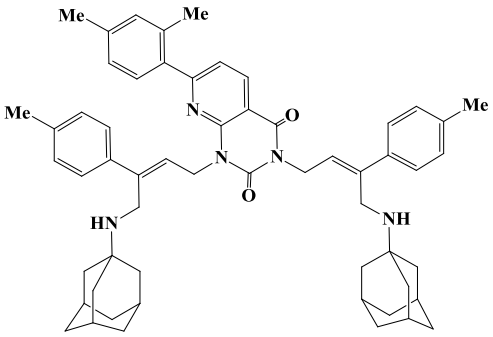
240k (68%)



240l (75%)



240m (58%)



240n (71%)

Reaction carried out at 80 ºC in MeCN for 1-4 h and employed bis-allene (1 equiv.), aryl iodide (2.4 equiv.), nucleophile (2.4 equiv.), $Pd_2(dba)_3$ (5 mol%), TFP (20 mol%), and K_2CO_3 (6 equiv.)

Chart 17. Pd catalysed 5-component cascades using splayed bisallenes.

All the NOE experiments showed the formation of two *Z*-double bonds (see experimental). The NOE data of **240c** (Chart 17) established the formation of two Z,Z-trisubstituted alkenes. Irradiation of 1-CH_2 (δ 5.03) resulted in 5.9 and 3.3% enhancements of 2-H and 4-CH_2, respectively, but no enhancement of the 3-pyridyl protons was observed. However, irradiation of 2-H (δ 5.92) caused 3.0, 6.5 and 4.6% enhancements of 1-CH_2, 3-pyridyl 2-H and 3-pyridyl 4-H, respectively, but no enhancement of the 4-CH_2 protons. Irradiation of 4-CH_2 (δ 3.76) caused 3.1, 3.6, 3.6 and 5.4% enhancements of 1-CH_2, 3-pyridyl 2-H, 3-pyridyl 4-H and 4-pyrrolidinyl 2-CH_2, respectively, but no enhancement of the 2-H proton was observed.

Irradiation of 1′-CH_2 (δ 5.41) resulted in 5.5, 3.4 and 1.7% enhancements of 2′-H, 4′-CH_2 and benzoquinoline 1-H, respectively, but no enhancement of the 3′-pyridyl protons were observed. However, irradiation of 2′-H (δ 6.03) caused 2.7, 6.4 and 4.2% enhancements of 1′-CH_2, 3′-pyridyl 2-H and 3′-pyridyl 4-H, respectively, but no enhancement of 4′-CH_2 protons. Irradiation of 4′-CH_2 (δ 3.81) caused 3.4, 4.0, 4.1, 2.1 and 8.7% enhancements of 1′-CH_2, 3′-pyridyl 2-H, 3′-pyridyl 4-H,

benzoquinoline 1-H and 4′-pyrrolidinyl 2-CH_2, respectively, but no enhancement of the 2′-H proton was observed.

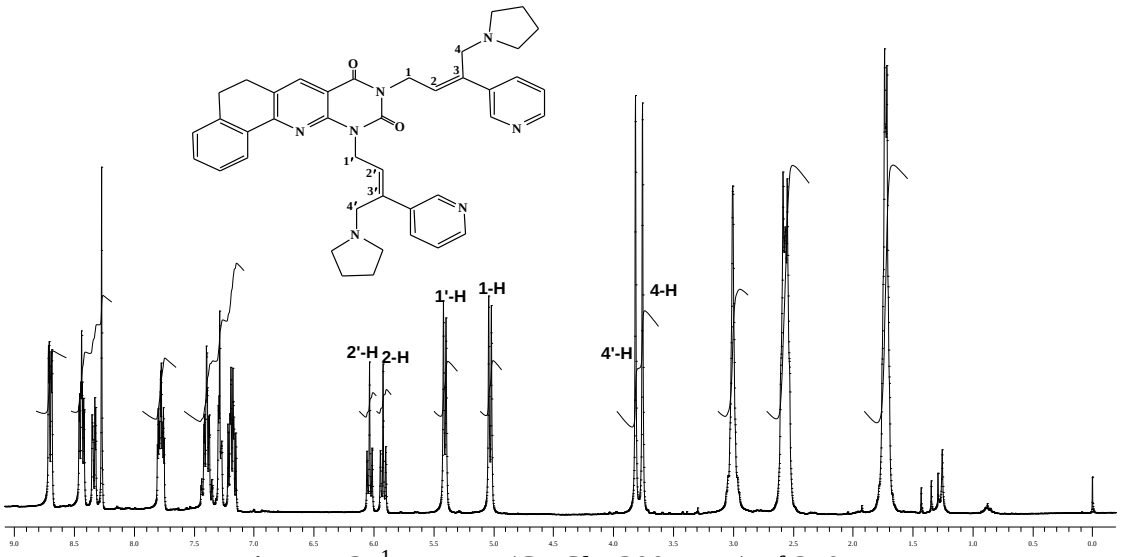


Figure 13. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **240c**.

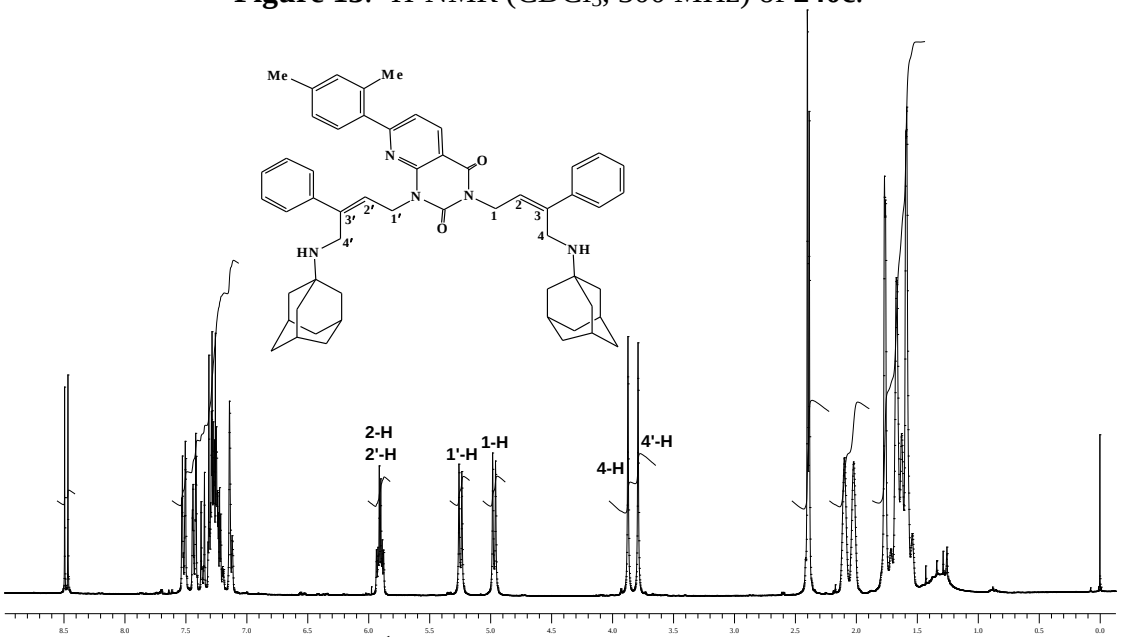


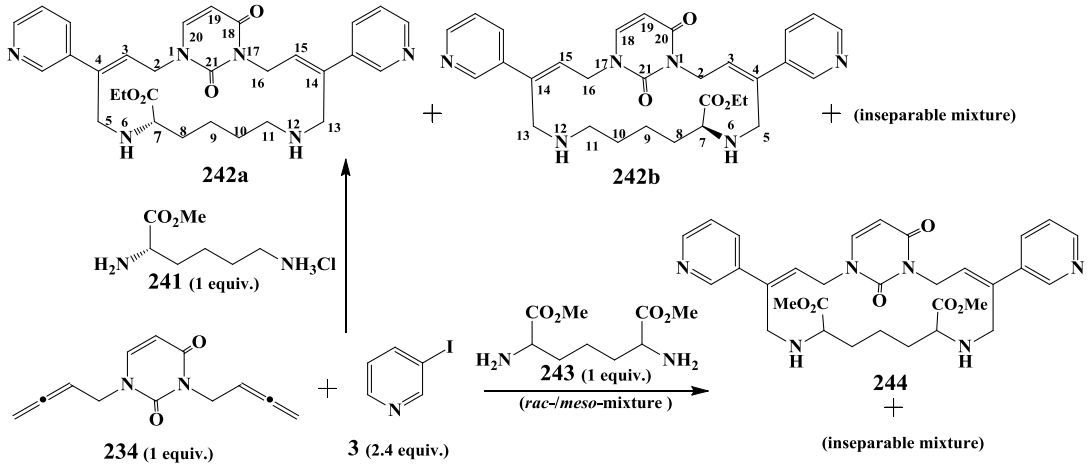
Figure 14. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **240l**.

2.2.3.3 Pd(0) Catalysed formation of macrocycles *via* bisallenes *vs* bisamines: preliminary studies.

Synthesis of macrocycles continues to attract the interest of synthetic chemists and biologists.[149] However, to our knowledge, there are only a few strategies that generate macrocycles using allene chemistry e.g. intramolecular cyclisation of allene tethered nucleophile or aryl iodide,[150] macrocyclisation of 1,n-diallenyl diketones[151] and a four component reaction[152] of bisallene (1 component) with a primary amine (1 component) and an aryl iodide (2 components). This encouraged us to explore

such processes using splayed bisallenes as a key scaffold. Two bisallene strategies were considered to accomplish this target. The first is the reaction of a bisallene with a dinucleophile and an aryl iodide (2 equiv.) and the second involves reaction of a bisallene with an aryl diiodide and a nucleophile (2 equiv.). Furthermore, the reaction of dinucleophile (1 equiv.) with aryl diiodide (1 equiv.) and mono-allene (2 equiv.) could also provide access to macrocycles.

The first strategy was applied to the reaction of (*S*)-lysine ethyl ester hydrochloride **241** (1 equiv.) as di-nucleophile with bisallene **234** (1 equiv.) and 3-iodopyridine **3** (2.4 equiv.) in a four component cascade reaction. The product comprise a mixture of two 18-membered macrocycles **242a** (29%) and **242b** (25%) together with an inseparable complex mixture which contains 36-membered macrocycles (supported by HRMS) (Scheme 81). Thus, the rate of formation of **242a** and **242b** is approximately equal. This result paralleled the previous observation (Scheme 79) that the reactivity of the N^1- and N^3- allenyl groups in **234** are similar. We expect the terminal basic (*S*)-lysine amino group (conjugate acid pK_a 10.47)[118] to react first with either of the allene groups in **234** followed by the second (*S*)-lysine amino group (conjugate acid pK_a 7.46,[118] and more hindered) to react intramolecularly with the second allene group to give the two 18-membered macrocycles **242a** and **242b**.



Scheme 81. Macrocycles *via* reaction of splayed bisallene **234** with bis-amine nucleophiles.

Interestingly, using 2,6-diaminopimelic acid dimethyl ester **243**[153] (commercial 50:50 *rac*-/*meso*-mixture) as the di-nucleophile gave the 18-memberd macrocycle **244** as a mixture of *rac*- and *meso*-isomers in 48% yield together with an inseparable mixture which may contain 36-membered macrocycles.

From these results we can predict the following: (1) bis-symmetrical triggers (allene, aryl iodide, nucleophile) containing an appropriate linker between them may direct the reaction to form only one macrocycle, (2) the formation of 36-membered macrocycles might be reasoned to the strain which could exist in 18-membered macrocycles and directed the reaction toward the stable 36-membered ring.

The structure of macrocycle **242a** was assigned based on spectroscopic data. The HRMS spectrum provided crucial evidence of the 18-membered macrocycle which has molecular ion peak at *m*/*z* 545 $(M+H)^+$. The ^{1}H-NMR (Fig. 15) showed the same coupling constant between the triplet at δ 5.86 (15-H, *J* 6.2) and the two doublet of doublets, which have similar coupling between each other, at δ 4.84 (16-H_A, *J* 6.2 and 14.3) and δ 4.78 (16-H_B, *J* 6.2 and 14.3). There is also a good coupling relation between the triplet at δ 5.72 (3-H, *J* 6.7) and the two methylene doublet of doublets, which have the same relationship to each other, at δ 4.94 (2-H_A, *J* 6.7 and 15.7) and δ 4.59 (2-H_B, *J* 6.7 and 15.7). ^{1}H-NMR results were confirmed with a ^{1}H-^{1}H COSY spectrum which presented a correlation between the proton at δ 5.86 (15-H) and the two protons at δ 4.84 (16-H_A) and δ 4.78 (16-H_B) which showed a good relation between each other. Also, a relationship was observed between the proton at δ 5.72 (3-H) and the two methylene protons at δ 4.94 (2-H_A) and δ 4.59 (2-H_B) which had a good relation between each other. Furthermore, the protons at δ 3.77 (13-H_A) and δ 3.73 (5-H_A) correlate with the protons at δ 3.55 (13-H_B) and δ 3.44 (5-H_B), respectively.

The HMBC spectrum ($CDCl_3$) (Fig. 16) delivered useful long range correlations between the protons and the neighbouring carbons, which support the 18-membered macrocycle **242a** structure. The correlations between the 2-H proton and 3-C, 20-C and 21-C support the connection of 2-C to the pyrimidinyl 1-N. Also, the correlations between 16-H and 15-C, 21-C and 18-C support the connection of 16-C to the pyrimidinyl 17-N and the relation between 5-$H_{A,B}$ and 7-C confirmed the connection of 5-C with the 6-N amino ester (*S*)-lysine amino group.

Finally, NOE data provided a strong evidence for the formation of **242a** with two *Z*,*Z*-double bonds (see Appendix 1). Thus, irradiation the proton at δ 5.86 (15-H) caused 1.32, 3.36 and 2.58% enhancements to the protons at δ 4.80 (16-H_A), 8.75 (Py-β) and 7.86 (Py-β), respectively but there was no effect on the protons at δ 3.77 (13-H_A) and δ 3.55 (13-H_B). Also, irradiation at δ 4.80 (16-$H_{A,B}$) resulted in 5.07,

1.52 and 1.01% enhancements of the protons at δ 5.86 (15-H), 3.77 (13-H_A) and 3.55 (13-H_B), respectively, but no enhancement of the pyridyl (Py-β) protons was observed. Furthermore, irradiation the protons at δ 3.77 (13-H_A) and δ 3.55 (13-H_B) caused 2.78 and 2.87% enhancements to the protons at δ 4.80 (16-$H_{A,B}$), 2.28 and 2.38% enhancements to the two methylene protons at δ 2.76 (11-H), 1.46 and 2.38% enhancements to the pyridyl protons (Py-β) at δ 8.75 and 1.52, 2.88% enhancements to the pyridyl protons (Py-β) at δ 87.86, respectively, but no enhancement of the 15-H proton at δ 5.86 was observed. These results support the formation of a 14-C *Z*-double bond and the connection of 13-C to the terminal (*S*)-lysine nitrogen (12-N).

At the other end of the macrocycle, irradiation the proton at δ 5.72 (3-H) caused 1.02, 1.20, 7.02, 3.34 and 2.56% enhancements to the protons at δ 4.94 (2-H_A), 4.59 (2-H_B), 8.70 (Py-α), 7.96 (Py-α) and 7.33 (20-H), respectively, but no enhancements of the protons at δ 3.73 (5-H_A) and δ 3.44 (5-H_B) was observed. However, irradiation the protons at δ 4.94 (2-H_A) and δ 4.59 (2-H_B) caused 2.97 and 3.70% enhancements to the proton at δ 5.72 (3-H), 2.93 and 2.20 % enhancements to the protons at δ 3.75 (5-H_A) and δ 3.44 (5-H_B) and 3.35, 7.43% enhancements to the proton at δ 7.33 (20-H), respectively, but no enhancement of the pyridyl (Py-α) protons was observed. Finally, irradiation at δ 3.44 (5-H_B) afforded 2.52, 12.87, 2.05 and 2.86% enhancements to δ 4.59 (2-H_B), 3.73 (5-H_A), 8.70 (Py-α) and 7.96 (Py-α), respectively, but no enhancement of δ 5.72 (3-H) was observed. These results supported the formation of a 3-C *Z*-double bond and the proximity of 2-C to the pyrimidinyl nitrogen (1-N).

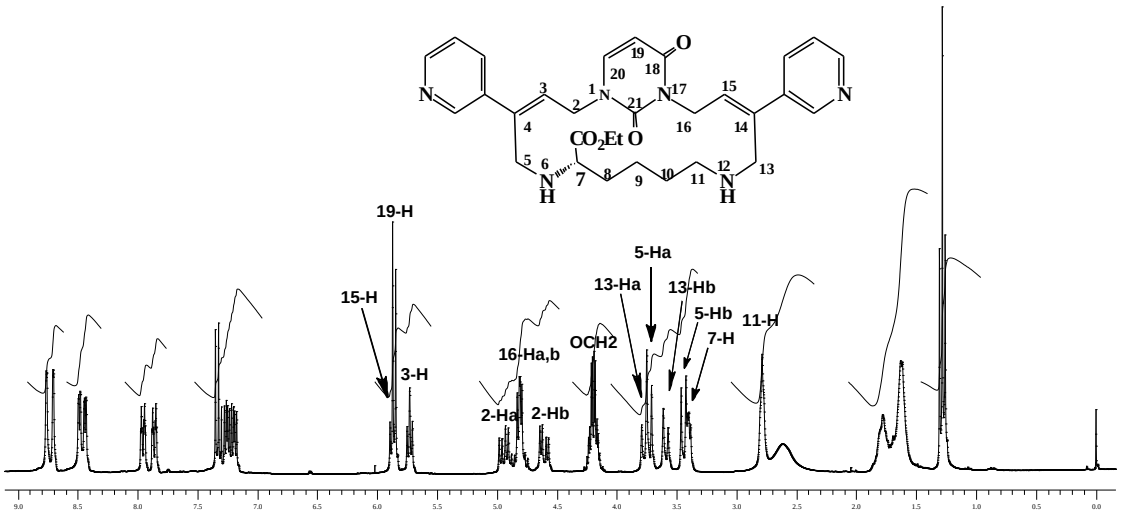


Figure 15. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **242a**.

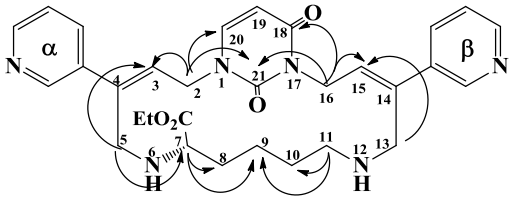


Figure 16. Important HMBC correlation of **242a** (H→C).

Similarly, the macrocycle **242b** was assigned by HRMS, ^{1}H-NMR, ^{13}C-NMR, DEPT135, ^{1}H-^{1}H COSY, HMQC and HMBC data. The high resolution mass spectrum gave a molecular ion at *m*/*z* 545 $(M+H)^{+}$ in agreement with the 18-membered macrocycle structure. The ^{1}H-NMR (Fig. 17) showed similar coupling constants between the triplet at δ 5.80 (3-H, *J* 6.7) and the doublet at δ 4.92 (2-H, *J* 6.7). There is a coupling correlation between the doublet of doublets at δ 5.73 (15-H, *J* 6.2 and 8.1) and the two methylene doublet of doublets, which have the similar coupling constants between each other, at δ 4.83 (16-H_A, *J* 8.1 and 15.0) and δ 4.44 (16-H_B, *J* 6.2 and 15.0). Also, the doublet signals at δ 3.76 (13-H_A, *J* 12.2) and δ 3.72 (5-H_A, *J* 11.2) closely correlate with the two doublets at δ 3.57 (13-H_B, *J* 12.2) and δ 3.50 (5-H_B, *J* 11.2), respectively. ^{1}H-^{1}H COSY spectrum data was in agreement with ^{1}H-NMR results. Thus, a correlation between the proton at δ 5.80 (3-H) and the methylene protons at δ 4.92 (2-H) was assigned. Also, a relationship between the proton at δ 5.73 (15-H) and the two protons at δ 4.83 (16-H_A) and δ 4.44 (16-H_B), which had a good relation between each other, was observed.

Crucial HMBC evidence supporting structure **242b** was delivered with long range H-C correlations (Fig. 18). The correlations between 2-H proton and 3-C, 20-C and 21-C supported the connection of 2-C to the pyrimidinyl 1-N. Also, the correlations between 16-$H_{A,B}$ and 15-C, 21-C and 18-C support the connection of 16-C to the pyrimidinyl 17-N whilst the relation between 5-$H_{A,B}$ and 7-C confirms the connection of 5-C with 6-N (*S*)-lysine amino group.

The NOE analysis (see Appendix 2) of the first part of **242b** afforded a relationship between the 3-H proton and the 2-H, pyridyl (Py-β) protons, but no correlation was observed with the 5-H protons. The 2-H protons correlated with 3-H and 5-$H_{A,B}$ but no correlation with the pyridyl (Py-β) protons was observed. Also, irradiation of 5-H_B enhanced the 2-H, pyridyl (Py-β) protons, but no enhancement of the 3-H proton was observed. The previous NOE results predicted the formation of 3-C *Z*-double

bond. Analogously, the NOE data of the second part of **242b** delivered correlations between the 15-H proton and 16 $H_{A,B}$, 18-H and pyridyl (Py-α) protons but no correlation with 13-$H_{A,B}$ was observed. Irradiation of 16-$H_{A,B}$ caused enhancements to 15-H, 13-$H_{A,B}$ and 18-H protons but no enhancement of the pyridyl (Py-α) protons was detected. Finally, irradiation of 13-$H_{A,B}$ afforded enhancements to 16-$H_{A,B}$, 11-H, pyridyl (Py-α) protons but no enhancement of 15-H was observed. These results support the existence of 14-C in a *Z*-stereochemistry, the attaching of 13-C to the basic amino group 12-N of (*S*)-lysine ester and the connection of 16-C with the pyrimidinyl 17-N.

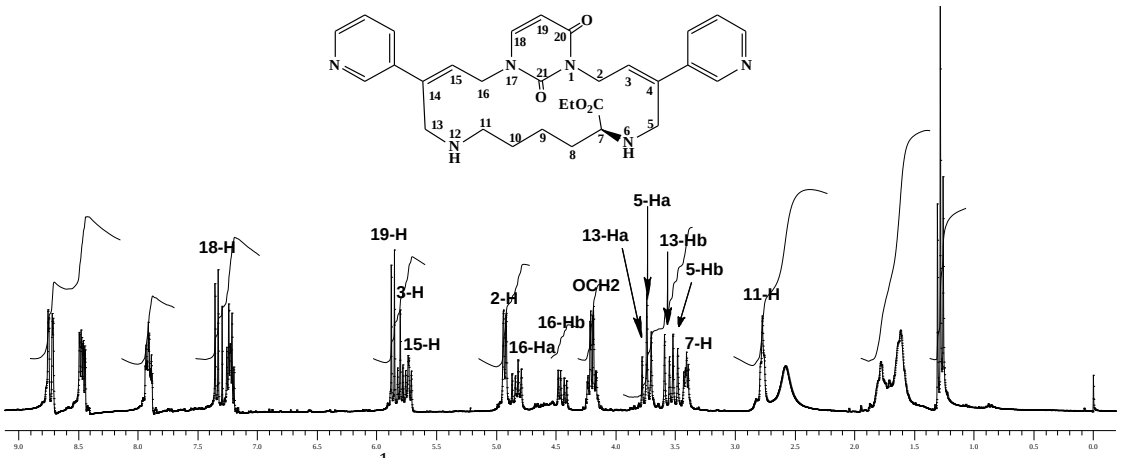


Figure 17. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **242b**.

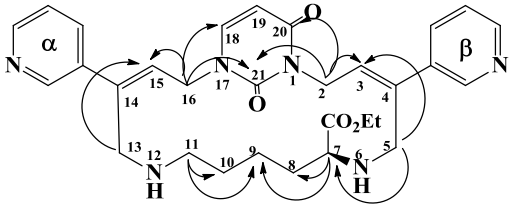
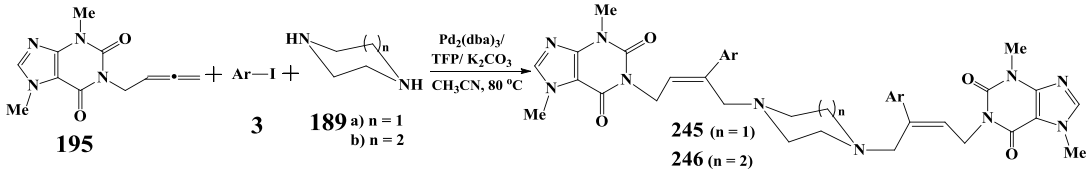


Figure 18. Important HMBC correlation of **242b** (H→C).

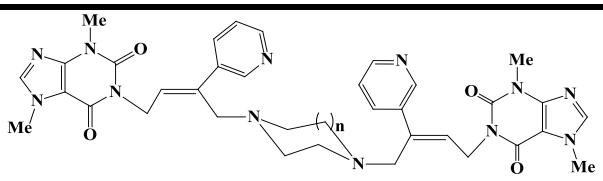
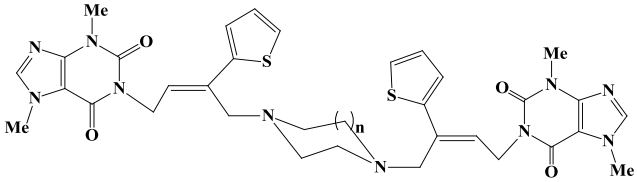
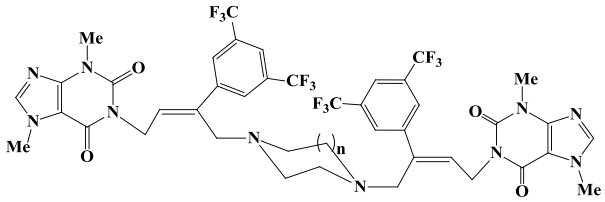
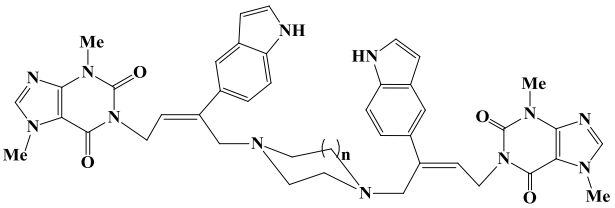
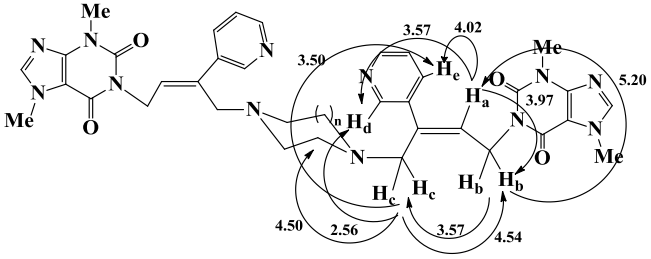
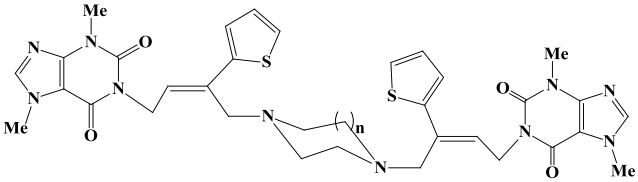
2.2.3.4 Pd(0) catalysed five component cascades using di-amines (piperazine and homopiperazine).

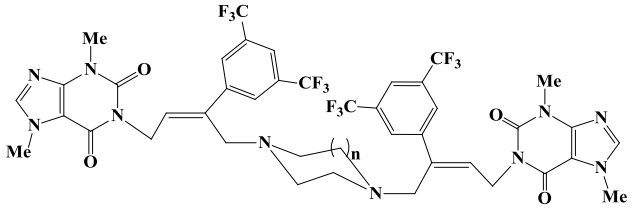
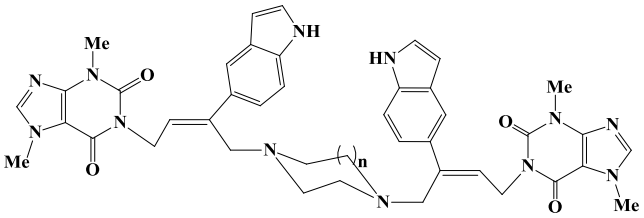
Piperazine **189a** and homopiperazine **189b** are privileged structure existing in a broad range of biologically active compounds.[154] They were explored as bidentate nucleophiles (Scheme 82). They reacted with **195** and aryl/heteroaryl-iodides **3** under our cascade conditions to afford the corresponding *Z,Z*-products **245** and **246** *via* 5-component cascades (Table 2). Compounds **245a-d** (Table 2, entries 1-4) precipitated from hot solution in 80-92% yield whereas compounds **246a-d** (entries 5-8) were separated by chromatography and gave 47-66% yields.



Scheme 82. 5-component cascades of di-amine nucleophiles **189**.

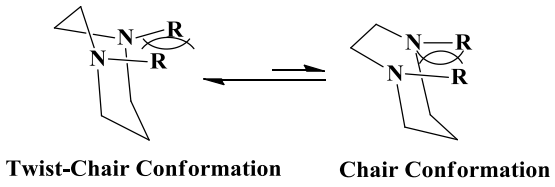
Table 2. Five component cascade products with diamine nucleophiles.[a]

Entry	n	Compound	Yield (%)[b]
1	1	 **245a**	88
2	1	 **245b**	92
3	1	 **245c**	80
4	1	 **245d**	80
5	2	 **246a**	58
6	2	 **246b**	53

7	2	 **246c**	47 (89:11)[c]
8	2	 **246d**	66

a) Reaction carried out at 80 ºC in MeCN (5 mL) for 3-11 h and employed piperazine or homopiperazine (0.5 mmol), *N*-allenylpurine (1 mmol), ArI (1.1 mmol), $Pd_2(dba)_3$ (5 mol%), TFP (20 mol%), and K_2CO_3 (6 equiv.). b) Isolated yield. c) Mixture of two isomers with the *Z*,*Z*-product as the major isomer.

The variation in yield of **245** and **246** is attributed to the different conformations of the piperazine and homopiperazine scaffolds. Piperazine favours the chair conformation in which the two *N*,*N*-substituents are far from each other with no steric problems resulting in excellent yields (Table 2, entries 1-4). However, homopiperazine favours twist chair and chair conformations (Scheme 83).[155] In both conformations there is steric clash between the two substituents which leads to low yields (Table 2, entries 5-8) and an isomeric mixture in case of 1-iodo-bis(3,5-trifluoromethyl)benzene as an aryl iodide (Table 2, entry 7).



Scheme 83. Stable conformations of homopiperazine.

Product stereochemistry was assigned by ^{1}H-NMR spectra e.g. Fig. 20 and 21. NOE data for **246a** (n = 2) established the formation of the *Z*,*Z*-product (Table 2, entry 5). Irradiation of H_a (δ 5.85) caused a 3.97% enhancement of H_b, a 3.57% enhancement of pyridinyl H_d, and 4.02% enhancement of pyridinyl H_e but no enhancement of H_c. However, irradiation of H_b (δ 4.88) resulted in 5.20% enhancement of H_a and 3.57% enhancement of H_c but no enhancement of the pyridinyl protons was observed. Irradiation of H_c (δ 3.33) caused a 4.54% enhancement of H_b, 2.56% enhancement of

pyridinyl H_d, 3.50% enhancement of pyridinyl H_e and 4.50% enhancement of the diazepane protons (δ 2.64) but also no enhancement of H_a was observed.

The NOE data was confirmed by an X-ray crystal structure of **245d** which showed the formation of *Z*,*Z*-product (Fig. 19, Appendix 3). Accordingly, *Z*,*Z*-stereochemistry was assigned the remaining five component products (Table 2).

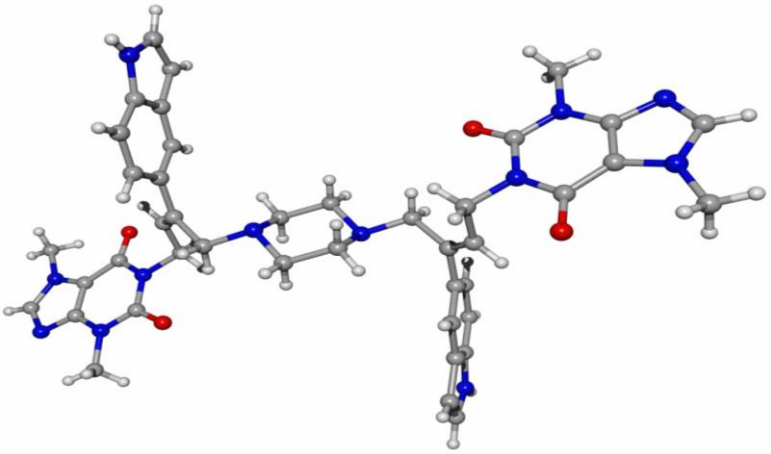


Figure 19. X-ray crystal structure of **245d** (Appendix 3).

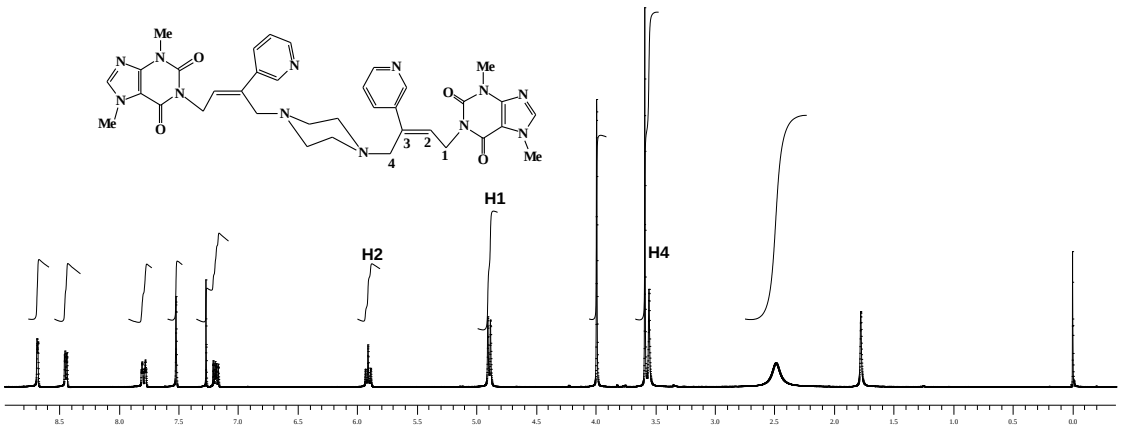


Figure 20. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **245a**.

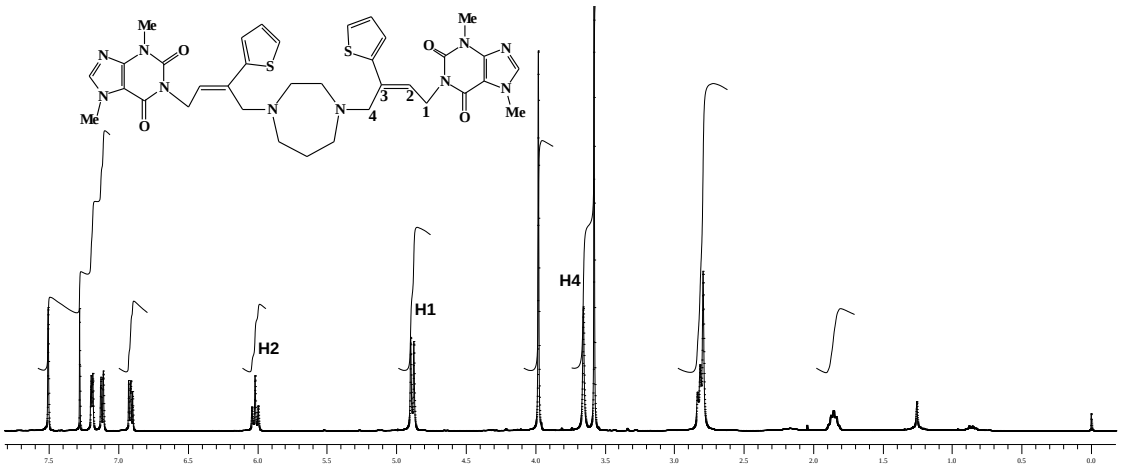


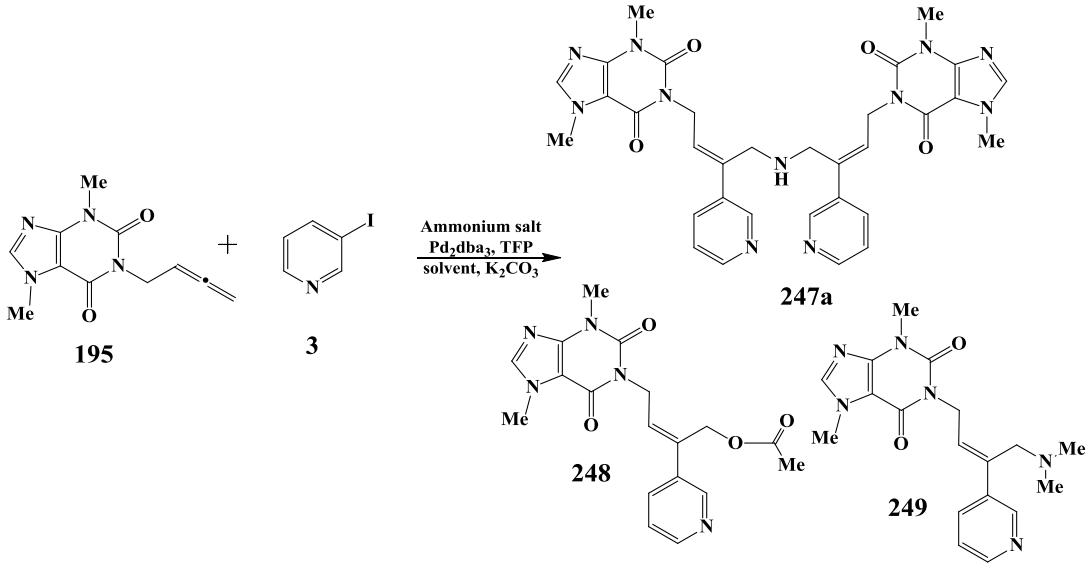
Figure 21. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **246b**.

2.2.3.5 Catalytic reactions of ammonia surrogates.

2.2.3.5.1 Pd(0) catalysed 5-component cascade synthesis of complex Z,Z-bisallylamines using ammonium tartrate.

Ammonia and its equivalents are among the most attractive nitrogen sources from a cost and industrial point of view. Thus, creating efficient methods for the synthesis of amines using commercial cheap nitrogen sources have attracted attention.[156] The former literature work invariably used special catalytic systems,[157] high loading of ammonia,[157b] handling of ammonia gas and most of the work was done in sealed vessels under high temperature and pressure.[158] These disadvantages might restrict the application of these methods. Our approach was targeted at developing Pd catalysed cascade alkylation of ammonia using commercially available cheap ammonia surrogates and ambient pressure. A preliminary exploratory reaction of purine allene **195** (1 equiv.), 3-iodopyridine **3** (1.2 equiv.) and ammonium carbonate (11 equiv.) in the presence of $Pd_2(dba)_3$, TFP and K_2CO_3 in MeCN at 80 °C was carried out (Scheme 83). After 38 h, monitoring by TLC, a new product was observed together with unreacted purine allene **195**. Workup afforded the diallylamine **247a** in 25% yield (Table 3, entry 1). Thus, ammonium carbonate is thermally unstable under these conditions and liberates ammonia which reacts as a nucleophile and affords the primary allylamine. The primary allylamine is highly nucleophilic and reacted in situ to give diallylamine **247a**. Increasing the amount of ammonium carbonate (25 equiv.) and heating for 102 h in the absence of K_2CO_3 produced the desired diallylamine **247a** in 58% yield (Table 3, entry 2). The long reaction time is attributed to the sublimation of ammonium carbonate on the inside wall of the condenser. A mixed aqueous solvent kept ammonium carbonate in the reaction and reduced the amount of ammonium salt needed and the reaction time (Table 3, entries 3-7). In case of DMF/H_2O or 1,4-dioxane/H_2O (2:1) and ammonium carbonate (6 equiv.) and in the absence of K_2CO_3, the desired product **247a** was obtained in 58 and 65% yield, respectively, (Table 3, entries 4 and 7). Increasing the amount of water lead to increased reaction time and lower yield (entry 5). Addition of K_2CO_3 gave a mixture of products in the case of DMF/H_2O (2:1) (entry 3) and did not affect the yield and the time in case of 1,4-dioxane/H_2O (2:1) (entry 6). Repeat of entry 4 with ammonium carbonate (100 equiv.) in a sealed tube in order to try and isolate the primary allylamine failed but compound **249** was

isolated in 45% yield (entry 8) via transamidation of DMF with ammonia to produce dimethylamine which reacted as nucleophile to afford **249**.[157a, 159]



Scheme 83. Pd Catalysed reaction of **195** with 3-iodopyridine **3** and ammonia surrogates.

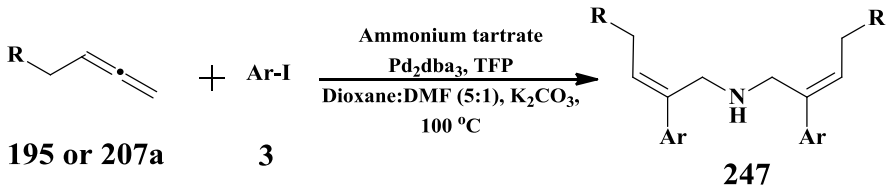
Table 3. The scope of ammonia surrogates as nucleophiles.

Entry	Ammonia surrogate (equiv.)	Solvent	K_2CO_3	Time (h)	Temp.	Yield[a]
1	$(NH_4)_2CO_3$ (11 equiv.)	MeCN	3 equiv.	38	80	**247a** (25%)
2	$(NH_4)_2CO_3$ (25 equiv.)	MeCN	-	102	80	**247a** (58%)
3	$(NH_4)_2CO_3$ (6 equiv.)	DMF/H_2O (2:1)	3 equiv.	3	80	mixture[b]
4	$(NH_4)_2CO_3$ (6 equiv.)	DMF/H_2O (2:1)	-	3	80	**247a** (58%)
5	$(NH_4)_2CO_3$ (6 equiv.)	DMF/H_2O (1:2)	-	7	80	**247a** (24%)
6	$(NH_4)_2CO_3$ (6 equiv.)	dioxane/H_2O (2:1)	3 equiv.	8	80	**247a** (65%)
7	$(NH_4)_2CO_3$ (6 equiv.)	dioxane/H_2O (2:1)	-	8	80	**247a** (65%)
8[c]	$(NH_4)_2CO_3$ (100 equiv.)	DMF/H_2O (2:1)	-	5	80	**249** (45%)
9	$AcONH_4$ (6 equiv.)	DMF/H_2O (2:1)	-	3	80	**247a** (7%) **248** (37%)
10	NH_2CONH_2 (12 equiv.)	DMF/H_2O (2:1)	3 equiv.	4	80	**249** (79%)
11[d]	Ammonium tartrate (6 equiv.)	dioxane/DMF (5:1)	2 equiv.	22	100	**247a** (80%)
12[d]	Ammonium tartrate (3 equiv.)	dioxane/DMF (5:1)	2 equiv.	22	100	**247a** (77%)

a) Isolated yield. b) Unseparated mixture of products. c) Sealed tube reaction. d) Reaction was done by my colleague.

Screening ammonium acetate as an ammonia equivalent, gave a mixture of **247a** and **248** in 7 and 37% yield, respectively (entry 9). The formation of **248** is due to the reaction of acetate anion as a nucleophile. Testing urea as the ammonia source afforded **249** in 79% yield (entry 10). In this case urea accelerates transamidation of DMF to liberate dimethylamine. Finally, one of my colleagues repeated entry 4 with dibasic ammonium tartrate (3 and 6 equiv.) in the presence of K_2CO_3 (2 equiv.) and 1,4-dioxane/DMF (5:1) as reaction solvent at 100 °C. This gave the diallylamine **247a** in 77-80% yield, respectively, (entries 11 and 12).

With optimum conditions in hand, the scope of the reaction was expanded to include purine and uridine allenes **195** and **207a** (1 equiv.) with diverse aryl iodides **3** (1.2 equiv.) and ammonium tartrate (3-6 equiv.). The diallylamines **247** were obtained in 67-93% yield (Scheme 84, Table 4). ^{1}H-NMR experiments (e.g. Fig. 22 and 23) showed a single product in each case with four new bonds (2 x C-C and 2 x C-N) and NOE studies (see experimental) confirmed the *Z*,*Z*-configuration of the two double bonds generated.



Scheme 84. Pd Catalysed 5-component cascades using ammonia equivalent as a nucleophile.

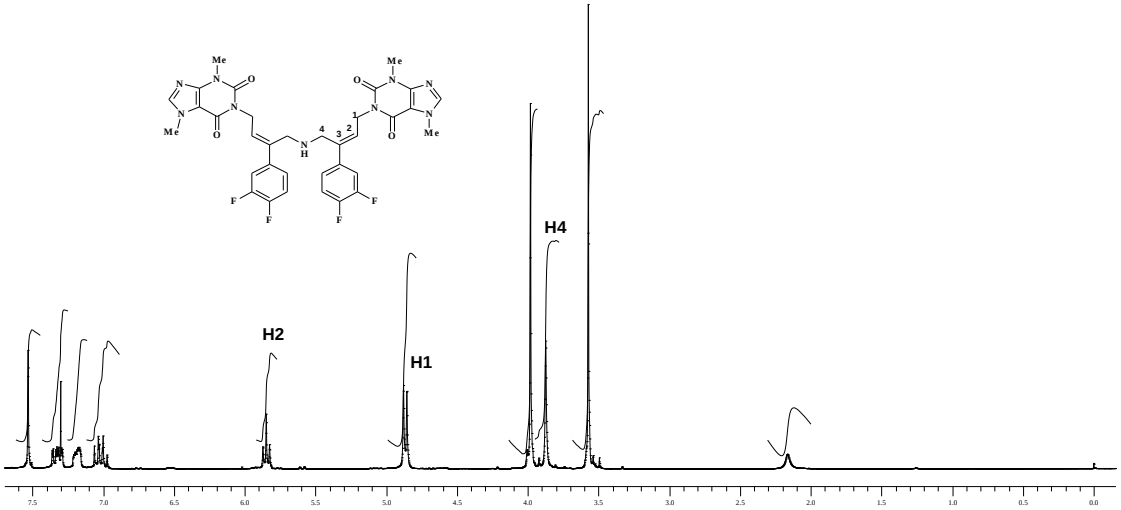


Figure 22. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **247c**.

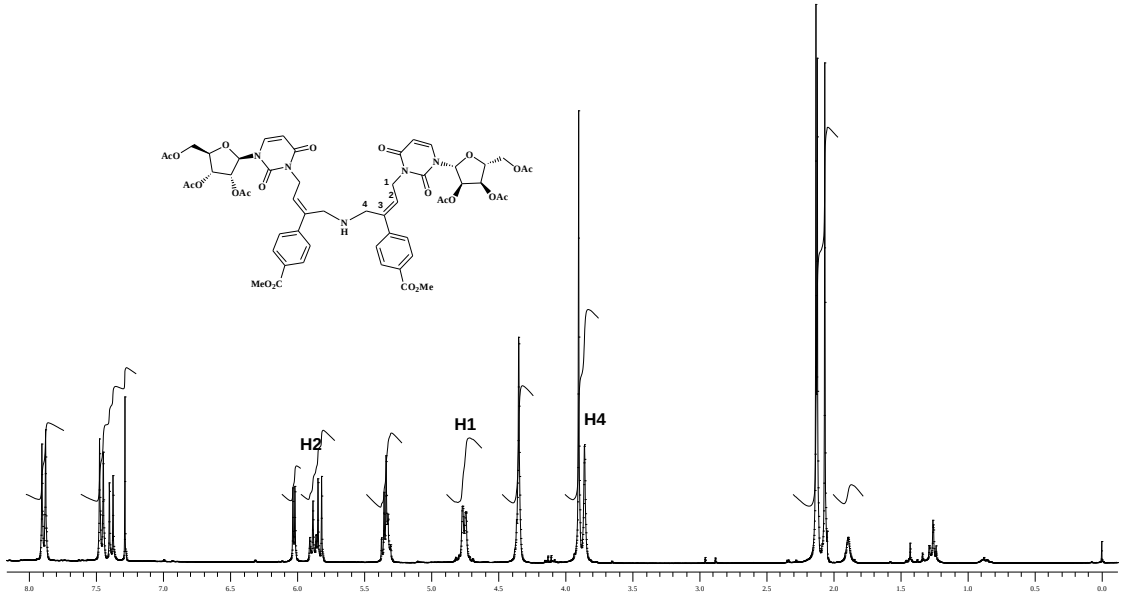
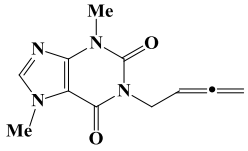
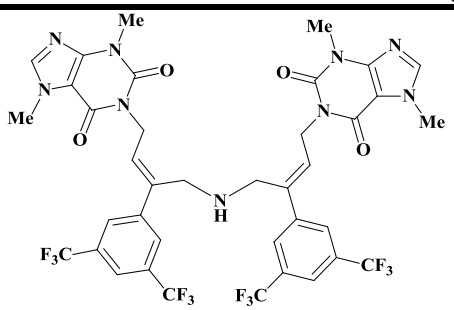
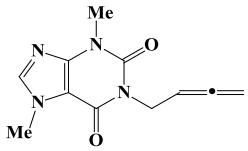
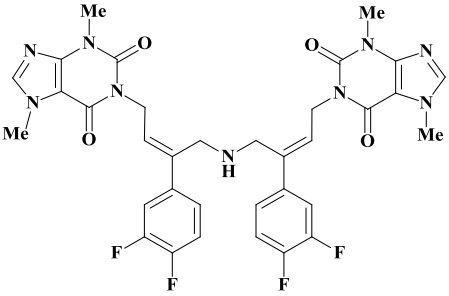
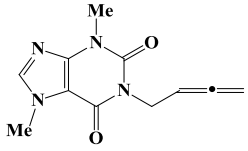
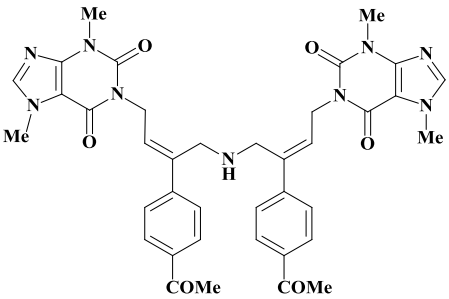
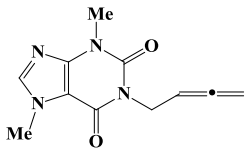
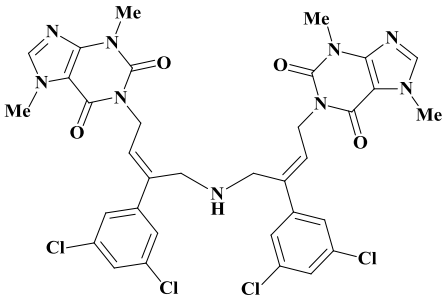
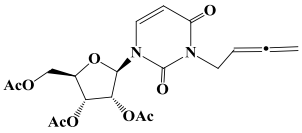
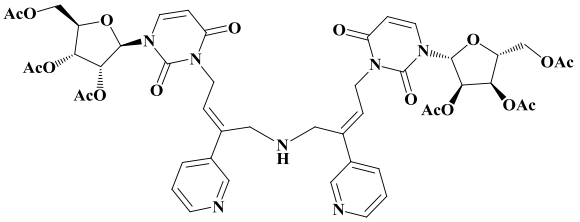
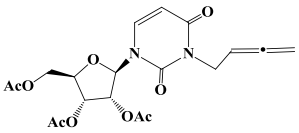
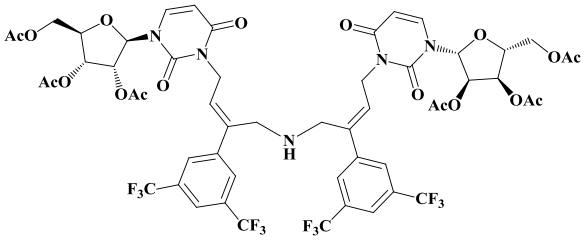
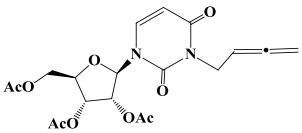
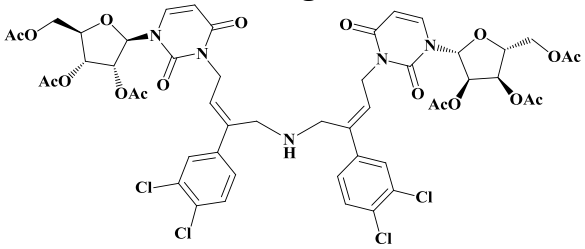
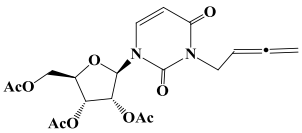
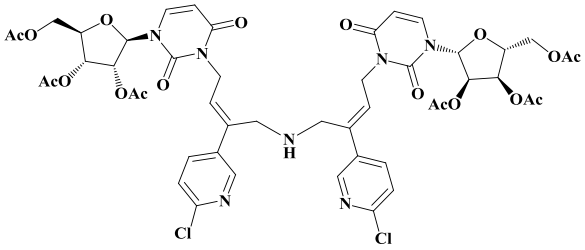
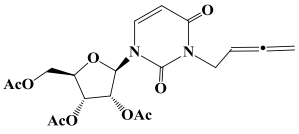
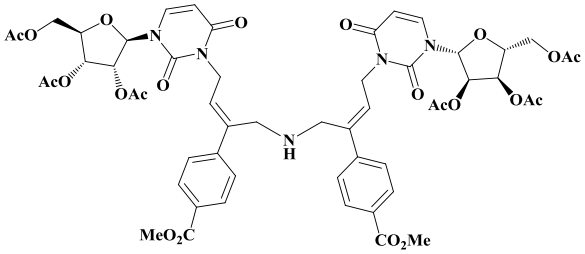


Figure 23. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **247j**.

Table 4. Pd Catalysed *Z*,*Z*-diallylamine formation.[a]

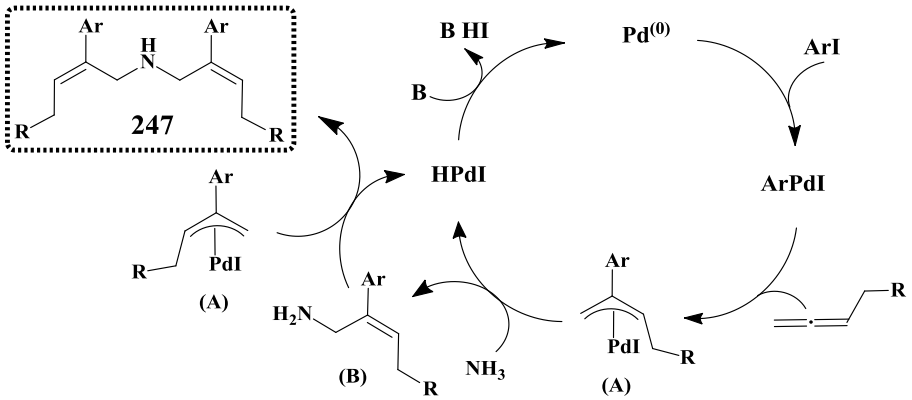
Entry	Allene	Product	Ammonium tartrate (equiv.)	Yield (%)[b]
1	 **195**	 **247b**	3	86
2	 **195**	 **247c**	6	93
3	 **195**	 **247d**	6	67

(continued)

4	 **195**	 **247e**	6	87
5	 **207a**	 **247f**	3	71
6	 **207a**	 **247g**	3	74
7	 **207a**	 **247h**	3	71
8	 **207a**	 **247i**	3	77
9	 **207a**	 **247j**	3	62

a) Reaction carried out at 100 ºC in 1,4-dioxane/DMF (5:1) for 9-29 h and employed substituted allene (1 equiv.), aryl iodide (1.2 equiv.), ammonium tartrate (3-6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (2 equiv.). b) Isolated yield

A plausible mechanism for the cascade (Scheme 85) involves oxidative addition followed by allene coordination and migratory insertion to furnish the π-allyl complex (**A**) which is attacked by the *in situ* generated ammonia to afford a mono-allylamine intermediate (**B**) which reacts with the π-complex (**A**) faster than ammonia to give the desired *Z*,*Z*-bisallylamine **247**. The created H−Pd^{II}-I species regenerates Pd(0) *via* reductive elimination in the presence of K_2CO_3. The mechanism requires the intermediate allyl amine (**B**) to be more nucleophilic than ammonia. This has already been commented on by Hartwig[156a, 157b,e] for Ir-catalysed allylic amination whilst Kobayashi and Nagano[160] reported optimization of a Pd-catalysed process for monoallylic aminations. We note that the calculated pK_a's using the ACD/I-Lab web service give conjugate acid pK_a's for the monoallyl amines of ~8.58-9.08 and 9.24 for ammonia.[118] Furthermore, reaction of **247**-NH group with the π-allyl intermediate (**A**) to give triallyl amine is not detected due to both steric hindrance and lower nucleophilicity of bisallyl amine NH group (pK_a ~8.0-8.3).



Scheme 85. Plausible mechanism for *Z*,*Z*-bisallylamine synthesis.

2.2.3.5.2 Pd(0) catalysed synthesis of isoquinolinone and isoquinoline using ammonium tartrate.

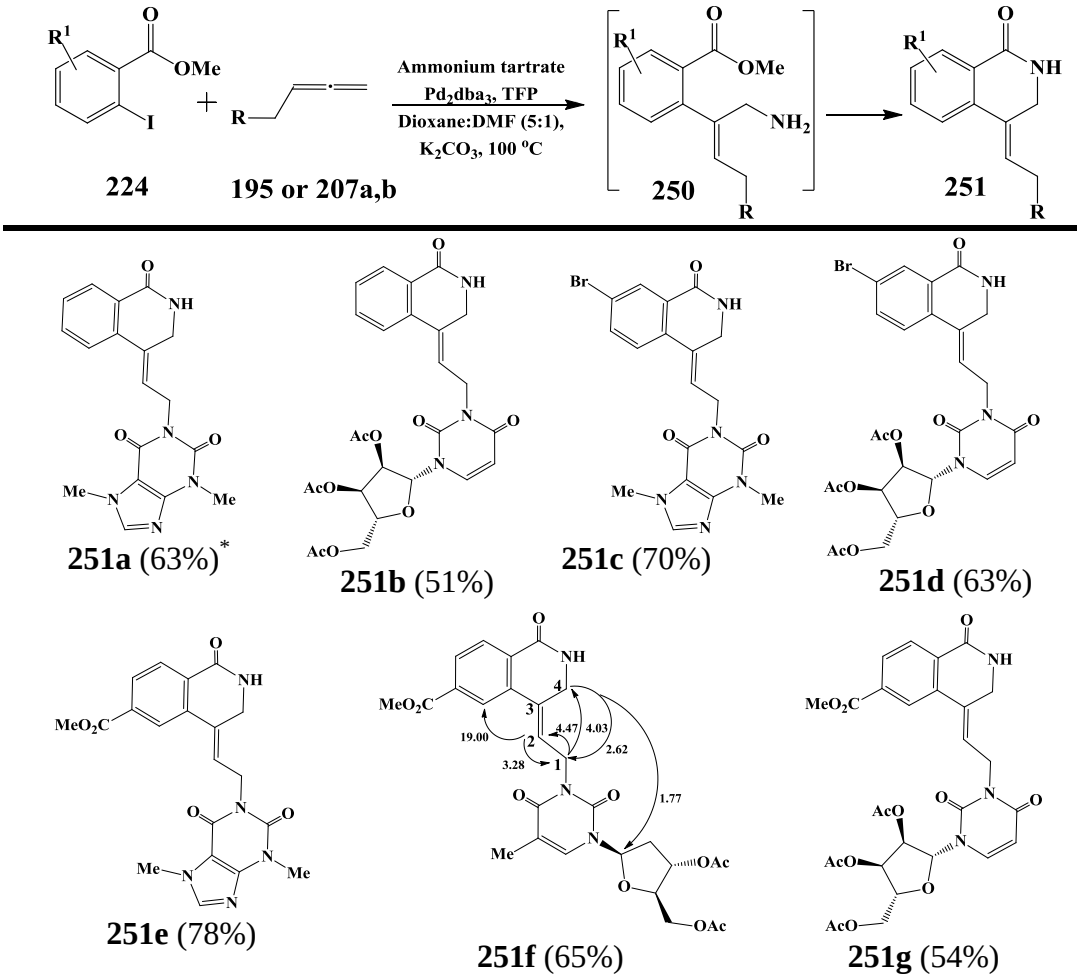
Despite the natural occurrence,[161] biological importance[161a,162] and existing broad synthetic methods[163] for the isoquinolines and isoquinolinones, little attention has been paid to the incorporation of allenes as a new building block in this area. The first application was published by Larock in which a substituted allene annulated with *N*-tosyl-2-iodobenzylamine under Pd(II) catalysis to afford isoquinolines as a mixture of three regio- and stereo-isomers.[164] 2-Iodobenzaldehyde imines have also been used with Pd(0) catalysis to annulate substituted allenes giving isoquinoline

derivatives.[165] Ni(0)/chiral phosphine ligand mediated regio- and enantioselective synthesis of isoquinoline-1(2*H*)-one derivatives has been reported *via* denitrogenation or decarbonylation of *N*-aryl-1,2,3-benzotriazin-4(3*H*)-ones or *N*-substituted phthalimide, respectively, followed by intermolecular annulation with substituted allenes.[166] Recently, Glorius et al., employed Rh(III) to catalyse C-H activation of *N*-(pivaloyloxy)benzamide involving intermolecular annulation with substituted allenes to furnish isoquinoline-1(2*H*)-ones.[111]

Synthesis of isoquinolinones: Grigg et al designed three types of cascades to furnish isoquinolinone derivatives. The first was the palladium catalysed intermolecular insertion of allene into 2-iodobenzoate (C-I bond) followed by intermolecular *N*-nucleophile addition and intramolecular cyclisation.[52b] The second type was achieved by designing nitrogen tethered three functional groups (aryl iodide, allene and *N*-nucleophile) to facilitate Pd mediated intramolecular allene insertion and intramolecular nucleophilic addition to give tetra-fused ring systems containing an isoquinolinone centre.[167a] The third type involved *N*-allenyl-2-iodobenzamide as a model for intramolecular allene insertion catalysed by Pd(0) followed by intermolecular nucleophilic addition.[167b,c]

This new approach utilises our "ammonium surrogate" technology to furnish isoquinolinone derivatives **251** (Scheme 86). Methyl 2-iodobenzoate derivatives **224** were reacted with substituted allenes **195/207a,b** in the presence of ammonium tartrate (ammonia equivalent) under the previously developed optimum conditions (Table 3, entry 11) to give a 51-70% yield of isoquinolinones **251** *via* intramolecular cyclisation of the intermediate **250**. ^{1}H-NMR spectra (e.g. Fig. 24) showed only one set of protons and NOE data supported *Z*-configuration of the exocyclic double bonds (see compound **251f**, Scheme 86). The reaction sequence is analogous to previous work from the Grigg group[52b] and this was further confirmed by reacting 2-iodobenzamide with purine allene **195** under the same conditions in Scheme 86 except heating for 24 h and the absence of ammonium tartrate when no reaction was observed and the starting materials recovered. This experiment supported the addition of ammonia to the π-allyl intermediate forming allyl amine **250** which subsequently cyclised to give **251**. Thus, the cyclisation step in **250→251** is faster than further allylation of the allyl-NH_2 group. In case of methyl 5-bromo-2-iodobenzoate, the reaction is chemoselective for oxidative addition at the C-I bond

leaving the C-Br bond intact. It is worth notice that the additional methyl ester group in **251e-g** was untouched under the reaction conditions.



Reaction carried out at 100 ºC in 1,4-dioxane/DMF (5:1) for 21-31 h and employed substituted allene (1 equiv.), **224** (1.2 equiv.), ammonium tartrate (6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (3 equiv.). *This reaction used ammonium carbonate (6 equiv.) and DMF/H_2O (2:1, 3 mL) (see experimental).

Scheme 86. Pd(0) catalysed annulation of allenes with methyl 2-iodobenzoates in the presence of ammonium tartrate generates isoquinolinones **251a-g**.

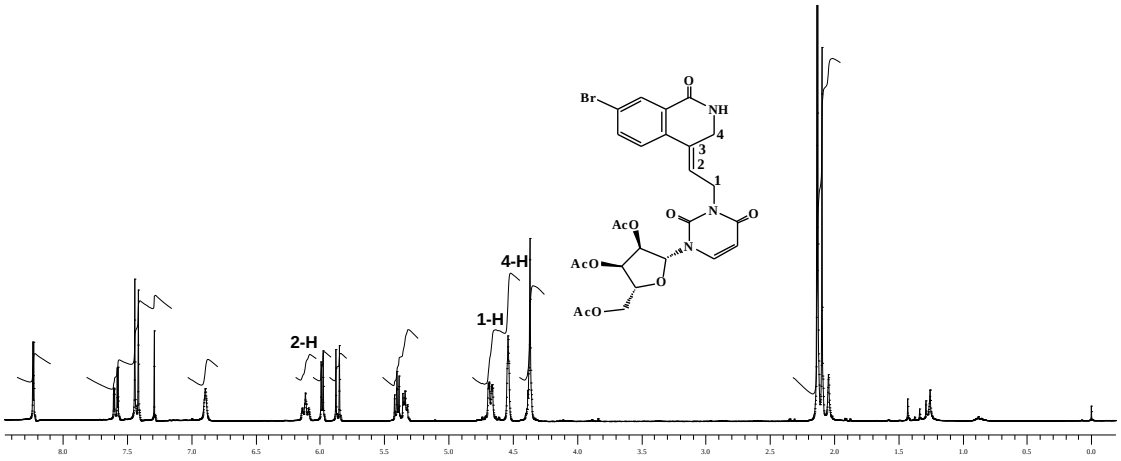
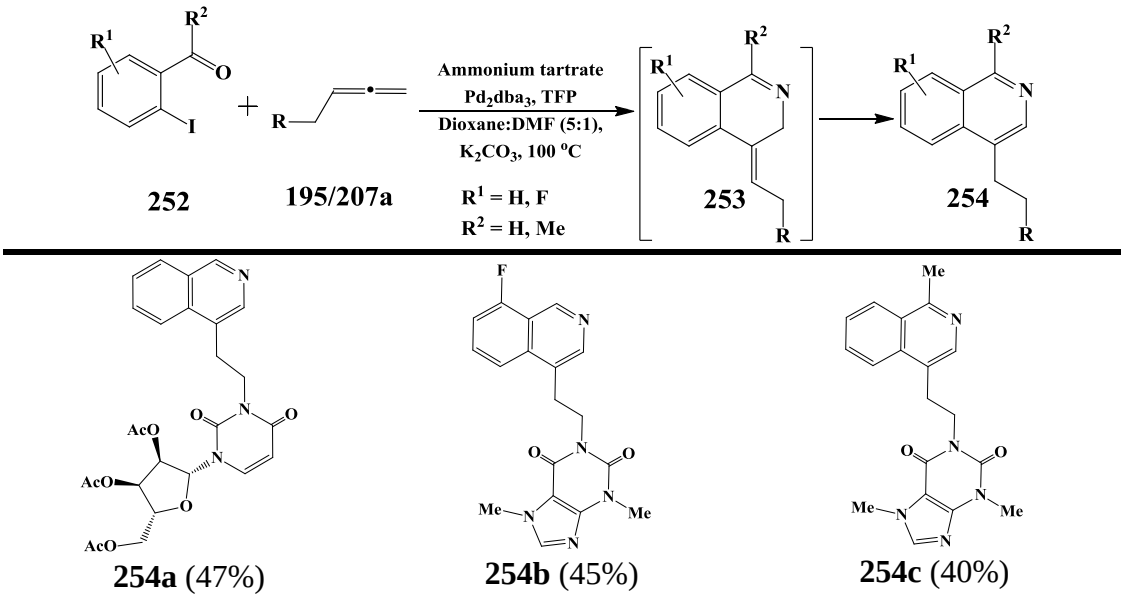


Figure 24. ^{1}H-NMR ($CDCl_3$, 300 MHz) experiment of **251d**.

Synthesis of isoquinolines: Isoquinoline/tetrahydroisoquinoline derivatives were prepared by Grigg and his co-workers *via* designing two types of cascade reactions; (i) intermolecular allene insertion into the C-I bond of an aryl iodide linked *N*-nucleophile then intramolecular *N*-addition to the generated π-allyl,[52a,61d] (ii) intermolecular allene insertion to an aryl iodide carrying a dipolarophile/Michael acceptor followed by intermolecular *N*-addition of azide/amine and finally intramolecular 1,3-dipolar cycloaddition/Michael addition, respectively.[28a,b,61c] This previous work prompted the application of the optimum conditions in Table 3 (entry 11) to the reaction of 2-iodobenzaldehydes/2′-iodoacetophenone **252** with substituted allenes **195/207a** to give intermediate **253** which undergoes a 1,3-hydrogen rearrangement generating the aromatized isoquinolines **254** (Scheme 87). ^{1}H-NMR data (e.g. Fig. 25) showed no indication of allyl signals (triplet at ~6-6.5 ppm and doublet at ~4.5-5 ppm) but instead comprised an AA′BB′ nmr pattern for the two methylene groups at 3-3.5 and 4-4.5 ppm. The low yields may reflect the thermal instability of the substrates or the products and this hypothesis is supported by isolation of theobromine **155** in the case of **254b,c** and of 2',3',5'-tri-*O*-acetyluridine **205a** in the case of **254a** as byproducts. This evidence suggests a competition between the 1,3-H shift and a degradation mechanism of some kind. Unfortunately, there was insufficient time to follow up this process.



Reaction carried out at 100 ºC in 1,4-dioxane/DMF (5:1) for 12-26 h and employed substituted allene (1 equiv.), **224** (1.2 equiv.), ammonium tartrate (6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (2-3 equiv.).

Scheme 87. Pd catalysed preparation of isoquinoline derivatives.

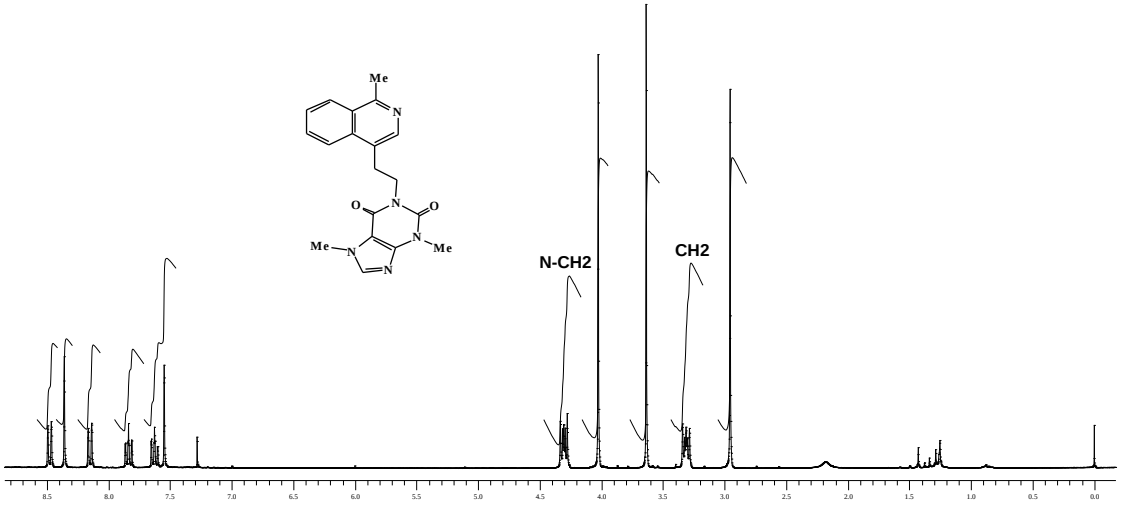


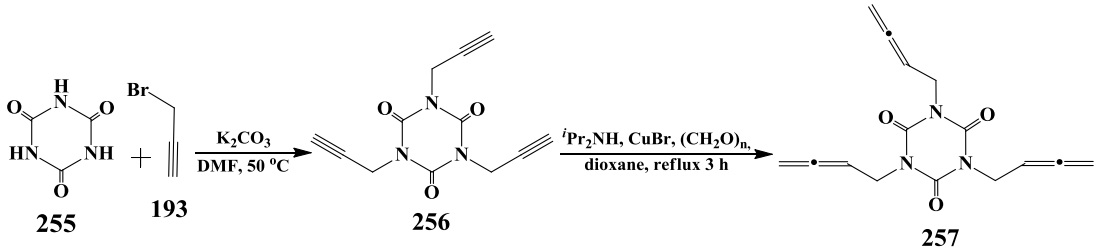
Figure 25. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **254c**.

2.2.3.6 Pd catalysed seven component cascades.

The chemical space of allene chemistry can be expanded by enhancing the multivalence of the products using novel splayed trisallenes to prepare trivalent compounds. Also, it may in the future prove possible to use trisaryl iodides or trisamino-nucleophiles to create different skeletons containing three recognition groups.

2.2.3.6.1 Design and preparation of a novel splayed trisallene 257.

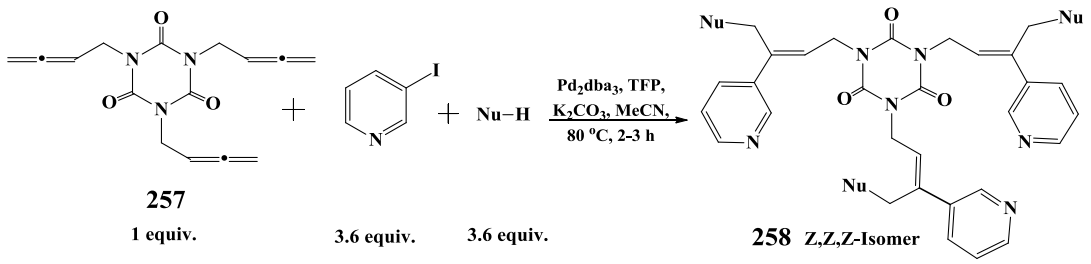
To the authors knowledge there is only one, very recent, example of a trisallene in the literature.[168a] This is a cyclododeca-1,2,5,6,9,10-hexaene. Thus a manipulatable functionalised trisallene for incorporation into Pd cascade chemistry is very attractive from a synthetic point of view and from its potential biochemical outlets. The unknown 1,3,5-tri(buta-2,3-dien-1-yl)-1,3,5-triazinane-2,4,6-trione **257** was selected as a splayed trisallene target to explore this area. It was prepared by heating a mixture of cyanuric acid **255** and propargyl bromide **193** in DMF at 50 °C which afforded the trisalkyne **256** (46%) (Scheme 88). This was then converted to the splayed trisallene **257** (37%) in one step using the Crabbé reaction (Scheme 88).



Scheme 88. Preparation of trisallene **257**.

2.2.3.6.2 Incorporation of the splayed trisallene 257 in 7-component cascade reactions.

The reaction of **257** (1 equiv.), 3-iodopyridine (3.6 equiv.), a nucleophile (3.6 equiv.), $Pd_2(dba)_3$, TFP and K_2CO_3 in MeCN at 80 °C gave the products **258a-c** in 66-70% yield (Scheme 89, Table 5). In this multicomponent cascade, six new bonds (3 x C-C and 3 x C-N) and three double bonds were formed. In case of γ-carboline **187** and 1-aminoadamantane **180** as nucleophiles the reaction afforded only one product **258a** and **258b**, respectively, (e.g. Fig. 26). However, when maraviroc amine **188** was used as the nucleophile, a mixture of *E*/*Z*-isomers of **258c** was formed (Fig. 27). All attempts to separate this mixture failed and it is not possible to calculate the isomer ratio due to peak overlap. The isomeric mixture in the latter case is attributed, as mentioned earlier, to the steric congestion around the secondary amine centre in **188** which impedes the addition to the π-allyl intermediate and permits *anti*/*syn*-equilibrium to give *E*/*Z*-isomers. Also, the existence of three flexible allenyl groups close to each other in **257** could cause steric hindrance during the addition of maraviroc amine **188** to the π-allyl intermediate which would decrease the stereoselectivity.



Scheme 89. General 7-Component cascade using trisallene **257**.

The *Z,Z,Z*-stereochemistry of **258a** was assigned on the basis of NOE studies (Table 5, entry 1). Irradiation of 2-H (δ 6.07) caused -11.18% enhancement of 1-CH_2 and -3.02 and -1.91% enhancement of two of the pyridyl-H but no enhancement of 4-CH_2 protons. However, irradiation of 1-CH_2 (δ 4.77) resulted in -10.58% enhancement of 2-H and -5.77% enhancement of 4-CH_2 protons but no enhancement of pyridyl protons. Irradiation of 4-CH_2 (δ 3.76) caused 2.52% enhancement of pyridyl-H, -4.71% enhancement of 1-CH_2 and -4.22, 4.79 and 3.07% enhancement of tetrahydropyridoindolyl-CH_2 protons but no enhancement of the 2-H proton was observed. The negative NOE enhancements might be due to the shape, temperature,

molecular weight and slow reorientation of the molecule.[131] The stereochemistry of **258b** was assigned on the basis of the stereochemistry of **258a**.

To our knowledge, the carboamination of trisallenes using Pd(0) catalysed cascades is a previously unknown process. This type of cascade is very attractive to both chemists and biologists because we can install three bioactive recognition groups (six groups are also possible by using both aryl iodide and nucleophile as bioactive moieties) at once in a stereoselective manner.

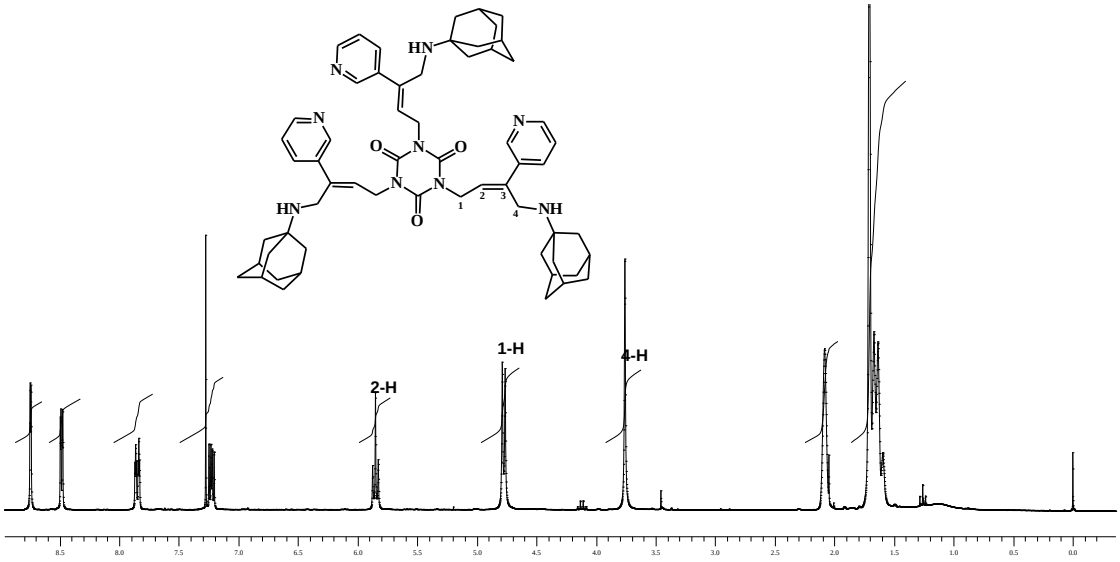


Figure 26. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **258b**.

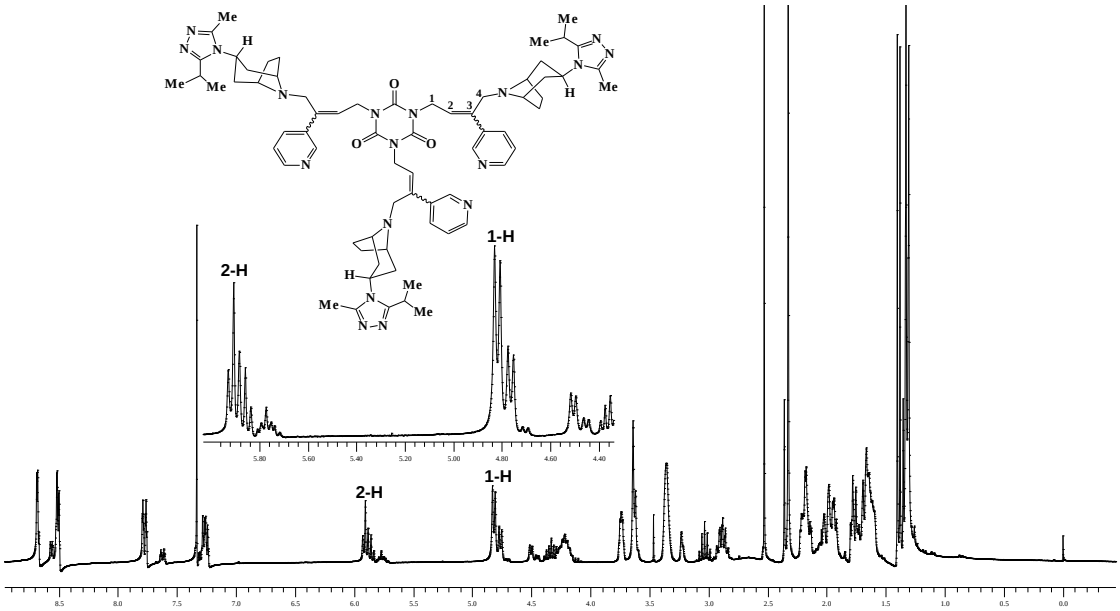
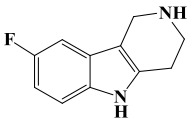
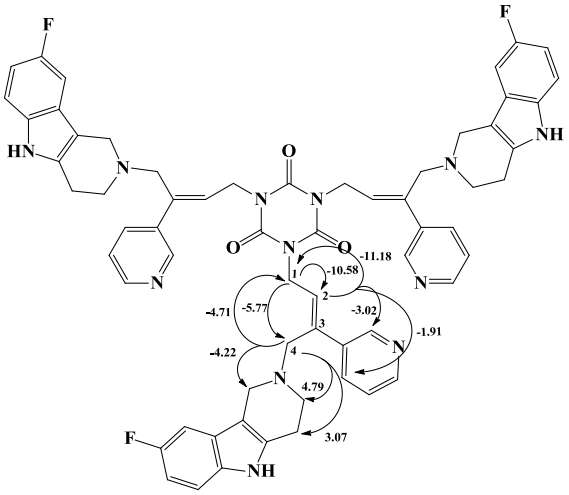
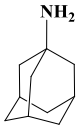
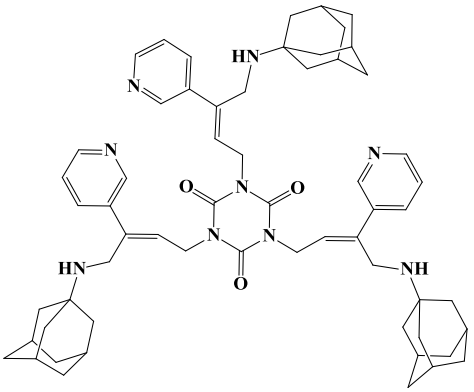
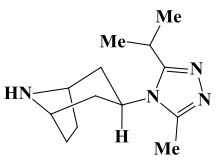
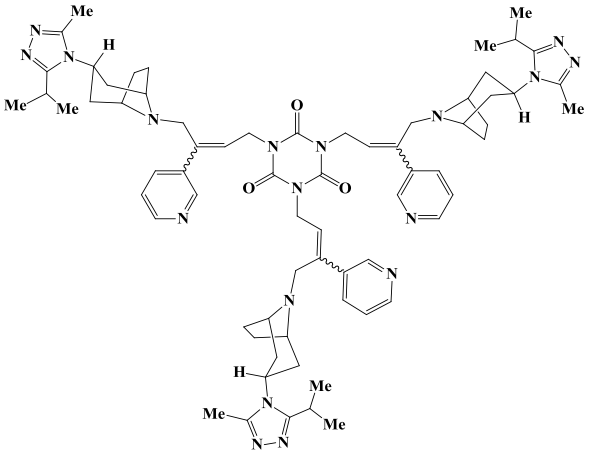


Figure 27. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **258c**.

Table 5. Seven component cascades with trisallene **257**.[a]

Entry	Nucleophile	Product	Yield (%)[b]
1	 **187**	 **258a**	70
2	 **180**	 **258b**	66
3	 **188**	 **258c**	69 (mixture of *E*/*Z* isomers)

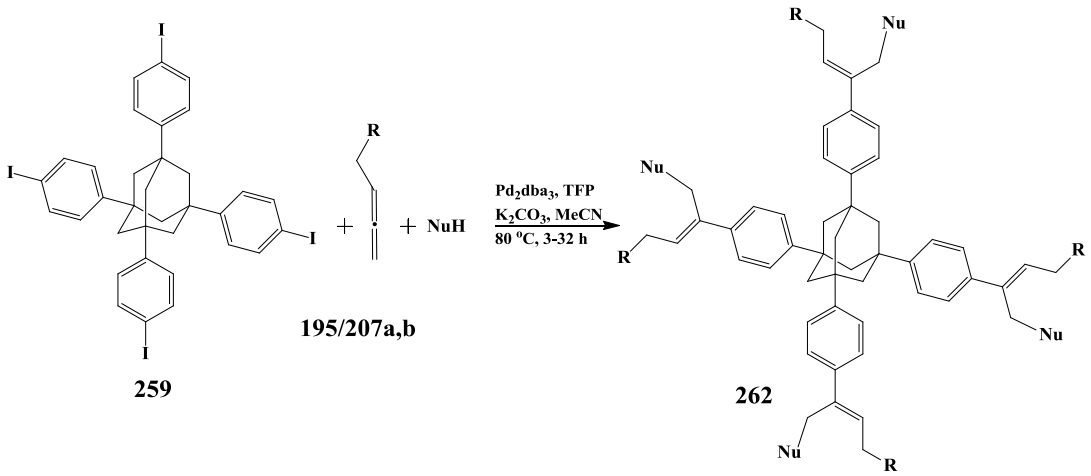
a) Reaction carried out at 80 ºC in MeCN (5 mL) for 2-3 h and employed trisallene **257** (0.25 mmol), 3-iodopyridine (0.9 mmol), nucleophile (0.9 mmol), $Pd_2(dba)_3$ (7.5 mol%), TFP (30 mol%), and K_2CO_3 (9 equiv.). b) Isolated yield

2.2.3.7 1,3,5,7-tetrakis-(4-iodophenyl)adamantane as a splayed tetra-aryl iodide.

1,3,5,7-Tetrakis-(4-iodophenyl)adamantane **259**[168b] was used as a tetrahedral aryl iodide core (1 equiv.) in reactions with various substituted allenes (4 equiv.) and nucleophiles (4 equiv.) enabling nine component cascades populating four orthogonal regions of space (Scheme 90). *N*-Allenylpurine **195** and *N*-allenyl nucleosides, uridine **207a** and thymidine **207b**, were reacted as substituted allenes with a range of amine nucleophiles, e.g. maraviroc amine **188**, γ-carboline **187** and 1-aminoadamantane **180**, generating compounds **262a-g** in 45-87% yield (Table 6, entries 1-6). In this case, maraviroc amine **188** reacted smoothly and produced 9-component cascade products contaminated with only a trace amount of another isomer (Fig. 28) which is in contrast with the previous 3, 5- and 7-component results (Scheme 73, Chart 16 (compounds **235e-g**), Table 5, entry 3 (Fig. 27)). This variation can be attributed to the geometry of the multitrigger scaffold. Thus, tetrahedral arrangement of the 4-iodophenyl groups on the rigid adamantane core in **259** afforded products directed in four dimensions, far from each other, which minimises the steric clash between their substituents and leads exclusively to the *Z*-product. In the same vein, the aryl iodide **259** is very bulky and restricts the formation of *syn*-π-allyl complex (see Scheme 69) thus inhibiting the *E*-configuration of the double bonds.

Further incorporation of **259** as a tetraiodo rigged tecton in a fourfold 3-component cascade strategy was carried out to probe reactivity of chiral amines. We used representative amino acid esters, (*S*)-tryptophan methyl ester hydrochloride **260** and (*S*)-serine methyl ester hydrochloride **210**, as nucleophiles to afford **262g** and **262h**, respectively, (Table 6, entries 7 and 8). Scaffold **210** was involved as a model for the reaction of an NH_2 group in the presence of an unprotected OH. The reaction went exclusively, and only once, **262h** at the NH_2 site with no reaction of OH group as a nucleophile. Also, we involved a simple representative peptide, glycyl-(*S*)-leucine methyl ester hydrochloride **261**, as a nucleophile under the same conditions. We observed no effect on the peptide bond and the reaction moved smoothly to afford **262i**. It is worth noting that the chirality of **260**, **210** and **261** are retained in the cascade product **262g-i** under the reaction conditions (see experimental). Finally, 1-

aminomethylnaphthalene **212** was incorporated as both nucleophile and fluorophore under the same conditions to afford **262j** in 51% yield. It is worth mentioning that, the mild cascade conditions generate four *Z*-double bonds and eight new bonds (4 x C and 4 x N). Additionally, a broad range of privileged structures are readily installed four times stereoselectively on the tetrahedral tecton.

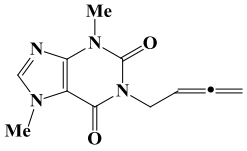
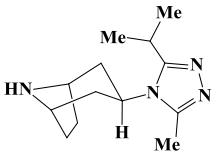
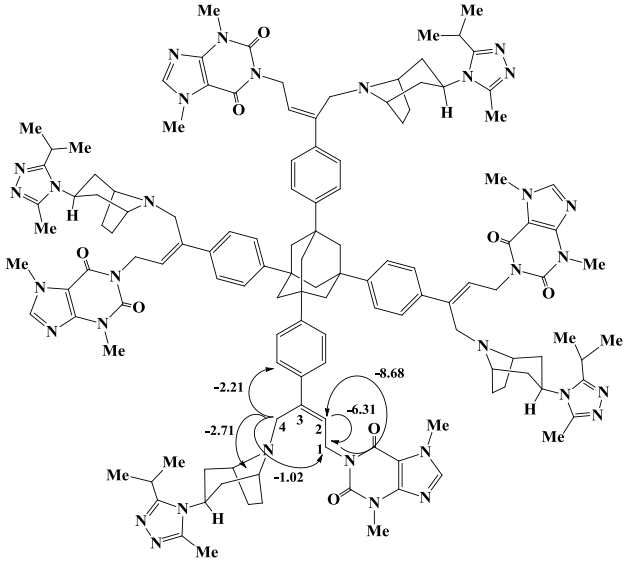
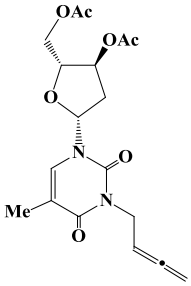
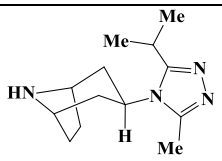
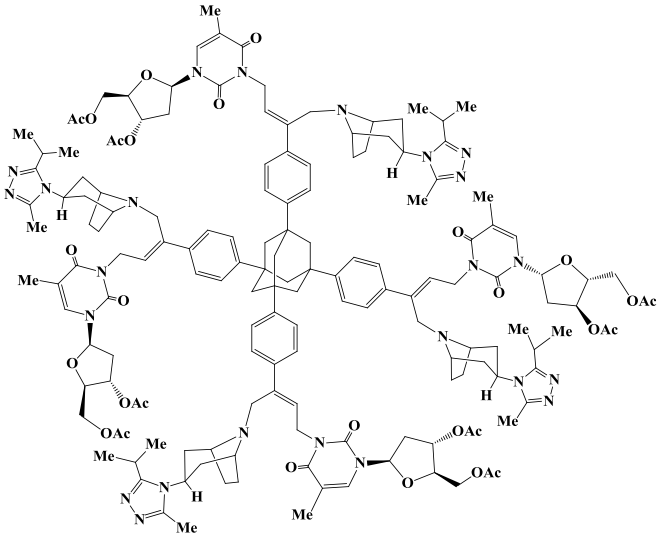
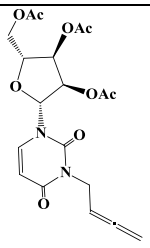
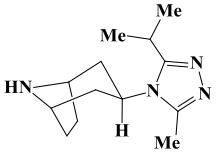
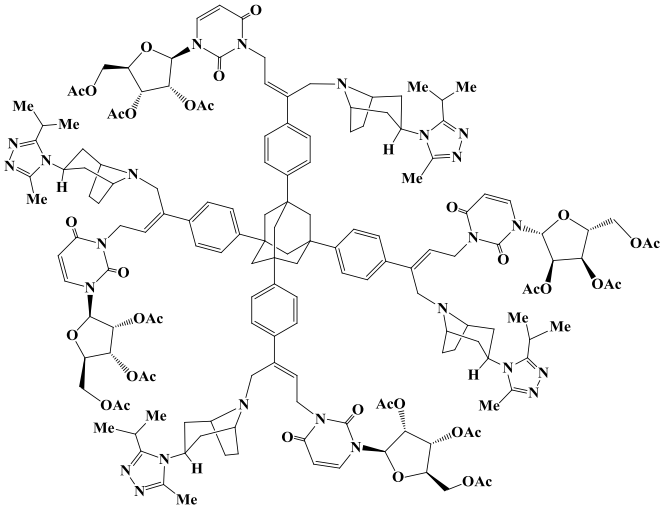


Scheme 90. 9-Component cascades using tetraiodo-scaffold **259**.

The four-fold assembling of substituted allenes and nucleophiles on tetrahedral 1,3,5,7-tetrakis-(4-iodophenyl)adamantane was confirmed by high resolution mass spectrometry. It is worth mentioning that, due to the high molecular mass >1200, we see double and triple charge molecular ions beside the common mono-charge molecular ion (see experimental).

The configuration of the double bonds in the 9-component products was assigned based on NOE studies on **262a**,**b** and **262e** (see experimental). The stereochemistry of **262a** (Table 6, entry 1) was assigned as follows: irradiation of 1-H (δ 4.93) caused a -8.68% enhancement of 2-H and irradiation of 2-H (δ 5.88) resulted in a -6.31% enhancement of 1-H. Irradiation of 4-H (δ 3.68) caused -1.02% enhancement of 1-H, -2.21% enhancement of *o*-phenyl protons and -2.71% enhancement of the azabicyclooctyl proton at (δ 3.46). The negative NOE enhancements normally arise for several reasons, e.g. shape of the molecule, molecular weight, viscosity of the solvent, temperature and slow reorientation of the molecule.[131]

Table 6. Nine component cascade reactions of **259**. [a]

Entry	Allene / Nucleophile	Product	Yield (%)[b]
1	 **195** /  **188**	 **262a**	52
2	 **207b** /  **188**	 **262b**	69
3	 **207a** /  **188**	 **262c**	56

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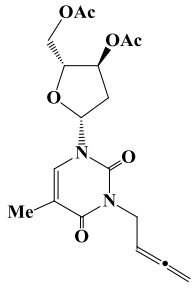
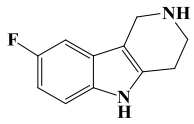
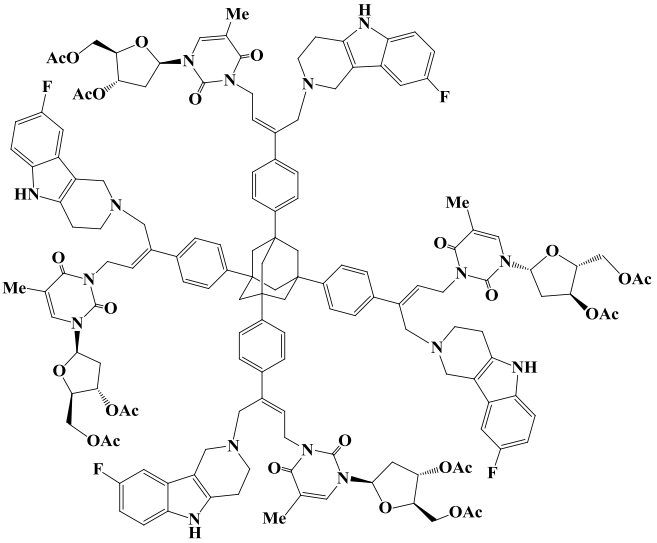
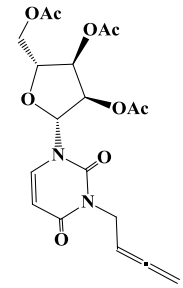
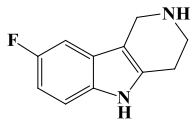
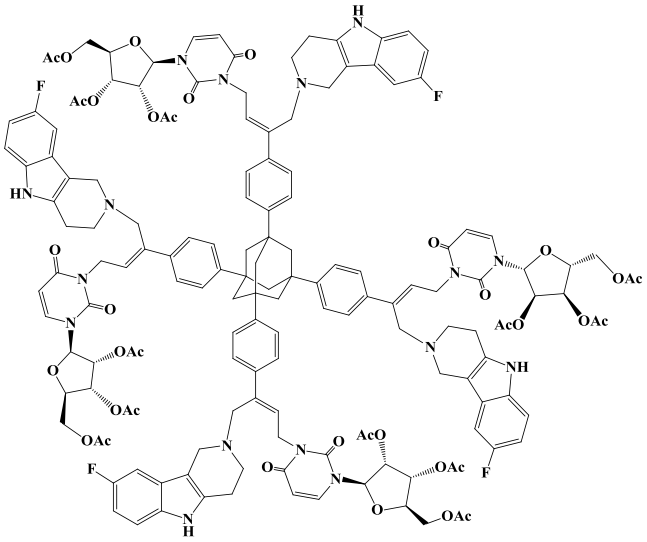
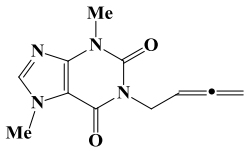
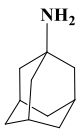
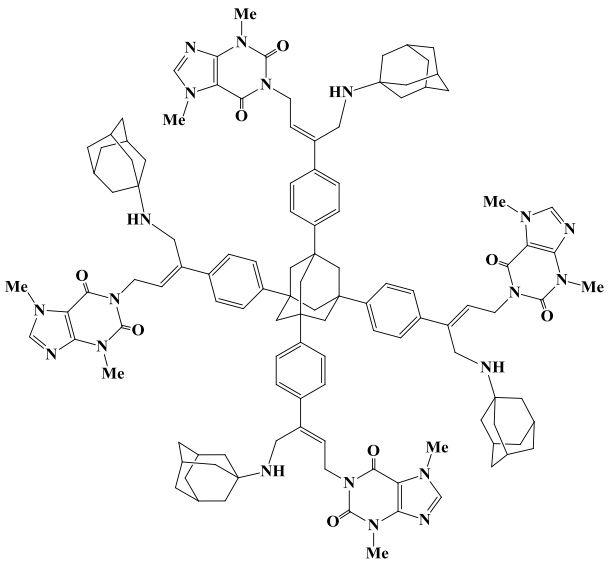
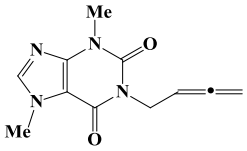
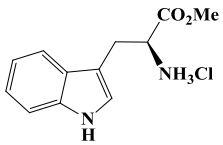
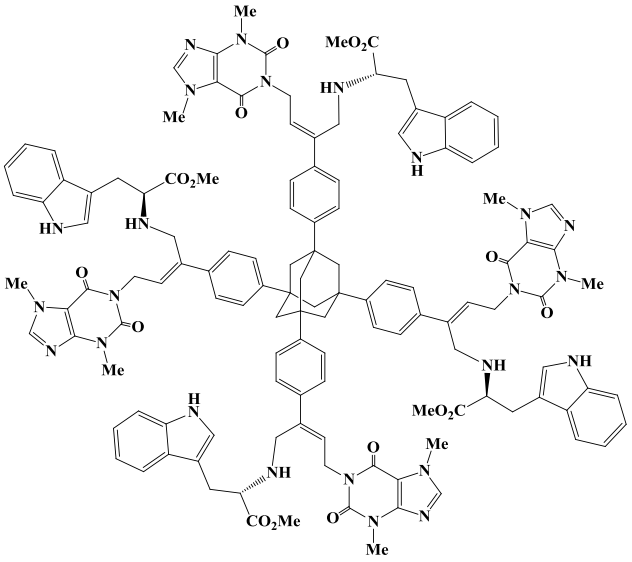
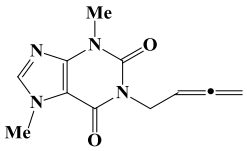
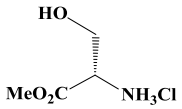
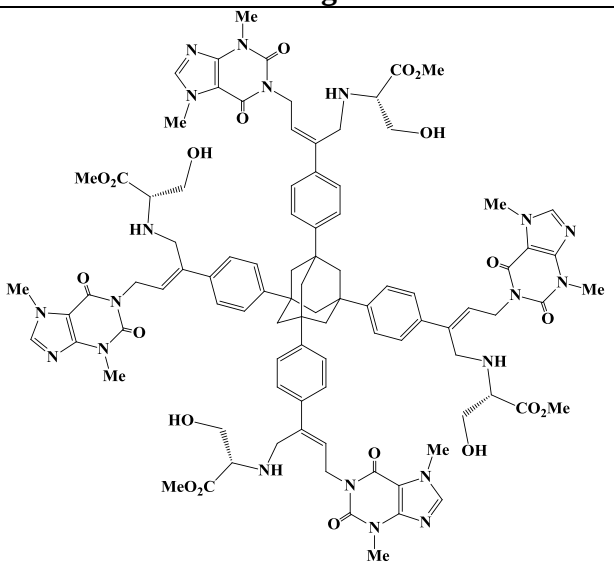
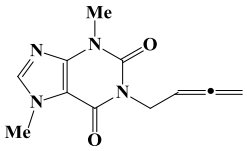
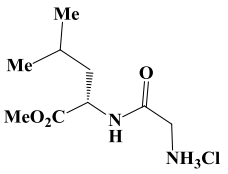
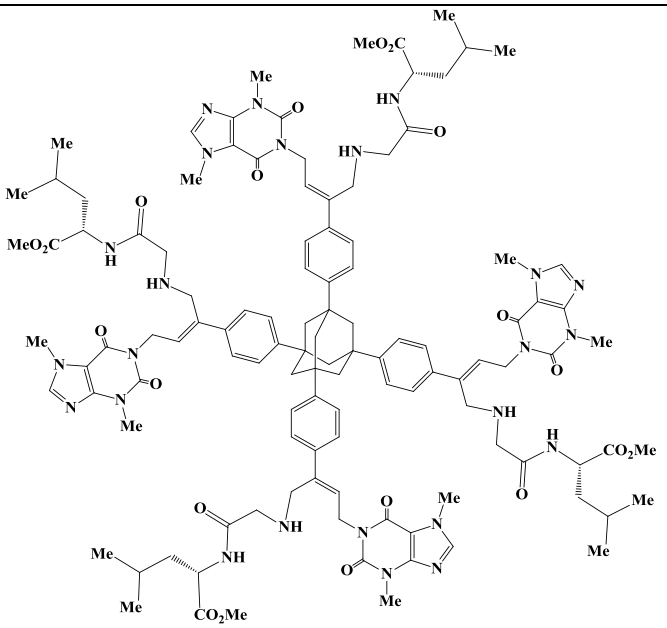
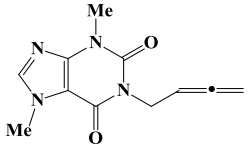
4	 **207b**  **187**	 **262d**	74
5	 **207a**  **187**	 **262e**	62
6	 **195**  **180**	 **262f**	87

(continued)

7	 **195**  **260**	 **262g**	45
8	 **195**  **210**	 **262h**	49
9	 **195**  **261**	 **262i**	55

(continued)



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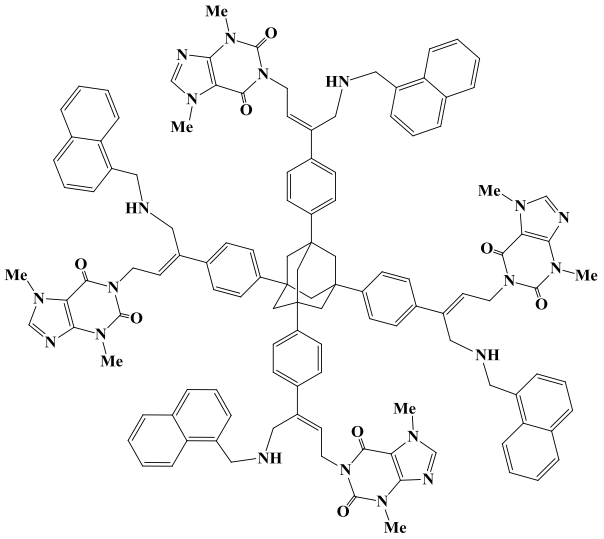
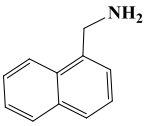


262j



212

a) Reaction carried out at 80 ºC in MeCN (3 mL) for 3-32 h and employed substituted allene (0.4 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane (0.1 mmol), nucleophile (0.48 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (6 equiv.). b) Isolated yield.

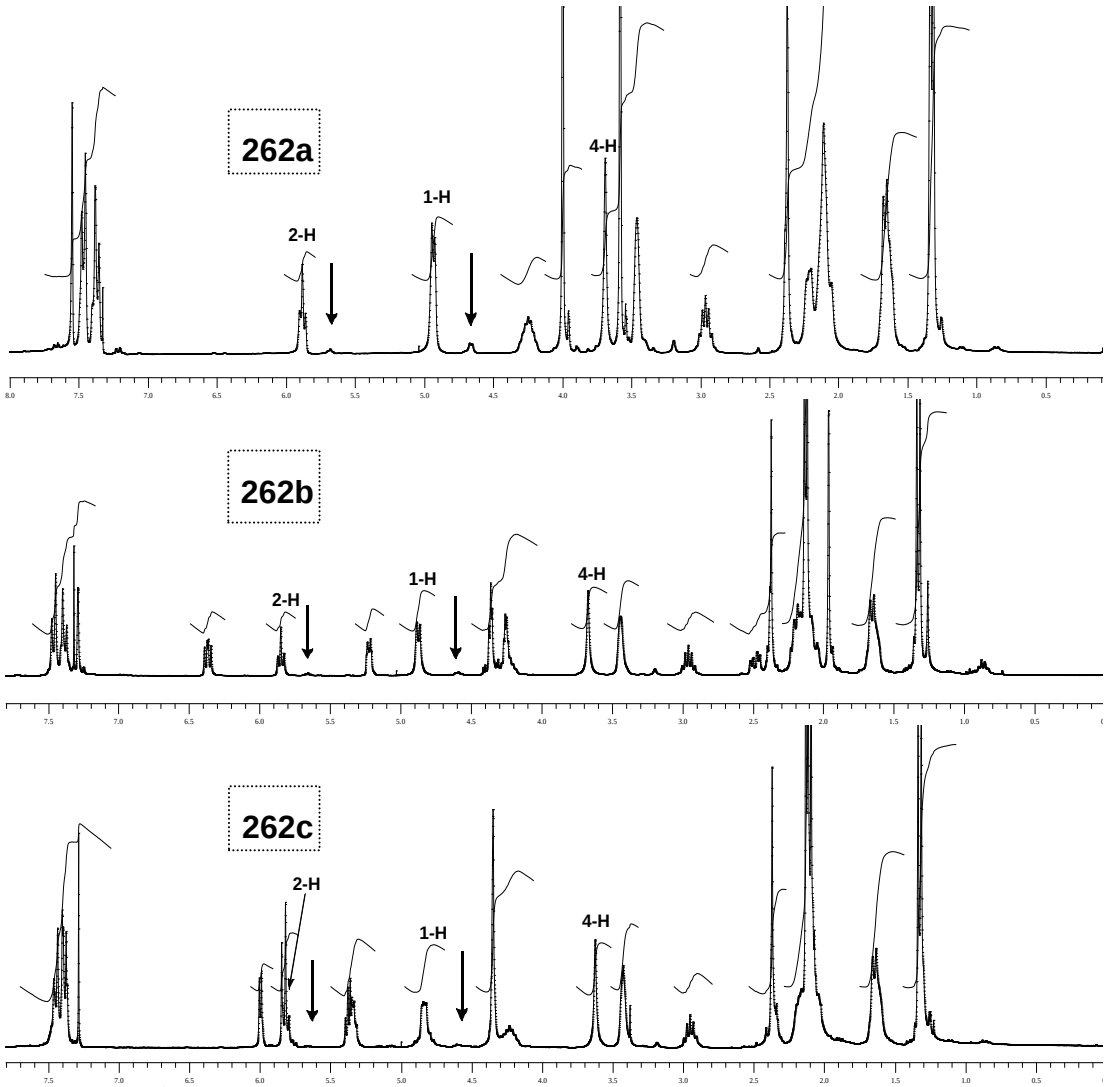


Figure 28. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **262a-c** arranged from the top. The arrows are directed toward suspected minor isomers.

The previous success encouraged us to determine the chemoselectivity of the 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** and the possibility of sequentially attaching both four different nucleophiles and allenes on **259**. In a preliminary study, the reaction of **259** (1.2 equiv.) with purine allene **195** (1 equiv.) and 1-aminoadamantane **180** (1.2 equiv.) under the same conditions afforded a mixture of the 3-component product **263a** (36%) and the 5-component product **263b** (29%) but none of the 7- and 9-component products (Chart 18). This result indicated that the first and second step functionalisations of **259** are selectively accessible. Additionally, the formation rate of **263a** is slightly faster than **263b**. Unfortunately, there was insufficient time to develop this study further.

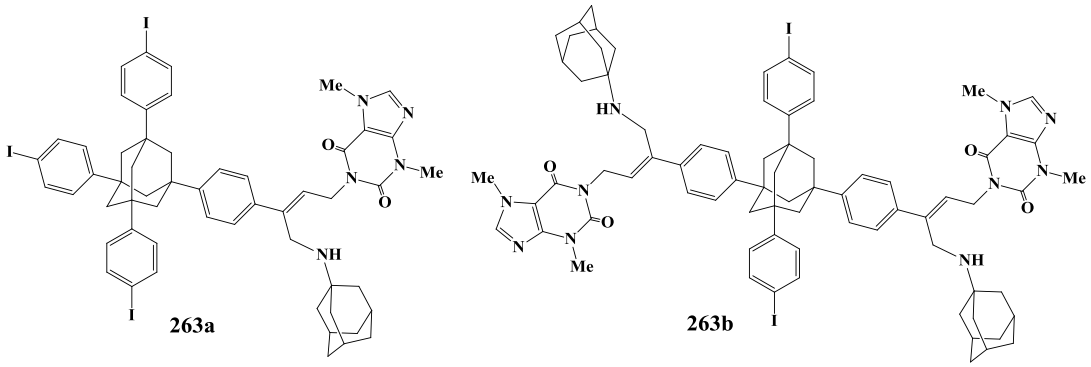


Chart 18. Chemoselectivity of **259**.

2.3 Conclusion

The main objective of my work was to develop new Pd chemistry applicable to drug design and discovery. One way to do this is to use biologically active compounds as building blocks. Thus drugs or parts of drugs were used as scaffolds and incorporated regio- and stereoselectively in multicomponent cascades. Also, amino acids and short peptides were successfully involved as nucleophiles and these results will encourage our group to try short proteins/DNA or sugars as scaffolds. In the same vein, zinc binding benzamide scaffolds were incorporated into 3-component cascades in order to increase the inhibition of HDAC enzymes and the metal chelator di-(2-picolyl)amine was employed as a nucleophile in the cascades to provide a modified metal scavenger. This latter reaction opens a link to organometallic chemistry. Furthermore, I developed (in collaboration with two Thai students) a range of new bivalent ligands based on bisallylamines that are generated catalytically and employ ammonium salts as an NH_3 source. Splayed bisallenes and

piperazine/homopiperazine were successfully incorporated into 5-component cascades. Additionally, a splayed bisallene reacted with bis-amine nucleophiles in an exploratory creation of macrocycles which clearly requires further work. Splayed trisallene was designed and involved in 7-component cascades. Interestingly, I achieved the first stereoselective 9-component cascade synthesis based on the adamantyl core and demonstrated (a) its potential for attachment of peptide ligands (b) the selectivity for amine nucleophiles over oxygen nucleophiles (c) the ability to cleanly generate *Z*-trisubstituted alkenes. Screening samples have been sent to universities in USA, Australia, Holland as well as Leeds University (Biomedical Sciences), Sheffield University (Department of Chemistry), Leeds Institute of Molecular Medicine (LIMM), and Scottish Biomedical. Three compounds have been tested so far at 10 µM, 100 nM and 10 nM against Human HDACs 1-3 by Scottish biomedical. No inhibition was observed over 10% against Human HDAC 1. Compounds **223a**, **223b** and **223f** showed 63.9, 54.3 and 69.3% inhibition, respectively, at 10 µM against Human HDAC 2. Furthermore, **223a**, **223b** and **223f** showed 92.5, 71.6 and 97.6% inhibition, respectively, at 10 µM and **223f** showed 32.3% inhibition at 100 nM against Human HDAC3.

Hence, the new versatile catalytic multicomponent reactions have provided access to potentially bioactive products stereo and regioselectively with high atom economy. I believe that this allene chemistry is capable of substantial further development and will afford diverse and complex molecular materials in a stereoselective fashion. At the moment we have only scratched the surface of its power and reach.

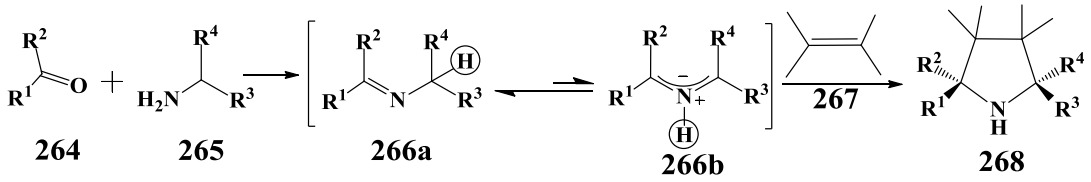
Chapter 3

Results and Discussion

1,3-Dipolar cycloaddition approach to pyrimidinylpyrrolidine

Chapter 3 (Results and Discussion): 1,3-dipolar cycloaddition approach to pyrimidinylpyrrolidines

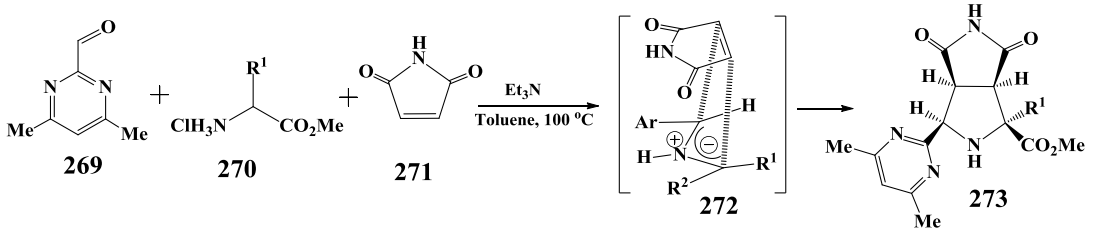
Pyrimidine-based compounds find many applications in medicine and agrochemistry.[169] Several authors have developed methods for the synthesis of pyrimidinylpyrrolidines and have evaluated their biological activity[170] but hardly any have employed 1,3-dipolar cycloaddition reactions. Such an approach provides an efficient method for the construction of highly functionalized five-membered heterocycles.[171] The author's work seeks to employ azomethine ylides which are a cornerstone of work in the Grigg group. These versatile 1,3-dipoles provide access to a multitude of nitrogen-containing heterocycles with wide ranging applications.[172] A number of methods have been developed for the generation of azomethine ylides. One of these methods is the formal 1,2-prototropic shift method, in which an aldehyde or ketone **264** reacts with an amine **265** that has an α-hydrogen through a condensation process to afford an imine **266a** (Scheme 91)[173] which generates the azomethine ylide **266b** *via* a formal 1,2-prototropic shift. This process is catalysed by both Bronsted acids and bases. Subsequently, the azomethine ylide **266b** cycloadds to a wide variety of dipolarophiles **267** to furnish pyrrolidine cycloadducts **268**. The conversion of **266a** to **266b** probably occurs by a bimolecular process.

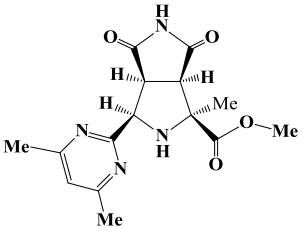


Scheme 91. Azomethine ylide generation *via* a 1,2-prototropic shift.

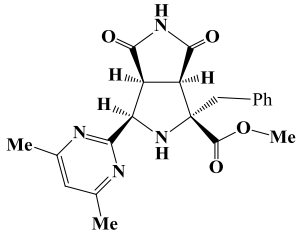
We have used 4,6-dimethyl-2-formylpyrimidine **269** to prepare a library of pyrimidinylpyrrolidines *via* the 1,3-dipolar cycloaddition methodology. Thus, a one pot reaction of a mixture of **269**, α-amino acid ester hydrochloride **270**, and maleimide **271** in toluene containing Et_3N at 100 ºC gave *endo*-cycloadducts **273a-d** as sole products in 66-83% yield (Scheme 92) *via endo*-transition state **272**. It is worth noting that the cycloadducts **273a-d** precipitated from hot solution during the reaction and afforded pure products after filtering and washing with water. The proton NMR spectra (DMSO-d_6) of **273a-c** showed a singlet for the maleimide NH

proton at δ 11.14-11.16 ppm and doublet for the pyrrolidine NH proton at δ 3.68-3.38 ppm. The corresponding signals for **273d** in $CDCl_3$ occurred at δ 8.29 and 4.14 ppm.

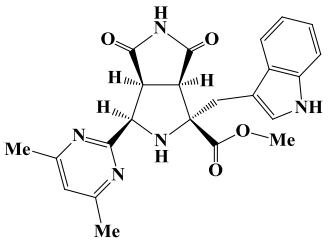




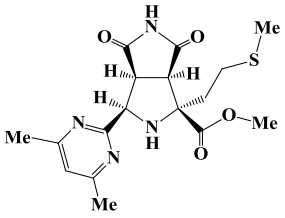
273a (66%)



273b (83%)



273c (74%)



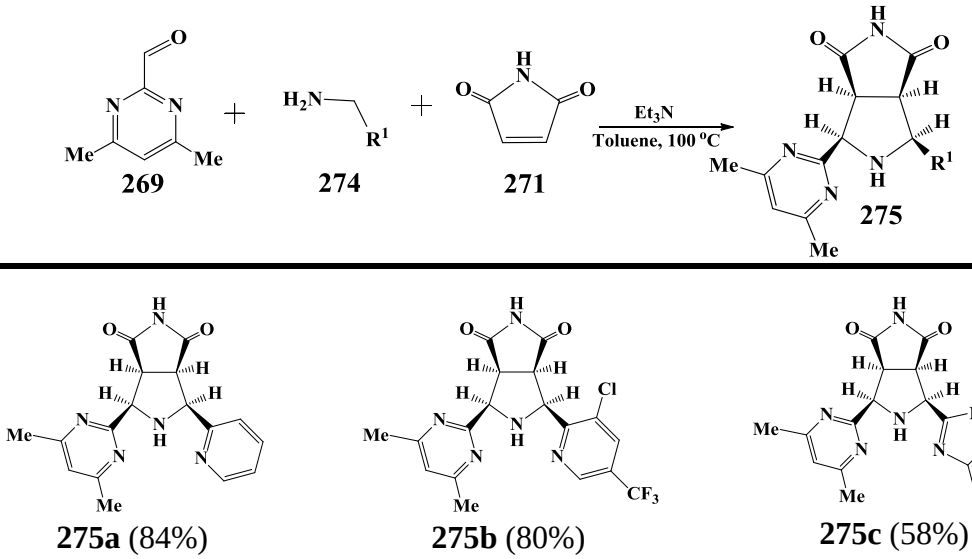
273d (64%)

The reaction was carried out using an equimolar mixture of 4,6-dimethyl-2-formylpyrimidine (1 mmol), α-amino acid ester hydrochloride (1 mmol), maleimide (1 mmol) and Et_3N (1 mmol) in toluene (7 mL) at 100 °C for 1-2 h.

Scheme 92. Cycloaddition products of α-amino acid ester **270**.

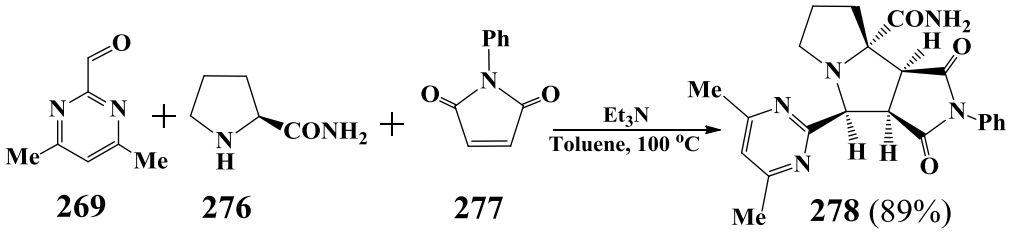
Furthermore, 4,6-dimethyl-2-formylpyrimidine **269** reacted with 2-aminomethyl heteroaromatic compounds **274** and maleimide **271** under the same conditions (Et_3N, toluene, 100 ºC) to produce the corresponding *endo*-cycloadducts **275** in 58-84% yield, (Scheme 93).

The scope of **269** in cycloaddition reactions was extended by reacting it with (*S*)-prolinamide **276** and *N*-phenylmaleimide **277** in toluene containing Et_3N at 100 °C for 2 h to afford the corresponding tricyclic cycloadduct **278** in 89% yield (Scheme 94**)**. The stereochemistry of **278** was established by an X-ray crystal structure (Fig. 29, Appendix 4**)**. The high yield of a single isomer suggests that a series of prolinamide peptides would react similarly. It is interesting to note that the proton n.m.r. of **278** clearly shows the well known restricted rotation about the amide bond showing two doublet signals for the NH_2 protons at δ 7.63 and 7.32 (J = 2.3 Hz).



The reaction was carried out using an equimolar mixture of 4,6-dimethyl-2-formylpyrimidine (1 mmol), aminomethyl heteroaromatic (1 mmol), maleimide (1 mmol) and Et_3N (1 mmol) in toluene (7 mL) at 100 °C for 10 min-1.5 h.

Scheme 93. Cycloadducts of 2-aminomethyl heteroaromatic compounds **274**.



Scheme 94. Formation of fused tricyclic product **278**.

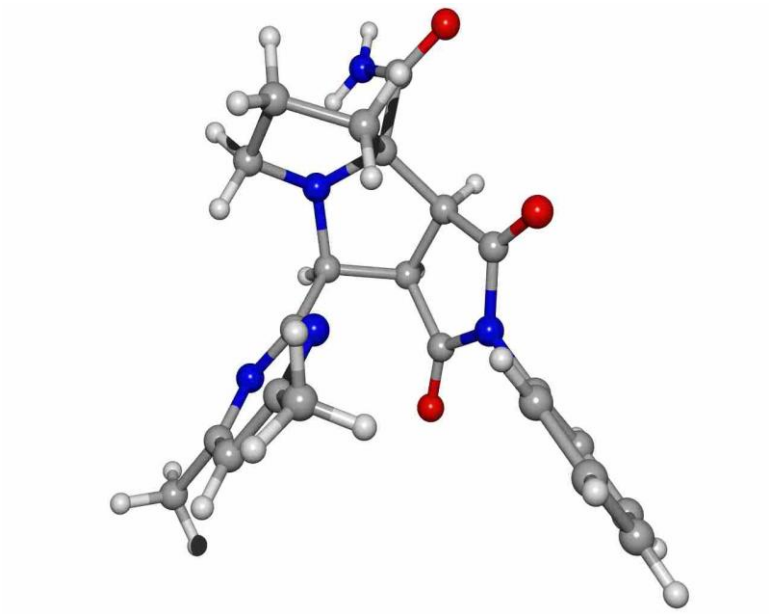
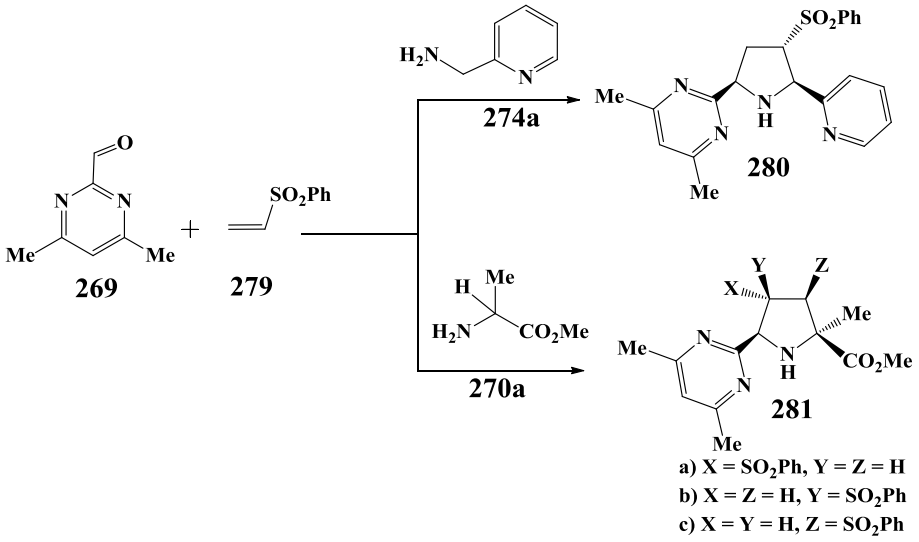


Figure 29. X-ray crystal structure of **278** (Appendix 4).

The high stereoselectivity of 4,6-dimethyl-2-formylpyrimidine **269** in these cycloadditions encouraged us to study the regioselectivity in more details. The reaction of **269** with 2-aminomethylpyridine **274a** and phenyl vinylsulfone **279** under the same conditions (Et_3N, toluene, 100 °C) gave the corresponding cycloadduct **280** regio- and stero-selectively in 64% yield (Scheme 95). Thus, the ability of the pyrimidinyl group to stabilise the azomethine ylide negative charge is greater than the pyridyl group. Furthermore, steric congestion between the $PhSO_2$ group on the dipolarophile and the pyridyl group on the dipole in the *endo*-transition state directed the cycloaddition toward the favourable *exo*-cycloadduct **280**. The regio- and stereochemistry of **280** was confirmed by an X-ray crystal structure (Fig 30).



Scheme 95. Reaction of **279** as dipolarophile.

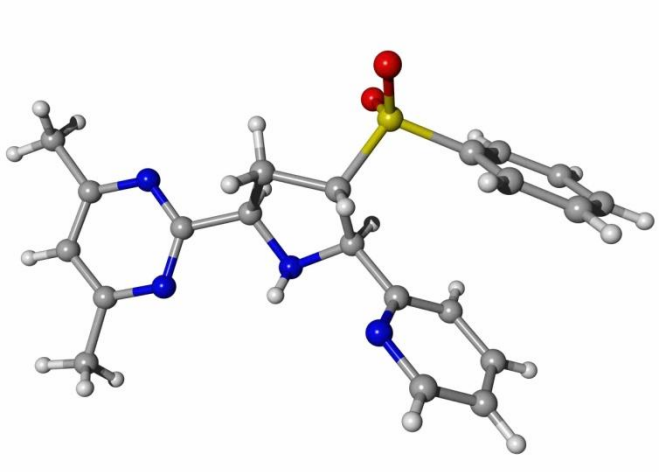


Figure 30. X-ray crystal structure of **280** (Appendix 5).

The reaction of **269** with (*R*)-alanine methyl ester **270a** and phenyl vinylsulfone **279** under the same conditions afforded a 2.5:1.3:1 mixture of three isomers **281a-c** in 54% combined yield. From this result, the capability of the carboxylic ester group in the azomethine ylide to stabilise the negative charge on the dipole is 3.8 times more favourable than the pyrimidinyl group. Furthermore, the 2.5:1.3 ratio of **281a** and **281b**, respectively, reflects favourable *exo*-cycloaddition over *endo*-cycloaddition. The regiochemistry of **281a** was suggested on the basis of its ^{1}H-NMR spectrum and NOE data (Fig. 31, **281a**). The 5-H proton appeared as a doublet (δ 4.72, *J* 6.4) and 4-H proton appeared as a doublet of triplets (δ 4.61, *J* 6.4 and 8.9). Furthermore, irradiation of 5-H (δ 4.72) caused a 3.9% enhancement of the *o*-phenyl protons whilst irradiation of 4-H (δ 4.61) resulted in 6.4% enhancement of 3-Ha and 4.6% enhancement of the *o*-phenyl protons. Irradiation of 3-H_a (δ 2.86) caused 11.6% enhancement of 4-H and 25.5% enhancement of 3-H_b. Irradiation of 3-H_b (δ 2.44) effected a 27.4% enhancement of 3-H_a, 3.8% enhancement of 5-H and 2.8% enhancement of the *o*-phenyl protons.

The NOE data was confirmed by an X-ray crystal structure of **281a** which showed a *trans*-relation between phenylsulphonyl group and pyrimidinyl group (Fig. 32).

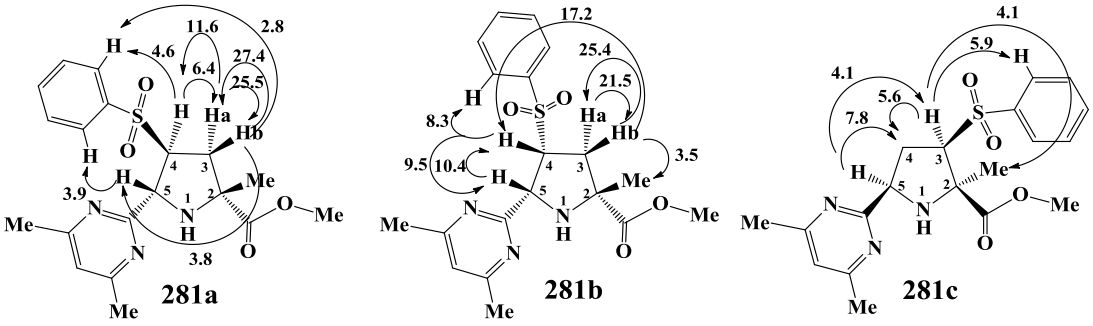


Figure 31. NOE data for **281a-c**.

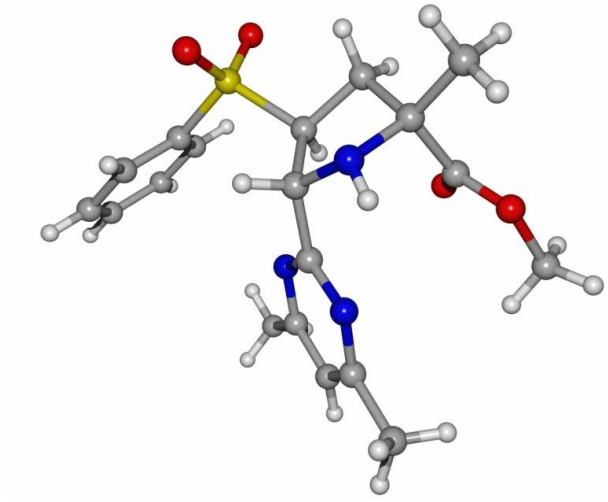


Figure 32. X-ray crystal structure of **281a** (Appendix 6).

The ^{1}H-NMR spectrum of **281b** showed the appearance of 5-H as a doublet (δ 4.69, *J* 5.6) and 4-H as doublet of triplets (δ 4.17, *J* 5.6 and 7.8). The NOE data (Fig. 31, **281b**) showed that irradiation of 5-H (δ 4.69) caused 10.4% enhancement of 4-H whilst irradiation of 4-H (δ 4.17) resulted in 9.5% enhancement of 5-H and 8.3% enhancement of the *o*-phenyl protons. Irradiation of 3-H_a (δ 3.38) caused 21.5% enhancement of 3-H_b proton whilst irradiation of 3-H_b proton (δ 2.25) effected a 25.4% enhancement of 3-H_a, 17.2% enhancement of 4-H and 3.5% enhancement of the 2-Me protons.

In contrast with the regiochemistry of **281a** and **281b**, the minor adduct **281c** had opposite regiochemistry. Thus, 5-H appeared as double of doublets (δ 4.38, *J* 7.2 and 9.7) as did the 3-H (δ 3.70, *J* 7.2 and 9.7). NOE data (Fig. 31, **218c**) showed irradiation of 5-H (δ 4.38) caused 7.9 and 4.1% enhancements of 4-H and 3-H, respectively whilst irradiation of 3-H resulted in 5.6, 4.1 and 5.9% enhancements of 4-H, 2-Me and *o*-phenyl protons, respectively.

Conclusion

We have established 4,6-dimethyl-2-formylpyrimidine as an important carbonyl component in 1,3-dipolar cycloadditions and demonstrated its reactivity with a range of primary and secondary amino acids in the presence of maleimide as dipolarophile. Additionally, phenyl vinylsulfone was incorporated as an unsymmetrical dipolarophile to determine the regioselectivity of the cycloaddition process. In case of 2-aminomethylpyridine, the reaction was regio- and stereo-selective affording a single product whereas (*R*)-alanine methyl ester afforded a mixture of three regio- and stereo-isomers. Future work will focus on combinations of 1,3-dipolar cycloaddition chemistry with allene chemistry in super cascade reactions.

Chapter 4

Experimental

Experimental

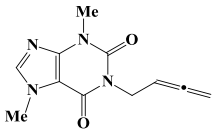
General details: Thin layer chromatography (TLC) was carried out on aluminium plates pre-coated with silica gel 60 F254 (Merck), and were visualised using ultraviolet light and/or aqueous $KMnO_4/I_2$. Flash column chromatography employed silica gel 60 (Merck, 230-400 mesh). Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Microanalyses were performed on a Carlo Erba 1108 elemental analyser. Optical rotations measured on a Polartronic H 532 (Schmidt + Haensch) instrument. Infrared spectra were recorded on a Perkin-Elmer Spectrum FT-IR spectrometer either as thin films on sodium chloride discs or as solids using a golden gate apparatus. The former were created by dissolving the compound in $CHCl_3$ and transfering the solution to a sodium chloride disc and allowing the solvent to evaporate. Proton nuclear magnetic resonance spectra were recorded at 300MHz on a Bruker DPX300 instrument. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (δ = 0.00) and coupling constants are given in hertz (Hz). The following abbreviations are used: s = singlet, br = broad, d = doublet, dd = doublet of doublets, ddd = doublet of double doublets, dt = doublet of triplets, m = multiplet, t = triplet, td = triplet of doublets. ^{13}C-NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument and chemical shifts are reported in parts per million (ppm). ^{1}H-NMR peak assignments are mainly based on DEPT135, COSY, HMQC and HMBC spectral data. Accurate masses were obtained using a Bruker Daltonics micrOTOF spectrometer. The m/z data mentioned in the case of 9-component cascade products are the result of two runs one using the auto sampler technique and the other by injecting the sample directly into the machine using a syringe pump. All compounds are named according to the IUPAC system using the ACD/ILAB (ACD/IUPAC v.12.0 programme) web service (http:/www.acdlabs.com).

General Procedure A: Allene formation.[116]

A mixture of alkyne (1 equiv.), dicyclohexylamine (1.8 equiv.), paraformaldehyde (2.5 equiv.) and CuI (0.5 equiv.) in dry dioxane was refluxed for 3 h. The reaction mixture was cooled and the solvent removed under reduced pressure. The residue was dissolved in $CHCl_3$ and the organic layer washed three times with 10% aqueous

NH_4OH three times then with water, dried over anhydrous $MgSO_4$, filtered and the filtrate evaporated under *vacuo* to give the crude allene which was purified by flash column chromatography.

1-(Buta-2,3-dien-1-yl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (195).[115]



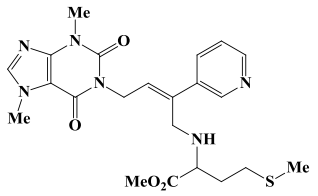
Prepared by general procedure A from 3,7-dimethyl-1-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione **194**[174] (2.34 g, 11.1 mmol), dicyclohexylamine (4.0 mL, 20.1 mmol), paraformaldehyde (0.84 g, 27.9 mmol) and CuI (1.06 g, 5.6 mmol) in dioxane (50 mL). Flash column chromatography eluting with EtOAc gave **195** as colourless fine needles (2.14 g, 83%), mp. 128-130 °C; (Found: C, 56.70; H, 5.10; N, 24.15; $C_{11}H_{12}N_4O_2$ requires C, 56.89; H, 5.21; N, 24.12%); δ_H (300 MHz, $CDCl_3$); 7.53 (1H, s, purine 8-H), 5.36-5.27 (1H, m, CH_2CH=), 4.83-4.78 (2H, m, NCH_2CH=), 4.65-4.61 (2H, m, $=CH_2$), 4.00 (3H, s, NMe), 3.58 (3H, s, NMe); δ_c (75 MHz, $CDCl_3$); 208.8, 154.9, 151.2, 148.8, 141.5, 107.6, 86.3, 77.0, 39.5, 33.6, 29.7; υ_{max}/cm^{-1} (film); 3115, 2950, 1701, 1654, 1598, 1477, 1332; *m/z* (ESI^+) 255.1 (100%, MNa^+); (Found MNa^+, 255.0844. $C_{11}H_{12}N_4NaO_2$ requires *MNa*, 255.0852).

General Procedure B: Pd catalysed 3-component cascades.

A mixture of substituted allene (1 equiv.), aryl/heteroaryl iodide (1.2 equiv.), nucleophile (1.2 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (tri-(2-furyl)phosphine) (10 mol%) and K_2CO_3 (3 equiv.) in MeCN or DMF was stirred and heated at 80 °C (oil bath temperature). The mixture was then cooled, evaporated under reduced pressure and the resulting residue dissolved in $CHCl_3$ and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography.

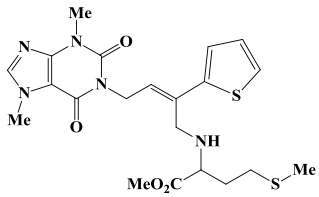
Methyl 2-{[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(pyridin-3-yl)but-2-en-1-yl]amino}-4-(methylthio)butanoate (200a).

Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), *rac*-methionine methyl ester hydrochloride **199** (0.149 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.5 mmol) in MeCN (5 mL) at 80 ºC for 18 h. Flash column



chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **200a** (0.39 g, 82%) as a pale yellow gum; δ_H (300 MHz, C_6D_6); 9.03 (1H, d, *J* 1.5, pyridinyl-H), 8.45 (1H, d, *J* 3.9, pyridinyl-H), 7.66 (1H, d, *J* 7.8, pyridinyl-H), 6.78 (1H, dd, *J* 7.8 and 4.8, pyridinyl-H), 6.71 (1H, s, purine 8-H), 6.03 (1H, t, *J* 6.9, NCH_2CH=), 4.99 (2H, d, *J* 6.9, NCH_2CH=), 3.94 (1H, d, *J* 12, =CCH_2NH), 3.58 (1H, d, *J* 12, =CCH_2NH), 3.50 (1H, dd, *J* 8.6 and 4.7, $NHCHCO_2CH_3$), 3.45 (3H, s, purine 3-NCH_3), 3.36 (3H, s, CO_2CH_3), 3.20 (3H, s, purine 7-NCH_3), 2.53 (2H, t, *J* 7.3, CH_2SCH_3), 2.42 (1H, br s, $NHCHCO_2CH_3$), 1.98 (1H, m, CH_2CH_2S), 1.83 (1H, m, CH_2CH_2S), 1.81 (3H, s, SCH_3); δ_C (75 MHz, $CDCl_3$); 175.8, 155.3, 151.7, 149.2, 148.7, 148.0, 142.1, 138.3, 137.2, 134.1, 127.5, 123.4, 107.9, 60.2, 52.3, 47.0, 39.9, 34.0, 33.0, 30.9, 30.1, 15.7; υ_{max}/cm^{-1} (film); 3310, 3104, 2950, 2912, 2851, 1732, 1704, 1661, 1604, 1549, 1455, 1356, 1314, 1285, 1234; *m/z* (ESI^+) 473.2 (100%, MH^+); (Found MH^+, 473.1973. $C_{22}H_{29}N_6O_4{}^{32}S$ requires *MH*, 473.1966).

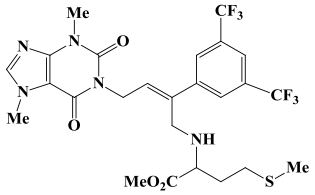
Methyl 2-{[(2*E*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(2-thienyl)but-2-en-1-yl]amino}-4-(methylthio)butanoate (200b).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 2-iodothiophine (0.066 mL, 0.60 mmol), *rac*-methionine methyl ester hydrochloride **199** (0.149 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 11 h. Flash column chromatography eluting with EtOAC gave the product **200b** (0.18, 75%) as a pale yellow gum; δ_H (300 MHz, C_6D_6); 7.29 (1H, t, *J* 2.2, thienyl-H), 6.73 (2H, d, *J* 2.4, 2 x thienyl-H), 6.47 (1H, s, purine 8-H), 6.42 (1H, t, *J* 7.2, NCH_2CH=), 5.01 (2H, d, *J* 7.2, NCH_2CH=), 4.07 (1H, d, *J* 11.6, =CCH_2NH), 3.80 (1H, d, *J* 11.6, =CCH_2NH), 3.61 (1H, dd, *J* 8.6 and 4.7, $NHCHCO_2CH_3$), 3.42 (3H, s, purine 3-NCH_3), 3.31 (3H, s, CO_2CH_3), 3.06 (3H, s, purine 7-NCH_3), 2.61 (2H, m, CH_2SCH_3), 2.02 (1H, m, CH_2CH_2S), 1.85 (1H, m, CH_2CH_2S), 1.80 (3H, s, SCH_3); δ_C (75 MHz, $CDCl_3$); 175.5, 155.0, 151.4, 148.9, 144.9, 141.5, 135.0, 127.3, 124.3, 124.0, 123.3, 107.7, 60.1, 51.9, 47.0, 39.3, 33.6, 32.8, 30.6, 29.8, 15.3; υ_{max}/cm^{-1} (film); 3310, 3110, 2949, 1733, 1704, 1660, 1604,

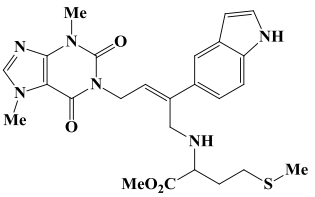
1549, 1487, 1454, 1432, 1359, 1233; *m/z* (ESI^+) 478.2 (100%, MH^+); (Found MH^+, 478.1599. $C_{21}H_{28}N_5O_4{}^{32}S_2$ requires *MH*, 478.1577).

Methyl 2-{[(2*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-en-1-yl]amino}-4-(methylthio)butanoate (200c).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.11 mL, 0.60 mmol), *rac*-methionine methyl ester hydrochloride **199** (0.149 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 10 h. Flash column chromatography eluting with EtOAc gave the product **200c** (0.26 g, 85%) as a pale yellow gum; δ_H (300 MHz, $CDCl_3$); 8.02 (2H, s, phenyl 2-H and 6-H), 7.74 (1H, s, phenyl 4-H), 7.55 (1H, s, purine 8-H), 5.94 (1H, t, *J* 6.9, NCH_2CH=), 4.95 (2H, d, *J* 6.9, NCH_2CH=), 4.01 (3H, s, purine 7-NCH_3), 3.98 (1H, d, *J* 11.9, =CCH_2NH), 3.79 (3H, s, CO_2CH_3), 3.60 (3H, s, purine 3-NCH_3), 3.59 (1H, d, *J* 11.9, =CCH_2NH), 3.52 (1H, dd, *J* 8.9 and 4.4, $NHCHCO_2CH_3$), 2.63 (2H, m, CH_2SCH_3), 2.15 (1H, br s, $NHCHCO_2CH_3$), 2.08 (3H, s, SCH_3), 2.00 (1H, m, CH_2CH_2S), 1.87 (1H, m, CH_2CH_2S); δ_C (75 MHz, $CDCl_3$); 174.1, 153.7, 150.1, 147.7, 142.4, 140.5, 137.1, 130.1 (*J* 32.2), 127.6 (*J* 2.3), 125.3 (*J* 4.6), 122.2 (*J* 272.8), 119.6 (*J* 4.6), 106.4, 58.6, 50.7, 45.7, 38.3, 32.4, 31.3, 29.4, 28.5, 14.0; υ_{max}/cm^{-1} (film); 3307, 3109, 2953, 2829, 1734, 1708, 1661, 1605, 1550, 1456, 1381, 1280, 1234; *m/z* (ESI^+) 608.2 (100%, MH^+); (Found MH^+, 608.1782. $C_{25}H_{28}F_6N_5O_4{}^{32}S$ requires *MH*, 608.1761).

Methyl 2-{[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(1H-indol-5-yl)but-2-en-1-yl]amino}-4-(methylthio)butanoate (200d).



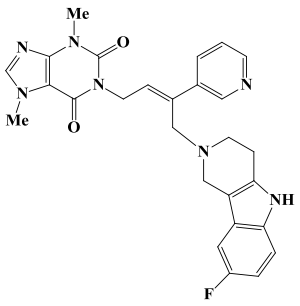
Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 5-iodoindole (0.145 g, 0.60 mmol), *rac*-methionine methyl ester hydrochloride **199** (0.149 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 18 h. Flash column chromatography eluting with EtOAc gave the product **200d**

(0.18 g, 72%) as a pale yellow gum; δ_H (300 MHz, $CDCl_3$); 8.36 (1H, s, indolyl-NH), 7.74 (1H, s, indolyl-H), 7.49 (1H, s, purine 8-H), 7.30-7.28 (2H, m, 2 x indolyl-H), 7.15 (1H, t, *J* 2.5, indolyl-H), 6.49 (1H, t, *J* 2.3, indolyl-H), 5.87 (1H, t, *J* 7.2, NCH_2CH=), 4.91 (2H, d, *J* 7.2, NCH_2CH=), 3.99 (1H, d, *J* 11.4, =CCH_2NH), 3.97 (3H, s, purine 7-NCH_3), 3.79 (1H, d, *J* 11.4, =CCH_2NH), 3.75 (3H, s, CO_2CH_3), 3.57 (3H, s, purine 3-NCH_3), 3.53 (1H, dd, *J* 8.7 and 4.8, $NHCHCO_2CH_3$), 2.57 (2H, t, *J* 7.5, CH_2SCH_3), 2.13 (1H, brs, $NHCHCO_2CH_3$), 2.04 (3H, s, SCH_3), 2.01 (1H, m, CH_2CH_2S), 1.85 (1H, m, CH_2CH_2S); υ_{max}/cm^{-1} (film); 3318, 3104, 2922, 2853, 1725, 1703, 1660, 1602, 1549, 1456, 1312, 1234; *m/z* (ESI^+) 511.2 (100%, MH^+); (Found MH^+, 511.2137. $C_{25}H_{31}N_6O_4{}^{32}S$ requires *MH*, 511.2122).

General Procedure C: Pd catalysed 3-component cascades.

As for general procedure A except the reaction time was 2-3 h and the cascade product precipitated out of the hot solution. The solution was filtered and the precipitate was washed with water and crystallized from MeOH.

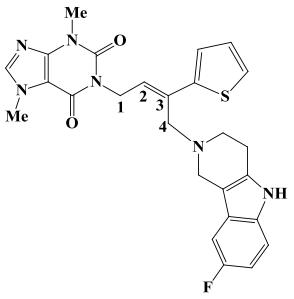
1-[(2*Z*)-4-(8-Fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-b]indol-2-yl)-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (201a).



Prepared by general procedure C from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) for 3 h. The product **201a** precipitated from MeOH as an off-white amorphous powder (0.23 g, 92%), mp 262-264 °C; δ_H (300 MHz, DMSO-d_6); 10.86 (1H, s, pyridoindolyl-NH), 8.71 (1H, d, *J* 1.0 pyridinyl-H), 8.40 (1H, d, *J* 4.6, pyridinyl-H), 8.04 (1H, s, purine 8-H), 7.91 (1H, d, *J* 8.2, pyridinyl-H), 7.29 (1H, dd, *J* 7.7 and 4.6, pyridinyl-H), 7.22 (1H, dd, *J* 9.0 and 4.9, pyridoindolyl-H), 7.10 (1H, dd, *J* 9.5 and 1.8, pyridoindolyl-H), 6.80 (1H, td, *J* 9.4, and 2.6, pyridoindolyl-H), 5.98 (1H, t, *J* 6.1, NCH_2CH=), 4.83 (2H, d, *J* 6.1, NCH_2CH=), 3.91 (3H, s, purine 7-NCH_3), 3.81 (2H, s, =CCH_2N), 3.66 (2H, s, pyridoindoly 1-CH_2), 3.45 (3H, s, purine 3-NCH_3), 2.86 (2H, brt, *J* 5.5,

pyridoindolyl-CH_2), 2.71 (2H, brt, *J* 5.5, pyridoindolyl-CH_2); δ_C (75 MHz, DMSO-d_6); 156.5 (*J* 229.9), 154.2, 150.8, 148.3, 147.8, 147.4, 142.8, 136.5, 135.5, 134.9, 133.6, 132.4, 129.1, 125.6 (*J* 9.2), 123.0, 111.3 (*J* 9.2), 107.7 (*J* 27.6), 107.5 (*J* 4.6), 106.7, 101.9 (*J* 25.3), 54.8, 49.5, 48.9, 39.0, 33.1, 29.3, 23.5; υ_{max}/cm^{-1} (solid); 2917, 1698, 1650, 1544, 1454, 1407, 1360, 1293, 1231; *m/z* (ESI^+) 500.2 (100%, MH^+); (Found MH^+, 500.2198. $C_{27}H_{27}FN_7O_2$ requires *MH*, 500.2205).

1-[(2*E*)-4-(8-Fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-b]indol-2-yl)-3-(2-thienyl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (201b).

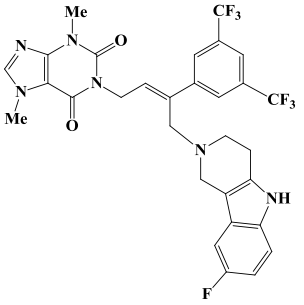


Prepared by general procedure C from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 2-iodothiophene (0.066 mL, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) for 3 h. The product **201b** crystallized from MeOH as off-white needles (0.18 g, 71%), mp 243-245 °C; δ_H (300 MHz, $CDCl_3$); 7.76 (1H, s, pyridoindolyl-NH), 7.49 (1H, s, purine 8-H), 7.23 (1H, d, *J* 3.6, thienyl-H), 7.18 (1H, dd, *J* 8.7 and 4.2, pyridoindolyl-H), 7.11 (1H, d, *J* 5.7, thienyl-H), 7.07 (1H, dd, *J* 9.7 and 2.1, pyridoindolyl-H), 6.91 (1H, dd, *J* 4.9 and 3.8, thienyl-H), 6.83 (1H, td, *J* 9.3 and 2.4, pyridoindolyl-H), 6.13 (1H, t, *J* 6.8, NCH_2CH=), 4.92 (2H, d, *J* 6.8, NCH_2CH=), 3.99 (3H, s, purine 7-NCH_3), 3.84 (2H, s, =CCH_2N), 3.80 (2H, s, pyridoindolyl 1-CH_2), 3.59 (3H, s, purine 3-NCH_3), 2.98 (2H, brt, *J* 5.6, pyridoindolyl-CH_2), 2.84 (2H, brt, *J* 5.6, pyridoindolyl-CH_2); δ_C (75 MHz, DMSO-d_6); 156.6 (*J* 229.3), 154.2, 150.8, 148.3, 144.6, 142.9, 135.0, 132.5, 132.4, 127.1, 125. 8 (*J* 9.7), 125.5, 124.8, 124.0, 111.3 (*J* 9.7), 107.7 (*J* 26), 107.4 (*J* 4.3), 106.7, 101.9 (*J* 23.1), 55.9, 49.6, 49.0, 38.8, 33.1, 29.3, 23.6; υ_{max}/cm^{-1} (solid); 3305, 1699, 1560, 1550, 1457, 1426, 1283, 1233; *m/z* (ESI^+) 505.2 (100%, MH^+); (Found MH^+, 505.1806. $C_{26}H_{27}FN_6O_2{}^{32}S$ requires *MH*, 505.1816).

NOE data for **201b**:

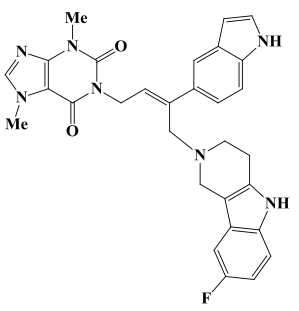
	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Thienyl 3-H	Pyridoindolyl 3-H
1-H		6.6	3.5	-	-
2-H	3.7		-	4.2	-
4-H	4.4	-		4.2	3.4

1-[(2*Z*)-3-[3,5-Bis(trifluoromethyl)phenyl]-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-b]indol-2-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (201c).



Prepared by general procedure C from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.1 mL, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 °C for 3 h. The product **201c** crystallized from MeOH as off-white needles (0.19 g, 60%), mp 148-250 °C; δ_H (300 MHz, $CDCl_3$); 7.96 (2H, s, phenyl 2-H and 6-H), 7.75 (1H, s, pyridoindolyl-NH), 7.70 (1H, s, phenyl 4-H), 7.53 (1H, s, purine 8-H), 7.17 (1H, dd, *J* 8.7 and 4.1, pyridoindolyl-H), 7.08 (1H, dd, *J* 9.5 and 2.3, pyridoindolyl-H), 6.83 (1H, td, *J* 9.0 and 2.6, pyridoindolyl-H), 6.02 (1H, t, *J* 6.4, NCH_2CH=), 4.98 (2H, d, *J* 6.4, NCH_2CH=), 4.01 (3H, s, purine 7-NCH_3), 3.89 (2H, s, =CCH_2N), 3.77 (2H, s, pyridoindolyl 1-CH_2), 3.61 (3H, s, purine 3-NCH_3), 2.98 (2H, t, *J* 5.5, pyridoindolyl-CH_2), 2.81 (2H, brt, *J* 5.5, pyridoindolyl-CH_2);); δ_C (75 MHz, DMSO-d_6); 156.6 (*J* 228.8), 154.3, 150.9, 148.4, 143.6, 142.9, 135.1, 134.8, 132.4, 131.7, 129.9 (*J* 32.2), 126.9, 125.6 (*J* 9.2), 123.4 (*J* 273.6), 120.2, 111.4 (*J* 9.2), 107.8 (*J* 27.6), 107.4 (*J* 4.6), 106.8, 101.9 (*J* 23.0), 54.6, 49.7, 48.7, 39.2, 33.1, 29.4, 23.5; υ_{max}/cm^{-1} (film); 3313, 3241, 2939, 2824, 1708, 1660, 1602, 1551, 1455, 1381, 1278, 1233; *m/z* (ESI^+) 635.2 (100%, MH^+); (Found MH^+, 635.1985. $C_{30}H_{26}F_7N_6O_2$ requires *MH*, 635.2000).

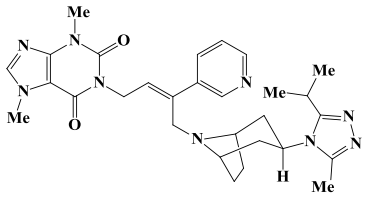
1-[(2*Z*)-4-(8-Fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-b]indol-2-yl)-3-(1*H*-indol-5-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (201d).



Prepared by general procedure C (the product was precipitated from cold solution) from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 5-iodoindole (0.145 g, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (tri-(2-furyl)phosphine) (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) for 2 h. The product **201d** crystallized from MeOH as an off-white powder (0.21 g, 78%), mp 250-252 °C; δ_H (300 MHz,

$CDCl_3$/MeOH-d_4); 7.73 (1H, s, NH), 7.64 (1H, s, indolyl-H), 7.47 (1H, s, purine 8-H), 7.31 (2H, dd, *J* 4.1 and 1.5, 2 x indolyl-H), 7.19-7.16 (2H, m, indolyl-H and pyridoindolyl-H), 7.01 (1H, dd, *J* 9.7 and 2.6, pyridoindolyl-H), 6.78 (1H, td, *J* 9.2 and 2.6, pyridoindolyl-H), 5.94 (1H, t, *J* 7.1, NCH_2CH=), 4.95 (2H, d, *J* 7.1, NCH_2CH=), 3.86 (2H, s, =CCH_2N), 3.82 (3H, s, purine 7-NCH_3), 3.62 (2H, s, pyridoindolyl 1-CH_2), 3.40 (3H, s, purine 3-NCH_3), 2.76 (2H, t, *J* 5.4, pyridoindolyl-CH_2), 2.61 (2H, brt, *J* 5.4, pyridoindolyl-CH_2); δ_C (75 MHz, DMSO-d_6); 156.5 (*J* 229.1), 154.3, 150.8,148.3, 142.8, 139.5, 135.1, 135.0, 132.7, 132.4, 127.4, 125.7 (*J* 10.3), 125.6, 125.4, 120.0, 117.7, 111.3 (*J* 9.7), 110.7, 107.7 (*J* 4.3), 107.6 (*J* 25.4), 106.7, 101.8 (*J* 23.0), 101.2, 56.1, 49.6, 49.1, 39.3, 33.1, 29.3, 23.6; υ_{max}/cm^{-1} (solid); 3314, 2919, 1695, 1647, 1544, 1454, 1434, 1410, 1358, 1227; *m/z* (ESI^+) 538.2 (100%, MH^+); (Found MH^+, 538.2353. $C_{30}H_{29}F_1N_7O_2$ requires *MH*, 538.2361).

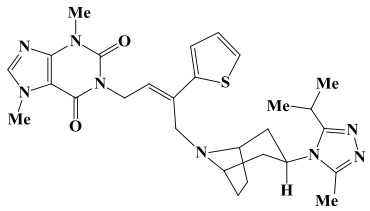
1-[(2*Z*)-4-[3-(3-Isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (202a).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.149 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 8 h. Flash column chromatography gradient elution with EtOAc to 10:5 v/v EtOAc/MeOH gave the product **202a** (0.25 g, 92%, *Z*:*E* 93:7) as a colourless amorphous solid, mp 112-114 °C; δ_H (300 MHz, $CDCl_3$); 8.71 (1H, d, *J* 2.1, pyridinyl-H), 8.47 (1H, dd, *J* 1.4 and 4.7, pyridinyl-H), 7.80 (1H, dt, *J* 1.9 and 7.9, pyridinyl-H), 7.60 (1H, s, purine 8-H), 7.23 (1H, dd, *J* 4.9 and 7.9, pyridinyl-H), 5.92 (1H, t, *J* 6.6, NCH_2CH=), 4.90 (2H, d, *J* 6.6, NCH_2CH=), 4.25 (1H, m, azabicyclooctyl-H), 4.01 (3H, s, purine 7-NCH_3), 3.70 (2H, s, =CCH_2N), 3.59 (3H, s, purine 3-NCH_3), 3.42 (2H, brs, 2 × azabicyclooctyl-H), 2.91 (1H, m, triazolyl 3-$CH(CH_3)_2$), 2.34 (3H, s, triazolyl 5-CH_3), 2.27-2.24 (2H, brdd, *J* 4.6 and 6.1, 2 × azabicyclooctyl-H), 2.06-1.97 (2H, brdt, *J* 2.3 and 12.0, 2 x azabicyclooctyl-H), 1.74-1.63 (4H, brm, 4 × azabicyclooctyl-H), 1.33 (6H, d, *J* 6.9, triazolyl 3-$CH(CH_3)_2$); δ_C (75 MHz, $CDCl_3$); 159.1, 154.9, 151.4, 150.7, 148.9, 148.3, 148.0,

141.9, 138.1, 137.2, 134.4, 127.7, 122.6, 107.6, 58.8, 50.9, 47.2, 39.3, 37.6, 33.7, 29.8, 26.6, 25.7, 21.6, 12.7; υ_{max}/cm^{-1} (film); 3109, 2962, 2868, 1704, 1660, 1602, 1550, 1455, 1357, 1287, 1235; *m/z* (ESI^+) 544.3 (100%, MH^+); (Found MH^+, 544.3162. $C_{29}H_{38}N_9O_2$ requires *MH*, 544.3143).

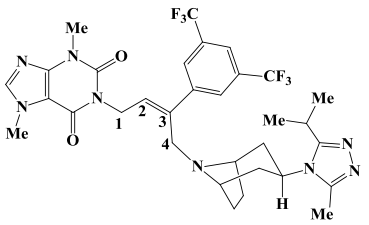
1-[(2*E*)-4-[3-(3-Isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-(2-thienyl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (202b).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 2-iodothiophene (0.066 mL, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.149 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 10 h. Flash column chromatography gradient elution with EtOAc to 5:1 v/v EtOAc/MeOH gave the product **202b** (0.24 g, 88%, *Z*:*E* 90:10) as a colourless amorphous solid, mp 118-120 °C; δ_H (300 MHz, $CDCl_3$); 7.53 (1H, s, purine 8-H), 7.20 (1H, d, *J* 3.4, thienyl-H), 7.18 (1H, d, *J* 5.1, thienyl-H), 6.94 (1H, t, *J* 4.7, thienyl-H), 6.06 (1H, t, *J* 6.8, NCH_2CH=), 4.88 (2H, d, *J* 6.8, NCH_2CH=), 4.31 (1H, m, azabicyclooctyl-H), 4.00 (3H, s, purine 7-NCH_3), 3.59 (5H, s, purine 3-NCH_3 and $=CCH_2N$), 3.53 (2H, brs, 2 × azabicyclooctyl-H), 3.07 (1H, m, triazolyl 3-C*H*$(CH_3)_2$), 2.53 (3H, s, triazolyl 5-CH_3), 2.34-2.28 (4H, brm, 4 × azabicyclooctyl-H), 1.74-1.71 (4H, brm, 4 × azabicyclooctyl-H), 1.38 (6H, d, *J* 6.8, triazolyl 3-CH(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$); 159.2, 155.0, 151.4, 150.8, 148.9, 144.9, 141.7, 134.3, 126.6, 125.1, 124.5, 123.9, 107.7, 59.0, 51.9, 47.5, 39.4, 37.4, 33.7, 29.8, 26.7, 25.8, 21.7, 13.0; υ_{max}/cm^{-1} (film); 3051, 2963, 2873, 1704, 1652, 1603, 1549, 1455, 1361, 1312, 1286, 1234; *m/z* (ESI^+) 549.3 (100%, MH^+); (Found MH^+, 549.2756. $C_{28}H_{37}N_8O_2{}^{32}S$ requires *MH*, 549.2755).

1-{(2*Z*)-3-[3,5-Bis(trifluoromethyl)phenyl]-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]but-2-en-1-yl}-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (202c).

Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.11 mL, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.149 g, 0.60 mmol),

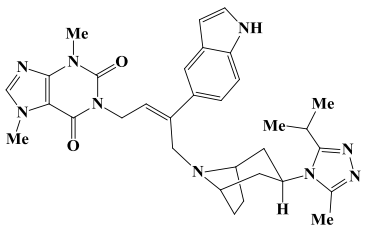


$Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 11 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **202c** (0.29 g, 86%, *Z*:*E* 90:10) as a colourless amorphous solid, mp 118-120 °C; δ_H (300 MHz, $CDCl_3$); 8.04 (2H, s, phenyl 2-H and 6-H), 7.76 (1H, s, phenyl 4-H), 7.58 (1H, s, purine 8-H), 6.00 (1H, t, *J* 6.7, NCH_2CH=), 4.89 (2H, d, *J* 6.7, NCH_2CH=), 4.26 (1H, m, azabicyclooctyl-H), 4.01 (3H, s, purine 7-NCH_3), 3.69 (1H, s, =CCH_2NH), 3.61 (3H, s, purine 3-NCH_3), 3.46 (2H, brs, 2 × azabicyclooctyl-H), 2.89 (1H, m, triazolyl 3-$CH(CH_3)_2$), 2.41-2.28 (2H, brm, 2 × azabicyclooctyl-H), 2.34 (3H, s, triazolyl 5-CH_3), 2.04 (2H, brdt, *J* 2.1 and 12.3, 2 × azabicyclooctyl-H), 1.75-1.66 (4H, brm, 4 × azabicyclooctyl-H), 1.33 (6H, d, *J* 7.2, triazolyl 3-$CH(CH_3)_2$; δ_C (75 MHz, $CDCl_3$); 159.5, 155.4, 151.8, 151.1, 149.5, 144.1, 142.3, 138.5, 131.5 (*J* 33.0), 129.5, 127.5 (*J* 4.6), 123.8 (*J* 271.0), 121.0 (*J* 4.6), 108.0, 59.4, 51.6, 47.6, 39.6, 38.1, 34.1, 30.3, 27.0, 26.2, 22.0, 13.0; υ_{max}/cm^{-1} (film); 3055, 2969, 2882, 1708, 1661, 1604, 1550, 1515, 1455, 1416, 1381, 1279, 1234; *m/z* (ESI^+) 679.2 (100%, MH^+); (Found MH^+, 679.2950. $C_{32}H_{37}F_6N_8O_2$ requires *MH*, 679.2938).

NOE data for **202c**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Ph	Azabicyclooctyl-H
1-H		5.92	-	-	-
2-H	3.26		-	1.95	-
4-H	4.35	-		7.13	5.66 (δ 3.46) and 3.97(δ 2.30)

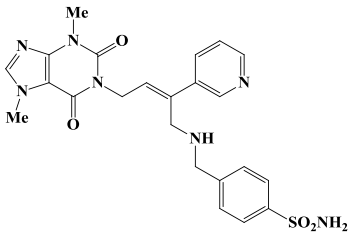
1-{(2*Z*)-3-(1*H*-Indol-5-yl)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]but-2-en-1-yl}-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (202d).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 5-iodoindole (0.145 g, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.149 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21

g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 11 h. Flash column chromatography gradient elution with EtOAc to 5:1 v/v EtOAc/MeOH gave the product **202d** (0.24 g, 72%, *Z*:*E* 88:12) as a colourless amorphous solid, mp 148-150 °C; δ_H (300 MHz, $CDCl_3$); 9.81 (1H, brs, indolyl-NH), 7.72 (1H, s, indolyl-H), 7.53 (1H, s, purine 8-H), 7.25 (2H, d, J 3.8, 2 x indolyl-H), 7.16 (1H, brt, *J* 2.7, indolyl-H), 6.42 (1H, brs, indolyl-H), 5.88 (1H, t, *J* 6.6, NCH_2CH=), 4.96 (2H, d, *J* 6.6, NCH_2CH=), 4.23 (1H, m, azabicyclooctyl-H), 3.96 (3H, s, purine 7-NCH_3), 3.75 (1H, s, =CCH_2NH), 3.58 (3H, s, purine 3-NCH_3), 3.48 (2H, brs, 2 × azabicyclooctyl-H), 2.90 (1H, m, triazolyl 3-$CH(CH_3)_2$), 2.29 (3H, s, triazolyl 5-CH_3), 2.21 (2H, brdd, *J* 3.1and 7.7, 2 × azabicyclooctyl-H), 2.07 (2H, brdt, *J* 2.8 and 12.0, 2 × azabicyclooctyl-H), 1.72-1.58 (4H, brm, 4 × azabicyclooctyl-H), 1.27 (6H, d, *J* 7.2, triazolyl 3-$CH(CH_3)_2$; δ_C (75 MHz, $CDCl_3$); 159.7, 155.5, 151.9, 151.2, 149.2, 142.4, 142.2, 135.8, 134.1, 128.1, 125.4, 125.1, 121.5, 119.1, 111.0, 108.1, 102.4, 59.0, 52.1, 47.9, 40.3, 37.8, 34.0, 30.2, 27.1, 26.1, 22.1, 13.0; υ_{max}/cm^{-1} (film); 3333, 3038, 2969, 2873, 1704, 1660, 1602, 1549, 1455, 1415, 1357, 1233; *m/z* (ESI^+) 582.3 (100%, MH^+); (Found MH^+, 582.3314. $C_{32}H_{40}N_9O_2$ requires *MH*, 582.3299).

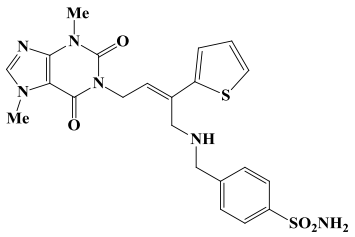
4-({[(2*Z*)-4-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(pyridin-3-yl)but-2-en-1-yl]amino}methyl)benzenesulfonamide (203a).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), mafenide hydrochloride **174** (0.133 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.5 mmol) in DMF (2 mL) at 80 ºC for 2 h. Flash column chromatography eluting with 10:2 v/v EtOAC/MeOH gave the product **203a** (0.11 g, 44%) as a colourless amorphous solid, mp 96-98 °C; δ_H (300 MHz, $CDCl_3$); 8.56 (1H, brs, pyridinyl-H), 8.45 (1H, d, *J* 3.6, pyridinyl-H), 7.83 (2H, d, *J* 8.2, 2 x phenyl-H), 7.75 (1H, dt, *J* 8.0 and 1.8, pyridinyl-H), 7.53 (1H, s, purine 8-H), 7.48 (2H, d, *J* 8.2, 2 x phenyl-H), 7.21 (1H, dd, *J* 7.9 and 4.9, pyridinyl-H), 5.87 (1H, t, *J* 7.1, NCH_2CH=), 5.27 (1H, s, NH), 4.83 (2H, d, *J* 7.1, NCH_2CH=), 3.97 (3H, s, purine 7-NCH_3), 3.93 (2H, s, $NHCH_2$), 3.80 (2H, s, =CCH_2NH), 3.57 (3H, s, purine 3-NCH_3), 2.04 (1H, brs, NH); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 149.0, 148.3, 147.5, 145.6, 141.8, 140.7, 138.5, 136.8,

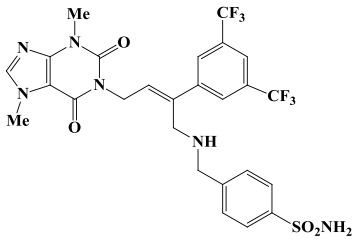
133.9, 128.9, 126.8, 126.4, 123.2, 107.6, 53.2, 47.2, 39.4, 33.7, 28.9; υ_{max}/cm^{-1} (film); 3303, 2927, 2252, 1703, 1658, 1603, 1550, 1455, 1414, 1332, 1234; *m/z* (ESI^+) 496.2 (100%, M^+); (Found M^+, 496.1707. $C_{23}H_{25}N_7O_4{}^{32}S$ requires *M*, 495.1683).

4-({[(2*E*)-4-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(2-thienyl)but-2-en-1-yl]amino}methyl)benzenesulfonamide (203b).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 2-iodothiophene (0.066 mL, 0.60 mmol), mafenide hydrochloride **174** (0.133 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.5 mmol) in DMF (2 mL) at 80 ºC for 3 h. Flash column chromatography gradient eluting with EtOAc and then 50:1 v/v EtOAc/MeOH gave the product **203b** (0.13 g, 52%) as a colourless amorphous solid, mp 103-105 °C; δ_H (300 MHz, $CDCl_3$/MeOH-d_4); 7.87 (2H, d, *J* 8.2, 2 x phenyl-H), 7.64 (1H, s, purine 8-H), 7.53 (2H, d, *J* 8.4, 2 x phenyl-H), 7.18 (1H, dd, *J* 5.1 and 1.0, thienyl-H), 7.07 (1H, dd, *J* 3.6 and 1.0, thienyl-H), 6.97 (1H, dd, J 5.1 and 3.6, thienyl-H), 6.02 (1H, t, *J* 7.3, NCH_2CH=), 4.78 (2H, d, *J* 7.3, NCH_2CH=), 4.01 (2H, brs, NH), 3.98 (3H, s, purine 7-NCH_3), 3.94 (2H, s, $NHCH_2$), 3.82 (2H, s, =CCH_2NH), 3.57 (3H, s, purine 3-NCH_3); δ_C (75 MHz, $CDCl_3$/MeOH-d_4); 159.3, 155.8, 153.1, 148.9, 148.8, 146.4, 145.7, 139.4, 133.1, 131.7, 130.5, 129.0, 128.2, 127.6, 112.0, 57.1, 51.7, 43.7, 37.9, 34.0; υ_{max}/cm^{-1} (film); 3300, 2924, 1702, 1655, 1549, 1451, 1330, 1231; *m/z* (ESI^+) 501.1 (100%, MH^+); (Found MH^+, 501.1375. $C_{22}H_{25}N_6O_4{}^{32}S_2$ requires *MH*, 501.1373).

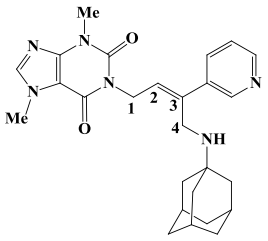
4-({[(2*Z*)-2-[3,5-Bis(trifluoromethyl)phenyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-en-1-yl]amino}methyl)benzenesulfonamide (203c).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.10 mL, 0.60 mmol), mafenide hydrochloride **174** (0.133 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.5

mmol) in DMF (2 mL) at 80 ºC for 3 h. Flash column chromatography gradient eluting with EtOAc to 10:1 v/v EtOAc/MeOH gave the product **203c** (0.17 g, 54%) as a colourless amorphous solid, mp 139-141 °C; δ_H (300 MHz, $CDCl_3$); 7.96 (2H, s, 2 x bis-3,5-trifluoromethylphenyl-H), 7.88 (2H, d, *J* 8.4, 2 x phenyl-H), 7.73(1H, s, bis-3,5-trifluoromethylphenyl-H), 7.56 (2H, d, *J* 8.4, 2 x phenyl-H), 7.53 (1H, s, purine 8-H), 5.94 (1H, t, *J* 7.1, NCH_2CH=), 4.86 (2H, d, *J* 7.1, NCH_2CH=), 4.82 (1H, brs, NH), 4.00 (2H, s, NCH_2), 3.98 (3H, s, purine NCH_3), 3.74 (2H, s, NCH_2), 3.58 (3H, s, purine NCH_3); δ_C (75 MHz, DMSO-d_6); 154.7, 151.2, 148.7, 145.3, 144.2, 143.3, 142.9, 137.4, 130.4 (*J* 32.2), 130.3, 126.5, 127.2 (brs), 123.8 (*J* 273.6), 120.7 (*J* 4.6), 107.2, 52.5, 47.0, 39.5, 33.5, 29.8; υ_{max}/cm^{-1} (solid); 3320, 1703, 1668, 1551, 1458, 1384, 1331, 1282, 1237; *m/z* (ESI^+) 631.2 (100%, MH^+); (Found MH^+, 631.1559. $C_{26}H_{25}F_6N_6O_4{}^{32}S$ requires *MH*, 631.1557).

1-[(2*Z*)-4-(Adamantan-1-ylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (204a).

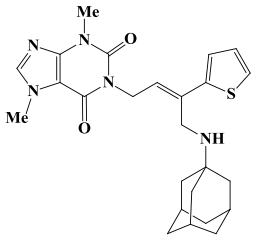


Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 1-aminoadamantane **180** (0.091 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 5 h. Flash column chromatography gradient eluting with EtOAc and then 10:1 v/v EtOAc/MeOH gave the product **204a** (0.18 g, 78%) as a colourless froth, mp 91-93 °C; δ_H (300 MHz, $CDCl_3$); 8.77 (1H, d, *J* 1.5, pyridyl-H), 8.45 (1H, dd, *J* 1.5 and 4.9, pyridyl-H), 7. 87 (1H, td, *J* 2.1 and 8.0, pyridyl-H), 7.55 (1H, s, purine-H), 7.21 (1H, ddd, *J* 0.5, 4.9 and 8.0, pyridinyl-H), 5.90 (1H, t, *J* 7.1, NCH_2CH=), 4.90 (2H, d, *J* 7.1, NCH_2CH=), 4.00 (3H, s, NMe), 3.82 (2H, s, =CCH_2N), 3.59 (3H, s, NMe), 2.10 (3H, br s, adamantyl-H), 1.78 (6H, d, *J* 2.3, adamantyl-H), 1.67 (6H, br s, adamantyl-H); δ_C (75 MHz, $CDCl_3$); 155.4, 151.7, 149.3, 148.7, 148.1, 142.0, 139.6, 137.5, 134.1, 126.1, 123.4, 108.0, 51.4, 42.9 (3 x C), 39.9, 39.6, 37.2 (3 x C), 34.0, 30.2, 30.0 (3 x C); υ_{max}/cm^{-1} (film); 2906, 2848, 1704, 1661, 1550, 1455, 1358, 1310, 1234; *m/z* (ESI^+) 461.3 (100%, MH^+); (Found MH^+, 461.2675. $C_{26}H_{33}N_6O_2$ requires *MH*, 461.2660).

NOE data for **204a**:

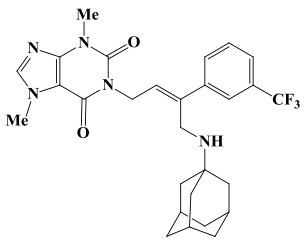
	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Pyridyl 2-H	Pyridyl 4-H
1-H		6.8	3.6	-	-
2-H	3.2		-	8.4 (δ 8.77)	6.1 (δ 7.87)
4-H	4.3	-		4.4 (δ 8.77)	3.6 (δ 7.87)

1-[(2*E*)-4-(Adamantan-1-ylamino)-3-(2-thienyl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (204b).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 2-iodothiophene (0.066 mL, 0.60 mmol), 1-aminoadamantane **180** (0.091 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 2 h. Flash column chromatography eluting with EtOAc gave the product **204b** (0.16 g, 69%) as a colourless froth, mp 155-157 °C; δ_H (300 MHz, $CDCl_3$); 7.50 (1H, s, purine-H), 7.17 (1H, dd, *J* 1.0 and 3.6, thienyl-H), 7.11 (1H, dd, *J* 1.0 and 5.1, thienyl-H), 6.93 (1H, dd, *J* 3.6 and 5.1, thienyl-H), 5.97 (1H, t, *J* 7.2, NCH_2CH=), 4.85 (2H, d, *J* 7.2, NCH_2CH=), 3.98 (3H, s, NMe), 3.81 (2H, s, =CCH_2N), 3.57 (3H, s, NMe), 2.11 (3H, br s, adamantyl-H), 1.80 (6H, d, *J* 2.6, adamantyl-H), 1.68 (6H, d, *J* 2.1, adamantyl-H); δ_C (75 MHz, $CDCl_3$); 154.9, 151.2, 148.7, 145.3, 141.5, 136.4, 127.2, 124.1, 123.8, 122.1, 107.5, 50.9, 42.5 (3 x C), 39.7, 39.2, 36.8 (3 x C), 33.5, 29.7, 29.4 (3 x C); υ_{max}/cm^{-1} (film); 2903, 2846, 1702, 1660. 1549, 1454, 1361, 1310, 1233; *m/z* (ESI^+) 466.2 (100%, MH^+); (Found MH^+, 466.2289. $C_{25}H_{32}N_5O_2{}^{32}S$ requires *MH*, 466.2271).

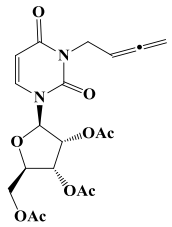
1-{(2*Z*)-4-(Adamantan-1-ylamino)-3-[3-(trifluoromethyl)phenyl]but-2-en-1-yl}-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (204c).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodobenzotrifluoride (0.09 mL, 0.60 mmol), 1-aminoadamantane **180** (0.09 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 2 h. Work up by flash column chromatography eluting with 30:1 v/v $CHCl_3$/MeOH gave the product **204c**

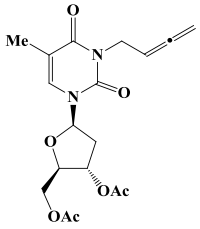
(0.24 g, 91%) as a colourless froth, mp 68-70 °C; δ_H (300 MHz, $CDCl_3$); 7.86 (1H, s, phenyl-H), 7.75 (1H, d, *J* 7.7, phenyl-H), 7.52 (1H, s, purine-H), 7.47 (1H, d, *J* 7.7, phenyl-H), 7.39 (1H, t, *J* 7.7, phenyl-H), 5.90 (1H, t, *J* 7.1, NCH_2CH=), 4.90 (2H, d, *J* 7.1, NCH_2CH=), 3.99 (3H, s, NMe), 3.82 (2H, s, =CCH_2N), 3.59 (3H, s, NMe), 2.11 (3H, br s, 3 × adamantyl-CH), 1.79 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.68 (6H, br d, *J* 1.6, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.9, 142.5, 141.6, 140.9, 130.4 (*J* 32.1), 129.6, 128.6, 125.5, 124.2 (*J* 272.0), 123.8 (*J* 4.4), 123.2 (*J* 4.4), 107.6, 50.9, 42.5, 39.6, 39.4, 36.8, 33.6, 29.8, 29.7; υ_{max}/cm^{-1} (film); 3310, 2907, 2849, 1702, 1661, 1604, 1550, 1487, 1455, 1415, 1334, 1258, 1234; *m/z* (ESI^+) 528.3 (100%, MH^+); (Found MH^+, 528.2575. $C_{28}H_{33}F_3N_5O_2$ requires *MH*, 528.2581).

2',3',5'-Tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine (207a).



Prepared by general procedure A from 2',3',5'-tri-*O*-acetyl-3-prop-2-yn-1-yluridine **206a**[117] (1.50 g, 3.67 mmol), dicyclohexylamine (1.32 mL, 6.61 mmol), paraformaldehyde (0.28 g, 9.18 mmol) and CuI (0.35 g, 1.86 mmol) in dioxane (15 mL). Flash column chromatography eluting with 2:1 v/v EtOAc/*n*-hexane gave **207a** as a colourless gum (1.24 g, 80%), $[\alpha]_D^{20}$ + 30.6 (*c*, 4.2 mg/1 mL CH_2Cl_2); (Found: C, 53.85; H, 5.00; N, 6.45; $C_{19}H_{22}N_2O_9$ requires C, 54.03; H, 5.25; N, 6.63%); δ_H (500 MHz, $CDCl_3$); 7.37 (1H, d, *J* 8.1, pyrimidinyl 6-H), 6.01 (1H, d, *J* 4.3, ribosyl 1-H), 5.82 (1H, d, *J* 8.1, pyrimidinyl 5-H), 5.38 (1H, dd, *J* 5.9 and 4.3, ribosyl 2-H), 5.35-5.31 (1H, m, ribosyl 3-H), 5.29-5.23 (1H, m, CH_2CH=), 4.83-4.80 (2H, m, NCH_2CH=), 4.55-4.51 (2H, m, =CH_2), 4.36 (3H, br s, ribosyl 4-H and 5-CH_2), 2.15 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 2.11 (3H, s, OCOMe); δ_c (75 MHz, $CDCl_3$); 209.2, 170.6, 170.5, 169.9, 162.1, 150.8, 137.8, 103.1, 89.2, 86.0, 80.0, 77.6, 73.3, 71.3, 63.3, 39.6, 21.4, 21.1, 20.8 ; υ_{max}/cm^{-1} (film); 2107, 1960, 1746, 1666, 1457, 1423, 1388, 1229; *m/z* (ESI^+) 445.1 (100%, MNa^+); (Found MNa^+, 445.1220. $C_{19}H_{22}NaN_2O_9$ requires *MNa*, 445.1218).

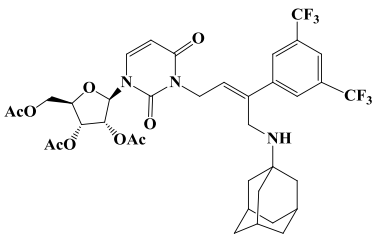
3',5'-Di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine (207b).



Prepared by general procedure A from 3',5'-di-*O*-acetyl-3-prop-2-yn-1-ylthymidine **206b**[117] (1.82 g, 5.0 mmol), dicyclohexylamine (1.80 mL, 9.0 mmol), paraformaldehyde (0.38 g, 12.5 mmol) and CuI (0.48 g, 2.5 mmol) in dioxane (20 mL). Flash column chromatography eluting

with 1:1 v/v EtOAc/*n*-hexane gave **207b** as a colourless gum (1.51 g, 75%), $[\alpha]_D^{20}$ + 17.0 (*c*, 10 mg/1 mL CH_2Cl_2); (Found: C, 57.05; H, 5.85; N, 7.40; $C_{18}H_{22}N_2O_7$ requires C, 57.14; H, 5.86; N, 7.40%); δ_H (500 MHz, $CDCl_3$); 7.27 (1H, br s, pyrimidinyl 6-H), 6.35 (1H, dd, *J* 8.6 and 5.6, deoxyribosyl 1-H), 5.27 (1H, tt, *J* 12.8 1nd 6.4, CH_2CH=), 5.23-5.21 (1H, m, deoxyribosyl 3-H), 4.80 (2H, dt, *J* 6.4 and 3.0, NCH_2CH=), 4.56 (2H, dt, *J* 6.4 and 3.0, =CH_2), 4.36 (2H, d, *J* 3.9, deoxyribosyl 5-CH_2), 4.25 (1H, dt, *J* 5.9 and 3.9, deoxyribosyl 4-H), 2.49 (1H, ddd, *J* 14.1, 5.6 and 2.0, deoxyribosyl 2-H_A), 2.18-2.15 (1H, m, deoxyribosyl 2-H_B), 2.13 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 1.96 (3H, s, pyrimidinyl 5-Me); δ_c (75 MHz, $CDCl_3$); 209.5, 170.8, 170.5, 163.1, 150.9, 132.9, 111.0, 86.1, 85.8, 82.4, 77.3, 74.5, 64.2, 39.9, 38.0, 21.4, 21.2, 13.8; υ_{max}/cm^{-1} (film); 2954, 1957, 1744, 1703, 1671, 1647, 1466, 1367, 1232; *m/z* (ESI^+) 401.1 (100%, MNa^+); (Found MNa^+, 401.1334. $C_{18}H_{22}NaN_2O_7$ requires *MNa*, 401.1319).

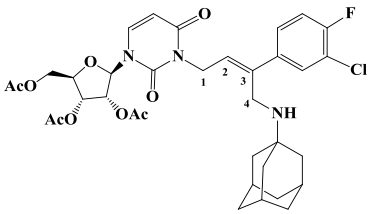
2',3',5'-Tri-*O*-acetyl-3-{(2*Z*)-4-(adamantan-1-ylamino)-3-[3,5-bis(trifluoromethyl)phenyl]but-2-en-1-yl}uridine (208a).



Prepared by general procedure B from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.33 g, 0.78 mmol), 1-iodo-3,5-bis(trifluoromethyl)benzene (0.152 mL, 0.86 mmol), 1-aminoadamantane **180** (0.13 g, 0.86 mmol), $Pd_2(dba)_3$ (0.0179 g, 2.5 mol%), TFP (0.0181 g, 10 mol%) and K_2CO_3 (0.324 g, 2.34 mmol) in MeCN (5 mL) at 80 ºC for 5 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **208a** (0.47 g, 77%) as a pale yellow gum; $[\alpha]_D^{20}$ + 19.5 (*c*, 16 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 8.00 (2H, s, 2 × phenyl-H), 7.61 (1H, s, phenyl-H), 7.33 (1H, d, *J* 8.2, pyrimidinyl 6-H), 5.91 (1H, d, *J* 4.9, ribosyl 1-H), 5.78 (1H, t, *J* 7.1, NCH_2CH=), 5.74 (1H, d, *J* 8.2, pyrimidinyl 5-H), 5.28 (1H, dd, *J* 6.0 and 4.9, ribosyl 2-H), 5.23-5.19 (1H, m, ribosyl 3-H), 4.69 (2H, d, *J* 7.1, NCH_2CH=), 4.24 (3H, s, ribosyl 4-H and 5-CH_2), 3.62 (2H, s, =CCH_2N), 2.00 (9H, s, 2 × OCOMe and 3 × adamantyl-CH), 1.96 (3H, s, OCOMe), 1.64 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.56 (6H, br s, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.1 (CO), 169.5 (2 × CO), 161.9, 150.7, 144.0, 140.3, 137.5, 131.2 (q, *J* 33.2), 126.6 (brd, *J* 3.3), 125.9, 123.5 (q, *J* 237.1), 120.7 (q, *J* 3.9), 102.7, 88.7, 79.7, 73.0, 69.9, 62.8, 50.8,

42.5, 39.5, 39.4, 36.7, 29.6, 20.7, 20.4, 20.3; υ_{max}/cm^{-1} (film); 3313, 3023, 2908, 2850, 1755, 1713, 1668, 1455, 1383, 1310, 1280, 1227; *m/z* (ESI^+) 786.3 (100%, MH^+); (Found MH^+, 786.2941. $C_{37}H_{41}F_6N_3O_9$ requires *MH*, 786.2820).

2',3',5'-Tri-*O*-acetyl-3-[(2*Z*)-4-(adamantan-1-ylamino)-3-(3-chloro-4-fluorophenyl)but-2-en-1-yl]uridine (208b).

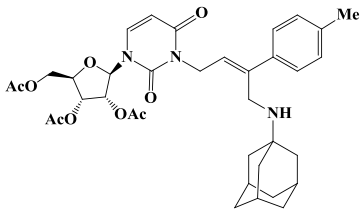


Prepared by general procedure B from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.16 g, 0.38 mmol), 3-chloro-4-fluoroiodobenzene (0.054 mL, 0.42 mmol), 1-aminoadamantane **180** (0.063 g, 0.42 mmol), $Pd_2(dba)_3$ (0.0087 g, 2.5 mol%), TFP (0.0088 g, 10 mol%) and K_2CO_3 (0.157 g, 1.14 mmol) in MeCN (3 mL) at 80 ºC for 4 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **208b** (0.23 g, 86%) as a pale yellow gum; $[\alpha]_D^{20}$ + 19.7 (*c*, 14 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.62 (1H, dd, *J* 7.1 and 2.2, phenyl-H), 7.44-7.39 (1H, m, phenyl-H), 7.40 (1H, d, *J* 8.2, pyrimidinyl 6-H), 7.05 (1H, t, *J* 8.5, phenyl-H), 6.00 (1H, d, *J* 4.4, ribosyl 1-H), 5.84 (1H, d, *J* 8.2, pyrimidinyl 5-H), 5.74 (1H, t, *J* 7.1, NCH_2CH=), 5.39 (1H, dd, *J* 5.5 and 4.4, ribosyl 2-H), 5.34-5.33 (1H, m, ribosyl 3-H), 4.75 (2H, d, *J* 7.1, NCH_2CH=), 4.35 (3H, s, ribosyl 4-H and 5-CH_2), 3.70 (2H, s, =CCH_2N), 2.13 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 2.10 (6H, s, OCOMe and 3 × adamantyl-CH), 1.74 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.67 (6H, br s, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.1 (CO), 169.6 (2 × CO), 162.0, 157.5 (*J* 248.8), 150.7, 140.8, 139 (*J* 4.4), 137.4, 128.6, 126.1 (*J* 6.6), 123.9, 120.5 (*J* 17.7), 116.1 (*J* 21.0), 102.8, 88.8, 79.7, 73.0, 69.9, 62.8, 50.8, 42.5, 39.54, 39.51, 36.8, 29.6, 20.8, 20.5, 20.4; υ_{max}/cm^{-1} (film); 3312, 2906, 2849, 1751, 1711, 1668, 1497, 1455, 1386, 1310, 1228; *m/z* (ESI^+) 702.3 (100%, MH^+); (Found MH^+, 702.2606. $C_{35}H_{42}{}^{35}ClFN_3O_9$ requires *MH*, 702.2588).

NOE data ($CDCl_3$) for **208b**:

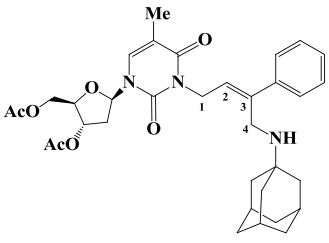
	% Enhancement				
Irradiated proton	1-H	2-H	4-H	phenyl-H	adamantyl-CH_2
1-H		6.8	4.0	-	-
2-H	3.7		-	8.3 (δ 7.62) 6.6 (δ 7.41)	-
4-H	4.1	-		4.3 (δ 7.62) 3.3 (δ 7.41)	5.8 (δ 1.74)

2',3',5'-Tri-*O*-acetyl-3-[(2*Z*)-4-(adamantan-1-ylamino)-3-(4-methylphenyl)but-2-en-1-yl]uridine (208c).



Prepared by general procedure B from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.213 g, 0.50 mmol), 4-iodotoluene (0.132 g, 0.60 mmol), 1-aminoadamantane **180** (0.092 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 3 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **208c** (0.29 g, 87%) as a pale yellow gum; $[\alpha]_D^{20}$ + 19.0 (*c*, 11 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.38 (2H, d, *J* 8.2, 2 × phenyl-H), 7.37 (1H, d, *J* 8.2, pyrimidinyl 6-H), 7.10 (2H, d, *J* 7.7, 2 × phenyl-H), 6.02 (1H, d, *J* 4.9, ribosyl 1-H), 5.82 (1H, d, *J* 8.2, pyrimidinyl 5-H), 5.76 (1H, t, *J* 7.1, NCH_2CH=), 5.37 (1H, dd, *J* 6.0 and 4.9, ribosyl 2-H), 5.35-5.31 (1H, m, ribosyl 3-H), 4.77 (2H, d, *J* 7.1, NCH_2CH=), 4.34 (3H, s, ribosyl 4-H and 5-CH_2), 3.79 (2H, s, =CCH_2N), 2.32 (3H, s, phenyl-Me), 2.13 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 2.08 (6H, s, OCOMe and 3 × adamantyl-CH), 1.73 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.66 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.1 (CO), 169.6 (2 × CO), 162.0, 150.7, 142.7, 138.4, 137.3, 137.1, 129.0, 126.2, 122.3, 102.9, 88.5, 79.6, 72.9, 69.9, 62.9, 50.8, 42.5, 39.8, 39.2, 36.8, 29.7, 21.1, 20.8, 20.5, 20.4; υ_{max}/cm^{-1} (film); 3313, 3022, 2906, 2849, 1748, 1712, 1668, 1511, 1455, 1371, 1310, 1228; *m/z* (ESI^+) 664.3 (100%, MH^+); (Found MH^+, 664.3252. $C_{36}H_{46}N_3O_9$ requires *MH,* 664.3229).

3',5'-Di-*O*-acetyl-3-[(2*Z*)-4-(adamantan-1-ylamino)-3-phenylbut-2-en-1-yl]thymidine (208d).



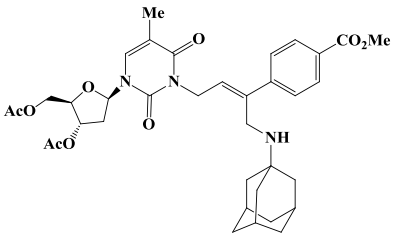
Prepared by general procedure B from 3',5'-di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine **207b** (0.189 g, 0.50 mmol), iodobenzene (0.062 mL, 0.60 mmol), 1-aminoadamantane **180** (0.083 g, 0.55 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 3 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **208d** (0.30 g, 99%) as a pale yellow gum; $[\alpha]_D^{20}$ + 5.2 (*c*, 12 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.50 (2H, dd, *J* 8.0 and 1.4, 2 × phenyl-H), 7.31-7.22 (3H, m, 3 × phenyl-H

and pyrimidinyl 6-H), 6.37 (1H, dd, *J* 8.5 and 5.8, deoxyribosyl 1-H), 5.82 (1H, t, *J* 7.1, NCH_2CH=), 5.21 (1H, dt, *J* 6.6 and 2.2, deoxyribosyl 3-H), 4.82 (2H, d, *J* 7.1, NCH_2CH=), 4.38 (1H, dd, *J* 12.1 and 3.8, deoxyribosyl 5-H_A), 4.32 (1H, dd, *J* 12.1 and 3.8, deoxyribosyl 5-H_B), 4.24 (1H, dt, *J* 6.6 and 3.8, deoxyribosyl 4-H), 3.83 (2H, s, $=CCH_2N$), 2.48 (1H, ddd, *J* 13.7, 5.5 and 1.6, deoxyribosyl 2-H_A), 2.20-2.08 (1H, ddd, *J* 13.7 ,5.5 and 1.6, deoxyribosyl 5-H_B), 2.12 (3H, s, OCOMe), 2.10 (3H, s, OCOMe), 2.09 (3H, s, 3 × adamantyl-CH), 1.95 (3H, s, pyrimidinyl 5-Me), 1.74 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.66 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.4, 170.2, 162.9, 150.7, 142.6, 141.4, 132.6, 128.3, 127.4, 126.3, 123.5, 110.8, 85.4, 82.0, 74.1, 63.9, 50.9, 42.6, 39.9, 39.3, 37.6, 36.8, 29.7, 20.9, 20.8, 13.5; υ_{max}/cm^{-1} (film); 3312, 3020, 2906, 2848, 1747, 1704, 1668, 1644, 1464, 1367, 1310, 1233; *m/z* (ESI^+) 606.3 (100%, MH^+); (Found MH^+, 606.3194. $C_{34}H_{44}N_3O_7$ requires *MH*, 606.3174).

NOE data ($CDCl_3$) for **208d**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	phenyl-H (δ 7.50)	adamantyl-CH_2 (δ 1.74)
1-H		5.8	3.6	-	-
2-H	4.3		-	11.9	-
4-H	4.3	-		6.8	7.0

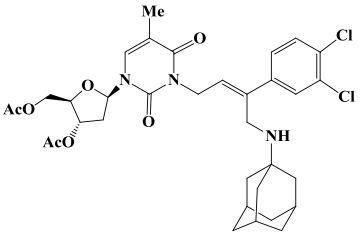
3',5'-Di-*O*-acetyl-3-{(2*Z*)-4-(adamantan-1-ylamino)-3-[4-(methoxycarbonyl)phenyl]but-2-en-1-yl}thymidine (208e).



Prepared by general procedure B from 3',5'-di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine **207b** (0.189 g, 0.50 mmol), methyl 4-iodobenzoate (0.157 mL, 0.60 mmol), 1-aminoadamantane **180** (0.091 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 4 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **208e** (0.31 g, 93%) as a pale yellow gum; $[\alpha]_D^{20}$ + 7.6 (*c*, 13 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.96 (2H, d, *J* 8.5, 2 × phenyl-H), 7.59 (2H, d, *J* 8.5, 2 × phenyl-H), 7.29 (1H, s, pyrimidinyl 6-H), 6.38 (1H, dd, *J* 5.8 and 8.5, deoxyribosyl 1-H), 5.90 (1H, t, *J* 7.1, NCH_2CH=), 5.22 (1H, dt, *J* 6.6 and 2.2, deoxyribosyl 3-H), 4.83 (2H, d, *J* 7.1, NCH_2CH=), 4.39 (1H, dd, *J* 4.4 and 12.1,

deoxyribosyl 5-H_A), 4.33 (1H, dd, *J* 3.3 and 12.1, deoxyribosyl 5-H_B), 4.25 (1H, dt, *J* 3.6 and 6.3, deoxyribosyl 4-H), 3.89 (3H, s, CO_2Me), 3.81 (2H, s, =C*CH_2*N), 2.49 (1H, ddd, *J* 1.6, 5.5 and 13.7, deoxyribosyl 2-H_A), 2.20 (1H, ddd, *J* 1.6, 6.6 and 13.7, deoxyribosyl 2-H_B), 2.12 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 2.10 (3H, s, 3 × adamantyl-CH), 1.96 (3H, s, pyrimidinyl 5-Me), 1.75 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.67 (6H, br s, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.3, 170.1, 166.9, 162.9, 150.6, 146.1, 141.8, 132.8, 129.6, 128.8, 126.3, 125.3, 110.8, 85.4, 82.0, 74.1, 63.8, 52.0, 50.8, 42.5, 39.8, 39.2, 37.5, 36.8, 29.6, 20.9, 20.8, 13.4; υ_{max}/cm^{-1} (film); 3311, 3018, 2906, 2848, 1746, 1704, 1669, 1645, 1606, 1465, 1366, 1278, 1233; *m/z* (ESI^+) 664.3 (100%, MH^+); (Found MH^+, 664.3239. $C_{36}H_{46}N_3O_9$ requires *MH*, 664.3229).

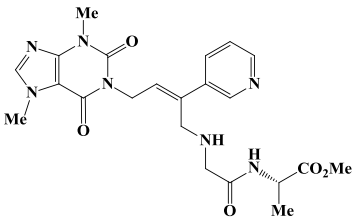
3',5'-Di-*O*-acetyl-3-[(2*Z*)-4-(adamantan-1-ylamino)-3-(3,4-dichlorophenyl)but-2-en-1-yl]thymidine (208f).



Prepared by general procedure B from 3',5'-di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine **207b** (0.189 g, 0.50 mmol), 1,2-dichloro-4-iodobenzene (0.164 g, 0.60 mmol), 1-aminoadamantane **180** (0.091 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 2 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **208f** (0.29 g, 87%) as a pale yellow gum; $[\alpha]_D^{20}$ + 7.7 (*c*, 11 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.56 (1H, d, *J* 1.6, phenyl-H), 7.28 (1H, dd, *J* 8.2 and 1.6, 2 × phenyl-H), 7.19 (1H, d, *J* 8.2, phenyl-H), 7.18 (1H, s, pyrimidinyl 6-H), 6.27 (1H, dd, *J* 8.2 and 6.0, deoxyribosyl 1-H), 5.70 (1H, t, *J* 7.1, NCH_2CH=), 5.12 (1H, dt, *J* 6.6 and 2.2, deoxyribosyl 3-H), 4.68 (2H, d, *J* 7.1, N*CH_2*CH=), 4.28 (1H, dd, *J* 12.3 and 3.6, deoxyribosyl 5-H_A), 4.23 (1H, dd, *J* 12.3 and 3.6, deoxyribosyl 5-H_B), 4.15 (1H, dt, *J* 6.6 and 3.6, deoxyribosyl 4-H), 3.62 (2H, s, =C*CH_2*N), 2.38 (1H, ddd, *J* 14.3, 6.6 and 2.2, deoxyribosyl 2-H_A), 2.09 (1H, ddd, *J* 14.3, 8.2 and 1.6, deoxyribosyl 2-H_B), 2.02 (3H, s, OCOMe), 2.00 (6H, s, OCOMe and 3 × adamantyl-CH), 1.86 (3H, s, pyrimidinyl 5-Me), 1.64 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.56 (6H, br s, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.3, 170.1, 162.9, 150.6, 141.8, 140.5, 132.8, 132.2, 130.9, 130.0, 128.3, 125,7, 124.8, 110.8, 85.4, 82.0, 74.1, 63.8, 50.9, 42.5, 39.7, 39.3, 37.5, 36.8, 29.6, 20.9, 20.8, 13.4; υ_{max}/cm^{-1} (film); 3310, 3018,

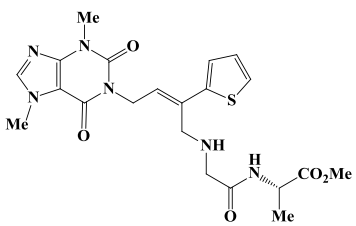
2906, 2848, 1746, 1702, 1670, 1644, 1550, 1466, 1366, 1336, 1310, 1233; *m/z* (ESI^+) 674.2 (100%, MH^+); (Found MH^+, 674.2410. $C_{34}H_{42}{}^{35}Cl_2N_3O_7$ requires *MH*, 674.2394).

Methyl *N*-[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(pyridin-3-yl)but-2-en-1-yl]glycyl-L-alaninate (215a).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), methyl (2*S*)-2-[(aminoacetyl)amino]propanoate hydrochloride **209** (0.147 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 13 h. Flash column chromatography eluting with 5:1 v/v EtOAc/MeOH gave the product **215a** (0.26 g, 85%) as a pale yellow froth; $[\alpha]_D{}^{24}$ + 6.8 (*c*, 11 mg/1 mL $CHCl_3$); mp 57-59 °C; δ_H (300 MHz, $CDCl_3$); 8.68 (1H, dd, *J* 0.8 and 2.3, pyridyl-H), 8.50 (1H, dd, *J* 1.5 and 4.8, pyridyl-H), 7.78 (1H, ddd, *J* 1.7, 2.3 and 7.9, pyridyl-H), 7.63 (1H, d, *J* 7.9, CO*NH*), 7.56 (1H, s, purine-H), 7.25 (1H, ddd, *J* 0.8, 4.8 and 7.9, pyridinyl-H), 5.89 (1H, t, *J* 7.1, NCH_2CH=), 4.93 (1H, dd, *J* 7.1 and 14.5, H_A, NCH_2CH=), 4.86 (1H, dd, *J* 7.1 and 14.5, H_B, NCH_2CH=), 4.59 (1H, m, *CH*CO_2Me), 4.00 (3H, s, NMe), 3.93 (1H, d, *J* 12.7, H_A, =CCH_2N), 3.81 (1H, d, *J* 12.7, H_B, =CCH_2N), 3.72 (3H, s, CO_2Me), 3.6 (3H, s, NMe), 3.37 (2H, s, NHCH_2CO), 2.23 (1H, s, NH), 1.34 (3H, d, *J* 7.4, CH*Me*); δ_C (75 MHz, $CDCl_3$); 173.3, 171.4, 155, 151.4, 149, 148.7, 147.9, 141.8, 138.3, 136.6, 133.9, 127.1, 123.2, 107.6, 52.3, 52.2, 47.9, 47.4, 39.3, 33.7, 29.8, 18.1; υ_{max}/cm^{-1} (film); 3331, 2951, 1742, 1703, 1658, 1550, 1455, 1355, 1233; *m/z* (ESI^+) 470.2 (100%, MH^+); (Found MH^+, 470.2134. $C_{22}H_{28}N_7O_5$ requires *MH*, 470.2146).

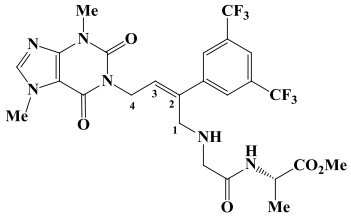
Methyl (2*S*)-2-[({[(2*E*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(2-thienyl)but-2-en-1-yl]amino}acetyl)amino]propanoate (215b).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 2-iodothiophene (0.066 mL, 0.60 mmol), methyl (2*S*)-2-[(aminoacetyl)amino]propanoate hydrochloride **209** (0.147 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%),

TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 6 h. Work up followed by flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **215b** (0.19 g, 76%) as a colourless gum; $[\alpha]_D^{24}$ + 3.3 (*c*, 13 mg/1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.87 (1H, d, *J* 8.2, CO*NH*), 7.55 (1H, s, purine-H), 7.16 (2H, br s, 2 x thienyl-H), 7.95 (1H, m, thienyl-H), 6.01 (1H, t, *J* 7.4, NCH_2CH=), 4.89 (1H, dd, *J* 7.4 and 14.3, H_A, NCH_2CH=), 4.82 (1H, dd, *J* 7.4 and 14.3, H_B, NCH_2CH=), 4.64 (1H, m, *CH*CO_2Me), 3.99 (3H, s, NMe), 3.90 (1H, d, *J* 12.5, H_A, =CCH_2N), 3.79 (1H, d, *J* 12.5, H_B, =CCH_2N), 3.72 (3H, s, CO_2Me), 3.43 (3H, s, NMe), 3.37 (2H, s, $NHCH_2CO$), 2.31 (1H, s, NH), 1.40 (3H, d, *J* 7.2, CH*Me*); δ_C (75 MHz, $CDCl_3$); 173.7, 172.0, 155.4, 151.7, 149.3, 145.0, 142.2, 135.1, 127.8, 125.0, 124.3, 124.0, 108.0, 52.7, 52.6, 48.4, 47.9, 39.6, 34.0, 30.2, 18.4; υ_{max}/cm^{-1} (film); 3332, 3111, 3005, 2951, 1742, 1704, 1659, 1604, 1549, 1454, 1365, 1316, 1286, 1234; *m/z* (ESI^+) 475.2 (100%, MH^+); (Found MH^+, 475.1745. $C_{21}H_{27}N_6O_5\,^{32}S$ requires *MH*, 475.1758).

Methyl (2*S*)-2-[({[(2*Z*)-2-[3,5-bis(trifluoromethyl)phenyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-en-1yl]amino}acetyl)amino] propanoate (215c).



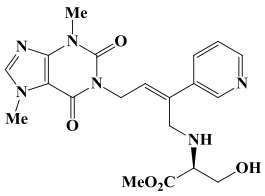
Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.10 mL, 0.60 mmol), methyl (2*S*)-2-[(aminoacetyl)amino]propanoate hydrochloride **209** (0.147 g, 0.75 mmol), $Pd_2(dba)_3$ (0.0115 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 5 h. Work up by flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **215c** (0.23 g, 76%) as a pale yellow froth, $[\alpha]_D^{24}$ + 11.0 (*c*, 11 mg/1 mL $CHCl_3$); mp 138-140 °C; δ_H (300 MHz, $CDCl_3$); 7.93 (2H, s, 2 x phenyl-H), 7.78 (1H, s, phenyl-H), 7.60 (1H, s, purine-H), 7.55 (1H, d, *J* 7.9, CO*NH*), 5.94 (1H, t, *J* 7.2, NCH_2CH=), 4.97 (1H, dd, *J* 7.2 and 14.6, H_A, NCH_2CH=), 4.90 (1H, dd, *J* 7.2 and 14.6, H_B, NCH_2CH=), 4.60 (1H, m, *CH*CO_2Me), 4.02 (3H, s, NMe), 4.00 (1H, d, *J* 12.5, H_A, =CCH_2N), 3.83 (1H, d, *J* 12.5, H_B, =CCH_2N), 3.71 (3H, s, CO_2Me), 3.69 (3H, s, NMe), 3.33 (2H, s, $NHCH_2CO$) 2.37 (1H, s, NH), 1.33 (3H, d, *J* 7.2, CH*Me*); δ_C (75 MHz, $CDCl_3$); 173.5, 171.7, 155.3, 151.8, 149.4, 143.9, 142.6,

139.3, 131.9 (2 x C, *J* 33.0), 129.2, 127.1 (2 x C, *J* 4.6), 123.7 (2 x C, *J* 272.8), 121.5 (*J* 4.6), 108.0, 52.7, 52.6, 48.3, 47.8, 39.7, 34.0, 30.2, 18.2; υ_{max}/cm^{-1} (film); 3333, 2954, 1744, 1706, 1661, 1550, 1455, 1382, 1279; *m/z* (ESI^+) 605.2 (100%, MH^+); (Found MH^+, 605.1946. $C_{25}H_{27}F_6N_6O_5$ requires *MH*, 605.1942).

NOE data ($CDCl_3$) for **215c**:

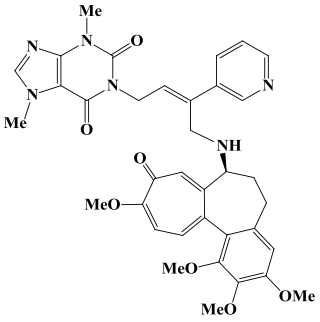
	% Enhancement				
Irradiated proton	4-H	3-H	1-H_A	1-H_B	phenyl-H
4-H		5.7	4.4	1.6	-
3-H	3.2		-		11.6 (δ 7.93)
1-H_A	2.9	-		13.2	-
1-H_B	4.7		5.9		6.2 (δ 7.93)

Methyl *N*-[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(pyridin-3-yl)but-2-en-1-yl]serinate (216).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), (*S*)-serine methyl ester hydrochloride **210** (0.093 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.272 g, 2.00 mmol) in MeCN (4 mL) at 80 ºC for 8 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **216** (0.15 g, 70%) as a colourless amorphous solid; $[\alpha]_D^{20}$ + 7.1 (*c*, 15 mg/1 mL $CHCl_3$); mp 119-121 °C; δ_H (300 MHz, pyridine-d_5); 9.14 (1H, d, *J* 2.2, pyridinyl-H), 8.57 (1H, dd, *J* 1.6 and 4.9, pyridinyl-H), 8.00 (1H, dt, *J*, 8.2 and 1.6, pyridinyl-H), 7.83 (1H, s, purine-H), 7.14 (1H, dd, *J* 4.9 and 8.2, pyridinyl-H), 6.67 (1H, br s, OH), 6.27 (1H, t, *J* 6.7, NCH_2CH=), 5.18 (1H, dd, *J* 6.7 and 14.3, H_A, NCH_2CH=), 5.13 (1H, d, *J* 6.7 and 14.3, H_B, NCH_2CH=), 4.27 (1H, d, *J* 11.8, H_A, =CCH_2N), 4.20 (2H, br s, $NCHCH_2OH$), 4.07 (1H, d, *J* 11.8, H_B, =CCH_2N), 3.83 (1H, br s, $NCHCH_2OH$), 3.82 (3H, s, purine 7-Me), 3.72 (3H, s, CO_2Me), 3.54 (3H, s, purine 3-Me), 2.91 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$); 173.3, 155.0, 151.4, 148.9, 148.7, 147.6, 141.8, 138.0, 136.5, 133.7, 127.1, 123.1, 107.6, 62.7, 62.66, 52.1, 46.2, 39.4, 33.7, 29.8; υ_{max}/cm^{-1} (film); 3316, 2952, 1732, 1704, 1660, 1604, 1550, 1456, 1415, 1356, 1315, 1286, 1234; *m/z* (ESI^+) 429.2 (100 %, MH^+); (Found MH^+, 429.1891. $C_{20}H_{25}N_6O_5$ requires *MH*, 429.1881).

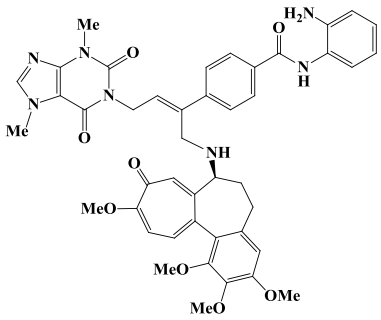
3,7-Dimethyl-1-[(2*Z*)-3-(pyridin-3-yl)-4-{[(7*S*)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]amino}but-2-en-1-yl]-3,7-dihydro-1*H*-purine-2,6-dione (217a).



Prepared by general procedure B from *N*-allenylpurine **195** (0.075 g, 0.32 mmol), 3-iodopyridine (0.08 g, 0.39 mmol), *N*-deacetylcolchicine **211**[122] (0.127 g, 0.36 mmol), $Pd_2(dba)_3$ (0.0074 g, 2.5 mol%), TFP (0.0075 g, 10 mol%) and K_2CO_3 (0.134 g, 0.96 mmol) in MeCN (3 mL) at 80 ºC for 7 h. Flash column chromatography eluting with 5:1 v/v EtOAc/MeOH gave the product **217a** (0.20 g, 94%) as a pale yellow froth; $[\alpha]_D^{20}$ -118.6 (*c*, 13 mg/1 mL $CHCl_3$); mp 106-108 °C; δ_H (300 MHz, $CDCl_3$); 8.59 (1H, d, *J* 2.2, pyridinyl-H), 8.45 (1H, dd, *J* 1.6 and 4.48, pyridinyl-H), 7.91 (1H, s, colchicine-H), 7.81 (1H, dt, *J* 7.7 and 1.6, pyridinyl-H), 7.53 (1H, s, purine 8-H), 7.27 (1H, dd, *J* 3.8 and 7.7, pyridinyl-H), 7.24 (1H, d, *J* 10.7, colchicine-H), 6.80 (1H, d, *J* 10.7, colchicine-H), 6.55 (1H, s, colchicine-H), 5.81 (1H, t, *J* 7.1, NCH_2CH=), 4.82 (1H, dd, *J* 7.1 and 13.2, NCH_ACH=),4.77 (1H, dd, *J* 7.1 and 13.2, NCH_BCH=), 3.99 (3H, s, Me), 3.97 (3H, s, Me), 3.95 (3H, s, Me), 3.93 (3H, s, Me), 3.68 (3H, s, Me), 3.64 (1H, d, *J* 12.6, =CCH_AN), 3.56 (3H, s, Me), 3.51 (1H, d, *J* 12.6, =CCH_BN), 3.50-3.41 (1H, m, colchicines-*CH*NH), 2.52-2.21 (3H, m, 3 × colchicine-H), 2.14 (1H, br s, NH), 1.77-1.67 (1H, m, colchicine-H); δ_C (75 MHz, $CDCl_3$); 179.6, 163.9, 154.9, 153.2, 151.3, 151.1, 150.7, 148.9, 148.5, 147.6, 141.6, 141.2, 138.5, 137.0, 136.9, 135.2, 134.5, 133.8, 132.5, 126.5, 125.6, 123.3, 111.6, 107.6, 107.2, 61.3, 61.26, 61.0, 56.2, 56.0, 46.7, 39.5, 38.4, 33.6, 30.4, 29.7; υ_{max}/cm^{-1} (film); 3318, 2939, 1702, 1659, 1588, 1553, 1487, 1457, 1396, 1345, 1318, 1248; *m/z* (ESI^+) 667.3 (100%, MH^+); (Found MH^+, 667.2883. $C_{36}H_{39}N_6O_7$ requires *MH*, 667.2875).

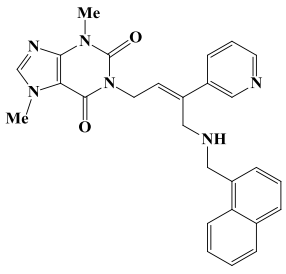
***N*-(2-Aminophenyl)-4-[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-1-{[(7*S*)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]amino}but-2-en-2-yl]benzamide (217b).**

Prepared by general procedure B from *N*-allenylpurine **195** (0.103 g, 0.44 mmol), *N*-(2-aminophenyl)-4-iodobenzamide (0.18 g, 0.53 mmol), *N*-deacetylcolchicine **211** (0.158 g, 0.44 mmol), $Pd_2(dba)_3$ (0.01 g, 2.5 mol%), TFP (0.011 g, 10 mol%) and K_2CO_3 (0.183 g, 1.33 mmol) in MeCN (3 mL) at 80 ºC for 5 h. Flash column



chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **217b** (0.29 g, 85%) as a pale yellow froth; $[\alpha]_D^{20}$ -73.2 (*c*, 14 mg/1 mL $CHCl_3$); mp 151-153 °C; δ_H (300 MHz, $CDCl_3$); 8.68 (1H, br s, CONH), 7.76 (2H, d, *J* 8.2, 2 × phenyl-H), 7.68 (1H, s, colchicine-H), 7.53 (1H, s, purine 8-H), 7.50 (1H, d, *J* 8.2, phenyl-H), 7.36 (2H, d, *J* 8.2, 2 × phenyl-H),7.24 (1H, d, *J* 10.4, colchicine-H), 7.02 (1H, dt, *J* 1.1 and 8.2, phenyl-H), 9.79 (1H, d, *J* 8.2, phenyl-H), 6.78 (1H, d, *J* 10.4, colchicine-H), 6.77 (1H, dt, *J* 1,1 and 8.2, phenyl-H), 6.54 (1H, s, colchicine-H), 5.80 (1H, t, *J* 7.7, NCH_2CH=), 4.40 (1H, dd, *J* 7.7 and 14.2, NCH_ACH=), 4.73 (1H, dd, *J* 7.7 and 14.2, NCH_BCH=), 3.95 (6H, s, 2 × Me), 3.92 (3H, s, Me), 3.91 (3H, s, Me), 3.76 (1H, d, *J* 12.1, =CCH_AN), 3.68 (3H, s, Me), 3.54 (3H, s, Me), 3.49-3.41 (1H, m, colchicines-*CH*NH), 3.44 (1H, d, *J* 12.6, =CCH_BN), 2.48-2.17 (3H, m, 3 × colchicine-H), 1.69-1.59 (1H, m, colchicine-H); δ_C (75 MHz, $CDCl_3$); 179.4, 166.6, 163.8, 154.9, 153.2, 151.8, 151.3, 150.7, 148.9, 144.5, 141.8, 141.5, 141.1, 140.6, 137.2, 135.2, 134.5, 133.8, 132.9, 127.5, 126.8, 126.5, 125.5, 125.4, 125.0, 124.7, 118.9, 117.6, 111.8, 107.6, 107.3, 61.3, 61.0, 60.95, 56.2, 56.0, 47.0, 39.4, 38.4, 33.6, 30.4, 29.7; υ_{max}/cm^{-1} (film); 3329, 2940, 1703, 1660, 1589, 1552, 1487, 1456, 1396, 1345, 1317, 1249; *m/z* (ESI^+) 800.3 (100%, MH^+); (Found MH^+, 800.3426. $C_{44}H_{46}N_7O_8$ requires *MH*, 800.3402).

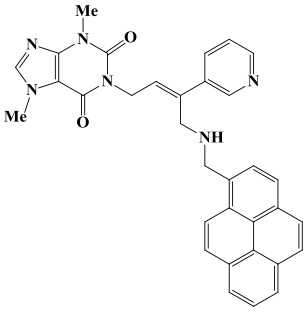
3,7-Dimethyl-1-[(2*Z*)-4-[(1-naphthylmethyl)amino]-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dihydro-1*H*-purine-2,6-dione (218).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 1-naphthalenemethylamine **212** (0.088 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 3 h. The reaction was cooled, evaporated under vacuum, and the residue dissolved in $CHCl_3$ (30 mL). The organic layer washed with water (10 mL), separated, dried over anhydrous $MgSO_4$ and evaporated under vacuum to afford viscous oil. The crude product was dissolved in MeCN (5 mL) and left at room temperature over night to give the product **218** (0.20 g, 86%) as colourless needles, mp 146-148 °C; δ_H (300 MHz, $CDCl_3$); 8.72

(1H, d, *J* 2.2, pyridinyl-H), 8.45 (1H, dd, *J* 1.6 and 4.9, pyridinyl-H), 8.13-8.07 (1H, m, naphthyl-H). 7.86-7.82 (1H, m, naphthyl-H), 7.77-7.72 (2H, m, pyridinyl-H and naphthyl-H), 7.49-7.37 (5H, m, purine-H and 4 × naphthyl-H), 7.12 (1H, dd, *J* 4.9 and 8.2, pyridinyl-H), 5.95 (1H, t, *J* 7.1, NCH_2CH=), 4.90 (2H, s, NCH_2CH=), 4.31 (3H, s, naphthyl-CH_2NH), 3.97 (2H, s, =CCH_2NH), 3.94 (3H, s, purine 7-Me), 3.57 (3H, s, purine 3-Me), 1.91 (1H, brs, NH); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.9, 148.5, 147.9, 141.6, 139.0, 136.9, 135.8, 133.9, 133.8, 131.9, 128.5, 127.8, 126.4, 126.3, 125.9, 125.6, 125.3, 124.1, 123.0, 107.6, 51.6, 47.8, 39.4, 33.6, 29.8; υ_{max}/cm^{-1} (film); 1312, 3009, 2948, 1702, 1658, 1603, 1550, 1455, 1413, 1356, 1315, 1286, 1233; *m/z* (ESI^+) 467.2 (100%, MH^+); (Found MH^+, 467.2201. $C_{27}H_{27}N_6O_2$ requires *MH*, 467.2190).

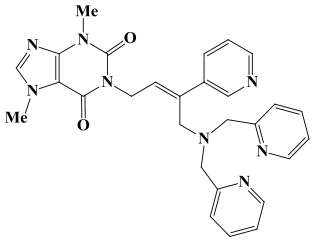
3,7-Dimethyl-1-[(2*Z*)-4-[(pyren-1-ylmethyl)amino]-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dihydro-1*H*-purine-2,6-dione (219).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 1-pyrenemethylamine hydrochloride **213** (0.134 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (5 mL) at 80 ºC for 4 h. The product precipitated from hot solution. The reaction was cooled, filtered and the precipitate washed with water to give the crude product. Crystallisation from 5:1 v/v MeCN/$CHCl_3$ gave the product **219** (0.24 g, 89%) as colourless needles, mp 166-168 °C; δ_H (300 MHz, $CDCl_3$); 8.78 (1H, d, *J* 1.6, pyridinyl-H), 8.45 (1H, dd, *J* 1.6 and 4.9, pyridinyl-H), 8.35 (1H, d, *J* 9.3, pyrenyl-H). 8.17-7.96 (8H, m, pyrenyl-H), 7.76 (1H, dt, *J* 7.7and 1.6, pyridinyl-H), 7.44 (1H, s, purine-H), 7.10 (1H, dd, *J* 4.9 and 7.7, pyridinyl-H), 5.96 (1H, t, *J* 7.1, NCH_2CH=), 4.90 (2H, s, NCH_2CH=), 4.57 (3H, s, pyrenyl-CH_2NH), 4.02 (2H, s, =CCH_2NH), 3.87 (3H, s, purine 7-Me), 3.55 (3H, s, purine 3-Me), 2.09 (1H, brs, NH); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.9, 148.5, 147.9, 141.5, 139.0, 137.0, 133.9, 133.7, 131.3, 130.8, 130.7, 129.3, 127.4, 127.35, 127.3, 127.0, 126.4, 125.8, 125.0, 124.8, 124.6, 123.6, 123.0, 107.6, 51.8, 47.9, 39.4, 33.5, 29.7 (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3304, 3011, 2948, 1703, 1659, 1603, 1550, 1486, 1455, 1429, 1413, 1355, 1314, 1287,

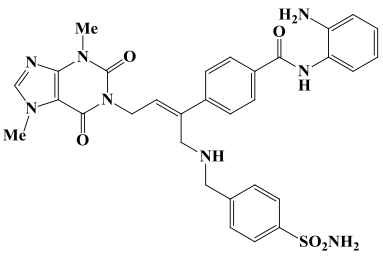
1234; *m/z* (ESI$^+$) 541.2 (100%, MH$^+$); (Found MH$^+$, 541.2366. $C_{33}H_{29}N_6O_2$ requires *MH*, 541.2347).

1-[(2*Z*)-4-[Bis(pyridin-2-ylmethyl)amino]-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (220).



Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 3-iodopyridine (0.246 g, 1.1 mmol), di-(2-picolyl)amine **214** (0.09 mL, 0.50 mmol), $Pd_2(dba)_3$ (0.0228 g, 5.0 mol%), TFP (0.023 g, 20 mol%) and K_2CO_3 (0.414 g, 6.0 mmol) in MeCN (5 mL) at 80 ºC for 7.5 h. Work up by flash column chromatography gradient elution with EtOAc and then 10:1 v/v EtOAc/MeOH gave the product **220** (0.23 g, 91%) as a colourless froth, mp 144-146 °C; δ_H (300 MHz, $CDCl_3$); 8.52-8.46 (4H, m, 4 × pyridyl-H), 7.56 (2H, dt, *J* 1.4 and 7.6, 2 × pyridyl-H), 7.52 (1H, s, purine-H), 7.47 (1H, td, *J* 1.9, 8.1, pyridyl-H), 7.17-7.11 (3H, m, 3 × pyridinyl-H), 7.06 (2H, d, J 7.6, 2 × pyridinyl-H), 5.86 (1H, t, *J* 6.7, NCH_2CH=), 4.91 (2H, d, *J* 6.7, NCH_2CH=), 3.98 (3H, s, NMe), 3.86 (2H, s, =CCH_2N), 3.81 (4H, s, 2 × NCH_2-pyridyl), 3.57 (3H, s, NMe); δ_C (75 MHz, $CDCl_3$); 159.4, 154.9, 151.3, 148.9, 148.8, 148.4, 148.2, 141.6, 138.0, 137.0, 136.3, 134.4, 128.9, 123.1, 122.6, 122.0, 107.6, 60.1 (2 × C), 52.5, 39.4, 33.6, 29.7, ; υ_{max}/cm^{-1} (film); 2926, 2854, 1705, 1660, 1590, 1550, 1474, 1455, 1433, 1414, 1358, 1313, 1234; *m/z* (ESI$^+$) 509.2 (100%, MH$^+$); (Found MH$^+$, 509.2413. $C_{28}H_{29}N_8O_2$ requires *MH*, 509.2408).

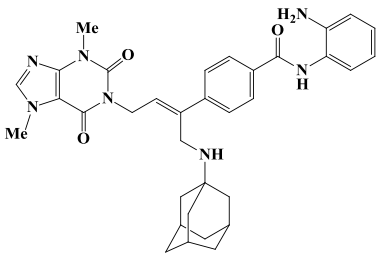
***N*-(2-Aminophenyl)-4-{(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-1-[(4-sulfamoylbenzyl)amino]but-2-en-2-yl}benzamide (223a).**



Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), *N*-(2-aminophenyl)-4-iodobenzamide **221**[130c] (0.406 g, 1.20 mmol), mafenide hydrochloride **174** (0.266 g, 1.20 mmol), $Pd_2(dba)_3$ (0.0228 g, 2.5 mol%), TFP (0.023 g, 10 mol%) and K_2CO_3 (0.414 g, 3.00 mmol) in DMF (4 mL) at 80 ºC for 5 h. Work up by flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **223a** (0.42 g, 67%) as a colourless froth, mp 224-226 °C; δ_H (300

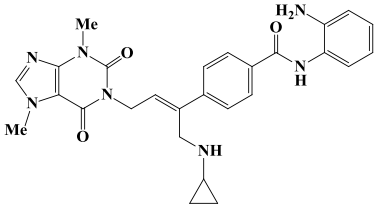
MHz, DMSO-d_6); 9.67 (1H, s, CONH), 8.08 (1H, s, purine-H), 7.93 (2H, d, *J* 8.1, 2 × phenyl-H), 7.78 (2H, d, *J* 8.1, 2 × phenyl-H), 7.59 (2H, d, *J* 8.1, 2 × phenyl-H), 7.55 (2H, d, *J* 8.1, 2 × phenyl-H), 7.32 (2H, s, SO_2NH_2), 7.15 (1H, d, *J* 7.6, phenyl-H), 6.97 (1H, t, *J* 8.1, phenyl-H), 6.78 (1H, d, *J* 8.1, phenyl-H), 6.60 (1H, t, *J* 7.6, phenyl-H), 5.90 (1H, t, *J* 6.7, NCH_2CH=), 4.89 (2H, br s, phenyl-NH_2), 4.73 (2H, d, *J* 6.7, NCH_2CH=), 3.88 (3H, s, NMe), 3.85 (2H, s, $NHCH_2$-phenyl), 3.74 (2H, s, =CCH_2N), 3.46 (3H, s, NMe); δ_C (75 MHz, DMSO-d_6); 164.9, 154.3, 150.9, 148.4, 145.0, 144.0, 143.2, 143.0, 142.4, 139.4, 133.0, 128.2, 127.7, 127.2, 126.7, 126.5, 125.9, 125.5, 123.3, 116.2, 116.1, 106.8, 52.2, 46.8, 39.0, 33.2, 29.4; υ_{max}/cm^{-1} (solid); 3282, 1697, 1626, 1539, 1506, 1492, 1456, 1411, 1325, 1227; *m/z* (ESI^+) 629.2 (41%, MH^+); (Found MH^+, 629.2291. $C_{31}H_{33}N_8O_5{}^{32}S$ requires *MH*, 629.2289).

4-[(2*Z*)-1-(Adamantan-1-ylamino)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-en-2-yl]-*N*-(2-aminophenyl)benzamide (223b).



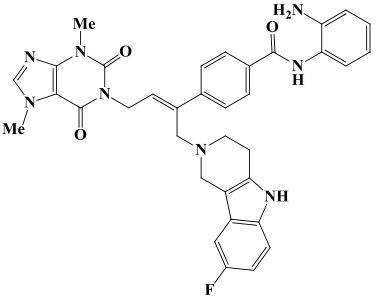
Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), *N*-(2-aminophenyl)-4-iodobenzamide **221**[130c] (0.406 g, 1.20 mmol), 1-aminoadamantane **180** (0.182 g, 1.20 mmol), $Pd_2(dba)_3$ (0.0228 g, 2.5 mol%), TFP (0.023 g, 10 mol%) and K_2CO_3 (0.414 g, 3.00 mmol) in MeCN (7 mL) at 80 ºC for 2 h. Work up by flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **223b** (0.49 g, 83%) as a colourless froth, mp 151-153 °C; δ_H (300 MHz, $CDCl_3$); 8.15 (1H, s, CONH), 7.70 (2H, d, *J* 8.1, 2 × phenyl-H), 7.47 (2H, d, *J* 8.1, 2 × phenyl-H), 7.40 (1H, s, purine-H), 7.14 (1H, d, *J* 7.6, phenyl-H), 6.93 (1H, dt, *J* 1.4 and 8.1, phenyl-H), 6.68 (1H, d, *J* 7.6, phenyl-H), 6.67 (1H, t, *J* 8.1, phenyl-H), 5.80 (1H, t, *J* 7.2, NCH_2CH=), 4.78 (2H, d, *J* 7.2, NCH_2CH=), 3.85 (3H, s, NMe), 3.72 (2H, s, =CCH_2N), 3.46 (3H, s, NMe), 2.00 (3H, br s, 3 × adamantyl-CH), 1.66 (6H, d, *J* 1.9, 3 × adamantyl-CH_2), 1.57 (6H, br s, 3 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 165.7, 155.0, 151.4, 148.9, 145.1, 141.7, 141.2, 141.0, 132.7, 127.4, 127.1, 126.5, 125.9, 125.4, 124.5, 119.4, 118.1, 107.6, 51.0, 42.5, 39.7, 39.2, 36.8, 33.6, 29.8, 29.6; υ_{max}/cm^{-1} (film); 3314, 3009, 2906, 2848, 1704, 1660, 1605, 1549, 1504, 1455, 1414, 1358, 1311, 1234; *m/z* (ESI^+) 594.3 (100%, MH^+); (Found MH^+, 594.3179. $C_{34}H_{40}N_7O_3$ requires *MH*, 594.3187).

***N*-(2-Aminophenyl)-4-[(2*Z*)-1-(cyclopropylamino)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-en-2-yl]benzamide (223c).**



Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), *N*-(2-aminophenyl)-4-iodobenzamide **221**[130c] (0.406 g, 1.20 mmol), cyclopropylamine (0.10 mL, 1.50 mmol), $Pd_2(dba)_3$ (0.0228 g, 2.5 mol%), TFP (0.023 g, 10 mol%) and K_2CO_3 (0.414 g, 3.00 mmol) in MeCN (7 mL) at 80 ºC for 3 h. Work up by flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **223c** (0.38 g, 76%) as a colourless froth, mp 117-119 °C; δ_H (300 MHz, $CDCl_3$); 8.12 (1H, s, CONH), 7.81 (2H, d, *J* 8.1, 2 × phenyl-H), 7.52 (2H, d, *J* 8.1, 2 × phenyl-H), 7.51 (1H, s, purine-H), 7.26 (1H, d, *J* 7.6, phenyl-H), 7.06 (1H, dt, *J* 1.4 and 8.1, phenyl-H), 6.80 (1H, d, *J* 7.6, phenyl-H), 6.79 (1H, t, *J* 7.6, phenyl-H), 5.92 (1H, t, *J* 7.2, NCH_2CH=), 4.91 (2H, d, *J* 7.2, NCH_2CH=), 3.97 (3H, s, NMe), 3.94 (2H, s, =CCH_2N), 3.57 (3H, s, NMe), 2.23-2.16 (1H, m, cyclopropyl-CH), 0.49-0.37 (4H, m, 2 × cyclopropyl-CH_2); δ_C (75 MHz, $CDCl_3$); 165.6, 155.0, 151.4, 148.9, 145.0, 141.7, 140.9, 140.6, 132.8, 127.5, 127.2, 126.7, 126.4, 125.3, 124.5, 119.6, 118.2, 107.7, 47.6, 39.7, 33.6, 30.4, 29.8, 6.5; υ_{max}/cm^{-1} (film); 3319, 3007, 1703, 1657, 1504, 1455, 1358, 1313, 1234; *m/z* (ESI^+) 500.2 (100%, MH^+); (Found MH^+, 500.2416. $C_{27}H_{30}N_7O_3$ requires *MH*, 500.2405).

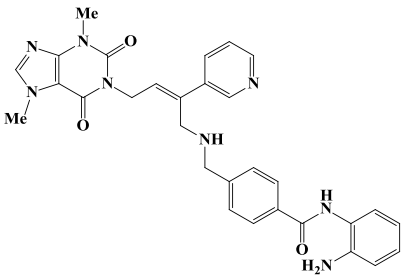
***N*-(2-Aminophenyl)-4-[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-1-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)but-2-en-2-yl]benzamide (223d).**



Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), *N*-(2-aminophenyl)-4-iodobenzamide **221**[130c] (0.406 g, 1.20 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.228 g, 1.20 mmol), $Pd_2(dba)_3$ (0.0228 g, 2.5 mol%), TFP (0.023 g, 10 mol%) and K_2CO_3 (0.414 g, 3.00 mmol) in MeCN (7 mL) at 80 ºC for 2 h. The product precipitated out of the hot solution. Work up by flash column chromatography eluting with 5:1 v/v EtOAc/MeOH gave the product **223d** (0.52 g, 82%) as a colourless amorphous solid,

mp > 230 °C; δ_H (300 MHz, DMSO-d_6); 10.86 (1H, s, pyridoindolyl-NH), 9.61 (1H, s, CONH), 8.03 (1H, s, purine 8-H), 7.90 (2H, d, *J* 8.6, 2 × phenyl-H), 7.64 (2H, d, *J* 8.6, 2 × phenyl-H), 7.22 (1H, dd, *J* 4.5 and 8.8, pyridoindolyl-H), 7.14 (1H, d, *J* 8.1, phenyl-H), 7.10 (1H, dd, *J* 2.9 and 10.0, pyridoindolyl-H), 6.95 (1H, dt, *J* 1.4 and 7.6, phenyl-H), 6.80 (1H, dt, *J* 2.9 and 9.5, pyridoindolyl-H), 6.76 (1H, dd, *J* 1.4 and 8.1, phenyl-H), 6.57 (1H, dt, *J* 1.4 and 7.6, phenyl-H), 6.02 (1H, t, *J* 6.2, NCH_2CH=), 4.88 (2H, s, phenyl-NH_2), 4.85 (2H, d, *J* 6.2, NCH_2CH=), 3.91 (3H, s, purine 7-NCH_3), 3.83 (2H, s, =CCH_2N), 3.67 (2H, s, pyridoindoly 1-CH_2), 3.45 (3H, s, purine 3-NCH_3), 2.87 (2H, t, *J* 5.2, pyridoindolyl-CH_2), 2.70 (2H, t, *J* 5.2, pyridoindolyl-CH_2); δ_C (75 MHz, DMSO-d_6); 165.0, 156.6 (*J* 230.0), 154.3, 150.9, 148.4, 144.2, 143.1, 142.9, 137.7, 135.9, 132.9, 132.4, 129.1, 127.6, 126.6, 126.4, 126.1, 125.7 (*J* 10.0), 123.3, 116.2, 116.0, 111.4 (*J* 10.0), 107.8 (*J* 21.0), 107.6 (*J* 4.4), 106.8, 101.9 (*J* 22.1), 55.1, 49.6, 49.1, 39.2, 33.2, 29.4, 23.6; υ_{max}/cm^{-1} (solid); 3413, 1687, 1641, 1550, 1504, 1448, 1318, 1234; *m/z* (ESI^+) 633.3 (100%, MH^+); (Found MH^+, 633.2732. $C_{35}H_{34}FN_8O_3$ requires *MH*, 633.2732).

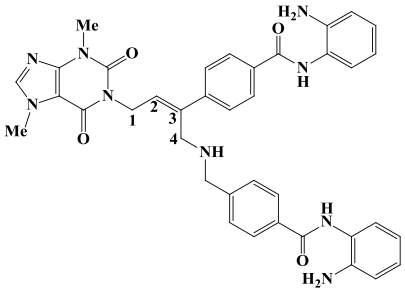
_N_-(2-Aminophenyl)-4-({[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(pyridin-3-yl)but-2-en-1-yl]amino}methyl)benzamide (223e).



Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 3-iodopyridine (0.246 g, 1.20 mmol), 4-(aminomethyl)-*N*-(2-aminophenyl)benzamide **222**[130b] (0.362 g, 1.50 mmol), $Pd_2(dba)_3$ (0.0228 g, 2.5 mol%), TFP (0.023 g, 10 mol%) and K_2CO_3 (0.414 g, 3.00 mmol) in MeCN (7 mL) at 80 ºC for 7 h. Work up by flash column chromatography eluting with 10:3 v/v EtOAc/MeOH gave the product **223e** (0.33 g, 60%) as a colourless froth, mp 99-101 °C; δ_H (300 MHz, $CDCl_3$); 8.66 (1H, s, CONH), 8.64 (1H, d, *J* 2.4, pyridyl-H), 8.42 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 7.82 (2H, d, *J* 8.1, 2 × phenyl-H), 7.75 (1H, td, *J* 1.9 and 8.1, pyridyl-H), 7.50 (1H, s, purine 8-H), 7.38 (2H, d, *J* 8.1, 2 × phenyl-H), 7.21 (1H, d, *J* 8.1, phenyl-H), 7.18 (1H, dd, *J* 4.8 and 8.1, pyridyl-H), 7.00 (1H, dt, *J* 1.4 and 8.1, phenyl-H), 6.76 (1H, d, *J* 8.1, phenyl-H), 6.72 (1H, dt, *J* 1.4 and 8.1, phenyl-H), 5.87 (1H, t, *J* 6.7, NCH_2CH=), 4.79 (2H, d, *J* 6.7, NCH_2CH=), 4.01 (1H, br s, NH), 3.90 (3H, s, NMe), 3.88 (2H, s, CH_2), 3.76 (2H, s,

CH_2), 3.53 (3H, s, NMe); δ_C (75 MHz, $CDCl_3$); 166.0, 154.9, 151.3, 148.9, 148.4, 147.7, 144.4, 141.8, 141.2, 138.5, 136.9, 133.8, 132.9, 128.4, 127.6, 127.1, 126.7, 125.6, 124.4, 123.1, 119.2, 117.9, 107.6, 53.3, 50.3, 47.3, 39.4, 33.6, 29.8; υ_{max}/cm^{-1} (film); 3332, 3008, 1703, 1652, 1549, 1504, 1455, 1414, 1355, 1314, 1234; *m/z* (ESI^+) 551.3 (100%, MH^+); (Found MH^+, 551.2529. $C_{30}H_{31}N_8O_3$ requires *MH*, 551.2514).

_N_-(2-Aminophenyl)-4-[(2*Z*)-1-({4-[(2-aminophenyl)carbamoyl]benzyl} -amino)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-en-2-yl]benzamide (223f).

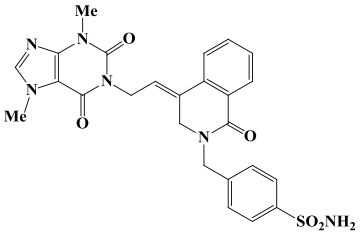


Prepared by general procedure B from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), *N*-(2-aminophenyl)-4-iodobenzamide **221**[130c] (0.406 g, 1.20 mmol), 4-(aminomethyl)-*N*-(2-aminophenyl)benzamide **222**[130b] (0.362 g, 1.50 mmol), $Pd_2(dba)_3$ (0.0228 g, 2.5 mol%), TFP (0.023 g, 10 mol%) and K_2CO_3 (0.414 g, 3.00 mmol) in MeCN (7 mL) at 80 ºC for 4 h. Work up by flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **223f** (0.35 g, 51%) as a colourless froth, mp 215-217 °C; δ_H (300 MHz, DMSO-d_6); 9.67 (1H, s, CONH), 9.66 (1H, s, CONH), 8.04 (1H, s, purine-H), 7.96 (2H, d, *J* 8.1, 2 × phenyl-H), 7.94 (2H, d, *J* 8.1, 2 × phenyl-H), 7.62 (2H, d, *J* 8.1, 2 × phenyl-H), 7.51 (2H, d, *J* 8.1, 2 × phenyl-H), 7.16 (2H, br d, *J* 8.1, 2 × phenyl-H), 6.98 (1H, t, *J* 7.6, phenyl-H), 6.97 (1H, t, *J* 8.1, phenyl-H), 6.79 (1H, d, *J* 7.6, phenyl-H), 6.78 (1H, d, *J* 8.1, phenyl-H), 6.60 (1H, t, *J* 7.6, phenyl-H), 6.59 (1H, t, *J* 8.1, phenyl-H), 5.91 (1H, t, *J* 6.7, NCH_2CH=), 4.90 (4H, br s, 2 × phenyl-NH_2), 4.74 (2H, d, *J* 6.7, NCH_2CH=), 3.89 (3H, s, NMe), 3.87 (2H, s, $NHCH_2$-phenyl), 3.75 (2H, s, =CCH_2N), 3.44 (3H, s, NMe); δ_C (75 MHz, DMSO-d_6); 165.13, 164.91, 154.33, 150.87, 148.39, 144.45, 144.07, 143.16, 143.13, 142.98, 139.44, 132.97, 132.86, 127.72, 127.68, 127.16, 126.68, 126.42, 125.90, 123.34, 123.28, 116.21, 116.08, 106.77, 52.36, 46.78, 39.06, 33.17, 29.44, (Five aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (solid); 3336, 1697, 1662, 1625, 1505, 1456, 1352, 1302, 1225; *m/z* (ESI^+) 706.3 (74%, MNa^+); (Found MNa^+, 706.2871. $C_{38}H_{37}N_9NaO_4$ requires *MNa*, 706.2861).

NOE data (DMSO-d_6) for **223f**:

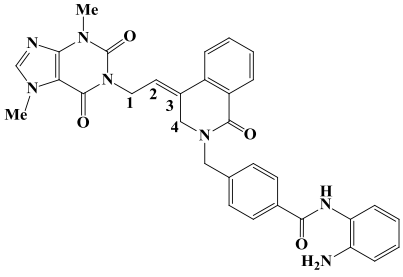
	% Enhancement			
Irradiated proton	1-H	2-H	4-H	phenyl-H
1-H		-6.74	-	-
2-H	-3.17		-	-
4-H	-1.58	-		-1.83 (δ 7.62)

4-{[(4*Z*)-4-[2-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)ethylidene]-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}benzenesulfonamide (226a).



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), methyl 2-iodobenzoate **224** (0.09 mL, 0.60 mmol), mafenide hydrochloride **174** (0.122 g, 0.55 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.204 g, 1.50 mmol) in DMF (3 mL) at 80 ºC for 9 h. The crude product, without chromatography, was dissolved in $CHCl_3$ and left overnight to give the product **226a** (0.14 g, 54%) as a colourless amorphous solid, mp 194-196 °C; δ_H (300 MHz, DMSO-d_6); 8.03 (1H, s, purine-H), 7.99 (1H, d, *J* 7.7, isoquinolin-H), 7.82 (2H, d, *J* 7.7, Ph-H), 7.64 (1H, d, *J* 7.7, isoquinolin-H), 7.54 (2H, d, *J* 7.7, Ph-H), 7.53 (1H, t, *J* 7.7, isoquinolin-H), 7.43 (1H, t, *J* 7.7, isoquinolin-H), 7.36 (2H, s, SO_2NH_2), 6.13 (1H, t, *J* 6.6, NCH_2CH=), 4.86 (2H, s, NCH_2Ph), 4.63 (2H, d, *J* 6.6, NCH_2CH=), 4.54 (2H, s, =CCH_2N), 3.86 (3H, s, NMe), 3.41 (3H, s, NMe); δ_C (75 MHz, DMSO-d_6); 162.2, 154.2, 150.8, 148.4, 143.0, 142.9, 141.3, 135.9, 132.3, 129.7, 128.3, 127.8, 127.78, 126.8, 125.9, 123.3, 123.2, 106.7, 49.7, 47.0, 38.1, 33.2, 29.4; υ_{max}/cm^{-1} (solid); 3287, 2948, 1697, 1641, 1599, 1546, 1492, 1431, 1412, 1360, 1334, 1227; *m/z* (ESI^+) 543.1 (100%, MNa^+); (Found MNa^+, 543.1397. $C_{25}H_{24}N_6NaO_5{}^{32}S$ requires *MNa*, 543.1421).

***N*-(2-Aminophenyl)-4-{[(4*Z*)-4-[2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)ethylidene]-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}benzamide (226b).**



Prepared by general procedure B from *N*-allenylpurine **195** (0.116 g, 0.50 mmol), methyl 2-iodobenzoate **224** (0.09 mL, 0.60 mmol), 4-(aminomethyl)-*N*-(2-aminophenyl)benzamide

222[130b] (0.169 g, 0.70 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.204 g, 1.50 mmol) in MeCN (4 mL) at 80 ºC for 3 h. The product precipitated from hot solution during the reaction. The reaction mixture was cooled, filtered and the precipitate washed with water to give the crude product which crystallised from $CHCl_3$ to give the product **226b** (0.16 g, 56%) as fine colourless needles, mp 222-224 °C; δ_H (300 MHz, $CDCl_3$); 8.15 (1H, dd, *J* 1.4 and 7.4, Ar-H), 8.11 (1H, br s, NH), 7.84 (2H, d, *J* 8.2, Ar-H), 7.54-7.37 (6H, m, Ar-H), 7.31 (1H, d, *J* 7.7, Ar-H), 7.08 (1H, dt, *J* 1.4 and 8.2, Ar-H), 6.83 (1H, d, *J* 7.7, Ar-H), 6.82 (1H, t, *J* 7.2, Ar-H), 6.20 (1H, t, *J* 7.2, NCH_2CH=), 4.94 (2H, s, NCH_2), 4.66 (2H, d, *J* 7.2, NCH_2CH=), 4.51 (2H, s, =CCH_2N), 3.96 (2H, br s, NH_2), 3.90 (3H, s, NMe), 3.54 (3H, s, NMe); δ_C (75 MHz, $CDCl_3$); 163.6, 154.8, 151.3, 148.9, 141.8, 141.3, 140.8, 136.4, 133.3, 132.2, 131.9, 128.7, 128.6, 128.0, 127.7, 127.6, 127.2, 125.3, 124.5, 123.1, 122.0, 119.6, 118.3, 107.5, 50.4, 47.2, 38.2, 33.6, 29.8 (one aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3345, 3008, 1704, 1645, 1548, 1505, 1455, 1413, 1361, 1313, 1234; *m/z* (ESI^+) 598.2 (74%, MNa^+); (Found MNa^+, 598.2164. $C_{32}H_{29}N_7NaO_4$ requires *MNa*, 598.2173). NOE data ($CDCl_3$) for **226b**:

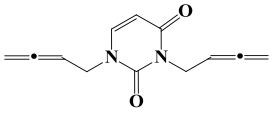
	% Enhancement				
Irradiated proton	1-H	2-H	4-H	NCH_2	phenyl-H
1-H		5.02	3.43	-	-
2-H	3.82		-	-	14.25 (δ 7.52)
4-H	3.63	-		2.42	2.38 (δ 7.46)

General procedure D: preparation of bisallene.

A mixture of dialkyne (1 equiv.), paraformaldehyde (5 equiv.), dicyclohexylamine (3.6 equiv.) and CuI (1 equiv.) in dry dioxane was refluxed and magnetically stirred for 40 min-3 h. The mixture was then cooled, filtered and the filtrate evaporated under vacuum. The residue was dissolved in $CHCl_3$ and the organic layer washed with 10% v/v ammonia solution and finally with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate evaporated under vacuum. The residue was purified by flash column chromatography.

1,3-Di(buta-2,3-dien-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (234).

Prepared by general procedure D from dialkyne **233** (0.5 g, 2.66 mmol), paraformaldehyde (0.5 g, 13.30 mmol),

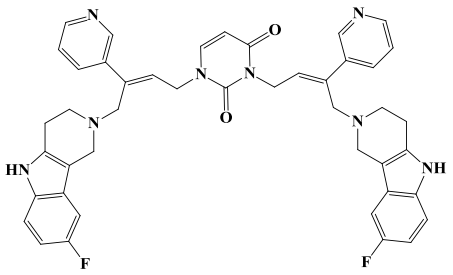


dicyclohexylamine (1.90 mL, 9.57 mmol) and CuI (0.51 g, 2.66 mmol) in dioxane (15 mL) for 3 h. Flash column chromatography eluting with 3:1 v/v hexane/EtOAc gave pure N^1,N^3-diallenyluracil **234** (0.39 g, 68%) as a pale yellow viscous oil; δ_H (300 MHz, $CDCl_3$); 7.22 (1H, d, *J* 7.9, pyrimidinyl-H), 5.75 (1H, d, *J* 7.9, pyrimidinyl-H), 5.72 (2H, m, 2 x NCH_2CH=), 4.90 (2H, m, NCH_2), 4.80 (2H, m, NCH_2), 4.55 (2H, m, $=CH_2$). 4.36 (2H, m, $=CH_2$); δ_C (75 MHz, $CDCl_3$); 205.5, 205.1, 159.0, 147.3, 138.3, 98.1, 82.6, 82.2, 74.4, 73.5, 43.7, 35.6; υ_{max}/cm^{-1} (film); 2952, 1957, 1709, 1661, 1454, 1391, 1347, 1220; *m/z* (ESI^+) 217.1 (100%, MH^+); (Found MH^+, 217.0976. $C_{12}H_{13}N_2O_2$ requires *MH*, 217.0972).

General procedure E: Pd catalysed 5-component cascades using splayed bisallenes.

A mixture of bisallene (1 equiv.), aryl/heteroaryl iodide (2.4 equiv.), nucleophile (2.4 equiv.), $Pd_2(dba)_3$ (5 mol%), TFP (tri-(2-furyl)phosphine) (20 mol%), and K_2CO_3 (6 equiv.) in MeCN was stirred and heated at 80 °C (oil bath temperature). The mixture was cooled and the solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ and washed with H_2O (1 x 20 mL). The organic layer was dried (anhydrous $MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography.

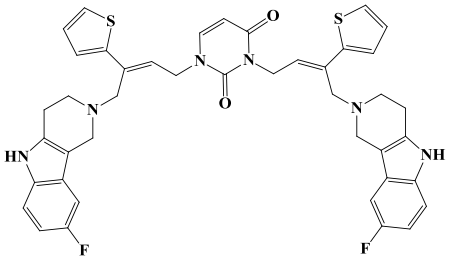
1,3-Bis[(2*Z*)-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)-3-(pyridin-3-yl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235a).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 1 h. Flash column chromatography gradient eluting with EtOAc and then 10:1 v/v EtOAc/MeOH gave the product **235a** (0.18 g, 96%) as a colourless amorphous solid, mp 127-129 °C; δ_H (300 MHz, $CDCl_3$); 8.71 (2H, d, *J* 2.0, pyridyl-H), 8.50 (1H, dd, *J* 1.4 and 4.7, pyridyl-H), 8.42 (1H, dd, *J* 1.4 and 4.7, pyridyl-H), 8.25 (1H, s, NH), 8.13 (1H, s, NH), 7,78 (2H, m, 2H, pyridinyl-H), 7.25 (1H, d, *J* 7.9, pyrimidinyl-H), 7.25-7.22 (1H, m, pyridinyl-H), 7.18-7.11 (3H, m, 2 x

pyridoindolyl-H and pyridinyl-H), 7.01 (2H, dt, *J* 9.2 and 2.4, pyridoindolyl-H), 6.80 (2H, dq, *J* 9.0 and 2.2, pyridoindolyl-H), 6.00 (1H, t, *J* 7.1, NCH_2CH=), 5.94 (1H, t, *J* 6.6, NCH_2CH=), 5.58 (1H, d, *J* 7.9, pyrimidinyl-H), 4.85 (2H, d, *J* 6.6, NCH_2CH=), 4.69 (2H, d, *J* 7.1, NCH_2CH=), 3.80 (2H, s, =CCH_2N), 3.72 (2H, s, =CCH_2N), 3.68 (4H, s, pyridoindolyl-H), 2.90-2.84 (4H, m, pyridoindolyl-H), 2.76-2.69 (4H, m, pyridoindolyl-H); δ_C (75 MHz, $CDCl_3$); 163.1, 158.2 (*J* 239.1), 158.1 (*J* 239.1), 151.8, 149.3, 148.6, 148.3, 148.1, 142.7, 139.7, 137.8, 137.7, 137.5, 134.8, 134.6, 134.4, 134.3, 132.9, 132.8, 128.5, 127.6, 126.8 (*J* 9.1), 126.5 (*J* 9.1), 123.6, 123.4, 111.7 (*J* 9.1), 111.4 (*J* 9.1), 109.7 (*J* 27.6), 109.4 (*J* 29.9), 109.4 (*J* 4.6), 108.8 (*J* 4.6), 103.1 (*J* 25.3), 102.7 (*J* 25.3), 102.2, 56.7, 56.2, 50.2, 50.0, 49.7, 47.6, 40.0, 24.2, 24.1, (One aliphatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2930, 1703, 1656, 1455, 1390, 1325, 1231; *m/z* (ESI^+) 751.3 (100%, MH^+); (Found MH^+, 751.3336. $C_{44}H_{41}F_2N_8O_2$ requires *MH*, 751.3315).

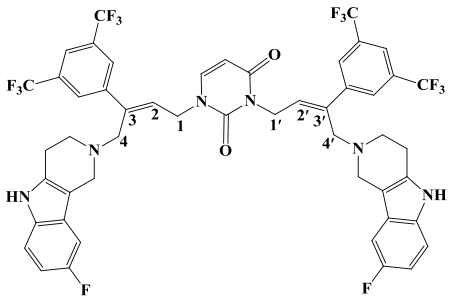
1-[(2*E*)-4-(8-Fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)-3-(2-thienyl)but-2-en-1-yl]-3-[(2*Z*)-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)-3-(3-thienyl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235b).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 2-iodothiophene (0.066 mL, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Flash column chromatography gradient eluting with 1:1 v/v EtOAc/hexane and then EtOAc gave the product **235b** (0.15 g, 79%) as a colourless amorphous solid, mp 137-139 °C; δ_H (300 MHz, $CDCl_3$); 7.94 (1H, s, NH), 7.88 (1H, s, NH), 7.34 (1H, d, *J* 7.9, pyrimidinyl-H), 7.22-6.79 (12H, m, 6 x pyridoindolyl-H and 6 x thienyl-H), 6.14 (1H, t, *J* 7.4, NCH_2CH=), 6.09 (1H, t, *J* 7.0, NCH_2CH=), 5.72 (1H, d, *J* 7.9, pyrimidinyl-H), 4.85 (2H, d, *J* 7.0, NCH_2CH=), 4.79 (2H, d, *J* 7.4, NCH_2CH=), 3.77 (2H, s, CH_2), 3.75 (2H, s, CH_2), 3.70 (2H, s, CH_2), 3.68 (2H, s, CH_2), 2.92-2.88 (4H, m, pyridoindolyl-H), 2.77 (4H, brs, pyridoindolyl-H); δ_C (75 MHz, $CDCl_3$); 162.6, 157.7 (*J* 234.5) (2C), 151.4, 145.1,

144.8, 142.4, 135.9, 134.4, 133.9, 132.4, 127.5, 127.0, 126.5 (*J* 9.8), 126.2 (*J* 9.8), 125.4, 124.7, 124.5, 124.4, 124.1, 123.1, 111.2 (*J* 11.2), 111.0 (*J* 9.2), 109.3 (*J* 25.3), 109.1 (*J* 4.6), 109.0 (*J* 25.3), 108.5 (*J* 4.6), 102.8 (*J* 23.0), 1102.7 (*J* 23.0), 101.5, 56.7, 56.3, 49.7, 49.5, 49.3, 46.8, 39.5, 23.8, (Two aromatic and two aliphatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2927, 1700, 1652, 1481, 1455, 1380, 1324, 1231; *m/z* (ESI^+) 761 (100%, MH^+); (Found MH^+, 761.2548. $C_{42}H_{39}F_2N_6O_2{}^{32}S_2$ requires *MH*, 761.2538).

1,3-Bis[(2*Z*)-3-[3,5-bis(trifluoromethyl)phenyl]-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235c).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.0.1 mL, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.114 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 4 h. Flash column chromatography eluting with 1:1 v/v EtOAc/hexane gave the product **235c** (0.14 g, 55%) as a colourless amorphous solid, mp 115-117 °C; δ_H (300 MHz, $CDCl_3$); 8.00 (1H, s, NH), 7.91 (5H, d, *J* 7.4, 4 x bis-3,5-trifluoromethylphenyl-H and NH), 7.78 (1H, s, bis-3,5-trifluoromethylphenyl-H), 7.70 (1H, s, bis-3,5-trifluoromethylphenyl-H), 7.25 (1H, d, *J* 7.9, pyrimidinyl-H), 7.16- 7.10 (2H, m, pyridoindolyl-H), 6.98 (2H, dt, *J* 11.4 and 2.3, pyridoindolyl-H), 6.82 (2H, dq, *J* 9.3 and 2.2, pyridoindolyl-H), 6.06 (1H, t, *J* 6.8, NCH_2CH=), 5.98 (1H, t, *J* 6.4, NCH_2CH=), 5.63 (1H, d, *J* 7.9, pyrimidinyl-H), 4.87 (2H, d, *J* 6.4, NCH_2CH=), 4.71 (2H, d, *J* 6.8, NCH_2CH=), 3.83 (2H, s, =CCH_2N), 3.77 (2H, s, =CCH_2N), 3.70 (4H, s, 2 x pyridoindolyl-CH_2), 2.94-2.86 (4H, m, 2 x pyridoindolyl-CH_2), 2.80-2.74 (4H, m, 2 x pyridoindolyl-CH_2); δ_C (75 MHz, $CDCl_3$); 162.7, 157.8 (*J* 234.5), 157.7 (*J* 232.2), 151.4, 143.7, 143.4, 142.3, 139.8, 138.0, 134.1, 133.8, 132.2 (*J* 32.2), 131.3 (*J* 32.2), 129.5, 128.7, 126.8 (*J* 4.6), 126.7 (*J* 4.6), 126.1 (*J* 9.2), 126.2 (*J* 9.2), 123.8, 123.5, 123.4 (*J* 273.6), 123.3 (*J* 273.6), 120.9 (*J* 4.6), 120.8 (*J* 4.6), 111.3 (*J* 9.2), 111.0 (*J* 9.2), 109.4 (*J* 29.9), 109.1 (*J* 27.6), 108.7 (*J* 4.2), 108.1 (*J* 4.2), 102.8 (*J* 25.3), 102.6 (*J* 23.0), 102.0, 56.2, 55.7,

50.0, 49.9, 49.0 (2 x C), 47.4, 39.6, 23.7, 23.5. υ_{max}/cm^{-1} (film); 2927, 1707, 1659, 1481, 1455, 1382, 1324, 1278; *m/z* (ESI^+) 1021.3 (100%, MH^+); (Found MH^+, 1021.2924. $C_{50}H_{39}F_{14}N_6O_2$ requires *MH*, 1021.2905).

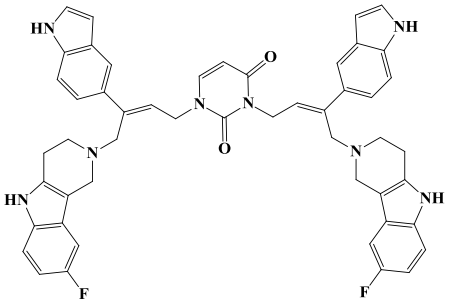
NOE data for **235c**:

	% Enhancement					
Irradiated proton	1-H	2-H	4-H	BTFMP-H*	pyridoindolyl-H	Pyrimidyl-H
1-H (δ 4.71)		1.38	-	-	-	1.97 (δ 7.25)
2-H (δ 6.06)	-		-	8.87 (δ 7.91)	-	-
4-H (δ 3.77)	1.40	-		5.88 (δ 7.91)	1.45 (δ 2.91)	-

	% Enhancement				
Irradiated proton	1′-H	2′-H	4′-H	BTFMP-H*	pyridoindolyl-H
1′-H (δ 4.87)		-	1.74	-	-
2′-H (δ 5.98)	1.34		-	7.73 (δ 7.91)	-
4′-H (δ 3.83)	1.86	-		3.71 (δ 7.91)	1.59 (δ 2.91)

*BTFMP = bis-3,5-trifluoromethylphenyl

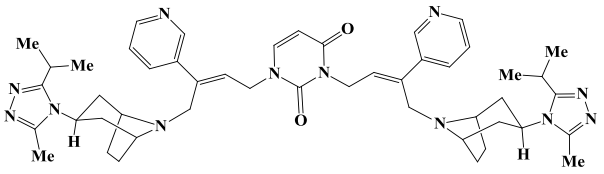
1,3-Bis[(2*Z*)-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)-3-(1*H*-indol-5-yl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235d).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 5-iodoindole (0.145 g, 0.60 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.14 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 1 h. The solvent was cooled to precipitate cascade product, filter and wash the precipitate with water to dissolve K_2CO_3. The product **235d** (0.12 g, 58%) crystallized from $CHCl_3$ as pale yellow needles, mp 175-177 °C; δ_H (300 MHz, DMSO-d_6); 11.06 (1H, brs, NH), 10.01 (1H, brs, NH), 10.86 (1H, s, NH), 10.84 (1H, s, NH), 7.80 (1H, d, *J* 7.9, pyrimidinyl-H), 7.70 (1H, s, Ar-H), 7.64 (1H, s, Ar-H), 7.32-7.18 (8H, m, Ar-H), 7.08 (1H, t, *J* 2.8, Ar-H), 7.05 (1H, t, *J* 2.6, Ar-H), 6.79 (2H, brt, *J* 9.2, Ar-H), 6.36 (2H, brs, Ar-H), 5.96 (1H, t, *J* 6.4, NCH_2CH=), 5.79 (1H, t, *J* 6.5, NCH_2CH=), 5.70 (1H, d, *J* 7.2, pyrimidinyl-H), 4.75 (2H, d, *J* 7.2, NCH_2CH=), 4.72 (2H, d, *J* 7.2, NCH_2CH=), 3.78 (4H, s, 2 x =CCH_2N), 3.63 (4H, s, 2 x pyridoindolyl-CH_2), 2.83

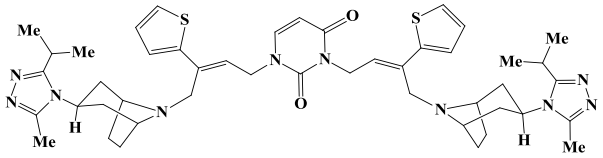
(4H, brs, 2 x pyridoindolyl-CH_2), 2.69 (4H, brs, 2 x pyridoindolyl-CH_2); υ_{max}/cm^{-1} (film); 3406, 1697, 1649, 1453, 1391, 1323, 1231; *m/z* (ESI^+) 827.4 (100%, MH^+); (Found MH^+, 827.3640. $C_{50}H_{45}F_2N_8O_2$ requires *MH*, 827.3628).

1,3-Bis[(2*Z*)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-(pyridin-3-yl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235e).



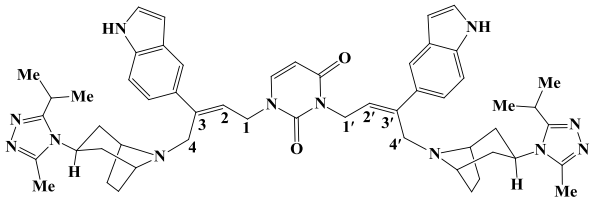
Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.14 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 2.5 h. Flash column chromatography eluting with 2:1 v/v EtOAc/MeOH gave the product **235e** (0.16 g, 76%) as a colourless amorphous solid, mp 112-115 °C; δ_H (300 MHz, $CDCl_3$); 8.69 (2H, s, pyridinyl-H), 8.54 (1H, dd, *J* 4.7 and 1.4, pyridinyl-H), 8.48 (1H, dd, *J* 4.7 and 1.4, pyridinyl-H), 7.78 (2H, dd, *J* 7.9 and 1.8, pyridinyl-H), 7.29 (1H, d, *J* 7.9, pyrimidinyl-H), 7.29-7.22 (2H, m, pyridinyl-H), 5.89 (1H, t, *J* 6.7, NCH_2CH=), 5.88 (1H, t, *J* 6.7, NCH_2CH=), 5.83 (1H, d, J 6.7, pyrimidinyl-H), 4.83 (2H, d, *J* 6.7, NCH_2CH=), 4.71 (2H, d, *J* 6.7, NCH_2CH=), 4.22 (2H, m, azabicyclooctyl-H), 3.66 (2H, s, $=CCH_2N$), 3.60 (2H, s, $=CCH_2N$), 3.40 (2H, brs, azabicyclooctyl-H), 3.35 (2H, brs, azabicyclooctyl-H), 2.88 (2H, m, 2 x triazolyl 3-$CH(CH_3)_2$), 2.34 (3H, s, triazolyl 5-CH_3), 2.32 (3H, s, triazolyl 5-CH_3), 2.24-2.21 (2H, m, azabicyclooctyl-H), 2.18-2.14 (2H, m, azabicyclooctyl-H), 1.98 (4H, dt, *J* 12.2 and 1.7, azabicyclooctyl-H), 1.71-1.60 (8H, m, azabicyclooctyl-H), 1.32 (6H, d, *J* 6.9, triazolyl 3-$CH(CH_3)_2$), 1.31 (6H, d, *J* 6.7, triazolyl 3-$CH(CH_3)_2$); δ_C (75 MHz, $CDCl_3$); 162.9, 159.5, 159.5, 151.7, 151.0, 150.9, 149.2, 148.7, 148.6, 148.5, 142.1, 141.0, 139.2, 137.5, 137.0, 134.8, 134.7, 127.0, 126.3, 123.3, 123.1, 102.8, 59.3, 59.2, 51.6, 51.3, 47.5, 47.3, 47.2, 39.7, 37.9, 37.8, 27.0, 26.9, 26.2, 22.0, 13.2, 13.1, (Two of the aliphatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2964, 1703, 1660, 1513, 1453, 1415, 1346, 1222; *m/z* (ESI^+) 839.3 (11%, MH^+); (Found MH^+, 839.5176. $C_{48}H_{63}N_{12}O_2$ requires *MH*, 839.5191).

1,3-Bis[(2*Z*)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-(3-thienyl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235f).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 3-iodothiophene (0.066 mL, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.14 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 2 h. Flash column chromatography gradient elution with EtOAc and then 10:3 v/v EtOAc/MeOH gave the product **235f** (0.18 g, 85%) as a colourless amorphous solid, mp 105-107 °C; δ_H (300 MHz, $CDCl_3$); 7.34 (1H, d, *J* 7.9, pyrimidinyl-H), 7.25-7.18 (4H, m, thienyl-H), 7.00-6.93 (2H, m, thienyl-H), 6.05 (1H, t, *J* 6.7, NCH_2CH=), 6.03 (1H, t, *J* 7.0, NCH_2CH=), 5.79 (1H, d, *J* 7.9, pyrimidinyl-H), 4.81 (2H, d, *J* 6.7, NCH_2CH=), 4.70 (2H, d, *J* 7.0, NCH_2CH=), 4.29 (2H, m, azabicyclooctyl-H), 3.53 (2H, s, $=CCH_2N$), 3.48 (2H, brs, azabicyclooctyl-H), 3.45 (2H, s, $=CCH_2N$), 3.40 (2H, brs, azabicyclooctyl-H), 3.11-2.99 (2H, m, 2 x triazolyl 3-C*H*$(CH_3)_2$), 2.52 (3H, s, triazolyl 5-CH_3), 2.51 (3H, s, triazolyl 5-CH_3), 2.33-2.19 (8H, m, azabicyclooctyl-H), 1.73-1.67 (8H, m, azabicyclooctyl-H), 1.37 (12H, d, *J* 6.7, triazolyl 3-CH(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$); 163.0, 159.6, 159.5, 151.7, 151.2, 151.0, 145.1, 144.4, 142.2, 136.6, 135.1, 127.2, 126.7, 126.3, 125.7, 124.9, 124.4, 124.0, 122.8, 102.5, 59.4, 52.3, 52.2, 47.8, 47.6, 47.0, 39.7, 37.8, 37.7, 27.0, 27.9, 26.2, 22.1, 13.4, 13.3, (three of the aliphatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2964, 1704, 1660, 1514, 1453, 1390, 1343, 1216; *m/z* (ESI^+) 849.4 (8%, MH^+); (Found MH^+, 849.4441. $C_{46}H_{61}N_{10}O_2{}^{32}S_2$ requires *MH*, 849.4415).

1,3-Bis{(2*Z*)-3-(1*H*-indol-5-yl)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]but-2-en-1-yl}pyrimidine-2,4(1*H*,3*H*)-dione (235g).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 5-iodoindole (0.145 g, 0.60 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]-octane **188** (0.14 g,

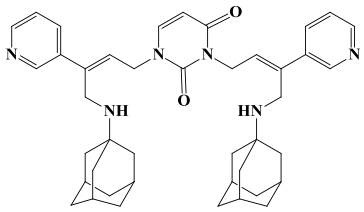
0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 2 h. Flash column chromatography gradient eluting with 10:1 to 10:3 v/v EtOAc/MeOH gave the product **235g** (0.17 g, 74%) as a colourless amorphous solid, mp 152-154 °C; δ_H (300 MHz, $CDCl_3$); 10.31 (1H, brs, NH), 9.98 (1H, brs, NH), 7.71 (1H, s, indolyl-H), 7.66 (1H, s, indolyl-H), 7.35-7.14 (7H, m, 6 x indolyl-H and pyrimidinyl-H), 6.42 (2H, d, *J* 6.9, 2 x indolyl-H), 5.87 (1H, t, *J* 6.0, NCH_2CH=), 5.81 (1H, t, *J* 6.4, NCH_2CH=), 5.75 (1H, d, *J* 7.9, pyrimidinyl-H), 4.90 (2H, d, *J* 6.0, NCH_2CH=), 4.70 (2H, d, *J* 6.4, NCH_2CH=), 4.22 (2H, m, azabicyclooctyl-H), 3.71 (2H, s, $=CCH_2N$), 3.62 (2H, s, $=CCH_2N$), 3.44 (2H, brs, azabicyclooctyl-H), 3.36 (2H, brs, azabicyclooctyl-H), 2.92-2.84 (2H, m, 2 x triazolyl 3-$CH(CH_3)_2$), 2.30 (3H, s, triazolyl 5-CH_3), 2.28 (3H, s, triazolyl 5-CH_3), 5.17 (2H, brs, azabicyclooctyl-H), 2.06-1.99 (6H, m, azabicyclooctyl-H), 1.60 (8H, brs, azabicyclooctyl-H), 1.24 (6H, d, *J* 6.7, triazolyl 3-$CH(CH_3)_2$), 1.1.23 (6H, d, *J* 6.7, triazolyl 3-$CH(CH_3)_2$); υ_{max}/cm^{-1} (film); 2963, 1702, 1657, 1514, 1453, 1388, 1344, 1215; *m/z* (ESI^+) 915.6 (5%, $MH)^+$; (Found MH^+, 915.5544. $C_{54}H_{67}N_{12}O_2$ requires *MH*, 915.5504).

NOE data for **235g**.

	% Enhancement					
Irradiated proton	**1-H**	**2-H**	**4-H**	**Indolyl-H**	**Azabicyclooctyl-H**	**Pyrimidinyl-H**
1-H (δ 4.90)		-14.2	-9.52	-2.59 (δ 7.71)	-5.03 (δ 3.44)	-4.83 (δ 7.25)
2-H (δ 5.87)	-18.02		-5.19	-11.22 (δ 7.71)	-	-18.01 (δ 7.25)
4-H (δ 3.71)	-16.79	-5.21		-8.60 (δ 7.71), and -2.20 (δ 6.42)	-17.07 (δ 3.44), -12.92 (δ 2.28), -5.33 (δ 2.18) and -9.45 (δ 1.60)	-15.01 (δ 7.25)

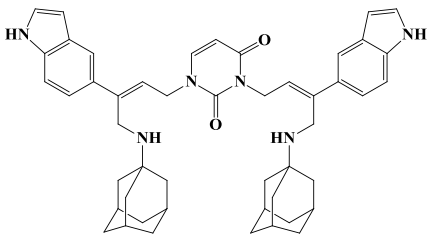
Irradiated proton	**1′-H**	**2′-H**	**4′-H**	**Indolyl-H**	**Azabicyclooctyl-H**	**Pyrimidinyl-H**
1′-H (δ 4.70)		-14.4	-10.0	-3.18 (δ 7.66) and -16.45 (δ 7.34)	-	-7.57 (δ 5.75)
2′-H (δ 5.81)	-14.55		-	-10.51 (δ 7.66), -13.46 (δ 7.33), -11.37 (δ 7.18) and -3.00 (δ 6.43)	-	-
4′-H (δ 3.62)	-12.88	-4.05		-7.30 (δ 7.66), -7.21 (δ 7.33), and -7.87 (δ 7.18)	-15.29 (δ 3.36), -3.75 (δ 2.30), -7.29 (δ 2.08), -5.57 (δ 1.99) and -10.86 (δ 1.58)	-2.07 (δ 5.75)

1,3-Bis[(2*Z*)-4-(adamantan-1-ylamino)-3-(pyridin-3-yl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235h).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054 g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 1-aminoadamantane **180** (0.182 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Flash column chromatography gradient eluting with EtOAc and then 10:3 v/v EtOAc/MeOH gave the product **235h** (0.14 g, 83%) as a colourless amorphous solid, mp 93-95 °C; δ_H (300 MHz, $CDCl_3$); 8.77 (1H, d, *J* 1.9, pyridyl-H), 8.68 (1H, d, *J* 2.4, pyridyl-H), 8.52 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 8.46 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 7.88 (1H, dt, *J* 8.1 and 1.9, pyridyl-H), 7.76 (1H, dt, *J* 8.1 and 2.4, pyridyl-H), 7.53 (1H, d, *J* 8.1, pyrimidinyl-H), 7.29-7.19 (2H, m, 2 x pyridinyl-H), 5.87 (1H, t, *J* 7.2, NCH_2CH=), 5.86 (1H, t, *J* 7.2, NCH_2CH=), 5.77 (1H, d, *J* 8.1, pyrimidinyl-H), 4.83 (2H, d, *J* 7.2, NCH_2CH=), 4.67 (2H, d, *J* 7.2, NCH_2CH=), 3.78 (2H, s, =CCH_2N), 3.72 (2H, s, =CCH_2N), 2.09 (6H, br s, 6 x adamantyl-H), 1.75 (6H, d, *J* 2.4, 6 x adamantyl-H), 1.67 (18H, d, *J* 2.4, 18 x adamantyl-H); δ_C (75 MHz, $CDCl_3$); 162.8, 151.4, 149.1, 148.4, 147.7, 147.5, 142.2, 141.4, 139.8, 137.2, 136.4, 133.7, 133.6, 125.0, 124.9, 123.3, 123.1, 102.1, 51.0, 50.9, 46.8, 42.7, 42.6, 39.6, 39.4, 39.3, 36.8, 36.7, 29.7, 29.5; υ_{max}/cm^{-1} (film); 3309, 2906, 2848, 1704, 1660, 1567, 1453, 1415, 1391, 1358, 1343, 1310, 1222; *m/z* (ESI^+) 673.4 (100%, MH^+); (Found MH^+, 673.4240. $C_{42}H_{56}N_6O_2$ requires *MH*, 673.4225).

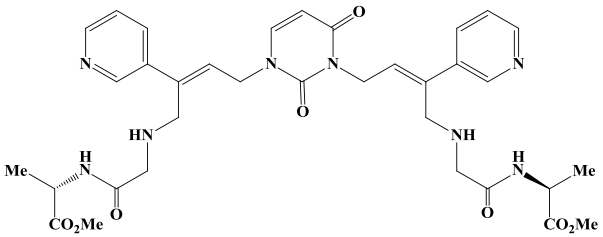
1,3-Bis[(2*Z*)-4-(adamantan-1-ylamino)-3-(1*H*-indol-5-yl)but-2-en-1-yl]pyrimidine-2,4(1*H*,3*H*)-dione (235i).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054 g, 0.25 mmol), 5-iodoindol (0.146 g, 0.60 mmol), 1-aminoadamantane **180** (0.182 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.21 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 2 h. Flash column chromatography eluting with EtOAc gave the product **235i** (0.13 g, 70%) as a colourless amorphous solid, mp

145-147 °C; δ_H (300 MHz, $CDCl_3$/MeOH-*d*$_4$); 8.86 (1H, br s, NH), 8.71 (1H, NH), 7.70 (1H, d, *J* 1.0, indolyl-H), 7.63 (1H, d, *J* 1.0, indolyl-H), 7.58 (1H, d, *J* 8.1, pyrimidinyl-H), 7.32-7.15 (6H, m, 6 x indolyl-H), 6.51 (1H, d, *J* 2.9, indolyl-H), 6.48 (1H, d, *J* 3.3, indolyl-H), 5.84 (1H, t, *J* 7.2, NCH_2CH=), 5.74 (1H, t, *J* 7.2, NCH_2CH=), 5.73 (1H, d, *J* 8.1, pyrimidinyl-H), 4.83 (2H, d, *J* 7.2, NCH_2CH=), 4.63 (2H, d, *J* 7.2, NCH_2CH=), 3.93 (2H, s, =CCH_2N), 3.76 (2H, s, =CCH_2N), 2.06 (6H, br s, 6 x adamantyl-H), 1.73 (6H, d, *J* 1.9, 6 x adamantyl-H), 1.65 (18H, br d, *J* 5.2, 18 x adamantyl-H); δ_C (75 MHz, $CDCl_3$/MeOH-*d*$_4$); 163.3, 151.6, 144.7, 143.3, 142.6, 135.6, 135.4, 132.7, 131.7, 128.0, 127.9, 125.0, 124.5, 122.2, 121.9, 121.0, 120.7, 118.6 118.5, 111.3, 110.9, 102.6, 101.6, 51.1, 51.0, 46.7, 42.4 (3 x C), 42.2 (3 x C), 40.0, 39.2, 36.7 (3 x C), 36.6 (3 x C), 29.6 (3 x C), 29.5 (3 x C) (One aliphatic and one aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (solid); 2902, 2847, 1703, 1651, 1454, 1390, 1356, 1310, 1215; *m/z* (ESI^+) 749.5 (12.5%, MH^+); (Found MH^+, 749.4537. $C_{48}H_{57}N_6O_2$ requires *MH*, 749.4538).

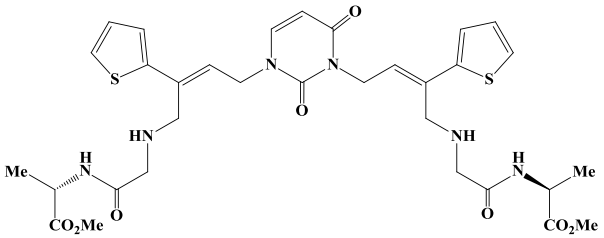
Dimethyl (2*S*,2'*S*)-2,2'-[(2,4-dioxopyrimidine-1,3(2*H*,4*H*)-diyl)bis{[(2*Z*)-2-(pyridin-3-yl)but-2-ene-4,1-diyl]imino(1-oxoethane-2,1-diyl)imino}]dipropanoate (235j).



Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), methyl (2*S*)-2-[(aminoacetyl)amino]propanoate hydrochloride **209** (0.118 g, 0.60 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Work up by flash column chromatography gradient elution with EtOAc and then 10:4 v/v EtOAc/MeOH gave the product **235j** (0.12 g, 70%) as a colourless gum; $[\alpha]_D^{26}$ -3.1 (*c*, 31 mg/ 1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 8.67 (2H, d, *J* 1.5, 2 x pyridyl-H), 8.56 (1H, dd, *J* 1.5 and 5.1, pyridyl-H), 8.51 (1H, dd, *J* 1.5 and 5.1, pyridyl-H), 7.77 (2H, m, 2 x pyridyl-H), 7.55 (1H, d, *J* 7.7, CO*NH*), 7.39 (1H, d, *J* 7.7, pyrimidinyl-H), 7.34-7.24 (2H, m, 2 x pyridinyl-H), 5.88 (1H, t, *J* 7.2, NCH_2CH=), 5.85 (1H, t, *J* 7.2, NCH_2CH=), 5.82 (1H, d, *J* 7.7, pyrimidinyl-H), 4.85 (1H, dd, 7.2 and 14.3, H_A, NCH_2CH=), 4.79 (1H, dd, 7.2 and 14.3, H_B, NCH_2CH=), 4.67 (2H, t, *J* 7.2, NCH_2CH=),4.60-4.54 (2H, m, 2 x $CHCO_2Me$), 3.91-3.72 (4H, m, 2 x =CCH_2N),

3.73 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.35 (2H, s, NH*CH*$_2$CO), 3.27 (2H, d, *J* 9.7, NH*CH*$_2$CO), 1.99 (2H, br s, 2 x NH), 1.37 (3H, d, *J* 7.7, CH*Me*), 1.31 (3H, d, *J* 7.2, CH*Me*); δ_C (75 MHz, $CDCl_3$); 173.9, 173.7, 171.8, 171.6, 163.1, 151.8, 149.7, 149.2, 148.3, 148.2, 142.9, 139.8, 139.2, 137.0, 136.0, 134.5, 134.4, 126.8, 126.7, 123.9, 123.6, 102.7, 52.9, 52.8, 52.5, 51.8, 48.2, 48.0, 47.9, 47.6, 39.7, 18.2 (2 x C), (One aliphatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3331, 2928, 1742, 1653, 1520, 1455, 1348, 1221; *m/z* (ESI^+) 691.3 (100%, MH^+); (Found MH^+, 691.3215. $C_{34}H_{43}N_8O_8$ requires *MH*, 691.3198).

Dimethyl (2*S*,2'*S*)-2,2'-[(2,4-dioxopyrimidine-1,3(2*H*,4*H*)-diyl)bis{[(2*E*)-2-(2-thienyl)but-2-ene-4,1-diyl]imino(1-oxoethane-2,1-diyl)imino}]dipropa-noate (235k).

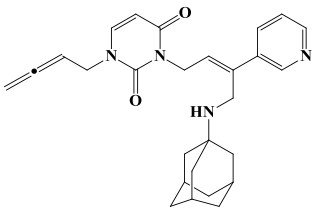


Prepared by general procedure E from N^1,N^3-diallenyluracil **234** (0.069 g, 0.319 mmol), 2-iodothiophene (0.084 mL, 0.76 mmol), methyl (2*S*)-2-[(aminoacetyl)amino]propanoate hydrochloride **209** (0.15 g, 0.76 mmol), $Pd_2(dba)_3$ (0.0145 g, 5 mol%), TFP (0.0147 g, 20 mol%) and K_2CO_3 (0.264 g, 1.91 mmol) in MeCN (3 mL) at 80 ºC for 1.5 h. Work up by flash column chromatography gradient elution with EtOAc and then 20:1 v/v EtOAc/MeOH gave the product **235k** (0.15 g, 67%) as a colourless gum; $[\alpha]_D^{24}$ -3.6 (*c*, 14 mg/ 1 mL $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.82 (1H, d, *J* 8.1, CO*NH*), 7.55 (1H, d, *J* 7.6, CO*NH*), 7.39 (1H, d, *J* 7.6, pyrimidinyl-H), 7.22 (1H, d, *J* 5.2, thienyl-H), 7.18-7.15 (3H, m, 3 x thienyl-H), 7.02-6.95 (2H, m, 2 x thienyl-H), 5.99 (2H, t, *J* 7.4, 2 x NCH$_2$*CH*=), 5.79 (1H, d, *J* 7.6, pyrimidinyl-H), 4.81 (1H, dd, *J* 7.4 and 14.3, H_A, N*CH*$_2$CH=), 4.76 (1H, dd, *J* 7.4 and 14.3, H_B, N*CH*$_2$CH=), 4.65-4.54 (4H, m, 2 x N*CH*$_2$CH= and 2 x *CH*CO_2Me), 3.88-3.71 (4H, m, 2 x =C*CH*$_2$N), 3.72 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.40 (2H, s, NH*CH*$_2$CO), 3.35 (2H, d, *J* 6.7, NH*CH*$_2$CO), 2.27 (2H, br s, 2 x NH), 1.39 (3H, d, *J* 7.2, CH*Me*), 1.38 (3H, d, *J* 7.2, CH*Me*); δ_C (75 MHz, $CDCl_3$); 173.7, 173.3, 171.6, 171.2, 162.8, 151.4, 144.5, 143.4, 142.5, 135.6, 135.1, 127.7, 127.4, 125.3, 124.7, 124.6, 124.1, 122.9, 122.7, 102.1, 52.4, 52.3, 52.2, 51.7, 48.4, 47.8, 47.6, 47.5, 47.1, 39.2, 18.01, 18.00 ; υ_{max}/cm^{-1} (film); 3333, 3007, 2953, 1742,

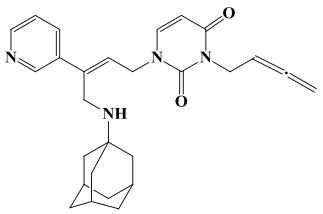
1660, 1525, 1453, 1343, 1215; *m/z* (ESI^+) 723.2 (100%, MNa^+); (Found MNa^+, 723.2252. $C_{32}H_{40}N_6Na_1O_8{}^{32}S_2$ requires *MNa*, 723.2241).

3-[(2*Z*)-4-(Adamantan-1-ylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-1-(buta-2,3-dien-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (236a) and 1-[(2*Z*)-4-(Adamantan-1-ylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-3-(buta-2,3-dien-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (236b).

Prepared by general procedure B from N^1,N^3-diallenyluracil **234** (0.051 g, 0.236 mmol), 3-iodopyridine (0.058 g, 0.283 mmol), 1-aminoadamantane **180** (0.036 g, 0.236 mmol), $Pd_2(dba)_3$ (0.0054 g, 2.5 mol%), TFP (0.0055 g, 10 mol%) and K_2CO_3 (0.11 g, 0.708 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Flash column chromatography gradient elution with EtOAc and then 10:2 v/v EtOAc/MeOH gave the first two products **236a** and **236b**. Increasing the elution polarity to 10:3 v/v EtOAc/MeOH gave the third product **235h** (0.031 g, 19%).



Compound **236a** was obtained as a pale yellow gum (0.026 g, 25%); δ_H (300 MHz, $CDCl_3$); 8.77 (1H, d, *J* 1.6, pyridinyl-H), 8.46 (1H, dd, *J* 1.1 and 4.4, pyridinyl-H), 7.88 (1H, dt, *J* 1.6 and 7.7, pyridinyl-H), 7.23 (1H, dd, *J* 4.4 and 7.7, pyridinyl-H), 7.19 (1H, d, *J* 8.2, pyrimidinyl-H), 5.86 (1H, t, *J* 7.1, $NCH_2CH{=}CCH_2$), 5.78 (1H, d, *J* 8.2, pyrimidinyl-H), 5.33-5.24 (1H, m, $NCH_2CH{=}C{=}$), 4.91-4.87 (2H, m, $=C{=}CH_2$), 4.82 (2H, d, *J* 7.1, $NCH_2CH{=}$), 4.38-4.34 (2H, m, $NCH_2CH{=}C{=}$), 3.78 (2H, s, $CH{=}CCH_2N$), 2.09 (3H, br s, 3 × adamantyl-CH), 1.75 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.66 (6H, br s, 3 × adamantyl-CH_2); δ_c (75 MHz, $CDCl_3$); 209.3, 162.8, 151.2, 148.4, 147.7, 141.9, 139.7, 137.2, 133.7, 124.9, 123.1, 102.0, 86.2, 78.1, 51.0, 47.4, 42.5, 39.5, 39.3, 36.8, 29.6; υ_{max}/cm^{-1} (film); 3308, 2906, 2848, 1957, 1705, 1661, 1454, 1416, 1391, 1358, 1310, 1219; *m/z* (ESI^+) 445.3 (100%, MH^+); (Found MH^+, 445.2608. $C_{27}H_{33}N_4O_2$ requires *MH*, 445.2598).



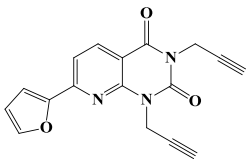
Compound **236b** was obtained as a pale yellow gum (0.024 g, 23%); δ_H (300 MHz, $CDCl_3$); 8.69 (1H, d, *J* 2.2, pyridinyl-H), 8.52 (1H, dd, *J* 1.6 and 4.9, pyridinyl-H), 7.77 (1H, dt, *J* 2.2 and 8.2, pyridinyl-H), 7.50 (1H, d, *J* 8.0, pyrimidinyl-H), 7.27 (1H, dd, *J* 4.9 and 8.2, pyridinyl-H), 5.85 (1H, t, *J* 7.1,

NCH_2CH=CCH_2), 5.76 (1H, d, *J* 8.0, pyrimidinyl-H), 5.33-5.24 (1H, m, NCH_2CH=C=), 4.82-4.78 (2H, m, =C=CH_2), 4.67 (2H, d, *J* 7.1, NCH_2CH=), 4.59-4.55 (2H, m, NCH_2CH=C=), 3.73 (2H, s, CH=CCH_2N), 2.11 (3H, br s, 3 × adamantyl-CH), 1.70-1.60 (12H, br m, 6 × adamantyl-CH_2); δ_c (75 MHz, $CDCl_3$); 208.9, 162.6, 151.3, 149.0, 147.5, 142.2, 141.0, 136.4, 133.7, 125.3, 123.3, 102.0, 85.9, 77.1, 51.2, 46.9, 42.6, 39.4 (2 × C), 36.6, 29.5; υ_{max}/cm^{-1} (film); 3312, 2906, 2848, 1957, 1706, 1661, 1454, 1416, 1391, 1358, 1224; *m/z* (ESI^+) 445.3 (100%, MH^+); (Found MH^+, 445.2619. $C_{27}H_{33}N_4O_2$ requires *MH*, 445.2598).

General procedure F: preparation of more complex bis-alkynes 238.

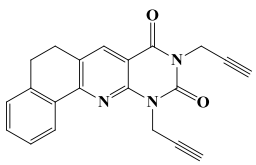
A mixture of pyridopyrimidine **237** (1 equiv.), K_2CO_3 (6 equiv.) and propargyl bromide **193** (4 equiv.) in DMF was magnetically stirred at rt for 16 h. The reaction mixture was poured into ice cold water and the solid product collected by filtration, washed with cold water and dried under vacuum. The crude solid was crystallised to give the dialkyne **238.**

7-(2-Furyl)-1,3-di(prop-2-yn-1-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (238a).



Prepared by general procedure F from **237a** (1g, 4.37 mmol), propargyl bromide (2.10 mL, 17.47 mmol), K_2CO_3 (3.60 g, 26.20 mmol) in DMF (20 mL). The product **238a** crystallized from MeOH as colourless needles (0.92 g, 71%), mp 220-222 °C; δ_H (300 MHz, DMSO-d_6); 8.44 (1H, d, *J* 8.2, pyrido-H), 8.01 (1H, d, *J* 1.6, furyl-H), 7.69 (1H, d, *J* 8.2, pyrido-H), 7.45 (1H, d, *J* 3.5, furyl-H), 6.77 (1H, dd, *J* 1.6 and 3.5, furyl-H), 5.05 (2H, d, *J* 2.2, NCH_2), 4.68 (2H, d, *J* 2.2, NCH_2), 3.21-3.19 (2H, m, 2 × ≡CH); δ_C (75 MHz, DMSO-d_6); 159.3, 151.7, 151.6, 149.4, 149.3, 146.6, 138.7, 113.9, 113.5, 113.1, 108.3, 79.2, 78.8, 73.6, 73.5, 31.6, 30.7; υ_{max}/cm^{-1} (solid); 3268, 1713, 1667, 1601, 1552, 1472, 1451, 1416, 1336; *m/z* (ESI^+) 328.1 (100%, MNa^+); (Found MNa^+, 328.0708. $C_{17}H_{11}N_3NaO_3$ requires *MNa*, 328.0693).

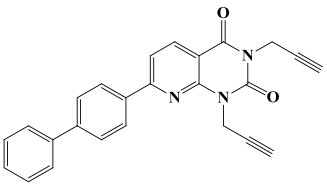
9,11-Di(prop-2-yn-1-yl)-6,11-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(5*H*,9*H*)-dione (238b).



Prepared by general procedure F from **237b** (1g, 3.77 mmol), propargyl bromide (1.81 mL, 16.29 mmol), K_2CO_3 (3.10 g,

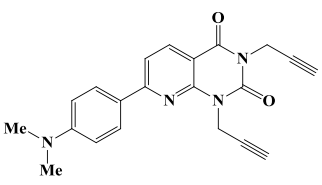
22.79 mmol) in DMF (25 mL). The product **238b** crystallized from MeOH as colourless needles (1.15 g, 89%), mp 212-214 °C; δ_H (300 MHz, DMSO-d_6); 8.33-8.30 (1H, m, aryl-H), 8.30 (1H, s, 7-H), 7.49-7.42 (2H, m, 2 × aryl-H), 7.38-7.35 (1H, m, aryl-H), 5.10 (2H, d, *J* 2.2, NCH_2), 4.69 (2H, d, *J* 2.2, NCH_2), 3.21 (2H, t, *J* 2.2, 2 × ≡CH), 3.05-2.89 (4H, m, 5-CH_2 and 6-CH_2); δ_C (75 MHz, DMSO-d_6); 159.5, 155.9, 149.4, 148.0, 139.7, 136.5, 132.5, 131.1, 128.3, 127.8, 127.2, 125.9, 108.6, 79.3, 78.9, 73.6, 73.5, 31.7, 30.7, 26.9, 25.9; υ_{max}/cm^{-1} (film); 3287, 1712, 1667, 1612, 1599, 1567, 1497, 1465, 1441, 1411, 1386, 1339, 1296, 1272; *m/z* (ESI^+) 364.1 (100%, MNa^+); (Found MNa^+, 364.1067. $C_{21}H_{11}N_3NaO_2$ requires *MNa*, 364.1054).

7-(Biphenyl-4-yl)-1,3-di(prop-2-yn-1-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (238c).



Prepared by general procedure F from **237c** (1g, 3.17 mmol), propargyl bromide (1.40 mL, 12.6 mmol), K_2CO_3 (2.60 g, 19.12 mmol) in DMF (20 mL). The product **238c** crystallized from $CHCl_3$ as colourless needles (0.85 g, 69%), mp 218-220 °C; δ_H (300 MHz, DMSO-d_6); 8.40 (1H, d, *J* 8.2, pyrido-H), 8.28 (2H, d, *J* 8.2, aryl-H), 7.97 (1H, d, *J* 8.2, pyrido-H), 7.82 (2H, d, *J* 8.2, aryl-H), 7.73 (2H, d, *J* 7.1, aryl-H), 7.48 (2H, t, *J* 7.1, aryl-H), 7.40 (1H, d, *J* 7.1, aryl-H), 5.08 (2H, d, *J* 2.2, NCH_2), 4.66 (2H, d, *J* 2.2, NCH_2), 43.26 (1H, t, *J* 2.2, ≡CH), 43.23 (1H, t, *J* 2.2, ≡CH); δ_C (75 MHz, DMSO-d_6); 159.6, 159.4, 149.4, 149.0, 142.2, 138.9, 138.5, 135.4, 129.0, 128.1, 127.9, 127.1, 126.7, 115.7, 108.7, 79.2, 78.8, 72.7, 73.5, 31.7, 30.7; υ_{max}/cm^{-1} (solid); 3259, 1710, 1667, 1598, 1454, 1412, 1341, 1266, 1231; *m/z* (ESI^+) 414.1 (70%, MNa^+); (Found MNa^+, 414.1195. $C_{25}H_{17}N_3NaO_2$ requires *MNa*, 414.1213).

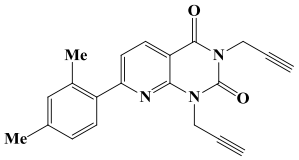
7-[4-(Dimethylamino)phenyl]-1,3-di(prop-2-yn-1-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (238d).



Prepared by general procedure F from **237d** (0.846 g, 3.00 mmol), propargyl bromide (1.33 mL, 11.97 mmol), K_2CO_3 (2.48 g, 18.26 mmol) in DMF (20 mL). The product **238d** crystallized from MeOH as yellow needles (0.79 g, 74%), mp 220-222 °C; δ_H (300 MHz, DMSO-d_6); 8.27 (1H, d, *J* 8.2,

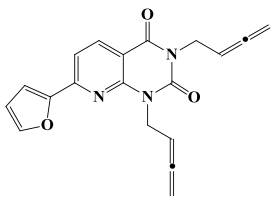
pyrido-H), 8.10 (2H, d, *J* 8.8, 2 × phenyl-H), 7.78 (1H, d, *J* 8.2, pyrido-H), 6.80 (2H, d, *J* 8.8, phenyl-H), 5.05 (2H, d, *J* 2.2, NCH_2), 4.67 (2H, d, *J* 2.2, NCH_2), 3.20 (2H, br s, 2 × ≡CH), 3.2 (3H, s, NMe_2); δ_C (75 MHz, DMSO-d_6); 160.6, 159.5, 152.0, 149.5, 149.0, 137.6, 128.7, 128.2, 123.3, 114.0, 111.7, 106.5, 79.3, 79.0, 73.44, 73.4, 39.6, 21.0; υ_{max}/cm^{-1} (film); 3285, 1711, 1667, 1590, 1446, 1415, 1394, 1347, 1281, 1232; *m/z* (ESI^+) 359.1 (53%, MH^+); (Found MH^+, 359.1498. $C_{21}H_{19}N_4O_2$ requires *MH*, 359.1503).

7-(2,4-Dimethylphenyl)-1,3-di(prop-2-yn-1-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (238e).



Prepared by general procedure F from **237e** (0.69g, 2.58 mmol), propargyl bromide (1.25 mL, 11.25 mmol), K_2CO_3 (2.29 g, 16.84 mmol) in DMF (20 mL). The product **238e** crystallized from 1:1 v/v $CHCH_3$/*n*-hexane as colourless needles (0.85 g, 96%), mp 190-192 °C; δ_H (300 MHz, $CDCl_3$); 8.52 (1H, d, *J* 8.2, pyrido-H), 7.43 (1H, d, *J* 7.2, phenyl-H), 7.41 (1H, d, *J* 8.2, pyrido-H), 7.16 (1H, s, phenyl-H), 7.15 (1H, d, *J* 7.2, phenyl-H), 5.18 (2H, d, *J* 2.7, NCH_2), 4.89 (2H, d, *J* 2.7, NCH_2), 2.50 (2H, s, Me), 2.40 (3H, s, Me), 2.23 (1H, t, *J* 2.7, ≡CH), 2.19 (1H, t, *J* 2.7, ≡CH); δ_C (75 MHz, $CDCl_3$); 165.2, 160.3, 150.0, 149.0, 139.8, 138.1, 136.6, 135.6, 132.2, 130.0, 126.9, 119.9, 108.5, 78.6, 77.9, 71.1(2 × C), 31.9, 31.0, 21.2, 21.0; υ_{max}/cm^{-1} (film); 3271, 1715, 1673, 1601, 1442, 1416, 1338, 1263, 1227; *m/z* (ESI^+) 366.1 (100%, MNa^+); (Found MNa^+, 366.1205. $C_{21}H_{17}N_3NaO_2$ requires *MNa*, 366.1213).

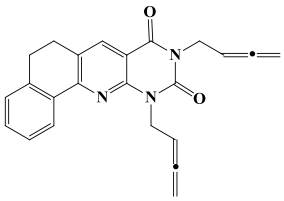
1,3-Di(buta-2,3-dien-1-yl)-7-(2-furyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (239a).



Prepared by general procedure D from dialkyne **238a** (0.85 g, 2.79 mmol), $(CH_2O)_n$ (0.418 g, 13.95 mmol), dicyclohexylamine (1.99 mL, 10.04 mmol) and CuI (0.53 g, 2.79 mmol) in 1,4-dioxane (4 mL) for 1.5 h. Flash column chromatography eluting with 6:1 v/v *n*-hexane/EtOAc gave the product **239a** (0.56 g, 59%) as a colourless amorphous solid, mp 126-128 °C; δ_H (300 MHz, $CDCl_3$); 8.46 (1H, d, *J* 8.2, pyrido-H), 7.61 (1H, d, *J* 1.6, furyl-H), 7.59 (1H, d, *J* 8.2, pyrido-H), 7.28 (1H, dd, *J* 1.1 and 3.3, furyl-H), 6.60 (1H, dd, *J* 1.6 and 3.3, furyl-H), 5.43-5.29 (2H, m, 2 ×

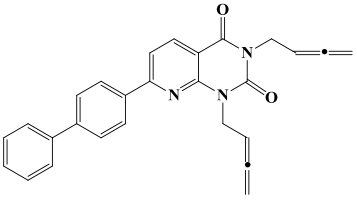
NCH_2CH=), 5.04-5.00 (2H, m, NCH_2), 4.83-4.74 (4H, m, 2 × =CH_2), 4.72-4.68 (2H, m, NCH_2); δ_C (75 MHz, $CDCl_3$); 209.6, 208.9, 160.6, 152.8, 152.7, 150.6, 150.3, 145.1, 138.6, 113.4, 112.7, 112.5, 108.7, 86.0, 77.2, 76.8, 40.8, 39.9 (One aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (solid); 1953, 1707, 1660, 1599, 1558, 1473, 1445, 1421, 1289; *m/z* (ESI^+) 356.1 (100%, MNa^+); (Found MNa^+, 356.1021. $C_{19}H_{15}N_3NaO_3$ requires *MNa*, 356.1006).

9,11-Di(buta-2,3-dien-1-yl)-6,11-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(5*H*,9*H*)-dione (239b).



Prepared by general procedure D from dialkyne **238b** (0.95 g, 2.79 mmol), $(CH_2O)_n$ (0.418 g, 13.95 mmol), dicyclohexylamine (1.99 mL, 10.04 mmol) and CuI (0.53 g, 2.79 mmol) in 1,4-dioxane (4 mL) for 40 min. Flash column chromatography eluting with 10:1 v/v *n*-hexane/EtOAc gave the product **239b** (0.61 g, 60%) as a colourless amorphous solid, mp 118-120 °C; δ_H (300 MHz, $CDCl_3$); 8.37-8.34 (1H, m, aryl-H), 8.22 (1H, s, 7-H), 7.42-7.34 (2H, m, 2 × aryl-H), 7.29-7.25 (1H, m, aryl-H), 5.47-5.39 (1H, m, NCH_2CH=), 5.38-5.30 (1H, m, NCH_2CH=), 5.10-5.06 (2H, m, NCH_2), 4.82-4.76 (4H, m, 2 × =CH_2), 4.71-4.67 (2H, m, NCH_2), 2.99 (4H, br s, 5-CH_2 and 6-CH_2); δ_C (75 MHz, $CDCl_3$); 209.5, 208.9, 160.9, 156.7, 150.6, 149.0, 139.5, 136.5, 133.2, 130.9, 128.1, 127.3, 127.26, 126.4, 109.0, 86.3, 86.1, 77.2, 76.9, 40.9, 39.9, 27.9, 27.0; υ_{max}/cm^{-1} (film); 2948, 1956, 1712, 1667, 1599, 1567, 1498, 1471, 1445, 1417, 1385, 1353, 1297, 1259, 1219; *m/z* (ESI^+) 392.1 (30%, MNa^+); (Found MNa^+, 392.1364. $C_{23}H_{19}N_3NaO_2$ requires *MNa*, 392.1369).

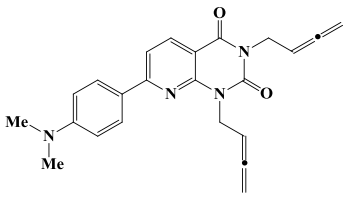
7-(Biphenyl-4-yl)-1,3-di(buta-2,3-dien-1-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (239c).



Prepared by general procedure D from dialkyne **238c** (1.0 g, 2.56 mmol), $(CH_2O)_n$ (0.38 g, 12.8 mmol), dicyclohexylamine (1.83 mL, 9.21 mmol) and CuI (0.49 g, 2.56 mmol) in a mixture of 1,4-dioxane (4 mL) and DMF (2 mL) for 2.5 h. Flash column chromatography eluting with 5:1 v/v *n*-hexane/EtOAc gave the product **239c** (0.40 g, 42%) as a colourless amorphous solid, mp 112-114 °C; δ_H (300 MHz, $CDCl_3$); 8.45 (1H, d, *J* 8.2, pyrido-H), 8.22 (2H, d, *J* 8.8, aryl-H), 7.75-

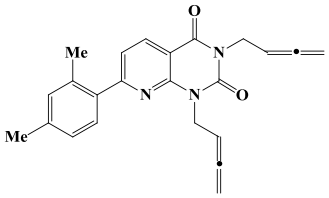
7.64 (5H, m, 4 × aryl-H and pyrido-H), 7.51-7.37 (3H, m, aryl-H), 5.49-5.40 (1H, m, NCH_2CH=), 5.40-5.32 (1H, m, NCH_2CH=), 5.12-5.09 (2H, m, NCH_2), 4.84-4.77 (4H, m, 2 × =CH_2), 4.43-4.69 (2H, m, NCH_2); δ_C (75 MHz, $CDCl_3$); 209.5, 208.9, 160.72, 160.7, 150.6, 150.2, 143.4, 140.1, 138.5, 136.2, 128.9, 128.0, 127.97, 127.6, 127.1, 115.1, 109.0, 86.2, 86.0, 77.3, 77.0, 40.8, 39.9; υ_{max}/cm^{-1} (film); 30.29, 1956, 1712, 1667, 1597, 1558, 1492, 1455, 1423, 1319, 1354, 1262, 1227; *m/z* (ESI^+) 442.2 (18%, MNa^+); (Found MNa^+, 442.1515. $C_{27}H_{21}N_3NaO_2$ requires *MNa*, 442.1526).

1,3-Di(buta-2,3-dien-1-yl)-7-[4-(dimethylamino)phenyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (239d).



Prepared by general procedure D from di-alkyne **238d** (0.70 g, 1.95 mmol), $(CH_2O)_n$ (0.29 g, 9.8 mmol), dicyclohexylamine (1.39 mL, 7.02 mmol) and CuI (0.37 g, 1.95 mmol) in 1,4-dioxane (3 mL) for 1.5 h. Flash column chromatography eluting with 5:1 v/v *n*-hexane/EtOAc and crystallization from 5:1 v/v n-hexane/EtOAc gave the product **239d** (0.51 g, 68%) as yellow needles, mp 130-132 °C; δ_H (300 MHz, $CDCl_3$); 8.37 (1H, d, *J* 8.2, pyrido-H), 8.09 (2H, d, *J* 9.1, 2 × phenyl-H), 7.56 (1H, d, *J* 8.2, pyrido-H), 6.78 (2H, d, *J* 9.1, phenyl-H), 5.48-5.40 (1H, m, NCH_2CH=), 5.39-5.31 (1H, m, NCH_2CH=), 5.11-5.07 (2H, m, NCH_2), 4.83-4.76 (4H, m, 2 × =CH_2), 4.72-4.68 (2H, m, NCH_2), 3.08 (6H, s, NMe_2); δ_C (75 MHz, $CDCl_3$); 209.5, 208.9, 161.4, 161.0, 152.1, 150.9, 150.1, 137.8, 128.9, 124.7, 113.6,111.8, 107.8, 86.3, 86.2, 77.2, 76.8, 40.7, 40.2, 39.8; υ_{max}/cm^{-1} (film); 1956, 1705, 1661, 1590, 1450, 1422, 1392, 1349, 1229; *m/z* (ESI^+) 387.2 (100%, MH^+); (Found MH^+, 387.1813. $C_{23}H_{23}N_4O_2$ requires *MH*, 387.1816).

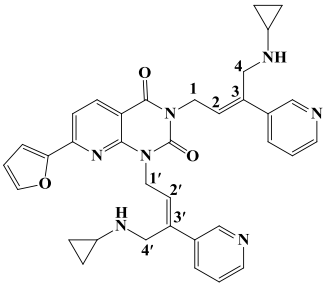
1,3-Di(buta-2,3-dien-1-yl)-7-(2,4-dimethylphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (239e).



Prepared by general procedure D from dialkyne **238e** (0.75 g, 2.19 mmol), $(CH_2O)_n$ (0.33 g, 11.00 mmol), dicyclohexylamine (1.56 mL, 7.88 mmol) and CuI (0.42 g, 2.19 mmol) in 1,4-dioxane (4 mL) for 1.5 h. Flash column chromatography eluting with 5:1 v/v *n*-hexane/EtOAc followed by crystallization from 5:1 v/v *n*-

hexane/$CHCl_3$ gave the product **239e** (0.45 g, 56%) as colourless needles, mp 67-69 °C; δ_H (300 MHz, $CDCl_3$); 8.48 (1H, d, *J* 8.2, pyrido-H), 7.40 (1H, d, *J* 7.7, phenyl-H), 7.35 (1H, d, *J* 8.2, pyrido-H), 7.14 (1H, s, phenyl-H), 7.13 (1H, d, *J* 7.7, phenyl-H), 5.41-5.31 (2H, m, 2 × NCH_2*CH*=), 5.02-4.98 (2H, m, NCH_2), 4.84-4.79 (2H, m, NCH_2), 4.74-4.69 (4H, m, 2 × $=CH_2$), 2.46 (3H, s, Me), 2.39 (3H, s, Me); δ_C (75 MHz, $CDCl_3$); 209.0, 208.9, 164.8, 160.9, 150.6, 149.7, 139.6, 137.9, 136.4, 136.0, 132.1, 130.0, 126.9, 119.4, 108.4, 86.6, 86.0, 77.2 (2 × C), 40.5, 40.0, 21.2, 20.9; υ_{max}/cm^{-1} (film); 2957, 1957, 1713, 1667, 1598, 1563, 1447, 1390, 1354, 1260, 1221; *m/z* (ESI^+) 372.2 (48%, MH^+); (Found MH^+, 372.1696. $C_{23}H_{12}N_3O_2$ requires *MH*, 372.1707).

1,3-Bis[(2*Z*)-4-(cyclopropylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-7-(2-furyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240a).



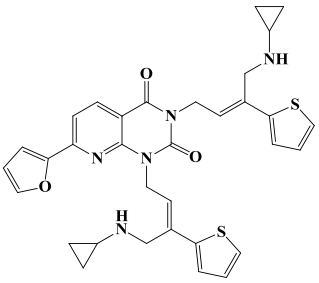
Prepared by general procedure E from **239a** (0.08 g, 0.24 mmol), 3-iodopyridine (0.118 g, 0.57 mmol), cyclopropylamine (0.04 mL, 0.57 mmol), $Pd_2(dba)_3$ (0.011 g, 5 mol%), TFP (0.011 g, 20 mol%) and K_2CO_3 (0.196 g, 1.44 mmol) in MeCN (3 mL) at 80 ºC for 2 h. Flash column chromatography eluting with 5:1 v/v EtOAc/MeOH gave the product **240a** (0.09 g, 63%) as a colourless froth, mp 70-72 °C; δ_H (300 MHz, $CDCl_3$); 8.71 (1H, d, *J* 1.6, aryl-H), 8.68 (1H, d, *J* 1.6, aryl-H), 8.49-8.46 (3H, m, 3 × aryl-H), 7.80-7.74 (2H, m, 2 × aryl-H), 7.64 (1H, d, *J* 1.3, furyl-H), 7.61 (1H, d, *J* 8.2, aryl-H), 7.28 (1H, d, *J* 3.5, furyl-H), 7.24-7.19 (2H, m, 2 × aryl-H), 6.61 (1H, dd, *J* 1.3 and 3.5, furyl-H), 6.04 (1H, t, *J* 7.1, NCH_2*CH*=), 5.94 (1H, t, *J* 7.1, NCH_2*CH*=), 5.32 (2H, d, *J* 7.1, NCH_2), 5.00 (2H, d, *J* 7.1, NCH_2), 4.04 (2H, s, NH*CH*$_2$C=), 3.95 (2H, s, NH*CH*$_2$C=), 2.27-2.20 (2H, m, 2 × cyclopropyl-CH), 2.11 (2H, br s, 2 × NH), 0.51-0.39 (8H, m, 4 × cyclopropyl-CH_2); δ_C (75 MHz, $CDCl_3$); 160.7, 152.8, 152.5, 150.9, 150.3, 148.6, 148.57, 147.8, 145.3, 139.3, 139.1, 138.6, 136.9, 136.8, 133.8, 126.1, 125.6, 123.2, 123.1, 113.9, 112.8, 112.7, 108.8, 47.7, 47.6, 40.7, 40.1, 30.5, 30.4, 6.6, 6.5 (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3319, 3007, 2933, 1708, 1660, 1598, 1563, 1475, 1449, 1417, 1399, 1360, 1334, 1291, 1265, 1224; *m/z* (ESI^+) 602.3 (100%, MH^+); (Found MH^+, 602.2879. $C_{35}H_{36}N_7O_3$ requires *MH*, 602.2874).

NOE data ($CDCl_3$) for **240a**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	pyridinyl-H	cyclopropyl-H
1-H (δ 5.00)		5.07	3.82	-	-
2-H (δ 5.94)	2.79		-	6.64 (δ 8.71), 4.37 (δ 7.77)	-
4-H (δ 3.95)	4.76	-		4.20 (δ 8.71), 3.55 (δ 7.77)	4.05 (δ 2.22)

	% Enhancement					
Irradiated proton	1′-H	2′-H	4′-H	pyridinyl-H	furyl-H	cyclopropyl-H
1′-H (δ 5.32)		5.49	3.63	-	-	-
2′-H (δ 6.04)	3.46		-	6.65 (δ 8.68), 4.21 (δ 7.75)	-	-
4′-H (δ 4.04)	3.36	-		3.62 (δ 8.68), 3.18 (δ 7.75)	1.16 (δ 7.28)	2.61 (δ 2.23)

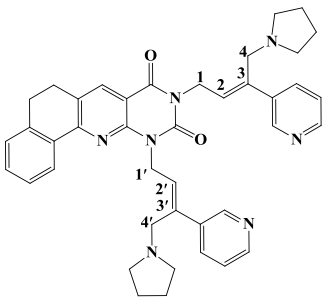
1,3-Bis[(2*E*)-4-(cyclopropylamino)-3-(2-thienyl)but-2-en-1-yl]-7-(2-furyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240b).



Prepared by general procedure E from **239a** (0.08 g, 0.24 mmol), 2-iodothiophene (0.06 mL, 0.57 mmol), cyclopropylamine (0.04 mL, 0.57 mmol), $Pd_2(dba)_3$ (0.011 g, 5 mol%), TFP (0.011 g, 20 mol%) and K_2CO_3 (0.196 g, 1.44 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Flash column chromatography eluting with 6:1 v/v *n*-hexane/EtOAc gave the product **240b** (0.08 g, 55%) as a colourless froth; mp 94-96 °C; δ_H (300 MHz, $CDCl_3$); 8.46 (1H, d, *J* 8.2, pyrido-H), 7.62 (1H, d, *J* 1.4, furyl-H), 7.60 (1H, d, *J* 8.2, pyrido-H), 7.28 (1H, d, *J* 3.3, furyl-H), 7.15-7.11 (4H, m, 4 × thienyl-H), 7.00-6.94 (2H, m, 2 × thienyl-H), 6.61 (1H, dd, *J* 1.4 and 3.3, furyl-H), 6.17 (1H, t, *J* 7.1, NCH_2CH=), 6.06 (1H, t, *J* 7.7, NCH_2CH=), 5.28 (2H, d, *J* 7.1, NCH_2), 4.96 (2H, d, *J* 7.7, NCH_2), 4.04 (2H, s, $NHCH_2C$=), 3.96 (2H, s, $NHCH_2C$=), 2.32-2.24 (2H, m, 2 × cyclopropyl-CH), 1.95 (2H, br s, 2 × NH), 0.51-0.47 (8H, m, 4 × cyclopropyl-CH_2); δ_C (75 MHz, $CDCl_3$); 160.8, 152.8, 152.6, 150.9, 150.4, 145.2, 145.0, 144.9, 138.6, 135.9, 135.6, 127.4, 127.36, 124.5, 123.9, 123.8, 122.7, 122.1, 113.8, 112.8, 112.6, 108.9, 48.1, 48.0, 40.6, 40.0, 30.3, 30.2, 6.7, 6.6 (one aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2926, 1706, 1661, 1597, 1562, 1475, 1448, 1399, 1367, 1335,

1267, 1224; *m/z* (ESI^+) 612.2 (50%, MH^+); (Found MH^+, 612.2084. $C_{33}H_{34}N_5O_3{}^{32}S_2$ requires *MH*, 612.2098).

9,11-Bis[(2*Z*)-3-(pyridin-3-yl)-4-(pyrrolidin-1-yl)but-2-en-1-yl]-6,11-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(5*H*,9*H*)-dione (240c)



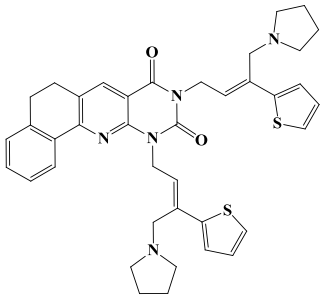
Prepared by general procedure E from **239b** (0.092 g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), pyrrolidine (0.05 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 1 h. Flash column chromatography eluting with 2:1 v/v EtOAc/MeOH gave the product **240c** (0.13 g, 78%) as a colourless froth, mp 64-66 °C; δ_H (300 MHz, $CDCl_3$); 8.70 (2H, 2d, *J* 2.2, 2 × pyridinyl-H), 8.46-8.42 (2H, m, 2 × pyridinyl-H), 8.34 (1H, dd, *J* 2.2 and 7.4, benzo-H), 8.27 (1H, s, 7-H), 7.81-7.75 (2H, m, 2 × pyridinyl-H), 7.44-7.35 (2H, m, 2 × benzo-H), 7.30-7.27 (1H, m, benzo-H), 7.27-7.15 (2H, m, 2 × pyridinyl-H), 6.03 (1H, t, *J* 6.6, NCH_2CH=), 5.92 (1H, t, *J* 6.6, NCH_2CH=), 5.41 (2H, d, *J* 6.6, NCH_2), 5.03 (2H, d, *J* 6.6, NCH_2), 3.81 (2H, s, =CCH_2N), 3.76 (2H, s, =CCH_2N), 3.00 (4H, br s, 5-CH_2 and 6-CH_2), 2.58-2.55 (8H, m, 4 × pyrrolidinyl-CH_2), 1.73-1.72 (8H, m, 4 × pyrrolidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 161.0, 157.0, 150.9, 149.2, 148.2, 148.0, 147.9, 139.6, 138.6, 138.1, 137.6, 135.5, 136.6, 134.0, 133.9, 133.2, 131.0, 128.3, 127.6, 127.57, 127.3, 126.8, 126.3, 122.9, 109.2, 54.4, 54.1, 54.0, 53.95, 40.9, 40.1, 27.8, 27.1, 23.63, 26.6 (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2958, 2786, 1706, 1660, 1611, 1599, 1567, 1497, 1471, 1443, 1415, 1384, 1354, 1295, 1259, 1219; *m/z* (ESI^+) 666.4 (47%, MH^+); (Found MH^+, 666.3554. $C_{41}H_{44}N_7O_2$ requires *MH*, 666.3551).

NOE data ($CDCl_3$) for **240c**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	pyridinyl-H	pyrrolidinyl -H
1-H (δ 5.03)		5.86	3.26	-	-
2-H (δ 5.92)	2.98		-	6.45 (δ 8.70), 4.58 (δ 7.76)	-
4-H (δ 3.76)	3.06	-		3.57 (δ 8.70), 3.57 (δ 7.76)	5.44 (δ 2.55)

	% Enhancement					
Irradiated proton	1′-H	2′-H	4′-H	pyridinyl-H	Benzo-H	pyrrolidinyl - H
1′-H (δ 5.41)		5.48	3.35	-	1.65 (δ 8.34)	-
2′-H (δ 6.03)	2.68		-	6.42 (δ 8.70), 4.22 (δ 7.76)	-	-
4′-H (δ 3.81)	3.42	-		4.00 (δ 8.70), 4.05 (δ 7.76)	2.12 (δ 8.34)	8.68 (δ 2.58)

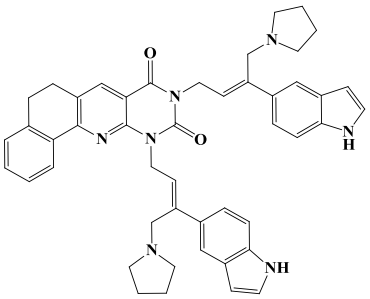
9,11-Bis[(2*E*)-4-(pyrrolidin-1-yl)-3-(2-thienyl)but-2-en-1-yl]-6,11-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(5*H*,9*H*)-dione (240d).



Prepared by general procedure E from **239b** (0.092 g, 0.25 mmol), 2-iodothiophene (0.066 g, 0.60 mmol), pyrrolidine (0.05 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Flash column chromatography eluting with EtOAc gave the product **240d** (0.09 g, 53%) as a colourless froth, mp 66-68 °C; δ_H (300 MHz, $CDCl_3$); 8.36 (1H, m, benzo-H), 8.26 (1H, s, 7-H), 7.44-7.35 (2H, m, 2 × benzo-H), 7.29-7.26 (1H, m, benzo-H), 7.20-7.17 (2H, m, 2 × thienyl-H), 7.12-7.08 (2H, m, 2 × thienyl-H), 6.94-6.89 (2H, m, 2 × thienyl-H), 6.21 (1H, t, *J* 6.6, NCH_2CH=), 6.08 (1H, t, *J* 7.1, NCH_2CH=), 5.36 (2H, d, *J* 6.6, NCH_2), 4.99 (2H, d, *J* 7.1, NCH_2), 3.78 (2H, s, =CCH_2N), 3.73 (2H, s, =CCH_2N), 3.00 (4H, br s, 5-CH_2 and 6-CH_2), 2.64 (8H, br dd, *J* 2.7 and 6.6, 4 × pyrrolidinyl-CH_2), 1.77 (8H, dr d, *J* 5.5, 4 × pyrrolidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 161.1, 156.9, 150.9, 149.3, 145.5, 145.45, 139.6, 136.6, 135.1, 134.7, 133.3, 130.9, 128.2, 127.5, 127.3, 127.0, 127.01, 126.4, 124.5, 124.1, 124.0, 123.9, 123.3, 109.3, 54.9, 54.5, 54.0, 53.9, 40.9, 40.1, 27.9, 27.1, 23.74, 23.7 (one aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2960, 2785, 1705, 1660, 1611, 1599, 1567, 1497, 1470, 1443, 1383, 1294, 1269, 1216; *m/z* (ESI^+) 676.3 (14%, MH^+); (Found MH^+, 676.2783. $C_{39}H_{42}N_5O_2{}^{32}S_2$ requires *MH*, 676.2774).

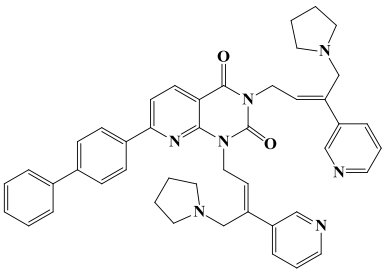
9,11-Bis[(2*Z*)-3-(1*H*-indol-5-yl)-4-(pyrrolidin-1-yl)but-2-en-1-yl]-6,11-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(5*H*,9*H*)-dione (240e).

Prepared by general procedure E from **239b** (0.09 g, 0.25 mmol), 5-iodoindole (0.146 g, 0.60 mmol), pyrrolidine (0.05 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5



mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 1 h. The product precipitated from hot solution. The reaction was cooled, filtered and the precipitate washed with water to give the crude product crystallisation from DMF gave **240e** (0.12 g, 65%) as an amorphous solid, mp 187-189 °C; δ_H (300 MHz, DMSO-d_6); 11.01 (1H, br s, NH), 10.98 (1H, br s, NH), 8.25 (1H, d, *J* 7.1, aryl-H), 8.20 (1H, s, 7-H), 7.59 (2H, d, *J* 11.0, 2 × aryl-H), 7.44-7.13 (9H, m, 9 × aryl-H), 6.33 (2H, dt, *J* 13.2 and 2.2, 2 × indolyl-H), 5.87 (1H, t, *J* 5.9, NCH_2CH=), 5.79 (1H, t, *J* 6.2, NCH_2CH=), 5.19 (2H, d, *J* 5.9, NCH_2), 4.81 (2H, d, *J* 6.2, NCH_2), 3.73 (2H, s, =CCH_2N), 3.66 (2H, s, =CCH_2N), 2.92 (4H, br s, 5-CH_2 and 6-CH_2), 2.49 (8H, br s, 4 × pyrrolidinyl-CH_2), 1.60 (8H, br d, *J* 4.4, 4 × pyrrolidinyl-CH_2); δ_C (75 MHz, DMSO-d_6); 160.3, 155.3, 150.4, 148.9, 140.7, 140.3, 139.6, 136.2, 135.2, 135.1, 132.8, 132.7, 132.69, 130.8, 128.3, 127.44, 127.4, 127.0, 125.6, 125.5, 124.7, 123.9, 120.0, 119.9, 117.7, 117.6, 110.7 (2 × C), 109.2, 101.3, 101.2, 54.4, 54.1, 53.4 (2 × C), 40.7, 39.7, 27.0, 26.0, 23.1 (2 × C) (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (solid); 3246, 2973, 2790, 1706, 1651, 1614, 1567, 1442, 1384, 1355, 1223; *m/z* (ESI^+) 742.4 (12%, MH^+); (Found MH^+, 742.3890. $C_{47}H_{48}N_7O_2$ requires *MH*, 742.3864).

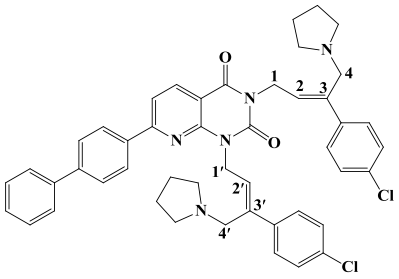
7-(Biphenyl-4-yl)-1,3-bis[(2*Z*)-3-(pyridin-3-yl)-4-(pyrrolidin-1-yl)but-2-en-1-yl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240f).



Prepared by general procedure E from **239c** (0.058 g, 0.138 mmol), 3-iodopyridine (0.068 g, 0.33 mmol), pyrrolidine (0.035 mL, 0.33 mmol), $Pd_2(dba)_3$ (0.006 g, 5 mol%), TFP (0.006 g, 20 mol%) and K_2CO_3 (0.113 g, 0.83 mmol) in MeCN (2 mL) at 80 ºC for 1 h. The product precipitated from the cooled solution. The reaction mixture was filtered, and the precipitate washed with water to give the crude product. Crystallization from MeCN gave the product **240f** (0.07 g, 71%) as a colourless amorphous solid, mp 172-174 °C; δ_H (300 MHz, $CDCl_3$); 8.71 (2H, 2d, *J* 2.2, aryl-H), 8.53 (1H, d, *J* 8.2, aryl-H), 8.45 (2H, td, *J* 1.6 and 4.9, aryl-H), 8.18 (2H, d, *J* 8.2, aryl-H), 7.81-7.72 (5H, m, aryl-H), 7.66 (2H, d, *J* 7.1, aryl-H), 7.49 (2H, t, *J* 7.1, aryl-H), 7.41 (1H, d, *J* 7.1, aryl-H),

7.22-7.15 (2H, m, aryl-H), 6.03 (1H, t, *J* 6.6, NCH_2CH=), 5.92 (1H, t, *J* 6.6, NCH_2CH=), 5.43 (2H, d, *J* 6.6, NCH_2), 5.04 (2H, d, *J* 6.6, NCH_2), 3.80 (2H, s, =CCH_2N), 3.73 (2H, s, =CCH_2N), 2.55 (8H, br d, *J* 3.3, 4 × pyrrolidinyl-CH_2), 1.71 (8H, br s, 4 × pyrrolidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 159.2, 159.0, 149.1, 148.4, 146.4, 146.1, 146.0, 141.7, 138.1, 136.9, 136.7, 136.4, 135.6, 135.55, 134.4, 132.0, 131.9, 127.0, 126.1, 126.09, 125.7, 125.4, 125.2, 124.6,121.0, 113.7, 107.4, 52.5, 52.2, 52.1, 52.0, 39.1, 38.3, 21.7, 21.5 (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3030, 2963, 3876, 2787, 1712, 1667, 1595, 1455, 1417, 1392, 1344, 1264, 1227; *m/z* (ESI^+) 716.4 (58%, MH^+); (Found MH^+, 716.3712. $C_{45}H_{46}N_7O_2$ requires *MH*, 716.3708).

7-(Biphenyl-4-yl)-1,3-bis[(2*Z*)-3-(4-chlorophenyl)-4-(pyrrolidin-1-yl)but-2-en-1-yl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240g).



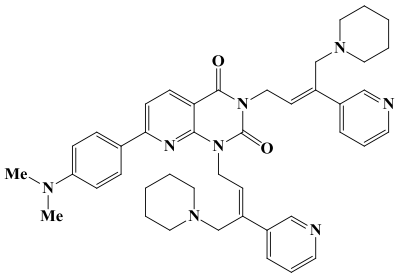
Prepared by general procedure E from **239c** (0.05 g, 0.119 mmol), 1-chloro-4-iodobenzene (0.07 g, 0.286 mmol), pyrrolidine (0.03 mL, 0.286 mmol), $Pd_2(dba)_3$ (0.005 g, 5 mol%), TFP (0.006 g, 20 mol%) and K_2CO_3 (0.10 g, 0.71 mmol) in MeCN (2 mL) at 80 ºC for 1 h. The product precipitated from the hot solution. The reaction mixture was cooled, filtered, and the precipitate washed with water to give the crude product. Crystallization from 3:1 v/v MeCN/$CHCl_3$ gave the product **240g** (0.08 g, 86%) as colourless needles, mp 164-166 °C; δ_H (300 MHz, $CDCl_3$); 8.51 (1H, 2d, *J* 8.2, pyrido-H), 8.18 (2H, d, *J* 8.8, aryl-H), 7.73 (1H, d, *J* 8.2, pyrido-H), 7.75-7.65 (4H, m, aryl-H), 7.49 (2H, t, *J* 7.4, aryl-H), 7.43-7.37 (5H, m, aryl-H), 7.25-7.20 (4H, m, aryl-H), 5.96 (1H, t, *J* 6.6, NCH_2CH=), 5.87 (1H, t, *J* 6.6, NCH_2CH=), 5.39 (2H, d, *J* 6.6, NCH_2), 5.00 (2H, d, *J* 6.6, NCH_2), 3.77 (2H, s, =CCH_2N), 3.73 (2H, s, =CCH_2N), 2.54 (8H, br d, *J* 4.9, 4 × pyrrolidinyl-CH_2), 1.72 (8H, br s, 4 × pyrrolidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 161.1, 160.97, 151.1, 150.4, 143.6, 140.7, 140.6, 140.5, 140.1, 138.6, 136.4, 133.0, 129.0, 128.3, 128.2, 128.1, 128.0, 127.98, 127.9, 127.6, 127.2, 126.6, 125.8, 115.5, 109.3, 54.7, 54.3, 54.1, 54.07, 41.1, 30.4, 23.6, 23.59 (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3030, 2964, 2784, 1710, 1661, 1595, 1557, 1490, 1454, 1422, 1390, 1344, 1263; *m/z* (ESI^+) 782.3 (21%, MNa^+); (Found MNa^+, 782.3003. $C_{45}H_{47}Cl_2N_5NaO_2$ requires *MNa*, 782.2999).

NOE data ($CDCl_3$) for **240g**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	*p*-chlorophenyl-H	pyrrolidinyl-H
1-H (δ 5.00)		4.48	1.75	-	-
2-H (δ 5.87)	2.06		-	8.66 (δ 7.40)	-
4-H (δ 3.73)	1.98	-		6.40 (δ 7.40)	4.12 (δ 2.54)

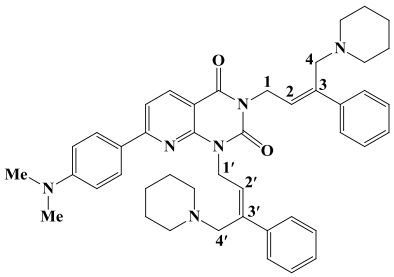
	% Enhancement				
Irradiated proton	1′-H	2′-H	4′-H	*p*-chlorophenyl-H	pyrrolidinyl-H
1′-H (δ 5.39)		5.05	2.86	-	-
2′-H (δ 5.96)	2.35		-	9.75 (δ 7.36) 1.06 (δ 8.18)	-
4′-H (δ 3.77)	1.60	-		6.25 (δ 7.38) 0.76 (δ 8.18)	4.86 (δ 2.54)

7-[4-(Dimethylamino)phenyl]-1,3-bis[(2*Z*)-4-(piperidin-1-yl)-3-(pyridin-3-yl)but-2-en-1-yl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240h).



Prepared by general procedure E from **239d** (0.096 g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), piperidine (0.06 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 1 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **240h** which crystallizated from MeCN as yellow needles (0.13 g, 78%), mp 149-151 °C; δ_H (300 MHz, $CDCl_3$); 8.72 (2H, d, *J* 2.2, 2 × pyridinyl-H), 8.43 (2H, td, *J* 1.3 and 4.9, 2 × pyridinyl-H), 8.38 (1H, d, *J* 8.2, pyrido-H), 8.04 (2H, d, *J* 8.8, 2 × phenyl-H), 7.82-7.76 (2H, m, 2 × pyridinyl-H), 7.56 (1H, d, *J* 8.2, pyrido-H), 7.20-7.14 (2H, m, 2 × pyridinyl-H), 6.75 (2H, d, *J* 8.8, 2 × phenyl-H), 6.08 (1H, t, *J* 6.2, NCH_2CH=), 5.96 (1H, t, *J* 6.6, NCH_2CH=), 5.36 (2H, d, *J* 6.2, NCH_2), 5.00 (2H, d, *J* 6.6, NCH_2), 3.61 (2H, s, =CCH_2N), 3.56 (2H, s, =CCH_2N), 3.06 (6H, s, NMe_2), 2.46 (8H, br s, 4 × piperidinyl-CH_2), 1.51 (8H, br d, *J* 4.4, 4 × piperidinyl-CH_2), 1.41 (4H, br s, 2 × piperidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 161.6, 161.1, 152.1, 151.2, 150.3, 148.1 (4 × C), 137.8, 137.7, 137.6, 137.5, 136.9, 134.03, 134.0, 128.9, 128.7, 127.8, 124.6, 122.8, 122.76, 114.0, 111.8, 107.4, 57.9, 57.6, 54.34, 54.3, 41.0, 40.2 (2 × C), 26.1 (2 × C), 24.4 (2 × C); υ_{max}/cm^{-1} (film); 2935, 2853, 1704, 1660, 1589, 1446, 1417, 1392, 1347, 1269, 1229; *m/z* (ESI^+) 711.4 (42%, MH^+); (Found MH^+, 711.4133. $C_{43}H_{51}N_8O_2$ requires *MH*, 711.4129).

7-[4-(Dimethylamino)phenyl]-1,3-bis[(2*Z*)-3-phenyl-4-(piperidin-1-yl)but-2-en-1-yl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240i).



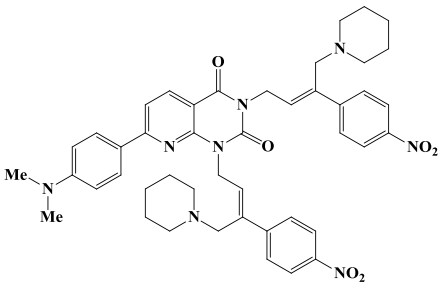
Prepared by general procedure E from **239d** (0.096 g, 0.25 mmol), iodobenzene (0.067 mL, 0.60 mmol), piperidine (0.06 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 1 h. The product precipitated from the cooled solution and was filtered, washed with water and crystallized from MeCN to give the product **240i** (0.14 g, 79%) as a yellow amorphous solid, mp 142-144 °C; δ_H (300 MHz, $CDCl_3$); 8.37 (1H, d, *J* 8.2, pyrido-H), 8.05 (2H, d, *J* 9.3, 2 × 7-phenyl-H), 7.54 (1H, d, *J* 8.2, pyrido-H), 7.46 (4H, td, *J* 1.6 and 8.2, 4 × phenyl-H), 7.29-7.18 (6H, m, 6 × phenyl-H), 6.68 (2H, d, *J* 9.3, 2 × 7-phenyl-H), 6.01 (1H, t, *J* 6.0, NCH_2CH=), 5.91 (1H, t, *J* 6.6, NCH_2CH=), 5.36 (2H, d, *J* 6.0, NCH_2), 5.01 (2H, d, *J* 6.6, NCH_2), 3.62 (2H, s, =CCH_2N), 3.58 (2H, s, =CCH_2N), 3.06 (6H, s, NMe_2), 2.47 (8H, br s, 4 × piperidinyl-CH_2), 1.58-1.49 (8H, br m, 4 × piperidinyl-CH_2), 1.41 (4H, br s, 2 × piperidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 161.5, 161.3, 152.1, 151.2, 150.4, 142.7, 142.69, 140.2, 139.5, 137.8, 128.9, 128.0 (2 × C), 127.95, 127.7, 126.9, 126.7 (2 × C), 126.6, 124.9, 113.8, 111.8, 107.5, 58.4, 58.1, 54.5, 54.4, 41.3, 40.5, 40.2, 26.2, 26.1, 24.5 (2 × C); υ_{max}/cm^{-1} (film); 3020, 2934, 2851, 2802, 1704, 1660, 1589, 1557, 1530, 1490, 1446, 1422, 1391, 1346, 1300, 1267, 1227; *m/z* (ESI^+) 709.4 (40%, MH^+); (Found MH^+, 709.4218. $C_{45}H_{53}N_6O_2$ requires *MH*, 709.4225).

NOE data ($CDCl_3$) for **240i**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	phenyl-H	piperidinyl-H
1-H (δ 5.01)		5.59	3.27	-	-
2-H (δ 5.91)	2.79		-	9.37 (δ 7.46)	-
4-H (δ 3.58)	2.89	-		6.47 (δ 7.46)	6.15 (δ 2.47)

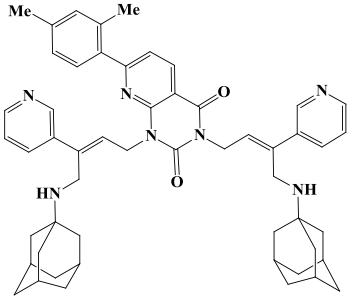
	% Enhancement				
Irradiated proton	1′-H	2′-H	4′-H	phenyl-H	piperidinyl-H
1′-H (δ 5.36)		-	3.02	1.12 (δ 8.05)	-
2′-H (δ 6.01)	2.60		-	9.32 (δ 7.46), 0.92 (δ 8.05)	-
4′-H (δ 3.62)	2.76	-		5.90 (δ 7.46), 1.06 (δ 8.05)	5.89 (δ 2.47)

7-[4-(Dimethylamino)phenyl]-1,3-bis[(2*Z*)-3-(4-nitrophenyl)-4-(piperidin-1-yl)but-2-en-1-yl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240j).



Prepared by general procedure E from **239d** (0.096 g, 0.25 mmol), 4-iodonitrobenzene (0.149 g, 0.60 mmol), piperidine (0.06 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 1 h. The product precipitated from the hot solution. The reaction mixture was cooled, filtered and the precipitate washed with water to give the crude product. Crystallization from MeCN gave the product **240j** (0.16 g, 80%) as a brownish yellow amorphous solid, mp 166-168 °C; δ_H (300 MHz, $CDCl_3$); 8.39 (1H, d, *J* 8.2, pyrido-H), 8.10 (4H, dd, *J* 6.6 and 8.8, 4 × phenyl-H), 8.04 (2H, d, *J* 9.3, 2 × 7-phenyl-H), 7.66-7.57 (5H, m, pyrido-H and 4 × phenyl-H), 6.75 (2H, d, *J* 9.3, 2 × 7-phenyl-H), 6.17 (1H, t, *J* 6.0, NCH_2CH=), 6.04 (1H, t, *J* 6.6, NCH_2CH=), 5.38 (2H, d, *J* 6.0, NCH_2), 5.02 (2H, d, *J* 6.6, NCH_2), 3.61 (2H, s, =CCH_2N), 3.56 (2H, s, =CCH_2N), 3.07 (6H, s, NMe_2), 2.46 (8H, br s, 4 × piperidinyl-CH_2), 1.56-1.49 (8H, br m, 4 × piperidinyl-CH_2), 1.42 (4H, br s, 2 × piperidinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 161.7, 161.1, 152.2, 151.2, 150.3, 148.9, 148.8, 146.7, 146.69, 138.8, 138.2, 137.9, 130.6, 129.6, 128.9, 127.5, 127.4, 124.5, 123.3, 123.27, 114.1, 111.8, 107.4, 57.9, 57.6, 54.4, 54.3, 41.1, 40.3, 40.2, 26.1 (2 × C), 24.4 (2 × C); υ_{max}/cm^{-1} (film); 3020, 2935, 2852, 1704, 1660, 1589, 1557, 1515, 1446, 1418, 1392, 1344, 1270, 1229; *m/z* (ESI^+) 799.4 (39%, MH^+); (Found MH^+, 799.3960. $C_{45}H_{51}N_8O_6$ requires *MH*, 799.3926).

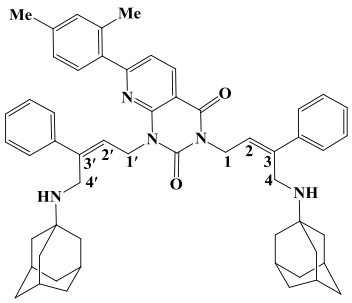
1,3-Bis[(2*Z*)-4-(adamantan-1-ylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-7-(2,4-dimethylphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240k).



Prepared by general procedure E from **239e** (0.093 g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 1-aminoadamantane (0.091 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 1 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **240k** (0.14 g, 68%) as a colourless froth,

mp 102-104 °C; δ_H (300 MHz, $CDCl_3$); 8.77 (1H, d, *J* 1.6, pyridinyl-H), 8.68 (1H, d, *J* 2.2, pyridinyl-H), 8.51 (1H, d, *J* 8.2, pyrido-H), 8.47-8.44 (2H, m, aryl-H), 7.88 (1H, dt, *J* 7.7and 1.6, pyridinyl-H), 7.81 (1H, dt, *J* 8.2 and 2.2, pyridinyl-H), 7.35 (1H, d, *J* 8.2, pyrido-H), 7.33 (1H, d, *J* 8.2, aryl-H), 7.23-7.18 (2H, m, aryl-H), 7.14 (1H, br s, aryl-H), 7.13 (1H, br d, *J* 6.0, aryl-H), 5.95 (2H, t, *J* 6.9, 2 × NCH_2CH=), 5.27 (2H, d, *J* 6.7, NCH_2), 4.99 (2H, d, *J* 7.1, NCH_2), 3.85 (2H, s, =CCH_2N), 3.78 (2H, s, =CCH_2N), 2.40 (3H, s, Me), 2.39 (3H, s, Me), 2.11 (3H, br s, 3 × adamantyl-CH), 2.04 (3H, br s, 3 × adamantyl-CH), 1.78 (6H, br s, 3 × adamantyl-CH_2), 1.68 (6H, br s, 3 × adamantyl-CH_2), 1.61 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 165.1, 161.0, 150.9, 148.4, 147.7, 147.67, 139.9, 139.6, 139.5, 138.0, 137.1, 137.0, 136.2, 136.0, 133.8, 133.7, 132.0, 129.7, 126.9, 125.8, 125.1, 123.1, 123.09, 119.7, 108.7, 51.0, 50.8, 42.6, 42.5, 41.0, 40.2, 39.4, 39.3, 36.8, 36.7, 29.6, 29.58, 21.2, 20.7 (two aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3313, 2905, 2848, 1708, 1661, 1598, 1446, 1423, 1390, 1357, 1310, 1259, 1217; *m/z* (ESI^+) 828.5 (63%, MH^+); (Found MH^+, 828.4959. $C_{53}H_{62}N_7O_2$ requires *MH*, 828.4960).

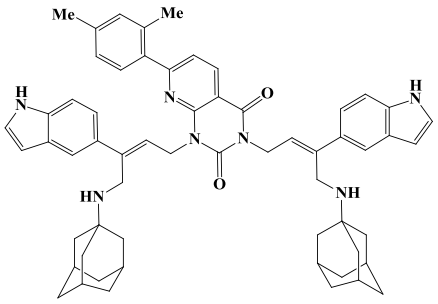
1,3-Bis[(2*Z*)-4-(adamantan-1-ylamino)-3-phenylbut-2-en-1-yl]-7-(2,4-dimethylphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240l).



Prepared by general procedure E from **239e** (0.054 g, 0.145 mmol), iodobenzene (0.04 mL, 0.35 mmol), 1-aminoadamantane (0.053 mL, 0.35 mmol), $Pd_2(dba)_3$ (0.006 g, 5 mol%), TFP (0.007 g, 20 mol%) and K_2CO_3 (0.118 g, 0.87 mmol) in MeCN (2 mL) at 80 ºC for 1 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **240l** (0.09 g, 75%) as a colourless froth, mp 99-101 °C; δ_H (300 MHz, $CDCl_3$); 8.48 (1H, d, *J* 8.2, pyrido-H), 7.51 (2H, dd, *J* 1.4 and 8.5, aryl-H), 7.42 (2H, dd, *J* 1.4 and 8.0, aryl-H), 7.36 (1H, d, *J* 8.2, pyrido-H), 7.31-7.19 (7H, m, aryl-H), 7.14 (1H, br s, aryl-H7.13 (1H, br d, aryl-H), 5.91 (1H, t, *J* 7.1, NCH_2CH=), 5.90 (1H, t, *J* 7.1, NCH_2CH=), 5.24 (2H, d, *J* 7.1, NCH_2), 4.97 (2H, d, *J* 7.1, NCH_2), 3.87 (2H, s, =CCH_2N), 3.79 (2H, s, =CCH_2N), 2.40 (3H, s, Me), 2.38 (3H, s, Me), 2.10 (3H, br s, 3 × adamantyl-CH), 2.02 (3H, br s, 3 × adamantyl-CH), 1.76 (6H, br d, *J* 2.1, 3 × adamantyl-CH_2), 1.66 (6H, br d, *J* 1.1, 3 × adamantyl-

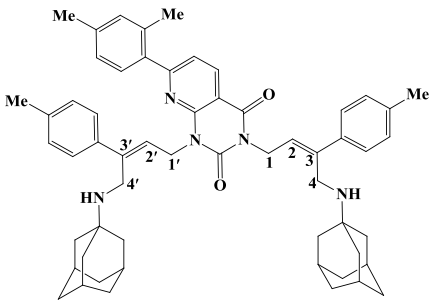
CH_2), 1.58 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 164.9, 161.1, 150.9, 149.9, 142.8, 142.4, 141.4, 141.3, 139.3, 137.9, 136.4, 136.0, 132.0, 129.7, 128.34, 128.3, 127.4, 126.8, 126.4, 126.37, 124.3, 123.6, 119.5, 108.7, 50.9, 50.7, 42.6, 42.5, 41.2, 40.4, 39.4, 39.37, 36.9, 36.7, 29.7, 29.6, 21.3, 20.8 (one aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3314, 2905, 2848, 1707, 1661, 1598, 1446, 1390, 1340, 1310, 1258, 1216; *m/z* (ESI^+) 826.5 (9 %, MH^+); (Found MH^+, 826.5034. $C_{55}H_{64}N_5O_2$ requires *MH*, 826.5055).

1,3-Bis[(2*Z*)-4-(adamantan-1-ylamino)-3-(1*H*-indol-5-yl)but-2-en-1-yl]-7-(2,4-dimethylphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240m).



Prepared by general procedure E from **239e** (0.093 g, 0.25 mmol), 5-iodoindole (0.146 g, 0.60 mmol), 1-aminoadamantane (0.091 mL, 0.60 mmol), $Pd_2(dba)_3$ (0.0114 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.20 g, 1.5 mmol) in MeCN (3 mL) at 80 ºC for 4 h. Flash column chromatography eluting with 2:1 v/v EtOAc/*n*-hexane gave the product **240m** (0.13 g, 58%) as a colourless froth, mp 138-140 °C; δ_H (300 MHz, $CDCl_3$); 8.71 (2H, br s, 2 × NH), 8.45 (1H, d, *J* 8.2, pyrido-H), 7.68 (1H, s, aryl-H), 7.60 (1H, s, aryl-H), 7.36 (1H, d, *J* 8.2, aryl-H), 7.26 (1H, d, *J* 8.2, pyrido-H), 7.22-7.10 (8H, m, aryl-H), 6.42 (2H, br s, aryl-H), 5.87 (1H, t, *J* 7.1, NCH_2CH=), 5.86 (1H, t, *J* 7.1, NCH_2CH=), 5.24 (2H, d, *J* 7.1, NCH_2), 4.96 (2H, d, *J* 7.1, NCH_2), 3.96 (2H, s, =CCH_2N), 3.86 (2H, s, =CCH_2N), 2.40 (3H, s, Me), 2.38 (3H, s, Me), 2.06 (3H, br s, 3 × adamantyl-CH), 1.98 (3H, br s, 3 × adamantyl-CH), 1.74 (6H, br s, 3 × adamantyl-CH_2), 1.63 (6H, br s, 3 × adamantyl-CH_2), 1.57 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 164.8, 161.2, 151.0, 149.95, 143.7, 143.4, 139.2, 137.8, 136.4, 136.0, 135.5, 135.4, 132.8, 131.9, 129.8, 127.9, 126.8, 124.7, 124.6, 122.7, 122.0, 121.0, 120.9, 119.4, 118.6, 118.5, 111.0, 108.8, 102.7, 102.6, 51.0, 50.9, 42.5, 42.3, 41.3, 40.6, 39.6, 39.5, 36.8, 36.7, 29.7, 29.6, 21.3, 20.8 (three aromatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3407, 3017, 2906, 2848, 1704, 1660, 1652, 1598, 1446, 1392, 1343, 1311, 1259, 1216; *m/z* (ESI^+) 904.5 (12%, MH^+); (Found MH^+, 904.5259. $C_{59}H_{66}N_7O_2$ requires *MH*, 904.5273).

1,3-Bis[(2*Z*)-4-(adamantan-1-ylamino)-3-(4-methylphenyl)but-2-en-1-yl]-7-(2,4-dimethylphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (240n).



Prepared by general procedure E from **239e** (0.068 g, 0.183 mmol), 4-iodotoluene (0.10 g, 0.44 mmol), 1-aminoadamantane (0.066 mL, 0.44 mmol), $Pd_2(dba)_3$ (0.008 g, 5 mol%), TFP (0.009 g, 20 mol%) and K_2CO_3 (0.15 g, 1.1 mmol) in MeCN (2 mL) at 80 ºC for 2 h. Flash column chromatography eluting with 1:1 v/v EtOAc/*n*-hexane gave the product **240n** (0.11 g, 71%) as a colourless froth, mp 102-104 °C; δ_H (300 MHz, $CDCl_3$); 8.47 (1H, d, *J* 8.2, pyrido-H), 7.40-7.29 (5H, m, aryl-H), 7.28 (1H, d, *J* 8.2, pyrido-H), 7.13-7.06 (6H, m, aryl-H), 5.88 (1H, t, *J* 7.1, NCH_2CH=), 5.87 (1H, t, *J* 7.1, NCH_2CH=), 5.23 (2H, d, *J* 7.1, NCH_2), 4.95 (2H, d, *J* 7.1, NCH_2), 3.86 (2H, s, =CCH_2N), 3.77 (2H, s, =CCH_2N), 2.39 (3H, s, Me), 2.38 (3H, s, Me), 2.31 (3H, s, Me), 2.30 (3H, s, Me), 2.09 (3H, br s, 3 × adamantyl-CH), 2.02 (3H, br s, 3 × adamantyl-CH), 1.76 (6H, br d, *J* 2.2, 3 × adamantyl-CH_2), 1.66 (6H, br s, 3 × adamantyl-CH_2), 1.58 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 164.9, 161.2, 150.9, 150.0, 142.6, 142.3, 139.3, 138.4, 138.3, 137.8, 137.1, 137.06, 136.4, 136.0, 132.0, 129.7, 129.1, 129.0, 126.8, 126.3, 126.25, 123.5, 122.8, 119.5, 108.8, 50.9, 50.7, 42.7, 42.6, 42.5, 41.2, 40.4, 39.3, 36.9, 36.8, 29.7, 29.65, 21.5, 21.3, 21.1, 20.9; υ_{max}/cm^{-1} (film); 3313, 2905, 2848, 1707, 1662, 1598, 1511, 1447, 1389, 1357, 1310, 1260, 1218; *m/z* (ESI^+) 854.5 (44 %, MH^+); (Found MH^+, 854.5377. $C_{57}H_{68}N_5O_2$ requires *MH,* 854.5368).

NOE data ($CDCl_3$) for **240n**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	tolyl-H	adamantyl-H
1-H (δ 4.95)		3.50	2.62	-	-
2-H (δ 5.88)	1.20		-	3.55 (δ 7.31), 5.51 (δ 7.39)	-
4-H (δ 3.86)	2.54	-		5.42 (δ 7.39)	5.45 (δ 1.76)

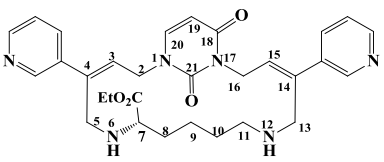
	% Enhancement				
Irradiated proton	1′-H	2′-H	4′-H	tolyl-H	adamantyl-H
1′-H (δ 5.23)		3.13	2.34	-	-
2′-H (δ 5.87)	1.30		-	3.75 (δ 7.31), 4.03 (δ 7.39)	-
4′-H (δ 3.77)	3.00	-		5.57 (δ 7.31)	5.77 (δ 1.58)

General Procedure G: Pd catalysed 4-component cascades.

A mixture of N^1,N^3-diallenyluracil **234** (0.25 mmol), 3-iodopyridine (0.60 mmol), nucleophile (0.25 mmol), $Pd_2(dba)_3$ (5 mol%), TFP (tri-(2-furyl)phosphine) (20 mol%), and K_2CO_3 (1.50 mmol) in MeCN (3 mL) was stirred and heated at 80 °C (oil bath temperature) for 3-5 h. The mixture was filtered through a filter paper and the solid washed with MeCN (5 mL). The solvent was removed under reduced pressure, the residue dissolved in $CHCl_3$ and washed with H_2O (1 x 20 mL). The organic layer was dried (anhydrous $MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography gradient elution with 10:3 v/v EtOAc/MeOH then 10:5 v/v EtOAc/MeOH and then 1:1 v/v EtOAc/MeOH to give the 18-membered macrocycles. Changing the eluting solvent to MeOH and then DMF gave inseparable mixtures of products.

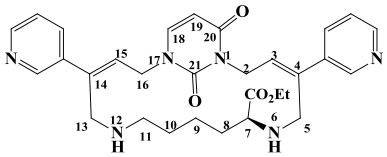
Ethyl (3*Z*,7*S*,14*Z*)-18,21-dioxo-4,14-di(pyridin-3-yl)-1,6,12,17-tetraazabicyclo-[15.3.1]henicosa-3,14,19-triene-7-carboxylate (242a) and Ethyl (3*Z*,7*S*,14*Z*)-20,21-dioxo-4,14-di(pyridin-3-yl)-1,6,12,17-tetraazabicyclo[15.3.1]henicosa-3,14,18-triene-7-carboxylate (242b).

Prepared by general procedure G from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), (*S*)-lysine ethyl ester dihydrochloride **241** (0.0617 g, 0.25 mmol), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.276 g, 2.00 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Work up by flash column chromatography gradient elution with 10:3 v/v EtOAc/MeOH then 10:5 v/v EtOAc/MeOH and then 1:1 v/v EtOAc/MeOH gave **242a** and then **242b**. Further elution with DMF afforded a complex mixture of 36-membered macrocycles; *m/z* (ESI^+) 1089.6 (10%, MH^+); (Found MH^+, 1089.5682. $C_{60}H_{73}N_{12}O_8$ requires *MH*, 1089.5669); 1111.6 (10%, M+Na); 545.3 (100%, $[M+2H]^{2+}$).



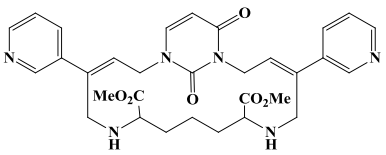
Compound **242a** was obtained as a colourless froth (0.039 g, 29%), mp 81-83 °C; δ_H (300 MHz, $CDCl_3$); 8.75 (1H, d, *J* 1.9, pyridyl-H), 8.70 (1H, d, *J* 1.4, pyridyl-H), 8.49 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 8.45 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 7.96 (1H, td, *J* 1.9 and 8.1, pyridyl-H), 7.86 (1H, td, *J* 1.9 and 8.1, pyridyl-H), 7.33 (1H, d, *J* 7.9, pyrimidinyl-H, 20-H), 7.26 (1H, dd, *J* 4.9 and 8.2, pyridinyl-H), 7.20 (1H, dd, *J* 4.9 and 8.2, pyridinyl-H), 5.86 (1H, t, *J* 6.2,

NCH_2CH=, 15-H), 5.85 (1H, d, *J* 7.9, pyrimidinyl-H, 19-H), 5.72 (1H, t, *J* 6.7, NCH_2CH=, 3-H), 4.94 (1H, dd, *J* 6.7 and 15.7, NCH_2CH=, 2-H_A), 4.84 (1H, dd, *J* 6.2 and 14.3, NCH_2CH=, 16-H_A), 4.78 (1H, dd, *J* 6.2 and 14.3, NCH_2CH=, 16-H_B), 4.59 (1H, dd, *J* 6.7 and 15.7, NCH_2CH=, 2-H_B), 4.27-4,12 (2H, m, CO_2CH_2Me), 3.77 (1H, d, 12.4, =CCH_2N, 13-H_A), 3.73 (1H, d, 12.1, =CCH_2N, 5-H_A), 3.55 (1H, d, *J* 12.4, =CCH_2N, 13-H_B), 3.44 (1H, d, *J* 12.1, =CCH_2N, 5-H_B), 3.40 (1H, dd, *J* 4.4 and 7.1, NH$CHCO_2Et$, 7-H), 2.76 (2H, br s, =CH_2NHCH_2, 11-H), 2.55 (2H, br s, 2 x NH), 1.79 (2H, br s, $NHCHCH_2$, 8-H), 1.61 (4H, br d, *J* 3.3, $CH_2CH_2CH_2NH$, 9-H and 10-H), 1.29 (3H, t, *J* 7.2, CO_2CH_2Me); δ_C (75 MHz, $CDCl_3$); 175.0, 162.8, 151.4, 148.8, 148.4, 147.6, 147.2, 142.6, 139.6, 138.4, 137.0, 136.9, 133.7 (2 x C), 125.3, 125.0, 123.3, 123.1, 102.5, 61.2, 60.6, 49.6, 48.9 48.6, 47.4, 39.8, 32.4, 28.6, 22.7, 14.3; υ_{max}/cm^{-1} (film); 3320, 2930, 1702, 1655, 1567, 1453, 1416, 1392, 1364, 1224; *m/z* (ESI^+) 545.3 (100%, MH^+); (Found MH^+, 545.2894. $C_{30}H_{37}N_6O_4$ requires *MH*, 545.2871).



Compound **242b** was obtained as a colourless froth (0.034 g, 25%), mp 69-71 °C; δ_H (300 MHz, $CDCl_3$); 8.75 (1H, d, *J* 1.9, pyridyl-H), 8.71 (1H, d, *J* 1.9, pyridyl-H), 8.48 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 8.45 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 7.93-7.88 (2H, m, 2 x pyridyl-H), 7.34 (1H, d, *J* 8.1, pyrimidinyl-H, 18-H), 7.25-7.20 (2H, m, 2 x pyridinyl-H), 5.86 (1H, d, *J* 8.1, pyrimidinyl-H, 19-H), 5.80 (1H, t, *J* 6.7, NCH_2CH=, 3-H), 5.73 (1H, dd, *J* 6.2 and 8.1, NCH_2CH=, 15-H), 4.92 (2H, d, *J* 6.7, NCH_2CH=, 2-H), 4.83 (1H, dd, *J* 8.1 and 15.0, NCH_2CH=, 16-H_A), 4.44 (1H, dd, *J* 6.2 and 15.0, NCH_2CH=, 16-H_B), 4.25-415 (2H, m, CO_2CH_2Me), 3.76 (1H, d, *J* 12.2, =CCH_2N, 13-H_A), 3.72 (1H, d, *J* 11.2, =CCH_2N, 5-H_A), 3.57 (1H, d, *J* 12.2, =CCH_2N, 13-H_B), 3.50 (1H, d, *J* 11.2, =CCH_2N, 5-H_B), 3.41 (1H, dd, *J* 4.1 and 6.9, NH$CHCO_2Et$, 7-H), 2.77 (2H, br s, =CH_2NHCH_2, 11-H), 2.58 (2H, br s, 2 x NH), 1.78 (2H, br s, $NHCHCH_2CH_2$, 8-H), 1.61 (4H, br s, $CHCH_2CH_2$ CH_2CH_2NH, 9-H and 10-H), 1.28 (3H, t, *J* 7.2, CO_2CH_2Me); δ_C (75 MHz, $CDCl_3$); 174.9, 162.7, 151.4, 148.9, 148.3, 147.5, 147.4, 142.3, 140.1, 138.0, 137.2, 136.7, 133.9, 133.5, 126.1, 124.1, 123.3, 123.1, 102.6, 61.5, 60.6, 49.5, 48.8, 48.0, 47.1, 40.1, 32.4, 28.7, 22.8, 14.3; υ_{max}/cm^{-1} (film); 3321, 2932, 1703, 1658, 1567, 1454, 1416, 1392, 1360, 1223; *m/z* (ESI^+) 545.3 (100%, MH^+); (Found MH^+, 545.2847. $C_{30}H_{37}N_6O_4$ requires *MH*, 545.2871).

Dimethyl (3*Z*,14*Z*)-20,21-dioxo-4,14-di(pyridin-3-yl)-1,6,12,17-tetraazabicyclo[15.3.1]henicosa-3,14,18-triene-7,11-dicarboxylate (244).



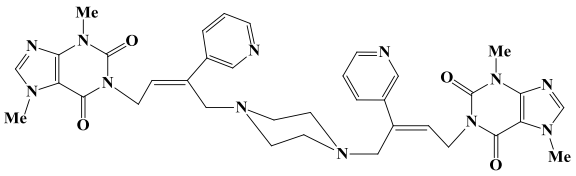
Prepared by general procedure G from N^1,N^3-diallenyluracil **234** (0.054g, 0.25 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), 2,6-diaminopimelic acid dimethyl ester **243** (0.055 g, 0.25 mmol) (1:1 *rac*-/*meso*-mixture), $Pd_2(dba)_3$ (0.0115 g, 5 mol%), TFP (0.0116 g, 20 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in MeCN (3 mL) at 80 ºC for 5 h. Work up by flash column chromatography gradient elution with 10:3 v/v EtOAc/MeOH then 10:5 v/v EtOAc/MeOH and then 1:1 v/v EtOAc/MeOH gave **244** (1:1 *rac*-/*meso*-mixture) as a colourless amorphous solid (0.071 g, 48%), mp 79-81°C. Due to the presence of both *meso*- and *rac*-isomers, two separate proton and/or carbon NMR signals are frequently observed and noted in the NMR data by asterisks. These assignments are based on DEPT135, HMBC, HMQC and also comparison with similar systems **242a** and **242b**. δ_H (300 MHz, $CDCl_3$); 8.76 (1H, dd, *J* 1.4 and 2.4, pyridyl-H), 8.71 (1H, d, *J* 2.4, pyridyl-H), 8.49 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 8.46 (1H, dd, *J* 1.4 and 4.8, pyridyl-H), 7.98-7.90 (2H, m, 2 x pyridyl-H), 7.32 (1H, dd, *J* 1.9 and 8.1, pyrimidinyl-H), 7.29-7.19 (2H, m, 2 x pyridinyl-H), 5.86 (1H, d, *J* 8.1, pyrimidinyl-H), 5.82 (1H, t, *J* 7.4, NCH_2CH=), 5.74-5.70 (1H, m, NCH_2CH=), 5.08-4.45 (4H, 2 x NCH_2CH=)*, 3.74 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.77-3.66 (2H, m, =CCH_2N), 3.51-3.38 (4H, m, =CCH_2N and 2 x $CHCO_2Me$), 2.43 (2H, br s, 2 x NH), 1.80-1.67 (6H, br m, 3 x CH_2); δ_C (75 MHz, $CDCl_3$); 175.17*, 175.14*, 175.02*, 174.97*, 162.85, 151.33, 148.86, 148.41, 147.44*, 147.41*, 147.27, 142.49*, 142.38*, 139.43, 137.78*, 137.74*, 137.03*, 136.98*, 136.77*, 136.70*, 133.73, 133.51*, 133.49*, 126.26*, 126.01*, 125.05*, 124.73*, 133.24, 123.10, 102.41*, 102.39*, 61.33*, 61.14*, 61.04*, 60.72*, 51.78*, 51.75*, 51.74*, 51.70*, 48.83*, 48.60*, 47.37*, 47.20*, 47.08*, 46.94*, 40.15*, 40.03*, 32.76*, 32.72*, 32.42*, 32.34*, 21.35*, 20.78*; υ_{max}/cm^{-1} (film); 3321, 2951, 2855, 1732, 1704, 1660, 1567, 1455, 1393, 1354; *m/z* (ESI^+) 589.3 (100%, MH^+); (Found MH^+, 589.2780. $C_{31}H_{37}N_6O_6$ requires *MH*, 589.2769). *Two sets of NCH_2CH= protons were observed in the presence of the chiral $Eu(fod)_3$ reagent one for the *meso*-isomer [5.04 (0.5H, dd, *J* 7.6 and 15.7), 4.80 (0.5H, dd, *J* 6.9 and 15.7), 4.69 (0.5H, dd, *J* 6.7 and 15.7) and 4.49 (0.5H, dd, *J* 5.7 and 15.7)] and the second for the *rac*-isomer [4.95-4.89 (2H, m)]. *Some of

carbons appeared as two peaks, and the assignment based on DEPT 135, HMQC, comparison with similar systems.

General Procedure H: Pd catalysed 5-component cascades using piperazine as a dinucleophile.

A mixture of *N*-allenylpurine **195** (1.00 mmol), aryl/heteroaryl iodide (1.10 mmol), piperazine **189a** (0.50 mmol), $Pd_2(dba)_3$ (5 mol%), TFP (tri-(2-furyl)phosphine) (20 mol%) and K_2CO_3 (3.00 mmol) in MeCN (5 mL) was stirred and heated at 80 °C (oil bath temperature) for 3-5 h. The product precipitated from the hot solution. The cooled solution was filtered, the precipitate washed with water and crystallized from $CHCl_3$.

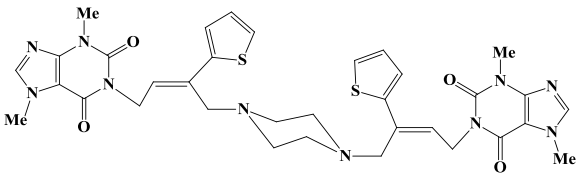
1,1'-{Piperazine-1,4-diylbis[(2*Z*)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (245a).



Prepared by general procedure H from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 3-iodopyridine (0.246 g, 1.10 mmol), piperazine **189a** (0.043 g, 0.50 mmol), $Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (0.023 g, 20 mol%) and K_2CO_3 (0.40 g, 3.00 mmol) in MeCN (5 mL) at 80 °C for 3 h. The product **245a** crystallized from $CHCl_3$ as colourless needles (0.31 g, 88%), mp 248-250 °C; δ_H (300 MHz, $CDCl_3$); 8.68 (2H, d, *J* 2.6, 2 × pyridinyl-H), 8.44 (2H, dd, *J* 4.6 and 1.5, 2 × pyridinyl-H), 7.79 (2H, dt, *J* 7.9 and 2.0, 2 × pyridinyl-H), 7.52 (2H, s, 2 × purine 8-H), 7.18 (2H, dd, *J* 7.9 and 4.9, 2 × pyridinyl-H), 5.91 (2H, t, *J* 6.7, 2 × NCH_2CH=), 4.89 (4H, d, *J* 6.7, 2 × NCH_2CH=), 3.99 (6H, s, 2 × purine 7-NCH_3), 3.58 (6H, s, 2 × purine 3-NCH_3), 3.55 (4H, s, 2 × =CCH_2N), 2.48 (8H, brs, 4 x piperazinyl-CH_2); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.9, 148.1, 148.0, 141.6, 137.4, 136.7, 134.0, 128.5, 122.8, 107.7, 56.7, 52.9, 39.6, 33.7, 29.8; υ_{max}/cm^{-1} (film); 3104, 3038, 2943, 2812, 1704, 1659, 1603, 1549, 1456, 1359, 1312, 1234; *m/z* (ESI^+) 705.3 (19%, MH^+); (Found MH^+, 705.3339. $C_{36}H_{41}N_{12}O_4$ requires *MH*, 705.3368).

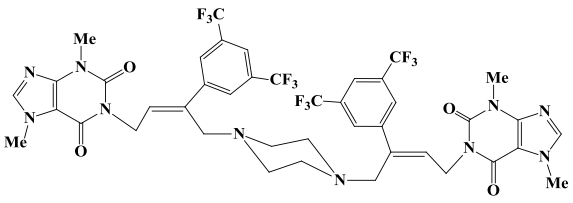
1,1'-{Piperazine-1,4-diylbis[(2*E*)-3-(2-thienyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (245b).

Prepared by general procedure H from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 2-iodothiophene (0.132 mL, 1.10 mmol), piperazine **189a** (0.043 g, 0.50 mmol),



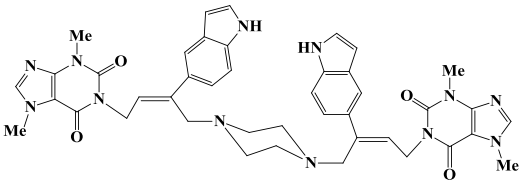
$Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (tri-(2-furyl)phosphine) (0.023 g, 20 mol%) and K_2CO_3 (0.40 g, 3.00 mmol) in MeCN (5 mL) at 80 °C for 3 h. The product **245b** crystallized from $CHCl_3$ as colourless needles (0.33 g, 92%), mp 265-267 °C; δ_H (300 MHz, $CDCl_3$); 7.50 (2H, s, 2 × purine 8-H), 7.2 (2H, d, *J* 3.6, 2 × thienyl-H), 7.11 (2H, d, *J* 4.1, 2 × thienyl-H), 6.92 (2H, dd, *J* 5.1 and 3.6, 2 × thienyl-H), 6.04 (2H, t, *J* 6.7, 2 × NCH_2CH=), 4.87 (4H, d, *J* 6.7, 2 × NCH_2CH=), 3.98 (6H, s, 2 × purine 7-NCH_3), 3.58 (6H, s, 2 × purine 3-NCH_3), 3.55 (4H, s, 2 × =CCH_2N), 2.59 (8H, brs, 4 x piperazinyl-CH_2); δ_C (75 MHz, DMSO-d_6); 154.6, 151.2, 148.7, 144.9, 143.3, 132.5, 127.6, 125.9, 125.3, 124.5, 197.1, 56.8, 52.9, 39.2, 33.6, 29.8; υ_{max}/cm^{-1} (solid); 2814, 1706, 1659, 1602, 1547, 1450, 1324, 1290, 1231; *m/z* (ESI^+) 715.3 (100%, MH^+); (Found MH^+, 715.2587. $C_{34}H_{39}N_{10}O_4{}^{32}S_2$ requires *MH*, 715.2592).

1,1'-(Piperazine-1,4-diylbis{(2*Z*)-3-[3,5-bis(trifluoromethyl)phenyl]but-2-ene-4,1-diyl})bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (245c).



Prepared by general procedure H from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.20 mL, 1.10 mmol), piperazine **189a** (0.043 g, 0.50 mmol), $Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (tri-(2-furyl)phosphine) (0.023 g, 20 mol%) and K_2CO_3 (0.40 g, 3.00 mmol) in MeCN (5 mL) for 5 h. The product **245c** crystallized from $CHCl_3$ as colourless needles (0.39 g, 80%), mp 256-258 °C; δ_H (300 MHz, $CDCl_3$); 7.96 (4H, s, 2 × phenyl 2-H and 6-H), 7.72 (2H, s, 2 × phenyl 4-H), 7.27 (2H, s, 2 × purine 8-H), 5.96 (2H, t, *J* 6.3, 2 × NCH_2CH=), 4.90 (4H, d, *J* 6.3, 2 × NCH_2CH=), 4.00 (6H, s, 2 × purine NCH_3), 3.60 (6H, s, 2 × purine NCH_3), 3.58 (4H, s, 2 × =CCH_2N), 2.52 (8H, brs, 4 x piperazinyl-CH_2); δ_C (75 MHz, AcOH-d_4); 155.3, 152.0, 148.5, 143.6, 142.3, 138.0, 131.8, 131.7 (J 32.9), 128.1 (brs), 123.8 (J 272.0), 122.2 (brs), 108.1, 53.8, 49.6, 40.3, 33.7, 30.0; υ_{max}/cm^{-1} (solid); 2919, 1705, 1660, 1547, 1458, 1383, 1352, 1279; *m/z* (ESI^+) 975.3 (100%, MH^+); (Found MH^+, 975.2965. $C_{42}H_{39}F_{12}N_{10}O_4$ requires *MH*, 975.2959).

1,1'-{Piperazine-1,4-diylbis[(2*Z*)-3-(1*H*-indol-5-yl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (245d).



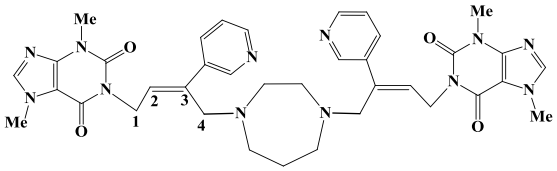
Prepared by general procedure H from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 5-iodoindole (0.267, 1.10 mmol), piperazine **189a** (0.043 g, 0.50 mmol), $Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (tri-(2-furyl)phosphine) (0.023 g, 20 mol%) and K_2CO_3 (0.40 g, 3.00 mmol) in MeCN (5 mL) for 3.5 h. The product **245d** crystallized from $CHCl_3$ as colourless needles (0.31 g, 80%), mp 187-189 °C; δ_H (300 MHz, DMSO-d_6); 11.02 (2H, brs, 2x indolyl-NH), 8.00 (2H, d, *J* 0.5, 2 × indolyl-H), 7.60 (2H, brs, 2 × indolyl-H), 7.29 (2H, t, *J* 2.7, 2 × indolyl-H), 7.26 (2H, s, 2 × purine 8-H), 7.18 (2H, dd, *J* 8.6 and 1.7, 2 x indolyl-H), 6.37 (2H, m, 2 × indolyl-H), 5.75 (2H, t, *J* 6.4, 2 × NCH_2CH=), 4.74 (4H, d, *J* 6.4, 2 × NCH_2CH=), 3.87 (6H, s, 2 × purine 7-NCH_3), 3.51 (4H, s, 2 × =CCH_2N), 3.41 (6H, s, 2 × purine 3-NCH_3), 2.43 (8H, brs, 4 × piperazinyl-CH_2); δ_C (75 MHz, DMSO-d_6); 154.2, 150.8, 148.2, 142.7, 138.9, 135.1, 132.7, 127.4, 125.6, 125.4, 119.9, 117.5, 110.7, 106.7, 101.3, 56.8, 52.7, 39.2, 33.1, 29.3; υ_{max}/cm^{-1} (solid); 3332, 2822, 1700, 1652, 1548, 1454, 1309, 1233; *m/z* (ESI^+) 781.4 (100%, MH^+); (Found MH^+, 781.3692. $C_{42}H_{45}N_{12}O_4$ requires *MH*, 781.3681).

General Procedure I: Pd catalysed 5-component cascades using homopiperazine as a dinucleophile.

As for general procedure H except the reaction time was 6-11 h. The mixture was filtered through a filter paper and the K_2CO_3 precipitate washed with MeCN (5 mL). The solvent was removed under reduced pressure and the resulting gum dissolved in $CHCl_3$ and washed with saturated NH_4Cl (1 x 20 mL) and then with saturated NaCl (1 x 20 mL). The organic layer was dried (anhydrous $MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography.

1,1'-{1,4-Diazepane-1,4-diylbis[(2*Z*)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (246a).

Prepared by general procedure I from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 3-iodopyridine (0.246 g, 1.10 mmol), homopiperazine **189b** (0.05 g, 0.50 mmol),

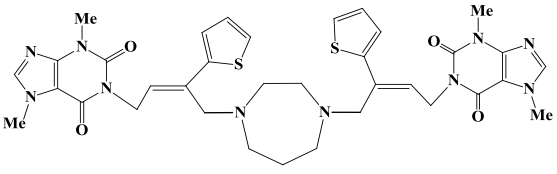


$Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (0.023 g, 20 mol%), and K_2CO_3 (0.4 g, 3.00 mmol) in MeCN (5 mL) at 80 ºC for 6 h. Flash column chromatography eluting with 1:1 v/v EtOAc/MeOH gave the product **246a** (0.21 g, 58%) as a colourless amorphous solid, mp 93-95 °C; δ_H (300 MHz, $CDCl_3$); 8.65 (2H, d, *J* 1.8, 2 × pyridinyl-H), 8.43 (2H, dd, *J* 4.9 and 1.5, 2 × pyridinyl-H), 7.74 (2H, dt, *J* 7.9 and 1.7, 2 × pyridinyl-H), 7.52 (2H, s, 2 × purine 8-H), 7.18 (2H, dd, *J* 7.7 and 4.9, 2 × pyridinyl-H), 5.85 (2H, t, *J* 6.7, 2 × NCH_2CH=), 4.88 (4H, d, *J* 6.7, 2 × NCH_2CH=), 3.99 (6H, s, 2 × purine 7-NCH_3), 3.33 (4H, s, 2 × C=CH_2N), 3.59 (6H, s, 2 × purine 3-NCH_3), 2.65 (4H, t, *J* 5.6, diazepane 5- and 7-CH_2), 2.61 (4H, s, diazepane 2- and 3-CH_2), 1.67 (2H, quin, *J* 5.6, diazepane 6-CH_2); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.9, 148.0 (2 x C), 141.5, 138.0, 137.3, 134.1, 127.8, 122.7, 107.7, 56.1, 54.6, 53.5, 39.7, 33.7, 29.8, 27.8; υ_{max}/cm^{-1} (film); 3104, 3048, 2941, 2828, 1704, 1659, 1603, 1550, 1455, 1414, 1359, 1234; *m/z* (ESI^+) 719.4 (100%, MH^+); (Found MH^+, 719.3525. $C_{37}H_{43}N_{12}O_4$ requires *MH*, 719.3525).

NOE data for **246a**:

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Pyridinyl-H (δ 8.65 and 7.74)	Diazepanyl-H (δ 2.64)
1-H		5.20	3.57	-	-
2-H	3.97		-	4.02 and 3.57	-
4-H	4.54	-		3.50 and 2.56	4.50

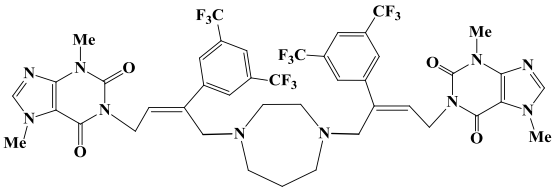
1,1'-{1,4-Diazepane-1,4-diylbis[(2*E*)-3-(2-thienyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (246b).



Prepared by general procedure I from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 2-iodothiophene (0.132 mL, 1.10 mmol), homopiperazine **189b** (0.05 g, 0.50 mmol), $Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (0.023 g, 20 mol%), and K_2CO_3 (0.4 g, 3.00 mmol) in MeCN (5 mL) at 80 ºC for 10 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **246b** (0.19 g, 53%) as colourless amorphous solid, mp 110-112 °C; δ_H (300 MHz, $CDCl_3$); 7.50

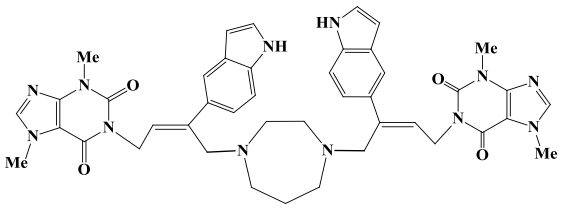
(2H, s, 2 × purine 8-H), 7.19 (2H, d, *J* 3.8, 2 x thienyl-H), 7.11 (2H, d, *J* 5.1, 2 x thienyl-H), 6.91 (2H, dd, *J* 5.1 and 3.7, 2 x thienyl-H), 6.01 (2H, t, *J* 6.9, 2 × NCH_2CH=), 4.88 (4H, d, *J* 6.9, 2 × NCH_2CH=), 3.97 (6H, s, 2 × purine 7-NCH_3), 3.65 (4H, s, 2 × C=CH_2N), 3.57 (6H, s, 2 × purine 3-NCH_3), 2.81 (4H, t, *J* 5.6, diazepane 5- and 7-CH_2), 2.79 (4H, s, diazepane 2- and 3-CH_2), 1.85 (2H, quin, *J* 5.6, diazepane 6-CH_2); δ_C (75 MHz, $CDCl_3$); 155.4, 151.8, 149.3, 145.7, 141.9, 135.0, 127.1, 125.0, 124.7, 124.4, 108.1, 57.3, 55.1, 54.2, 40.0, 34.0, 30.2, 28.2; υ_{max}/cm^{-1} (film); 3104, 2943, 2824, 1703, 1659, 1604, 1550, 1455, 1363, 1311, 1233; *m/z* (ESI^+) 729.3 (100%, MH^+); (Found MH^+, 729.2751. $C_{35}H_{41}N_{10}O_4{}^{32}S_2$ requires *MH*, 729.2748).

1,1'-(1,4-Diazepane-1,4-diylbis{(2Z)-3-[3,5-bis(trifluoromethyl)phenyl]but-2-ene-4,1-diyl})bis(3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione) (246c).



Prepared by general procedure I from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 1-iodo-bis(3,5-trifluoromethyl)benzene (0.2 mL, 1.10 mmol), homopiperazine **189b** (0.05 g, 0.50 mmol), $Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (0.023 g, 20 mol%) and K_2CO_3 (0.4 g, 3.00 mmol) in MeCN (5 mL) at 80 ºC for 11 h. Flash column gradient elution chromatography from 6:1 to 3:1 v/v EtOAc/MeOH gave the product **246c** (0.23 g, 47%) as a colourless amorphous solid, mp 95-97 °C; δ_H (300 MHz, $CDCl_3$); 7.97 (4H, s, 2 × phenyl 2-H and 6-H), 7.73 (2H, s, 2 × phenyl 4-H), 7.56 (2H, s, 2 × purine 8-H), 5.95 (2H, t, *J* 6.6, 2 × NCH_2CH=), 4.90 (4H, d, *J* 6.6, 2 × NCH_2CH=), 4.01 (6H, s, 2 × purine 7-NCH_3), 3.70 (4H, s, 2 × C=CH_2N), 3.60 (6H, s, 2 × purine 3-NCH_3), 2.68 (4H, t, *J* 5.8, diazepane 5- and 7-CH_2), 2.62 (4H, s, diazepane 2- and 3-CH_2), 1.72 (2H, quin, *J* 5.8, diazepane 6-CH_2); δ_C (75 MHz, $CDCl_3$); 154.0, 150.5, 148.1, 142.7, 140.7, 137.3, 129.9 (*J* 33.0), 128.4, 126.0 (*J* 3.0), 122.6 (*J* 271.0), 119.7 (*J* 3.0), 106.7, 55.3, 53.9, 52.3, 38.54, 32.7, 28.8, 26.9; υ_{max}/cm^{-1} (film); 3056, 2944, 2828, 1712, 1667, 1605, 1551, 1456, 1415, 1381, 1314, 1279, 1234; *m/z* (ESI^+) 989.3 (100%, MH^+); (Found MH^+, 989.3109. $C_{43}H_{41}F_{12}N_{10}O_4$ requires *MH*, 989.3115).

1,1'-{1,4-Diazepane-1,4-diylbis[(2Z)-3-(1H-indol-5-yl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione) (246d).

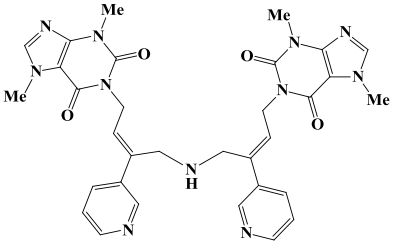


Prepared by general procedure I from *N*-allenylpurine **195** (0.232 g, 1.00 mmol), 5-iodoindole (0.267 g, 1.10 mmol), homopiperazine **189b** (0.05 g, 0.50 mmol), $Pd_2(dba)_3$ (0.022 g, 5 mol%), TFP (0.023 g, 20 mol%), and K_2CO_3 (0.4 g, 3.00 mmol) in MeCN (5 mL) at 80 ºC for 9 h. Flash column gradient elution chromatography from EtOAC to 1:1 v/v EtOAc/MeOH gave the product **246d** (0.26 g, 66%) as a colourless amorphous solid, mp 107-110 °C; δ_H (300 MHz, $CDCl_3$); 8.27 (2H, s, 2 × indolyl-NH), 7.66 (2H, s, 2 × indolyl-H),7.46 (2H, s, 2 × purine 8-H), 7.20 (4H, s, 4 × indolyl-H), 7.09 (2H, t, *J* 2.9, 2 × indolyl-H), 6.44 (2H, t, *J* 2.5, 2 × indolyl-H), 5.79 (2H, t, *J* 6.5, 2 × NCH_2CH=), 4.89 (4H, d, *J* 6.5, 2 × NCH_2CH=), 3.95 (6H, s, 2 × purine 7-NCH_3), 3.75 (4H, s, 2 × C=CH_2N), 3.56 (6H, s, 2 × purine 3-NCH_3), 2.70 (8H, brs, diazepane 2-, 3-, 5- and 7-CH_2), 1.71 (2H, quin, *J* 5.1, diazepane 6-CH_2); δ_C (75 MHz, $CDCl_3$); 154.7, 151.0, 148.3, 141.3, 140.9, 134.7, 134.1, 127.2, 124.7, 123.8, 121.0, 118.2, 109.9, 107.3, 102.3, 56.5, 54.0, 53.4, 39.8, 33.2, 29.3, 27.2; υ_{max}/cm^{-1} (film); 3333, 3109, 3038, 2939, 2829, 1704, 1659, 1602, 1549, 1454, 1366, 1312, 1233; *m/z* (ESI^+) 795.4 (100%, MH^+); (Found MH^+, 795.3824. $C_{43}H_{47}N_{12}O_4$ requires *MH*, 795.3838).

General procedure J: ammonia surrogates as nucleophiles.

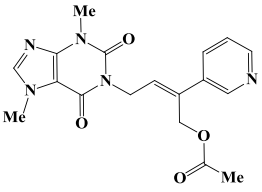
A mixture of substituted allene (1 equiv.), aryl/heteroaryl iodide (1.2 equiv.), ammonia equivalent (3-6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (tri-(2-furyl)phosphine) (10 mol%) and K_2CO_3 (2 equiv.) in 1,4-dioxane/DMF (5:1) was stirred and heated at 100 °C (oil bath temperature). The mixture was cooled, evaporated under reduced pressure and the resulting residue dissolved in $CHCl_3$ and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography.

1,1'-{Iminobis[(2*Z*)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (247a).



Prepared by general procedure J from purine allene **195** (0.102 g, 0.439 mmol), 3-iodopyridine (0.108 g, 0.53 mmol), ammonium carbonate (0.253 g, 2.6 mmol), $Pd_2(dba)_3$ (0.01 g, 2.5 mol%) and TFP (0.01 g, 10 mol%) in 2:1 v/v 1,4-dioxane/water (3 mL) at 80 ºC for 8 h. Flash column chromatography eluting with 5:3 v/v EtOAc/MeOH gave the product **247a** (0.09 g, 65%) as a colourless froth, mp 106-108 °C; δ_H (300 MHz, $CDCl_3$); 8.70 (2H, br s, 2 × pyridinyl-H), 8.44 (2H, br d, *J* 4.4, 2 × pyridinyl-H), 7.76 (2H, dt, *J* 7.7 and 1.6, 2 × pyridinyl-H), 7.52 (2H, s, 2 × purine-H), 7.15 (2H, dd, *J* 4.4 and 7.7, 2 × pyridinyl-H), 5.92 (2H, t, *J* 7.1, 2 × NCH_2CH=), 4.90 (4H, d, *J* 7.1, 2 × NCH_2CH=), 3.98 (6H, s, 2 × purine 7-Me), 3.93 (4H, s, 2 × =CCH_2N), 3.57 (6H, s, 2 × purine 3-Me), 2.19 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$);155.0, 151.4, 148.9, 148.3, 147.8, 141.6, 138.7, 137.0, 133.8, 126.5, 123.0, 107.6, 48.1, 39.5, 33.7, 29.8; υ_{max}/cm^{-1} (film); 3312, 2950, 1704, 1658, 1603, 1550, 1455, 1414, 1356, 1314, 1286, 1234; *m/z* (ESI^+) 636.3 (100%, MH^+); (Found MH^+, 636.2804. $C_{32}H_{34}N_{11}O_4$ requires *MH*, 636.2790).

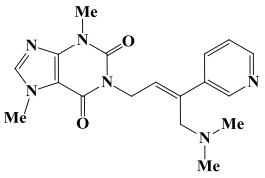
(2*Z*)-4-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-2-(pyridin-3-yl)but-2-en-1-yl acetate (248).



Prepared by general procedure J from purine allene **195** (0.102 g, 0.439 mmol), 3-iodopyridine (0.108 g, 0.53 mmol), ammonium acetate (0.203 g, 2.60 mmol), $Pd_2(dba)_3$ (0.01 g, 2.5 mol%) and TFP (0.01 g, 10 mol%) in 2:1 v/v DMF/water (3 mL) at 80 ºC for 3 h. Flash column chromatography gradient eluting with 10:1 then 5:3 v/v EtOAc/MeOH gave the products **248** (0.06 g, 37%) and **247a** (0.01 g, 7%), respectively, as a colourless froth. Product **248**: mp 106-108 °C; δ_H (300 MHz, $CDCl_3$); 8.65 (1H, d, *J* 2.2, pyridinyl-H), 8.50 (1H, dd, *J* 1.6 and 4.9, pyridinyl-H), 7.72 (1H, dt, *J* 7.7 and 1,6, pyridinyl-H), 7.57 (1H, s, purine-H), 7.25 (1H, dd, *J* 4.9 and 7.7, pyridinyl-H), 6.07 (1H, t, *J* 6.6, NCH_2CH=), 5.29 (2H, s, =CCH_2O), 4.94 (2H, d, *J* 6.6, NCH_2CH=), 4.01 (3H, s, purine 7-Me), 3.59 (3H, s, purine 3-Me), 2.04 (3H, s, CO_2Me); δ_C (75 MHz, $CDCl_3$); 170.7, 154.9, 151.3, 148.9, 148.7, 147.7, 141.7, 135.3, 153.1, 133.7, 127.7, 123.1, 107.6, 60.7, 39.2, 33.6, 29.7, 20.9; υ_{max}/cm^{-}

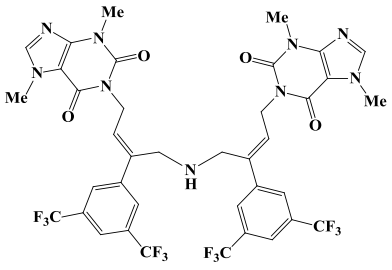
^{1} (film); 2949, 1737, 1704, 1660, 1603, 1459, 1455, 1415, 1364, 1316, 1286, 1232; *m/z* (ESI^{+}) 370.2 (100%, MH^{+}); (Found MH^{+}, 370.1516. $C_{18}H_{20}N_5O_4$ requires *MH*, 370.1510).

1-[(2*Z*)-4-(Dimethylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (249).



Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), 3-iodopyridine (0.123 g, 0.60 mmol), urea (0.36 g, 6.00 mmol), $Pd_2(dba)_3$ (0.011 g, 2.5 mol%), TFP (0.012 g, 10 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in 2:1 v/v DMF/water (3 mL) at 80 ºC for 4 h. Flash column chromatography eluting with 5:1 v/v EtOAc/MeOH gave the product **249** (0.14 g, 79%) as a colourless amorphous solid, mp 172-174 °C; δ_H (300 MHz, $CDCl_3$); 8.68 (1H, d, *J* 1.6, pyridinyl-H), 8.45 (1H, dd, *J* 1.6 and 4.9, pyridinyl-H), 7.76 (1H, dt, *J* 7.7 and 1.6, pyridinyl-H), 7.54 (1H, s, purine-H), 7.21 (1H, dd, *J* 4.9 and 7.7, pyridinyl-H), 5.92 (1H, t, *J* 6.6, NCH_2CH=), 4.93 (2H, d, *J* 6.6, NCH_2CH=), 4.00 (3H, s, purine 7-Me), 3.59 (3H, s, purine 3-Me), 3.56 (2H, s, =CCH_2N), 2.27 (6H, s, NMe_2); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.9, 148.3, 147.8, 141.6, 137.6, 137.1, 133.8, 128.1, 122.9, 107.6, 57.6, 45.3, 39.5, 33.6, 29.8; υ_{max}/cm^{-1} (film); 2943, 2818, 2766, 1704, 1660, 1603, 1549, 1455, 1414, 1366, 1315, 1286, 1234; *m/z* (ESI^{+}) 355.2 (100%, MH^{+}); (Found MH^{+}, 355.1886. $C_{18}H_{23}N_6O_2$ requires *MH*, 355.1877).

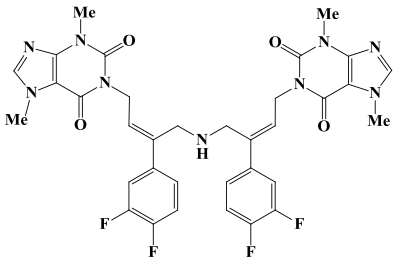
1,1'-(Iminobis{(2*Z*)-3-[3,5-bis(trifluoromethyl)phenyl]but-2-ene-4,1-diyl})bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (247b).



Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), 1-iodo-3,5-bis-(trifluoromethyl)benzene (0.11 mL, 0.60 mmol), ammonium tartrate (0.276 g, 1.50 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.138 g, 1.00 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 14 h. Flash column chromatography eluting with 20:1 v/v EtOAc/MeOH gave the product **247b** (0.194 g, 86%) as a colourless froth, mp 94-96 °C; δ_H (300 MHz, $CDCl_3$); 7.94 (2H, s, 4 × phenyl-H), 7.70 (2H, s, 2 × phenyl-H), 7.54 (2H, s, 2 ×

purine-H), 5.95 (2H, t, *J* 7.1, 2 × NCH_2CH=), 4.92 (4H, d, *J* 7.1, 2 × NCH_2CH=), 3.98 (10H, s, 2 × purine 7-Me and 2 × =CCH_2N), 3.58 (6H, s, 2 × purine 3-Me); δ_C (75 MHz, $CDCl_3$);155.0, 151.3, 149.0, 143.8, 141.7, 139.3, 131.3 (*J* 33.2), 128.3, 126.6 (*J* 3.3), 123.3 (*J* 273.1), 120.9 (*J* 3.3), 107.6, 48.4, 39.5, 33.6, 29.8; υ_{max}/cm^{-1} (film); 3312, 3017, 2952, 1710, 1660, 1605, 1550, 1456, 1430, 1415, 1382, 1312, 1279, 1235; *m/z* (ESI^+) 906.2 (100%, MH^+); (Found MH^+, 906.2366. $C_{38}H_{32}F_{12}N_9O_4$ requires *MH*, 906.2380).

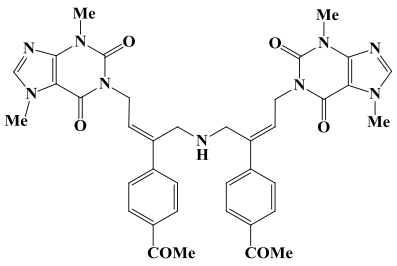
1,1'-{Iminobis[(2*Z*)-3-(3,4-difluorophenyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (247c).



Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), 3,4-difluoroiodobenzene (0.144 gm, 0.60 mmol), ammonium tartrate (0.552 g, 3.00 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.138 g, 1.00 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 13 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **247c** (0.164 g, 93%) as a colourless froth, mp 92-94 °C; δ_H (300 MHz, $CDCl_3$); 7.53 (2H, s, 2 × purine-H), 7.36-7.29 (2H, m, 2 × phenyl-H), 7.21-7.16 (2H, m, 2 × phenyl-H), 7.06-6.97 (2H, m, 2 × phenyl-H), 5.85 (2H, t, *J* 7.1, 2 × NCH_2CH=), 4.87 (4H, d, *J* 7.1, 2 × NCH_2CH=), 3.98 (6H, s, 2 × purine 7-Me), 3.87 (4H, s, 2 × =CCH_2N), 3.57 (6H, s, 2 × purine 3-Me), 2.17 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$); 154.9, 151.3, 150.0 (dd, *J* 246.6 and 13.3), 149.6 (dd, *J* 248.2 and 12.7), 148.9, 141.6, 139.6, 138.6 (dd, *J* 5.5 and 4.4), 125.8, 122.5 (dd, *J* 5.5 and 3.3), 116.7 (d, *J* 16.6), 115.5 (d, *J* 17.7), 107.6, 48.1, 39.5, 33.6, 29.7; υ_{max}/cm^{-1} (film); 3313, 3015, 2950, 1704, 1660, 1602, 1549, 1515, 1487, 1455, 1415, 1357, 1287, 1234; *m/z* (ESI^+) 706.2 (100%, MH^+); (Found MH^+, 706.2475. $C_{34}H_{32}F_4N_9O_4$ requires *MH*, 706.2508).

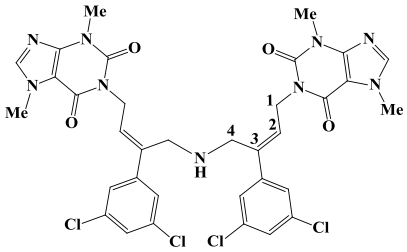
1,1'-{Iminobis[(2*Z*)-3-(4-acetylphenyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (247d).

Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), 4-iodoacetophenone (0.148 g, 0.60 mmol), ammonium tartrate (0.552 g, 3.00 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.138 g, 1.00



mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 13 h. Flash column chromatography eluting with 40:1 v/v $CHCl_3$/MeOH gave the product **247d** (0.12 g, 67%) as a colourless froth, mp 110-112 °C; δ_H (300 MHz, $CDCl_3$); 7.82 (4H, d, *J* 8.2, 4 × phenyl-H), 7.56 (2H, s, 2 × purine-H), 7.54 (4H,d, *J* 8.2, 4 × phenyl-H), 5.83 (2H, t, *J* 7.1, 2 × NCH_2CH=), 4.91 (4H, d, *J* 7.1, 2 × NCH_2CH=), 3.99 (6H, s, 2 × purine 7-Me), 3.97 (4H, s, 2 × =CCH_2N), 3.58 (6H, s, 2 × purine 3-Me), 2.58 (6H, s, 3 × COMe), 2.23 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$); 197.7, 154.9, 151.3, 148.8, 146.2, 141.7, 140.6, 135.7, 128.3, 127.1, 126.6, 107.6, 47.8, 39.6, 33.6, 29.7, 26.6; υ_{max}/cm^{-1} (film); 3320, 3114, 3012, 2945, 1704, 1659, 1602, 1549, 1487, 1455, 1428, 1412, 1358, 1312, 1270, 1234; *m/z* (ESI^+) 718.3 (100%, MH^+); (Found MH^+, 718.3111. $C_{38}H_{40}N_9O_6$ requires *MH*, 718.3096).

1,1'-{Iminobis[(2*Z*)-3-(3,5-dichlorophenyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (247e).

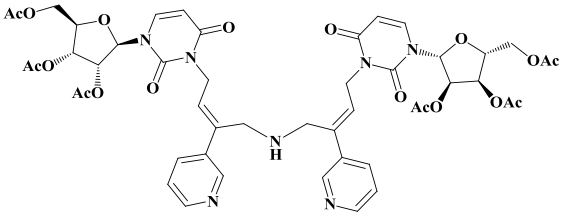


Prepared by general procedure J from purine allene **195** (0.109 g, 0.47 mmol), 3,5-dichloroiodobenzene (0.154 g, 0.60 mmol), ammonium tartrate (0.51 g, 2.82 mmol), $Pd_2(dba)_3$ (0.011 g, 2.5 mol%), TFP (0.011 g, 10 mol%) and K_2CO_3 (0.13 g, 0.94 mmol) in 4:1 v/v 1,4-dioxane/DMF (10 mL) at 100 ºC for 16 h. Flash column chromatography eluting with 20:1 v/v EtOAc/MeOH gave the product **247e** (0.157 g, 87%) as a colourless froth, mp 102-104 °C; δ_H (300 MHz, $CDCl_3$); 7.53 (2H, s, 2 × purine-H), 7.39 (4H, d, *J* 1.6, 4 × phenyl-H), 7.18 (2H, t, *J* 1.6, 2 × phenyl-H), 5.89 (2H, t, *J* 7.1, 2 × NCH_2CH=), 4.88 (4H, d, *J* 7.1, 2 × NCH_2CH=), 3.98 (6H, s, 2 × purine 7-Me), 3.87 (4H, s, 2 × =CCH_2N), 3.58 (6H, s, 2 × purine 3-Me), 2.17 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$); 154.9, 151.3, 148.9, 144.7, 141.6, 139.4, 134.6, 127.2, 127.1, 125.0, 107.6, 48.1, 39.5, 33.7, 29.8; υ_{max}/cm^{-1} (film); 3311, 3071, 3014, 2949, 1704, 1660, 1604, 1584, 1557, 1487, 1455, 1414, 1355, 1313, 1286, 1234; *m/z* (ESI^+) 770.1 (100%, MH^+); (Found MH^+, 770.1328. $C_{34}H_{32}Cl_4N_9O_4$ requires *MH*, 770.1326).

NOE data ($CDCl_3$) for **247e**.

	% Enhancement			
Irradiated proton	1-H	2-H	4-H	phenyl-H (δ 7.39)
1-H		5.87	2.91	-
2-H	4.09		-	16.75
4-H	4.79	-		11.38

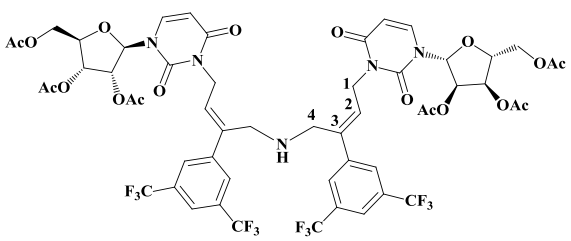
3,3'-{Iminobis[(2*Z*)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}bis(2',3',5'-tri-*O*-acetyluridine) (247f).



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.377 g, 0.89 mmol), 3-iodopyridine (0.22 g, 1.07 mmol), ammonium tartrate (0.493 g, 2.68 mmol), $Pd_2(dba)_3$ (0.02 g, 2.5 mol%), TFP (0.02 g, 10 mol%) and K_2CO_3 (0.25 g, 1.79 mmol) in 5:1 v/v 1,4-dioxane/DMF (18 mL) at 100 ºC for 29 h. Flash column chromatography eluting with 10:1 v/v EtOAc/MeOH gave the product **247f** (0.32 g, 71%) as a yellow froth; $[\alpha]_D^{20}$ + 32.0 (*c*, 10 mg/1mL $CHCl_3$); mp 76-78 °C; δ_H (300 MHz, $CDCl_3$); 8.68 (2H, d, *J* 2.2, 2 × pyridyl-H), 8.45 (2H, dd, *J* 1.6 and 4.9, 2 × pyridyl-H), 7.70 (2H, dt, *J* 8.0 and 2.2, 2 × pyridyl-H), 7.39 (2H, d, *J* 8.2, 2 × pyrimidinyl 6-H), 7.15 (2H, dd, *J* 4.9 and 8.0, 2 × pyridyl-H), 6.02 (2H, d, *J* 4.9, 2 × ribosyl 1-H), 5.84 (2H, t, *J* 7.1, 2 × NCH_2CH=), 5.83 (2H, d, *J* 8.2, 2 × pyrimidinyl 5-H), 5.37-5.30 (4H, m, 2 × ribosyl 2-H and 2 × ribosyl 3-H), 4.80 (2H, dd, *J* 7.1 and 14.3, 2 × NCH_ACH=), 4.74 (2H, dd, *J* 7.1 and 14.3, 2 × NCH_BCH=), 4.35 (6H, s, 2 × (ribosyl 4-H and 5-CH_2)), 3.85 (2H, s, 2 × =CCH_2N), 2.13 (6H, s, 2 × OCOMe), 2.12 (6H, s, 2 × OCOMe), 2.07 (6H, s, 2 × OCOMe); δ_C (75 MHz, $CDCl_3$); 170.1, 169.6 (2 × C), 161.9, 150.7, 148.4, 147.8, 139.2, 137.4, 136.9, 133.9, 125.6, 123.0, 102.9, 88.4, 79.7, 72.9, 70.0, 63.0, 47.8, 39.3, 20.8, 20.5, 20.46; υ_{max}/cm^{-1} (film); 3318, 3022, 1753, 1710, 1665, 1563, 1455, 1415, 1375, 1235; *m/z* (ESI^+) 1016.4 (100%, MH^+); (Found MH^+, 1016.3504. $C_{48}H_{54}N_7O_{18}$ requires *MH*, 1016.3520).

3,3'-(Iminobis{(2*Z*)-3-[3,5-bis(trifluoromethyl)phenyl]but-2-ene-4,1-diyl}]bis(2',3',5'-tri-*O*-acetyluridine) (247g).

Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.192 g, 0.455 mmol), 1-iodo-3,5-bis(trifluoromethyl)-benzene (0.10 mL, 0.55

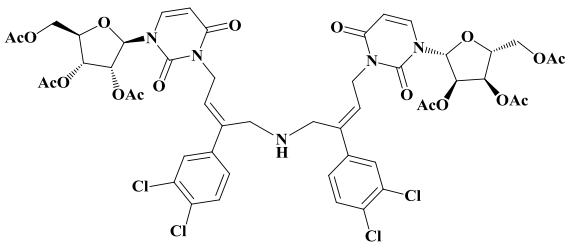


mmol), ammonium tartrate (0.250 g, 1.37 mmol), $Pd_2(dba)_3$ (0.011 g, 2.5 mol%), TFP (0.011 g, 10 mol%) and K_2CO_3 (0.126 g, 0.91 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 9 h. Flash column chromatography eluting with 1.5:1 v/v EtOAc/*n*-hexane gave the product **247g** (0.215 g, 74%) as a colourless froth; $[\alpha]_D^{20}$ + 27.2 (*c*, 10 mg/1mL $CHCl_3$); mp 72-74 °C; δ_H (300 MHz, $CDCl_3$); 7.90 (4H, d, *J* 1.1, 4 × phenyl-H), 7.71 (2H, br s, 2 × phenyl-H), 7.31 (2H, d, *J* 8.2, 2 × pyrimidinyl 6-H), 6.03 (2H, d, *J* 4.4, 2 × ribosyl 1-H), 5.89 (2H, t, *J* 7.1, 2 × NCH_2CH=), 5.84 (2H, d, *J* 8.2, 2 × pyrimidinyl 5-H), 5.37-5.30 (4H, m, 2 × ribosyl 2-H and 2 × ribosyl 3-H), 4.85 (2H, dd, *J* 7.1 and 14.5, 2 × NCH_ACH=), 4.76 (2H, dd, *J* 7.1 and 14.5, 2 × NCH_BCH=), 4.36 (6H, s, 2 × (ribosyl 4-H and 5-CH_2)), 3.92 (2H, d, *J* 15.6, 2 × =CCH_AN), 3.88 (2H, d, *J* 15.6, 2 × =CCH_BN), 2.13 (6H, s, 2 × OCOMe), 2.12 (6H, s, 2 × OCOMe), 2.06 (6H, s, 2 × OCOMe); δ_C (75 MHz, $CDCl_3$); 170.1, 169.7, 169.6, 161.9, 150.7, 143.6, 139.8, 137.4, 131.4 (q, *J* 33.2), 127.2, 126.6 (br d, *J* 2.2), 123.1 (q, *J* 273.1), 121.5 (br d, *J* 3.3), 102.9, 88.3, 79.8, 72.9, 70.0, 63.0, 48.2, 39.3, 20.8, 20.5, 20.3; υ_{max}/cm^{-1} (film); 3317, 3024, 1755, 1714, 1668, 1455, 1380, 1281, 1228; *m/z* (ESI^+) 1286.3 (100%, MH^+); (Found MH^+, 1286.3130. $C_{54}H_{52}F_{12}N_5O_{18}$ requires *MH*, 1286.3110).

NOE data ($CDCl_3$) for **247g**.

	% Enhancement			
Irradiated proton	1-H	2-H	4-H	phenyl-H (δ 7.90)
1-H		2.41	2.50	-
2-H	2.64		-	10.41
4-H	2.18	-		5.64

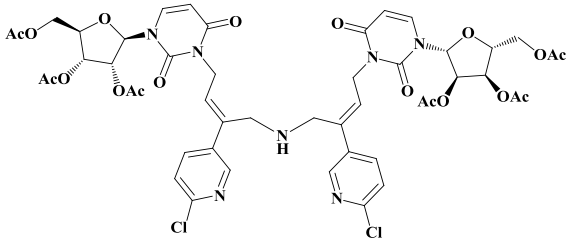
3,3'-{Iminobis[(2*Z*)-3-(3,4-dichlorophenyl)but-2-ene-4,1-diyl]}bis(2',3',5'-tri-*O*-acetyluridine) (247h).



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.134 g, 0.317 mmol), 1,2-dichloro-4-iodobenzene (0.104 g, 0.38 mmol), ammonium tartrate (0.175 g, 0.95 mmol), $Pd_2(dba)_3$ (0.007 g, 2.5 mol%), TFP (0.007 g, 10 mol%) and K_2CO_3 (0.09 g, 0.64 mmol) in 5:1 v/v 1,4-

dioxane/DMF (6 mL) at 100 ºC for 16 h. Flash column chromatography eluting with 2:1 v/v EtOAc/*n*-hexane gave the product **247h** (0.13 g, 71%) as a pale yellow froth; $[\alpha]_D^{20}$ + 32.9 (*c*, 10 mg/1 mL $CHCl_3$); mp 76-78 °C; δ_H (300 MHz, $CDCl_3$); 7.55 (2H, d, *J* 2.2, 2 × phenyl-H), 7.40 (2H, d, *J* 8.2, 2 × pyrimidinyl 6-H), 7.32-7.23 (4H, m, 4 × phenyl-H), 6.03 (2H, d, *J* 4.9, 2 × ribosyl 1-H), 5.84 (2H, d, *J* 8.2, 2 × pyrimidinyl 5-H), 5.81 (2H, t, *J* 7.1, 2 × NCH_2CH=), 5.38-5.30 (4H, m, 2 × ribosyl 2-H and 2 × ribosyl 3-H), 4.78 (2H, dd, *J* 7.1 and 14.3, 2 × NCH_ACH=), 4.72 (2H, dd, *J* 7.1 and 14.3, 2 × NCH_BCH=), 4.35 (6H, s, 2 × (ribosyl 4-H and 5-CH_2)), 3.79 (4H, s, 2 × =CCH_2N), 2.14 (6H, s, 2 × OCOMe), 2.13 (6H, s, 2 × OCOMe), 2.08 (6H, s, 2 × OCOMe), 1.88 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$); 170.1, 169.6 (2 × C), 161.9, 150.7, 141.4, 140.0, 137.4, 132.2, 131.1, 130.0, 128.5, 125.9, 125.4, 102.9, 88.4, 79.7, 72.9, 70.0, 63.0, 47.8, 39.3, 20.8, 20.5, 20.46; υ_{max}/cm^{-1} (film); 3318, 3021, 1752, 1711, 1665, 1552, 1455, 1376, 1232; *m/z* (ESI^+) 1150.2 (100%, MH^+); (Found MH^+, 1150.2002. $C_{50}H_{51}{}^{35}Cl_4N_5O_{18}$ requires *MH* 1150.2056).

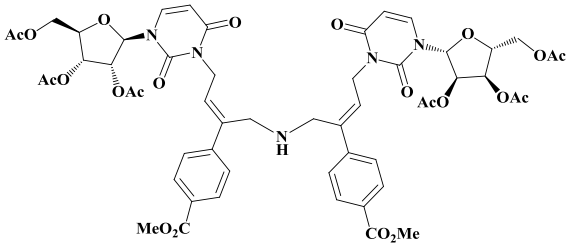
3,3'-{Iminobis[(2*Z*)-3-(6-chloropyridin-3-yl)but-2-ene-4,1-diyl]}bis(2',3',5'-tri-*O*-acetyluridine) (247i)



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.112 g, 0.265 mmol), 2-chloro-5-iodopyridine (0.076 g, 0.318 mmol), ammonium tartrate (0.293 g, 1.59 mmol), $Pd_2(dba)_3$ (0.006 g, 2.5 mol%), TFP (0.006 g, 10 mol%) and K_2CO_3 (0.07 g, 0.53 mmol) in 5:1 v/v 1,4-dioxane/DMF (6 mL) at 100 ºC for 19 h. Flash column chromatography eluting with 4:1 v/v EtOAc/*n*-hexane gave the product **247i** (0.11 g, 77%) as a colourless froth; $[\alpha]_D^{20}$ + 34.8 (*c*, 12 mg/ 1 mL $CHCl_3$); mp 80-82 °C; δ_H (300 MHz, $CDCl_3$); 8.43 (2H, d, *J* 2.4, 2 × pyridyl-H), 7.69 (2H, dd, *J* 8.2 and 2.4, 2 × pyridyl-H), 7.42 (2H, d, *J* 8.2, 2 × pyrimidinyl 6-H), 7.20 (2H, d, *J* 8.0, 2 × pyridyl-H), 6.01 (2H, d, *J* 4.9, 2 × ribosyl 1-H), 5.84 (2H, d, *J* 8.2, 2 × pyrimidinyl 5-H), 5.83 (2H, t, *J* 7.1, 2 × NCH_2CH=), 5.39-5.30 (4H, m, 2 × ribosyl 2-H and 2 × ribosyl 3-H), 4.80 (2H, dd, *J* 14.5 and 7.1, 2 × NCH_ACH=), 4.72 (2H, dd, *J* 14.5 and 7.1, 2 × NCH_BCH=), 4.36 (6H, s, 2 × (ribosyl 4-H and 5-CH_2)), 3.81 (2H, s, 2 × =CCH_2N), 2.14 (6H, s, 2 × OCOMe), 2.13 (6H, s, 2 × OCOMe), 2.09 (6H, s, 2 × OCOMe); δ_C (75 MHz, $CDCl_3$); 170.1, 169.6 (2 × C), 161.9, 150.7, 150.0, 147.6, 138.0, 137.6, 136.9, 135.9,

126.0, 123.5, 102.8, 88.6, 79.7, 72.9, 69.9, 62.9, 47.8, 39.2, 20.8, 20.5. 20.47; υ_{max}/cm^{-1} (film); 3320, 3019, 1748, 1712, 1668, 1580, 1553, 1456, 1376, 1228; *m/z* (ESI^+) 1084.3 (100%, MH^+); (Found MH^+, 1084.2752. $C_{47}H_{52}{}^{35}Cl_2N_7O_{18}$ requires *MH* 1084.2740).

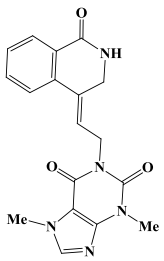
Dimethyl 4,4'-{Iminobis[(2*Z*)-4-(2',3',5'-tri-*O*-acetryuridine)but-2-ene-1,2-diyl]}dibenzoate (247j).



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.152 g, 0.36 mmol), methyl 4-iodobenzoate (0.113 g, 0.43 mmol), ammonium tartrate (0.199 g, 1.08 mmol), $Pd_2(dba)_3$ (0.008 g, 2.5 mol%), TFP (0.008 g, 10 mol%) and K_2CO_3 (0.10 g, 0.72 mmol) in 5:1 v/v 1,4-dioxane/DMF (6 mL) at 100 ºC for 21 h. Flash column chromatography eluting with 5:1 v/v EtOAc/*n*-hexane gave the product **247j** (0.125 g, 62%) as a pale yellow froth; $[\alpha]_D^{20}$ + 33.0 (*c*, 11 mg/ 1 mL $CHCl_3$); mp 78-80 °C; δ_H (300 MHz, $CDCl_3$); 7.90 (4H, d, *J* 8.5, 4 × phenyl-H), 7.47 (4H, d, *J* 8.5, 4 × phenyl-H), 7.39 (2H, d, *J* 8.2, 2 × pyrimidinyl 6-H), 6.03 (2H, d, *J* 4.4, 2 × ribosyl 1-H), 5.88 (2H, t, *J* 7.1, 2 × NCH_2CH=), 5.84 (2H, d, *J* 8.2, 2 × pyrimidinyl 5-H), 5.37-5.31 (4H, m, 2 × ribosyl 2-H and 2 × ribosyl 3-H), 4.79 (2H, dd, *J* 7.1 and 14.8, 2 × NCH_ACH=), 4.72 (2H, dd, *J* 7.1 and 14.8, 2 × NCH_BCH=), 4.35 (6H, s, 2 × (ribosyl 4-H and 5-CH_2)), 3.90 (6H, s, 2 × CO_2Me), 3.86 (4H, s, 2 × =CCH_2N), 2.13 (6H, s, 2 × OCOMe), 2.12 (6H, s, 2 × OCOMe), 2.07 (6H, s, 2 × OCOMe); δ_C (75 MHz, $CDCl_3$); 170.1, 169.6 (2 × C), 166.9, 161.9, 150.7, 145.9, 141.3, 137.3, 129.5, 128.8, 126.5, 125.8, 102.9, 88.4, 79.7, 72.9, 70.0, 63.0, 52.0, 47.7, 39.4, 20.8, 20.5, 20.45; υ_{max}/cm^{-1} (film); 3322, 3021, 2953, 1748, 1714, 1668, 1607, 1564, 1455, 1435, 1373, 1280, 1227; *m/z* (ESI^+) 1130.4 (100%, MH^+); (Found MH^+, 1130.3753. $C_{54}H_{60}N_5O_{22}$ requires *MH* 1130.3724).

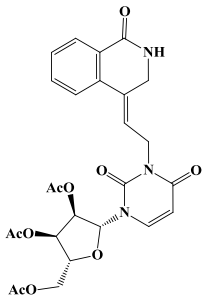
3,7-Dimethyl-1-[(2*Z*)-2-(1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione (251a).

A mixture of purine allene **195** (0.116 g, 0.50 mmol), methyl 2-iodobenzoate (0.088 mL, 0.60 mmol), ammonium carbonate (0.288 g, 3.0 mmol), $Pd_2(dba)_3$ (0.011 g, 2.5 mol%) and TFP (0.011 g, 10 mol%) in 2:1 v/v DMF/water (3 mL) was heated at 80



ºC for 7 h. the product precipitated from hot solution during the reaction. The reaction mixture was filtered and the precipitate washed with water (10 mL) and MeOH (3 mL) to give a first crop of product as a colourless amorphous solid (0.09 g). The reaction solvent was removed under *vacuo*, the residue dissolved in $CHCl_3$ (30 mL) and the organic layer washed with water (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate removed under *vacuo*. The residue was dissolved in $CHCl_3$ (5 mL) and left to stand giving a second crop precipitate as a colourless amorphous solid (0.02 g). Compound **251a** (0.11 g, 63%), mp 239-241 °C; δ_H (300 MHz, DMSO-d_6); 8.16 (1H, br s, NH), 8.03 (1H, s, purine-H), 7.90 (1H, dd, *J* 7.7 and 1.6, isoquinolinyl-H), 7.61 (1H, dd, *J* 7.7 and 1.6, isoquinolinyl-H), 7.50 (1H, td, *J* 7.7 and 1.6, isoquinolinyl-H),), 7.40 (1H, td, *J* 7.7 and 1.6, isoquinolinyl-H), 6.08 (1H, t, *J* 6.9, NCH_2CH=), 4.66 (2H, d, *J* 6.9, NCH_2CH=), 4.36 (2H, br s, =CCH_2NH), 3.89 (3H, s, purine 7-Me), 3.43 (3H, s, purine 3-Me); δ_C (75 MHz, DMSO-d_6); 163.0, 154.2, 150.8, 148.4, 143.0, 136.2, 132.1, 130.3, 128.2, 127.2, 123.2, 122.4, 106.7, 40.7, 38.2, 33.2, 29.4 (One aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (solid); 3197, 1660, 1607, 1552, 1495, 1451, 1361, 1317, 1289, 1232; *m/z* (ESI^+) 374.1 (100%, MNa^+); (Found MNa^+, 374.1239. $C_{18}H_{17}N_5NaO_3$ requires *MNa*, 374.1224).

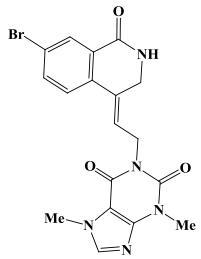
2',3',5'-Tri-O-acetyl-3-[(2Z)-2-(1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)ethyl]uridine (251b).



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.106 g, 0.25 mmol), methyl 2-iodobenzoate (0.046 g, 0.30 mmol), ammonium tartrate (0.277 g, 1.51 mmol), $Pd_2(dba)_3$ (0.006 g, 2.5 mol%), TFP (0.006 g, 10 mol%) and K_2CO_3 (0.11 g, 0.75 mmol) in 5:1 v/v 1,4-dioxane/DMF (6 mL) at 100 ºC for 31 h. Flash column chromatography eluting with EtOAc gave the product **251b** (0.07 g, 51%) as a pale yellow froth; $[\alpha]_D^{24}$ + 26.9 (*c*, 10 mg/ 1 mL $CHCl_3$); mp 78-80 °C; δ_H (300 MHz, $CDCl_3$); 8.10 (1H, dd, *J* 7.7 and 1.1, isoquinolinyl-H), 7.56 (1H, dd, *J* 7.7 and 1.1, isoquinolinyl-H), 7.49 (1H, td, *J* 7.7 and 1.1, isoquinolinyl-H),), 7.42 (1H, d, *J* 8.2, pyrimidinyl 6-H), 7.42 (1H, td, overlapped, isoquinolinyl-H), 6.68 (1H, br s, NH), 6.12 (1H, t, *J* 7.7, NCH_2CH=),

6.00 (1H, d, *J* 4.9, ribosyl 1-H), 5.86 (1H, d, *J* 8.2, pyrimidinyl 5-H), 5.42-5.32 (2H, m, ribosyl 2-H and ribosyl 3-H), 4.73 (1H, dd, *J* 14.6 and 7.7, N*CH*$_A$CH=), 4.66 (1H, dd, *J* 14.6 and 7.7, N*CH*$_B$CH=), 4.54 (2H, s, =C*CH*$_2$N), 4.36 (3H, s, ribosyl 4-H and 5-CH$_2$), 2.13 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 2.09 (3H, s, OCOMe); δ_C (75 MHz, $CDCl_3$); 170.2, 169.7 (2 × C),165.0, 161.9, 150.6, 137.7, 136.7, 132.5, 132.4, 128.7, 128.1, 127.2, 123.4, 120.4, 102.8, 88.8, 79.7, 73.0, 69.9, 62.9, 41.7, 38.4, ,20.8, 20.5, 20.28; υ_{max}/cm^{-1} (film); 3356, 3019, 1749, 1712, 1668, 1601, 1571, 1456, 1372, 1230; *m/z* (ESI$^+$) 564.2 (100%, MNa$^+$); (Found MNa$^+$, 564.1573. $C_{26}H_{27}N_3NaO_{10}$ requires *MNa* 564.1589).

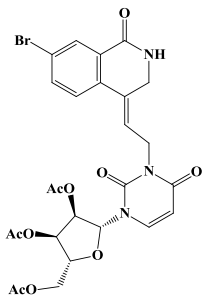
1-[(2*Z*)-2-(7-Bromo-1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene)ethyl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (251c).



Prepared by general procedure J from purine allene **195** (0.093 g, 0.40 mmol), methyl 5-bromo-2-iodobenzoate (0.164 g, 0.48 mmol), ammonium tartrate (0.442 g, 2.40 mmol), $Pd_2(dba)_3$ (0.009 g, 2.5 mol%), TFP (0.009 g, 10 mol%) and K_2CO_3 (0.166 g, 1.20 mmol) in 5:1 v/v 1,4-dioxane/DMF (6 mL) at 100 ºC for 24 h. The crude product dissolved in $CHCl_3$ and left overnight to give the product **251c** (0.12 g, 70%) as a white amorphous solid, mp 160-162 °C; δ_H (300 MHz, $CDCl_3$); 8.23 (1H, d, *J* 2.2, isoquinolinyl-H), 7.57 (1H, dd, *J* 8.4 and 2.2, isoquinolinyl-H), 7.54 (1H, s, purine-H), 7.42 (1H, d, *J* 8.4, isoquinolinyl-H),), 6.41 (1H, br s, NH), 6.18 (1H, t, *J* 7.7, NCH$_2$*CH*=), 4.78 (2H, d, *J* 7.7, N*CH*$_2$CH=), 4.61 (2H, br s, =C*CH*$_2$NH), 4.00 (3H, s, purine 7-Me), 3.59 (3H, s, purine 3-Me); δ_C (75 MHz, $CDCl_3$); 163.6, 154.9, 151.4, 149.0, 141.8, 135.5, 135.3, 131.0, 130.9, 128.8, 125.2, 122.8, 122.2, 107.6, 41.7, 38.5, 33.7, 29.8; υ_{max}/cm^{-1} (solid); 3523, 3400, 3308, 1702, 1660, 1553, 1491, 1431, 1321, 1286, 1233; *m/z* (ESI$^+$) 452.0 (100%, MNa$^+$); (Found MNa$^+$, 452.0327. $C_{18}H_{16}{}^{79}BrN_5NaO_3$ requires *MNa*, 452.0329).

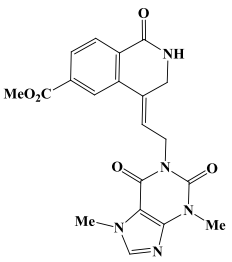
2',3',5'-Tri-*O*-acetyl-3-[(2*Z*)-2-(7-bromo-1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene)ethyl]uridine (251d).

Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.12 g, 0.284 mmol), methyl 5-bromo-2-iodobenzoate (0.116 g, 0.341 mmol), ammonium tartrate (0.314 g, 1.08 mmol), $Pd_2(dba)_3$ (0.007 g, 2.5 mol%), TFP (0.007 g, 10 mol%) and K_2CO_3 (0.08 g, 0.57 mmol) in 5:1 v/v 1,4-dioxane/DMF (6



mL) at 100 ºC for 24 h. Flash column chromatography eluting with 4:1 v/v EtOAc/*n*-hexane gave the product **251d** (0.11 g, 63%) as a colourless froth; $[\alpha]_D^{24}$ + 29.7 (*c*, 10 mg/ 1 mL $CHCl_3$); mp 90-92 °C; δ_H (300 MHz, $CDCl_3$); 8.23 (1H, d, *J* 2.2, isoquinolin-H), 7.59 (1H, dd, *J* 8.2 and 2.2, isoquinolin-H), 7.34 (2H, d, *J* 8.2, isoquinolin-H and pyrimidinyl 6-H), 6.89 (1H, br s, NH), 6.11 (1H, t, *J* 7.7, NCH_2CH=), 5.98 (1H, d, *J* 4.9, ribosyl 1-H), 5.86 (1H, d, *J* 8.2, pyrimidinyl 5-H), 5.42-5.32 (2H, m, ribosyl 2-H and ribosyl 3-H), 4.72 (1H, dd, *J* 14.3 and 7.7, NCH_ACH=), 4.64 (1H, dd, *J* 14.3 and 7.7, NCH_BCH=), 4.54 (2H, s, =CCH_2N), 4.37 (3H, s, ribosyl 4-H and 5-CH_2), 2.14 (3H, s, OCOMe), 2.13 (3H, s, OCOMe), 2.10 (3H, s, OCOMe); δ_C (75 MHz, $CDCl_3$); 170.2, 169.7 (2 × C), 163.7, 161.9, 150.6, 137.8, 135.4, 135.3, 131.5, 131.0, 128.8, 125.2, 122.8, 121.1, 102.7, 89.0, 79.7, 73.0, 69.9, 62.9, 41.6, 38.4, 20.8, 20.50, 20.51; υ_{max}/cm^{-1} (film); 3356, 3018, 1748, 1712, 1667, 1591, 1556, 1455, 1373, 1335, 1307, 1231; *m/z* (ESI^+) 642.1 (100%, MNa^+); (Found MNa^+, 642.0691. $C_{26}H_{26}{}^{79}BrN_3NaO_{10}$ requires *MNa* 642.0694).

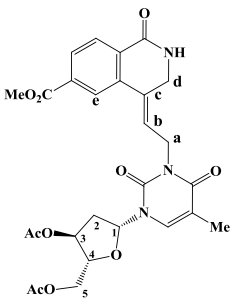
Methyl (4*Z*)-4-[2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)ethylidene]-1-oxo-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (251e).



Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), dimethyl iodoterephthalate (0.192 g, 0.60 mmol), ammonium tartrate (0.552 g, 3.00 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 23 h. Flash column chromatography eluting with 40:1 v/v $CHCl_3$/MeOH gave the product **251e** (0.16 g, 78%) as a white amorphous solid which crystallised from $CHCl_3$ as colourless fine needles; mp 202-204 °C; δ_H (300 MHz, $CDCl_3$/MeOH-d_4); 8.21 (1H, d, *J* 1.5, isoquinolin-H), 8.15 (1H, d, *J* 8.2, isoquinolin-H), 8.03 (1H, dd, *J* 8.2 and 1.5, isoquinolin-H), 7.60 (1H, s, purine-H), 6.24 (1H, tt, *J* 7.7 and 1.6, NCH_2CH=), 4.82 (2H, d, *J* 7.7, NCH_2CH=), 4.61 (2H, d, *J* 1.6, =CCH_2NH), 4.01 (3H, s, purine 7-Me), 3.95 (3H, s, purine 3-Me), 3.60 (3H, s, CO_2Me); δ_C (75 MHz, $CDCl_3$/MeOH-d_4); 166.3, 164.3, 154.9, 151.3, 148.9, 141.9, 137.0, 133.5, 130.8, 130.5, 129.1, 128.3, 124.9, 122.8, 107.6, 52.3, 41.4, 38.5, 33.7, 29.8; υ_{max}/cm^{-1} (solid); 3605,

3095, 2957, 1701, 1661, 1603, 1549, 1434, 1359, 1293, 1260, 1189; *m/z* (ESI^+) 432.13(100%, MNa^+); (Found MNa^+, 432.1296. $C_{20}H_{19}N_5NaO_5$ requires *MNa*, 432.1278).

3',5'-Di-*O*-acetyl-3-{(2*Z*)-2-[6-(methoxycarbonyl)-1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene]ethyl}thymidine (251f)

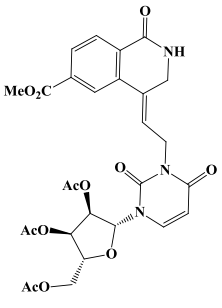


Prepared by general procedure J from 2'3',5'-di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine **207b** (0.189 g, 0.50 mmol), dimethyl iodoterephthalate (0.192 g, 0.60 mmol), ammonium tartrate (0.552 g, 3.00 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 21 h. Flash column chromatography eluting with EtOAc gave the product **251f** (0.18 g, 65%) as a colourless froth; $[\alpha]_D^{24}$ + 6.1 (*c*, 10 mg/ 1 mL $CHCl_3$); mp 84-86 °C; δ_H (300 MHz, $CDCl_3$); 8.20 (1H, d, *J* 1.6, isoquinolinyl-H), 8.17 (1H, d, *J* 8.2, , isoquinolinyl-H), 8.03 (1H, dd, *J* 8.2 and 1.6, isoquinolinyl-H), 7.33 (1H, d, *J* 1.1, pyrimidinyl 6-H), 7.07 (1H, br s, NH), 6.38 (1H, dd, *J* 8.2 and 5.5, deoxyribosyl 1-H), 6.21 (1H, t, *J* 7.1, NCH_2CH=), 5.25 (1H, dt, *J* 6.6 and 2.2, deoxyribosyl 3-H), 4.76 (2H, d, *J* 7.1, NCH_2CH=), 4.61 (2H, s, =CCH_2N), 4.41 (1H, dd, *J* 12.1 and 4.4, deoxyribosyl 5-H_A), 4.35 (1H, dd, *J* 12.1 and 4.4, deoxyribosyl 5-H_B), 4.28 (1H, dt, *J* 5.5 and 2.7, deoxyribosyl 4-H), 3.96 (3H, s, CO_2Me), 2.52 (1H, ddd, *J* 14.3, 5.5 and 1.6, deoxyribosyl 2-H_A), 2.23 (1H, ddd, *J* 14.8, 8.2 and 6.7, deoxyribosyl 2-H_B), 2.14 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 1.98 (3H, d, *J* 1.1, pyrimidinyl 5-Me); δ_C (75 MHz, $CDCl_3$); 170.4, 170.2, 166.2, 164.1, 162.9, 150.6, 136.8, 133.4, 133.1, 131.2, 130.7, 129.1, 128.3, 124.8, 122.0, 110.7, 85.5, 82.0, 74.1, 63.8, 52.5, 41.6, 38.6, 37.5, 20.9, 20.8, 13.4; υ_{max}/cm^{-1} (film); 3330, 3018, 2954, 1744, 1703, 1673, 1644, 1568, 1467, 1366, 1236, 1194; *m/z* (ESI^+) 578.2 (100%, MNa^+); (Found MNa^+, 578.1769. $C_{27}H_{29}N_3NaO_{10}$ requires *MNa*, 578.1745).

NOE data ($CDCl_3$) for **251f**.

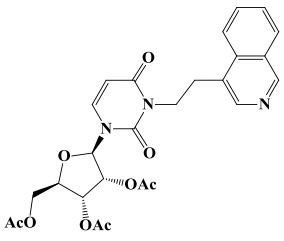
	% Enhancement				
Irradiated proton	Ha	Hb	Hd	isoquinolinyl-He (δ 8.20)	deoxyribosyl 1-H
Ha		4.47	4.03	-	-
Hb	3.28		-	19.00	-
Hd	2.62	-		-	1.77

2',3',5'-Tri-*O*-acetyl-3-{(2*Z*)-2-[6-(methoxycarbonyl)-1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene]ethyl}uridine (251g).



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.146 g, 0.345 mmol), dimethyl iodoterephthalate (0.133 g, 0.414 mmol), ammonium tartrate (0.381 g, 2.07 mmol), $Pd_2(dba)_3$ (0.008 g, 2.5 mol%), TFP (0.008 g, 10 mol%) and K_2CO_3 (0.143 g, 1.04 mmol) in 5:1 v/v 1,4-dioxane/DMF (8.5 mL) at 100 ºC for 21 h. Flash column chromatography eluting with EtOAc gave the product **251g** (0.11 g, 54%) as a colourless froth; $[\alpha]_D^{24}$ + 22.6 (*c*, 10 mg/ 1 mL $CHCl_3$); mp 86-88 °C; δ_H (300 MHz, $CDCl_3$); 8.21 (1H, d, *J* 1.4, isoquinolinyl-H), 8.18 (1H, dd, *J* 8.2, isoquinolinyl-H), 8.04 (1H, dd, *J* 8.2 and 1.4, isoquinolinyl-H),), 7.45 (1H, d, *J* 8.2, pyrimidinyl 6-H), 6.84 (1H, br s, NH), 6.21 (1H, t, *J* 7.7, NCH_2CH=), 6.03 (1H, d, *J* 4.4, ribosyl 1-H), 5.88 (1H, d, *J* 8.2, pyrimidinyl 5-H), 5.41-5.32 (2H, m, ribosyl 2-H and ribosyl 3-H), 4.74 (1H, dd, *J* 14.3 and 7.7, NCH_ACH=), 4.64 (1H, dd, *J* 14.3 and 7.7, NCH_BCH=), 4.57 (2H, s, =CCH_2N), 4.37 (3H, s, ribosyl 4-H and 5-CH_2), 3.95 (3H, s, isoquinoline-OCOMe), 2.14 (3H, s, OCOMe), 2.13 (3H, s, OCOMe), 2.10 (3H, s, OCOMe); δ_C (75 MHz, $CDCl_3$); 170.2, 169.7 (2 × C), 166.2, 164.1, 161.9, 150.6, 137.7, 136.8, 133.5, 131.5, 130.7, 129.2, 128.4, 124.9, 121.7, 102.8, 88.7, 79.8, 73.0, 69.9, 62.9, 52.5, 41.7, 38.4, 20.8, 20.5, 20.5; υ_{max}/cm^{-1} (film); 3346, 3020, 2954, 1749, 1667, 1456, 1372, 1234; *m/z* (ESI^+) 622.2 (100%, MNa^+); (Found MNa^+, 622.1672. $C_{28}H_{29}N_3NaO_{12}$ requires *MNa* 622.1643).

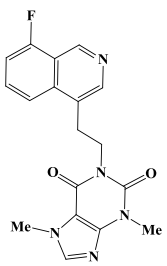
2',3',5'-Tri-*O*-acetyl-3-[2-(isoquinolin-4-yl)ethyl]uridine (254a).



Prepared by general procedure J from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.173 g, 0.41 mmol), 2-iodobenzaldehyde (0.114 g, 0.49 mmol), ammonium tartrate (0.453 g, 2.46 mmol), $Pd_2(dba)_3$ (0.01 g, 2.5 mol%), TFP (0.01 g, 10 mol%) and K_2CO_3 (0.113 g, 0.82 mmol) in 5:1 v/v 1,4-dioxane/DMF (6 mL) at 100 ºC for 12 h. Flash column chromatography gradient eluting with 2:1 to 3:1 v/v EtOAc/*n*-hexane gave the product **254a** (0.10 g, 47%) as a yellow froth; $[\alpha]_D^{24}$ + 18.0 (*c*, 11 mg/ 1 mL $CHCl_3$); mp 58-60 °C; δ_H (300 MHz, $CDCl_3$); 9.16 (1H, s, isoquinolinyl-H), 8.45 (1H, s, isoquinolinyl-H), 8.38

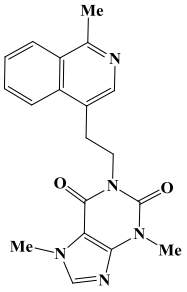
(1H, d, *J* 8.2, isoquinolinyl-H), 7.99 (1H, d, *J* 8.2, isoquinolinyl-H), 7.82 (1H, ddd, *J* 8.2, 7.1 and 1.1, isoquinolinyl-H), 7.63 (1H, ddd, *J* 8.2, 7.1 and 1.1, isoquinolinyl-H), 7.44 (1H, d, *J* 8.0, pyrimidinyl 6-H), 6.06 (1H, d, *J* 3.8, ribosyl 1-H), 5.87 (H, d, *J* 8.0, pyrimidinyl 5-H), 5.41-5.34 (2H, m, ribosyl 2-H and ribosyl 3-H), 4.38 (3H, s, ribosyl 4-H and 5-CH_2), 4.23 (2H, AA′BB′, *J* 8.2 and 5.5, -*CH_2*CH_2-), 3.32 (2H, AA′BB′, *J* 8.2 and 5.5, -CH_2*CH_2*-), 2.16 (3H, s, OCOMe), 2.14 (6H, s, 2 × OCOMe); δ_C (75 MHz, $CDCl_3$); 170.2, 169.64, 169.6, 162.1, 152.0, 150.8, 143.4, 137.6, 134.9, 130.8, 128.4, 128.2, 127.7, 127.1, 123.2, 102.8, 88.7, 79.7, 73.0, 70.0, 62.9, 41.7, 28.1, 20.8, 20.5 (2 × C); υ_{max}/cm^{-1} (film); 3020, 2963, 1748, 1712, 1673, 1585, 1504, 1456, 1390, 1373, 1231; *m/z* (ESI^+) 526.2 (100%, MH^+); (Found MH^+, 526.1830. $C_{26}H_{28}N_3O_9$ requires *MH*, 526.1820).

1-[2-(8-Fluoroisoquinolin-4-yl)ethyl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (254b).



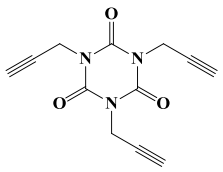
Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), 2-fluoro-6-iodobenzaldehyde (0.150 g, 0.60 mmol), ammonium tartrate (0.552 g, 3.00 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 26 h. Flash column chromatography eluting with 70:1 v/v EtOAc/MeOH gave the product **254b** (0.08 g, 45%) as a white amorphous solid; mp 236-238 °C; δ_H (300 MHz, $CDCl_3$); 9.47 (1H, br s, isoquinolinyl-H), 8.56 (1H, br s, isoquinolinyl-H), 8.26 (1H, d, *J* 8.2, isoquinolinyl-H), 7.78 (1H, td, *J* 8.2 and 5.8, isoquinolinyl-H), 7.56 (1H, s, purine-H), 7.27 (1H, dd, *J* 9.6 and 8.2, isoquinolinyl-H), 4.31 (2H, AA′BB′, *J* 8.2 and 4.9, N*CH_2*CH_2-), 4.03 (3H, s, purine 7-Me), 3.64 (3H, s, purine 3-Me), 3.35 (2H, AA′BB′, *J* 8.2 and 4.9, NCH_2*CH_2*-); δ_C (75 MHz, $CDCl_3$); 159.5 (*J* 255.4), 155.1, 151.5, 148.9, 145.5 (*J* 5.5), 144.4, 141.7, 136.4 (*J* 3.3), 131.1 (*J* 8.8), 127.7, 119.4 (*J* 4.4), 110.9 (*J* 18.8), 107.7, 41.8, 33.7, 29.8, 29.1(One aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2955, 1703, 1651, 1603, 1572, 1550, 1447, 1402, 1357, 1327, 1288, 1238; *m/z* (ESI^+) 354.1 (100%, MH^+); (Found MH^+, 354.1376. $C_{18}H_{17}FN_5O_2$ requires *MH*, 354.1361).

3,7-Dimethyl-1-[2-(1-methylisoquinolin-4-yl)ethyl]-3,7-dihydro-1H-purine-2,6-dione (254c).



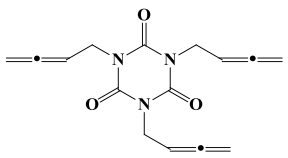
Prepared by general procedure J from purine allene **195** (0.116 g, 0.50 mmol), 2′-iodoacetophenone (0.086 mL, 0.60 mmol), ammonium tartrate (0.552 g, 3.00 mmol), $Pd_2(dba)_3$ (0.0114 g, 2.5 mol%), TFP (0.0116 g, 10 mol%) and K_2CO_3 (0.207 g, 1.50 mmol) in 5:1 v/v 1,4-dioxane/DMF (12 mL) at 100 ºC for 23 h. Flash column chromatography eluting with 20:1 v/v EtOAc/MeOH gave the product **254c** (0.07 g, 40%) as a white amorphous solid; mp 212-214 °C; δ_H (300 MHz, $CDCl_3$); 8.48 (1H, d, J 8.2, isoquinolin-H), 8.36 (1H, s, isoquinolin-H), 8.16 (1H, d, *J* 8.2, isoquinolin-H), 7.84 (1H, ddd, *J* 8.2 and 6.6 and 1.1, isoquinolin-H), 7.63 (1H, ddd, *J* 8.2, 6.6 and 1.1, isoquinolin-H), 7.55 (1H, s, purine-H), 4.31 (2H, AA′BB′, *J* 8.2 and 4.9, N*CH*$_2$CH$_2$-), 4.03 (3H, s, purine 7-Me), 3.64 (3H, s, purine 3-Me), 3.32 (2H, AA′BB′, *J* 8.2 and 4.9, NCH$_2$*CH*$_2$-), 2.96 (3H, s, isoquinoline-Me); δ_C (75 MHz, $CDCl_3$); 157.8, 155.2, 151.6, 148.9, 142.2, 141.6, 135.1, 130.4, 127.2, 126.8, 126.3, 126.1, 124.0, 107.7, 42.1, 33.7, 29.8, 28.8, 22.5; υ_{max}/cm^{-1} (solid); 1698, 1657, 1550, 1433, 1391, 1357, 1322, 1287, 1232; *m/z* (ESI^+) 350.2 (100%, MH^+); (Found MH^+, 350.1626. $C_{19}H_{20}N_5O_2$ requires *MH*, 350.1612).

1,3,5-Tri(prop-2-yn-1-yl)-1,3,5-triazinane-2,4,6-trione (256).



A mixture of cyanuric acid **255** (5.0 g, 38.76 mmol), K_2CO_3 (20.86 g, 151.16 mmol), DMF (90 mL), and propargyl bromide **193** (15.5 mL, 139.50 mmol) was magnetically stirred at 50 °C for 16 h. The solution was cooled, filtered and the filtrate removed under vacuum. The resultant residue was dissolved in $CHCl_3$ (200 mL) and the organic layer washed with 10% v/v NH_4Cl solution (3 x 100 mL) and finally with water (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was removed under vacuum. The resulted solid was crystallised from 1:1 v/v MeOH/$CHCl_3$ to give the pure trisalkyne **256** (4.3 g, 46%) as colourless plates, mp 164-166 °C; δ_H (300 MHz, $CDCl_3$); 4.70 (6H, d, *J* 2.4, 3 × CH_2), 2.31 (3H, t, *J* 2.4, 3 × ≡CH); δ_C (75 MHz, $CDCl_3$); 147.3, 76.7, 72.7, 32.6; υ_{max}/cm^{-1} (film); 3277, 3011, 2128, 1693, 1461, 1414, 1356, 1310; *m/z* (ESI^+) 266.1 (100%, MNa^+); (Found MNa^+, 266.0540. $C_{12}H_9N_3NaO_3$ requires *MNa*, 266.0536).

1,3,5-Tri(buta-2,3-dien-1-yl)-1,3,5-triazinane-2,4,6-trione (257).



A mixture of trisalkyne **256** (1.5 g, 6.17 mmol), paraformaldehyde (1.39 g, 46.3 mmol), diisopropylamine (5.22 mL, 37.11 mmol) and CuBr (1.30 g, 9.10 mmol) in dry dioxane (9 mL) was refluxed and magnetically stirred for 3 h. The mixture was then cooled, filtered and the filtrate evaporated under vacuum. The residue was dissolved in $CHCl_3$ (100 mL) and the organic layer washed with 10% ammonium hydroxide solution (2 x 100 mL), 10% HCl (3 x 100 mL) and finally with water (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate evaporated under vacuum. The residue was purified by flash column chromatography eluting with 2:1 v/v hexane/EtOAc to give the pure trisallene **257** (0.65, 37%) as a pale yellow viscous oil; δ_H (300 MHz, $CDCl_3$); 5.26 (3H, m, 3 × CH), 4.85 (6H, dt, *J* 2.9 and 6.4, 3 × CH_2), 4.50 (6H, dt, *J* 2.9 and 6.4, 3 × CH_2); δ_C (75 MHz, $CDCl_3$); 208.9, 148.3, 85.5, 77.6, 41.1; υ_{max}/cm^{-1} (film); 3384, 3066, 2991, 2959, 1957, 1685, 1458, 1361, 1317; *m/z* (ESI^+) 308.1 (100%, MNa^+); (Found MNa^+, 308.1003. $C_{15}H_{15}N_3NaO_3$ requires *MNa*, 308.1006).

General Procedure K: Pd catalysed 7-component cascades.

A mixture of trisallene **257** (0.25 mmol), 3-iodopyridine (0.90 mmol), nucleophile (0.90 mmol), $Pd_2(dba)_3$ (7.5 mol%), TFP (tri-(2-furyl)phosphine) (30 mol%), and K_2CO_3 (2.25 mmol) in MeCN (5 mL) was stirred and heated at 80 °C (oil bath temperature) for 2-3 h. The mixture was cooled, filtered through a filter paper and the solid washed with MeCN (5 mL). The solvent was removed under reduced pressure, the residue dissolved in $CHCl_3$ and washed with H_2O (1 x 20 mL). The organic layer was dried (anhydrous $MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography.

1,3,5-Tris[(2*Z*)-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)-3-(pyridin-3-yl)but-2-en-1-yl]-1,3,5-triazinane-2,4,6-trione (258a).

Prepared by general procedure K from trisallene **257** (0.0713 g, 0.25 mmol), 3-iodopyridine (0.185 g, 0.90 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.171 g, 0.90 mmol), $Pd_2(dba)_3$ (0.0172 g, 7.5 mol%), TFP (0.0174 g, 30 mol%) and K_2CO_3 (0.31 g, 2.25 mmol) in MeCN (5 mL) at 80 ºC for 2 h. Flash

column chromatography gradient eluting with EtOAc and then 5:1 v/v EtOAc/MeOH gave the product **258a** (0.19 g, 70%) as a colourless froth, mp 199-201 °C; δ_H (300 MHz, DMSO); 10.86 (3H, s, 3 × NH), 8.71 (3H, d, *J* 1.4, 3 × pyridyl-H), 8.41 (3H, dd, *J* 1.4 and 4.8, 3 × pyridyl-H), 7.89 (3H, td, *J* 1.4 and 8.1, 3 × pyridyl-H), 7.30 (3H, dd, *J* 4.8 and 8.1, 3 × pyridyl-H), 7.21 (3H, dd, *J* 4.5 and 9.1, 3 × pyridoindolyl-H), 7.07 (3H, dd, *J* 2.5 and 10.0, 3 × pyridoindolyl-H), 6.79 (3H, dt, *J* 2.5 and 9.1, 3 × pyridoindolyl-H), 6.07 (4H, t, *J* 5.7, 3 × NCH_2CH=), 4.77 (6H, d, *J* 5.7, 3 × NCH_2CH=), 3.76 (6H, br s, 3 × =CCH_2N), 3.63 (6H, br s, 3 × pyridoindolyl 1-CH_2), 2.84 (6H, br s, 3 × pyridoindolyl-CH_2), 2.68 (6H, br s, 3 × pyridoindolyl-CH_2); δ_C (75 MHz, DMSO); 156.6 (*J* 231.6), 149.0, 148.1, 147.5, 136.5, 136.0, 134.9, 133.7, 132.4, 128.1, 125.7 (*J* 9.9), 123.1, 111.4 (*J* 9.9), 107.8 (*J* 24.2), 107.5 (*J* 4.4), 101.9 (*J* 24.2), 54.9, 49.5, 48.9, 40.8, 23.5; υ_{max}/cm^{-1} (solid); 3183, 2923, 2385, 1688, 1634, 1588, 1455, 1369, 1324, 1286, 1234; *m/z* (ESI^+) 1087.5 (52%, MH^+); (Found MH^+, 1087.4675. $C_{63}H_{58}F_3N_{12}O_3$ requires *MH*, 1087.4701).

NOE data (DMSO) for **258a**:

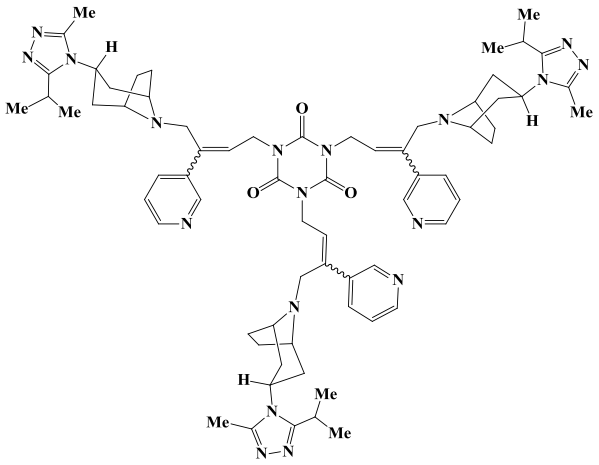
	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Pyridyl-H	pyridoindolyl-CH_2
1-H		-10.6	-5.8	-	-
2-H	-11.2		-	-3.0 (2-H, δ 8.71) -1.9 (4-H, δ 7.89)	-
4-H	-4.7	-		-	-4.2 (1-CH_2, δ 3.63) 4.8 (3-CH_2, δ 2.84) 3.1 (4-CH_2, δ 2.68)

1,3,5-Tris[(2*Z*)-4-(adamantan-1-ylamino)-3-(pyridin-3-yl)but-2-en-1-yl]-1,3,5-triazinane-2,4,6-trione (258b).

Prepared by general procedure K from trisallene **257** (0.0713 g, 0.25 mmol), 3-iodopyridine (0.185 g, 0.90 mmol), 1-aminoadamantane **180** (0.136 g, 0.90 mmol), $Pd_2(dba)_3$ (0.0172 g, 7.5 mol%), TFP (0.0174 g, 30 mol%) and K_2CO_3 (0.31 g, 2.25 mmol) in MeCN (5 mL) at 80 ºC for 2 h. Work up

by flash column chromatography gradient elution with EtOAc and then 10:3 v/v EtOAc/MeOH gave the product **258b** (0.16 g, 66%) which crystallized from $CHCl_3$ as a colourless fine needles, mp 111-113 °C; δ_H (300 MHz, $CDCl_3$); 8.75 (3H, d, *J* 1.9, 3 × pyridyl-H), 8.49 (3H, dd, *J* 1.9 and 4.8, 3 × pyridyl-H), 7.85 (3H, td, *J* 1.9, 8.1, pyridyl-H), 7.22 (3H, dd, *J* 4.8 and 8.1, 3 × pyridinyl-H), 5.85 (3H, t, *J* 7.2, 3 × NCH_2CH=), 4.78 (6H, d, *J* 7.2, 3 × NCH_2CH=), 3.76 (6H, s, 3 × =CCH_2N), 2.08 (9H, br s, 9 × adamantyl-CH), 1.71 (18H, br d, *J* 1.9, 9 × adamantyl-CH_2), 1.65 (18H, br q, *J* 10.5, 9 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 148.7, 148.69, 147.7, 140.8, 136.8, 133.7, 123.9, 123.1, 50.9, 42.6, 41.4, 39.3, 36.8, 29.6; υ_{max}/cm^{-1} (film); 3318, 2905, 2848, 1693, 1567, 1455, 1357, 1310, 1215; *m/z* (ESI^+) 970.6 (33%, MH^+); (Found MH^+, 970.6069. $C_{60}H_{76}N_9O_3$ requires *MH*, 970.6066).

1,3,5-Tris[(2*Z*)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-(pyridin-3-yl)but-2-en-1-yl]-1,3,5-triazinane-2,4,6-trione (258c).



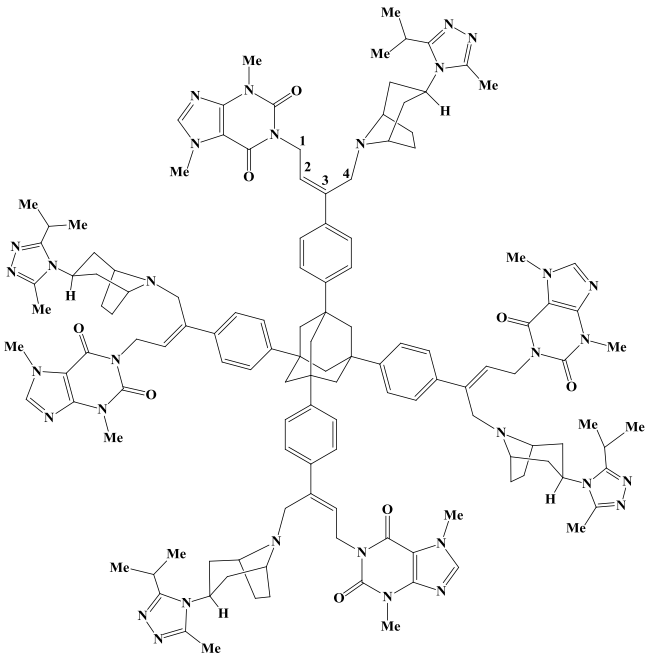
Prepared by general procedure K from trisallene **257** (0.0713 g, 0.25 mmol), 3-iodopyridine (0.185 g, 0.90 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.211 g, 0.90 mmol), $Pd_2(dba)_3$ (0.0172 g, 7.5 mol%), TFP (0.0174 g, 30 mol%) and K_2CO_3 (0.31 g, 2.25 mmol) in MeCN (5 mL) at 80 ºC for 3 h. Flash column chromatography gradient eluting with 10:7 v/v EtOAc/MeOH and then 1:1 v/v EtOAc/MeOH gave an inseparable mixture of *E*/*Z* isomeric products **258c** (0.21 g, 69%) as a colourless froth; δ_H (Major isomer from the isomeric mixture) (300 MHz, $CDCl_3$); 8.86 (3H, d, *J* 2.4, 3 pyridyl-H), 8.51 (3H, dd, *J* 1.4 and 4.8, 3 × pyridyl-H), 7.78 (3H, td, *J* 1.4 and 9.5, 3 × pyridyl-H), 7.26 (3H, dd, *J* 4.8 and 9.5, 3 × pyridyl-H), 5.91 (3H, t, *J* 6.7, 3 × NCH_2CH=), 4.82 (6H, d, *J* 6.7, 3 × NCH_2CH=), 4.28-4.15 (3H, m, 3 × azabicyclooctyl-H), 3.64 (6H, s, 3 × =CCH_2N), 3.36 (6H, br s, 6 × azabicyclooctyl-H), 2.94-2.84 (3H, m, 3 × triazolyl 3-$CH(CH_3)_2$), 2.34 (9H, s, 3 × triazolyl 5-CH_3),

2.23-2.13 (6H, m, 6 × azabicyclooctyl-H), 2.03-1.92 (6H, m, 6 × azbicyclooctyl-H), 1.69-1.59 (12H, m, 12 × azabicyclooctyl-H), 1.32 (18H, d, *J* 7.2, 3 × triazolyl 3-CH(*CH*$_3$)$_2$); υ_{max}/cm^{-1} (film) (isomeric mixture); 3383, 2965, 2878, 1693, 1567, 1514, 1462, 1417, 1345, 1315, 1286, 1251, 1215; *m/z* (ESI$^+$) (isomeric mixture) 1219.8 (50%, MH$^+$); (Found MH$^+$, 1219.7538. $C_{69}H_{91}N_{18}O_3$ requires *MH*, 1219.7516).

General Procedure L: Pd catalysed 9-component cascades.

A mixture of substituted allene (0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.10 mmol), nucleophile (0.48 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (tri-(2-furyl)phosphine) (10 mol%), and K_2CO_3 (0.6 mmol) in MeCN or DMF was stirred and heated at 80 °C (oil bath temperature) for 3-32 h. The mixture was filtered and the inorganic precipitate washed with MeCN. The solvent was removed under reduced pressure, the residue dissolved in $CHCl_3$ and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography.

1,1',1'',1'''-[Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis(4,1-phenylene{(2*Z*)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]-oct-8-yl]but-2-ene-3,1-diyl})]tetrakis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (262a).



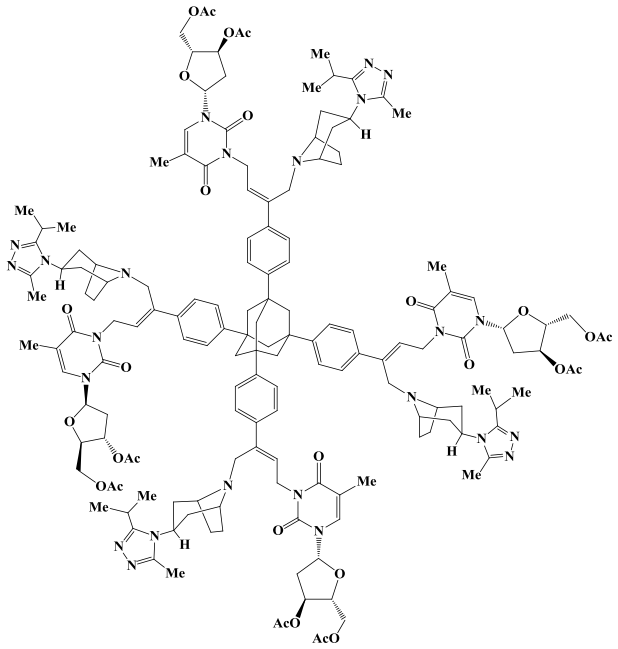
Prepared by general procedure L from *N*-allenylpurine **195** (0.0928 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.112 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP

(0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.60 mmol) in MeCN (3 mL) at 80 ºC for 24 h. Flash column chromatography gradient eluting with EtOAC, MeOH and then DMF gave the product **262a** (0.12 g, 52%) as a colourless froth, mp 199-201 °C; δ_H (300 MHz, $CDCl_3$); 7.54 (4H, s, 4 × purine-H), 7.46 (8H, d, *J* 8.2, 8 × phenyl-H), 7.37 (8H, d, *J* 8.2, 8 × phenyl-H), 5.88 (4H, t, *J* 6.2, 4 × NCH_2CH=), 4.93 (8H, d, *J* 6.2, 4 × NCH_2CH=), 4.24 (4H, m, 4 × azabicyclooctyl-H), 3.99 (12H, s, 4 × purine-NCH_3), 3.68 (8H, s, 4 × =CCH_2N), 3.58 (12H, s, 4 × purine-NCH_3), 3.46 (8H, br s, 8 × azabicyclooctyl-H), 2.96 (4H, m, 4 × triazolyl 3-$CH(CH_3)_2$), 2.37 (12H, s, 4 × triazolyl 5-CH_3), 2.21 (8H, br dd, *J* 8.7 and 3.6, 8 × azabicyclooctyl-H), 2.1 (20H, br s, 8 × azbicyclooctyl-H + 6 × adamantyl-CH_2), 1.66 (16H, br d, *J* 7.7, 16 × azabicyclooctyl-H), 1.32 (24H, d, *J* 6.7, 4 × triazolyl 3-$CH(CH_3)_2$); δ_C (75 MHz, $CDCl_3$);157.6, 153.5, 149.9, 149.3, 147.4, 146.7, 140.2, 138.9, 138.5, 125.3, 124.8, 123.0, 106.2, 57.2, 49.7, 45.8 (2 × C), 38.2, 37.5, 36.0, 32.2, 28.3, 25.2, 24.2, 20.2, 11.4; υ_{max}/cm^{-1} (film); 3384, 2935, 1704, 1661, 1603, 1549, 1513, 1455, 1415, 1357, 1314, 1286, 1234; *m/z* (ESI^+) 2321.3 (30%, $[M+Na]^+$); (Found $[M+Na]^+$, 2321.2911. $C_{130}H_{161}NaN_{32}O_8$ requires $[M+Na]^+$, 2321.3018); 2298.3 (28%, $[M+H]^+$); (Found $[M+H]^+$, 2298.3056. $C_{130}H_{161}N_{32}O_8$ requires $[M+H]^+$, 2298.3170); 1171.6 (34%, $[M+2Na]^{2+}$); (Found $[M+2Na]^{2+}$, 1171.6477. $C_{130}H_{160}Na_2N_{32}O_8$ requires $[M+2Na]^{2+}$, 1171.6441); 1160.7 (80%, $[M+H+Na]^{2+}$); (Found $[M+H+Na]^{2+}$, 1160.6560. $C_{130}H_{161}NaN_{32}O_8$ requires $[M+H+Na]^{2+}$, 1160.6531); 1149.7 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1149.6660. $C_{130}H_{162}N_{32}O_8$ requires $[M+2H]^{2+}$, 1149.6621).

NOE data ($CDCl_3$) for **262a**.

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Ph-H	Azabicyclooctyl-H
1-H		-8.7	-	-	-
2-H	-6.3		-	-	-
4-H	-1.0	-		-2.2 (δ 7.46)	-2.7 (δ 3.46)

1,1',1'',1'''-[Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis(4,1-phenylene{(2*Z*)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct -8-yl]but-2-ene-3,1-diyl})]tetrakis(3', 5'-di-*O*-acetylthymidine) (262b).



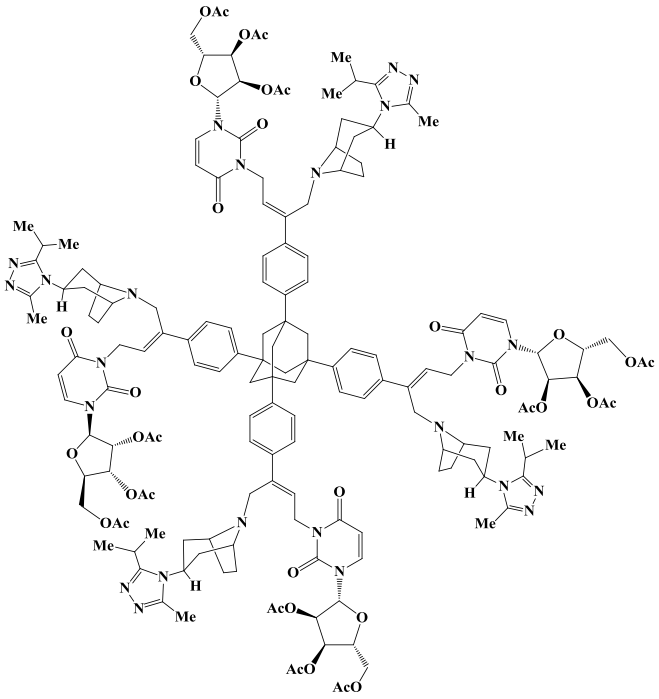
Prepared by general procedure L from 3',5'-di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine **207b** (0.151 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.112 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.6 mmol) in MeCN (3 mL) at 80 ºC for 4 h. Flash column chromatography gradient eluting with 4:1 v/v EtOAc/MeOH and then 1:1 v/v EtOAc/MeOH gave the product **262b** (0.20 g, 69%) as a colourless froth; $[\alpha]_D^{20}$ + 2.6 (*c*, 11 mg/1 mL $CHCl_3$); mp 146-148 °C; δ_H (300 MHz, $CDCl_3$); 7.46 (8H, d, *J* 8.6, 8 × phenyl-H), 7.37 (8H, d, *J* 8.6, 8 × phenyl-H), 7.29 (4H, s, 4 × pyrimidinyl 6-H), 6.37 (4H, dd, *J* 5.6 and 8.4, 4 × deoxyribosyl 1-H), 5.85 (4H, t, *J* 6.7, 4 × NCH_2CH=), 5.22 (4H, dd, *J* 4.5and 2.1, 4 × deoxyribosyl 3-H), 4.87 (8H, d, *J* 6.7, 4 × NCH_2CH=), 4.37 (4H, dd, *J* 12.2 and 3.6, 4 × deoxyribosyl 5-H_A), 4.35 (4H, dd, *J* 12.2 and 3.6, 4 × deoxyribosyl 5-H_B), 4.27-4.24 (8H, m, 4 × azabicyclooctyl-H + 4 × deoxyribosyl 4-H), 3.67 (8H, s, 4 × =CCH_2N), 3.44 (8H, br s, 8 × azabicyclooctyl-H), 2.98-2.93 (4H, m, 4 × triazolyl 3-$CH(CH_3)_2$), 2.51 (4H, dd, *J* 5.6 and 1.5, 4 × deoxyribosyl 2-H_A), 2.46 (4H, dd, *J* 5.6 and 1.5, 4 × deoxyribosyl 2-H_B), 2.37 (12H, s, 4 × triazolyl 5-CH_3), 2.23-2.05 (28H, m, 16 × azabicyclooctyl-H + 6 × adamantyl-CH_2), 2.14 (12H, s, 4 × deoxyribosyl OMe), 2.12 (12H, s, 4 × deoxyribosyl OMe), 1.96 (12H, s, 4 × pyrimidinyl 5-Me), 1.66 (16H, br d, *J* 7.9, 16 × azabicyclooctyl-H), 1.32 (24H, d, *J* 6.9, 4 × triazolyl 3-$CH(CH_3)_2$); δ_C (75 MHz, $CDCl_3$); 170.8, 170.6, 163.4, 159.5, 151.1, 151.0, 148.6, 141.2, 140.3, 133.2, 127.1, 125.9, 124.9, 111.2, 85.9, 82.5, 74.5, 64.3, 59.1, 51.6, 47.7 (2 x C), 40.2, 39.4, 37.9, 37.8, 27.1, 26.1, 22.0, 21.3, 21.2, 13.9, 13.3 ; υ_{max}/cm$^-$

^{1} (film); 3333, 2932, 1746, 1703, 1668, 1645, 1513, 1467, 1366, 1235; *m/z* (ESI^+) 2904.5 (8%, $[M+Na]^+$); (Found $[M+Na]^+$, 2904.4779. $C_{158}H_{200}NaN_{24}O_{28}$ requires *MNa*, 2904.4856); 2882.5 (15%, $[M+H]^+$); (Found $[M+H]^+$, 2882.4986. $C_{158}H_{201}N_{24}O_{28}$ requires *MH*, 2882.5037); 1493.7 (68%, $[M+2Na]^{2+}$); (Found $[M+2Na]^{2+}$, 1463.7397. $C_{158}H_{200}NaN_{24}O_{28}$ requires $[M+2Na]^{2+}$, 1463.7374); 1441.8 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1441.7615. $C_{158}H_{202}N_{24}O_{28}$ requires $[M+2H]^{2+}$, 1441.7555).

NOE data ($CDCl_3$) for **262b**.

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Ph-H	Azabicyclooctyl-H
1-H		-9.5	-1.1	-	-
2-H	-5.1		-	-	-
4-H	-2.1	-		-1.9 (δ 7.46)	-4.3 (δ 3.44)

1,1',1'',1'''-[Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis(4,1-phenylene{(2*Z*)-4-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]but-2-ene-3,1-diyl})]tetrakis(2', 3', 5'-tri-*O*-acetyluridine) (262c).

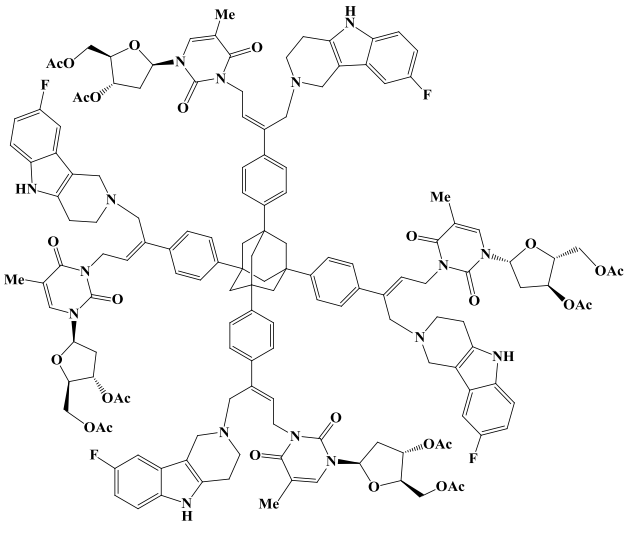


Prepared by general procedure L from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.169 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **188** (0.112 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.60 mmol) in MeCN (3 mL) at 80 ºC for 5 h. Flash column chromatography gradient eluting with EtOAc and then 2:1 v/v EtOAc/MeOH gave the product **262c** (0.17 g, 56%) as a colourless froth; $[\alpha]_D^{20}$ + 18.9 (*c*, 10 mg/1 mL

$CHCl_3$); mp 134-136 °C; δ_H (300 MHz, $CDCl_3$); 7.45 (8H, d, *J* 8.4, 8 × phenyl-H), 7.40 (8H, d, *J* 8.4, 8 × phenyl-H), 7.38 (4H, s, 4 × pyrimidinyl 6-H), 6.00 (4H, d, *J* 4.6, 4 × ribosyl 1-H), 5.83 (4H, s, 4 × pyrimidinyl 5-H), 5.82 (4H, t, *J* 7.0, 4 × NCH_2CH=), 5.40-5.32 (8H, m, 4 × ribosyl 2-H + 4 × ribosyl 3-H), 4.86 (4H, dd, *J* 14.8 and 7.0, 4 × NCH_ACH=), 4.82 (4H, dd, *J* 14.8 and 7.0, 4 × NCH_BCH=), 4.35 (12H, s, 4 × ribosyl 4-H + 4 × ribosyl 5-CH_2), 4.26-4.21 (4H, m, 4 × azabicyclooctyl-H), 3.62 (8H, s, 4 × =CCH_2N), 3.43 (8H, br s, 8 × azabicyclooctyl-H), 2.98-2.90 (4H, m, 4 × triazolyl 3-$CH(CH_3)_2$), 2.37 (12H, s, 4 × triazolyl 5-CH_3), 2.18-2.02 (28H, m, 16 × azabicyclooctyl-H + 6 × adamantyl-CH_2), 2.13 (12H, s, 4 × ribosyl OMe), 2.12 (12H, s, 4 × ribosyl OMe), 2.09 (12H, s, 4 × ribosyl OMe), 1.65 (16H, br d, *J* 7.7, 16 × azabicyclooctyl-H), 1.32 (24H, d, *J* 6.7, 4 × triazolyl 3-$CH(CH_3)_2$); δ_C (75 MHz, $CDCl_3$); 170.1 (CO), 169.6 (2 × CO), 162.0, 159.1, 150.7, 150.67, 148.2, 141.0, 139.9, 137.5, 126.8, 125.2, 124.5, 102.8, 88.8, 79.6, 72.9, 69.9, 62.9, 58.7, 51.2, 47.3 (2 x C), 39.6, 39.0, 37.4, 26.6, 25.7, 21.6, 20.8, 20.5, 12.9 (One aliphatic carbon could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 2934, 1750, 1711, 1669, 1512, 1455, 1386, 1228; *m/z* (ESI^+) 3058.5 (2%, $[M+H]^+$); (Found $[M+H]^+$, 3058.4522. $C_{162}H_{201}N_{24}O_{36}$ requires *MH*, 3058.4630); 1551.7 (100%, $[M+2Na]^{2+}$); (Found $[M+2Na]^{2+}$, 1551.7152. $C_{162}H_{200}Na_2N_{24}O_{36}$ requires $[M+2Na]^{2+}$, 1551.7171); 1529.7 (61%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1529.7358. $C_{162}H_{202}N_{24}O_{36}$ requires $[M+2H]^{2+}$, 1529.7351).

1,1',1'',1'''-(Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis{4,1-phenylene[(2*Z*)-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)but-2-ene-3,1-diyl]})tetrakis(3', 5'-di-*O*-acetylthymidine) (262d).

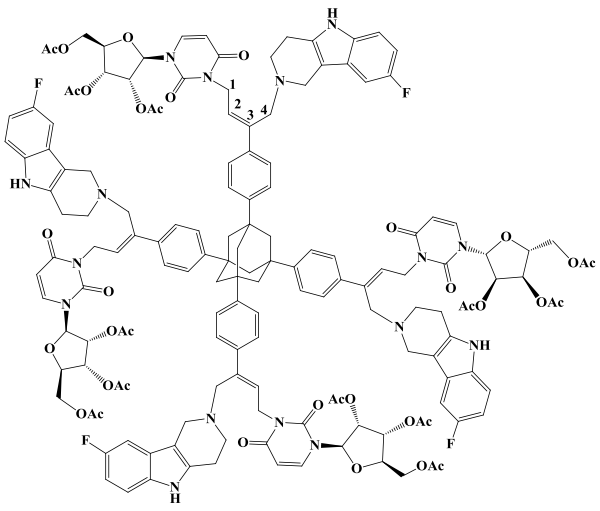
Prepared by general procedure L from 3',5'-di-*O*-acetyl-3-buta-2,3-dien-1-ylthymidine **207b** (0.151 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.0912 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003



g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.60 mmol) in MeCN (3 mL) at 80 ºC for 6 h. Flash column chromatography eluting with 20:1 v/v EtOAc/MeOH gave the product **262d** (0.20 g, 74%) as a colourless froth; $[\alpha]_D^{20}$ + 6.2 (*c*, 11 mg/1 mL $CHCl_3$); mp 155-157 °C; δ_H (300 MHz, $CDCl_3$); 8.18 (4H, br s, 4 × NH), 7.36 (8H, d, *J* 8.1, 8 × phenyl-H), 7.26 (4H, s, 4 × pyrimidinyl 6-H), 7.13 (8H, d, *J* 8.1, 8 × phenyl-H), 7.02 (4H, dd, *J* 8.5 and 4.4, 4 × pyridoindolyl-H), 6.95 (4H, dd, *J* 9.6 and 1.9, 4 × pyridoindolyl-H), 6.73 (4H, dt, *J* 9.2 and 2.4, 4 × pyridoindolyl-H), 6.36 (4H, dd, *J* 7.9 and 5.9, 4 × deoxyribosyl 1-H), 5.85 (4H, t, *J* 6.5, 4 × NCH_2CH=), 5.20 (4H, dd, *J* 4.4 and 1.8, 4 × deoxyribosyl 3-H), 4.82 (8H, d, *J* 6.5, 4 × NCH_2CH=), 4.38 (4H, dd, *J* 12.2 and 3.7, 4 × deoxyribosyl 5-H_A), 4.30 (4H, dd, *J* 12.2 and 3.7, 4 × deoxyribosyl 5-H_B), 4.23 (4H, dd, *J* 5.8 and 3.2, 4 × deoxyribosyl 4-H), 3.76 (8H, br s, 4 × =CCH_2N), 3.61 (8H, br s, 4 × pyridoindolyl 1-CH_2), 2.77 (8H, br s, 4 × pyridoindolyl-CH_2), 2.50-2.43 (16H, br m, 4 × pyridoindolyl-CH_2 + 4 × deoxyribosyl 2-CH_2), 2.12 (12H, s, 4 × deoxyribosyl OMe), 2.10 (12H, s, 4 × deoxyribosyl OMe), 1.95 (12H, s, 4 × pyrimidinyl 5-Me), 1.77 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 169.3, 169.1, 161.8, 156.3 (*J* 232.2), 149.5, 147.2, 138.9, 138.3, 133.2, 131.5, 131.2, 125.2 (*J* 9.2), 125.15, 124.7, 123.6, 109.7 (*J* 9.2), 109.5, 107.4 (*J* 4.5), 107.3 (*J* 25.2), 101.4 (*J* 23.0), 84.3, 80.9, 73.0, 62.7, 54.5, 48.6, 47.9, 45.7, 38.8, 37.5, 36.4, 22.3, 19.7, 19.66, 12.3; υ_{max}/cm^{-1} (film); 3346, 2927, 1744, 1702, 1643, 1465, 1366, 1325, 1232; *m/z* (ESI^+) 2706.1 (2%, $[M+H]^+$); (Found $[M+H]^+$, 2706.1237. $C_{150}H_{157}F_4N_{16}O_{28}$ requires *MH*, 2705.1284); *m/z* (ESI^+) 1353.6 (59%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1353.5679. $C_{150}H_{158}F_4N_{16}O_{28}$ requires $[M+2H]^{2+}$, 1353.5678); 902.7 (100%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 902.7141. $C_{150}H_{159}F_4N_{16}O_{28}$ requires $[M+3H]^{3+}$, 902.7143).

1,1',1'',1'''-(Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis{4,1-phenylene[(2*Z*)-4-(8-fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl)but-2-ene-3,1-diyl]})tetrakis(2', 3', 5'-tri-*O*-acetyluridine) (262e).

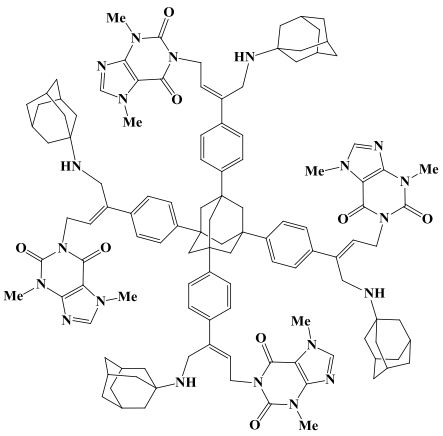
Prepared by general procedure L from 2',3',5'-tri-*O*-acetyl-3-buta-2,3-dien-1-yluridine **207a** (0.1794 g, 0.425 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.1003 g, 0.106 mmol), 8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole **187** (0.0969 g, 0.51 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.09 g, 0.636 mmol) in MeCN (3 mL) at 80 ºC for 3 h. Flash



column chromatography eluting with 30:1 v/v EtOAc/MeOH gave the product **262e** (0.19 g, 62%) as a colourless froth; $[\alpha]_D^{20}$ + 24.7 (*c*, 12 mg/1 mL $CHCl_3$); mp 144-146 °C; δ_H (300 MHz, $CDCl_3$); 8.02 (4H, br s, 4 × NH), 7.38 (8H, d, *J* 7.9, 8 × phenyl-H), 7.36 (4H, d, *J* 8.2, 4 × pyrimidinyl 6-H), 6.98 (8H, d, *J* 7.9, 8 × phenyl-H), 7.07 (4H, dd, *J* 8.6 and 4.5, 4 × pyridoindolyl-H), 6.98 (4H, dd, *J* 9.5 and 1.8, 4 × pyridoindolyl-H), 6.76 (4H, dt, *J* 9.1 and 2.3, 4 × pyridoindolyl-H), 6.04 (4H, d, *J* 4.4, 4 × ribosyl 1-H), 5.85 (4H, t, *J* 6.4, 4 × NCH_2CH=), 5.82 (4H, d, *J* 8.2, 4 × pyrimidinyl 5-H), 5.34 (8H, dd, *J* 8.7 and 6.1, 4 × ribosyl 2-H + 4 × ribosyl 3-H), 4.81 (8H, d, *J* 6.4, 4 × NCH_2CH=), 4.33 (12H, s, 4 × ribosyl 4-H + 4 × ribosyl 5-CH_2), 3.76 (8H, br s, 4 × =CCH_2N), 3.64 (8H, br s, 4 × pyridoindolyl 1-CH_2), 2.81 (8H, br s, 4 × pyridoindolyl-CH_2), 2.60 (8H, br s, 4 × pyridoindolyl-CH_2), 2.12 (12H, s, 4 × ribosyl OMe), 2.11 (12H, s, 4 × ribosyl OMe), 2.05 (12H, s, 4 × ribosyl OMe), 1.85 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 170.4 (CO), 169.8 (2 x CO), 162.2, 157.7 (*J* 232.2), 150.9, 148.6, 140.3, 139.6, 137.4, 134.6, 132.5, 126.6 (*J* 9.2), 126.57, 125.9, 125.0, 111.2 (*J* 9.2), 109.0 (*J* 4.5), 108.8 (*J* 25.3), 103.8, 102.9 (*J* 25.3), 88.5, 79.9, 73.1, 70.2, 63.2, 49.8, 49.3, 47.1, 40.0, 39.0, 29.9, 23.8, 21.0, 20.7, 20.6; υ_{max}/cm^{-1} (film); 3373, 3023, 2929, 1748, 1712, 1667, 1483, 1455, 1372, 1325, 1229; *m/z* (ESI^+) 2882.1 (10%, $[M+H]^+$); (Found $[M+H]^+$, 2882.0786. $C_{154}H_{157}F_4N_{16}O_{36}$ requires *MH*, 2882.0877); 1441.5 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1441.5480. $C_{154}H_{158}F_4N_{16}O_{36}$ requires $[M+2H]^{2+}$, 1441.5475); *m/z* (ESI^+) 961.4 (100%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 961.4. $C_{154}H_{159}F_4N_{16}O_{36}$ requires $[M+3H]^{3+}$, 961.3674). NOE data ($CDCl_3$) for **262e**.

	% Enhancement				
Irradiated proton	1-H	2-H	4-H	Ph-H	pyridoindolyl-H
1-H		-11.4	-4.6	-	-1.7 (δ 3.64)
2-H	-7.3		-	-6.5 (δ 7.38)	-
4-H	-7.0	-		-7.9 (δ 7.38)	-4.9 (δ 3.64) -5.8 (δ 2.81) -2.1 (δ 2.60)

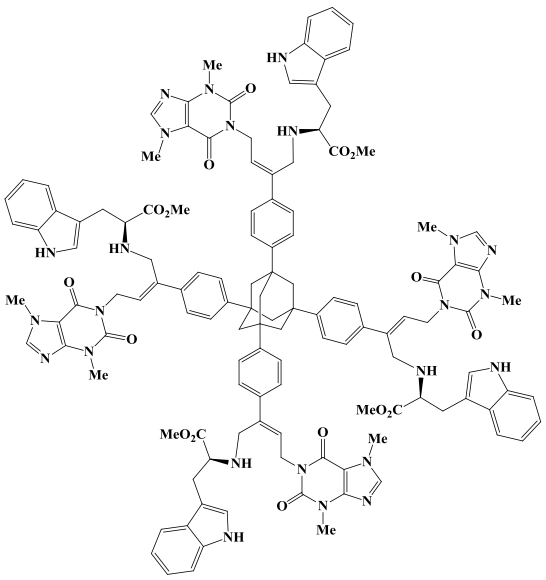
1,1',1'',1'''-(Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis{4,1-phenylene[(2*Z*)-4-(adamantan-1-ylamino)but-2-ene-3,1-diyl]})tetrakis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (262f).



Prepared by general procedure L from *N*-allenylpurine **195** (0.0928 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), 1-aminoadamantane **180** (0.0726 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.60 mmol) in MeCN (3 mL) at 80 ºC for 3 h. The product precipitated from hot solution during the reaction. The reaction mixture was cooled, filtered and the precipitate washed with water to give the crude product. Flash column chromatography gradient eluting with MeOH and then DMF gave the product **262f** (0.17 g, 87%) as a colourless froth, mp 217-219 °C; δ_H (300 MHz, $CDCl_3$); 7.50 (4H, s, 4 × purine-H), 7.49 (8 H, d, *J* 7.6, 8 × phenyl-H), 7.36 (8 H, d, *J* 7.6, 8 × phenyl-H), 5.85 (4H, t, *J* 7.2, 4 × NCH_2CH=), 4.87 (8H, d, *J* 7.2, 4 × NCH_2CH=), 3.98 (12H, s, 4 × NMe), 3.85 (8H, s, 4 × =CCH_2N), 3.57 (12H, s, 4 × NMe), 2.65 (4H, br s, 4 × NH), 2.08 (24H, br s, 12 × adamantyl-CH + 6 × adamantyl-CH_2), 1.77 (24H, br s, 12 × adamantyl-CH_2), 1.66 (24H, br s, 12 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 155.1, 151.4, 148.8, 148.6, 141.5, 141.2, 138.8, 126.3, 125.0, 124.1, 107.7, 51.3, 47.1, 42.2, 39.8, 39.0, 38.9, 36.8, 33.6, 29.8, 29.6; υ_{max}/cm^{-1} (film); 2903, 2847, 2366, 1704, 1660, 1604, 1549, 1486, 1454, 1413, 1357, 13101286, 1233; *m/z* (ESI$^+$) 1966.1097 (3%, $[M+H]^+$); (Found $[M+H]^+$, 1966.1097. $C_{118}H_{141}N_{20}O_8$ requires *[M+H]*$^+$, 1966.1236); 983.6 (93%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 983.5666. $C_{118}H_{142}N_{20}O_8$ requires *[M+2H]*$^{2+}$, 983.5654); 656.0 (100%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 656.0474. $C_{118}H_{143}N_{20}O_8$ requires *[M+3H]*$^{3+}$, 656.0460).

Tetramethyl (2*S*,2'*S*,2''*S*,2'''*S*)-2,2',2'',2'''-(tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis{4,1-phenylene[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-ene-2,1-diyl]imino})tetrakis[3-(1*H*-indol-3-yl)propanoate] (262g).

Prepared by general procedure L from *N*-allenylpurine **195** (0.0928 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), (*S*)-tryptophan

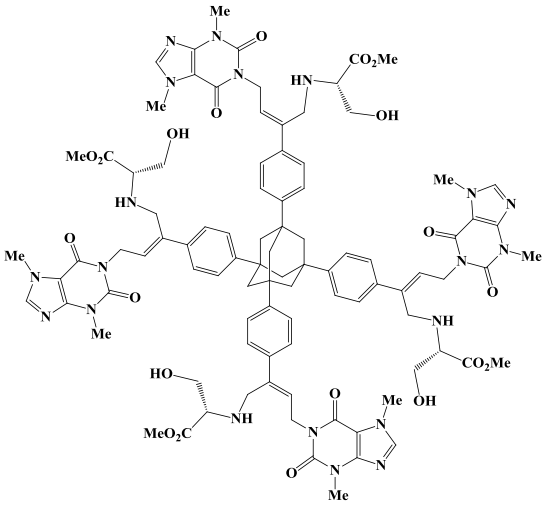


methyl ester hydrochloride **260** (0.122 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.6 mmol) in MeCN (3 mL) at 80 ºC for 24 h. Flash column chromatography eluting with 1:1 v/v EtOAc/MeOH gave the product **262g** (0.10 g, 45%) as a colourless froth; $[\alpha]_D^{20}$ + 9.1 (*c*, 12 mg/1 mL $CHCl_3$); mp 129-131 °C; δ_H (300 MHz, $CDCl_3$); 7.54 (4H, d, *J* 7.6, 4 × indolyl-H), 7.44 (4H, s, 4 × purine-H), 7.31 (8 H, d, *J* 8.6, 8 × phenyl-H), 7.24 (8 H, d, *J* 8.6, 8 × phenyl-H), 7.17 (4H, dd, *J* 8.6and 1.0, 4 × indolyl-H), 7.05 (8H, m, 8 × indolyl-H), 6.89 (4H, d, *J* 1.9, 4 × indolyl-H), 5.82 (4H, t, *J* 6.8, 4 × NCH_2CH=), 4.79 (8H, d, *J* 6.8, 4 × NCH_2CH=), 9.95-3.90 (4H, m, *CH*CO_2Me), 3.90 (12H, s, 4 × NMe), 3.75 (4H, d, *J* 6.7, 4 × =CCH_AN), 3.72 (4H, d, *J* 6.7, 4 × =CCH_BN), 3.65 (12H, s, CO_2Me), 3.52 (12H, s, 4 × NMe), 3.16 (4H, dd, *J* 14.3 and 6.6, 4 × CH_ACHCO_2Me), 3.05 (4H, dd, *J* 14.3 and 6.6, 4 × CH_BCHCO_2Me), 2.00 (16H, br s, 6 × adamantyl-CH_2 + 4 × NH); δ_C (75 MHz, $CDCl_3$); 175.4, 155.0, 151.4, 148.8, 148.4, 141.5, 140.5, 138.6, 136.1, 127.4, 126.3, 124.8 (2 x C), 123.0, 121.8, 119.3, 118.8, 111.3, 111.1, 107.6, 61.7, 51.8, 47.1, 46.6, 39.6, 38.9, 33.6, 32.0, 29.7; υ_{max}/cm^{-1} (film); 3330, 2926, 2853, 1701, 1659, 1549, 1456, 1355, 1233; *m/z* (ESI^+) 2234.0 (10%, $[M+H]^+$); (Found $[M+H]^+$, 2234.0270. $C_{126}H_{129}N_{24}O_{16}$ requires $[M+H]^+$, 2234.0013); 1117.5 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1117.5083. $C_{126}H_{130}N_{24}O_{16}$ requires $[M+2H]^{2+}$, 1117.5043); 745.3 (40%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 745.3410. $C_{126}H_{131}N_{24}O_{16}$ requires $[M+3H]^{3+}$, 745.3386).

Tetramethyl (2*S*,2'*S*,2''*S*,2'''*S*)-2,2',2'',2'''-(tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis{4,1-phenylene[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-ene-2,1-diyl]imino})tetrakis(3-hydroxypropanoate) (262h).

Prepared by general procedure L from *N*-allenylpurine **195** (0.0928 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), (*S*)-serine

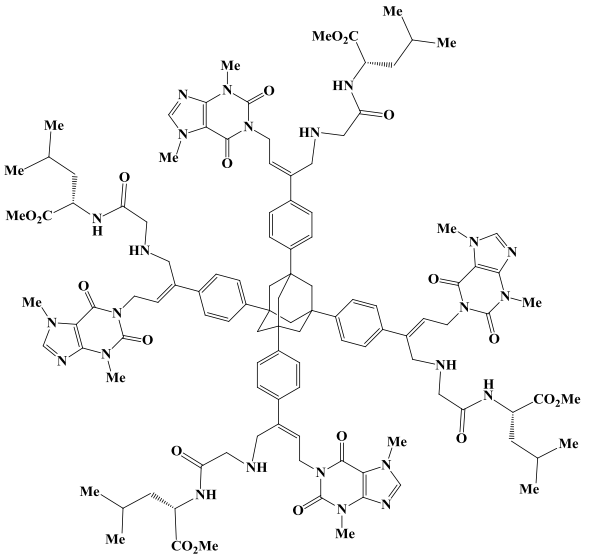
methyl ester hydrochloride **210** (0.075 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.60 mmol) in MeCN (3 mL) at 80 ºC for 32 h. Flash column chromatography eluting with 10:1 v/v $CHCl_3$/MeOH gave the product **262h** (0.09 g, 49%) as a colourless froth; $[\alpha]_D^{20}$ + 1.3 (*c*, 11 mg/1 mL $CHCl_3$); mp 136-138 °C; δ_H (300 MHz, $CDCl_3$);



7.50 (4H, s, 4 × purine-H), 7.44 (8H, d, *J* 8.5, 8 × phenyl-H), 7.38 (8H, d, *J* 8.5, 8 × phenyl-H), 5.91 (4H, t, *J* 7.1, 4 × NCH_2CH=), 4.95 (4H, dd, *J* 14.3 and 7.1, 4 × NCH_ACH=), 4.87 (4H, dd, *J* 14.3 and 7.1, 4 × NCH_BCH=), 3.98 (12H, s, 4 × NMe), 3.97 (4H, d, *J* 12.1, 4 × =CCH_AN), 3.87 (4H, dd, *J* 10.4 and 3.8, 4 × $CHCH_AOH$), 3.80 (4H, d, *J* 12.1, 4 × =CCH_BN), 3.75 (12H, s, 3 × CO_2Me), 3.63 (4H, dd, *J* 10.4 and 3.8, 4 × $CHCH_BOH$), 3.57 (12H, s, 4 × NMe), 3.58-3.51 (4H, m, 4 × $NHCHCH_2$), 2.07 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 173.2, 155.1, 151.4, 148.9, 148.7, 141.6, 140.4, 138.4, 126.2, 125.1, 124.8, 107.7, 62.7, 62.5, 52.1, 47.1, 46.3, 39.6, 39.0, 33.7, 29.8; υ_{max}/cm^{-1} (film); 3457, 2949, 1733, 1704, 1660, 1604, 1550, 1455, 1355, 1315, 1233; *m/z* (ESI^+) 1837.8 (14%, $[M+H]^+$); (Found $[M+H]^+$, 1837.8143. $C_{94}H_{109}N_{20}O_{20}$ requires *MH*, 1837.8122); 919.4 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 919.4139. $C_{94}H_{110}N_{20}O_{20}$ requires $[M+2H]^{2+}$, 919.4097); 613 (23%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 613.2781. $C_{94}H_{111}N_{20}O_{20}$ requires $[M+3H]^{3+}$, 613.2756).

Tetramethyl (2*S*,2'*S*,2''*S*,2'''*S*)-2,2',2'',2'''-(tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis{4,1-phenylene[(2*Z*)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)but-2-ene-2,1-diyl]imino(1-oxoethane-2,1-diyl)imino})tetrakis(4-methylpentanoate) (262i).

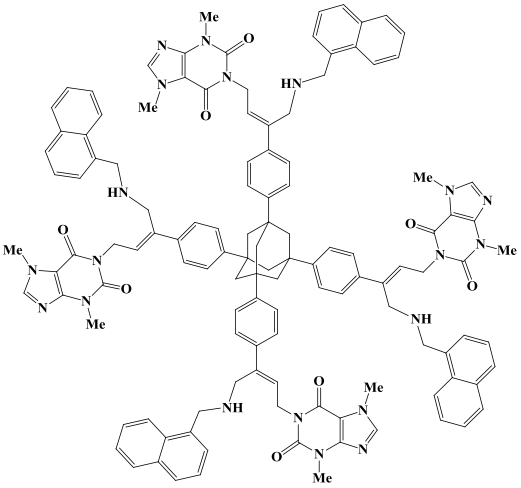
Prepared by general procedure L from *N*-allenylpurine **195** (0.0928 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), methyl glycyl-(*S*)-leucinate hydrochloride **261** (0.114 g, 0.48 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.083 mmol) in MeCN (3 mL)



at 80 ºC for 26 h. Flash column chromatography eluting with 20:1 v/v $CHCl_3$/MeOH gave the product **262i** (0.12 g, 55%) as a colourless froth; $[\alpha]_D^{20}$ + 0.7 (*c*, 20 mg/1 mL $CHCl_3$); mp 106-108 °C; δ_H (300 MHz, $CDCl_3$); 7.66 (4H, d, *J* 8.2, 4 × CONH), 7.53 (4H, s, 4 × purine-H), 7.41 (8H, d, *J* 8.5, 8 × phenyl-H), 7.37 (8H, d, *J* 8.5, 8 × phenyl-H), 5.85 (4H, t, *J* 7.1, 4 × NCH_2CH=), 4.91 (4H, dd, *J* 14.3 and 7.1, 4 × NCH_ACH=), 4.83 (4H, dd, *J* 14.3 and 7.1, 4 × NCH_BCH=), 4.64 (4H, td, *J* 8.2 and 4.4, 4 × CONH*CH*), 3.99 (12H, s, 4 × purine 7-NMe), 3.93 (4H, d, *J* 12.9, 4 × =CCH_AN), 3.82 (4H, d, *J* 12.9, 4 × =CCH_BN), 3.68 (12H, s, 3 × CO_2Me), 3.58 (12H, s, 4 × purine 3-NMe), 3.35 (8H, br s, 4 × NHCH_2CO), 2.08 (12H, br s, 6 × adamantyl-CH_2), 2.04 (4H, br s, 4 × NH), 1.67-1.44 (12H, m, CH_2CHMe$_2$), 0.90 (12H, d, *J* 4.4, 4 × CHMe_A), 0.88 (12H, d, *J* 4.4, 4 × CHMe_B); δ_C (75 MHz, $CDCl_3$); 173.4, 171.9, 155.0, 151.4, 148.9, 148.6, 141.6, 140.7, 138.7, 126.5, 125.1, 125.0, 107.7, 52.2 (2C, Me and CH_2), 50.1, 47.9, 47.2, 41.2, 39.5, 39.0, 33.7, 29.8, 24.9, 23.0, 21.8; υ_{max}/cm^{-1} (film); 3334, 3008, 2955, 1742, 1705, 1660, 1604, 1549, 1512, 1452, 1355, 1315, 1234; *m/z* (ESI^+) 2170.1 (6%, $[M+H]^+$); (Found $[M+H]^+$, 2170.1061. $C_{114}H_{145}N_{24}O_{20}$ requires *MH*, 2170.0946); 1085.6 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 1085.5578. $C_{114}H_{146}N_{24}O_{20}$ requires $[M+2H]^{2+}$, 1085.5567); 724.0 (63%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 724.0418. $C_{114}H_{147}N_{24}O_{20}$ requires $[M+3H]^{3+}$, 724.0402).

1,1',1'',1'''-[Tricyclo[3.3.1.1^{3,7}]decane-1,3,5,7-tetrayltetrakis(4,1-phenylene{(2*Z*)-4-[(1-naphthylmethyl)amino]but-2-ene-3,1-diyl})]tetrakis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (262j).

Prepared by general procedure L from *N*-allenylpurine **195** (0.0928 g, 0.40 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.0944 g, 0.1 mmol), 1-aminomethylnaphthalene **212** (0.065 mL, 0.44 mmol), $Pd_2(dba)_3$ (0.003 g, 2.5 mol%), TFP (0.003 g, 10 mol%) and K_2CO_3 (0.083 g, 0.083 mmol) in MeCN (3 mL)

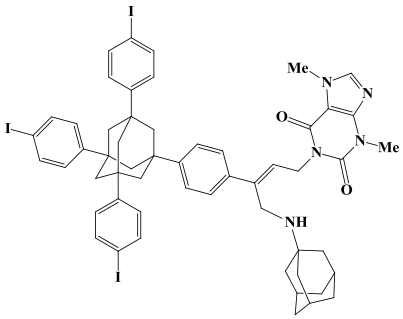


at 80 ºC for 24 h. Flash column chromatography eluting with 5:3 v/v EtOAc/MeOH gave the product **262j** (0.10 g, 51%) as a colourless froth, mp 138-140 °C; δ_H (300 MHz, $CDCl_3$); 8.05-8.01 (4H, m, 4 × naphthyl-H), 7.80-7.75 (4H, m, 4 × naphthyl-H), 7.71 (4H, d, *J* 8.2, 4 × naphthyl-H), 7.48-7.31 (36H, m, 16 × naphthyl-H, 16 × phenyl-H and 4 × purine-H), 5.93 (4H, t, *J* 7.1, 4 × NCH_2CH=), 4.88 (8H, d, *J* 7.1, 4 × NCH_2CH=), 4.26 (8H, s, 4 × naphthyl-CH_2NH), 4.01 (8H, s, 4 × =CCH_2NH), 3.91 (12H, s, 4 × purine 7-Me), 3.55 (12H, s, 4 × purine 3-Me), 2.06 (12H, br s, 6 × adamantyl-CH_2), 1.86 (4H, br s, NH); δ_C (75 MHz, $CDCl_3$); 155.0, 151.4, 148.8, 148.6, 141.42, 141.4, 138.8, 136.0, 133.7, 131.9, 128.5, 127.6, 126.5, 126.2, 125.8, 125.4, 125.3, 125.0, 124.5, 124.0, 107.6, 51.2, 47.7, 47.1, 39.6, 39.0, 33.6, 29.7; υ_{max}/cm^{-1} (film); 3313, 3009, 2937, 1701, 1655, 1603, 1550, 1453, 1412, 1355, 1314, 1286, 1233; *m/z* (ESI^+) 1989.9 (11%, MH^+); (Found MH^+, 1989.9334. $C_{122}H_{117}N_{20}O_8$ requires MH, 1989.9358); 995.5 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 995.4748. $C_{122}H_{118}N_{20}O_8$ requires $[M+2H]^{2+}$, 995.4715); 664.0 (19%, $[M+3H]^{3+}$); (Found $[M+3H]^{3+}$, 663.9856. $C_{122}H_{119}N_{20}O_8$ requires $[M+3H]^{3+}$, 663.9834).

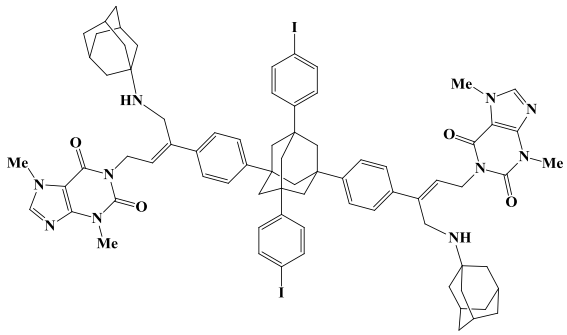
3,7-Dimethyl-1-[(2*Z*)-4-(tricyclo[3.3.1.1^{3,7}]dec-1-ylamino)-3-{4-[3,5,7-tris(4-iodophenyl)tricyclo[3.3.1.1^{3,7}]dec-1-yl]phenyl}but-2-en-1-yl]-3,7-dihydro-1*H*-purine-2,6-dione (263a) and 1,1'-([5,7-bis(4-iodophenyl)tricyclo[3.3.1.1^{3,7}]decane-1,3-diyl]bis{benzene-4,1-diyl[(2*Z*)-4-(tricyclo[3.3.1.1^{3,7}]dec-1-ylamino)but-2-ene-3,1-diyl]})bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (263b)

Prepared by general procedure B from *N*-allenylpurine **195** (0.0123 g, 0.053 mmol), 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **259** (0.06 g, 0.064 mmol), 1-aminoadamantane **180** (0.0096 g, 0.064 mmol), $Pd_2(dba)_3$ (0.0012 g, 2.5 mol%), TFP (0.0012 g, 10 mol%) and K_2CO_3 (0.022 g, 0.159 mmol) in DMF (2 mL) at 80 ºC for 16 h. Flash column chromatography gradient eluting with AcOEt afforded **263a** then eluting with 20:1 $CHCl_3$/MeOH gave **263b.**

Compound 263a: colourless froth, (0.023 g, 36%), mp 220-222 °C; δ_H (300 MHz, $CDCl_3$); 7.65 (6H, d, *J* 8.8, 7.49, 6 × phenyl-H), 7.52 (2H, d, *J* 8.2, 2 × phenyl-H), 7.50 (1H, s, purine-H), 7.35 (2H, d, *J* 8.2, 2 × phenyl-H), 7.19 (6H, d, *J* 8.8, 6 × phenyl-H), 5.86 (1H, t, *J* 7.1, NCH_2CH=), 4.88 (2H, d, *J* 7.1, NCH_2CH=), 3.98 (3H, s, purine 7-Me), 3.84 (2H, s, =CCH_2N), 3.57 (3H, s, purine 3-Me), 2.06 (15H, br d, *J* 7.1, 3 × adamantyl-CH + 6 × adamantyl-CH_2), 1.76 (6H, br s, 3 × adamantyl-CH_2), 1.66 (6H, br s, 3 × adamantyl-CH_2), 1.57 (1H, br s, NH); δ_C (75 MHz, $CDCl_3$); 155.1, 151.4, 148.9, 148.7, 147.7, 141.5, 139.4, 137.5, 127.2, 126.4, 124.8, 123.9, 107.7, 91.7, 50.9, 46.8, 42.6, 39.8, 39.1, 38.9, 36.9, 33.7, 29.8, 29.7 (One aromatic carbon atom could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3307, 2902, 2848, 1703, 1659, 1604, 1550, 1486, 1452, 1413, 1392, 1357, 1310, 1286, 1233; *m/z* (ESI^+) 1200.2 (100%, $[M+H]^+$); (Found $[M+H]^+$, 1200.1581. $C_{55}H_{57}{}^{127}I_3N_5O_2$ requires $[M+H]^+$, 1200.1641).



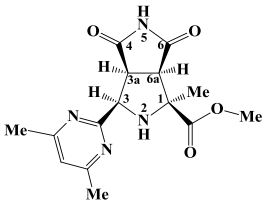
Compound 263b: colourless froth, (0.011 g, 29%), mp 212-214 °C; δ_H (300 MHz, $CDCl_3$); 7.65 (4H, d, *J* 8.2, 4 × phenyl-H), 7.51 (2H, s, 2 × purine-H), 7.50 (4H, d, *J* 8.2, 4 × phenyl-H), 7.36 (4H, d, *J* 8.2, 4 × phenyl-H), 7.19 (4H, d, *J* 8.2, 4 × phenyl-H), 5.87 (2H, t, *J* 7.1, 2 × NCH_2CH=), 4.87 (4H, d, *J* 7.1, 2 × NCH_2CH=), 3.99 (6H, s, 2 × purine 7-Me), 3.89 (4H, s, 2 × =CCH_2N), 3.58 (6H, s, 2 × purine 3-Me), 2.08 (20H, br d, *J* 7.1, 6 × adamantyl-CH + 6 × adamantyl-CH_2 + 2 × NH), 1.81 (12H, br s, 6 × adamantyl-CH_2), 1.66 (12H, br s, 6 × adamantyl-CH_2); δ_C (75 MHz, $CDCl_3$); 155.1, 151.4, 148.9, 148.2, 141.6, 139.0, 137.4, 127.3, 126.4, 125.0, 107.7, 91.5, 46.9, 42.0, 39.9, 39.1, 38.9, 36.7, 33.7, 29.8, 29.6 (three aromatic and one aliphatic carbon atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3309, 2905, 2848, 1704, 1660, 1604, 1550, 1486, 1454, 1413, 1392, 1357, 1310, 1286, 1233; *m/z* (ESI^+) 1455.5 (9%, $[M+H]^+$); (Found $[M+H]^+$, 1455.4814. $C_{76}H_{85}I_2N_{10}O_4$ requires $[M+H]^+$, 1455.4839); 728.2 (100%, $[M+2H]^{2+}$); (Found $[M+2H]^{2+}$, 728.2479. $C_{76}H_{86}{}^{127}I_2N_{10}O_4$ requires $[M+2H]^{2+}$, 728.2456).



General procedure M: 1,3-Dipolar cycloaddition reactions.

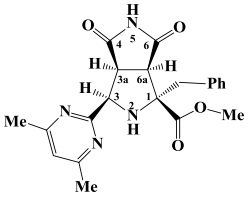
An equimolar mixture (1 mmol) of the aldehyde, amine hydrochloride, maleimide and Et_3N in toluene (7 mL) was heated at 100 °C for 10 min-3 h with stirring. The cycloadducts precipitated out of the hot solution. The solution was filtered and the precipitate washed with water to dissolve the Et_3NHCl salt. The resulting solid was crystallized.

Methyl 3-(4,6-dimethylpyrimidin-2-yl)-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (273a).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), (*R*)-alanine methyl ester hydrochloride (0.139 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1 h. The product **273a** (0.21 g, 66%) crystallized from MeOH as colourless needles, mp 258-260 °C; (Found: C, 56.65; H, 5.75; N, 17.65; $C_{15}H_{18}N_4O_4$ requires C, 56.60; H, 5.70; N, 17.60%); δ_H (300 MHz, DMSO-d_6); 11.15 (1H, s, NH), 7.16 (1H, s, pyrimidinyl-H), 4.66 (1H, dd, *J* 12.9 and 9.2, 3-H), 3.83 (1H, d, *J* 12.9, NH), 3.73 (3H, s, CO_2CH_3), 3.70 (1H, t, *J* 9.2, 3a-H), 3.36 (1H, d, *J* 9.2, 6a-H), 2.40 (6H, s, 2 x pyrimidinyl-CH_3), 1.43 (3H, s, 1-CH_3); δ_C (75 MHz, DMSO-d_6); 177.3, 176.5, 172.4, 166, 164.8, 118.8, 68.1, 64.4, 58.6, 52.8, 52.3, 23.9, 23.3; υ_{max}/cm^{-1} (film); 3302, 3148, 2990, 2758, 1772, 1721, 1598, 1539, 1437, 1344, 1270; *m/z* (ESI^+) 341.1 (100%, MNa^+); (Found MNa^+, 341.1219. $C_{15}H_{18}N_4NaO_4$ requires *MNa*, 341.1220.

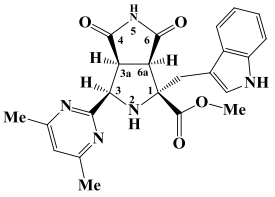
Methyl 1-benzyl-3-(4,6-dimethylpyrimidin-2-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (273b).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), (*S*)-phenylalanine methyl ester hydrochloride (0.215 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1 h. The product **273b** (0.32 g, 83%) crystallized from MeOH as colourless needles, mp 263-265 °C; (Found: C, 63.95; H, 5.60; N, 14.25; $C_{21}H_{22}N_4O_4$ requires C, 63.95; H, 5.62; N, 14.20%); δ_H (300 MHz, DMSO-d_6); 11.16 (1H, s, NH), 7.13-7.16 (6H, m, Ar-H), 4.84 (1H, dd, *J* 13.1 and 8.5, 3-H), 3.76 (1H, t, *J* 8.5, 3a-H),

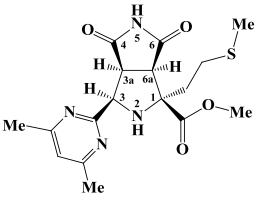
3.71 (3H, s, CO_2CH_3), 3.68 (1H, d, *J* 13.1, NH), 3.54 (1H, d, *J* 8.5, 6a-H), 3.21 (1H, d, *J* 13.8, 1-*CH*$_2$Ph), 3.10 (1H, d, *J* 13.8, 1-*CH*$_2$Ph), 2.39 (6H, s, 2 x pyrimidinyl-CH_3); δ_C (75 MHz, DMSO-*d*$_6$); 177.6, 177, 171.7, 166.5, 165.3, 137.2, 130.5, 128.0, 126.7, 119.3, 73.3, 64.5, 58, 53.2, 52.4, 40.7, 23.8; υ_{max}/cm^{-1} (film); 3300, 3248, 2956, 2741, 1776, 1745, 1718, 1598, 1435, 1374, 1348, 1263, 1231; *m/z* (ESI^+) 417.2 (100%, MNa^+); (Found MNa^+, 417.1534. $C_{21}H_{22}N_4NaO_4$ requires *MNa*, 417.1533.

Methyl 3-(4,6-dimethylpyrimidin-2-yl)-1-(1H-indol-3-ylmethyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (273c).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), (*S*)-tryptophan methyl ester hydrochloride (0.254 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1 h. The product **273c** (0.32 g, 74%) crystallized from EtOH as colourless needles, mp 257-259 °C; (Found: C, 63.70; H, 5.40; N, 16.20; $C_{23}H_{23}N_5O_4$ requires C, 63.73; H, 5.35; N, 16.16%); δ_H (300 MHz, DMSO-*d*$_6$); 11.14 (1H, s, NH), 10.80 (1H, d, *J* 2.05, NH), 7.53 (1H, d, *J* 7.5, indolyl-H), 7.29(1H, d, *J* 7.8, indolyl-H), 7.15 (1H, s, pyrimidinyl-H), 7.07 (1H, d, *J* 2.1, indolyl-H), 7.00 (1H, t, *J* 7.5, indolyl-H), 6.92 (1H, t, *J* 7.4, indolyl-H), 4.86 (1H, dd, *J* 13.2 and 8.5, 3-H), 3.79 (1H, t, *J* 8.5, 3a-H), 3.74 (1H, d, *J* 13.2, 2-NH), 3.66 (3H, s, CO_2CH_3), 3.58 (1H, d, *J* 8.5, 6a-H), 3.35 (1H, d, *J* 14.9, 1-C*H*$_2$-indolyl), 3.20 (1H, d, *J* 14.9, 1-C*H*$_2$-indolyl), 2.39 (6H, s, 2 x pyrimidinyl-CH_3); δ_C (75 MHz, DMSO-*d*$_6$); 177.3, 176.6, 171.8, 166, 164.9, 135.4, 128.0, 124.0, 120.4, 118.7, 118.5, 118.1, 111.0, 109.4, 73.2, 64.3, 58.2, 52.8, 51.9, 31.1, 23.3; υ_{max}/cm^{-1} (film); 3390, 3054, 2890, 2763, 1772, 1716, 1594, 1544, 1434, 1348, 1205; *m/z* (ESI^+) 434.2 (100%, MH^+); (Found MH^+,434.1827. $C_{23}H_{24}N_5O_4$ requires *MH*, 434.1823.

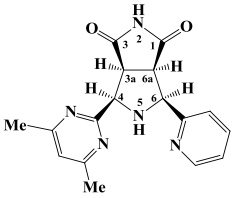
Methyl 3-(4,6-dimethylpyrimidin-2-yl)-1-[2-(methylthio)ethyl]-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (273d).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), *rac*-methionine methyl ester hydrochloride (0.199 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in

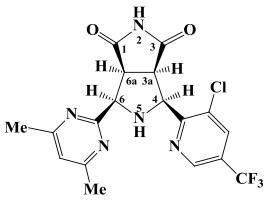
toluene (7 mL) at 100 °C for 2 h. The product **273d** (0.24 g, 64%) crystallized from MeOH as colourless needles, mp 213-215 °C; (Found: C, 54.10; H, 5.90; N, 14.50; S, 8.35; $C_{17}H_{22}N_4O_4S$ requires: C, 53.95; H, 5.86; N, 14.80; S, 8.47%); δ_H (300 MHz, $CDCl_3$); 8.29 (1H, s, 5-NH), 6.94 (1H, s, pyrimidinyl-H), 4.72 (1H, dd, *J* 12.9 and 8.3, 3-H), 4.13 (1H, d, *J* 12.9, 2-NH), 3.89 (3H, s, CO_2CH_3), 3.73 (1H, t, *J* 8.3, 3a-H), 3.35 (1H, d, *J* 8.3, 6a-H), 2.71-2.63 (1H, m, CH_2CH_2S), 2.50-2.36 (2H, m, CH_2CH_2S), 2.47 (6H, s, 2 x pyrimidinyl-CH_3), 2.10 (3H, s, SCH_3), 1.96-1.88 (1H, m, CH_2CH_2S); δ_C (75 MHz, $CDCl_3$); 175.4, 174.9, 171.1, 166.9, 164.1, 119.4, 72.6, 65.2, 58.7, 53, 52.7, 36.1, 28.8, 23.9, 15.6; υ_{max}/cm^{-1} (film); 3296, 3159, 2954, 2763, 1775, 1722, 1597, 1545, 1442, 1347, 1267, 1226; *m/z* (ESI^+) 379.1 (100%, MH^+); (Found MH^+, 379.1446. $C_{17}H_{23}N_4O_4{}^{32}S$ requires *MH*, 279.1435).

4-(4,6-Dimethylpyrimidin-2-yl)-6-(pyridin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (275a).



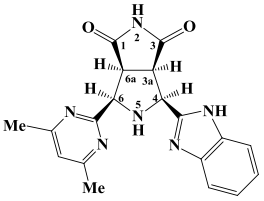
Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), 2-aminomethylpyridine (0.102 mL, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1.5 h. The solvent was removed under vacuum and the crude product was purified by flash chromatography with gradient elution from EtOAc to 1:1 v/v EtOAc/MeOH to afford the corresponding adduct **275a** which crystallized from $CHCl_3$ as colourless needles (0.27, 84%), mp 148-150 °C; (Found: C, 63.40; H, 5.25; N, 21.75; $C_{17}H_{17}N_5O_2$ requires C, 63.15; H, 5.30; N, 21.66%); δ_H (300 MHz, DMSO-d_6); 10.89 (1H, s, 2-NH), 8.53 (1H, d, *J* 4.6, pyridinyl-H), 7.77 (1H, dt, *J* 7.7 and 2.05, pyridinyl-H), 7.46 (1H, d, *J* 7.7, pyridinyl-H), 7.29 (1H, dd, *J* 7.7 and 4.6, pyridinyl-H), 7.16 (1H, s, pyrimidinyl-H), 4.62 (1H, dd, *J* 12.9 and 8.1, 6-H), 4.54 (1H, dd, *J* 12.9 and 8.1, 4-H), 4.03 (1H, t, *J* 12.9, 5-NH), 3.66 (1H, t, *J* 8.1, 3a-H), 3.56 (1H, t, *J* 8.1, 6a-H), 2.42 (6H, s, 2 x pyrimidinyl-CH_3); δ_C (75 MHz, $CDCl_3$); 175.8, 175.7, 166.6, 164.6, 155.6, 149.3, 136.5, 123.1, 122.9, 119.1, 66.9, 66.3, 53.8, 53.7, 24; υ_{max}/cm^{-1} (film); 3467, 3285, 3164, 3054, 2762, 1774, 1715, 1596, 1546, 1475, 1442, 1350; *m/z* (ESI^+) 324.1 (100%, MH^+); (Found MH^+, 324.1456. $C_{17}H_{18}N_5O_2$ requires *MH*, 324.1455.

4-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-6-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (275b).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), 2-aminomethyl-3-chloro-5-(trifluoromethyl)pyridine hydrochloride (0.246 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.26 mL, 2.00 mmol) in toluene (7 mL) at 100 °C for 10 min. The product **275b** (0.34 g, 80%) crystallized from MeOH as colourless needles, mp 262-264 °C; (Found: C, 50.55; H, 3.50; Cl, 8.35; N, 16.45; $C_{18}H_{15}ClF_3N_5O_2$ requires C, 50.77; H, 3.55;Cl, 8.33; N, 16.45%); δ_H (300 MHz, $CDCl_3$/MeOH-d_4); 8.77 (1H, d, *J* 1.3, pyridinyl-H), 8.00 (1H, d, *J* 1.5, pyridinyl-H), 6.99 (1H, s, pyrimidinyl-H), 5.07 (1H, d, *J* 8.0, 4-H), 4.77 (1H, d, *J* 8.0, 6-H), 3.93 (1H, t, *J* 8.0, 6a-H), 3.84 (1H, t, *J* 8.0, 3a-H), 2.82 (2H, br s, 2-NH and 5-NH), 2.51 (6H, s, 2 x pyrimidinyl-CH_3); δ_C (75 MHz, $CDCl_3$/MeOH-d_4); 176.3, 176.1, 166.9, 164.2, 157.0, 143.7 (q, *J* 3.8), 133.9 (q, *J* 3.5), 131.3, 126.9 (q, *J* 33.7), 120.4 (q, *J* 273.6), 119.4, 66.1, 62.6, 53.7, 51.7, 23.8; υ_{max}/cm^{-1} (film); 3407, 3054, 2758, 1776, 1714, 1595, 1544, 1410, 1344, 1321; *m/z* (ESI^+) 426.1 (100%, MH^+); (Found MH^+, 426.0947. $C_{18}H_{16}{}^{35}ClF_3N_5O_2$ requires *MH*, 426.0939.

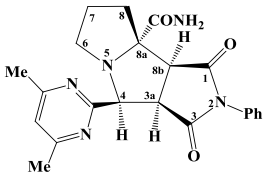
4-(1H-Benzimidazol-2-yl)-6-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (275c).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), 2-aminomethylbenzimidazole dihydrochloride (0.22 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.39 mL, 3.00 mmol) in toluene (7 mL) at 100 °C for 3 h. The product **275c** (0.21 g, 58%) was obtained as an amorphous off white powder from MeOH, mp 210-212 °C; δ_H (300 MHz, DMSO-d_6); 11.00 (1H, s, NH), 7.58 (1H, d, *J* 7.2 , benzimidazolyl-H), 7.51 (1H, d, *J* 7.5, benzimidazolyl-H), 7.20-7.13 (3H, m, 2 x benzimidazolyl-H and pyrimidinyl-H), 4.73 (1H, dd, *J* 12.3 and 8.0, 4-H), 4.60 (1H, dd, *J* 12.3 and 8.0, 6-H), 4.02 (1H, t, *J* 12.3, 5-NH), 3.71 (1H, t, *J* 8.0, 6a-H), 3.63 (1H, t, *J* 8.0, 3a-H), 2.44 (6H, s, 2 x pyrimidinyl-CH_3); δ_C (75 MHz, DMSO-d_6); 177.4, 177.0, 166.2, 165.4, 151.8, 121.7 (brs), 119.1, 66.3, 59.3, 53.8, 53.3, 23.9, (Two symmetrical benzimidazolyl carbon

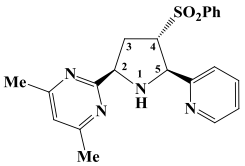
atoms could not be located due to peak overlaps); υ_{max}/cm^{-1} (film); 3478, 3297, 2950, 1868, 1761, 1713, 1599, 1542, 1485, 1437, 1360, 1276; *m/z* (ESI^+) 363.2 (53%, MH^+); (Found MH^+, 363.1563. $C_{19}H_{19}N_6O_2$ requires *MH*, 363.1564.

4-(4,6-Dimethylpyrimidin-2-yl)-1,3-dioxo-2-phenyloctahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxamide (278).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), (*S*)-prolinamide (0.114 g, 1.00 mmol), *N*-phenylmaleimide (0.173 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (5 mL) at 100 °C for 1 h. The solvent was removed under vacuum and the crude product was purified by gradient elution flash chromatography with EtOAc changing to 10:2 v/v EtOAc/EtOH to afford adduct **278**. Crystallization from CH_2Cl_2 gave colourless needles (0.36, 89%), mp 219-220 °C; (Found: C, 64.90; H, 5.70; N, 17.35; $C_{22}H_{23}N_5O_3$ requires C, 65.17; H, 5.72; N, 17.27%); δ_H (300 MHz, DMSO-d_6); 7.63 (1H, d, *J* 2.3, $CONH_2$), 7.47 (2H, t, *J* 7.5, phenyl-H), 7.38 (1H, t, *J* 7.5, phenyl-H), 7.32 (1H, d, *J* 2.3, $CONH_2$), 7.16 (1H, s, pyrimidinyl-H), 7.09 (2H, d, *J* 7.7, phenyl-H), 4.81 (1H, d, *J* 9.1, 4-H), 4.06 (1H, t, *J* 9.1, 3a-H), 3.97 (1H, d, *J* 9.1, 8b-H), 3.08-3.01 (1H, m, 6-H_A), 2.64-2.55 (2H, m, 6-$H_{B|}$ and 8-H_A), 2.34 (6H, s, 2 x pyrimidinyl-CH_3), 2.13-2.03 (1H, m, 8-H_B), 1.78-1.67 (2H, m, 7-CH_2); δ_C (75 MHz, DMSO-d_6); 176.9, 175.9, 174.9, 165.8, 165.5, 132.2, 128.7, 128, 126.2, 118.5, 80.1, 68.3, 51.9, 50, 48, 30.2, 25.4, 23.3; υ_{max}/cm^{-1} (film); 3425, 3060, 2964, 2873, 1775, 1712, 1679, 1594, 1543, 1499, 1440, 1379; *m/z* (ESI^+) 406.2 (100%, MH^+); (Found MH^+,406.1864. $C_{22}H_{24}N_5O_3$ requires *MH*, 406.1874.

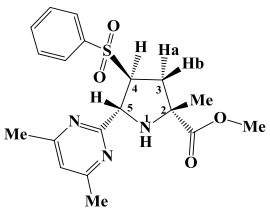
4,6-Dimethyl-2-[4-(phenylsulfonyl)-5-(pyridin-2-yl)pyrrolidin-2-yl]pyrimidine (280).



Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), 2-aminomethylpyridine (0.103 mL, 1.00 mmol), phenyl vinylsulfone (0.168 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 30 min. The solvent was removed under reduced pressure, the residue dissolved in $CHCl_3$, washed with water (3 x 20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography eluting with

AcOEt to give the product **280** which crystallized from $CHCl_3$ as colourless needles (0.25 g, 64%), mp 132-134 °C; δ_H (300 MHz, $CDCl_3$); 8.50 (1H, d, *J* 4.1, pyridinyl-H), 7.83 (2H, d, *J* 7.4, phenyl-H), 7.54 (2H, dt, *J* 2.1 and 7.7, pyridinyl-H), 7.43 (2H, t, *J* 7.6, phenyl-H), 7.22 (1H, d, *J* 7.7, pyridinyl-H), 7.15 (1H, dd, *J* 5.1 and 7.2, phenyl-H), 6.90 (1H, s, pyrimidinyl-H), 4.79 (1H, d, *J* 7.2, 5-H), 4.62 (1H, dd, *J* 7.4 and 9.2, 2-H), 4.25 (1H, ddd, *J* 4.6, 7.2 and 11.1, 4-H), 3.61 (1H, brs, NH), 2.93 (1H, ddd, *J* 4.6, 7.4 and 12.9, 3-Ha), 2.44 (6H, s, pyrimidinyl-CH_3), 2.34 (1H, ddd, *J* 9.2, 11.1 and 12.9, 3-Hb); δ_C (75 MHz, $CDCl_3$); 167.8, 166.8, 157.9, 149.4, 138.8, 136.6, 133.5, 129.1, 128.3, 123.9, 122.6, 118.6, 69.1, 65.4, 64.6, 36.2, 23.9; υ_{max}/cm^{-1} (film); 3276, 3061, 2925, 1593, 1544, 1474, 1446, 1384, 1348, 1304; *m/z* (ESI^+) 395.2 (100%, MH^+); (Found MH^+, 395.1553. $C_{21}H_{23}N_4O_2{}^{32}S$ requires *MH*, 395.1536.

Methyl 5-(4,6-dimethylpyrimidin-2-yl)-2-methyl-4-(phenylsulfonyl)-pyrrolidine-2-carboxylate (281a,b) and methyl 5-(4,6-dimethylpyrimidin-2-yl)-2-methyl-3-(phenylsulfonyl)pyrrolidine-2-carboxylate (281c).



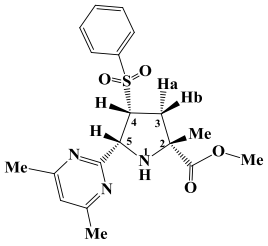
Prepared by general procedure M from 4,6-dimethyl-2-formylpyrimidine **269** (0.136 g, 1.00 mmol), (*R*)-alanine methyl ester hydrochloride (0.139 mL, 1.00 mmol), phenyl vinylsulfone (0.168 g, 1.00 mmol) and Et_3N (0.26 mL, 2.00 mmol) in toluene (7 mL) at 100 °C for 15 minutes. The solvent was removed under vacuum, the residue dissolved in $CHCl_3$ and washed with water (3 x 10 mL), dried ($MgSO_4$) and the solvent was removed under vacuum. The ^{1}H-NMR of the residue showed it to comprise a 2.5:1.3:1 mixture of **281a-c**. The residue was purified by column chromatography eluting with AcOEt which separated cycloadduct **281a** and then with EtOAc/MeOH (10:1) to separate first cycloadducts **281c** and then **281b**.

Compound **281a** crystallized from $CHCl_3$ as colourless needles (0.11 g, 28%), mp 121-123 °C; δ_H (300 MHz, $CDCl_3$); 7.86 (2H, d, *J* 7.7, phenyl-H), 7.51 (1H, t, *J* 7.4, phenyl-H), 7.42 (2H, t, *J* 7.4, phenyl-H), 6.73 (1H, s, pyrimidinyl-H), 4.72 (1H, d, *J* 6.4, 5-H), 4.61 (1H, dt, *J* 6.4 and 8.9, 4-H), 3.55 (3H, s, CO_2CH_3), 3.19 (1H, brs, NH), 2.86 (1H, dd, *J* 8.9 and 13.6, 3-Ha), 2.44 (1H, dd, *J* 8.9 and 13.6, 3-Hb), 2.31 (6H, s, pyrimidinyl-CH_3), 1.51 (3H, s, 2-CH_3); δ_C (75 MHz, $CDCl_3$); 175.6, 166.8, 166.6, 138.4, 133.4, 128.8 (2 x C), 118.4, 67.3, 66.0, 64.9, 52.3, 37.4, 25.6, 23.8;

υ_{max}/cm^{-1} (film); 3332, 2953, 1732, 1593, 1542, 1447, 1372, 1304, 1266; *m/z* (ESI^+) 390.2 (100%, MH^+); (Found MH^+, 390.1483. $C_{19}H_{24}N_3O_4{}^{32}S$ requires *MH*, 390.1482. NOE data ($CDCl_3$) for **281a**:

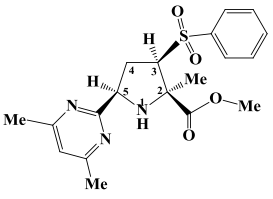
	% Enhancement					
Irradiated proton	5-H	4-H	3-Ha	3-Hb	Ph-H	Me
5-H		-	-	-	3.9	-
4-H	-		6.4	-	4.6	-
3-Ha	-	11.6		25.5	-	-
3-Hb	3.8	-	27.4		2.8	3.8

Compound **281b**: obtained as a yellow gum (0.06 g, 16%), δ_H (300 MHz, $CDCl_3$); 7.58 (2H, d, *J* 7.7, phenyl-H), 7.53 (1H, t, *J* 7.4, phenyl-H), 7.38 (2H, t, *J* 7.7, phenyl-H), 6.78 (1H, s, pyrimidinyl-H), 4.69 (1H, d, *J* 5.6, 5-H), 4.17 (1H, dt, *J* 5.6 and 7.8, 4-H), 3.86 (3H, s, CO_2CH_3), 3.38 (1H, dd, *J* 5.6 and 14.5, 3-Ha), 2.35 (6H, s, pyrimidinyl-CH_3), 2.25 (1H, dd, *J* 7.8 and 14.5, 3-Hb), 1.51 (3H, s, 2-CH_3); δ_C (75 MHz, $CDCl_3$); 176.3, 166.6, 165.0, 139.6, 133.5, 129.1, 128.5, 119.3, 67.5, 66.1, 65.5, 53.0, 38.3, 29.7, 24.1; υ_{max}/cm^{-1} (film); 3330, 2927, 1736, 1593, 1543, 1446, 1371, 1305. NOE data ($CDCl_3$) for **218b**:



	% Enhancement				
Irradiated proton	5-H	4-H	3-Ha	3-Hb	Ph-H
5-H		10.4	-	-	-
4-H	9.5		-	-	8.3
3-Ha	-	-		21.5	-
3-Hb	-	17.2	25.4		-

Compound **281c**: obtained as a yellow gum (0.04 g, 10%), δ_H (300 MHz, $CDCl_3$); 7.86 (2H, d, *J* 7.2, phenyl-H), 7.63 (1H, t, *J* 7.3, phenyl-H), 7.53 (2H, t, *J* 7.4, phenyl-H), 6.90 (1H, s, pyrimidinyl-H), 4.38 (1H, dd, *J* 7.2 and 9.7, 5-H), 3.82 (3H, s, CO_2CH_3), 3.70 (1H, dd, *J* 7.2 and 9.7, 3-H), 2.46-2.39 (2H, m, 4-CH_2), 2.45 (6H, s, pyrimidinyl-CH_3), 1.25 (3H, s, 2-CH_3); δ_C (75 MHz, $CDCl_3$); 173.4, 167.9, 167.2, 140.4, 134.2, 129.6, 128.6, 118.9, 74.7, 67.7, 61.8, 53.4, 37.4, 27.8, 24.3; υ_{max}/cm^{-1} (film); 3296, 2952, 1737, 1593, 1545, 1447, 1373, 1308.



NOE data ($CDCl_3$) for **281c**:

	% Enhancement				
Irradiated proton	5-H	4-CH_2	3-H	Ph-H	Me
5-H		7.8	4.1	-	-
3-H	-	5.6		5.9	4.1

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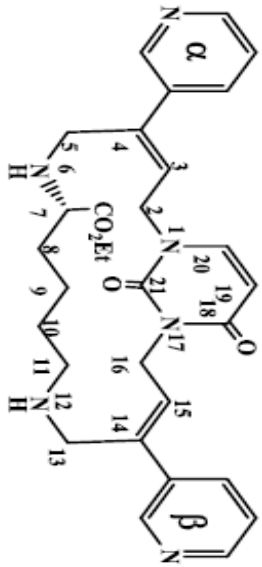
Appendices

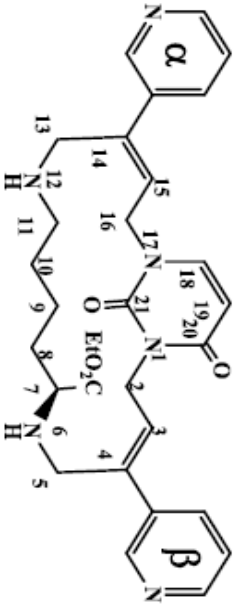
Appendix 1: NOE data ($CDCl_3$) for 242a.



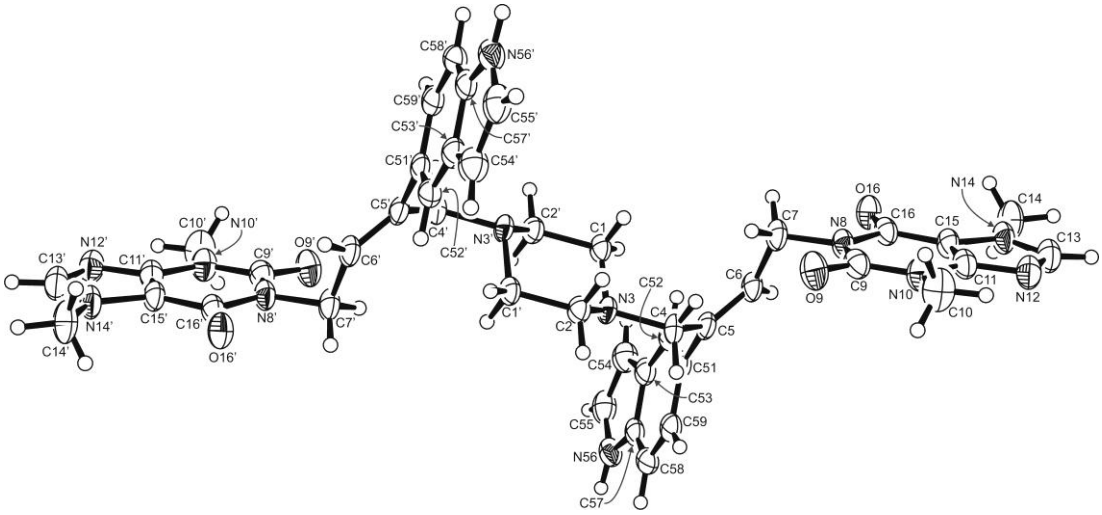
Irradiation Proton	Enhancement													
	15-H δ 5.86	**3-H** δ 5.72	**2-H$_A$** δ 4.94	**16H$_{A,B}$** δ 4.80	**2-H$_B$** δ 4.59	**13-H$_A$** δ 3.77	**5-H$_A$** δ 3.73	**13-H$_B$** δ 3.55	**5-H$_B$** δ 3.44	**11-H** δ 2.76	**Pγ-β** δ 8.75	**Pγ-α** δ 8.70	**Pγ-α** δ 7.96	**Pγ-β** δ 7.86	**20-H** δ 7.33
15-H δ 5.86				1.32							3.36			2.58	
3-H δ 5.72			1.02		1.20							7.02	3.34		2.56
2-H$_A$ δ 4.94		2.97			14.20		2.93								3.35
16H$_{A,B}$ δ 4.80	5.07					1.52		1.01							
2-H$_B$ δ 4.59		3.70	15.28						2.20						7.43
13-H$_A$ δ 3.77				2.78				5.19		2.28	1.46			1.52	
13-H$_B$ δ 3.55				2.87		5.93				2.38	2.38			2.88	
5-H$_B$ δ 3.44					2.52		12.87					2.05	2.86		

Appendix 2: NOE data ($CDCl_3$) for 242b.

Irradiation Proton	Enhancement												
	3-H δ 5.80	15-H δ 5.73	2-H_{AB} δ 4.92	16-H_A δ 4.83	16-H_B δ 4.44	13-H_A δ 3.76	5-H_A δ 3.72	13-H_B δ 3.57	5-H_B δ 3.50	11-H δ 2.77	Py-β δ 8.75	Py-α δ 8.71	Py-β δ 7.93	Py-α δ 7.88	18-H δ 7.34
3-H δ 5.80			2.19								5.34		3.96		
15-H δ 5.73				1.02	1.20							5.27		3.00	2.30
2-H δ 4.92	4.52						1.58		1.01						
16-H_A δ 4.83		2.98			9.65	1.52									2.19
16-H_B δ 4.44		3.27		12.04				1.99							4.63
13-H_A δ 3.76				2.99				8.90		2.10		1.49		1.70	
13-H_B δ 3.57					2.45	8.79				2.73		3.26		3.22	
5-H_B δ 3.50			4.00				12.11				4.05		3.68		



Appendix 3: X-ray crystallographic data for 245d.



Ortep view of 245d.

Table 1. Crystal data and structure refinement for EE77.

Archive code	10_11_06	
Identification code	EE77	
Formula	$C_{48}H_{50}Cl_{18}N_{12}O_4$	
Formula weight	1497.1	
Size	0.31 x 0.12 x 0.03 mm	
Crystal morphology	Colourless fragment	
Temperature	150(2) K	
Wavelength	0.71073 Å [Mo-K_α]	
Crystal system	Triclinic	
Space group	$P\ \bar{1}$	
Unit cell dimensions	a = 10.4541(10) Å	α = 107.624(5)°
	b = 12.9417(13) Å	β = 97.272(6)°
	c = 13.2135(14) Å	γ = 90.484(6)°
Volume	1688.0(3) Å^3	
Z	1	
Density (calculated)	1.473 Mg/m^3	
Absorption coefficient	0.779 mm^{-1}	
F(000)	760	
Data collection range	$1.93 \le \theta \le 26°$	
Index ranges	$-12 \le h \le 12$, $-15 \le k \le 15$, $-16 \le l \le 16$	
Reflections collected	56054	

Independent reflections	6530 [R(int) = 0.0634]
Observed reflections	4501 [$I > 2\sigma(I)$]
Absorption correction	multi-scan
Max. and min. transmission	0.977 and 0.5868
Refinement method	Full
Data / restraints / parameters	6530 / 36 / 453
Goodness of fit	1.048
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0597, wR_2 = 0.1569
R indices (all data)	R_1 = 0.0902, wR_2 = 0.1844
Largest diff. peak and hole	1.187 and -0.386e.Å^{-3}

Table 2. Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^4) with standard uncertainties (s.u.s) in parentheses. U_{eq} is defined as $^1/_3$ of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
C(1)	9443(3)	-365(3)	3897(3)	31.3(7)
Cl(1a)^{pd}	-2396(3)	-960(2)	105(3)	80.4(7)
Cl(1b)^{pd}	-2583(6)	1083(5)	1808(7)	80.0(13)
Cl(1c)^{pd}	-88(2)	164.6(19)	1451.1(19)	49.6(5)
Cl(1d)^{pd}	-3129(13)	-464(10)	247(6)	209(7)
Cl(1e)^{pd}	-452(12)	-225(9)	1265(9)	185(7)
Cl(1f)^{pd}	-2280(14)	1352(12)	2047(15)	88(4)
C(1s)^{d}	-1679(5)	361(4)	844(4)	63.4(12)
C(2)	10115(3)	-819(3)	5514(3)	32.2(7)
Cl(2a)^{pd}	5366(8)	2741(7)	165(6)	107(3)
Cl(2b)^{pd}	6043(7)	4658(6)	2031(7)	108(2)
Cl(2c)^{pd}	4571(4)	2860(3)	2206(3)	59.7(8)
Cl(2d)^{pd}	4674(13)	2965(10)	2262(9)	173(5)
Cl(2e)^{pd}	5336(7)	2739(5)	126(4)	48.8(16)
Cl(2f)^{pd}	6012(7)	4736(5)	1874(8)	90(3)
C(2s)^{d}	4863(4)	3628(4)	1325(4)	61.9(12)
N(3)	9023(3)	-894(2)	4654(2)	29.5(6)
Cl(3a)^{pd}	7419(10)	3265(6)	4640(7)	177(4)
Cl(3b)^{pd}	8570(6)	5139(5)	4307(5)	95.6(19)
Cl(3c)^{pd}	6774(5)	5406(7)	5799(4)	169(3)
Cl(3d)^{pd}	7974(4)	3203(3)	4223(4)	91.6(13)
Cl(3e)^{pd}	8141(7)	5525(4)	4726(5)	130(2)
Cl(3f)^{pd}	6323(3)	4470(4)	5617(3)	102.4(11)
C(3s)^{d}	7913(5)	4509(4)	5215(4)	65.4(13)
C(4)	8625(3)	-2069(2)	4111(3)	33.3(7)

C(5)	7566(3)	-2239(2)	3153(3)	32.3(7)
C(6)	7750(3)	-2761(3)	2126(3)	34.8(8)
C(7)	8995(3)	-3148(3)	1708(3)	37.4(8)
N(8)	8961(3)	-4355(2)	1216(2)	34.5(6)
O(9)	10246(3)	-4485(2)	2727(2)	50.3(7)
C(9)	9628(3)	-4954(3)	1841(3)	38.6(8)
N(10)	9579(3)	-6074(2)	1406(2)	41.5(7)
C(10)	10362(5)	-6715(3)	1985(4)	58.5(11)
C(11)	8899(3)	-6554(3)	391(3)	37.7(8)
N(12)	8761(3)	-7651(2)	-140(3)	44.1(8)
C(13)	8049(4)	-7690(3)	-1076(3)	44.9(9)
N(14)	7744(3)	-6706(2)	-1174(2)	40.8(7)
C(14)	6942(4)	-6487(3)	-2079(3)	55.4(11)
C(15)	8291(3)	-5949(3)	-205(3)	34.8(8)
O(16)	7796(2)	-4177.4(19)	-324.8(19)	42.7(6)
C(16)	8290(3)	-4785(3)	165(3)	34.6(8)
C(51)	6303(3)	-1732(2)	3364(3)	31.9(7)
C(52)	5800(3)	-1088(3)	2751(3)	34.5(8)
C(53)	4631(3)	-558(3)	2957(3)	36.4(8)
C(54)	3912(4)	202(3)	2523(3)	44.2(9)
C(55)	2892(4)	473(3)	3104(3)	45.9(9)
N(56)	2903(3)	-78(2)	3841(2)	41.8(7)
C(57)	3987(3)	-707(3)	3792(3)	35.7(8)
C(58)	4472(3)	-1365(3)	4408(3)	38.4(8)
C(59)	5626(3)	-1868(3)	4198(3)	35.8(8)

Key to superscripts on atoms with refinement constraints/restraints:
d - distance or angle restraint on site
p - partial occupancy constraint

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	28.6(17)	30.1(16)	27.6(15)	0.4(13)	-3.4(13)	-3.9(13)
Cl(1a)	92.9(16)	65.6(12)	70.5(15)	12.1(10)	-9.3(12)	-30.2(11)
Cl(1b)	67(3)	66(2)	118(4)	32.5(18)	40(3)	18.9(19)
Cl(1c)	56.8(9)	51.8(10)	36.6(8)	10.2(7)	1.2(7)	12.4(8)
Cl(1d)	333(18)	216(12)	57(4)	42(6)	-33(8)	-195(12)
Cl(1e)	315(16)	170(10)	154(9)	114(8)	167(10)	180(11)
Cl(1f)	75(7)	94(9)	108(8)	43(6)	26(6)	21(5)
C(1s)	77(3)	59(3)	54(3)	24(2)	-7(2)	-13(2)
C(2)	30.0(17)	30.7(16)	30.5(16)	3.5(13)	-0.7(14)	-3.8(14)
Cl(2a)	76(5)	123(6)	101(5)	2(4)	12(4)	-5(4)
Cl(2b)	70(4)	123(5)	101(3)	3(3)	-24(2)	-29(3)
Cl(2c)	64.4(17)	56.2(15)	58.8(19)	16.5(14)	12.2(14)	6.8(13)

Cl(2d)	210(11)	175(10)	128(8)	41(7)	14(7)	27(8)
Cl(2e)	36(3)	59(4)	41(3)	3(3)	-1(3)	-13(3)
Cl(2f)	43(4)	48(2)	146(7)	-27(3)	31(4)	-13(2)
C(2s)	42(2)	59(3)	73(3)	9(2)	-7(2)	-4(2)
N(3)	29.0(14)	24.7(13)	27.5(13)	0.4(10)	-3.8(11)	-6.8(11)
Cl(3a)	252(11)	99(5)	174(8)	73(5)	-68(6)	-93(6)
Cl(3b)	87(3)	117(5)	95(4)	62(3)	-14(3)	-28(3)
Cl(3c)	98(4)	291(9)	92(3)	16(5)	16(3)	99(5)
Cl(3d)	94(2)	52.5(17)	108(3)	2.3(16)	-7.5(19)	17.0(17)
Cl(3e)	183(6)	76(3)	136(5)	69(3)	-50(4)	-43(3)
Cl(3f)	74(2)	143(3)	83(2)	27(2)	5.2(15)	19(2)
C(3s)	70(3)	71(3)	50(2)	18(2)	-11(2)	10(2)
C(4)	37.3(19)	22.8(15)	30.9(16)	-2.2(13)	-1.5(14)	-3.3(13)
C(5)	31.5(18)	23.9(15)	34.0(17)	0.2(13)	-1.5(14)	-7.3(13)
C(6)	29.5(18)	29.9(16)	34.3(17)	-2.3(14)	-4.7(14)	-5.5(14)
C(7)	32.7(19)	30.1(17)	37.3(18)	-3.7(14)	-4.2(15)	-5.0(14)
N(8)	30.6(15)	31.4(14)	31.3(14)	-2.5(11)	-2.8(12)	-2.2(12)
O(9)	52.9(17)	49.0(15)	35.3(13)	-0.8(12)	-10.3(12)	-0.4(13)
C(9)	30.9(18)	41.6(19)	35.3(18)	1.4(15)	1.9(15)	-0.3(15)
N(10)	39.7(17)	37.2(16)	40.2(16)	4.6(13)	-3.9(14)	0.9(13)
C(10)	65(3)	47(2)	58(3)	14(2)	-11(2)	8(2)
C(11)	31.8(19)	34.1(18)	38.5(18)	-1.2(15)	3.5(15)	-0.3(14)
N(12)	41.5(18)	31.8(15)	50.1(18)	0.5(13)	3.4(15)	0.8(13)
C(13)	41(2)	34.6(19)	48(2)	-3.2(16)	2.2(17)	-2.1(16)
N(14)	38.3(17)	34.0(16)	36.6(16)	-5.9(12)	-2.6(13)	-4.1(13)
C(14)	58(3)	46(2)	44(2)	-4.3(17)	-17.2(19)	-6.0(19)
C(15)	27.4(17)	32.3(17)	34.2(17)	-2.5(14)	-2.4(14)	-3.9(14)
O(16)	45.0(15)	36.0(13)	38.0(13)	3.2(11)	-7.8(11)	-0.4(11)
C(16)	27.4(17)	35.3(18)	32.2(17)	-1.5(14)	0.6(14)	-1.4(14)
C(51)	27.1(17)	26.2(16)	31.5(16)	-4.9(13)	-1.0(14)	-6.7(13)
C(52)	31.4(18)	31.9(17)	32.3(17)	-2.0(14)	4.8(14)	-4.3(14)
C(53)	32.2(19)	31.7(17)	36.2(18)	-1.4(14)	0.9(15)	-5.5(14)
C(54)	38(2)	41(2)	46(2)	5.3(17)	0.4(17)	0.8(16)
C(55)	36(2)	39(2)	51(2)	0.6(17)	-5.1(18)	1.8(16)
N(56)	28.3(16)	43.3(17)	41.0(17)	-5.9(14)	4.2(13)	-3.8(13)
C(57)	27.9(18)	31.6(17)	35.2(17)	-7.0(14)	1.5(14)	-6.1(14)
C(58)	32.9(19)	41.6(19)	29.9(17)	-4.2(15)	2.8(15)	-11.0(15)
C(59)	34.9(19)	32.9(17)	30.3(16)	-0.7(14)	-3.4(14)	-8.0(15)

Table 4. Hydrogen atom co-ordinates (x 10^3) and isotropic displacement parameters (Å^2 x 10^2) with s.u.s in parentheses.

	x	y	z	U_{eq}
H(1a)	8719.	-395.	3327.	38.
H(1b)	10162.	-757.	3556.	38.
H(1s)	-1587.	781.	332.	76.
H(2a)	10845.	-1217.	5196.	39.
H(2b)	9844.	-1166.	6031.	39.

H(2s)	4049.	3963.	1125.	74.
H(3s)	8628.	4517.	5797.	78.
H(4a)	8309.	-2381.	4637.	40.
H(4b)	9388.	-2466.	3862.	40.
H(6)	7001.	-2900.	1607.	42.
H(7a)	9162.	-2797.	1165.	45.
H(7b)	9715.	-2924.	2305.	45.
H(10a)	10242.	-7487.	1575.	88.
H(10b)	10087.	-6599.	2691.	88.
H(10c)	11275.	-6484.	2072.	88.
H(13)	7784.	-8352.	-1622.	54.
H(14a)	6786.	-7157.	-2681.	83.
H(14b)	7390.	-5939.	-2298.	83.
H(14c)	6115.	-6218.	-1858.	83.
H(52)	6240.	-1001.	2194.	41.
H(54)	4104.	461.	1956.	53.
H(55)	2266.	974.	3007.	55.
H(56)	2321.	-41.	4276.	50.
H(58)	4024.	-1467.	4956.	46.
H(59)	5971.	-2309.	4615.	43.

Table 5. Interatomic distances (Å) with s.u.s in parentheses.

C(1)-N(3)	1.478(4)	C(1)-C(2)[(a)]	1.531(4)
Cl(1a)-C(1s)	1.795(5)	Cl(1b)-C(1s)	1.729(8)
Cl(1c)-C(1s)	1.807(5)	Cl(1d)-C(1s)	1.795(9)
Cl(1e)-C(1s)	1.620(10)	Cl(1f)-C(1s)	1.896(13)
C(2)-N(3)	1.485(4)	C(2)-C(1)[(a)]	1.531(4)
Cl(2a)-C(2s)	1.759(9)	Cl(2b)-C(2s)	1.759(7)
Cl(2c)-C(2s)	1.796(6)	Cl(2d)-C(2s)	1.736(10)
Cl(2e)-C(2s)	1.785(8)	Cl(2f)-C(2s)	1.774(7)
N(3)-C(4)	1.501(4)	Cl(3a)-C(3s)	1.607(8)
Cl(3b)-C(3s)	1.836(7)	Cl(3c)-C(3s)	1.753(7)
Cl(3d)-C(3s)	1.805(6)	Cl(3e)-C(3s)	1.660(6)
Cl(3f)-C(3s)	1.812(6)	C(4)-C(5)	1.532(4)
C(5)-C(6)	1.359(5)	C(5)-C(51)	1.499(5)
C(6)-C(7)	1.508(5)	C(7)-N(8)	1.497(4)
N(8)-C(16)	1.417(4)	N(8)-C(9)	1.422(5)
O(9)-C(9)	1.236(4)	C(9)-N(10)	1.386(5)
N(10)-C(11)	1.391(4)	N(10)-C(10)	1.476(5)
C(11)-C(15)	1.376(5)	C(11)-N(12)	1.377(4)
N(12)-C(13)	1.347(5)	C(13)-N(14)	1.355(5)
N(14)-C(15)	1.405(4)	N(14)-C(14)	1.473(5)
C(15)-C(16)	1.436(5)	O(16)-C(16)	1.238(4)
C(51)-C(52)	1.391(5)	C(51)-C(59)	1.435(5)
C(52)-C(53)	1.422(5)	C(53)-C(57)	1.423(5)
C(53)-C(54)	1.451(5)	C(54)-C(55)	1.378(6)
C(55)-N(56)	1.369(5)	N(56)-C(57)	1.398(5)

C(57)-C(58)	1.403(5)	C(58)-C(59)	1.394(5)

Key giving operations for symmetry related atoms:
(a) 2-x, -y, 1-z

Table 6. Angles between interatomic vectors (°) with s.u.s in parentheses.

N(3)-C(1)-C(2)[(a)]	110.3(3)	Cl(1e)-C(1s)-Cl(1b)	116.1(6)
Cl(1e)-C(1s)-Cl(1d)	117.4(7)	Cl(1b)-C(1s)-Cl(1d)	86.0(8)
Cl(1e)-C(1s)-Cl(1a)	88.5(9)	Cl(1b)-C(1s)-Cl(1a)	112.8(3)
Cl(1b)-C(1s)-Cl(1c)	110.7(4)	Cl(1d)-C(1s)-Cl(1c)	136.4(9)
Cl(1a)-C(1s)-Cl(1c)	107.0(3)	Cl(1e)-C(1s)-Cl(1f)	108.6(8)
Cl(1d)-C(1s)-Cl(1f)	100.1(7)	Cl(1a)-C(1s)-Cl(1f)	126.0(6)
Cl(1c)-C(1s)-Cl(1f)	99.7(6)	N(3)-C(2)-C(1)[(a)]	111.0(3)
Cl(2d)-C(2s)-Cl(2a)	111.2(7)	Cl(2d)-C(2s)-Cl(2b)	102.3(7)
Cl(2a)-C(2s)-Cl(2b)	112.5(5)	Cl(2d)-C(2s)-Cl(2f)	110.5(6)
Cl(2a)-C(2s)-Cl(2f)	109.1(5)	Cl(2d)-C(2s)-Cl(2e)	112.1(6)
Cl(2b)-C(2s)-Cl(2e)	113.3(4)	Cl(2f)-C(2s)-Cl(2e)	109.6(4)
Cl(2a)-C(2s)-Cl(2c)	108.4(4)	Cl(2b)-C(2s)-Cl(2c)	107.2(4)
Cl(2f)-C(2s)-Cl(2c)	115.5(6)	Cl(2e)-C(2s)-Cl(2c)	109.2(3)
C(1)-N(3)-C(2)	108.6(2)	C(1)-N(3)-C(4)	111.8(2)
C(2)-N(3)-C(4)	108.7(2)	Cl(3a)-C(3s)-Cl(3e)	131.6(5)
Cl(3a)-C(3s)-Cl(3c)	116.9(5)	Cl(3e)-C(3s)-Cl(3c)	79.0(4)
Cl(3e)-C(3s)-Cl(3d)	112.0(4)	Cl(3c)-C(3s)-Cl(3d)	139.7(5)
Cl(3a)-C(3s)-Cl(3f)	77.4(6)	Cl(3e)-C(3s)-Cl(3f)	112.7(4)
Cl(3d)-C(3s)-Cl(3f)	103.6(3)	Cl(3a)-C(3s)-Cl(3b)	113.0(5)
Cl(3c)-C(3s)-Cl(3b)	104.6(5)	Cl(3d)-C(3s)-Cl(3b)	88.6(3)
Cl(3f)-C(3s)-Cl(3b)	132.7(4)	N(3)-C(4)-C(5)	112.8(3)
C(6)-C(5)-C(51)	119.1(3)	C(6)-C(5)-C(4)	123.2(3)
C(51)-C(5)-C(4)	117.6(3)	C(5)-C(6)-C(7)	128.1(3)
N(8)-C(7)-C(6)	112.3(3)	C(16)-N(8)-C(9)	126.4(3)
C(16)-N(8)-C(7)	116.8(3)	C(9)-N(8)-C(7)	116.7(3)
O(9)-C(9)-N(10)	121.9(3)	O(9)-C(9)-N(8)	120.8(3)
N(10)-C(9)-N(8)	117.3(3)	C(9)-N(10)-C(11)	119.3(3)
C(9)-N(10)-C(10)	118.8(3)	C(11)-N(10)-C(10)	121.6(3)
C(15)-C(11)-N(12)	112.3(3)	C(15)-C(11)-N(10)	121.9(3)
N(12)-C(11)-N(10)	125.8(3)	C(13)-N(12)-C(11)	102.7(3)
N(12)-C(13)-N(14)	114.4(3)	C(13)-N(14)-C(15)	105.3(3)
C(13)-N(14)-C(14)	127.1(3)	C(15)-N(14)-C(14)	127.5(3)
C(11)-C(15)-N(14)	105.4(3)	C(11)-C(15)-C(16)	123.4(3)
N(14)-C(15)-C(16)	131.3(3)	O(16)-C(16)-N(8)	120.8(3)
O(16)-C(16)-C(15)	127.6(3)	N(8)-C(16)-C(15)	111.6(3)
C(52)-C(51)-C(59)	119.5(3)	C(52)-C(51)-C(5)	118.7(3)
C(59)-C(51)-C(5)	121.8(3)	C(51)-C(52)-C(53)	120.3(3)
C(52)-C(53)-C(57)	118.7(3)	C(52)-C(53)-C(54)	133.8(3)
C(57)-C(53)-C(54)	107.4(3)	C(55)-C(54)-C(53)	105.8(3)
N(56)-C(55)-C(54)	110.9(3)	C(55)-N(56)-C(57)	109.0(3)
N(56)-C(57)-C(58)	131.5(3)	N(56)-C(57)-C(53)	106.8(3)
C(58)-C(57)-C(53)	121.6(3)	C(59)-C(58)-C(57)	118.5(3)

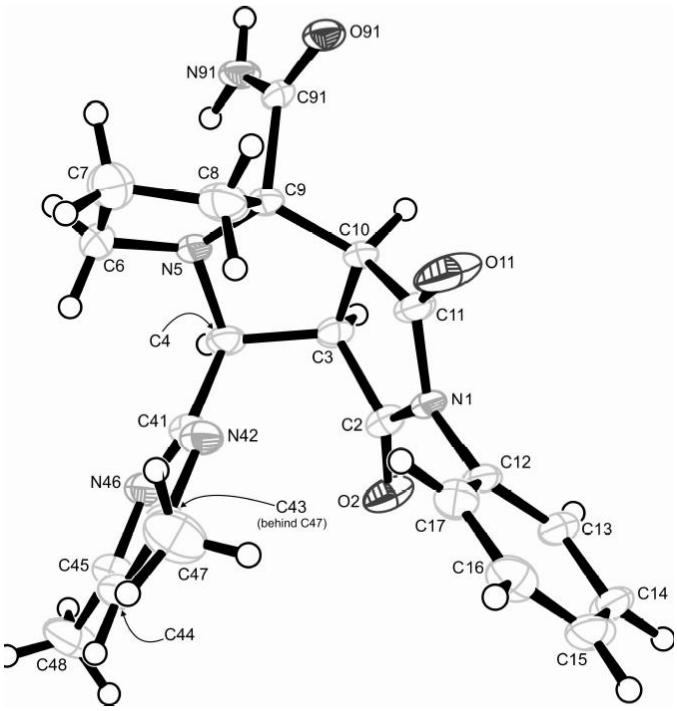
C(58)-C(59)-C(51)	121.3(3)

Key giving operations for symmetry related atoms:
(a) 2-x, -y, 1-z

Table 7. Torsion angles (°) with s.u.s in parentheses.

C(2)-C(1)-N(3)-C(2)	-58.1(4)	C(2)-C(1)-N(3)-C(4)	-178.1(3)
C(1)-C(2)-N(3)-C(1)	58.6(4)	C(1)-C(2)-N(3)-C(4)	-179.6(3)
C(1)-N(3)-C(4)-C(5)	-55.8(4)	C(2)-N(3)-C(4)-C(5)	-175.7(3)
N(3)-C(4)-C(5)-C(6)	114.9(3)	N(3)-C(4)-C(5)-C(51)	-60.7(4)
C(51)-C(5)-C(6)-C(7)	168.0(3)	C(4)-C(5)-C(6)-C(7)	-7.6(5)
C(5)-C(6)-C(7)-N(8)	117.8(4)	C(6)-C(7)-N(8)-C(16)	78.4(4)
C(6)-C(7)-N(8)-C(9)	-102.8(3)	C(16)-N(8)-C(9)-O(9)	175.7(3)
C(7)-N(8)-C(9)-O(9)	-2.9(5)	C(16)-N(8)-C(9)-N(10)	-2.9(5)
C(7)-N(8)-C(9)-N(10)	178.5(3)	O(9)-C(9)-N(10)-C(11)	-178.1(3)
N(8)-C(9)-N(10)-C(11)	0.5(5)	O(9)-C(9)-N(10)-C(10)	-4.4(6)
N(8)-C(9)-N(10)-C(10)	174.2(3)	C(9)-N(10)-C(11)-C(15)	1.2(5)
C(10)-N(10)-C(11)-C(15)	-172.3(4)	C(9)-N(10)-C(11)-N(12)	-179.7(3)
C(10)-N(10)-C(11)-N(12)	6.8(6)	C(15)-C(11)-N(12)-C(13)	0.0(4)
N(10)-C(11)-N(12)-C(13)	-179.2(4)	C(11)-N(12)-C(13)-N(14)	0.6(4)
N(12)-C(13)-N(14)-C(15)	-0.9(4)	N(12)-C(13)-N(14)-C(14)	-177.5(4)
N(12)-C(11)-C(15)-N(14)	-0.5(4)	N(10)-C(11)-C(15)-N(14)	178.8(3)
N(12)-C(11)-C(15)-C(16)	-179.9(3)	N(10)-C(11)-C(15)-C(16)	-0.7(6)
C(13)-N(14)-C(15)-C(11)	0.8(4)	C(14)-N(14)-C(15)-C(11)	177.4(4)
C(13)-N(14)-C(15)-C(16)	-179.8(4)	C(14)-N(14)-C(15)-C(16)	-3.2(6)
C(9)-N(8)-C(16)-O(16)	-176.3(3)	C(7)-N(8)-C(16)-O(16)	2.3(5)
C(9)-N(8)-C(16)-C(15)	3.2(5)	C(7)-N(8)-C(16)-C(15)	-178.2(3)
C(11)-C(15)-C(16)-O(16)	178.1(4)	N(14)-C(15)-C(16)-O(16)	-1.2(6)
C(11)-C(15)-C(16)-N(8)	-1.4(5)	N(14)-C(15)-C(16)-N(8)	179.3(3)
C(6)-C(5)-C(51)-C(52)	-47.7(4)	C(4)-C(5)-C(51)-C(52)	128.2(3)
C(6)-C(5)-C(51)-C(59)	134.3(3)	C(4)-C(5)-C(51)-C(59)	-49.9(4)
C(59)-C(51)-C(52)-C(53)	0.6(4)	C(5)-C(51)-C(52)-C(53)	-177.5(3)
C(51)-C(52)-C(53)-C(57)	-0.4(4)	C(51)-C(52)-C(53)-C(54)	175.5(3)
C(52)-C(53)-C(54)-C(55)	-176.1(3)	C(57)-C(53)-C(54)-C(55)	0.1(4)
C(53)-C(54)-C(55)-N(56)	-1.6(4)	C(54)-C(55)-N(56)-C(57)	2.4(4)
C(55)-N(56)-C(57)-C(58)	176.1(3)	C(55)-N(56)-C(57)-C(53)	-2.2(3)
C(52)-C(53)-C(57)-N(56)	178.2(3)	C(54)-C(53)-C(57)-N(56)	1.3(3)
C(52)-C(53)-C(57)-C(58)	-0.4(5)	C(54)-C(53)-C(57)-C(58)	-177.3(3)
N(56)-C(57)-C(58)-C(59)	-177.2(3)	C(53)-C(57)-C(58)-C(59)	1.0(5)
C(57)-C(58)-C(59)-C(51)	-0.8(4)	C(52)-C(51)-C(59)-C(58)	0.0(4)
C(5)-C(51)-C(59)-C(58)	178.0(3)		

Appendix 4: X-ray crystallographic data for 278.



Ortep view of 278.

Table 1. Crystal data and structure refinement of ELG28.

Archive code	10_07_06	
Identification code	ELG28	
Formula	$C_{22}H_{23}N_5O_3$	
Formula weight	405.45	
Size	0.36 x 0.20 x 0.05 mm	
Crystal morphology	Colourless plate	
Temperature	150(2) K	
Wavelength	0.71073 Å [Mo-K_α]	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	*a* = 25.8995(12) Å	α = 90°
	b = 7.0188(3) Å	β = 111.498(2)°
	c = 23.8259(11) Å	γ = 90°
Volume	4029.8(3) $Å^3$	
Z	8	
Density (calculated)	1.337 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	

F(000)	1712
Data collection range	$1.84 \leq \theta \leq 28.37°$
Index ranges	$-34 \leq h \leq 34,\ -8 \leq k \leq 9,\ -31 \leq l \leq 31$
Reflections collected	50253
Independent reflections	5038 [*R*(int) = 0.0581]
Observed reflections	3700 [$I > 2\sigma(I)$]
Absorption correction	none
Refinement method	Full
Data / restraints / parameters	5038 / 0 / 273
Goodness of fit	1.088
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0484$, $wR_2 = 0.1059$
R indices (all data)	$R_1 = 0.0773$, $wR_2 = 0.1279$
Largest diff. peak and hole	0.312 and -0.252e.Å^{-3}

Table 2. Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^4) with standard uncertainties (s.u.s) in parentheses. U_{eq} is defined as $^1/_3$ of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O(91)	2381.4(5)	8864.8(18)	573.2(5)	296(3)
N(1)	1772.4(5)	7500(2)	2398.4(5)	237(3)
N(42)	593.0(6)	8407(2)	1442.0(6)	313(3)
C(9)	1600.5(6)	8009(3)	845.3(7)	258(3)
O(2)	1281.8(6)	4787.6(19)	2422.8(5)	388(3)
N(91)	1858.0(6)	6375(2)	78.5(6)	305(3)
C(91)	1984.5(6)	7781(3)	480.4(6)	248(3)
C(41)	507.2(7)	6640(3)	1224.5(7)	278(4)
C(13)	2017.8(7)	7228(3)	3485.3(7)	275(3)
N(5)	1090.3(5)	6870(2)	569.7(6)	299(3)
N(46)	72.5(6)	5519(2)	1165.5(6)	331(3)
C(12)	1807.7(6)	8318(2)	2964.4(6)	242(3)
C(11)	1997.9(7)	8387(3)	2016.1(7)	336(4)
C(4)	950.3(7)	5756(3)	1020.6(7)	278(4)
C(2)	1502.8(7)	5803(2)	2169.4(7)	266(3)
C(17)	1635.0(7)	10180(3)	2977.0(8)	308(4)
C(3)	1523.8(7)	5502(3)	1544.6(7)	271(3)
C(43)	196.8(7)	9157(3)	1620.8(8)	337(4)
O(11)	2244.3(7)	9876(3)	2124.7(6)	637(5)
C(10)	1898.6(6)	7099(3)	1474.5(7)	283(4)
C(44)	-260.6(7)	8085(3)	1592.2(8)	372(4)

C(14)	2041.1(8)	8046(3)	4028.2(7)	351(4)
C(8)	1410.4(8)	10087(3)	793.7(9)	381(4)
C(16)	1664.3(7)	10962(3)	3524.4(9)	371(4)
C(15)	1861.3(8)	9886(3)	4045.7(8)	378(4)
C(45)	-312.8(7)	6257(3)	1364.4(8)	359(4)
C(6)	658.4(7)	8115(3)	145.1(8)	428(5)
C(48)	-792.1(8)	5000(4)	1328.6(11)	516(6)
C(7)	931.4(9)	10074(4)	178.6(10)	510(6)
C(47)	275.6(9)	11167(3)	1840.9(12)	527(6)

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(91)	316(6)	395(7)	239(5)	-30(5)	173(5)	-44(5)
N(1)	277(6)	300(8)	172(6)	-3(5)	126(5)	-7(5)
N(42)	312(7)	382(9)	298(7)	-18(6)	173(6)	-1(6)
C(9)	243(7)	379(10)	198(7)	-22(6)	135(6)	1(7)
O(2)	609(8)	338(8)	289(6)	-22(5)	251(6)	-134(6)
N(91)	315(7)	419(9)	255(7)	-66(6)	189(6)	-50(6)
C(91)	244(7)	368(10)	158(6)	29(6)	105(6)	36(7)
C(41)	268(8)	385(10)	218(7)	-11(7)	132(6)	-21(7)
C(13)	331(8)	307(9)	224(7)	-14(6)	145(6)	-15(7)
N(5)	238(6)	500(10)	189(6)	-14(6)	114(5)	-21(6)
N(46)	304(7)	421(9)	315(7)	-43(6)	169(6)	-39(6)
C(12)	260(7)	313(9)	199(7)	-34(6)	138(6)	-30(6)
C(11)	337(9)	510(12)	201(7)	-29(7)	146(7)	-128(8)
C(4)	289(8)	363(10)	230(7)	-71(7)	153(6)	-42(7)
C(2)	347(8)	273(9)	213(7)	1(6)	146(6)	19(7)
C(17)	307(8)	319(10)	317(8)	-11(7)	139(7)	15(7)
C(3)	309(8)	328(9)	217(7)	-33(6)	144(6)	23(7)
C(43)	344(9)	401(11)	304(8)	14(7)	165(7)	65(8)
O(11)	873(12)	822(13)	325(7)	-206(7)	349(8)	-595(10)
C(10)	234(7)	469(11)	183(7)	-18(7)	120(6)	-8(7)
C(44)	318(9)	498(12)	370(9)	11(8)	207(8)	73(8)
C(14)	410(10)	478(12)	200(7)	-41(7)	155(7)	-79(8)
C(8)	390(10)	406(12)	439(10)	2(8)	260(8)	57(8)
C(16)	358(9)	340(11)	456(10)	-132(8)	195(8)	-8(8)
C(15)	392(9)	501(12)	312(9)	-189(8)	215(8)	-101(8)
C(45)	288(8)	492(12)	344(9)	12(8)	169(7)	1(8)
C(6)	292(9)	776(16)	220(8)	60(9)	100(7)	88(9)
C(48)	354(10)	613(15)	682(14)	-114(11)	308(10)	-98(10)
C(7)	423(11)	627(16)	517(12)	193(11)	214(10)	186(10)
C(47)	509(12)	421(13)	740(15)	-91(11)	334(12)	40(10)

Table 4. Hydrogen atom co-ordinates (x 10^3) and isotropic displacement parameters ($Å^2$ x 10^2) with s.u.s in parentheses.

	x	y	z	U_{eq}
H(91a)	2063.	6177.	-140.	37.
H(91b)	1569.	5643.	31.	37.
H(13)	2142.	5962.	3473.	33.
H(4)	817.	4472.	846.	33.
H(17)	1499.	10913.	2617.	37.
H(3)	1686.	4228.	1519.	33.
H(10)	2260.	6543.	1493.	34.
H(44)	-534.	8599.	1727.	45.
H(14)	2183.	7325.	4390.	42.
H(8a)	1710.	10969.	796.	46.
H(8b)	1281.	10440.	1122.	46.
H(16)	1549.	12238.	3540.	45.
H(15)	1873.	10416.	4417.	45.
H(6a)	332.	8210.	266.	51.
H(6b)	536.	7601.	-270.	51.
H(48a)	-772.	3813.	1121.	77.
H(48b)	-1141.	5656.	1105.	77.
H(48c)	-776.	4709.	1737.	77.
H(7a)	664.	11109.	153.	61.
H(7b)	1072.	10231.	-153.	61.
H(47a)	559.	11210.	2249.	79.
H(47b)	-76.	11663.	1848.	79.
H(47c)	396.	11949.	1570.	79.

Table 5. Interatomic distances (Å) with s.u.s in parentheses.

O(91)-C(91)	1.232(2)	N(1)-C(2)	1.387(2)
N(1)-C(11)	1.396(2)	N(1)-C(12)	1.4376(18)
N(42)-C(41)	1.331(2)	N(42)-C(43)	1.354(2)
C(9)-N(5)	1.477(2)	C(9)-C(8)	1.530(3)
C(9)-C(10)	1.550(2)	C(9)-C(91)	1.5506(19)
O(2)-C(2)	1.206(2)	N(91)-C(91)	1.330(2)
C(41)-N(46)	1.338(2)	C(41)-C(4)	1.532(2)
C(13)-C(12)	1.388(2)	C(13)-C(14)	1.396(2)
N(5)-C(4)	1.477(2)	N(5)-C(6)	1.487(2)
N(46)-C(45)	1.355(2)	C(12)-C(17)	1.385(2)
C(11)-O(11)	1.203(2)	C(11)-C(10)	1.518(2)
C(4)-C(3)	1.561(2)	C(2)-C(3)	1.524(2)
C(17)-C(16)	1.391(2)	C(3)-C(10)	1.531(2)
C(43)-C(44)	1.384(3)	C(43)-C(47)	1.493(3)
C(44)-C(45)	1.381(3)	C(14)-C(15)	1.379(3)
C(8)-C(7)	1.534(3)	C(16)-C(15)	1.382(3)
C(45)-C(48)	1.499(3)	C(6)-C(7)	1.534(3)

Table 6. Angles between interatomic vectors (°) with s.u.s in parentheses.

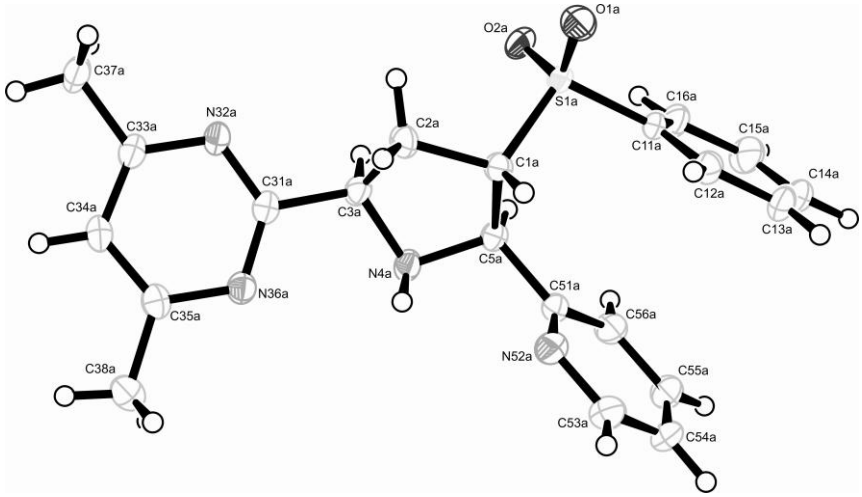
C(2)-N(1)-C(11)	113.38(13)	C(2)-N(1)-C(12)	124.18(13)
C(11)-N(1)-C(12)	122.42(14)	C(41)-N(42)-C(43)	116.58(15)
N(5)-C(9)-C(8)	105.74(14)	N(5)-C(9)-C(10)	104.73(13)
C(8)-C(9)-C(10)	120.14(14)	N(5)-C(9)-C(91)	110.37(12)
C(8)-C(9)-C(91)	107.88(14)	C(10)-C(9)-C(91)	107.77(12)
O(91)-C(91)-N(91)	123.83(14)	O(91)-C(91)-C(9)	120.00(14)
N(91)-C(91)-C(9)	116.17(14)	N(42)-C(41)-N(46)	127.08(15)
N(42)-C(41)-C(4)	117.60(14)	N(46)-C(41)-C(4)	115.32(16)
C(12)-C(13)-C(14)	118.14(17)	C(9)-N(5)-C(4)	112.42(12)
C(9)-N(5)-C(6)	108.16(15)	C(4)-N(5)-C(6)	118.82(13)
C(41)-N(46)-C(45)	115.95(17)	C(17)-C(12)-C(13)	121.64(15)
C(17)-C(12)-N(1)	119.16(14)	C(13)-C(12)-N(1)	119.20(15)
O(11)-C(11)-N(1)	124.27(15)	O(11)-C(11)-C(10)	127.72(15)
N(1)-C(11)-C(10)	107.95(15)	N(5)-C(4)-C(41)	115.36(15)
N(5)-C(4)-C(3)	103.09(12)	C(41)-C(4)-C(3)	113.35(12)
O(2)-C(2)-N(1)	125.00(14)	O(2)-C(2)-C(3)	126.93(16)
N(1)-C(2)-C(3)	108.05(13)	C(12)-C(17)-C(16)	119.03(17)
C(2)-C(3)-C(10)	104.85(13)	C(2)-C(3)-C(4)	113.66(12)
C(10)-C(3)-C(4)	106.55(13)	N(42)-C(43)-C(44)	120.46(18)
N(42)-C(43)-C(47)	117.16(17)	C(44)-C(43)-C(47)	122.38(17)
C(11)-C(10)-C(3)	105.05(12)	C(11)-C(10)-C(9)	116.48(16)
C(3)-C(10)-C(9)	107.23(13)	C(45)-C(44)-C(43)	118.92(16)
C(15)-C(14)-C(13)	120.83(17)	C(9)-C(8)-C(7)	101.22(16)
C(15)-C(16)-C(17)	120.19(18)	C(14)-C(15)-C(16)	120.14(16)
N(46)-C(45)-C(44)	120.95(17)	N(46)-C(45)-C(48)	117.11(19)
C(44)-C(45)-C(48)	121.94(17)	N(5)-C(6)-C(7)	105.90(15)
C(6)-C(7)-C(8)	104.55(16)		

Table 7. Torsion angles (°) with s.u.s in parentheses.

N(5)-C(9)-C(91)-O(91)	167.28(15)	C(8)-C(9)-C(91)-O(91)	52.20(19)
C(10)-C(9)-C(91)-O(91)	-78.90(19)	N(5)-C(9)-C(91)-N(91)	-13.0(2)
C(8)-C(9)-C(91)-N(91)	-128.10(16)	C(10)-C(9)-C(91)-N(91)	100.79(16)
C(43)-N(42)-C(41)-N(46)	-0.3(3)	C(43)-N(42)-C(41)-C(4)	-179.84(15)
C(8)-C(9)-N(5)-C(4)	-109.85(15)	C(10)-C(9)-N(5)-C(4)	18.00(18)
C(91)-C(9)-N(5)-C(4)	133.74(14)	C(8)-C(9)-N(5)-C(6)	23.33(16)
C(10)-C(9)-N(5)-C(6)	151.17(13)	C(91)-C(9)-N(5)-C(6)	-93.09(16)
N(42)-C(41)-N(46)-C(45)	-1.8(3)	C(4)-C(41)-N(46)-C(45)	177.68(15)
C(14)-C(13)-C(12)-C(17)	1.3(2)	C(14)-C(13)-C(12)-N(1)	-179.16(14)
C(2)-N(1)-C(12)-C(17)	-126.03(17)	C(11)-N(1)-C(12)-C(17)	52.2(2)
C(2)-N(1)-C(12)-C(13)	54.4(2)	C(11)-N(1)-C(12)-C(13)	-127.34(18)
C(2)-N(1)-C(11)-O(11)	179.4(2)	C(12)-N(1)-C(11)-O(11)	1.0(3)
C(2)-N(1)-C(11)-C(10)	-3.3(2)	C(12)-N(1)-C(11)-C(10)	178.32(14)
C(9)-N(5)-C(4)-C(41)	98.86(16)	C(6)-N(5)-C(4)-C(41)	-28.9(2)
C(9)-N(5)-C(4)-C(3)	-25.24(17)	C(6)-N(5)-C(4)-C(3)	-152.97(15)
N(42)-C(41)-C(4)-N(5)	-55.04(19)	N(46)-C(41)-C(4)-N(5)	125.38(16)

N(42)-C(41)-C(4)-C(3)	63.5(2)	N(46)-C(41)-C(4)-C(3)	-116.09(16)
C(11)-N(1)-C(2)-O(2)	179.32(18)	C(12)-N(1)-C(2)-O(2)	-2.3(3)
C(11)-N(1)-C(2)-C(3)	-2.29(19)	C(12)-N(1)-C(2)-C(3)	176.06(14)
C(13)-C(12)-C(17)-C(16)	-1.2(2)	N(1)-C(12)-C(17)-C(16)	179.34(15)
O(2)-C(2)-C(3)-C(10)	-174.89(17)	N(1)-C(2)-C(3)-C(10)	6.76(17)
O(2)-C(2)-C(3)-C(4)	69.1(2)	N(1)-C(2)-C(3)-C(4)	-109.21(16)
N(5)-C(4)-C(3)-C(2)	136.99(15)	C(41)-C(4)-C(3)-C(2)	11.6(2)
N(5)-C(4)-C(3)-C(10)	22.02(16)	C(41)-C(4)-C(3)-C(10)	-103.39(16)
C(41)-N(42)-C(43)-C(44)	2.1(2)	C(41)-N(42)-C(43)-C(47)	-177.43(17)
O(11)-C(11)-C(10)-C(3)	-175.4(2)	N(1)-C(11)-C(10)-C(3)	7.34(19)
O(11)-C(11)-C(10)-C(9)	-57.0(3)	N(1)-C(11)-C(10)-C(9)	125.80(15)
C(2)-C(3)-C(10)-C(11)	-8.36(17)	C(4)-C(3)-C(10)-C(11)	112.43(14)
C(2)-C(3)-C(10)-C(9)	-132.89(13)	C(4)-C(3)-C(10)-C(9)	-12.10(16)
N(5)-C(9)-C(10)-C(11)	-119.95(15)	C(8)-C(9)-C(10)-C(11)	-1.5(2)
C(91)-C(9)-C(10)-C(11)	122.52(15)	N(5)-C(9)-C(10)-C(3)	-2.69(16)
C(8)-C(9)-C(10)-C(3)	115.81(16)	C(91)-C(9)-C(10)-C(3)	-120.21(14)
N(42)-C(43)-C(44)-C(45)	-1.6(3)	C(47)-C(43)-C(44)-C(45)	177.87(19)
C(12)-C(13)-C(14)-C(15)	-0.1(3)	N(5)-C(9)-C(8)-C(7)	-36.44(16)
C(10)-C(9)-C(8)-C(7)	-154.42(15)	C(91)-C(9)-C(8)-C(7)	81.65(16)
C(12)-C(17)-C(16)-C(15)	-0.2(3)	C(13)-C(14)-C(15)-C(16)	-1.2(3)
C(17)-C(16)-C(15)-C(14)	1.4(3)	C(41)-N(46)-C(45)-C(44)	2.3(3)
C(41)-N(46)-C(45)-C(48)	-177.42(17)	C(43)-C(44)-C(45)-N(46)	-0.7(3)
C(43)-C(44)-C(45)-C(48)	179.00(18)	C(9)-N(5)-C(6)-C(7)	-0.24(17)
C(4)-N(5)-C(6)-C(7)	129.46(16)	N(5)-C(6)-C(7)-C(8)	-22.74(19)
C(9)-C(8)-C(7)-C(6)	35.79(18)		

Appendix 5: X-ray crystallographic data for 280.



Ortep view of 280.

Table 1. Crystal data and structure refinement for EE78.

Archive code	10_09_01	
Identification code	EE78	
Formula	$C_{21}H_{22}N_4O_2S$	
Formula weight	394.49	
Size	0.23 x 0.21 x 0.18 mm	
Crystal morphology	Colourless fragment	
Temperature	150(2) K	
Wavelength	0.71073 Å [Mo-K_α]	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.1200(9) Å	α = 90°
	b = 14.2859(8) Å	β = 96.051(2)°
	c = 18.2254(9) Å	γ = 90°
Volume	3914.8(4) Å^3	
Z	8	
Density (calculated)	1.339 Mg/m^3	
Absorption coefficient	0.19 mm^{-1}	
F(000)	1664	
Data collection range	$1.35 \leq \theta \leq 29.69°$	
Index ranges	$-21 \leq h \leq 17$, $-19 \leq k \leq 19$, $-25 \leq l \leq 25$	
Reflections collected	140682	

Independent reflections	11014 [R(int) = 0.0491]
Observed reflections	8377 [$I > 2\sigma(I)$]
Absorption correction	multi-scan
Max. and min. transmission	0.9666 and 0.8831
Refinement method	Full
Data / restraints / parameters	11014 / 0 / 510
Goodness of fit	1.082
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0480, wR_2 = 0.1171
R indices (all data)	R_1 = 0.0706, wR_2 = 0.1334
Largest diff. peak and hole	0.618 and -0.309e.Å^{-3}

Table 2. Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^4) with standard uncertainties (s.u.s) in parentheses. U_{eq} is defined as $^1/_3$ of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
S(1a)	-141(3)	-397(3)	34445(2)	232.7(10)
O(1a)	3699(9)	-3082(10)	27794(8)	351(3)
C(1a)	-11926(11)	-1394(12)	32682(10)	228(3)
O(2a)	2821(9)	-5308(9)	41177(8)	324(3)
C(2a)	-14937(12)	-11741(13)	32607(11)	292(4)
C(3a)	-20285(11)	-12346(12)	39371(10)	241(3)
N(4a)	-23989(10)	-3011(10)	40380(8)	255(3)
C(5a)	-16743(11)	3371(11)	38899(9)	224(3)
C(11a)	1583(11)	11719(11)	35881(9)	210(3)
C(12a)	-849(13)	17886(13)	30103(10)	284(4)
C(13a)	549(14)	27429(14)	31288(13)	367(5)
C(14a)	4428(13)	30628(13)	38007(14)	387(5)
C(15a)	6828(14)	24445(14)	43719(13)	387(5)
C(16a)	5275(13)	14854(13)	42699(11)	303(4)
C(31a)	-27094(12)	-20090(12)	38817(9)	241(3)
N(32a)	-23629(10)	-28735(10)	39312(9)	262(3)
C(33a)	-29500(12)	-35837(12)	39195(10)	259(3)
C(34a)	-38613(12)	-34118(13)	38846(10)	273(4)
C(35a)	-41559(12)	-24912(13)	38178(10)	255(3)
N(36a)	-35692(10)	-17757(10)	38021(8)	252(3)
C(37a)	-25721(14)	-45529(13)	39557(12)	333(4)
C(38a)	-51181(13)	-22255(15)	37759(12)	344(4)
C(51a)	-20156(11)	13067(12)	36749(10)	243(3)
N(52a)	-25296(10)	13587(11)	30347(9)	292(3)
C(53a)	-28281(13)	22078(14)	28145(12)	342(4)
C(54a)	-26239(14)	30214(14)	32170(13)	374(5)

C(55a)	-20935(14)	29522(14)	38763(13)	371(5)
C(56a)	-17843(13)	20783(13)	41168(11)	300(4)
S(1b)	50523(3)	38015(3)	35772(2)	231.1(10)
O(1b)	54121(9)	42152(9)	42664(8)	344(3)
C(1b)	38729(11)	39547(12)	34543(10)	232(3)
O(2b)	53999(9)	41255(10)	29115(8)	348(3)
C(2b)	36158(12)	50008(12)	35102(11)	292(4)
C(3b)	30589(12)	50235(12)	41794(10)	252(3)
N(4b)	26963(10)	40773(10)	42523(8)	247(3)
C(5b)	34058(11)	34423(11)	40665(10)	223(3)
C(11b)	51902(11)	25743(11)	36435(10)	220(3)
C(12b)	48164(12)	20135(13)	30643(10)	274(4)
C(13b)	49257(14)	10489(14)	31069(12)	343(4)
C(14b)	54007(14)	6540(14)	37186(14)	391(5)
C(15b)	57728(14)	12152(14)	42918(13)	378(5)
C(16b)	56657(12)	21864(13)	42625(11)	289(4)
C(31b)	23420(12)	57654(12)	41055(10)	245(3)
N(32b)	26455(10)	66498(10)	40848(9)	276(3)
C(33b)	20221(12)	73231(12)	40111(10)	262(4)
C(34b)	11199(12)	71100(13)	39774(10)	270(4)
C(35b)	8721(12)	61776(12)	40022(10)	253(3)
N(36b)	14932(10)	54932(10)	40567(9)	268(3)
C(37b)	23418(14)	83168(13)	39794(14)	382(5)
C(38b)	-821(12)	58760(14)	39710(12)	345(4)
C(51b)	30409(11)	24935(11)	38260(10)	215(3)
N(52b)	25660(10)	24614(11)	31660(9)	264(3)
C(53b)	22356(12)	16334(13)	29295(11)	291(4)
C(54b)	23666(13)	8157(13)	33333(12)	323(4)
C(55b)	28411(14)	8524(13)	40210(12)	337(4)
C(56b)	31911(12)	17098(13)	42761(10)	271(4)

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1a)	201.3(19)	145.5(18)	350(2)	-24.6(15)	24.1(15)	-8.5(14)
O(1a)	318(7)	287(7)	463(8)	-143(6)	114(6)	-38(6)
C(1a)	208(7)	199(8)	275(8)	-52(6)	16(6)	-20(6)
O(2a)	298(7)	194(6)	469(8)	69(6)	-13(6)	31(5)
C(2a)	256(8)	222(8)	405(10)	-101(7)	69(7)	-62(7)
C(3a)	246(8)	174(7)	293(9)	-26(6)	-9(6)	-16(6)
N(4a)	287(7)	182(7)	303(8)	-18(6)	65(6)	-26(6)
C(5a)	238(8)	182(7)	251(8)	-25(6)	22(6)	-15(6)
C(11a)	191(7)	150(7)	291(8)	-7(6)	32(6)	-13(6)
C(12a)	313(9)	253(9)	295(9)	43(7)	80(7)	11(7)
C(13a)	396(11)	214(9)	520(13)	129(8)	176(9)	32(8)
C(14a)	314(10)	155(8)	711(15)	-35(9)	139(10)	-35(7)

C(15a)	369(11)	239(9)	532(13)	-127(9)	-44(9)	-50(8)
C(16a)	316(9)	211(8)	363(10)	-12(7)	-55(7)	-19(7)
C(31a)	279(8)	201(8)	243(8)	-7(6)	25(6)	-34(6)
N(32a)	279(7)	192(7)	318(8)	-4(6)	46(6)	-39(6)
C(33a)	323(9)	193(8)	264(8)	-10(6)	51(7)	-32(7)
C(34a)	286(9)	235(8)	299(9)	-9(7)	40(7)	-80(7)
C(35a)	266(8)	265(8)	234(8)	-12(6)	23(6)	-53(7)
N(36a)	256(7)	219(7)	276(7)	1(6)	11(6)	-23(6)
C(37a)	394(10)	180(8)	438(11)	-5(7)	105(8)	-42(7)
C(38a)	259(9)	367(10)	407(11)	-10(8)	43(8)	-32(8)
C(51a)	219(8)	192(7)	328(9)	-19(6)	74(7)	-9(6)
N(52a)	286(8)	246(8)	343(8)	-13(6)	28(6)	11(6)
C(53a)	313(9)	322(10)	392(11)	58(8)	40(8)	49(8)
C(54a)	332(10)	210(9)	601(14)	70(9)	140(9)	72(7)
C(55a)	349(10)	208(9)	572(13)	-101(8)	123(9)	-2(8)
C(56a)	286(9)	258(9)	361(10)	-72(7)	62(7)	4(7)
S(1b)	197.3(19)	154.1(18)	344(2)	5.8(15)	38.7(15)	-6.0(14)
O(1b)	325(7)	237(7)	451(8)	-83(6)	-43(6)	-21(5)
C(1b)	200(7)	195(7)	302(9)	18(6)	33(6)	6(6)
O(2b)	327(7)	263(7)	473(8)	121(6)	133(6)	26(5)
C(2b)	267(9)	171(8)	448(11)	56(7)	82(7)	31(6)
C(3b)	254(8)	166(7)	330(9)	2(6)	9(7)	10(6)
N(4b)	263(7)	166(6)	320(8)	-4(6)	61(6)	23(5)
C(5b)	229(8)	173(7)	267(8)	14(6)	24(6)	3(6)
C(11b)	214(7)	155(7)	301(9)	2(6)	68(6)	10(6)
C(12b)	301(9)	234(8)	297(9)	-21(7)	77(7)	-5(7)
C(13b)	346(10)	237(9)	468(12)	-91(8)	144(8)	-12(7)
C(14b)	365(11)	174(8)	657(15)	23(9)	162(10)	56(7)
C(15b)	349(10)	288(10)	493(12)	116(9)	30(9)	71(8)
C(16b)	274(9)	252(9)	339(10)	22(7)	23(7)	24(7)
C(31b)	257(8)	178(7)	300(9)	-19(6)	35(7)	10(6)
N(32b)	272(7)	171(7)	390(9)	-16(6)	52(6)	5(6)
C(33b)	290(9)	170(7)	328(9)	-10(6)	45(7)	23(6)
C(34b)	280(9)	220(8)	308(9)	-16(7)	16(7)	55(7)
C(35b)	247(8)	240(8)	267(8)	-27(6)	9(6)	27(7)
N(36b)	248(7)	194(7)	361(8)	-21(6)	23(6)	13(6)
C(37b)	363(10)	173(8)	619(14)	4(8)	105(10)	12(7)
C(38b)	239(9)	310(10)	482(12)	-19(8)	13(8)	9(7)
C(51b)	201(7)	156(7)	292(8)	6(6)	45(6)	12(6)
N(52b)	246(7)	231(7)	311(8)	15(6)	17(6)	-12(6)
C(53b)	283(9)	277(9)	311(9)	-22(7)	26(7)	-33(7)
C(54b)	311(9)	217(8)	448(11)	-43(8)	71(8)	-47(7)
C(55b)	379(10)	196(8)	441(11)	86(8)	71(8)	-4(7)
C(56b)	288(9)	253(8)	272(9)	34(7)	37(7)	16(7)

Table 4. Hydrogen atom co-ordinates (x 10^3) and isotropic displacement parameters ($Å^2$ x 10^2) with s.u.s in parentheses.

	x	y	z	U_{eq}
H(1a)	-1396.	157.	2782.	27.
H(2a1)	-976.	-1602.	3314.	35.
H(2a2)	-1872.	-1327.	2799.	35.
H(3a)	-1596.	-1368.	4378.	29.
H(4a)	-2836.	-206.	3613.	38.(6)
H(5a)	-1246.	387.	4345.	27.
H(12a)	-341.	1563.	2545.	34.
H(13a)	-118.	3176.	2744.	44.
H(14a)	546.	3714.	3872.	46.
H(15a)	952.	2671.	4832.	46.
H(16a)	673.	1057.	4663.	36.
H(34a)	-4271.	-3912.	3906.	33.
H(37a)	-2263.	-4669.	3518.	50.
H(37b)	-3055.	-5008.	3972.	50.
H(37c)	-2152.	-4616.	4400.	50.
H(38a)	-5219.	-1842.	4205.	52.
H(38b)	-5483.	-2793.	3772.	52.
H(38c)	-5282.	-1868.	3323.	52.
H(53a)	-3197.	2256.	2361.	41.
H(54a)	-2846.	3611.	3041.	45.
H(55a)	-1941.	3495.	4163.	45.
H(56a)	-1423.	2010.	4573.	36.
H(1b)	3634.	3707.	2959.	28.
H(2b1)	3259.	5214.	3054.	35.
H(2b2)	4151.	5400.	3600.	35.
H(3b)	3470.	5162.	4633.	30.
H(4b)	2214.	4024.	3896.	33.(6)
H(5b)	3845.	3361.	4512.	27.
H(12b)	4490.	2289.	2645.	33.
H(13b)	4674.	661.	2716.	41.
H(14b)	5473.	-6.	3747.	47.
H(15b)	6103.	937.	4708.	45.
H(16b)	5912.	2572.	4657.	35.
H(34b)	685.	7592.	3938.	32.
H(37d)	2993.	8324.	4008.	57.
H(37e)	2148.	8670.	4395.	57.
H(37f)	2093.	8604.	3515.	57.
H(37g)	1830.	8741.	3937.	57.
H(37h)	2674.	8396.	3550.	57.
H(37j)	2730.	8461.	4430.	57.
H(38d)	-217.	5438.	3560.	52.
H(38e)	-469.	6425.	3897.	52.
H(38f)	-183.	5567.	4435.	52.
H(53b)	1894.	1605.	2461.	35.
H(54b)	2133.	239.	3140.	39.

H(55b)	2928.	305.	4315.	40.
H(56b)	3525.	1758.	4746.	32.

Table 5. Interatomic distances (Å) with s.u.s in parentheses.

S(1a)-O(2a)	1.4430(14)	S(1a)-O(1a)	1.4498(14)
S(1a)-C(11a)	1.7658(16)	S(1a)-C(1a)	1.7827(17)
C(1a)-C(2a)	1.546(2)	C(1a)-C(5a)	1.566(2)
C(2a)-C(3a)	1.546(3)	C(3a)-N(4a)	1.466(2)
C(3a)-C(31a)	1.507(2)	N(4a)-C(5a)	1.472(2)
C(5a)-C(51a)	1.515(2)	C(11a)-C(16a)	1.382(2)
C(11a)-C(12a)	1.392(2)	C(12a)-C(13a)	1.393(3)
C(13a)-C(14a)	1.379(3)	C(14a)-C(15a)	1.384(3)
C(15a)-C(16a)	1.399(3)	C(31a)-N(36a)	1.335(2)
C(31a)-N(32a)	1.341(2)	N(32a)-C(33a)	1.347(2)
C(33a)-C(34a)	1.394(3)	C(33a)-C(37a)	1.497(3)
C(34a)-C(35a)	1.390(3)	C(35a)-N(36a)	1.356(2)
C(35a)-C(38a)	1.498(3)	C(51a)-N(52a)	1.334(2)
C(51a)-C(56a)	1.388(2)	N(52a)-C(53a)	1.341(2)
C(53a)-C(54a)	1.392(3)	C(54a)-C(55a)	1.376(3)
C(55a)-C(56a)	1.388(3)	S(1b)-O(1b)	1.4418(14)
S(1b)-O(2b)	1.4482(14)	S(1b)-C(11b)	1.7682(17)
S(1b)-C(1b)	1.7871(17)	C(1b)-C(2b)	1.550(2)
C(1b)-C(5b)	1.564(2)	C(2b)-C(3b)	1.554(3)
C(3b)-N(4b)	1.470(2)	C(3b)-C(31b)	1.512(2)
N(4b)-C(5b)	1.471(2)	C(5b)-C(51b)	1.511(2)
C(11b)-C(16b)	1.388(3)	C(11b)-C(12b)	1.396(2)
C(12b)-C(13b)	1.389(3)	C(13b)-C(14b)	1.381(3)
C(14b)-C(15b)	1.388(3)	C(15b)-C(16b)	1.397(3)
C(31b)-N(36b)	1.335(2)	C(31b)-N(32b)	1.346(2)
N(32b)-C(33b)	1.344(2)	C(33b)-C(34b)	1.393(3)
C(33b)-C(37b)	1.503(3)	C(34b)-C(35b)	1.386(3)
C(35b)-N(36b)	1.352(2)	C(35b)-C(38b)	1.501(3)
C(51b)-N(52b)	1.335(2)	C(51b)-C(56b)	1.392(2)
N(52b)-C(53b)	1.338(2)	C(53b)-C(54b)	1.384(3)
C(54b)-C(55b)	1.378(3)	C(55b)-C(56b)	1.395(3)

Table 6. Angles between interatomic vectors (°) with s.u.s in parentheses.

O(2a)-S(1a)-O(1a)	117.81(9)	O(2a)-S(1a)-C(11a)	108.84(8)
O(1a)-S(1a)-C(11a)	108.50(8)	O(2a)-S(1a)-C(1a)	109.21(8)
O(1a)-S(1a)-C(1a)	108.00(8)	C(11a)-S(1a)-C(1a)	103.54(8)
C(2a)-C(1a)-C(5a)	105.25(14)	C(2a)-C(1a)-S(1a)	111.45(12)
C(5a)-C(1a)-S(1a)	111.54(11)	C(1a)-C(2a)-C(3a)	102.98(13)
N(4a)-C(3a)-C(31a)	114.14(14)	N(4a)-C(3a)-C(2a)	106.74(14)
C(31a)-C(3a)-C(2a)	113.48(14)	C(3a)-N(4a)-C(5a)	103.82(13)
N(4a)-C(5a)-C(51a)	111.95(14)	N(4a)-C(5a)-C(1a)	105.98(13)
C(51a)-C(5a)-C(1a)	112.45(14)	C(16a)-C(11a)-C(12a)	121.62(16)
C(16a)-C(11a)-S(1a)	119.36(13)	C(12a)-C(11a)-S(1a)	119.02(14)

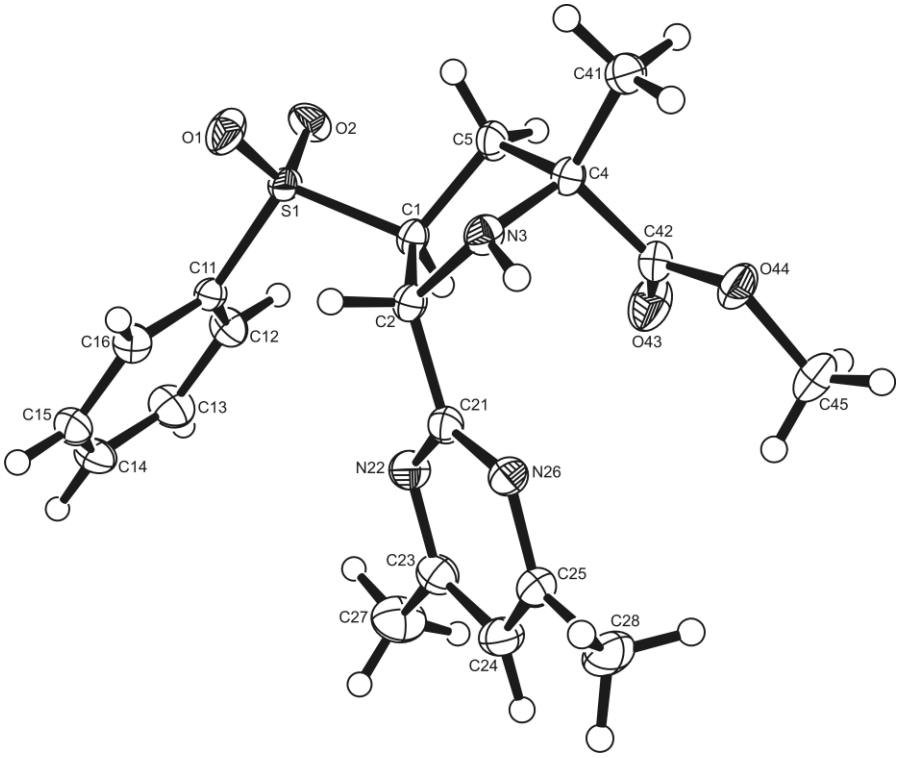
C(11a)-C(12a)-C(13a)	118.58(18)	C(14a)-C(13a)-C(12a)	120.37(19)
C(13a)-C(14a)-C(15a)	120.64(18)	C(14a)-C(15a)-C(16a)	119.9(2)
C(11a)-C(16a)-C(15a)	118.89(18)	N(36a)-C(31a)-N(32a)	127.32(16)
N(36a)-C(31a)-C(3a)	118.32(15)	N(32a)-C(31a)-C(3a)	114.35(15)
C(31a)-N(32a)-C(33a)	116.15(15)	N(32a)-C(33a)-C(34a)	120.97(16)
N(32a)-C(33a)-C(37a)	116.64(16)	C(34a)-C(33a)-C(37a)	122.39(16)
C(35a)-C(34a)-C(33a)	118.46(16)	N(36a)-C(35a)-C(34a)	120.72(16)
N(36a)-C(35a)-C(38a)	116.24(16)	C(34a)-C(35a)-C(38a)	123.02(16)
C(31a)-N(36a)-C(35a)	116.19(15)	N(52a)-C(51a)-C(56a)	123.45(17)
N(52a)-C(51a)-C(5a)	115.36(15)	C(56a)-C(51a)-C(5a)	121.19(17)
C(51a)-N(52a)-C(53a)	117.32(17)	N(52a)-C(53a)-C(54a)	123.3(2)
C(55a)-C(54a)-C(53a)	118.47(18)	C(54a)-C(55a)-C(56a)	119.11(19)
C(55a)-C(56a)-C(51a)	118.37(19)	O(1b)-S(1b)-O(2b)	117.52(9)
O(1b)-S(1b)-C(11b)	108.41(8)	O(2b)-S(1b)-C(11b)	108.88(8)
O(1b)-S(1b)-C(1b)	109.81(8)	O(2b)-S(1b)-C(1b)	107.54(8)
C(11b)-S(1b)-C(1b)	103.82(8)	C(2b)-C(1b)-C(5b)	105.61(14)
C(2b)-C(1b)-S(1b)	111.32(12)	C(5b)-C(1b)-S(1b)	111.90(12)
C(1b)-C(2b)-C(3b)	103.42(14)	N(4b)-C(3b)-C(31b)	112.46(14)
N(4b)-C(3b)-C(2b)	106.85(14)	C(31b)-C(3b)-C(2b)	112.80(15)
C(3b)-N(4b)-C(5b)	104.97(13)	N(4b)-C(5b)-C(51b)	111.54(14)
N(4b)-C(5b)-C(1b)	105.70(13)	C(51b)-C(5b)-C(1b)	113.05(14)
C(16b)-C(11b)-C(12b)	121.28(16)	C(16b)-C(11b)-S(1b)	119.92(14)
C(12b)-C(11b)-S(1b)	118.80(14)	C(13b)-C(12b)-C(11b)	119.38(18)
C(14b)-C(13b)-C(12b)	119.93(19)	C(13b)-C(14b)-C(15b)	120.43(18)
C(14b)-C(15b)-C(16b)	120.57(19)	C(11b)-C(16b)-C(15b)	118.40(18)
N(36b)-C(31b)-N(32b)	126.85(16)	N(36b)-C(31b)-C(3b)	118.48(15)
N(32b)-C(31b)-C(3b)	114.66(15)	C(33b)-N(32b)-C(31b)	115.92(15)
N(32b)-C(33b)-C(34b)	121.43(16)	N(32b)-C(33b)-C(37b)	117.07(16)
C(34b)-C(33b)-C(37b)	121.49(16)	C(35b)-C(34b)-C(33b)	118.40(16)
N(36b)-C(35b)-C(34b)	120.63(16)	N(36b)-C(35b)-C(38b)	116.91(16)
C(34b)-C(35b)-C(38b)	122.46(16)	C(31b)-N(36b)-C(35b)	116.72(15)
N(52b)-C(51b)-C(56b)	122.82(16)	N(52b)-C(51b)-C(5b)	115.94(15)
C(56b)-C(51b)-C(5b)	121.24(16)	C(51b)-N(52b)-C(53b)	117.90(16)
N(52b)-C(53b)-C(54b)	123.20(18)	C(55b)-C(54b)-C(53b)	118.90(18)
C(54b)-C(55b)-C(56b)	118.66(17)	C(51b)-C(56b)-C(55b)	118.51(17)

Table 7. Torsion angles (°) with s.u.s in parentheses.

O(2a)-S(1a)-C(1a)-C(2a)	-54.29(14)	O(1a)-S(1a)-C(1a)-C(2a)	74.95(14)
C(11a)-S(1a)-C(1a)-C(2a)	-170.12(12)	O(2a)-S(1a)-C(1a)-C(5a)	63.02(14)
O(1a)-S(1a)-C(1a)-C(5a)	-167.73(12)	C(11a)-S(1a)-C(1a)-C(5a)	-52.80(14)
C(5a)-C(1a)-C(2a)-C(3a)	-6.61(18)	S(1a)-C(1a)-C(2a)-C(3a)	114.45(13)
C(1a)-C(2a)-C(3a)-N(4a)	28.55(18)	C(1a)-C(2a)-C(3a)-C(31a)	155.16(14)
C(31a)-C(3a)-N(4a)-C(5a)	-166.30(14)	C(2a)-C(3a)-N(4a)-C(5a)	-40.08(17)
C(3a)-N(4a)-C(5a)-C(51a)	157.88(14)	C(3a)-N(4a)-C(5a)-C(1a)	34.94(17)
C(2a)-C(1a)-C(5a)-N(4a)	-17.00(18)	S(1a)-C(1a)-C(5a)-N(4a)	-138.00(12)
C(2a)-C(1a)-C(5a)-C(51a)	-139.62(15)	S(1a)-C(1a)-C(5a)-C(51a)	99.38(15)
O(2a)-S(1a)-C(11a)-C(16a)	0.13(17)	O(1a)-S(1a)-C(11a)-C(16a)	-129.21(15)
C(1a)-S(1a)-C(11a)-C(16a)	116.22(15)	O(2a)-S(1a)-C(11a)-C(12a)	-179.65(14)

O(1a)-S(1a)-C(11a)-C(12a)	51.01(16)	C(1a)-S(1a)-C(11a)-C(12a)	-63.55(15)
C(16a)-C(11a)-C(12a)-C(13a)	0.3(3)	S(1a)-C(11a)-C(12a)-C(13a)	-179.92(14)
C(11a)-C(12a)-C(13a)-C(14a)	1.3(3)	C(12a)-C(13a)-C(14a)-C(15a)	-1.3(3)
C(13a)-C(14a)-C(15a)-C(16a)	-0.3(3)	C(12a)-C(11a)-C(16a)-C(15a)	-1.9(3)
S(1a)-C(11a)-C(16a)-C(15a)	178.34(16)	C(14a)-C(15a)-C(16a)-C(11a)	1.9(3)
N(4a)-C(3a)-C(31a)-N(36a)	11.1(2)	C(2a)-C(3a)-C(31a)-N(36a)	-111.47(18)
N(4a)-C(3a)-C(31a)-N(32a)	-167.89(15)	C(2a)-C(3a)-C(31a)-N(32a)	69.5(2)
N(36a)-C(31a)-N(32a)-C(33a)	-2.0(3)	C(3a)-C(31a)-N(32a)-C(33a)	176.95(15)
C(31a)-N(32a)-C(33a)-C(34a)	-2.2(3)	C(31a)-N(32a)-C(33a)-C(37a)	178.54(16)
N(32a)-C(33a)-C(34a)-C(35a)	3.8(3)	C(37a)-C(33a)-C(34a)-C(35a)	-177.04(17)
C(33a)-C(34a)-C(35a)-N(36a)	-1.3(3)	C(33a)-C(34a)-C(35a)-C(38a)	-179.97(17)
N(32a)-C(31a)-N(36a)-C(35a)	4.3(3)	C(3a)-C(31a)-N(36a)-C(35a)	-174.58(15)
C(34a)-C(35a)-N(36a)-C(31a)	-2.4(2)	C(38a)-C(35a)-N(36a)-C(31a)	176.33(16)
N(4a)-C(5a)-C(51a)-N(52a)	-66.0(2)	C(1a)-C(5a)-C(51a)-N(52a)	53.2(2)
N(4a)-C(5a)-C(51a)-C(56a)	115.28(18)	C(1a)-C(5a)-C(51a)-C(56a)	-125.53(18)
C(56a)-C(51a)-N(52a)-C(53a)	0.3(3)	C(5a)-C(51a)-N(52a)-C(53a)	-178.39(16)
C(51a)-N(52a)-C(53a)-C(54a)	0.3(3)	N(52a)-C(53a)-C(54a)-C(55a)	-0.4(3)
C(53a)-C(54a)-C(55a)-C(56a)	-0.2(3)	C(54a)-C(55a)-C(56a)-C(51a)	0.8(3)
N(52a)-C(51a)-C(56a)-C(55a)	-0.9(3)	C(5a)-C(51a)-C(56a)-C(55a)	177.77(17)
O(1b)-S(1b)-C(1b)-C(2b)	55.11(15)	O(2b)-S(1b)-C(1b)-C(2b)	-73.86(14)
C(11b)-S(1b)-C(1b)-C(2b)	170.85(13)	O(1b)-S(1b)-C(1b)-C(5b)	-62.82(14)
O(2b)-S(1b)-C(1b)-C(5b)	168.22(12)	C(11b)-S(1b)-C(1b)-C(5b)	52.92(14)
C(5b)-C(1b)-C(2b)-C(3b)	2.90(18)	S(1b)-C(1b)-C(2b)-C(3b)	-118.76(13)
C(1b)-C(2b)-C(3b)-N(4b)	-24.17(18)	C(1b)-C(2b)-C(3b)-C(31b)	-148.24(14)
C(31b)-C(3b)-N(4b)-C(5b)	161.43(15)	C(2b)-C(3b)-N(4b)-C(5b)	37.15(18)
C(3b)-N(4b)-C(5b)-C(51b)	-157.84(14)	C(3b)-N(4b)-C(5b)-C(1b)	-34.59(17)
C(2b)-C(1b)-C(5b)-N(4b)	19.07(18)	S(1b)-C(1b)-C(5b)-N(4b)	140.35(12)
C(2b)-C(1b)-C(5b)-C(51b)	141.35(15)	S(1b)-C(1b)-C(5b)-C(51b)	-97.36(15)
O(1b)-S(1b)-C(11b)-C(16b)	-6.10(17)	O(2b)-S(1b)-C(11b)-C(16b)	122.84(15)
C(1b)-S(1b)-C(11b)-C(16b)	-122.83(15)	O(1b)-S(1b)-C(11b)-C(12b)	174.11(14)
O(2b)-S(1b)-C(11b)-C(12b)	-56.95(16)	C(1b)-S(1b)-C(11b)-C(12b)	57.39(16)
C(16b)-C(11b)-C(12b)-C(13b)	-0.3(3)	S(1b)-C(11b)-C(12b)-C(13b)	179.50(14)
C(11b)-C(12b)-C(13b)-C(14b)	0.0(3)	C(12b)-C(13b)-C(14b)-C(15b)	-0.2(3)
C(13b)-C(14b)-C(15b)-C(16b)	0.6(3)	C(12b)-C(11b)-C(16b)-C(15b)	0.7(3)
S(1b)-C(11b)-C(16b)-C(15b)	-179.07(15)	C(14b)-C(15b)-C(16b)-C(11b)	-0.9(3)
N(4b)-C(3b)-C(31b)-N(36b)	-5.1(2)	C(2b)-C(3b)-C(31b)-N(36b)	115.87(18)
N(4b)-C(3b)-C(31b)-N(32b)	175.93(15)	C(2b)-C(3b)-C(31b)-N(32b)	-63.1(2)
N(36b)-C(31b)-N(32b)-C(33b)	0.4(3)	C(3b)-C(31b)-N(32b)-C(33b)	179.29(16)
C(31b)-N(32b)-C(33b)-C(34b)	1.5(3)	C(31b)-N(32b)-C(33b)-C(37b)	-179.45(18)
N(32b)-C(33b)-C(34b)-C(35b)	-1.7(3)	C(37b)-C(33b)-C(34b)-C(35b)	179.36(18)
C(33b)-C(34b)-C(35b)-N(36b)	-0.1(3)	C(33b)-C(34b)-C(35b)-C(38b)	179.87(18)
N(32b)-C(31b)-N(36b)-C(35b)	-2.1(3)	C(3b)-C(31b)-N(36b)-C(35b)	179.06(16)
C(34b)-C(35b)-N(36b)-C(31b)	1.8(3)	C(38b)-C(35b)-N(36b)-C(31b)	-178.14(17)
N(4b)-C(5b)-C(51b)-N(52b)	71.31(19)	C(1b)-C(5b)-C(51b)-N(52b)	-47.7(2)
N(4b)-C(5b)-C(51b)-C(56b)	-108.12(18)	C(1b)-C(5b)-C(51b)-C(56b)	132.92(17)
C(56b)-C(51b)-N(52b)-C(53b)	-1.0(3)	C(5b)-C(51b)-N(52b)-C(53b)	179.55(15)
C(51b)-N(52b)-C(53b)-C(54b)	-0.3(3)	N(52b)-C(53b)-C(54b)-C(55b)	1.6(3)
C(53b)-C(54b)-C(55b)-C(56b)	-1.6(3)	N(52b)-C(51b)-C(56b)-C(55b)	1.0(3)
C(5b)-C(51b)-C(56b)-C(55b)	-179.63(16)	C(54b)-C(55b)-C(56b)-C(51b)	0.4(3)

Appendix 6: X-ray crystallographic data for 281a.



Ortep view of 281a.

Table 1. Crystal data and structure refinement for EE81_6_9

Archive code	10_11_13	
Identification code	EE81_6_9	
Formula	$C_{19}H_{23}N_3O_4S$	
Formula weight	389.46	
Size	0.33 x 0.19 x 0.09 mm	
Crystal morphology	Colourless fragment	
Temperature	150(2) K	
Wavelength	0.71073 Å [Mo-K_α]	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.0526(8) Å	α = 90°
	b = 8.2214(6) Å	β = 91.281(4)°
	c = 22.0941(16) Å	γ = 90°
Volume	2007.1(3) $Å^3$	
Z	4	
Density (calculated)	1.289 Mg/m^3	
Absorption coefficient	0.19 mm^{-1}	

F(000)	824
Data collection range	$1.84 \leq \theta \leq 30.63°$
Index ranges	$-15 \leq h \leq 15$, $-10 \leq k \leq 11$, $-31 \leq l \leq 31$
Reflections collected	34993
Independent reflections	6182 [*R*(int) = 0.0639]
Observed reflections	4954 [$I > 2\sigma(I)$]
Absorption correction	multi-scan
Max. and min. transmission	0.9831 and 0.7039
Refinement method	Full
Data / restraints / parameters	6182 / 1 / 251
Goodness of fit	1.028
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0414$, $wR_2 = 0.1059$
R indices (all data)	$R_1 = 0.0556$, $wR_2 = 0.1167$
Largest diff. peak and hole	0.387 and -0.426e.Å^{-3}

Table 2. Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^4) with standard uncertainties (s.u.s) in parentheses. U_{eq} is defined as $^1/_3$ of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
S(1)	6973.9(3)	3005.4(4)	2432.61(13)	200.3(8)
O(1)	5672.5(9)	3002.8(14)	2288.5(4)	320(2)
C(1)	7200.8(11)	3371.7(15)	3238.4(5)	191(2)
O(2)	7748.6(10)	4171.1(12)	2122.9(4)	309(2)
C(2)	6337.9(11)	2383.3(15)	3657.6(5)	194(2)
N(3)[d]	5606.3(10)	3654.3(14)	3962.1(5)	220(2)
C(4)	6348.9(12)	5168.5(16)	4006.1(5)	215(2)
C(5)	6931.5(12)	5196.9(16)	3371.6(5)	226(2)
C(11)	7558.1(11)	1030.2(15)	2287.1(5)	181(2)
C(12)	8808.7(12)	866.8(17)	2179.2(6)	250(3)
C(13)	9273.0(13)	-675.9(19)	2046.5(7)	334(3)
C(14)	8495.2(14)	-2027.7(18)	2021.5(7)	315(3)
C(15)	7254.6(13)	-1854.3(17)	2128.7(6)	278(3)
C(16)	6775.7(12)	-312.5(16)	2264.9(6)	234(2)
C(21)	7052.3(11)	1236.8(15)	4090.8(5)	208(2)
N(22)	8021.2(10)	470.1(14)	3856.2(5)	255(2)
C(23)	8629.7(12)	-576.3(17)	4232.5(6)	275(3)
C(24)	8249.4(13)	-832.1(18)	4831.7(6)	288(3)
C(25)	7212.0(13)	-8.4(17)	5030.3(6)	252(3)
N(26)	6607.3(10)	1053.3(14)	4655.1(5)	226(2)

C(27)	9715.3(15)	-1450(2)	3972.4(8)	404(4)
C(28)	6703.4(15)	-260(2)	5659.0(6)	348(3)
C(41)	5542.6(13)	6663.4(18)	4123.3(6)	285(3)
C(42)	7360.2(13)	4964.9(16)	4505.9(6)	248(3)
O(43)	8416.8(10)	4604.6(16)	4413.0(5)	386(3)
O(44)	6904.1(10)	5157.6(14)	5069.1(4)	323(2)
C(45)	7736.6(17)	4769(2)	5577.9(7)	425(4)

Key to superscripts on atoms with refinement constraints/restraints:

d - distance or angle restraint on site

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	251.0(15)	208.7(16)	141.4(13)	-8.7(10)	8.7(10)	45.4(11)
O(1)	281(5)	428(6)	249(5)	-99(4)	-67(4)	146(4)
C(1)	212(5)	220(6)	142(5)	-8(4)	6(4)	-8(4)
O(2)	516(6)	201(5)	214(4)	29(4)	104(4)	3(4)
C(2)	207(5)	218(6)	158(5)	-9(4)	13(4)	-5(4)
N(3)	228(5)	250(6)	183(5)	4(4)	34(4)	10(4)
C(4)	264(6)	226(6)	156(5)	-15(4)	3(4)	17(5)
C(5)	300(6)	213(6)	166(5)	-17(4)	21(4)	-27(5)
C(11)	210(5)	188(6)	146(5)	0(4)	16(4)	13(4)
C(12)	201(6)	240(6)	310(6)	-17(5)	25(5)	-22(5)
C(13)	236(6)	319(8)	448(8)	-32(6)	32(6)	78(5)
C(14)	408(8)	208(7)	329(7)	-9(5)	-11(6)	77(6)
C(15)	365(7)	205(6)	262(6)	21(5)	-11(5)	-59(5)
C(16)	231(6)	249(6)	223(6)	11(5)	32(4)	-31(5)
C(21)	234(6)	201(6)	189(5)	-4(4)	5(4)	-15(4)
N(22)	272(5)	258(6)	237(5)	3(4)	39(4)	30(4)
C(23)	269(6)	248(7)	308(7)	-6(5)	14(5)	27(5)
C(24)	303(7)	278(7)	282(6)	41(5)	-21(5)	39(5)
C(25)	307(7)	242(7)	207(6)	15(5)	-11(5)	-17(5)
N(26)	261(5)	230(5)	188(5)	17(4)	21(4)	-4(4)
C(27)	361(8)	392(9)	462(9)	15(7)	86(7)	130(7)
C(28)	431(8)	387(8)	226(6)	80(6)	36(6)	29(7)
C(41)	363(7)	276(7)	216(6)	-25(5)	-2(5)	89(6)
C(42)	312(7)	235(6)	194(5)	-34(4)	-25(5)	0(5)
O(43)	288(5)	553(7)	313(5)	-73(5)	-54(4)	44(5)
O(44)	418(6)	385(6)	164(4)	-18(4)	-41(4)	70(5)
C(45)	592(11)	463(10)	214(7)	0(6)	-134(7)	58(8)

Table 4. Hydrogen atom co-ordinates (x 10^3) and isotropic displacement parameters ($Å^2$ x 10^2) with s.u.s in parentheses.

	x	y	z	U_{eq}
H(1)	806.1	312.7	335.5	23.
H(2)	578.4	171.	339.6	23.
H(3)	537.2(14)	333.(2)	431.1(6)	26.
H(5a)	768.6	584.6	337.9	27.
H(5b)	636.5	565.7	306.3	27.
H(12)	932.6	178.9	219.6	30.
H(13)	1011.1	-80.7	197.4	40.
H(14)	881.3	-307.1	193.1	38.
H(15)	673.8	-277.7	210.9	33.
H(16)	593.8	-18.5	234.	28.
H(24)	868.4	-154.5	509.6	35.
H(27a)	977.5	-118.7	354.1	61.
H(27b)	961.5	-262.7	402.	61.
H(27c)	1045.5	-109.9	418.8	61.
H(28a)	695.8	64.	592.3	52.
H(28b)	700.8	-128.8	582.8	52.
H(28c)	581.8	-29.5	563.	52.
H(41a)	493.1	676.2	379.7	43.
H(41b)	604.4	764.6	413.6	43.
H(41c)	514.	653.1	451.1	43.
H(45a)	787.6	359.2	559.2	64.
H(45b)	738.	512.4	595.8	64.
H(45c)	850.8	533.2	552.3	64.

Table 5. Interatomic distances (Å) with s.u.s in parentheses.

S(1)-O(2)	1.4650(10)	S(1)-O(1)	1.4662(10)
S(1)-C(11)	1.7795(12)	S(1)-C(1)	1.8174(12)
C(1)-C(5)	1.5592(18)	C(1)-C(2)	1.5708(16)
C(2)-N(3)	1.4909(16)	C(2)-C(21)	1.5473(17)
N(3)-C(4)	1.4931(17)	N(3)-H(3)	0.861(13)
C(4)-C(41)	1.5435(18)	C(4)-C(5)	1.5557(17)
C(4)-C(42)	1.5625(18)	C(11)-C(16)	1.4024(17)
C(11)-C(12)	1.4143(17)	C(12)-C(13)	1.402(2)
C(13)-C(14)	1.405(2)	C(14)-C(15)	1.404(2)
C(15)-C(16)	1.409(2)	C(21)-N(22)	1.3556(16)
C(21)-N(26)	1.3590(15)	N(22)-C(23)	1.3632(18)
C(23)-C(24)	1.4137(19)	C(23)-C(27)	1.522(2)
C(24)-C(25)	1.410(2)	C(25)-N(26)	1.3678(17)
C(25)-C(28)	1.5243(19)	C(42)-O(43)	1.2265(17)
C(42)-O(44)	1.3623(16)	O(44)-C(45)	1.4718(18)

Table 6. Angles between interatomic vectors (°) with s.u.s in parentheses.

O(2)-S(1)-O(1)	118.70(7)	O(2)-S(1)-C(11)	107.12(6)
O(1)-S(1)-C(11)	108.52(6)	O(2)-S(1)-C(1)	106.25(6)
O(1)-S(1)-C(1)	109.04(6)	C(11)-S(1)-C(1)	106.59(6)
C(5)-C(1)-C(2)	105.40(9)	C(5)-C(1)-S(1)	108.77(8)
C(2)-C(1)-S(1)	114.81(8)	N(3)-C(2)-C(21)	114.97(10)
N(3)-C(2)-C(1)	104.25(10)	C(21)-C(2)-C(1)	111.82(10)
C(2)-N(3)-C(4)	108.11(9)	C(2)-N(3)-H(3)	111.4(11)
C(4)-N(3)-H(3)	112.0(11)	N(3)-C(4)-C(41)	110.86(11)
N(3)-C(4)-C(5)	101.06(9)	C(41)-C(4)-C(5)	113.04(10)
N(3)-C(4)-C(42)	109.89(10)	C(41)-C(4)-C(42)	111.92(10)
C(5)-C(4)-C(42)	109.54(10)	C(4)-C(5)-C(1)	103.90(10)
C(16)-C(11)-C(12)	121.57(11)	C(16)-C(11)-S(1)	119.91(9)
C(12)-C(11)-S(1)	118.49(9)	C(13)-C(12)-C(11)	119.01(12)
C(12)-C(13)-C(14)	119.83(13)	C(15)-C(14)-C(13)	120.79(13)
C(14)-C(15)-C(16)	120.03(12)	C(11)-C(16)-C(15)	118.78(12)
N(22)-C(21)-N(26)	127.18(12)	N(22)-C(21)-C(2)	116.32(10)
N(26)-C(21)-C(2)	116.43(11)	C(21)-N(22)-C(23)	116.33(11)
N(22)-C(23)-C(24)	120.80(12)	N(22)-C(23)-C(27)	116.74(12)
C(24)-C(23)-C(27)	122.46(13)	C(25)-C(24)-C(23)	118.74(12)
N(26)-C(25)-C(24)	120.50(12)	N(26)-C(25)-C(28)	116.98(12)
C(24)-C(25)-C(28)	122.51(12)	C(21)-N(26)-C(25)	116.42(11)
O(43)-C(42)-O(44)	123.65(12)	O(43)-C(42)-C(4)	125.20(12)
O(44)-C(42)-C(4)	111.07(11)	C(42)-O(44)-C(45)	115.76(12)