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Polypharmacology Approaches for Treatment of Idiopathic Pulmonary Fibrosis

A thesis submitted in partial fulfilment towards the degree of Doctor of Philosophy

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“The gratification comes in the doing, not in the results.”

James Dean, 1955

Abstract

Idiopathic pulmonary fibrosis (IPF) is a severe lung disease with a poor survival rate and it currently has no known cure. In this thesis, the signs and symptoms, diagnosis and epidemiology of IPF are discussed. Existing therapies for IPF are highlighted herein as well as new small molecule targets such as acylidene oxindoles, isatins and natural products such as febrifugine. These novel compounds can potentially be used for polypharmacology approaches for IPF treatment.

The preparation of isatin analogues has been explored with the motivation to screen them as potential treatments for IPF. Several types of biological and pharmacological activities are also associated with isatin derivatives which highlight their potential as novel drugs for the treatment of a number of diseases. Various methods for the synthesis of isatin have been reported which include early protocols involving aniline derivatives, the oxidation of indole, as well as more modern procedures employing transition metal catalysis. Previously reported strategies suffer from many disadvantages such as low yielding multi-step approaches and use of harsh conditions and toxic reagents which warrants a novel and much improved strategy.

In this research, a palladium-catalyzed cyclization of *o*-alkynylnitrobenzenes has been employed for the synthesis of different isatin analogues. An alternative strategy was developed in which a copper-catalyzed cycloisomerization of *o*-alkynylnitrobenzenes afforded 2-iodoisatogens in good yields. The corresponding isatins were then obtained via the reduction of the novel 2-iodoisatogens in a very efficient manner. In addition, alternative nitrogen-containing heterocycles have been prepared from 2-iodoisatogens to demonstrate the versatility of these substrates.

Finally, the preparation of febrifugine analogues has been explored with the incentive to identify polypharmacological mixtures of molecules which could potentially be combined into a single molecule. Using the reported model for the binding of febrifugine with its target receptor site, different analogues were designed to interrogate binding and potentially improve biological activity.

Acknowledgements

There's the old cliché "a journey of a thousand miles begins with a single step" and this thesis represents the culmination of a journey that started a few years back. I have so many people to thank for being a part of this extraordinary journey and I am indebted to every single one of you for supporting me every step of the way.

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Lastly, to my loved ones, I am so lucky to have you supporting me throughout this extraordinary journey called life. All that I do is to bring honour to our family and hopefully I have made you proud. I dedicate this thesis and this PhD to you.

Abbreviations

AA-AMP	aminoacyl adenylate
aq.	Aqueous
ATP	Adenosine triphosphate
n-Bu	*normal*-Butyl
t-Bu	*tert*-Butyl
cat.	catalytic
CI	Chemical Ionisation
DCM	dichloromethane
DIPA	diisopropylamine
DMAc	dimethylacetamide
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EDG	electron donating group
EI	electron impact
eq.	equivalents
EWG	electron withdrawing group
FAB	Fast Atom Bombardment
FTIR	Fourier Transform Infrared
h	hour(s)
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
HBTU	(2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide

HRMS	High-Resolution Mass Spectrum
Hz	Hertz
IBX	2-iodoxy benzoic acid
IPF	Idiopathic Pulmonary Fibrosis
J	coupling constant
LC-MS	Liquid Chromatography Mass Spectrum
m-CPBA	*meta*-chloroperoxybenzoic acid
mins.	minutes
mol	moles
m.p.	melting point
µw	microwave
MHz	mega-Hertz
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	nanometre
NMR	Nuclear Magnetic Resonance
PBPB	pyridinium bromide perbromide
ppm	parts per million
ProRS	prolyl-transfer RNA synthetase
RSM	recovered starting material
rt	room temperature
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
TMSA	trimethylsilylacetylene
tRNA	transfer ribonucleic acid

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Chapter 1: Idiopathic Pulmonary Fibrosis

Introduction

Idiopathic Pulmonary Fibrosis (IPF), also known as cryptogenic fibrosing alveolitis (CFA) is a clinical disease that belongs to a group of acute and chronic lung disorders referred to as interstitial lung diseases (ILDs). These interstitial pneumonias have varying degrees of pulmonary inflammation and scarring of lung tissue and IPF is one of a few cases where the origin of the disease is unknown, hence it is referred to as 'idiopathic'. Whilst major progress has been achieved over the past few years in our understanding of the pathogenesis of lung fibrosis, the diagnosis and treatment of patients with IPF remain significantly challenging and the cure for IPF continues to evade researchers. Hence, in 1999 a joint effort by the American Thoracic Society (ATS), European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP), resulted to an international consensus statement to define the epidemiology, diagnosis and management of IPF.[1]

According to the released statement, the definition of IPF is the chronic scarring of lung tissue in the interstitium which refers to the collection of support tissues within the lung surrounding the air sacs. Upon lung biopsy, a characteristic histopathological appearance of usual interstitial pneumonia (UIP) will be observed, although the etiology or cause remains unknown. IPF can only be diagnosed if UIP is evident from a high resolution CT scan or surgical lung biopsy and all the other known causes of interstitial lung diseases have been excluded. This includes usual recognised causes such as drug induced toxicities, environmental exposure to substances (e.g. asbestos) and finally, connective tissue disease.[1]

Common signs and symptoms associated with IPF include progressive exertional dyspnea which is shortness of breath when physically active. A persistent, dry and non-productive cough is observed in patients and there is an increased risk of developing chest infection. A distinct crackling sound in the lungs that can be associated with the

sound of Velcro being torn apart slowly is also characteristic and is used for the early diagnosis of IPF. Finally, chronic deficiency of oxygen in the blood may also lead to thickening and hardening of tissue at the base of finger and toe nails which causes disfigurement or clubbing of the digits.[2]

Patients diagnosed with IPF tend to be over the age of 50 although this is not a major criterion for diagnosis. Studies show that IPF is more prevalent with males than females and is more common with middle aged patients than children where diagnosis is very rare. In terms of geographical location or ethnicity, there is no general trend although variation is manifested by occupational or environmental exposures. The mortality rate for IPF is estimated to be 5-7 per 100,000 people and the length of survival from the time of diagnosis is 3-5 years.[1]

Current Treatments

The scarring of the lung tissue referred to as fibrosis is as a result of the production of fibroblasts going out of control as the body's response to repair damaged and inflamed alveolar epithelial cells. Since the cause of the initial inflammation is not known to begin with, strategies to treat IPF have been based on supressing the inflammation since there is currently no evidence that the fibrotic process can be reversed.[3] Realistically, existing treatments for IPF only involve reducing the symptoms, preventing acute exacerbations and essentially prolonging survival. Nonetheless, a few existing anti-inflammatory and antifibrotic drugs have been used for therapy over the years.

Initially, corticosteroids such as Prednisolone have been considered for therapy due to their anti-inflammatory effects but studies carried out as recently as 2010 have revealed that they have no beneficial effects in patients with IPF.[4] Similarly, the initial potential of immunosuppressant drugs such as Azathioprine and Cyclophosphamide to treat IPF was recently rendered as debatable.[4] Antioxidant drugs such as N-

acetylcysteine have also been studied based on the hypothesis that oxidant-induced epithelial cell injury could be repaired but placebo-controlled studies conducted in 2014 revealed “no significant benefit”.[5] Moreover, Etanercept, which is a type of antagonist for Tumour Necrosis Factor (TNF), has been used as an anti-inflammatory for arthritis and psoriasis but proved to be ineffective for IPF treatment.[4]

Anticoagulants such as Warfarin and Heparin have been tested to determine whether anticoagulant therapy with Prednisolone increases survival time of IPF patients but the trials had to be terminated due to increased mortality rates during the study.[6] Bosentan, a dual antagonist of endothelin 1A and B receptors, was also tested due to its known effectiveness in treating pulmonary artery hypertension but proved to be ineffective for IPF treatment.[7] A phosphodiesterase-5 inhibitor, Sildenafil, was hypothesised to improve gas exchange and reduce shortness of breath with IPF patients due to its ability to induce pulmonary vasodilation but again, showed negative results.[8] Moreover, Imatinib mesylate, which is a tyrosine kinase inhibitor demonstrated good inhibition of lung fibrosis in animals but proved to be ineffective in the subsequent clinical trials.[9]

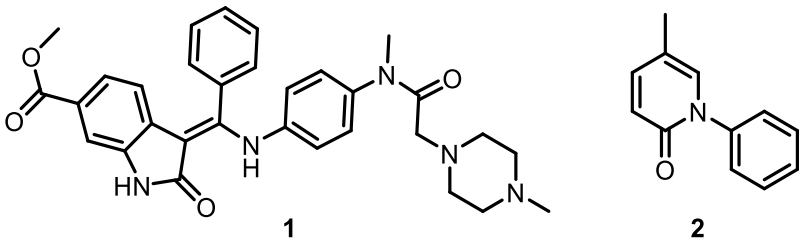


Figure 1

Nintedanib **1**, another tyrosine kinase inhibitor, targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet derived growth factor receptor (PDGFR). Formerly known as BIBF 1120, it was a clinical candidate for the treatment of nonsmall cell lung cancer alongside a similar analogue named BIBF 1000.[10] Nintedanib is a 6-substituted indolinone and its synthesis has been designed by Roth and co-workers in their research towards designing triple angiokinase

inhibitors.[11] Tyrosine kinases have previously been associated with the pathogenesis of IPF since they mediate fibroblast proliferation and differentiation therefore inhibitors such as Nintedanib are useful targets for IPF treatment.[12] Preliminary tests with mouse models of lung fibrosis indicated antifibrotic and anti-inflammatory activity of Nintedanib as a result of reduced levels of cytokines in the lung tissue.[12] Phase III clinical trials showed that there was a reduced decline in lung function in the Nintedanib group by around 50% compared to the placebo group which led to its approval by the FDA in 2014.[12]

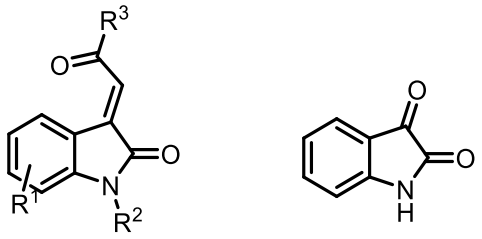
Initial studies have shown that Pirfenidone **2** demonstrates antifibrotic effects in animal models in addition to its anti-inflammatory and antioxidant properties. In these preliminary studies, it has been revealed that Pirfenidone inhibits transforming growth factor-β which is one of the several growth factors and cytokeins that initiate the migration and proliferation of fibroblasts.[13] Two subsequent phase III clinical trials then showed that Pirfenidone reduced disease progression by significantly decreasing the decline in Forced Vital Capacity (FVC) which was associated with decreased mortality.[14] This led to the drug being approved in Japan in 2008 but a third phase III clinical trial in 2011 failed to demonstrate a reduction in the deterioration of lung function and the FDA required further studies before approval.[15] In 2014, results of a randomized, double-blind, placebo-controlled trial were reported wherein 48% of the Pirfenidone group exhibited decrease in FVC decline compared to the placebo group. Although minor skin-related and gastrointestinal side-effects were reported with the Pirfenidone group, these seldom required treatment discontinuation therefore Pirfenidone was finally approved by the FDA for IPF treatment.[16]

Other Potential Targets

Various potential IPF treatments with different hypothesized mechanisms of action are still undergoing phase II or III clinical trials and results are expected by 2018. For instance, FG-3019 (FibroGen) is being investigated for its effectiveness in inhibiting Connective Tissue Growth Factor (CTGF) which plays roles in proliferation and differentiation of fibroblast.[3] Bristol-Myers Squibb is currently evaluating an antagonist of

Lysophosphatidic Acid Receptor-1 (LPA1) which is known to promote fibroblast migration and activation among other profibrotic effects.[3] Finally, Simtuzumab is undergoing phase II trials to test inhibition of lysyl oxidase-like 2 (LOXL2) which is a promoter of myofibroblast differentiation that can lead to fibrosis progression.[3]

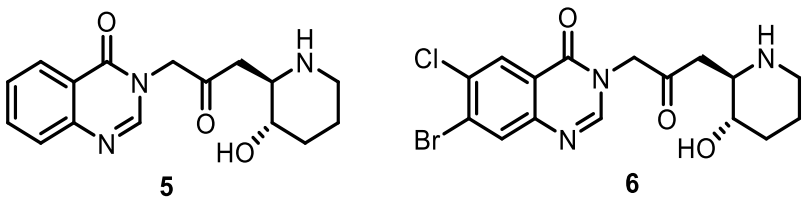
Klock recently reported the new roles of 3-acylidene-2-oxindoles **3** as potential inhibitors of human transglutaminase 2 (TG2).[17] TG2 is a multifunctional enzyme that has been implicated in the pathogenesis of multiple disorders including cystic fibrosis.[18] Moreover, Klock described the potential of isatin (indoline-2,3-dione) **4** as a candidate TG2 inhibitor due to the presence of the cyclic α-keto amide that could mimic the γ-carboxamide moiety of TG2 inhibitors.[17] Although TG2 has not been directly associated as a target for idiopathic pulmonary fibrosis, analogues of 3-acylidene-2-oxindoles and isatins could be interesting compounds to test for activity as potential IPF treatment.



3 **4**

Figure 2

Finally, febrifugine **5** and the related analogue halofuginone **6** have been primarily considered as treatments for malaria and they have been shown to target human prolyl-transfer RNA synthetase (ProRS), an important enzyme for protein synthesis. Febrifugine and halofuginone have demonstrated potential therapeutic applications in cancer and cystic fibrosis, but have not been directly considered as potential IPF treatments.



5 **6**

Figure 3

Chapter 2: Synthesis of Azaisatins

Introduction

Isatin (1*H*-indole-2,3-dione) is an indole derivative discovered independently by Erdman[19] and Laurent[20] in 1841 via the oxidation of indigo dye with nitric acid or chromic acids. The ring system of isatin comprises a pyrrole fused with benzene and it contains both the keto and lactam moiety which is significant for its biological activity.[21] In 1882, Baeyer distinguished two tautomers of isatin either as the lactam **4** or the lactim structure **7** (Figure 4).[22] At room temperature, isatin exists as a yellowish-red crystalline solid that is soluble in hot water, alcohol, acetic acid and benzene.

4 **7**

Figure 4

In Nature, the compound exists in plants such as *Isatis tinctoria* (Asp of Jerusalem),[23] in the orchid *Calanthe discolour,*[24] and in *Couroupita guianensis* (Cannonball tree).[25] Substituted isatins have also been found in plants and fungi such as the methoxy phenylpentyl isatins from *Melochia tomentosa*[26] and the methylbutenyl isatins isolated from *Streptomyces albus*[27] and *Chaetomium globosum.*[28] Furthermore, isatin can be found in the animal kingdom as a component of the parotin gland secretion from some species of *Bufo* frogs.[29] In addition, isatin has been found in humans as a metabolic derivative of adrenaline.[30]

Isatin and its metabolites are components of naturally occurring substances and as endogenous compounds, they have a wide spectrum of behavioural and metabolic effects. In the human body, they have a variety of biological targets and they have potential roles as functional agonists or antagonists.[31] As well as endogenous isatin, synthetic isatin derivatives are also known to exhibit a wide range of pharmacological

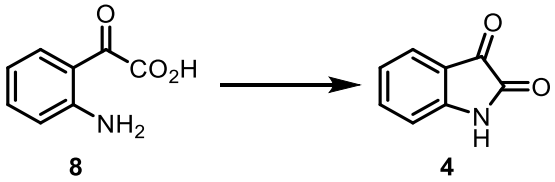
effects such as antimicrobial, antifungal, antiviral, anti-inflammatory, antidepressant and antianxiety. Moreover, the isatin moiety has been found in a range of compounds which are potential treatments for tuberculosis, HIV and cancer.

Isatins are known to be synthetically versatile substrates utilized as starting materials for the synthesis of a broad range of heterocyclic compounds such as indoles and quinolones.[21] In addition, the biological and pharmacological properties of some of their derivatives make them ideal substrates for the synthesis of potential new drugs. As a consequence of their synthetic versatility and their manifold significance in the field of medicinal chemistry, extensive research has been carried out to develop methods for the synthesis of this class of compound.[21] Since classical methods suffer from a few limitations including multistep sequences, toxic reagents, low reaction scope and harsh conditions, novel strategies are required to address these issues.

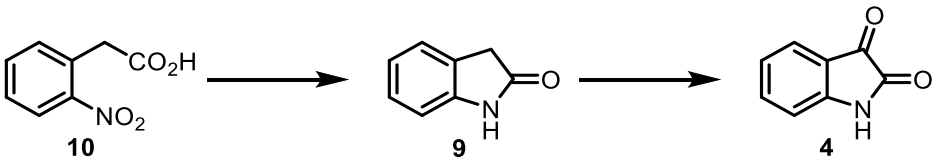
Synthetic Routes to Isatin

Early Methods

A review, published in 1944, by Sumpter summarizes early methodologies for the synthesis of isatin from the late 19th century when it was first discovered, up until the early 20th century.[22]

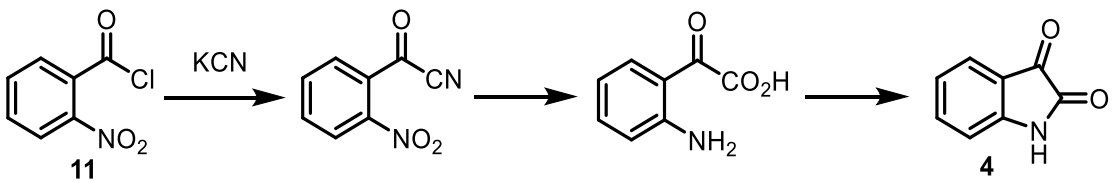


Scheme 1



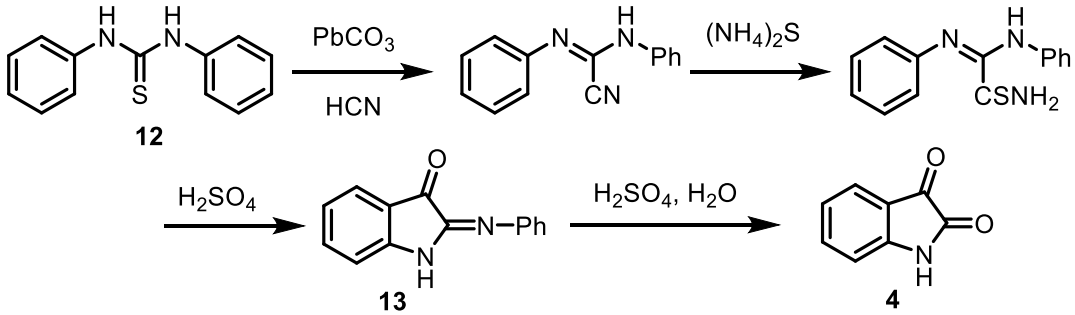
Scheme 2

In 1869, Kekule proposed that isatic acid was *o*-aminobenzoylformic acid and that the corresponding lactam was isatin, hence instigating the idea for the synthesis of isatin from *o*-aminophenylacetic acid **8** (Scheme 1).[32] Over a decade later, Baeyer confirmed Kekule's suggestion by synthesizing isatin from oxindole **9** which was in turn made via the reduction of *o*-nitrophenylacetic acid **10** (Scheme 2).[33] Furthermore, Claisen and Shadwell reported the preparation of isatin from *o*-nitrobenzoyl chloride **11** in 1879 which also confirmed Kekule's suggested structure (Scheme 3).[34] In 1884, Forrer also proposed a methodology based on the action of alkali on *o*-nitrophenylpropiolic acid.[35]

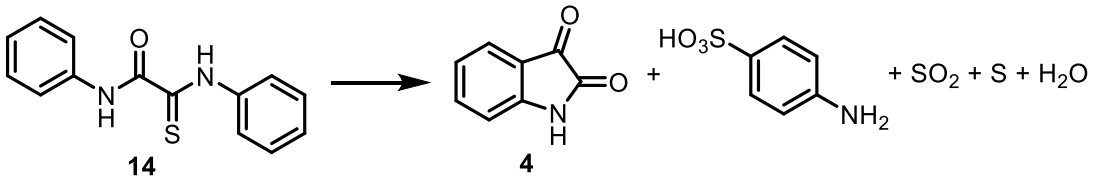


Scheme X

Sandmeyer's route, published in 1919, is commonly regarded as the oldest method for the synthesis of isatin.[22] However, an earlier procedure by Sandmeyer was actually reported in 1903 which involves thiocarbanilide **12** as the starting material and isatin-α-anilide **13** as an intermediate (Scheme 4).[36] A year later, Reissert developed a method which depends on heating thiooxanilide **14** with concentrated sulfuric acid (Scheme 5).[37] Bauer also utilized sulfuric acid for his synthesis which involves substituted imidoyl chlorides of oxalic acid.[38]

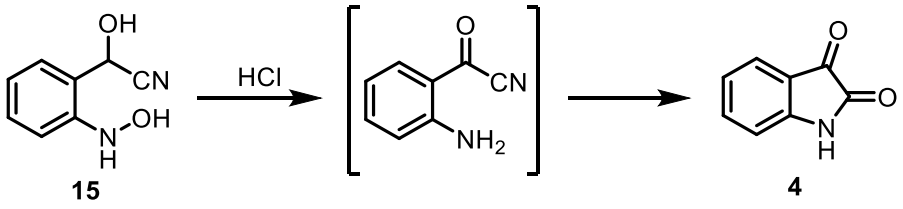


Scheme 4



Scheme 5

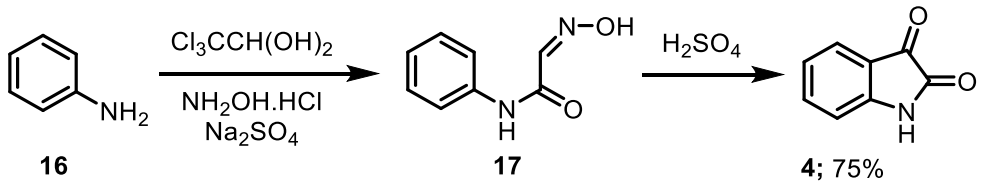
Heating *o*-hydroxylaminomandelonitrile **15** with hydrochloric acid was the basis for Heller's synthesis of isatin in 1906 (Scheme 6).[39] Succharda then obtained isatin-7-sulfonic acid via the oxidation of quinoline-8-sulfonic acid with alkaline potassium permanganate.[22] Burton and Stoves' methodology in 1937 also used alkali for the reaction with the azalactones of certain *o*-nitrobenzaldehydes.[40] Finally, in 1939, Fetscher and Bogert reported the synthesis of isatin from ethyl-6-aminoveratrate.[41]



Scheme 6

Sandmeyer's Method

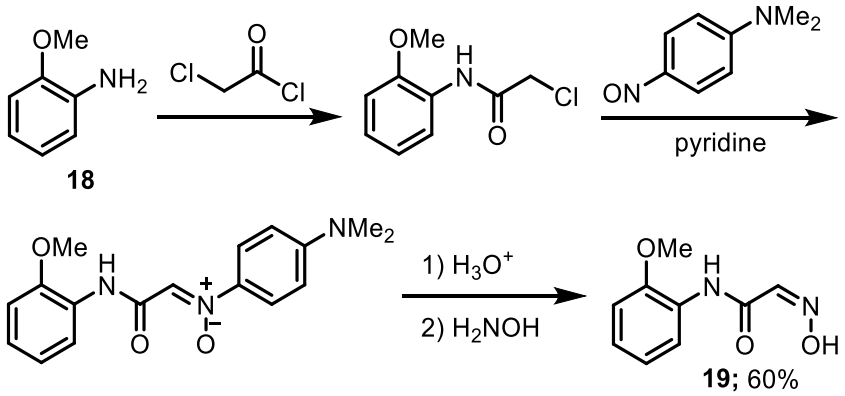
Sandmeyer's second, more well-known methodology for the synthesis of isatin is the most frequently used and has been employed for nearly a whole century (Scheme 7).[21] First reported in 1919, it is based on the reaction of aniline **16** with chloral hydrate and hydroxylamine hydrochloride in the presence of aqueous sodium sulfate.[42] The intermediate isonitrosoacetanilide **17** is then treated with concentrated sulfuric acid to afford isatin in yields usually greater than 75%. This method can be applied effectively with anilines containing electron-withdrawing substituents as well as a few heterocyclic amines such as 2-aminophenoxathine.



16 **17** **4;** 75%

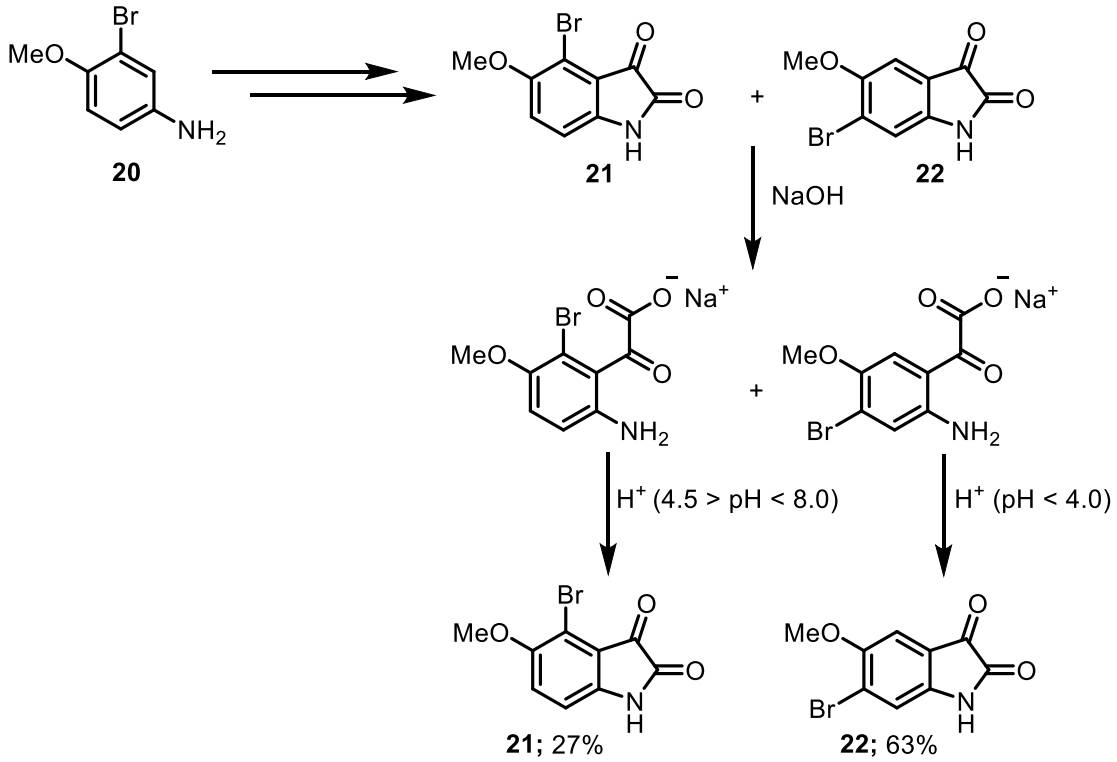
Scheme 7

Whilst this method is attractive from an economic point of view due to inexpensive and readily available starting materials, over the years a few modifications of the Sandmeyer route proved necessary. For example, in cases where the aniline starting material was insoluble using the conventional reaction conditions, ethanol was incorporated as a co-solvent.[43] The usefulness of this modification is most evident in the synthesis of 4,6-dibromoisatin in which a 700% enhancement in yield over the existing procedure was reported. This particular isatin derivative is a key intermediate for the synthesis of the marine natural product convolutamydine A.[44] Other significant modifications include using alternative reagents for the cyclization of the isonitrosoacetanilide other than concentrated sulfuric acid. Lackey's synthesis of benzo-oxygenated isatin derivatives as intermediates for the preparation of camptothecin provided a method which uses boron trifluoride etherate or the less toxic pyrophosphoric acid.[45]

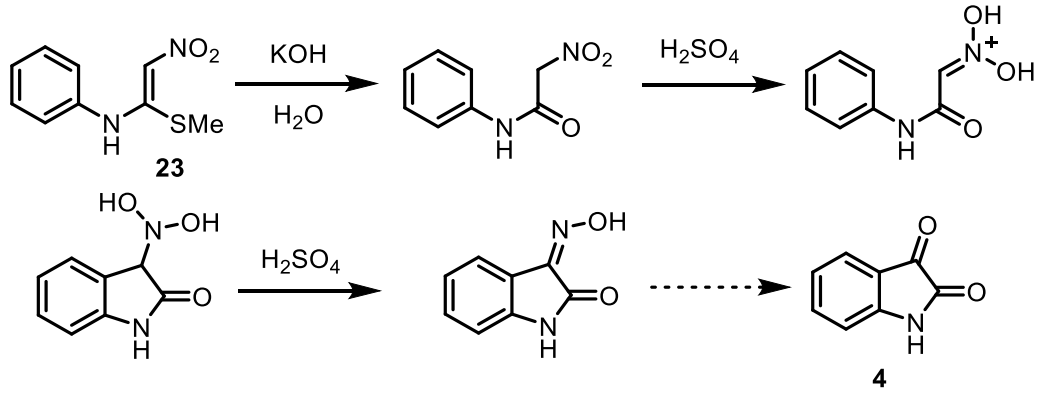


Scheme 8

Another difficulty associated with the Sandmeyer methodology is the ineffectiveness of this route with *ortho*-hydroxy or *ortho*-alkoxyanilines. A modified procedure was reported which involves reacting the alkoxyaniline **18** with chloroacetyl chloride followed by reaction with *N,N*-dimethyl-4-nitroaniline to eventually obtain the isonitroso-acetanilide **19** (Scheme 8).[46] Cyclization is then conducted under the same conditions using concentrated sulfuric acid to afford the corresponding isatins in 87-99% yield. Furthermore, *meta*-substituted anilines are known to yield two isomers, e.g. 3-bromo-4-methoxyaniline **20** gives 6-bromo-5-methoxyisatin **21** and 4-bromo-5-methoxyisatin **22** in a 2:1 ratio.[47] Separating these two isomers involves conversion to the corresponding sodium isatinates followed by acidification of the reaction medium. Controlled acidification will result in the cyclization of the two isomers at different pH values hence generating the corresponding isatins at different rates as they precipitate from the reaction mixture (Scheme 9). Lastly, nitroacetanilides have also been employed in another modified strategy which involves cyclization using sulfuric acid or trifluoromethanesulfonic acid.[48] The nitroacetanilides are obtained via the alkaline hydrolysis of 1-arylamino-1-methylthio-2-nitroethenes **23** (Scheme 10).



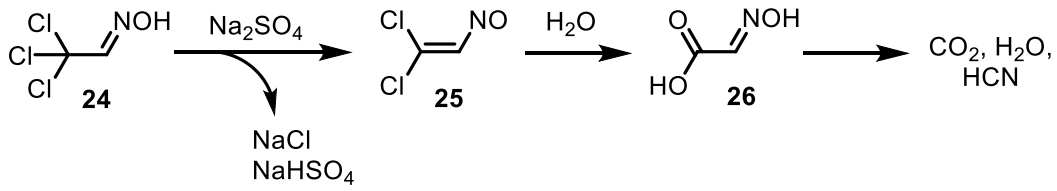
Scheme 9



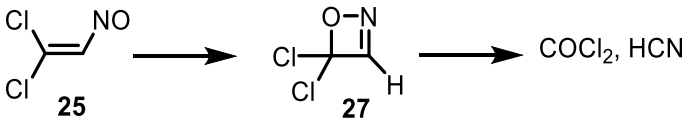
Scheme 10

The use of chloral as a starting material in the Sandmeyer methodology can be problematic, and may lead to the formation of the extremely poisonous gas hydrogen cyanide. Goodwin first detected this colourless liquid via the formation of Prussian blue on addition of ferrous sulfate and sodium hydroxide to the reaction mixture.[49] Gandy and Hill then reported a measured concentration of hydrogen cyanide in the mother liquors from the Sandmeyer reaction which was found to vary from 100 to 200 ppm.[49] A proposed mechanism for the formation of HCN is the addition of water to the nitrosoalkene **24** which yields glyoxylic acid oxime **25** that would decarboxylatively

decompose to water and HCN (Scheme 11).[50] Another reported mechanism is the decomposition of the nitrosoalkene via the formation of an oxazete **27** and subsequent retro-cyclization to yield carbonyl chloride and HCN (Scheme 12).[51] It is, therefore, highly recommended to take reasonable precautions when using the Sandmeyer procedure in the synthesis of isonitrosoacetanilides.



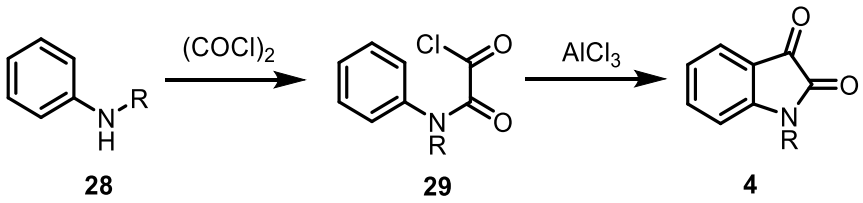
Scheme 11



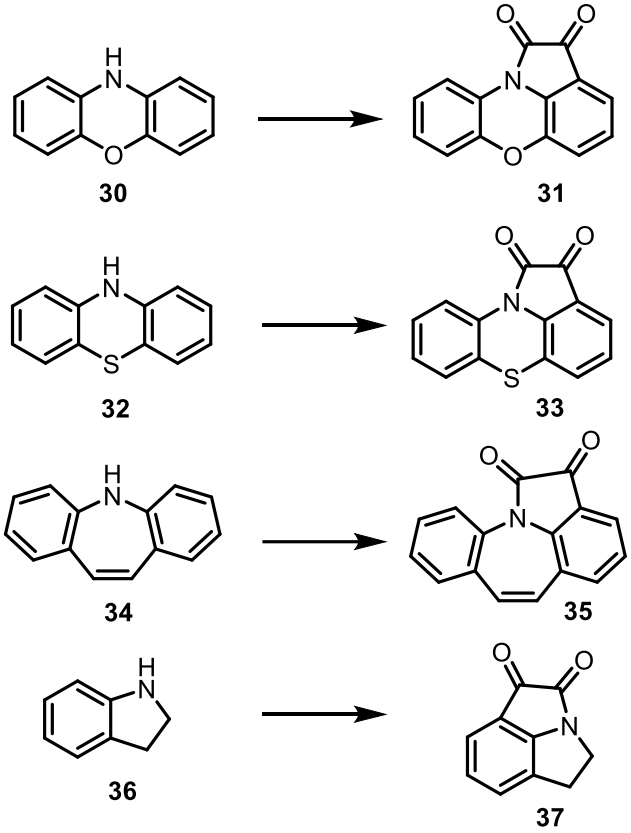
Scheme 12

Stolle's Method

A convenient methodology for the preparation of isatin derivatives was reported by Stolle and is regarded as the most important alternative to Sandmeyer's route. This synthesis involves the treatment of *N*-substituted anilines **28** with oxalyl chlorides resulting in a chlorooxalylanilide intermediate **29** which cyclizes to the isatin by treatment with anhydrous aluminium chloride (Scheme 13).[52] Other Lewis acids have also been employed in this reaction such as boron trifluoride diethyl ether complex[53] and titanium tetrachloride.[54] In some cases, spontaneous cyclization has also been observed in the absence of a Lewis acid; for example in the reaction of 2,3-dimethoxyaniline to afford the 2,3-dimethoxyisatin, albeit this transformation occurs in a diminished yield.[26] Using Stolle's method, the synthesis of polycyclic isatins has been accomplished from phenoxazine **30**, phenothiazine **32** and dibenzazepine **34** as reported by Silva.[55] Furthermore, Welstead has also reported a synthesis of isatin derived from indoline **36** which was used as a key intermediate for the preparation of an anti-inflammatory agent (Scheme 14).[56]



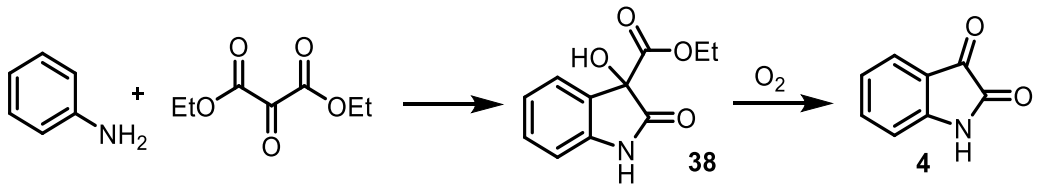
Scheme 13



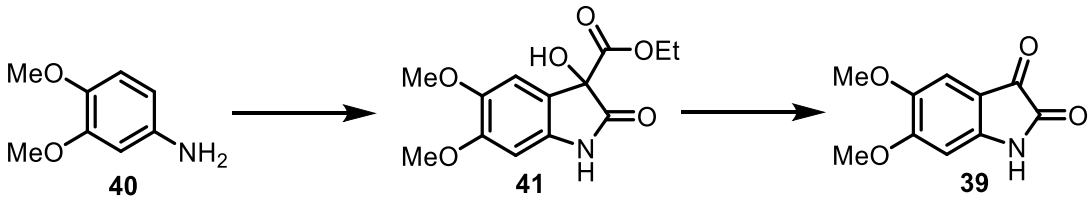
Scheme 14

Martinet's Method

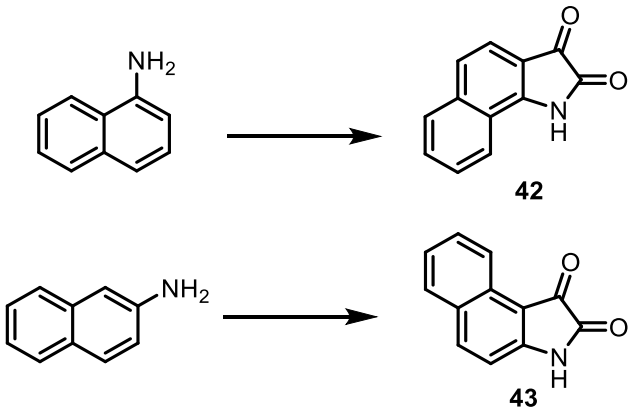
Martinet's original procedure for the synthesis of isatin derivatives involved aniline but is now applied to any substituted aromatic amine and their reaction with either the ethyl or the methyl ester of oxomalonic acid.[57] The condensation reaction proceeds in the presence of an acid to yield a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative **38** which in turn yields a dioxindole on treatment with alkali in the absence of oxygen. However, on treatment with alkali in the presence of air, oxidative decarboxylation takes place hence affording the isatin (Scheme 15). Examples of using Martinet's procedure include the synthesis of 5,6-dimethoxyisatin **39** from 4-aminoveratrole **40** (Scheme 16)[58] as well as the synthesis of α-**41** and β-naphthisatins **42** from naphthylamines (Scheme 17).[22]



Scheme 15



Scheme 16



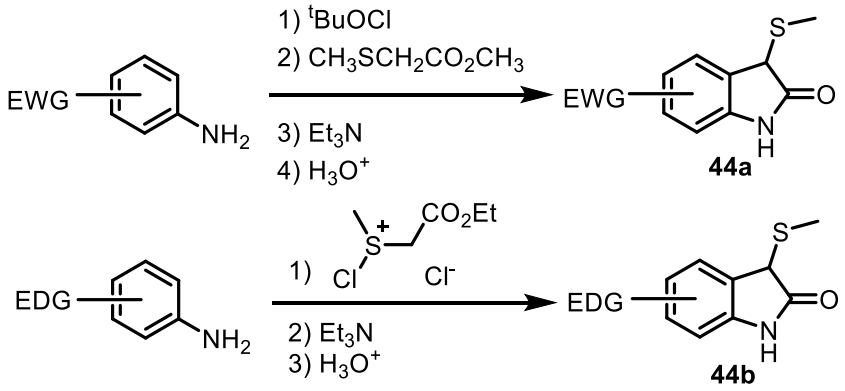
Scheme 17

Gassman's Method

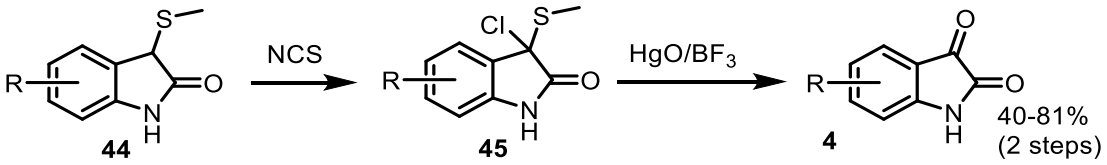
The formation of 3-methylthio-2-oxindoles and their subsequent oxidation is the basis of Gassman's procedure for the synthesis of substituted isatins.[59] In this method, the advantage of not utilizing a strong acid is emphasized which allows tolerance of a wide spectrum of electron-withdrawing and electron-donating substituents. Two corresponding methods for the preparation of the 3-methylthio-2-oxindole intermediate were developed initially and both allow the one-pot conversion of aniline to the required precursor. The procedure used depends on the electronic properties of the aniline substituents.

In the presence of electron-withdrawing substituents, the oxindole precursor **44** can be derived via an *N*-chloroaniline intermediate which is subsequently converted to an azasulfonium salt by treating with methylthioacetate ester (Scheme 18). However,

with electron-donating groups present, destabilization of the *N*-chloro intermediate is observed and it becomes necessary to use a chlorosulfonium salt to react with the appropriate aniline (Scheme 18). To convert the oxindole intermediate to the required isatin, 3-chloro-3-methylthio-2-oxindoles **45** were first synthesized by reaction of the oxindole with *N*-chlorosuccinimide. The hydrolysis step was then achieved in the presence of red mercuric oxide and $BF_3.Et_2O$ in aqueous THF to afford the isatin from good to excellent yields (Scheme 19).[59]

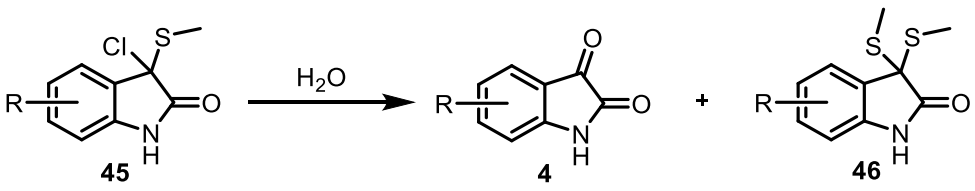


Scheme 18



Scheme 19

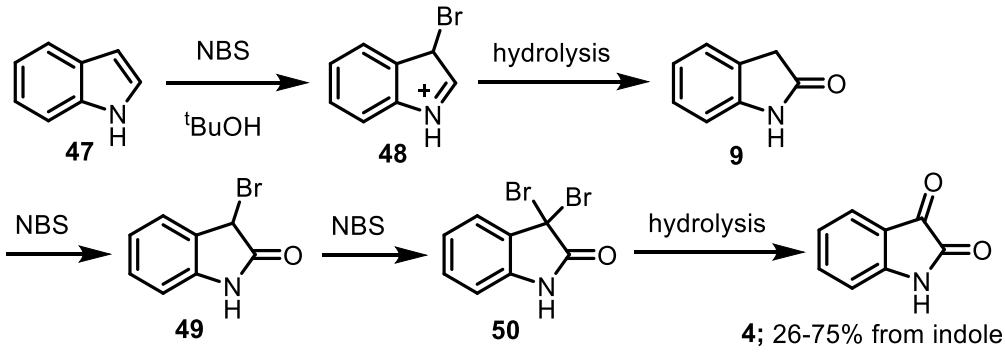
The hydrolysis was also attempted without the presence of the sulfur scavenging red mercuric oxide and boron trifluoride, which resulted in a mixture of the desired isatin and the 3,3-dimethylthio-2-oxindole ketal byproduct **46**.[59] It was presumed that the formation of this dithioketal is due to the reaction of either the isatin or the 3-chloro-3-methylthio-2-oxindole intermediate **45** with the methanethiol generated during the hydrolysis step (Scheme 20).



Scheme 20

Parrick's Method

The synthesis of isatin via the oxidation of the closely related indole is a methodology first reported by Parrick in 1989.[60] Previously, Noland and Rieke disclosed a method using chromium trioxide in acetic acid but these conditions gave poor yields in addition to causing modification of certain substituents.[61] Consequently, Parrick pursued a methodology which employs milder conditions that are applicable to a wider range of indoles. This procedure involves the bromination of either 3-bromoindoles or indoles in aqueous *t*-butyl alcohol followed by hydrolysis in aqueous methanol to furnish the required isatin.

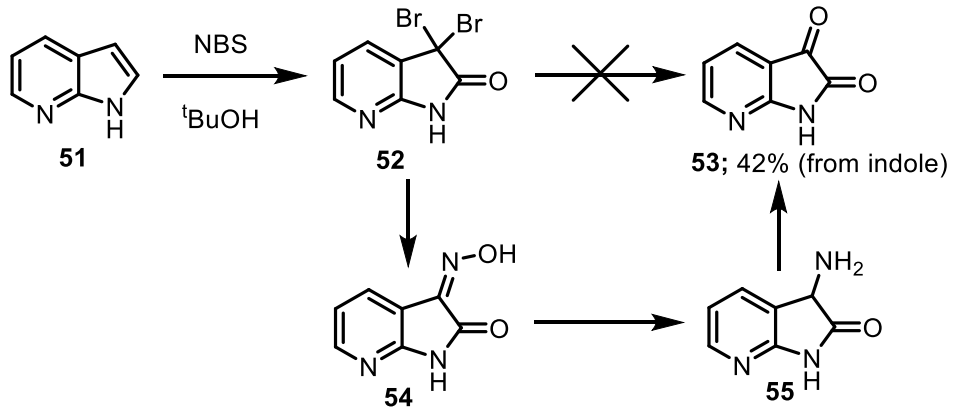


Scheme 21

When 1 equivalent of *N*-bromosuccinimide was used in aqueous *t*-butyl alcohol, the indole **47** was readily oxidized to the corresponding oxindole **48**. Remarkably, the use of 2 equivalents of NBS under mild conditions afforded the 3-bromo-oxindole **49** as the oxindole was brominated *in situ*. It was then conceived that the use of 3 equivalents of NBS would convert indole into 3,3-dibromooxindole **50** in a one-pot process (Scheme 21).

With the 3,3-dibromooxindole intermediate **50** in hand, the subsequent hydrolysis in aqueous methanol proceeded uneventfully producing the required isatin derivatives in excellent yields. However, an attempt to oxidize an azaindole system to the corresponding azaisatin proved to be ineffective using this bromination and hydrolysis sequence. Mild hydrolysis of 3,3-dibromo-7-azaoxindole **52** in aqueous methanol gave a red solid which was presumed to be the 7-azaisatin but all endeavours to isolate and

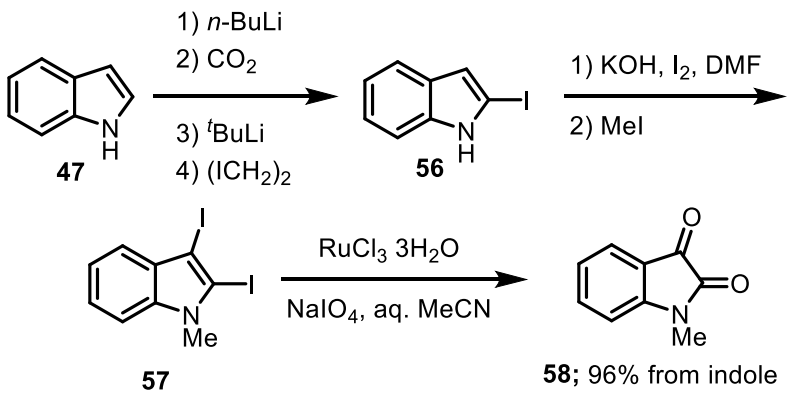
characterize the compound were unsuccessful. Nevertheless, Parrick claimed to have made the 7-azaisatin **53** by firstly converting the dibromo-oxindole **52** into its oxime **54** and subsequently converting the oxime into the isatin via the amine **55** in 42% overall yield (Scheme 22).[60]



Scheme 22

Gribble's Method

Gribble's synthesis of isatin, reported in 2001, involves the preparation of 2- and 3-haloindoles and their subsequent oxidation using a ruthenium catalyst.[62] Khan previously disclosed the conversion of vicinal dihaloalkenes to α-diketones via a ruthenium catalyzed oxidation reaction, which was readily extended to 2,3-dihaloindoles.[63]



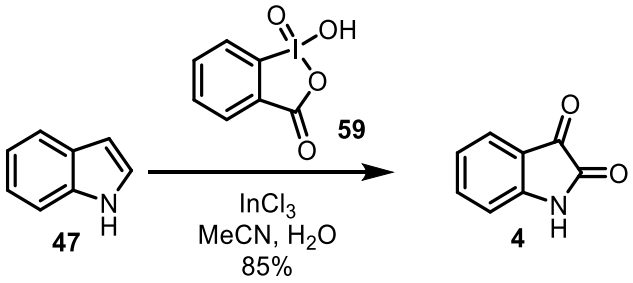
Scheme 23

Initially, Gribble described the preparation of 2,3-dibromo-1-methylindole from indole by employing the Katritzky indole C-2 lithiation protocol followed by Bergman's indole C-2 bromination method.[64] This sequence of reactions furnished 2-bromoindole

and a similar procedure was used in the synthesis of 2-iodoindole **56** which was subsequently iodinated and methylated to yield 2,3-diiodo-*N*-methylindole **57**. This intermediate was then treated with a ruthenium trichloride catalyst in aqueous acetonitrile in the presence of sodium periodate as a co-oxidant to afford the desired *N*-methylisatin **58** in 96% yield (Scheme 23). Beauchard employed Gribble's procedure for the oxidation of 6-nitroindole to the corresponding isatin which was a key intermediate for the synthesis of substituted indigoids.[65]

Yadav's Method

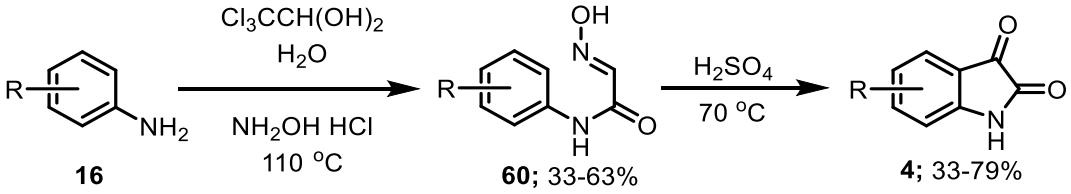
Yadav's procedure, published in 2007, is one of the most recently reported method involving the oxidation of indole to furnish isatin derivatives.[66] In this protocol, indole and azaindoles are oxidized using 2-iodoxybenzoic acid **59** (IBX) in the presence of indium (III) chloride at 80 °C (Scheme 24). The reaction takes place in aqueous media and provides a direct preparation of isatins from indoles in one step. Beauchard also took advantage of this procedure, in addition to Gribble's method, for the synthesis of 6-nitroisatin which was performed under microwave irradiation to give the product in a 54% yield.



Scheme 24

Mamun's Method

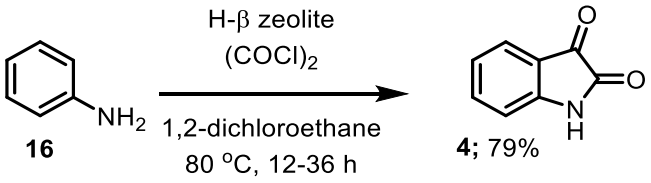
Mamun's microwave assisted synthesis of isatin is claimed to follow the Green Chemistry protocol.[67] Oximinoacetanilides **60** were prepared from primary aromatic amines under microwave irradiation using minimal amount of solvent. The cyclization was then carried out in concentrated H_2SO_4 under microwave irradiation for two 5 second pulses to furnish isatin (Scheme 25). The minimal use of solvent and toxic reagents, very short reaction times and increased yields make this procedure advantageous over classical heating methods as maintained by Mamun.



Scheme 25

Sudalai's Method

A recently published method for the synthesis of isatins involves an H-β Zeolite catalyst and a one-pot procedure.[68] Commercially available anilines are treated with the acylating reagent oxalyl chloride in the presence of the reusable catalyst under heterogeneous conditions (Scheme 26). Absence of the H-β Zeolite catalyst resulted in no reaction while a 10% wt loading proved to be the optimum amount required for the transformation. A wide range of anilines were employed and it was discovered that substrates containing electron withdrawing substituents required longer reaction times and provided the corresponding isatins in lower yields.

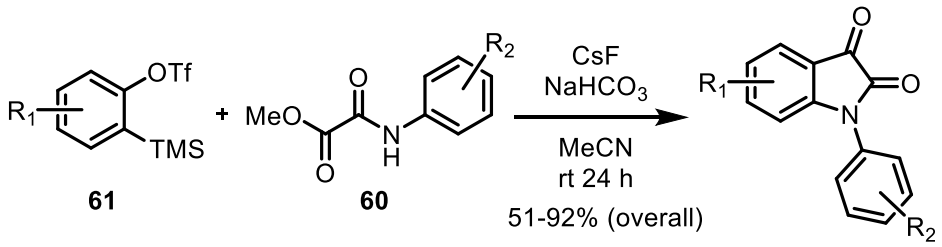


Scheme 26

The solvent of choice for the reaction was 1,2-dichloroethane while other solvents such as acetonitrile and nitrobenzene proved to be ineffective. After the reaction, the catalyst was recovered by simple filtration and calcinated at 823 K in air flow for 6 hours before being used for the next reaction. With aniline as the substrate, the catalyst was found to be active for a minimum of 5 reaction cycles without substantial loss of activity. This procedure is therefore more attractive than using homogeneous Lewis acid catalysts such as $SnCl_4$ and $BF_3.Et_2O$.[68]

Larock's Method

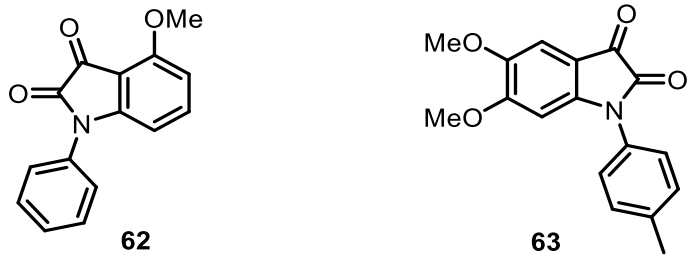
First published in 2011, Larock's methodology involves the synthesis of *N*-arylisatins by the reaction of arynes with methyl oxamates.[69] Aryne methodologies have been particularly useful not only in the synthesis of isatin but also in the preparation of a wide variety of heteroatom containing structures. Larock has previously disclosed related procedures where nucleophilic heteroatoms attack arynes to afford acridones, xanthones, thioxanthones and indoloindolones.[70] For the synthesis of *N*-aryl isatins, various methyl 2-oxo-2-(arylamino)acetates **60** were reacted with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **61** (Scheme 27).



Scheme 27

For the required transformation, 6 equivalents of CsF were needed as well as 2 equivalents of $NaHCO_3$. Acetonitrile proved to be the best solvent while ambient temperatures were found to be more effective than higher temperatures due to the avoidance of unidentified side reactions. A wide range of oxamates were used including substrates with electron-rich and electron-poor substituents giving moderate to excellent

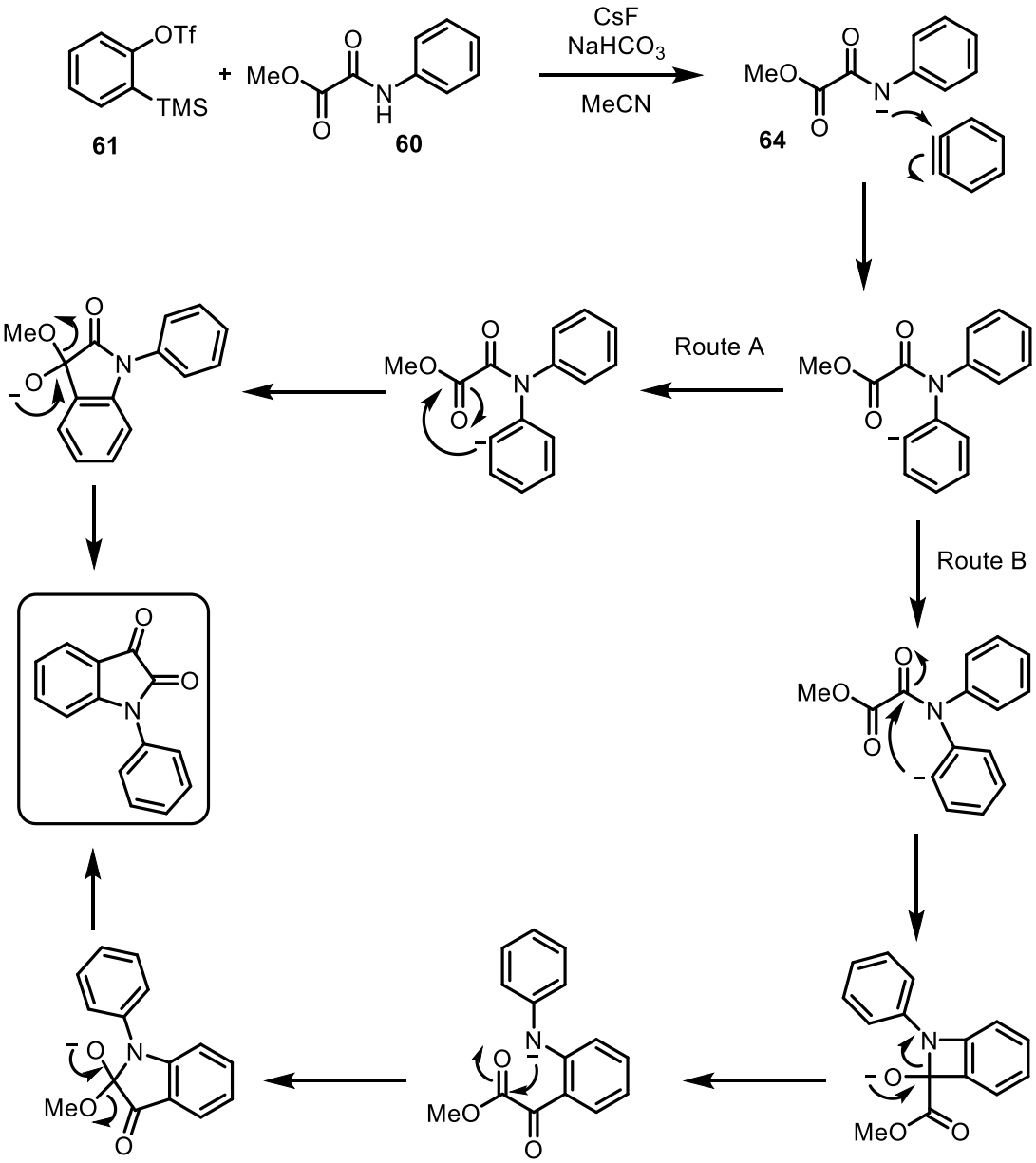
yields. Other benzyne precursors were also examined including unsymmetrical precursors which afforded a single regioisomer **62** in excellent yields, as well as using a symmetrical dimethoxybenzene precursor which produced the corresponding product **63** in an 86% yield (Figure 5).[69]



62 **63**

Figure 5

Two mechanistic pathways were suggested for this process with both routes sharing a common first step and both eventually leading to the desired isatin (Scheme 28). Firstly, an aryl carbanion results from the nucleophilic attack by the nitrogen of 2-oxo-2-(arylamino)acetate **64** on the benzyne. From there, the first possible route involves the attack of the aryl carbanion on the distal ester carbonyl which displaces a methoxy group. The alternative pathway involves attack onto the nearer amide carbonyl group forming a strained four-membered ring which fragments into a keto ester structure where the nitrogen can now attack the ester carbonyl.[69]

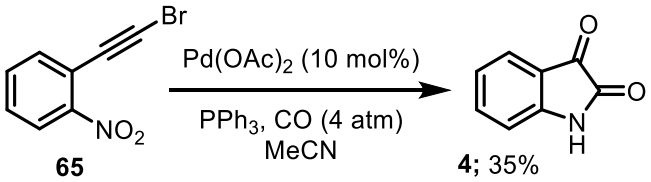


Scheme 28

Söderberg's Method

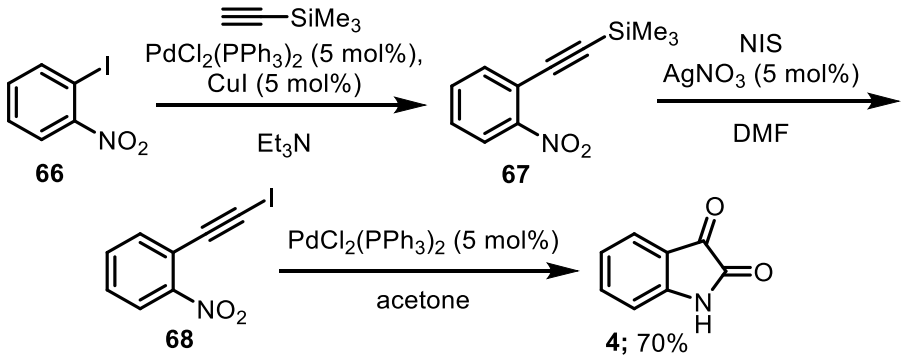
Söderberg's procedure reported in 2009 offers a unique method for the synthesis of isatins in which a palladium catalyst is used for the annulation of 1-(2-haloethynyl)-2-nitrobenzenes.[71] Initially, 1-(2-bromoethynyl)-2-nitrobenzene **65** was reacted with carbon monoxide in the presence of a palladium catalyst to synthesize indole but instead, a new product was observed and this was identified to be isatin (Scheme 29). The conditions for the annulation to form isatin were then optimised by varying the palladium catalyst,

the solvent system and the halogen on the haloethynyl nitrobenzene. Heating 1-(2-iodoethynyl)-2-nitrobenzene **65** to 60 °C with bis(triphenylphosphine) palladium chloride in acetone were found to be the best conditions for the required cyclization step (Scheme 29).



Scheme 29

The first step of this synthesis involves the Sonogashira coupling of 1-halo-2-nitrobenzene **66** with trimethylsilylacetylene to afford 1-[2-(trimethylsilyl)ethynyl] benzene **67** (Scheme 30). The TMS-alkynes were successfully iodinated using *N*-iodosuccinimide in the presence of a silver nitrate catalyst in *N,N*-dimethylformamide as the solvent. In one case, isatin was unexpectedly formed in very low yields from the iodination step in the presence of silver nitrate and NBS which also brominated at the 5 position. To furnish the isatin in good yields, the prepared iodoalkyne **68** was subjected to cyclization either as the crude product or immediately after purification due to the relative instability of the iodoalkyne at ambient temperature.



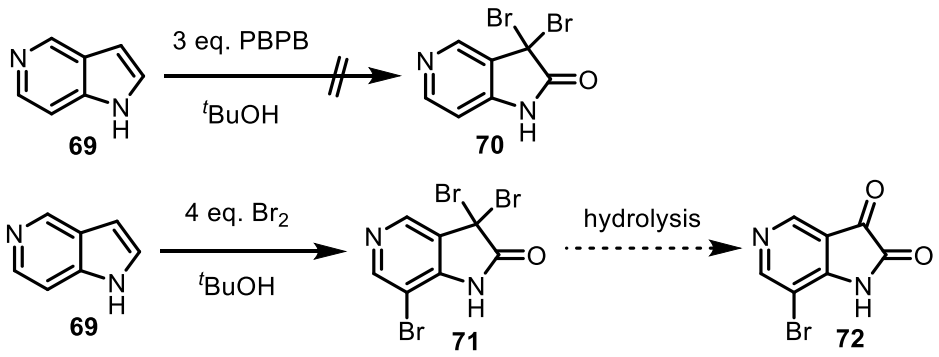
Scheme 30

Results and Discussion

Investigations into the Synthesis of Azaisatins

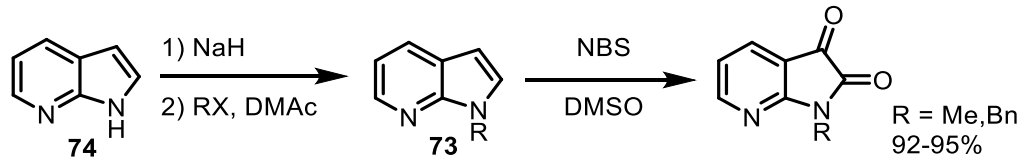
The initial objective of the project was to synthesise azaisatins which are the nitrogen containing analogues of isatin. Although the preparation of isatin has been extensively studied, there are far fewer methods reported for the synthesis of the aza-equivalents. The first attempted preparation of 7-azaisatin was reported by Parrick as described previously. However, this procedure was unsuccessful in generating the expected 7-azaisatin, and a revised 5-step method was necessary to obtain the product in a 42% overall yield (Scheme 22).

A modification of Parrick's method was reported by Robinson and Donahue in their effort to synthesize 5-azaoxindoles via the bromination of 5-azaindoles **69**.[72] Their initial attempt to prepare 5-azaoxindole involved treating 5-azaindole with a minimum of 3 equivalents of pyridinium bromide perbromide in *t*-butyl alcohol, but this afforded only the hydrobromide of 3-bromo-5-azaindole. Altering the solvent system produced small quantities of the 3,3-dibromo-5-azaoxindole **70** which is an intermediate for the synthesis of 5-azaisatin although the sample proved to be amorphous and unstable. To alleviate the problem, 4 equivalents of bromine in aqueous *t*-butyl alcohol were used to tribrominate 5-azaindole into 3,3,7-tribromo-5-azaoxindole **71** which is a possible intermediate for the synthesis of 7-bromo-5-azaisatin **72** (Scheme 31).



Scheme 31

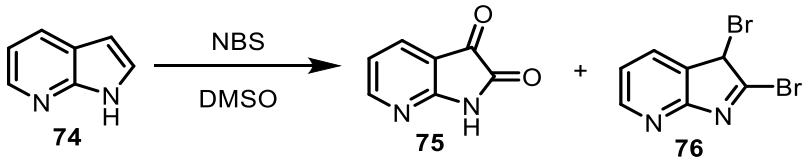
Tatsugi has also developed a procedure similar to Parrick's method of oxidizing indoles to synthesize isatin derivatives (Scheme 32).[73] Firstly, alkyl-7-azaindoles **73** were obtained by treating the sodium salt of 7-azaindole **74** with appropriate alkyl halides in dimethylacetamide. The 1-alkylated indoles were then oxidized using NBS in anhydrous DMSO at above 80 °C for 20 hours. When the reaction was performed at above 80 °C under normal pressure, hydrogen bromide was generated which subsequently led to the decomposition of DMSO. In order to prevent the acid-catalyzed DMSO decomposition, it became necessary to carry out the reaction under reduced pressure when temperatures above 80 °C were employed. However, in some cases, excellent yields could still be obtained when performing the reaction at 60 °C for 6 hours under normal pressure, e.g. 1-methyl-7-azaindole gave the corresponding isatin in a 95% yield.



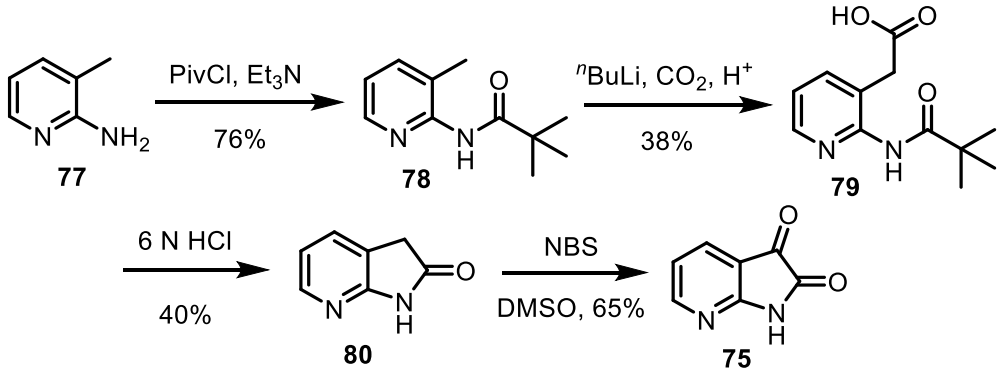
74 73

Scheme 32

Whilst Tatsugi's method gives excellent yields for the preparation of 1-substituted 7-azaisatins, it does not apply to the corresponding unsubstituted azaisatin. Kritsanida's attempt to synthesise 7-azaisatin by brominating 7-azaindole resulted to a mixture of the desired product and a dibrominated by-product **76** (Scheme 33).[74] The by-product was resubjected to the reaction conditions to obtain the desired 7-azaisatin albeit in a poor yield. Moreover, Cheng's attempt to apply this azaisatin synthesis in their effort to prepare 7-azaindirubin proved unsuccessful.[75] Cheng, therefore, reported a 4-step synthesis of 7-azaisatin starting from 2-amino-3-picoline **77** (Scheme 34). The final key step involved a bromination of 7-aza-2-indolinone **80** using NBS and DMSO under reduced pressure to afford 7-azaisatin in a 65% yield.

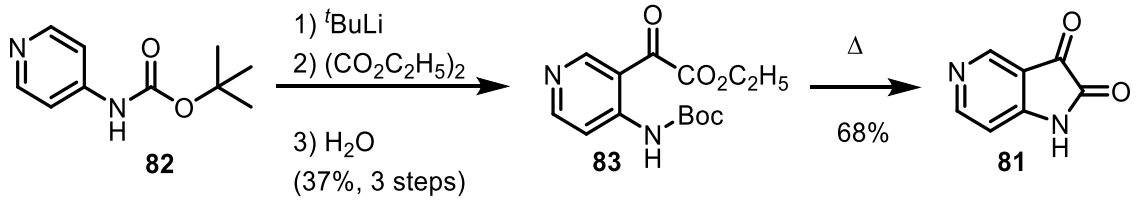


Scheme 33

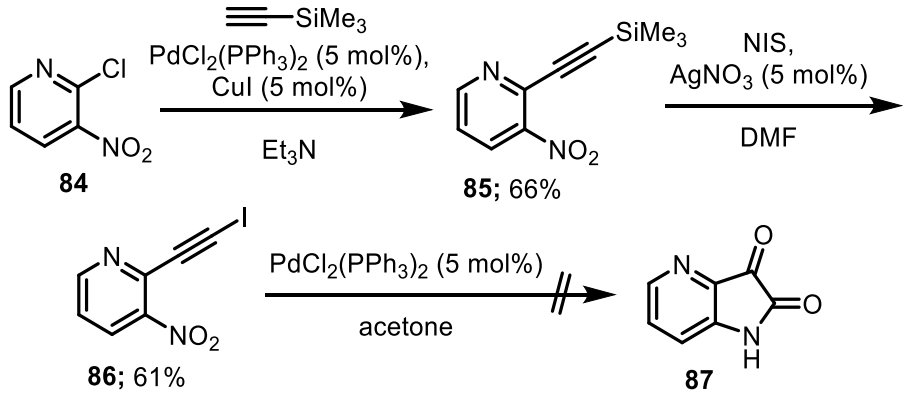


Scheme 34

Rivalle reported a preparation of 5-azaisatin **81** via ethyl 4-acyl-aminopyridineglyoxylate **82**.[76] The desired 5-azaisatin was obtained in a 68% yield via the cyclization of the keto-ester carbamate **83** (Scheme 35). Söderberg attempted the first synthesis of 4-azaisatin **87** through the Pd-catalyzed cyclization of 2-(2-iodoethynyl)-3-nitropyridine **86** (Scheme 36).[71] This proved to be unsuccessful as no identifiable product was observed although the starting material was fully consumed.

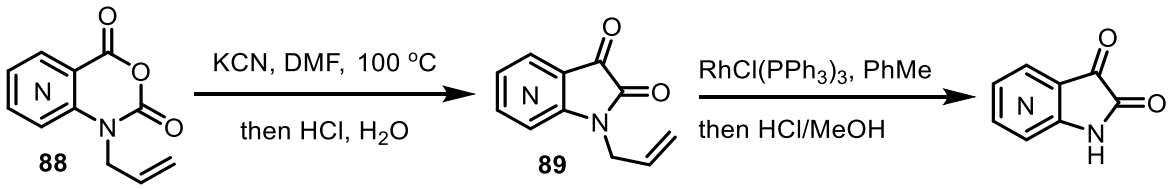


Scheme 35



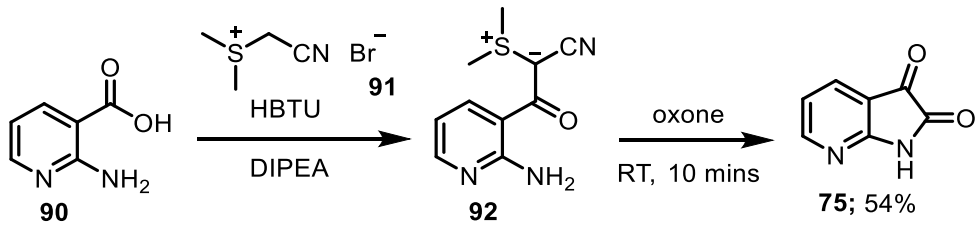
Scheme 36

A series of isatin analogues were used in the synthesis of tryptanthrin compounds as immunotherapeutics in the treatment of infectious diseases.[77] These analogues included azaisatins and their synthesis starting from azaisatoic anhydrides was reported. The *N*-protected azaisatoic anhydride **88** was transformed to the *N*-allyl azaisatin **89** via the reaction with potassium cyanide followed by acid hydrolysis (Scheme 37). The allyl group was removed by using Wilkinson's catalyst followed by treatment with acid to afford the desired azaisatin.



Scheme 37

Finally, the most recently reported synthesis of azaisatins involves a sulphur ylide-mediated carbonyl homologation as described by Lippert.[78] The required anthranillic acid was reacted with sulfonium salt **91** to make the sulfur ylide intermediate **92** which was then transformed to the azaisatin in the presence of oxone (Scheme 38).



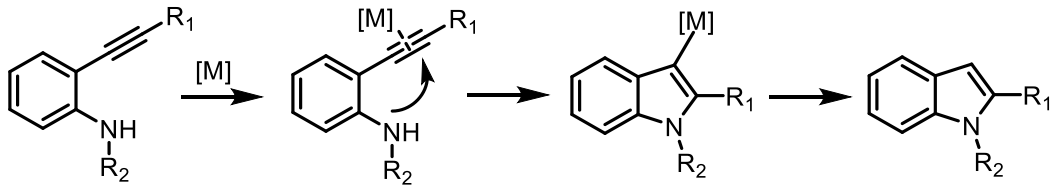
Scheme 38

With these different approaches to azaisatins available from the literature, the investigation commenced by choosing Parrick's method involving the bromination and oxidation of indoles. As azaindoles are relatively difficult to obtain commercially, efforts were turned towards the development of a synthesis of these substrates.

Approach 1: Via Oxidation of Azaindoles

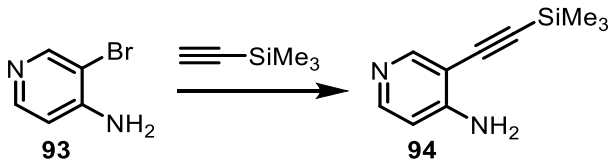
Synthesis of Azaindoles

Initial efforts to synthesise azaindoles focused on the transition-metal catalysed cycloisomerizations of 2-alkynyl anilines which has been extensively investigated for the construction of benzoheterocycles.[79] A wide range of transition metal catalysts have been used for the π-activation of the alkyne which forms an electrophilic species that can undergo nucleophilic attack by the pendant amine (Scheme 39).



Scheme 39

Before investigating the transition metal catalysed cyclization, the synthesis of the aromatic alkynylamine intermediate was required. Accordingly, the Sonogashira reaction of 3-bromo-4-aminopyridine **93** with trimethylsilylacetylene was examined using a variety of conditions reported in literature (Table 1). Initially, using 1 mol% of $PdCl_2(PPh_3)_2$ and 2 mol% of CuI did not give any of the desired product whilst increasing the loading of both catalysts to 10 mol% each still proved ineffective, even after heating. Changing the catalyst to $Pd(OAc)_2$ and adding triphenylphosphine ligand with tetrabutylammonium acetate did not aid the reaction. Finally, the use of diisopropylamine base was attempted, but again without success.

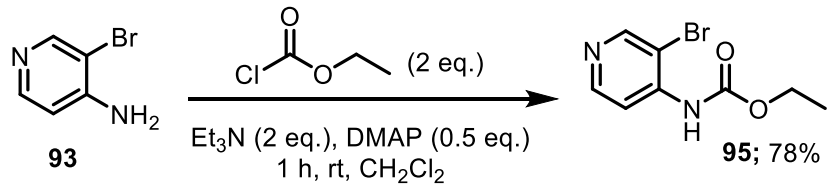


93 **94**

Entry	Conditions	Yield
1	1 mol% $PdCl_2(PPh_3)_2$, 2 mol% CuI, Et_3N, 24 h rt	0%
2	10 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, Et_3N, 2 h Δ	0%
3	2 mol% $Pd(OAc)_2$, 20 mol % PPh_3, 3 eq Bu_4NOAc, 24 h, rt	0%
4	5 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, 3 eq DIPA, THF, 30 min, 0 °C	0%

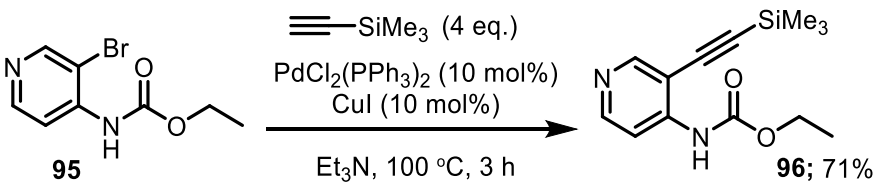
Table 1

The failure of the aminopyridine towards Sonogashira coupling prompted us to acylate the free amine in the hope that this would aid reactivity. Therefore, 3-bromo-4-aminopyridine **93** was reacted with ethyl chloroformate in the presence of excess pyridine to give ethyl carbanilate **95** in a 48% yield. The yield improved to 78% when triethylamine was used as the base in the presence of catalytic DMAP (Scheme 40). With the ethyl carbanilate in hand, the Sonogashira reaction with trimethylsilylacetylene was attempted.



Scheme 40

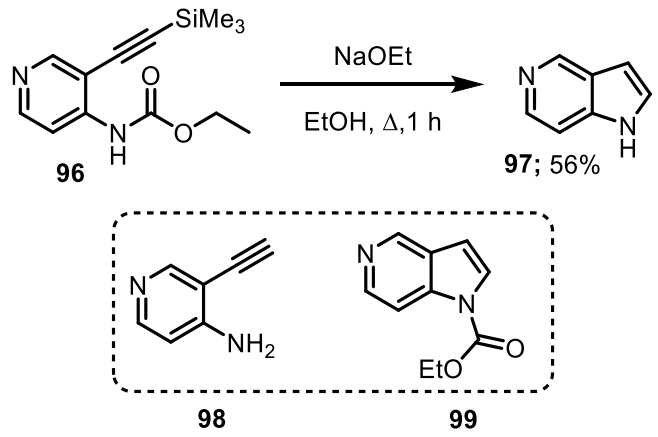
Treating acetanilide **95** with 1.5 eq. TMSA, 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% of CuI resulted in the recovery of starting material, and so an additional 2.5 eq. of TMSA and 5 mol% $PdCl_2(PPh_3)_2$ were added. Pleasingly, this afforded the alkyne product in 50% yield. Repeating the reaction with 4 eq. of TMSA and 10 mol% Pd catalyst at an elevated temperature of 100 °C gave the product in a 63% yield, while the product was generated in 71% if the CuI and TMSA were premixed before adding to the reaction mixture (Scheme 41).



Scheme 41

Yamanaka reported the cyclization of ethyl 2-(trimethylsilylethynyl)carbanilate **96** into 5-azaindole when treated with NaOEt, which eliminates the need to deprotect the carbanilate prior to cyclization (Scheme 42).[80] Interestingly, when the corresponding 2-(trimethylsilylethynyl)acetanilide was treated with NaOEt, the major product obtained is 2-ethynylaniline **98** instead of the indole. Moreover, when 2-ethynylaniline was

resubjected to NaOEt in EtOH, no indole was detected which suggested that the indole was formed via the acylindole **99**. Yamanaka's method was therefore used for the cyclization which gave the desired 5-azaindole **97** in a 56% yield (Scheme42).

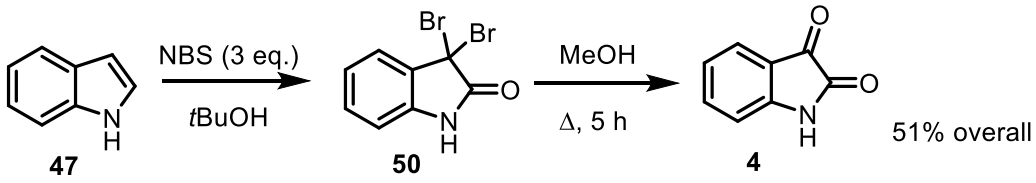


Scheme 42

Overall, a 3-step method was developed for the synthesis of 5-azaindole in good yields and from commercially available starting materials.

Bromination/Oxidation of Indoles

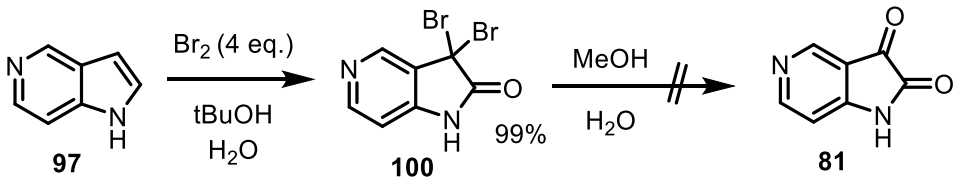
Before attempting to oxidise 5-azaindole **97**, we began by applying Parrick's conditions to the parent indole. Treatment of **47** with 3 equivalents of *N*-bromosuccinimide in *tert*-butanol gave the 3,3-dibromo-2-oxindole intermediate **50** which was hydrolysed in refluxing methanol to afford isatin **4** in a 51% overall yield (Scheme 43).



Scheme 43

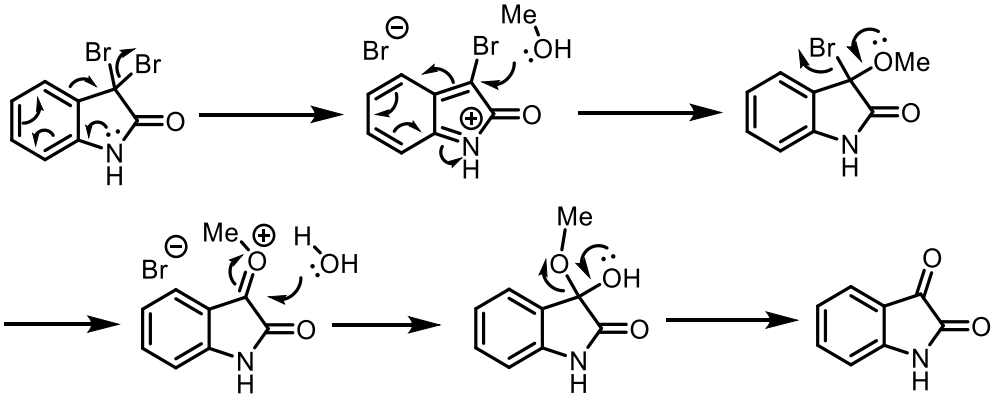
Encouraged by this promising result, the method was applied on the azaindole but treatment of **97** with 3 equivalents of NBS only gave the dibromo intermediate **100** in a poor yield. Fortunately, using Zou's conditions of 4 equivalents of bromine in aqueous

tert-butanol provided 3,3-dibromo-5-aza-2-oxindole in a quantitative yield (Scheme 44).[81] The subsequent hydrolysis was then attempted by refluxing in aqueous methanol for 24 h but this resulted in a complex mixture which included the starting dibromide. Likewise, when the reaction mixture was heated at 140 °C under microwave irradiation for 30 min, a complex mixture was obtained.

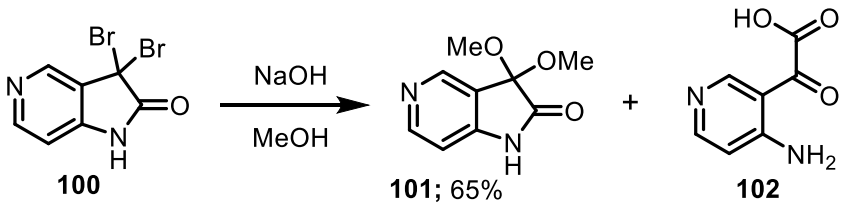


Scheme 44

It was then hypothesised that the reaction mechanism for the hydrolysis involves the deprotonation of the oxindole as the first step which would require a base (Scheme 45). Accordingly, the hydrolysis of oxindole **100** in methanol was attempted with the addition of an excess amount of NaOH at room temperature. After 1 h, full consumption of starting material was observed but the expected azaisatin was not detected. Instead, the isolated product was discovered to be 3,3-dimethoxy-5-aza-2-oxindole **101** (Scheme 46). Moreover, leaving the reaction for 16 h also formed a different product in addition to the acetal which was envisioned to be the corresponding oxalic acid **102**. However, attempts to conclusively characterize this product proved unsuccessful.

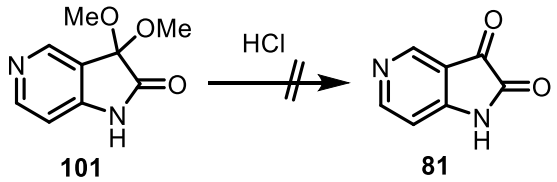


Scheme 45



Scheme 46

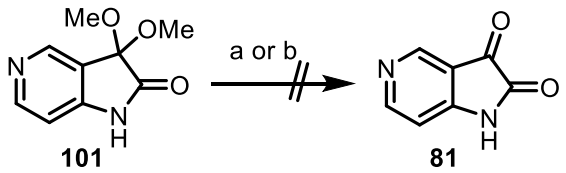
In an endeavour to prevent the formation of the acetal during the hydrolysis reaction, the methanol solvent was changed to *tert*-butanol. In addition, acetonitrile was also employed as an alternative solvent. Disappointingly, both sets of conditions resulted in a complex mixture with no indication of the expected product. Efforts were then turned to trying to convert the acetal to the required azaisatin. Initially, it was envisaged that the hydrolysis of the acetal could be achieved by acidifying the reaction mixture after the acetal formation. Regrettably, addition of 1 M HCl with further stirring for 1 h proved unsuccessful and gave a complex mixture which included the unreacted acetal (Scheme 47). The acetal was therefore isolated before treatment with acid but eventually, this proved to be ineffective as the acetal remained unreacted even after the application of heat. Furthermore, during the hydrolysis reaction using base in aqueous methanol, it was discovered that a different product was being formed after 5 minutes of reaction time which was not the acetal. It was anticipated to be the expected azaisatin but characterization of the obtained solid was unconvincing.



Scheme 47

With the conversion of the acetal to the isatin proving to be challenging, the idea of exploiting microwave irradiation was considered. Firstly, the dibromide **100** was subjected to microwave irradiation at 150 °C for 5 mins in the presence of acid (Scheme 48). Unfortunately, this resulted in a complex mixture and the desired azaisatin was not

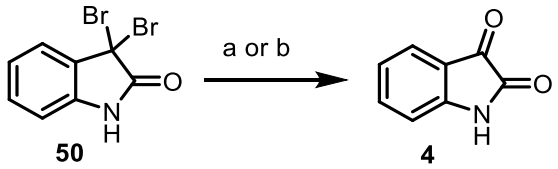
obtained. Moreover, the dibromide was subjected to microwave irradiation at 140 °C for 30 min using aqueous methanol as a solvent but the expected product was not observed.



a = HCl (aq 4M), microwave: 150 °C, 5 min
b = MeOH, H_2O (4:1), microwave: 140 °C, 30 min

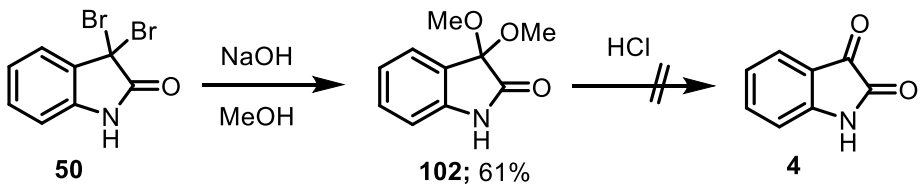
Scheme 48

In order to compare the results achieved for the oxidation of azaindole with that of the parent indole, the required dibromide intermediate **50** was prepared via the bromination of indole using literature conditions. The dibromide was then subjected to microwave irradiation at 150 °C for 5 mins in the presence of acid which gave the expected isatin in 64% yield (Scheme 49). The hydrolysis reaction in the presence of base was then performed in which the corresponding acetal was obtained in a 61% yield. The acetal was subsequently treated with acid in order to obtain the desired isatin but the acetal proved to be unreactive (Scheme 50). This mirrors the result obtained when 3,3-dimethoxy-5-aza-2-oxindole **101** was treated with acid, therefore suggesting that isatin acetals are quite stable and not susceptible to hydrolysis.



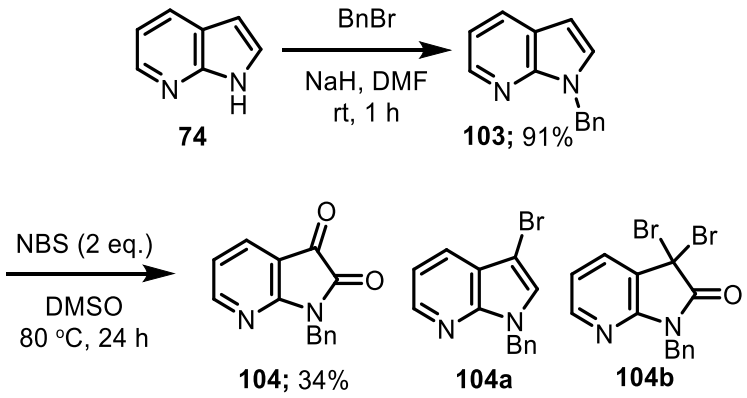
a = HCl (aq 4M), microwave: 150 °C, 5 min (64%)
b = MeOH, H_2O (4:1), microwave: 140 °C, 30 min (62%)

Scheme 49



Scheme 50

Since Parrick's bromination method had proved to be ineffective in the oxidation of azaindole, we turned our attention to Tatsugi's modification of Parrick's strategy. Although Tatsugi's method has not been successfully applied for the oxidation of unsubstituted indoles, it was anticipated that a removable protecting group on the amide might provide a solution. Before attempting the oxidation of 5-azaindole, we decided to reproduce Tatsugi's results using 7-azaindole to obtain 7-azaisatin.[73] Consequently, 7-azaindole **74** was benzylated to obtain 1-benzyl 7-azaindole in a 91% yield which was easily scaled up to 3 g. Using the reported conditions of heating at 80 °C for 24 h with 2 equivalents of NBS, 1-benzyl 7-azaisatin was obtained in a disappointing yield of 34%. Also observed in the LC-MS of the crude mixture was the 3-bromo indole **104a** and the dibromo oxindole intermediate **104b** (Scheme 51). The amount of NBS was therefore increased to 3 equivalents. This is to ensure complete conversion of the monobrominated indole to the oxindole intermediate and subsequently, the conversion of the oxindole intermediate into the isatin.



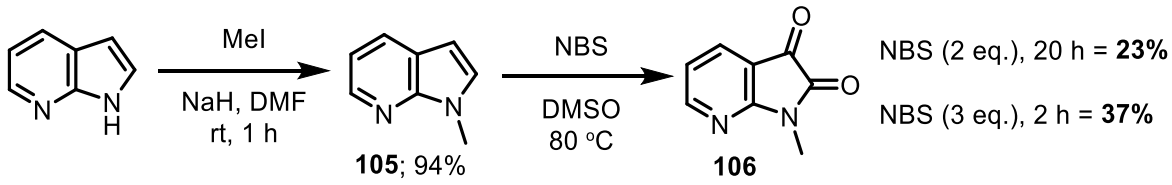
Scheme 51

Conducting the reaction with 3 equivalents of NBS at 80 °C resulted in complete consumption of the starting indole after 4 h according to TLC analysis. However, as other compounds were evident we decided to continue the reaction for another 1 h in the hope that these would converge to the product. Unfortunately, the reaction mixture started to become more complex so the reaction was stopped at that point. The expected isatin **104** was isolated in a 43% yield and was scaled up to 500 mg where the yield improved to 48% after stopping the reaction after 4 h.

103 **104;** 43%

Scheme 52

With 1-benzyl 7-azaisatin in hand, efforts were turned towards the deprotection of the benzyl group to obtain 7-azaisatin. Remarkably, attempts to hydrogenate with Pd/C proved ineffective as only starting material was recovered. The protected isatin was also treated with boron trichloride in dichloromethane for 24 h but this also turned out to be unsuccessful. Rombouts reported the decomposition of 1-benzyl isatin during their debenzylation attempts, leading them to conclude that the benzyl group is not the most suitable protecting group to use.[82]



105; 94% **106**

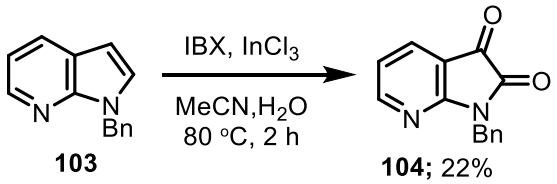
Scheme 53

Finally, 7-azaindole was methylated using iodomethane in the presence of sodium hydride which gave 1-methyl 7-azaindole **105** in a 94% yield. Unfortunately, attempts to brominate and oxidize this compound only gave the isatin **106** in a poor optimised yield of 37% (Scheme 53).

Other Oxidation Methods

After multiple failed attempts at oxidizing azaindole using the bromination method, efforts were turned towards alternative approaches involving other oxidizing agents. Krishna reported a preparation of 1-substituted 7-azaindoles using Yadav's method involving IBX as the oxidizing agent.[66] In the presence of catalytic $InCl_3$, the reactions proceeded uneventfully to obtain 1-substitited 7-azaisatins in excellent yields.

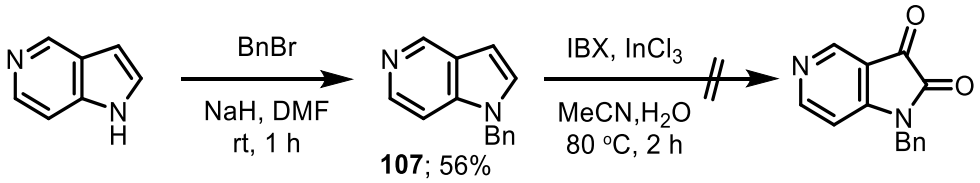
The previously prepared benzylated 7-azaindole was therefore subjected to Krishna's conditions. Disappointingly, when the oxidation was attempted, complex crude mixtures were observed and the desired isatin was only obtained in a 22% yield (Scheme 54).



103 **104;** 22%

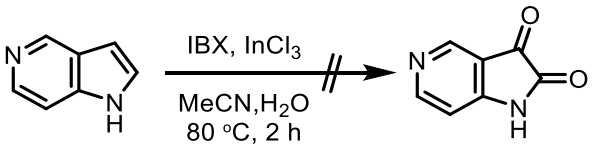
Scheme 54

We next attempted to apply this method for the synthesis of 5-azaisatins starting from the corresponding 1-substituted 5-azaindole. Accordingly, 5-azaindole was reacted with benzyl bromide and sodium hydride to obtain 1-benzyl 5-azaindole **107** in a 56% yield (Scheme 55). Disappointingly, the oxidation was unsuccessful when both this substrate and the free azaindole were employed, and only starting material was recovered (Scheme 56).



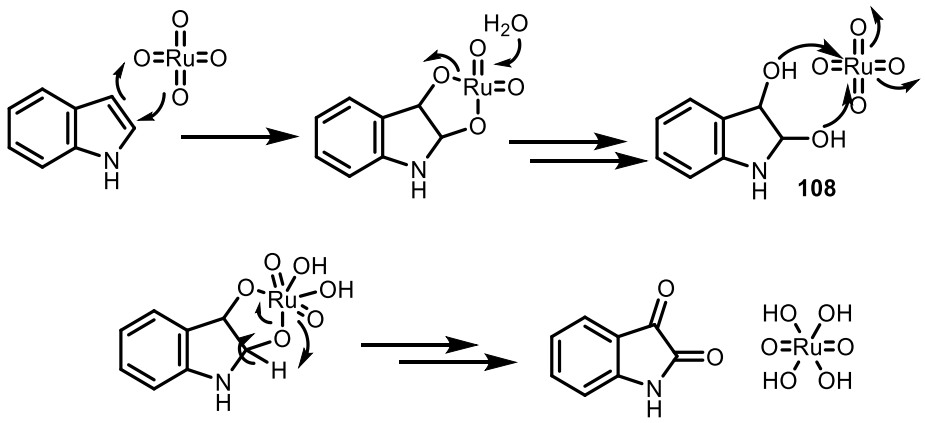
107; 56%

Scheme 55



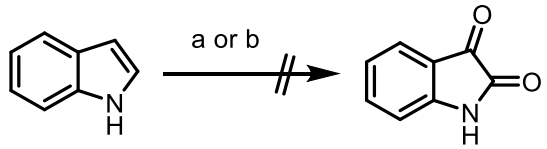
Scheme 56

Yang reported an oxidative cleavage of olefins to aldehydes using a ruthenium catalyst in the presence of an oxidant such as Oxone or $NaIO_4$.[83] Beauchard then investigated the suitability of this method for the oxidation of 6-nitroindole into 6-nitroisatin. In the event, $RuCl_3.2H_2O$ and $NaIO_4$ converted the substrate into the expected isatin, albeit in a low yield.[65] A proposed reaction mechanism for the transformation is depicted in Scheme 57. Firstly, the ruthenium catalyst and the oxidant forms RuO_4 which reacts with the indole. Instead of the expected oxidative cleavage, the presence of water forms the diol **108** which is further oxidized to the isatin by either the RuO_4 or the oxidant.



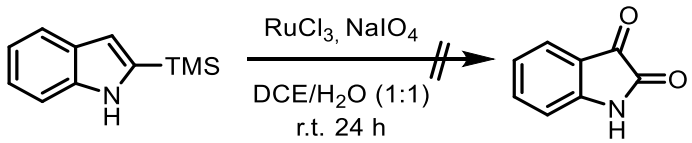
Scheme 57

Before we attempted this approach on our azaindole substrates, it was decided to try the chemistry on the parent indole first. Indole was therefore treated with $RuCl_3$ and $NaIO_4$ at ambient temperature for 24 h but a complex mixture was obtained. Likewise, using Yang's alternative conditions of $RuCl_3$ and Oxone in the presence of $NaHCO_3$ was ineffective (Scheme 58).[83] It was speculated that a more labile trimethylsilyl group at the 2-position would help the oxidation of indole, and therefore 2-trimethylsilylindole was treated with $RuCl_3$ and $NaIO_4$ at ambient temperature for 24 h (Scheme 59). Eventually, a complex mixture was obtained and therefore this approach was not applied in the oxidation of azaindoles.



a = $RuCl_3$, $NaIO_4$, DCE/H_2O (1:1) r.t. 24 h
b = $RuCl_3$, oxone, $NaHCO_3$, MeCN/H_2O (1.5:1) r.t. 24 h

Scheme 58



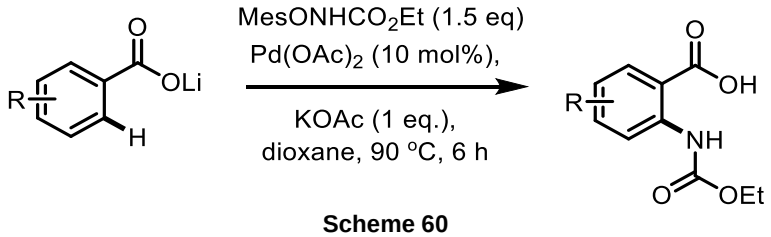
Scheme 59

Approach 2: Via Isatoic Anhydride

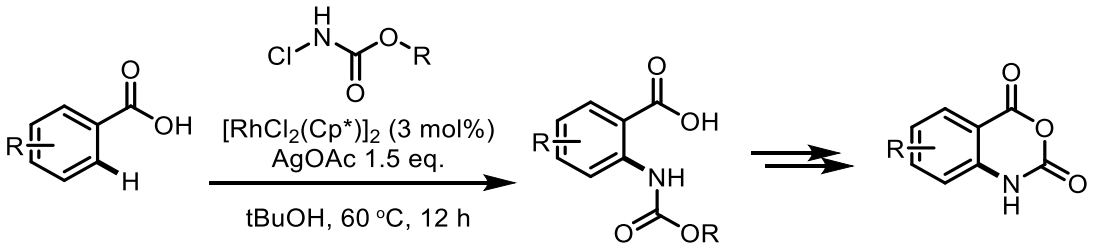
Synthesis of Azaisatoic Anhydride

The next strategy explored for the synthesis of azaisatin was the homologation of azaisatoic anhydride with cyanide, using the method previously described (Scheme 37). This approach was reported to allow the preparation of different analogues of isatin, including all four isomers of azaisatin. Whilst the patent suggested preparing the starting azaisatoic anhydride from azaphthalic anhydride or the corresponding anthranilic acid,[77] there appeared to be an opportunity to develop a new methodology to make the key azaisatoic anhydrides. Efforts were turned to developing a C-H activation strategy to these compounds. This novel approach would be efficient, and this area of research has received wide interest in organic synthesis in recent years.

Yu reported a carboxylate-directed amidation of benzoic acids using a palladium catalyst to afford anthranilic acids, which are important building blocks in heterocycle synthesis.[84] This C-H activation method employed ethyl N-mesityloxycarbamate as the amidation reagent while the carboxylic acid was used as the corresponding Li-carboxylate (Scheme 60). More recently, Yu also disclosed a Rh-catalyzed amidation of benzoic acids using N-chlorocarbamates as the amidating reagent (Scheme 61).[85] Not only is this a more convenient way to prepare functionalized anthranilic acids, but it was also shown to be a useful way to make isatoic anhydrides.

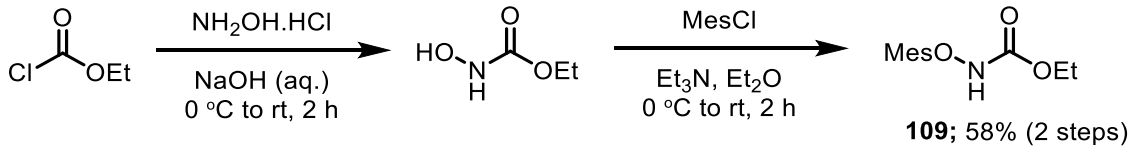


Scheme 60

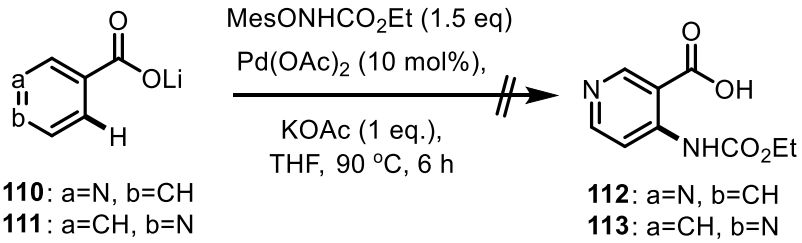


Scheme 61

We decided to investigate the Pd-catalyzed amidation first and this involved preparing the amidating reagent ethyl *N*-mesitoxycarbamate using the reported two-step method (Scheme 62).[84] Next, the pyridine carboxylic acid lithium salts were prepared by treating nicotinic acid and isonicotinic acid with lithium hydroxide. The C-H amidation was then attempted using Yu's conditions but none of the expected anthranilic acid products were observed in either case (Scheme 63). Some of the starting pyridine carboxylic acid starting materials were recovered but most of the material remained in the aqueous layer after the aqueous workup.

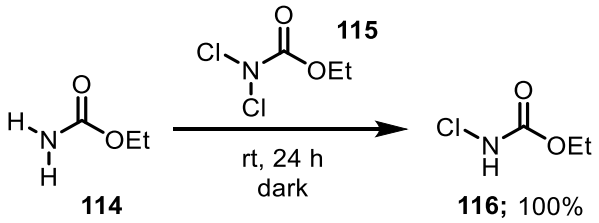


Scheme 62

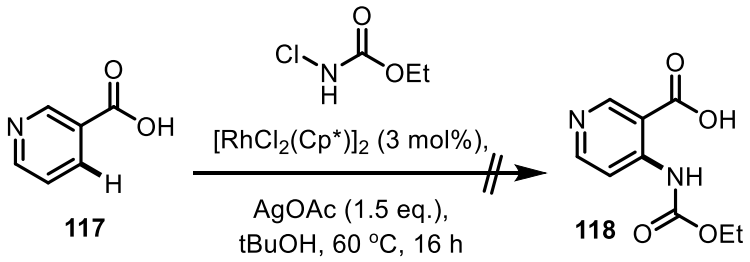


Scheme 63

The Rh-catalyzed amidation was then investigated which firstly required the synthesis of the *N*-chlorocarbamate as the amidating reagent.[85] Equimolar amounts of urethane **114** and *N*,*N*-dichlorourethane **115** were mixed in the dark for 24 h to afford ethyl *N*-monochlorocarbamate **116** after a disproportionation reaction (Scheme 64).[86] However, employing Yu's amidation procedure with nicotinic acid **117** only resulted in starting material being recovered (Scheme 65).



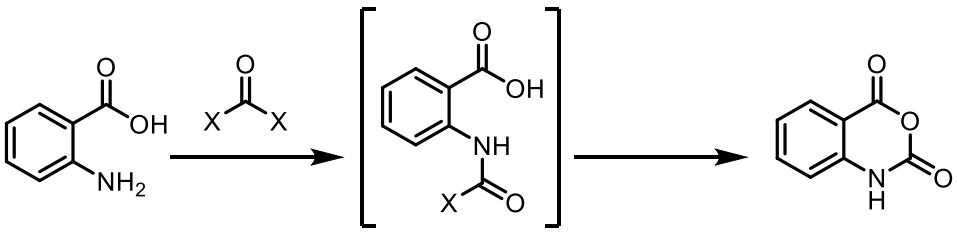
Scheme 64



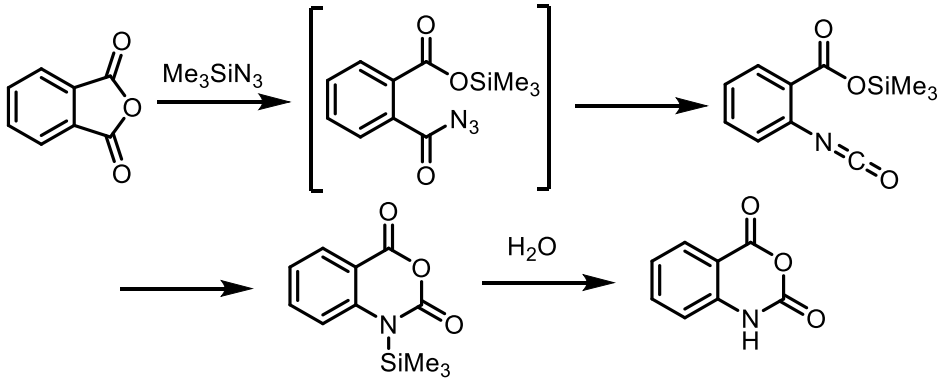
Scheme 65

Whilst the Rh-catalyzed amidation works well for benzoic acids, and appears to be more general than the Pd-catalyzed variant, carboxylic acids containing heteroaryl motifs are evidently not applicable for this method. In light of this, efforts were turned towards preparing azaisatoic anhydrides using more established methods.

Traditionally, isatoic anhydride is obtained via the oxidation of isatin by chromic acid or *m*-CPBA. In fact, the name isatoic acid was coined by Kolbe in 1884 when isatoic anhydride was first discovered because it was thought to be an acid product from the oxidation of isatin.[87] Coppola published a review surveying traditional methods to make isatoic anhydride including the aza-derivatives.[88] The two most useful strategies are the ring closure of anthranilic acid (Scheme 66) and the reaction of phthalic anhydride with azides (Scheme 67).

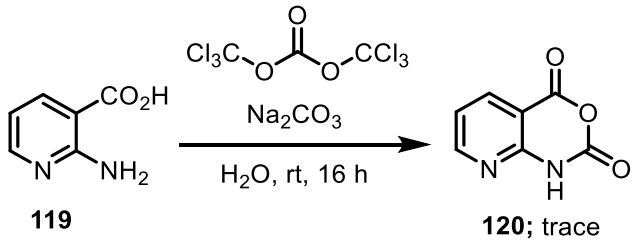


Scheme 66



Scheme 67

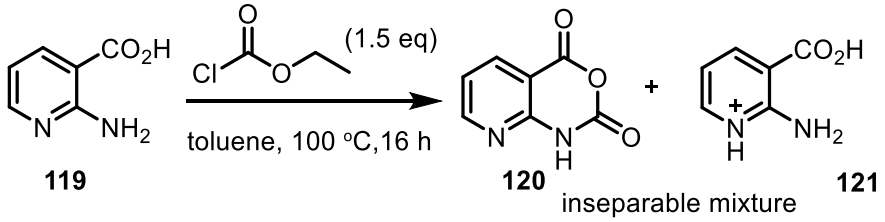
Commercially available 2-amino nicotinic acid **119** was initially treated with triphosgene in the presence of sodium carbonate in water at room temperature for 16 h (Scheme 68). Under these conditions however, only traces of product were observed and most of the unreacted starting material remained in the aqueous layer after work-up. The reaction was repeated in THF but in this case the starting material was fully recovered. Running the reaction at reflux resulted in about 50% conversion of starting material, but the product was difficult to separate from the salt of the unreacted nicotinic acid.



119 **120;** trace

Scheme 68

Triphosgene was substituted for ethyl chloroformate, which was the reagent used for one of the earliest reported syntheses of isatoic anhydride. Due to the poor recovery of mass balance when using water as the reaction solvent, an organic solvent was used for subsequent reactions. Accordingly, 2-amino nicotinic acid **119** was treated with ethyl chloroformate in toluene and then heated to 100 °C in the presence of triethylamine (Scheme 69). Whilst the product was indeed observed, unfortunately, removing the solvent directly to avoid aqueous work-up did not remove the triethylamine salt **121** from the reaction mixture. In an effort to avoid formation of the triethylamine salt, potassium carbonate was used as an alternative base but the reaction did not proceed under these conditions.

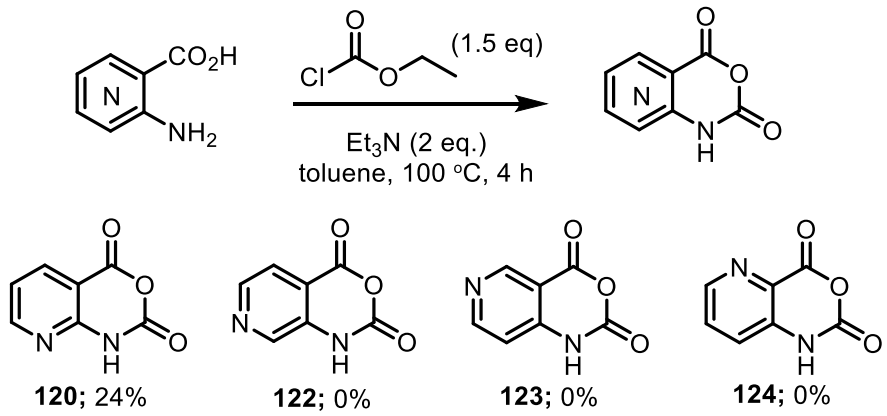


119 **120** **121**

inseparable mixture

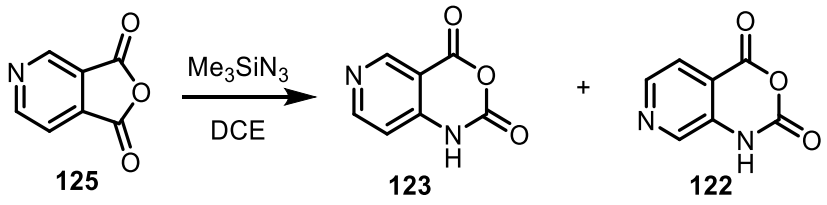
Scheme 69

To summarise, attempts to form the azaisatoic anhydride from all the aza-derivatives of the anthranilic acids were generally unsuccessful. Only one from the series was isolated cleanly, albeit in a low yield of 24%. In order to improve access to this class of compounds, we next explored the conversion of azaphthalic anhydrides to azaisatoic anhydrides.

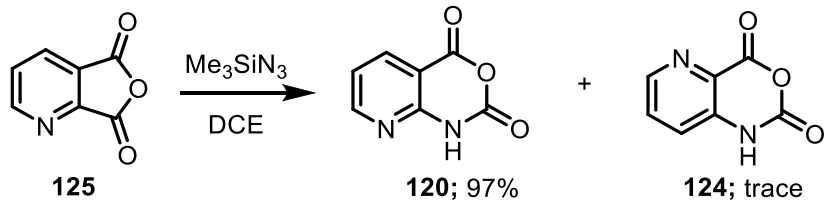


Scheme 70

The reaction of phthalic anhydride with azides involves an overall insertion of an N-H moiety between the carbonyl and the benzene ring. Initial addition of the azide forms an acyl azide intermediate which undergoes a Curtius rearrangement to produce an isocyanate. Subsequent ring closure gives the isatoic anhydride in a 91% yield according to the initial report by Coppola.[88] However, based on literature precedent, 3,4-pyridinedicarboxylic anhydride **125** would give an almost 1:1 mixture of both azaisatoic anhydride products **122** and **123** (Scheme 71). In contrast, it has been reported that the 2,3-pyridinedicarboxylic anhydride **125** gives one isomer as the major product, and this was indeed found to be the case when we attempted the reaction (Scheme 72).

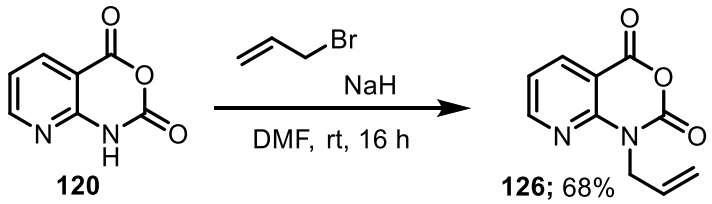


Scheme 71

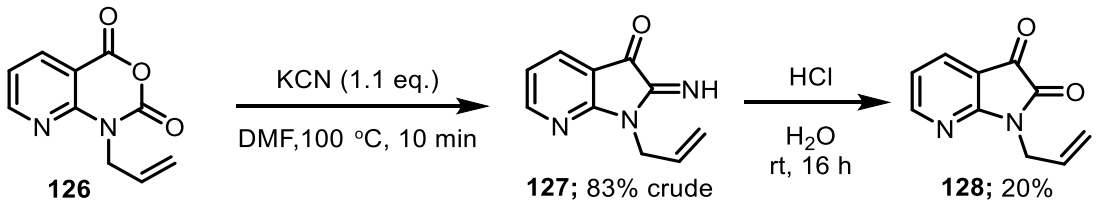


Scheme 72

With an optimal route to azaisatoic anhydride established, investigation of the transformation to azaisatin commenced. Firstly, 5-azaisatoic anhydride **120** was treated with allyl bromide in the presence of sodium hydride to obtain 1-allyl-5-azaisatoic anhydride in a 68% yield. This transformation could be performed on a multi-gram scale. This intermediate was then treated with potassium cyanide in DMF at 100 °C for 10 mins to obtain the imine intermediate **127**. The crude mixture observed after the reaction was complex but attempts to purify the imine via column chromatography were unsuccessful. Consequently, the crude material was used in the next step without further purification and an acid hydrolysis gave the *N*-allyl azaisatin **128** in a 20% yield (Scheme 74).



Scheme 73



Scheme 74

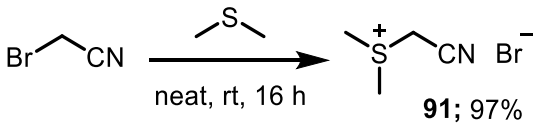
On further investigation of the reaction involving the addition of potassium cyanide to the azaisatoic anhydride, it was discovered that the reaction is time sensitive and running the reaction for longer than 10 mins led to decomposition. It was envisaged that performing the reaction at elevated temperatures might be detrimental and so it was decided to conduct the reaction at a lower temperature. Accordingly, the addition of

potassium cyanide was performed at room temperature and run for 24 h but this still led to a complex mixture. Nevertheless, the crude mixture was still subjected to the acid hydrolysis step but unfortunately, this resulted to unidentified products with none of the expected azaisatin observed.

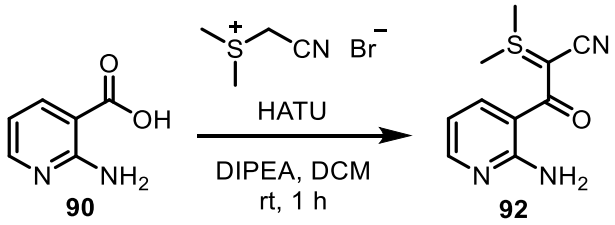
Whilst a viable route to azaisatin was developed, it was far from ideal and multiple problems arose that needed to be addressed. For instance, the initial reaction with potassium cyanide to form the imine intermediate was difficult to control and always led to complex mixtures. Moreover, after multiple attempts, the acid hydrolysis step remained challenging and the yields obtained were always below 20%. Consequently, scaling up the reaction to make multi-grams of azaisatin would require large quantities of cyanide which is not ideal.

Approach 3: Via Sulfur Ylide

The next strategy investigated for the synthesis of azaisatin was Lippert's method involving the sulfur ylide mediated carbonyl homologation previously described (Scheme 38).[78] They claimed to have synthesised 7-azaisatin in a 56% yield using their methodology and so the initial aim was to try to reproduce this result. The preparation of the required sulfonium bromide salt **91** via the reaction of dimethyl sulfide and bromoacetonitrile was quite convenient and the salt was found to be stable if stored at 0 °C, thereby allowing its preparation on multigram scale (Scheme 75). The synthesis of the sulfur ylide **92** from 2-amino nicotinic acid **90** was based on Lippert's conditions with a slight modification of using HATU instead of HBTU (Scheme 76).



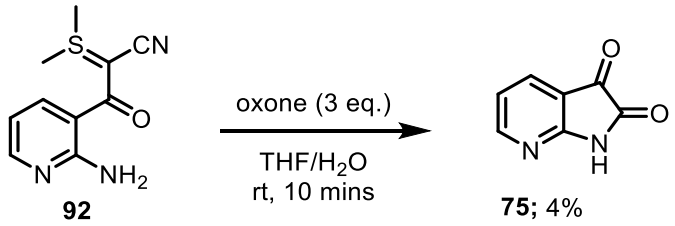
Scheme 75



Scheme 76

The sulfur ylide was not purified as it was reported that it is susceptible to forming fluorescent oxidation products via a spontaneous oxidation on silica gel. The crude ylide was therefore treated with 3 equivalents of oxone in THF/H_2O at room temperature for 10 mins and then the product was extracted. Low mass balance was obtained after the aqueous workup, however basifying the reaction mixture improved mass balance but at the expense of incorporating impurities obtained from HATU. Notwithstanding the report that the ylide intermediate decomposes on silica gel, the sulfur ylide was prepared again and purified by flash column chromatography to obtain pure product in an 81% yield. We next carried out the oxidation step using the clean ylide, and although the product was

observed in the NMR spectrum of the crude mixture, all attempts to purify it by column chromatography were unsuccessful. The product appeared to be unstable on silica gel as no desired azaisatin was isolated from chromatographic purification. Trituration of the crude mixture with ethanol gave the clean product in a very poor yield of 4%.

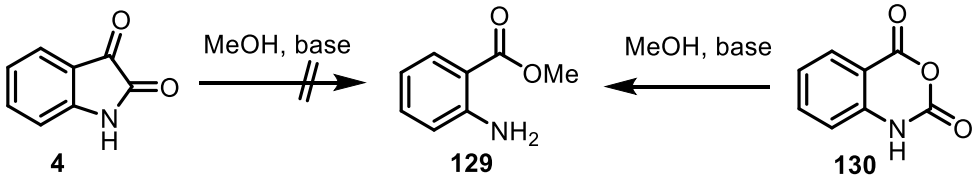


Scheme 77

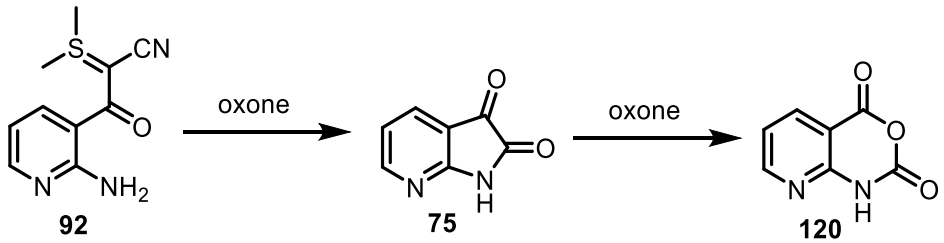
We speculated that an impurity in the crude mixture of the ylide from the previous step could be aiding the oxidation step which enabled Lippert to obtain the azaisatin in a 56% yield. Therefore, the preparation of the sulfur ylide was performed again using precisely the reported conditions where HATU was replaced with HBTU. The crude ylide was used directly for the oxidation step but after three separate attempts, the product was only obtained in a 15% yield on average. Efforts to identify what else may be in the crude mixture by analysing the LC-MS proved challenging and none of the expected by-products were observed. For instance, none of the pyridine *N*-oxide products which could have resulted from the oxidation of the pyridine moiety were detected and none of the starting anthranilic acid was observed.

Having failed to obtain the azaisatin in useful amounts, the stability of azaisatin was scrutinized in order to identify whether its decomposition was the main problem. Remarkably, it was discovered that when the isolated solid was stirred in methanol in the presence of a base (triethylamine), a new product was obtained in a 70% yield which was identified to be the methyl ester of the anthranilic acid **129** (Scheme 78). This was very surprising since there is no precedent for isatin ring opening under this set of conditions, and this transformation normally requires an oxidant such as oxone or hydrogen peroxide.[89] At this point, the results reported by Lippert appeared highly dubious and so further investigation was undertaken.

After searching for ways of preparing methyl anthranilate, we found a report that treating isatoic anhydride with base such as triethylamine, sodium hydride or sodium methoxide in methanol gives methyl anthranilate (Scheme 78).[90] Moreover, isatins are readily oxidized into isatoic anhydrides and this transformation has been shown to proceed using oxone.[91] We therefore concluded that the isatin being formed from the oxidation of the sulfur ylide is also being oxidized further to isatoic anhydride which explains the low yields obtained in this investigation.



Scheme 78

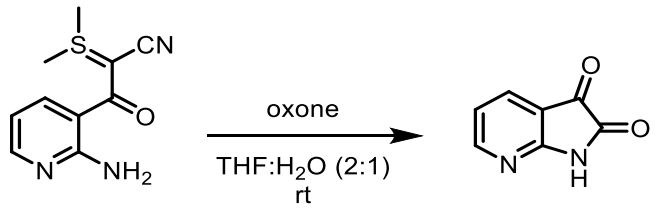


Scheme 79

Taking this new evidence into consideration, the spectroscopic data reported by Lippert was scrutinized in more detail. Firstly, the ^{1}H NMR spectrum published by the authors was performed in d^{4}-methanol and matched that of anthranilic acid ester **129**. However, the ^{1}H NMR spectrum of our product sample run in d^{6}-DMSO was found to match the data obtained for azaisatoic anhydride, which was synthesised earlier via a different method. Furthermore, the melting point and ^{13}C NMR spectrum obtained for this sample matched with literature data for azaisatoic anhydride. We therefore concluded that the compound isolated and reported by Lippert was in fact the azaisatoic anhydride, and that this has been erroneously identified as the azaisatin.

Returning to the oxidation of the sulfur ylide, and conducting a trituration of the crude material with ethanol, we discovered that the azaisatin was present in the mother

liquor. This material was purified by flash column chromatography and the azaisatin was isolated in a 26% yield. We next decided to carry out an optimization of the ylide oxidation reaction. Assuming that the isatin formation happens before oxidation to isatoic anhydride, it was envisaged that decreasing the equivalents of oxone used and reducing the reaction time might increase the yield of the isatin. Accordingly, the sulfur ylide was treated with 1.5 equivalents of oxone for 10 mins which stopped the formation of azaisatoic anhydride but only 17% of azaisatin was isolated and some unreacted starting material was observed. Increasing to 2 equivalents of oxone marginally increased the yield of azaisatin to 22% but the formation of small amounts of azaisatoic anhydride were noted. Increasing to 3 equivalents of oxone added in a portionwise manner was also ineffective. Finally, increasing the oxone equivalents to 4 but reducing the time to 5 mins resulted in complete consumption of starting material but only azaisatoic anhydride was observed. Evidently, it appears that the use of 3 equivalents of oxone over a 10 min reaction time offers the best conditions to obtain the azaisatin. As this yield was rather poor, a more efficient strategy to prepare azaisatin was sought and efforts were turned towards exploring Söderberg's transition metal catalysed method.



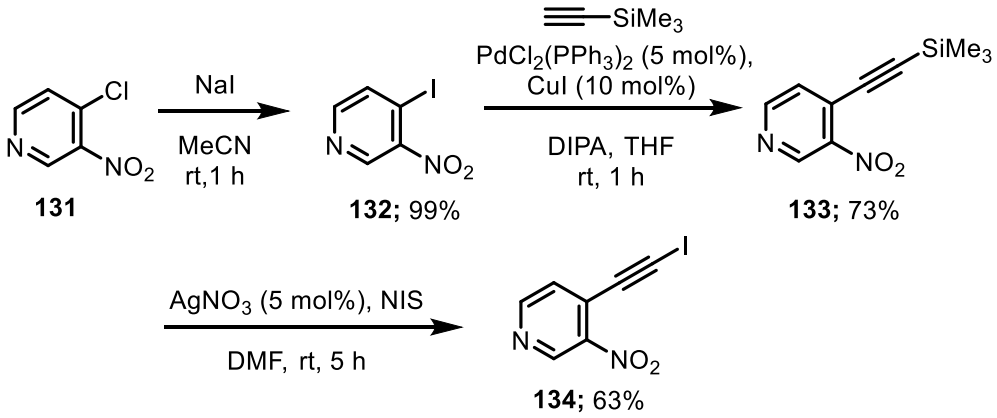
Entry	Reaction Time	Oxone Eq.	Azaisatin Yield	Azaisatoic Anhydride Yield	SM recovered
1	10 min	3	26%	16%	0%
2	10 min	1.5	17%	0%	36%
3	10 min	2	22%	13%	36%
4	10 min	3[a]	13%	10%	15%
5	5 min	4	0%	32%	0%

Table 2

[a] added portionwise

Approach 4: Via Palladium-Catalysed Cyclization of Iodoacetylenes

Based on the substantial interest in transition-metal catalysts for a variety of organic transformations, Söderberg's method was explored for the synthesis of 5-azaisatin and the novel 6-azaisatin. Although Söderberg was unsuccessful in their attempt to react the pyridine derivative, it was felt that there was an opportunity to further develop this reaction and to find a potentially cheaper metal to catalyze this transformation.

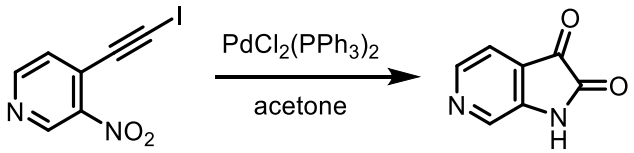


Scheme 80

The first objective was to develop an efficient starting material synthesis and our results are shown in Scheme 80. Starting from 4-chloro-3-nitropyridine **131**, a Sonogashira reaction was attempted to furnish the desired substrate **133** however the chloride coupling partner proved to be unreactive. The iodide counterpart was obtained via a Finkelstein reaction and the Sonogashira coupling of the resulting 4-iodo-3-nitropyridine **132** proceeded uneventfully giving the TMS-acetylene product **133** in a 73% yield. Finally, iodination of **133** furnished the iodoacetylene substrate **134** in a 63% yield (Scheme 80).

With the iodoacetylene precursor in hand, the cyclization was attempted using Söderberg's conditions (Table 3). The reaction proved to be slower than expected using 5 mol% of the palladium catalyst with most of the starting material recovered and only 24% of product **81** isolated after 4 h. Moreover, leaving the reaction for 24 h at room temperature showed complete consumption of starting material but a complex mixture

was observed and no identifiable product was isolated. We suggested that the low yield might be due to decomposition of the starting material since the iodoacetylene substrates are known to be relatively unstable. Doubling the loading of the catalyst to improve reaction rates however did not improve the yield and most of the starting material was still recovered. Further cyclization attempts were then performed using a different metal catalyst.

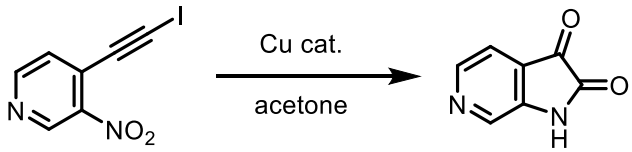


134 **81**

Entry	Conditions	Yield
1	5 mol% cat., 60 °C, 4 h	24%
2	5 mol% cat., rt, 24 h	0%
3	5 mol% cat., 60 °C, 24 h	36%
4	10 mol% cat., 60 °C, 48 h	10%

Table 3

As a substitute for palladium, it was speculated that copper salts could be used to catalyze the cyclization which would represent a cheaper alternative. A number of copper catalysts were tested and copper (II) chloride was found to be promising, giving the product in a 15% yield when 10 mol% of the catalyst was used (Table 3). However, most of the starting material was still recovered and leaving the reaction for longer only led to decomposition. Increasing the loading to 50 mol% only marginally increased the yield to 20% while using a stoichiometric amount of copper salt provided a 31% yield of product. Employing copper (I) iodide failed to promote the cyclisation, while adding zinc powder as a co-catalyst proved to be unsuccessful. It was then hypothesized that the copper or palladium catalyst might be coordinating to the nitrogen atom of the pyridine hence effectively hindering the cyclization process.

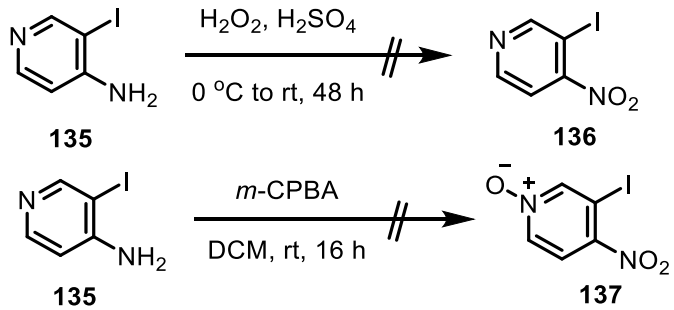


134 81

Entry	Conditions	Isolated Yield
1	10 mol% $CuCl_2$, 60 °C, 24 h	15%
2	50 mol% $CuCl_2$, 60 °C, 24 h	20%
3	1.5 eq. $CuCl_2$, 60 °C, 24 h	31%
4	1.5 eq. CuI, 60 °C, 24 h	0%
5	1.5 eq. CuI, 1.5 eq. Zn, 60 °C, 48 h	0%

Table 4

Attention was then turned to the synthesis of isomeric 5-azaisatin. Investigation began with the preparation of the 3-iodo-4-nitro pyridine **136** (Scheme 81). The oxidation of the commercially available 3-iodo-4-aminopyridine **135** was attempted using hydrogen peroxide in the presence of sulfuric acid at 0 °C to rt. This proved to be a sluggish reaction with only traces of product observed after 48 h. Reported oxidations of aminopyridines to nitropyridines involved using harsher conditions at higher temperatures.[92] Other oxidizing agents were considered such as *m*-CPBA but this resulted to a complex mixture. Moreover, obtaining the 3-iodo-4-nitropyridine from 3-iodopyridine was also envisioned but there is no precedent for the direct nitration of 3-halopyridines.



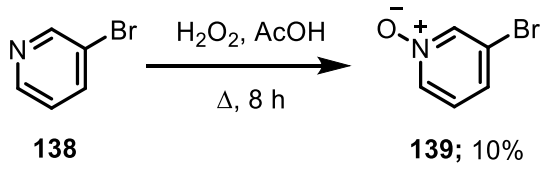
135 136

135 137

Scheme 81

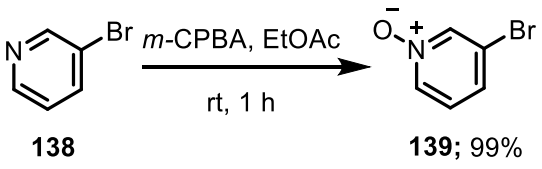
A different approach was employed which involved the initial oxidation of 3-bromopyridine **138** to obtain 3-bromopyridine *N*-oxide **139**. The direct nitration of this substrate has been previously achieved[93] and protecting the nitrogen atom of the pyridine was thought to be beneficial for the cyclization later on. Using hydrogen peroxide

as the oxidant in the presence of acetic acid gave the product in less than 10% yield however, most of the starting material was recovered even after heating under reflux (Scheme 82). Fortunately, replacing H_2O_2 with *m*-CPBA effected the reaction at room temperature after 1 h providing 3-bromopyridine *N*-oxide **139** in a quantitative yield (Scheme 83).



138 **139;** 10%

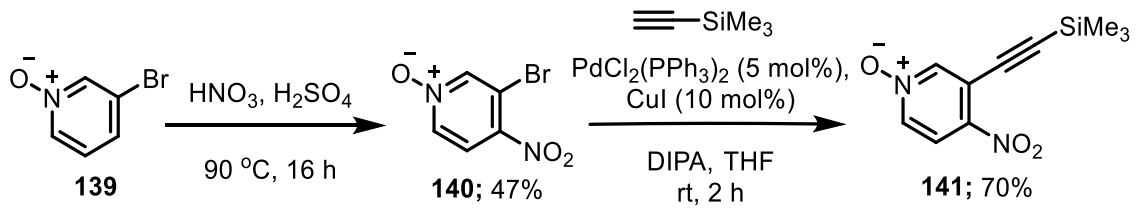
Scheme 82



138 **139;** 99%

Scheme 83

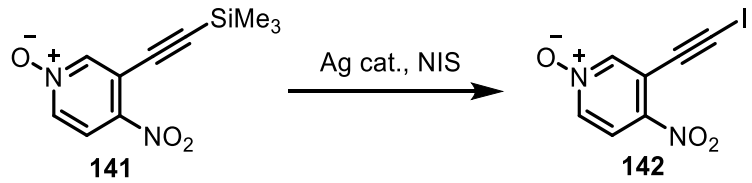
With the 3-bromopyridine *N*-oxide in hand, the nitration was performed using fuming nitric acid and concentrated sulfuric acid at 90 °C (Scheme 84). Conducting the reaction for 16 h gave 4-nitro-3-bromopyridine *N*-oxide **140** in a 33% yield. It appeared that the reaction was incomplete even after leaving for 48 h, and so it was speculated that the active reagent was decomposing. Therefore, nitric acid was added portion-wise over 16 h but unfortunately, this only improved the yield to 47%.



139 **140;** 47% **141;** 70%

Scheme 84

The Sonogashira reaction with the bromide then proceeded uneventfully to give the desired TMS-acetylene **141** in a 70% yield. However, the subsequent iodination proved to be more difficult using silver nitrate and 1.5 equivalents of *N*-iodosuccinimide in DMF. The high water solubility of the product made the aqueous work-up problematic and in addition, the succinimide by-product was difficult to separate from the desired substrate. Silver fluoride was then used with 1 eq. of NIS in acetonitrile which avoided an aqueous work-up and decreased the succinimide by-product to give the precursor **142** in a 65% yield (Table 5).

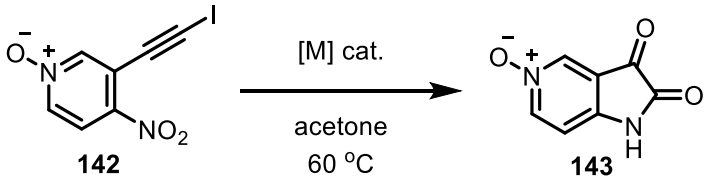


141 142

Entry	Conditions	Yield
1	5 mol% $AgNO_3$, 1.5 eq NIS, DMF	>5%
2	5 mol% $AgNO_3$, 3 eq NIS, MeCN	10%
3	1 eq AgF, 1 eq NIS, MeCN	65%

Table 5

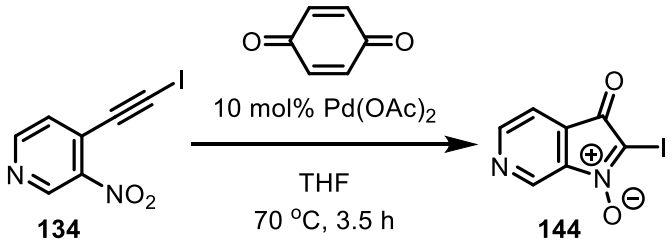
With the *N*-protected iodo-acetylene substrate **142** in hand, the cyclization was attempted with 5 mol% of $PdCl_2(PPh_3)_2$ over 24 h (Table 6). Disappointingly, the reaction did not proceed even when the catalyst loading was increased to 10 mol%. Likewise, using 10 mol% $CuCl_2$ did not afford any product and using stoichiometric amounts of copper salt led to a complex mixture. Furthermore, it was discovered that as the cyclization progresses, the pH drops considerably which signifies the generation of hydrogen iodide. The presence of this acid is also evident from the formation of diacetone alcohol and isobutenyl methyl ketone resulting from the acid-catalyzed self-condensation of acetone. The presence of acid is potentially one of the factors leading to the poor yields obtained in this work, and that of Söderberg.



142 143

Entry	Conditions	Result
1	$PdCl_2(PPh_3)_2$ (5 mol%), 24 h	No Reaction
2	$PdCl_2(PPh_3)_2$ (10 mol%), 24 h	No Reaction
3	$CuCl_2$ (10 mol%), 16 h	Complex Mixture

Table 6



134 **144**

Scheme 85

Cyclization of 4-(iodoethynyl)-3-nitropyridine **134** using $Pd(OAc)_2$ in the presence of benzoquinone gave a different product in trace amounts which was identified as the iodoisatogen **144** based on the ^1H NMR spectrum and LCMS (Scheme 85). Although the actual mechanism of forming isatin was ambiguous, Söderberg proposed that it is likely formed via this isatogen intermediate in accordance with Yamamoto's reported gold-catalyzed cyclization.[94] We then hypothesized that the efficient synthesis of this isatogen could lead to a better overall route to the corresponding isatin after reducing this intermediate. Accordingly, efforts were focused on finding conditions to prepare isatogen analogues and convert them to their isatin counterparts.

Conclusion

Isatin and its derivatives are versatile substrates which are important in the field of medicinal chemistry due to their biological and pharmacological properties. Since it was first discovered, the synthesis of isatin has been extensively investigated and reported methodologies have been modified over the years. Earlier routes to isatin have involved aniline and its derivatives as starting materials while more recently, the oxidation of indole to obtain isatin has been explored. Other modern procedures include the use of transition metal catalysts while innovative methods have also focused on following the Green Chemistry protocol.

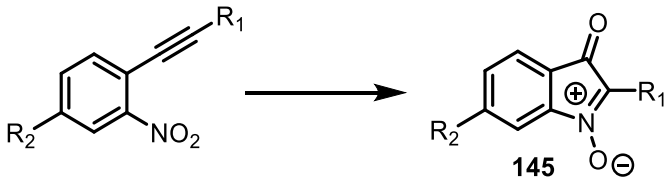
Traditional methods to prepare isatins suffer from a few limitations including multistep sequences, toxic reagents, low reaction scope and harsh conditions. In this investigation, a 3-step method was developed for the synthesis of 5-azaindole but the subsequent oxidation to the azaisatin proved unsuccessful or limited to the *N*-substituted isatins. The homologation of azaisatoic anhydride with cyanide provided *N*-allyl azaisatin but only in poor yields. Finally, the sulfur-ylide mediated carbonyl homologation gave azaisatin in poor yields due to the formation of azaisatoic anhydride which is a competing side reaction.

A transition-metal catalyzed cyclization of iodoacetylenes also resulted in unsatisfactory yields of azaisatins. However, a 2-iodoisatogen intermediate was isolated which could be a useful intermediate for the novel synthesis of isatins.

Chapter 3: Synthesis of 2-Iodoisatogens

Introduction

Isatogens or 3-oxo-3*H*-indole 1-oxides **145** are interesting compounds that do not occur naturally and were first synthesised by Baeyer in 1881 in line with his research involving the synthesis of indigo and isatin.[95] 2-Substituted isatogens were prepared via the cyclization of 2-nitrophenylacetylene derivatives in the presence of concentrated sulfuric acid at room temperature. Further work by Pfeiffer demonstrated that the cyclization could also be effected by refluxing in pyridine, whilst Ruggli reported irradiation with a mercury lamp as an alternative.[96] Moreover, it has been shown that the cyclization proceeds by refluxing with nitrosobenzene in an inert solvent such as chloroform.

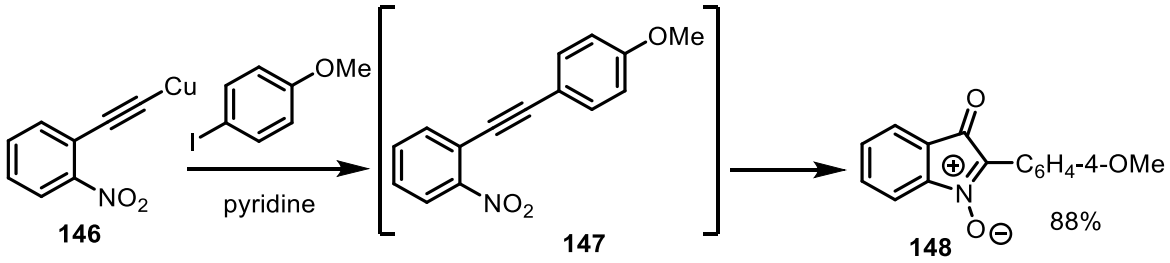


Entry	Conditions	R_1	R_2	Yield
1	conc. H_2SO_4, rt, 10-15 mins	CO_2Et	H	44%
2	pyridine, Δ, 3 mins	Ph	NO_2	75%
3	pyridine, hV, 21 days	2-Py	H	30%
4	nitrosobenzene, chloroform, Δ, 72 h	1-Naph	H	70%

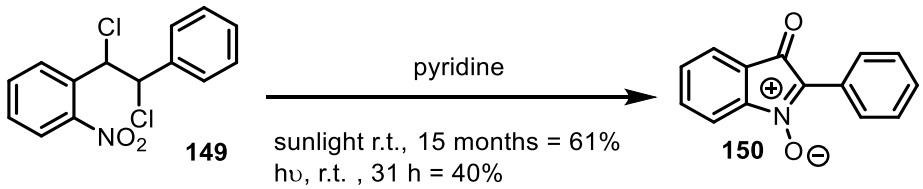
Table 7

Bond and Hooper reported the synthesis of 2-arylisatogens via the reaction of copper o-nitrophenylacetylides **146** with aryliodides in pyridine (Scheme 86).[97] It has been proposed that the cyclization involves the tolan (diphenylacetylene) intermediate **147** although this is not isolated from the reaction. Another way to synthesise 2-arylisatogens involves exposing 2-nitrostilbene dichlorides **149** in sunlight with pyridine for a long period of time.[98] This process could be accelerated by irradiation with a mercury vapour lamp to furnish 2-phenylisatogen **150** in a 40% yield. Also, *o*-nitro

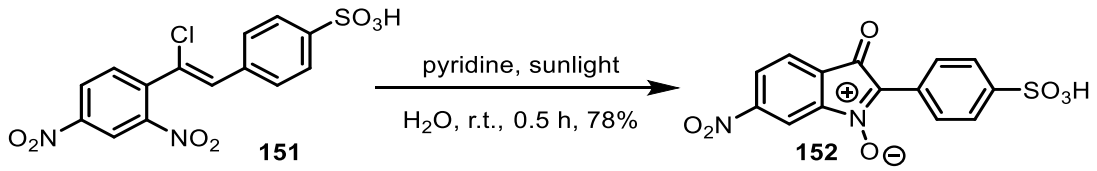
monochlorostilbenes **151** react faster when exposed to sunlight in the presence of pyridine to give the desired 2-arylisatogen **152** (Scheme 88).[99]



Scheme 86

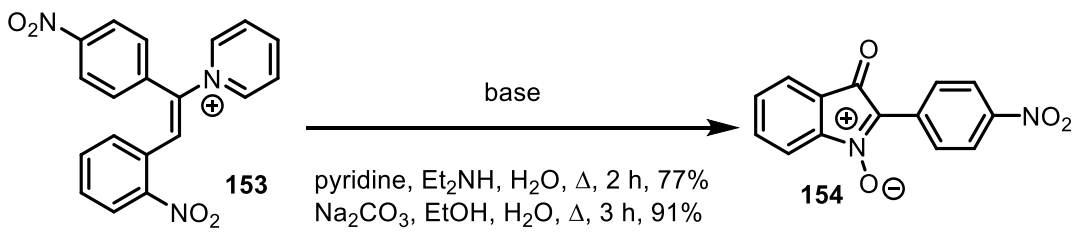


Scheme 87

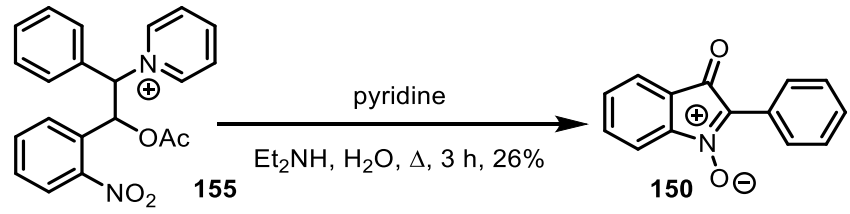


Scheme 88

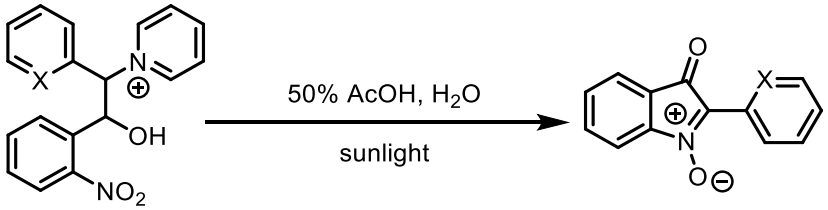
Krohnke reported the synthesis of 2-arylisatogens using *o*-nitrostyrylpyridinium salts **153** and treating them with base such as pyridine, sodium carbonate or diethylamine (Scheme 89).[96] The related acetoxy compound **155** has also been converted to an 2-arylisatogen using the same conditions (Scheme 90). For the corresponding alcohols, *o*-nitrophenylpyridinium ethanols **156** were transformed to the isatogens by exposing them to sunlight in 50% aq. AcOH (Scheme 91).[100] A pyridine derivative has also been successfully prepared using these conditions albeit with a prolonged reaction time of 18 days.[101]



Scheme 89



Scheme 90

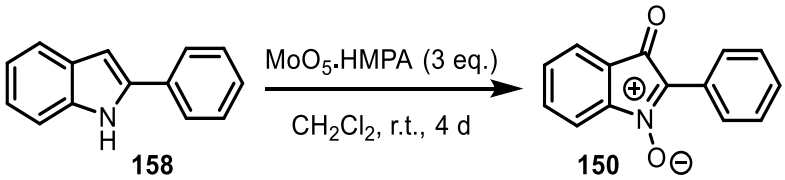


156a = X: CH
156b = X: N

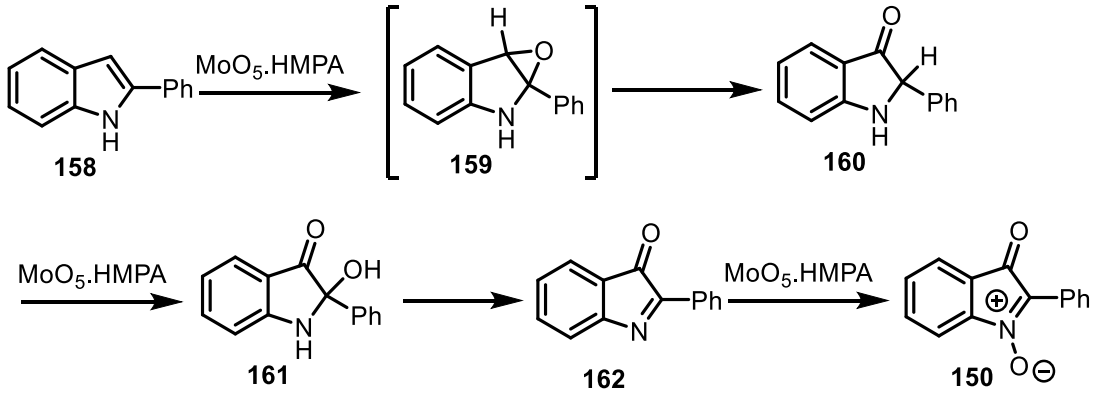
157a = X: CH, 82% (18 h)
157b = X: N, 27% (18 days)

Scheme 91

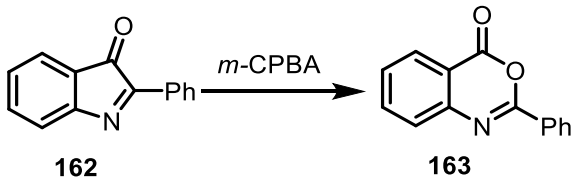
A unique strategy for the synthesis of isatogen derivatives that does not require a cyclization method was reported by Sakamoto.[102] This involved the oxidation of 2-substituted indoles with 3 equivalents of oxodiperoxomolybdenum (VI) to afford 2-aryl isatogens (Scheme 92). Whilst this transformation is not possible using peracids, MoO_5.HMPA was able to oxidize 2-phenylindole **158** to obtain 2-hydroxyindoxyl **160** which could undergo spontaneous dehydration to form indolone **161** (Scheme 93). Further oxidation of the indolone intermediate by MoO_5.HMPA gives the isatogen whereas using a peracid for the oxidation results in a Baeyer-Villiger-type rearrangement to generate 1,3-benzoxazine **163** (Scheme 94).



Scheme 92

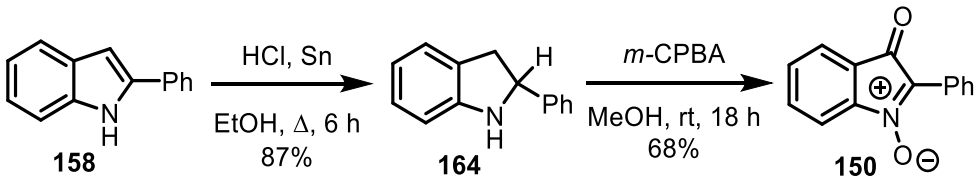


Scheme 93

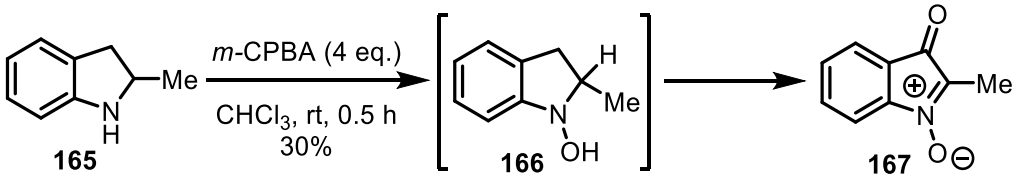


Scheme 94

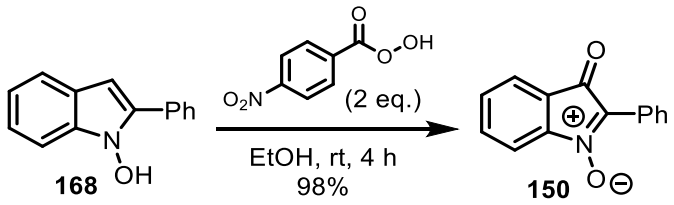
Bergman recently reported the use of *m*-CPBA and indoles to prepare 2-substituted isatogens but with 2,3-dihydroindoles **164** as the intermediates to avoid the unwanted Baeyer-Villiger rearrangement observed with the indolone **162**.[103] 2-Arylindoles were prepared via Fischer indole synthesis and then reduced to indoline derivatives **164** by treatment with hydrochloric acid, ethanol and an excess of tin. The indolines were oxidized with 3 equivalents of *m*-CPBA in methanol to obtain the 2-substituted isatogens in good yields (Scheme 95). Previously, Hooper reported the oxidation of 2-alkyl indolines **165** via the *N*-hydroxy indoline intermediate **166** to obtain the 2-alkylisatogens **167**, the first report of such compounds (Scheme 96).[104] Moreover, in a separate report, Hooper also described the oxidation of 2-substituted 1-hydroxyindoles **168** with 4-nitrobenzoperoxoic acid to afford isatogens which suggests that the hydroxyindole could be an intermediate in the oxidation of indolines to isatogens (Scheme 97).[105]



Scheme 95

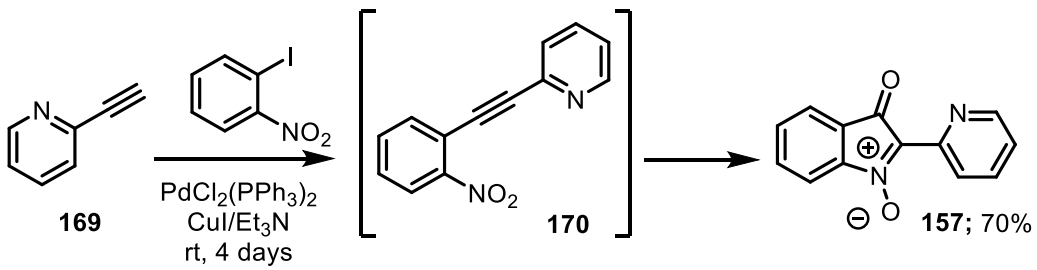


Scheme 96



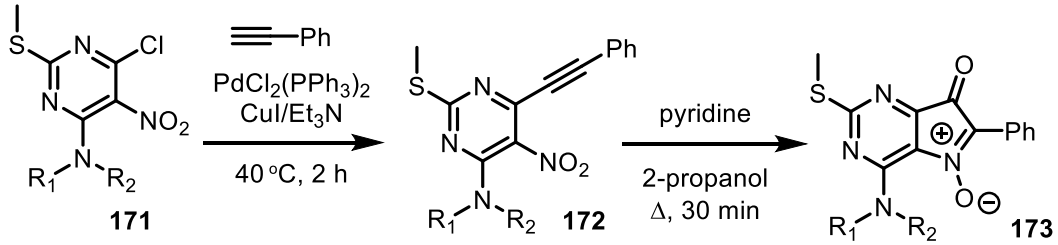
Scheme 97

With the emergence of transition metal catalysis as an important tool for many organic transformations, strategies to synthesise isatogens using transition metal catalysts started to appear more recently. Rosen reported what is effectively Bond and Hooper's method but applying a Sonogashira reaction to couple iodonitrobenzene with the aryl acetylide **169**.[106] The initial idea was to use Pd catalyst to prepare the diarylacetylene intermediate **170** and then cyclize it to the isatogen using previously reported methods. Remarkably, after running the reaction at prolonged times, the desired isatogen **157** was isolated in satisfactory yields (Scheme 98).



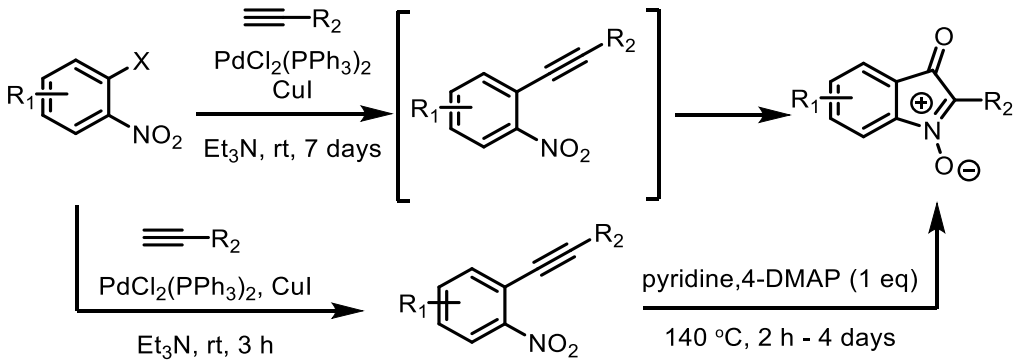
Scheme 98

Cikotiene also attempted a similar approach involving a diarylacetylene intermediate to synthesise isatogens containing pyrimidines.[107] Whilst the Pd-catalyzed coupling of the aryl acetylene with the *o*-nitro chloropyrimidine **171** proceeded uneventfully, the subsequent cyclization was not observed under the reaction conditions. The diarylacetylene intermediates were isolated and traditional conditions were explored for the required cyclization to the isatogen. Eventually, the cyclization was effected using pyridine in ethanol to obtain the isatogens in excellent yields (Scheme 99).

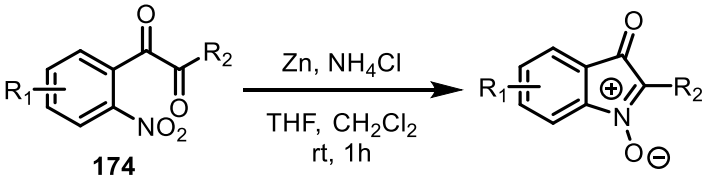


Scheme 99

In their attempt to prepare a small library of isatogen derivatives, Nepveu employed three different strategies based on transition-metal catalysed reactions.[108] One method involved Rosen's approach where the Sonogashira coupling of the *ortho*-nitro arenes with terminal alkynes was followed by the cyclization of the diarylacetylene intermediate to obtain the isatogens in a one-pot procedure. The second method was applied for the cases where the concomitant cyclization did not occur therefore the diarylacetylene intermediates were treated with pyridine and DMAP at 140 °C to afford the isatogens (Scheme 100). Finally, the third strategy involved 1,2-diketone intermediates **174** which were treated with Zn and NH_4Cl to effect a reduction of the nitro group and cyclize to the corresponding isatogen products (Scheme 101).

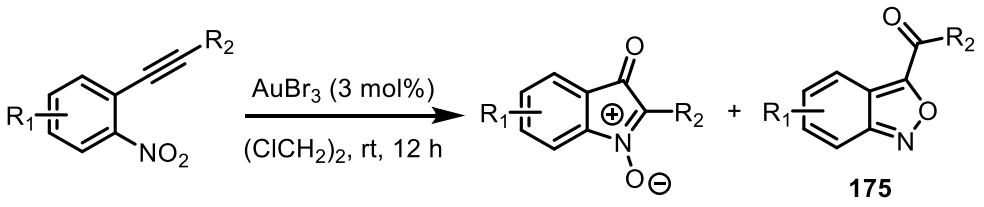


Scheme 100



Scheme 101

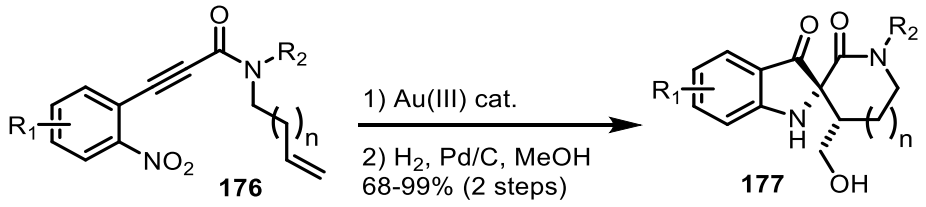
Gold catalysis has also been employed for the preparation of various 2-substituted isatogens. Yamamoto described the $AuBr_3$-catalyzed cyclization of *ortho*-substituted nitrobenzene precursors which either resulted in isatogen formation or the generation of anthranils **175,** depending on the substrate.[94] With the alkyl substituted alkynes, anthranils are obtained selectively whilst analogues bearing aryl substituents gave the isatogens (Scheme 102). Employing more common Lewis acids such as $BF_3.OEt_2$ and $TiCl_4$ were ineffective for the cyclization whilst the complete absence of a Lewis acid led to the corresponding products in moderate yields over prolonged times and elevated temperatures.



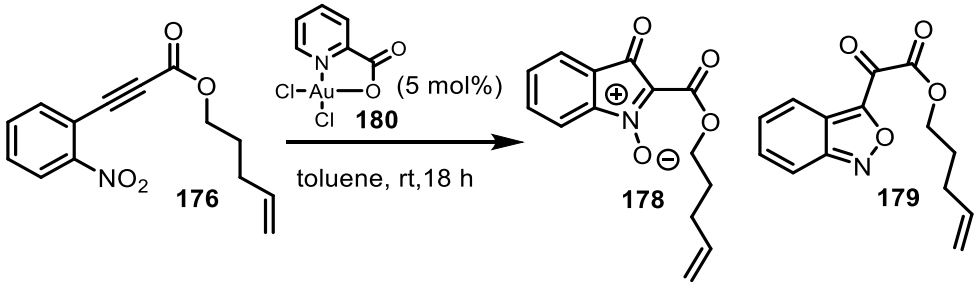
Scheme 102

Verniest reported the gold-catalyzed cyclization of *o*-nitrophenyl-propiolamides **176** followed by an intramolecular dipolar cycloaddition to obtain 2-spiropseudoindoxyls **177** (Scheme 103).[109] The required intermediate for the [3 + 2] intramolecular

cycloaddition is an isatogen therefore efforts were focused on finding suitable conditions to prepare the required isatogens. The major problem encountered was the formation of both the desired isatogen **178** and the anthranil derivative **179** using Au (I) catalysis (Scheme 104). Fortunately, Au (III) catalysts were more effective for the transformation in which selectivity towards the isatogen was observed with $AuBr_3$ or an Au (III) catalyst with a nicotine ligand **180**.

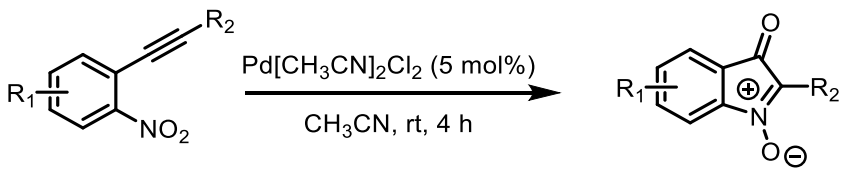


Scheme 103



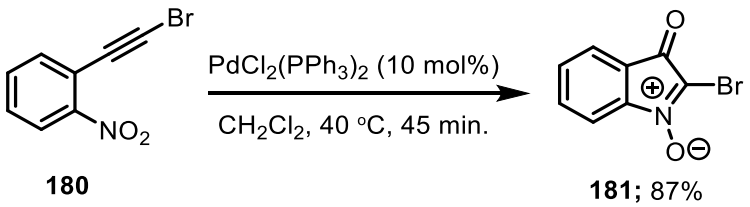
Scheme 104

Ramana carried out extensive investigations to understand the mechanism of the cyclization of *o*-alkynylnitrobenzenes to obtain both the isatogen and the anthranil derivatives.[110] Using DFT calculations, it has been shown that anthranil formation proceeds via a 6-*endo*-dig cyclization in the presence of the gold catalyst. On the other hand, Ramana also demonstrated that using Pd catalyst afforded the isatogen product exclusively via a 5-*exo*-dig cyclization. Consequently, a wide range of 2-substituted isatogens bearing alkyl and aryl substituents were prepared in moderate to excellent yields (Scheme 105).

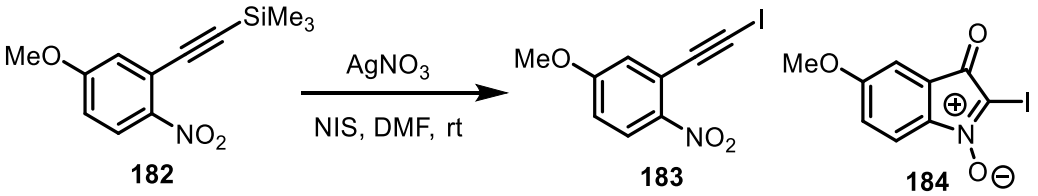


Scheme 105

Finally, Söderberg first reported the preparation of an isatogen bearing a substituent at the 2-position other than an aryl or an alkyl group.[71] During their investigation to cyclize 1-(2-haloethynyl)-2-nitrobenzenes to the corresponding isatins using palladium catalysis, 2-bromoisatogen **181** was isolated in an 87% yield (Scheme 106). Simultaneously, 2-iodoisatogen **184** was also observed when trimethylsilyl-alkyne **182** was treated with $AgNO_3$ alongside the expected iodo-alkyne product **183** (Scheme 107). These 2-halogenated isatogens have not been previously reported and their chemistry was, therefore, unexplored.



Scheme 106



	183	184
100 mol%, 5 min:	95%	0%
5 mol%, 24 h:	0%	83%

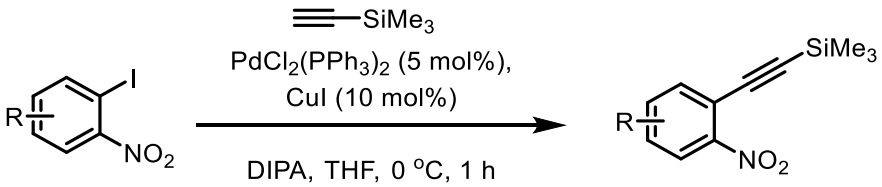
Scheme 107

Although the mechanism of isatin formation remains ambiguous, Söderberg proposed that the cyclization proceeds via 2-haloisatogens. It was then envisaged that developing an efficient methodology for the synthesis of 2-iodoisatogens and their subsequent reduction could provide a novel and innovative way to access isatins. Moreover, there was an opportunity to develop an alternative protocol involving a catalyst cheaper than palladium such as copper salts. Even more enticing was the prospect to investigate the unexplored chemistry of 2-iodoisatogens and unlock their potential as useful intermediates in organic synthesis.

Results and Discussion

Investigations into the Synthesis of Trimethylsilylacetylene Precursors

Our unsuccessful attempts to prepare azaisatin derivatives prompted us to target alternative benzene fused substrates, with a particular emphasis on establishing the scope of isatin formation with a range of electron withdrawing and donating groups. To begin with, methods to synthesize the required TMS-acetylene precursors were explored.



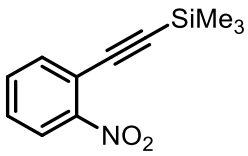
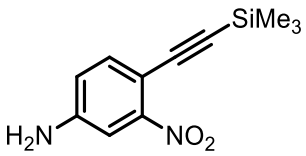
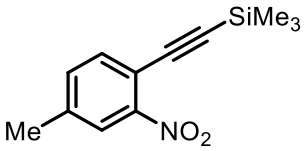
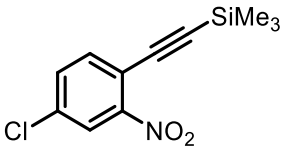
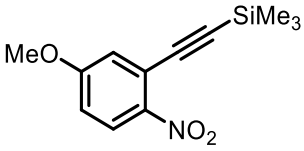
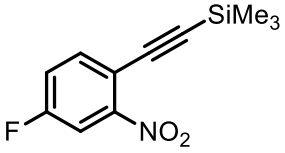
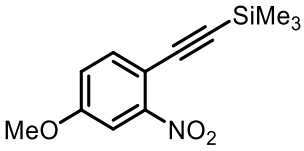
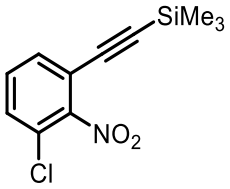
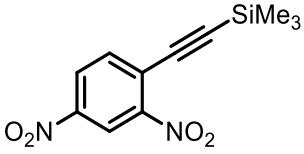
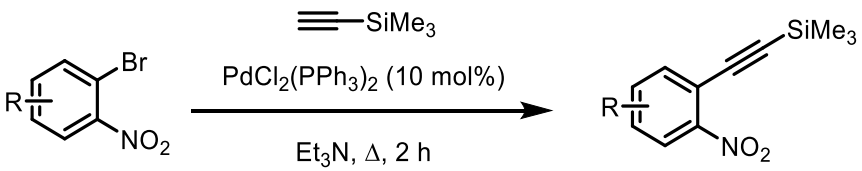
	Product	Yield		Product	Yield
67		81%	**188**		91%
185		93%	**189**		99%
182		96%	**190**		98%
186		97%	**191**		99%
187		83%			

Table 8



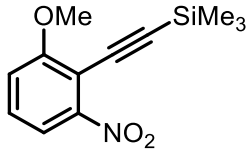
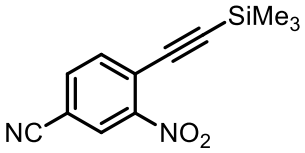
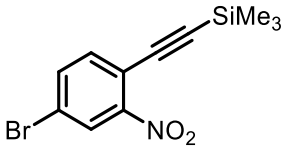
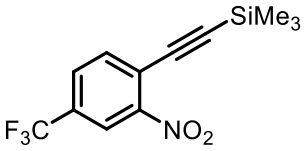
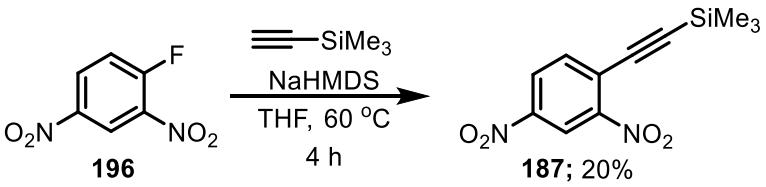
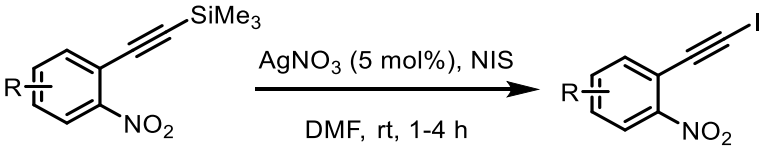
	Product	Yield		Product	Yield
192		68%	**194**		67%
193		91%*	**195**		99%

Table 9 *ca. 80% purity

A range of *o*-halo nitrobenzenes were used for Sonogashira coupling reactions to prepare the desired TMS-acetylene substrates. For the iodide coupling partners, the reaction proceeded uneventfully using $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) in the presence of DIPA at 0 °C. The TMS-acetylene products were obtained in excellent yields as summarized in Table 8. In contrast, the bromide coupling partners did not react effectively using the same conditions employed for the iodide counterparts. Subsequently, the conditions were varied by increasing the Pd catalyst loading to 10 mol% and by heating the reaction under reflux in triethylamine. However, in the presence of 10 mol% CuI as a co-catalyst, Glaser coupling was observed which diminished the product yields. The reaction was therefore performed without CuI which generated the TMS-acetylene substrates in good yields as summarized in Table 9. Finally, a fluoride precursor **196** was used in a nucleophilic aromatic substitution reaction to obtain the corresponding TMS-acetylene. Yoakim reported a S_NAr reaction between aryl nitrofluorides and triethylsilylacetylene in the presence of NaHMDS.[111] Unfortunately, using these conditions only gave the expected TMS-acetylene **187** in a 20% yield (Scheme 108) therefore the iodide precursor was used for the Sonogashira reaction to obtain **187** in 83% yield.



Scheme 108



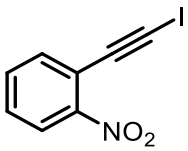
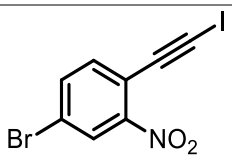
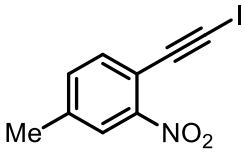
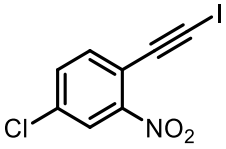
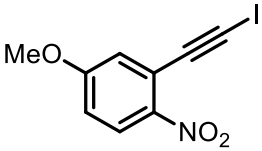
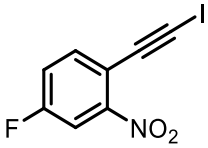
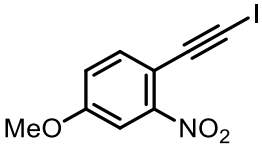
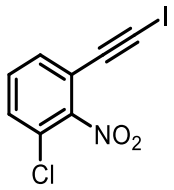
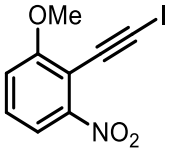
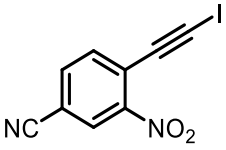
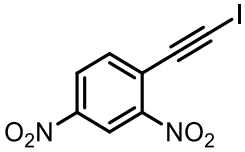
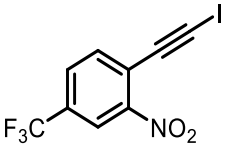
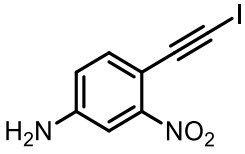
	Product	Yield		Product	Yield
68		81%	**202**		42%
197		79%	**203**		69%
183		68%	**204**		70%
198		75%	**205**		64%
199		62%	**206**		83%
200		94%	**207**		85%
201		42%			

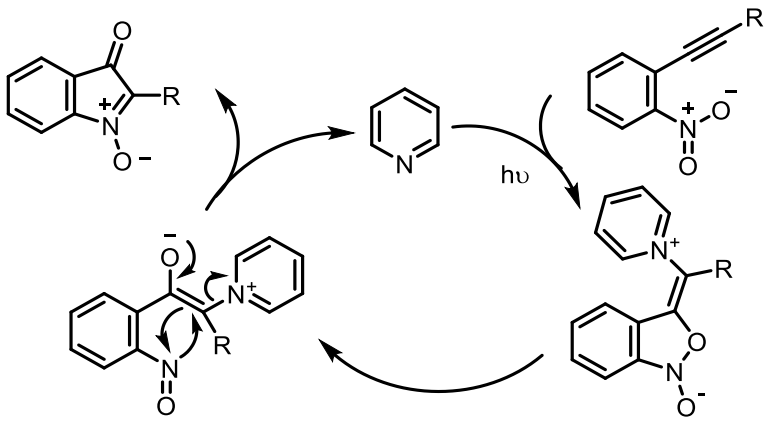
Table 10

Investigations into the Synthesis of Iodoacetylene Precursors

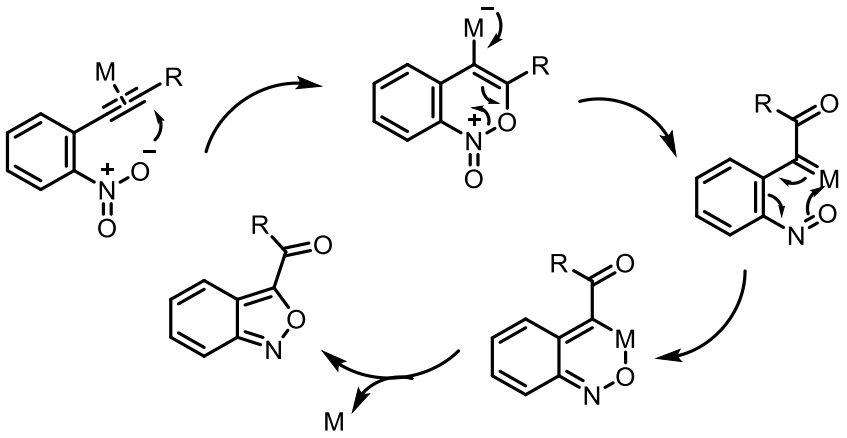
With the TMS-acetylene precursors in hand, the iodination reactions were performed using *N*-iodosuccinimide in the presence of silver nitrate. Most of the reactions proceeded uneventfully with the iodoacetylene substrates obtained in moderate to good yields as summarized in Table 10. However, it was observed that the iodoacetylene intermediates are relatively unstable to air and light with decomposition apparent upon standing at room temperature. It was then investigated whether the more stable TMS-acetylene precursors could undergo cyclization to generate TMS-isatogens, with the objective of transforming these compounds into the corresponding iodoisatogens at a later stage.

Investigations into the Synthesis of Trimethylsilyl-isatogens

As described earlier, Ramana reported a general synthesis of alkyl and aryl isatogens via the palladium catalyzed cycloisomerization of *o*-alkynylnitrobenzenes.[110] Previously, Yamamoto reported that this nitro-alkyne cyclization proceeded in the presence of gold (III) bromide or an iridium hydride complex, although a mixture of the desired isatogen and anthranil was obtained.[94] Huisgen proposed a mechanism leading to the formation of isatogens (Scheme 109)[112] while Crabtree suggested a different mechanism to access anthranils (Scheme 110).[113] Ramana then investigated the feasibility of exclusively forming the isatogen by using a variety of palladium catalysts.

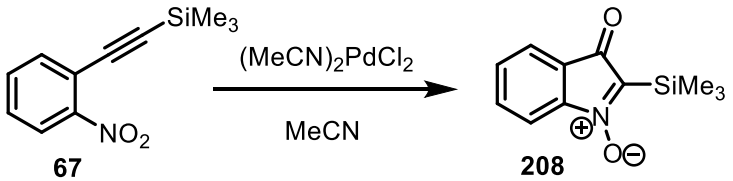


Scheme 109



Scheme 110

Whilst $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ were found to be ineffective, the cyclization proceeded uneventfully using $PdCl_2$ or $PdBr_2$. The yields were further improved by employing the acetonitrile and benzonitrile complexes of these Pd catalysts. A wide range of *o*-alkynylnitrobenzenes were subjected to the reaction conditions, highlighting the compatibility of substituents such as free alcohols, alkenes, and electron-rich and electron-poor aryl groups.[110] However, the synthesis of trimethylsilyl-isatogen **208** had not been described in their investigation and it was decided to explore the cycloisomerization of TMS-alkynylnitrobenzene using Ramana's conditions.



67 **208**

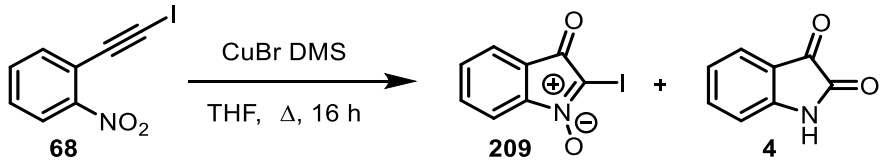
Entry	Cat. loading	Temp.	Time	Result
1	10 mol%	25 °C	4 h	No reaction
2	10 mol%	Reflux	24 h	No reaction
3	50 mol%	Reflux	24 h	No reaction
4	100 mol%	Reflux	24 h	No reaction

Table 11

Treatment of TMS-alkynylnitrobenzene **67** with 10 mol% of $Pd(CH_3CN)_2Cl_2$ at rt for 4 h showed no reaction while heating the reaction at reflux for 24 h proved to be ineffective (Table 11). Increasing the catalyst loading to 50 mol% and subsequently using stoichiometric amounts of transition metal catalyst also gave no reaction. With efforts to synthesise the TMS-isatogen proving to be futile, attention was turned to the cycloisomerization of the iodoacetylene precursors to obtain iodoisatogens. Efforts were also focused on whether a cheaper copper catalyst can be employed to achieve the desired cyclization.

Investigations into the Copper-catalyzed Synthesis of Iodoisatogens

Using 1-(iodoethynyl)-2-nitrobenzene **68** as the model substrate, the viability of the cyclization was investigated using a number of palladium and copper catalysts (Table 12). Initially employing Söderberg's conditions did result to the isatin but only with a moderate yield of 46%.

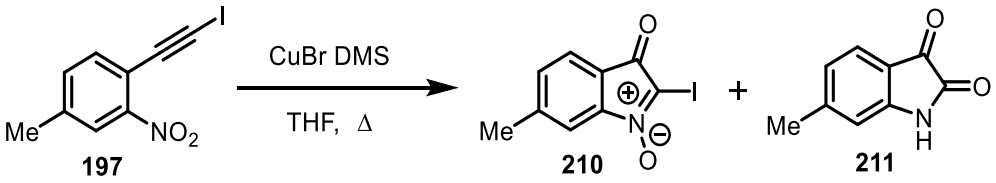


68 **209** **4**

Entry	Catalyst	Loading	Solvent	Isatogen Yield	Isatin Yield
1	$PdCl_2(PPh_3)_2$	5 mol%	acetone	0%	46%
2	CuI	10 mol%	acetone	0%	27%
3	$CuCl_2$	10 mol%	acetone	0%	22%
4	$PdCl_2(PPh_3)_2$	5 mol%	CH_2Cl_2	0%	30%
5	$PdCl_2(PPh_3)_2$	5 mol%	THF	0%	55%
6	CuBr.DMS	50 mol%	THF	73%	13%
7	CuBr.DMS	25 mol%	THF	89%	8%
8	CuBr.DMS	100 mol%	THF	0%	60%

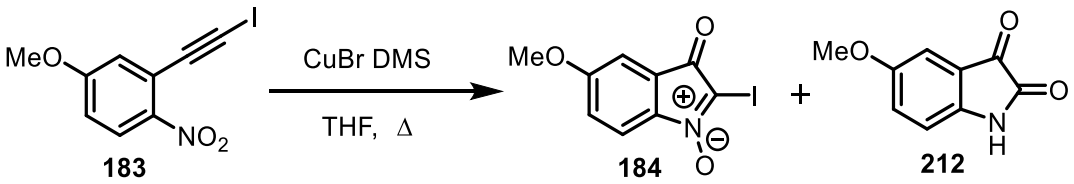
Table 12

Substituting the Pd catalyst with copper salts resulted to poor yields of isatin with no isatogen detected. Changing the solvent from acetone to THF to enable use of anhydrous conditions only resulted to a marginal improvement of the isatin yield. Remarkably however, using 50 mol% of CuBr.DMS in THF afforded the desired iodoisatogen in a 73% yield with only 13% of isatin isolated. The selectivity for the isatogen further improved by decreasing the loading to 25 mol%. However, increasing the loading to 1 equivalent gave the isatin exclusively with a moderate yield of 60%. It was then hypothesised that the copper salt not only catalyzes the cycloisomerization to the iodoisatogen but it also effects the transformation of iodoisatogen to isatin.



Entry	Cat. loading	Time	Isatogen Yield	Isatin Yield
1	25 mol%	16 h	63%	23%
2	25 mol%	1.5 h	91%	0%
3	10 mol%	5 h	70%	16%

Table 13

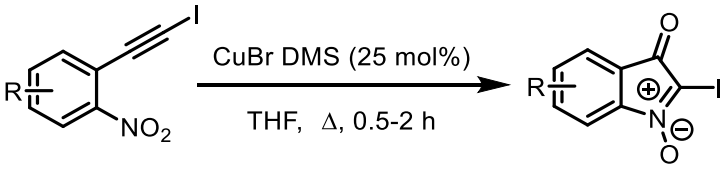


Entry	Cat. loading	Time	Isatogen Yield	Isatin Yield
1	25 mol%	16 h	56%	44%
2	25 mol%	0.5 h	99%	0%
3	10 mol%	5 h	77%	16%

Table 14

With an effective copper-catalyzed cyclization in hand, the cycloisomerizations of a range of electron-rich and electon-poor iodoacetylenes were attempted. Starting with iodo-acetylene **197**, the desired isatogen **210** was obtained in a 63% yield and the corresponding isatin **211** in a 23% yield after running the reaction for 16 h (Table 13). Similar results were observed with the cyclization of iodoacetylene **183** which furnished the isatogen **184** in a 56% yield and the isatin **212** in a 44% yield after a reaction time of 16 h (Table 14). It was then discovered that the reactions with the electron-rich substrates proceeded much faster compared to the electron-neutral aryl iodoacetylenes, with the cyclizations found to be complete within 2 h. The desired 6-methyl-2-iodo-isatogen **210** and 5-methoxy-2-iodo-isatogen **184** were then obtained in excellent yields with only traces of the corresponding isatin observed after 0.5-2 h. As expected, running the reaction for longer times led to the formation of the corresponding isatins.

The subsequent cyclizations were then carefully monitored by TLC analysis in order to stop the reaction as soon as complete consumption of the starting material was observed. The reaction was also attempted using 10 mol% of the catalyst but this led to longer reaction times which resulted to the formation of isatin. Further examples of electron-rich analogues were explored and pleasingly, the iodoisatogens were synthesized in excellent yields as summarized in Table 15. In all cases, the cyclizations are reproducible on a gram scale and the isatogen products are stable for a few weeks if stored below ambient temperature in the absence of light. Problems were encountered when the cyclization of the aniline substrate **201** was attempted which could be as a result of the copper catalyst coordinating to the free amine. Accordingly, the corresponding acetanilide **215** was prepared and the cyclization proceeded to obtain the isatogen **216** in a 76% yield (Scheme 111).



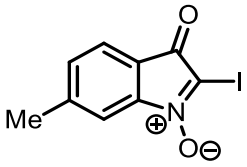
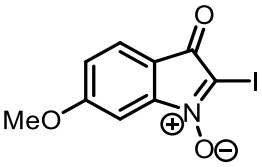
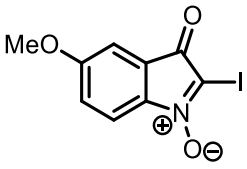
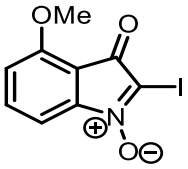
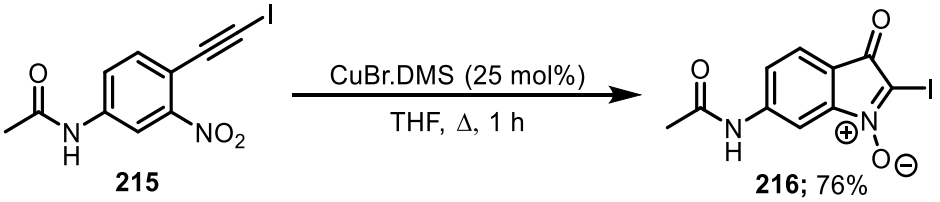
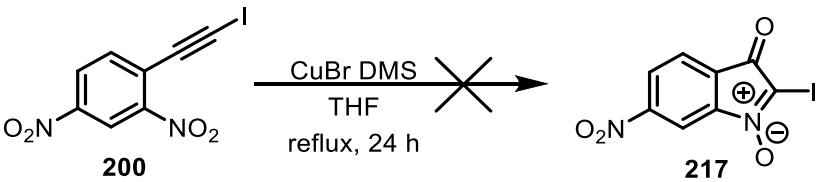
	Product	Yield		Product	Yield
210		91%	**213**		95%
184		99%	**214**		64%

Table 15

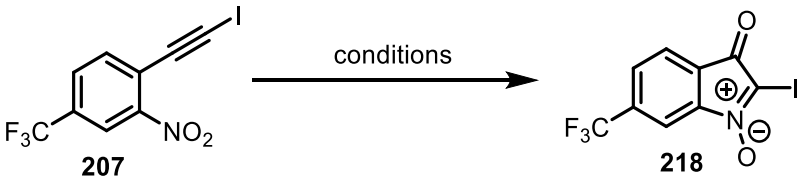


Scheme 111

With these promising results, the cyclizations were then attempted with the electron-poor iodoacetylenes using the same conditions. Unfortunately, treating the nitro- substituent **200** with 25 mol% of CuBr.DMS gave no reaction (Scheme 112). Doubling the catalyst loading to 50 mol% also returned starting material whereas using a stoichiometric amount of Cu-salt and running the reaction for long times led to a complex mixture. Similarly, with the trifluoromethyl-substituent **207**, performing the reaction for long times with 25 mol% of catalyst led to no reaction and decomposition of starting material (Table 16). Increasing the catalyst loading to 50 mol% and then using stoichiometric amounts did not show improvement. Moreover, using microwave irradiation led to a complex mixture and Glaser coupling of starting material was also observed.



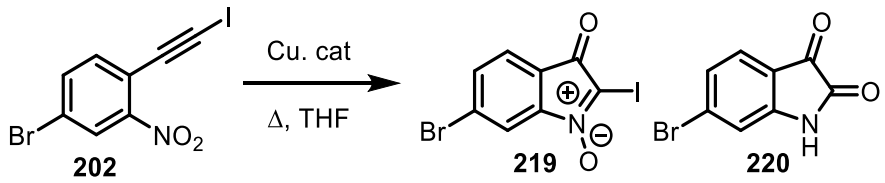
Scheme 112



	Conditions	Time	Result
1	25 mol% CuBr.DMS, THF, reflux	24 h	Complex mixture
2	50-100 mol% CuBr.DMS, THF, reflux	6 h	Complex mixture
3	1 eq. CuBr.DMS, DMF, µw:200W, 150 °C	1 h	Complex mixture
4	1 eq. CuBr.DMS, DMF, µw:200W, 100 °C	3 min	Glaser coupled product

Table 16

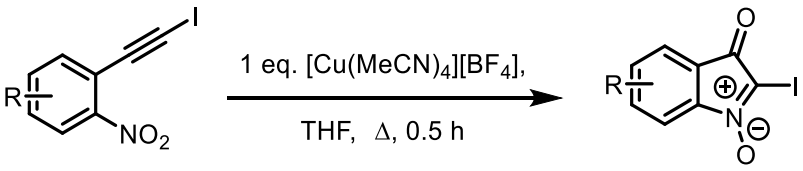
Efforts were therefore turned to finding a more active copper catalyst to achieve the cyclization more efficiently. Treatment of the bromo-substituent **202** with 25 mol% of copper (I) iodide, a more electrophilic copper source, for 24 h gave no reaction. Fortunately, employing 25% of $[Cu(MeCN)_4][BF_4]$ after 8 h gave the desired isatogen **219** albeit as a mixture with isatin and starting material (Table 17). Increasing the catalyst loading to 50 mol% gave the same results while running the reaction for 24 h with catalytic $[Cu(MeCN)_4][BF_4]$ resulted to a mixture of isatin and starting material. These results suggested that the isatogen being formed is converted to the corresponding isatin if left for a long period of time and even if the starting iodoacetylene is not fully converted to isatogen. It is therefore essential to ensure that the isatogen-forming reaction is fast and that the reaction is stopped before conversion to the isatin is observed.



	Conditions	Time	Result*
1	25 mol% $[Cu(MeCN)_4][BF_4]$	8 h	Isatogen + isatin + starting material
2	50 mol% $[Cu(MeCN)_4][BF_4]$	24 h	Isatin + starting material

Table 17 (*based on NMR of crude mixture)

Gratifyingly, the use of 1 eq. of the copper complex led to full conversion of the starting iodoacetylene after 30 min. and furnished the isatogen **219** in a 64% yield. However, the cyclization of the nitro-substituted analogue led to complete disappearance of starting material but with no identifiable product isolated. Nonetheless, the reaction of the other electron-poor substrates proceeded reasonably well, delivering the corresponding isatogens in moderate yields as summarized in Table 18.



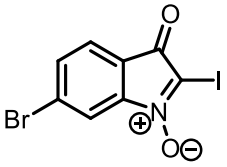
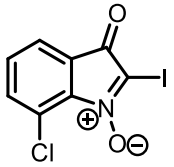
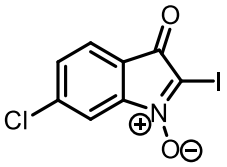
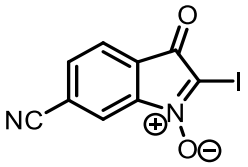
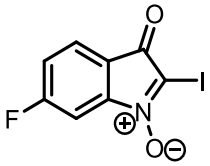
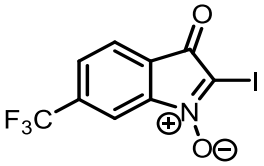
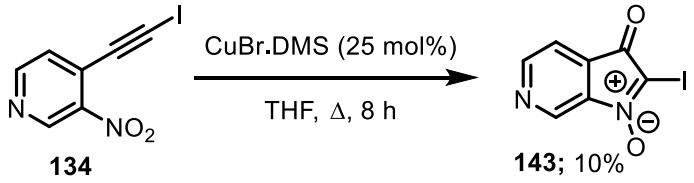
	Product	Yield		Product	Yield
219		64%	**223**		55%
221		59%	**224**		68%
222		53%	**218**		36%

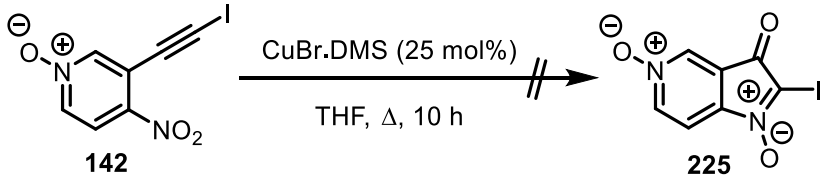
Table 18

Finally, the cycloisomerization of the pyridine analogues was reinvestigated using these conditions. Treating 4-(iodoethynyl)-3-nitropyridine **134** with 25 mol% of CuBr.DMS after 8 h gave the corresponding isatogen albeit in less than 10% yield (Scheme 113). Running the reaction for 24 h and using super-stoichiometric amounts of CuBr.DMS (1.2 eq.) resulted in a complex mixture. The cyclization of 3-(iodoethynyl)-4-nitropyridine 1-oxide **142** was also attempted using 25 mol% of CuBr.DMS with the anticipation that the *N*-oxide would act as an electron-donating substituent hence making the reaction facile (Scheme 114). Disappointingly, the reaction did not proceed after 10

h and running the reaction for more than 24 h led to decomposition of starting material. Moreover, the same problems were encountered when the substrates were treated with catalytic amounts of $[Cu(MeCN)_4][BF_4]$.

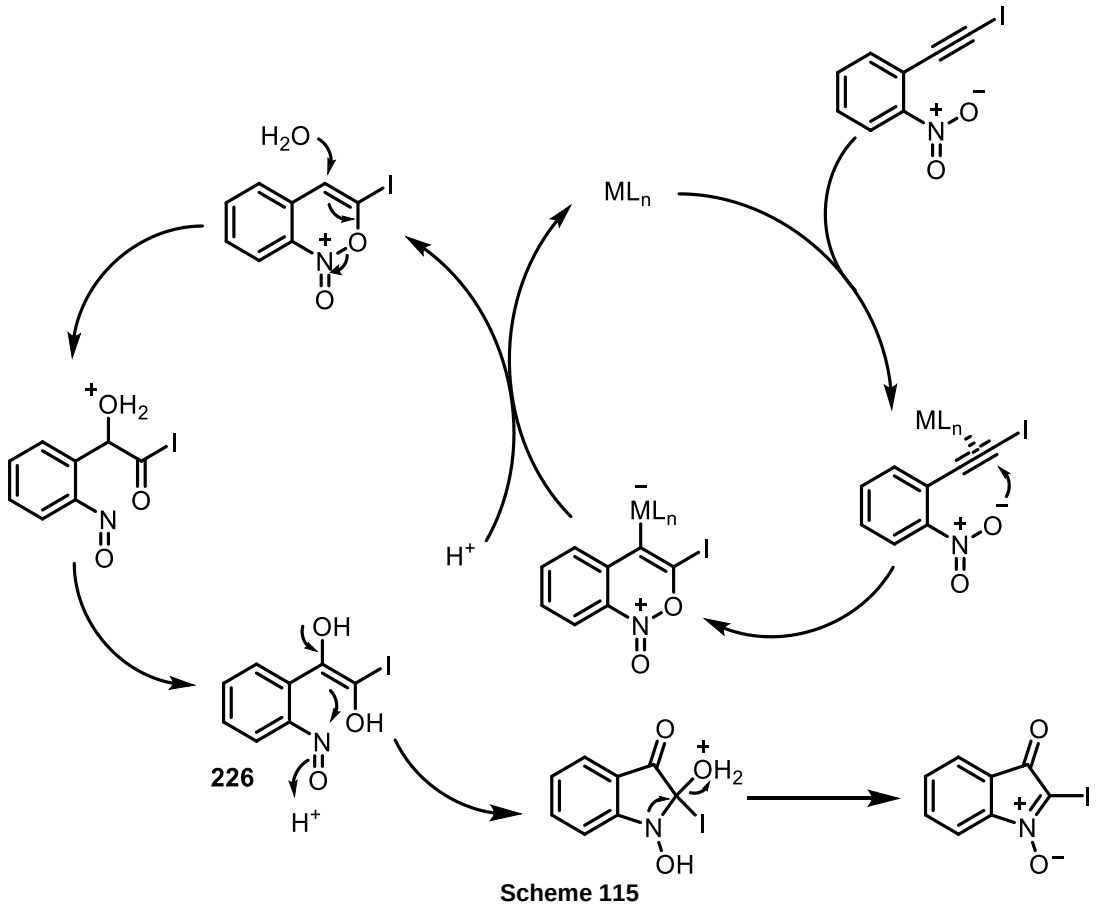


Scheme 113



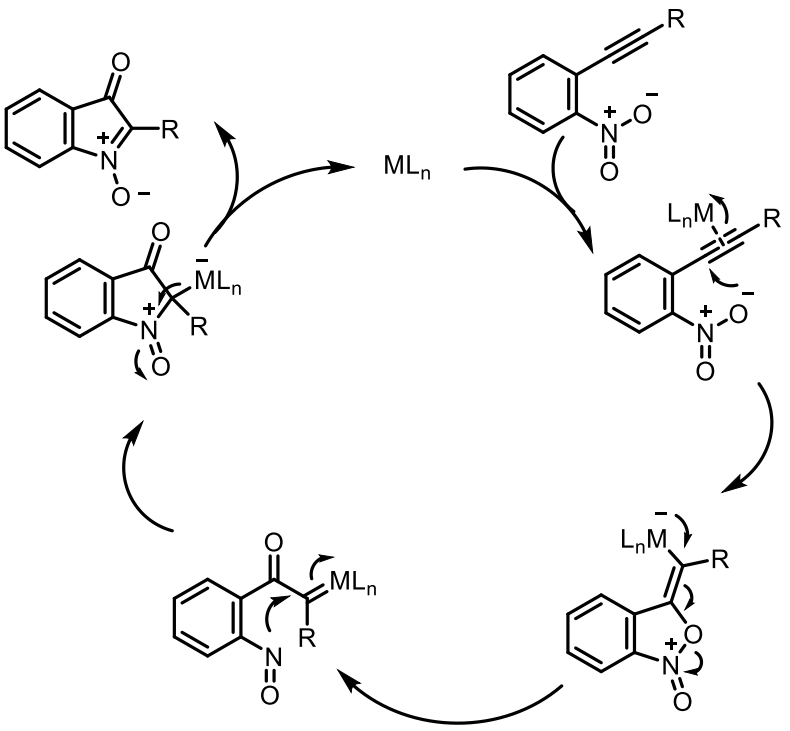
Scheme 114

Söderberg proposed a mechanism for the formation of isatogen based on the mechanism suggested by Yamamoto (Scheme 115).[94]



Scheme 115

According to the proposed mechanism, a metal complex undergoes protonolysis, followed by hydrolysis to form a nitrosobenzene derivative **226** which can cyclize and undergo dehydration to yield the isatogen. On the other hand, Ramana suggested a different mechanism involving the addition of nitro oxygen to the alkyne in a 5-*exo*-dig manner (Scheme 116).[110]



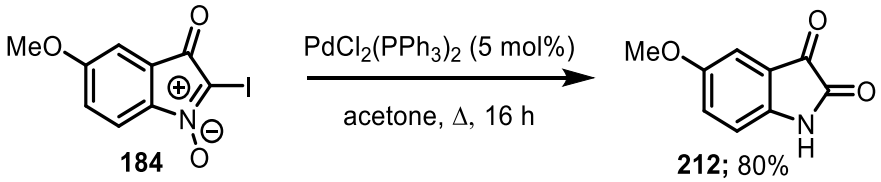
Scheme 116

Based on both hypotheses, the reactivities of the electron-rich and electron-poor iodoacetylene precursors can be explained by considering the first step of the mechanism involving the attack of the nitro group to the metal-alkyne complex. By incorporating an electron donating substituent into the aryl ring, the nucleophilicity of the nitro group is enhanced hence enabling a more facile nucleophilic attack. Moreover, increasing electron density on the aromatic ring may also promote binding of Cu-to the alkyne. On the other hand, the incorporation of electron-withdrawing groups would retard these processes (but would nevertheless enhance electrophilicity of the alkyne). It is worth bearing in mind that electron deficient substrates do react, but don't provide clean product and so it may be that they simply offer alternative reaction pathways. Lastly, the

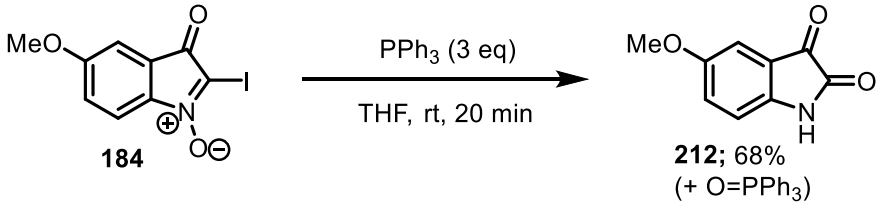
competing isatin-forming reaction remains a significant factor which influences the yield of the desired isatogens.

Investigations into the Reduction of Isatogen to Isatin

There are no established protocols in the literature for the direct conversion of isatogen to isatin. Söderberg suggested that their Pd-catalyzed synthesis of isatin most likely proceeds via the isatogen, although a mechanism was not proposed.[71] Nonetheless, 5-methoxy-2-iodoisatogen, the most reactive substrate in this investigation, was subjected to Söderberg's conditions to see whether this would convert the substrate to the corresponding isatin. Unsurprisingly, treatment of the isatogen **184** with 5 mol% of $PdCl_2(PPh_3)_2$ after 16 h gave 5-methoxy-isatin **212** in an excellent yield (Scheme 117).



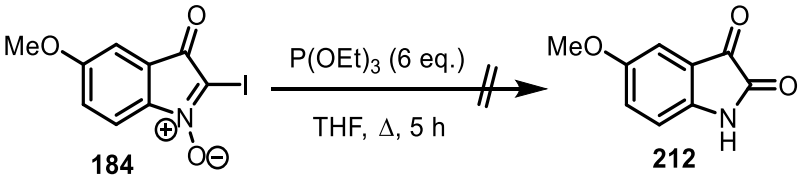
Scheme 117



Scheme 118

Analysis of the reaction mixture obtained after reduction of the isatogen with $PdCl_2(PPh_3)_2$ provided evidence for the formation of triphenylphosphine oxide (^{1}H NMR spectrum of the crude material). This led to the hypothesis that triphenylphosphine might be acting as a reducing agent in the same way that it reduces aromatic *N*-oxides to the corresponding amines. Accordingly, 5-methoxy-2-iodoisatogen was treated with 3 eq. of PPh_3 which encouragingly led to the formation of the desired isatin **212** (Scheme 118).

However, the resulting triphenylphosphine oxide by-product proved to be very difficult to separate from the desired product by flash column chromatography.



Scheme 119

In an endeavour to avoid the triphenylphosphine oxide which proved to be problematic, the reducing agent was replaced with triethylphosphite (Scheme 119). The resulting by-product, triethylphosphate, is a liquid which is easier to remove hence isolation of the desired isatin would be more facile. Unfortunately, although all the starting material was consumed after 5 h, no isatin was detected after treatment of the isatogen with excess triethylphosphite. The crude mixture contained a number of intensely coloured compounds and we have speculated that indigo related products[114-116] could be formed (Figure 6) although no compounds have been isolated and characterized.

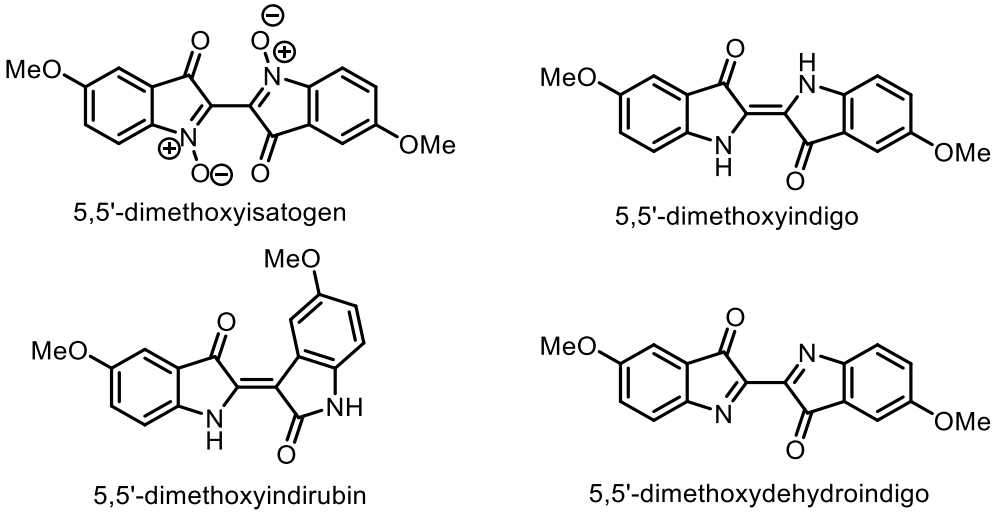
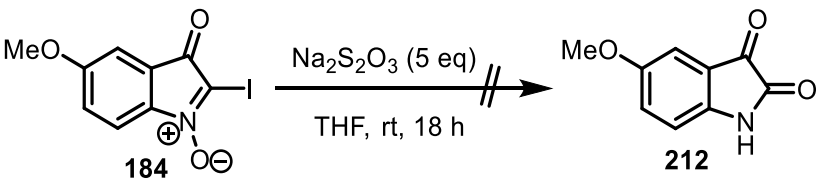


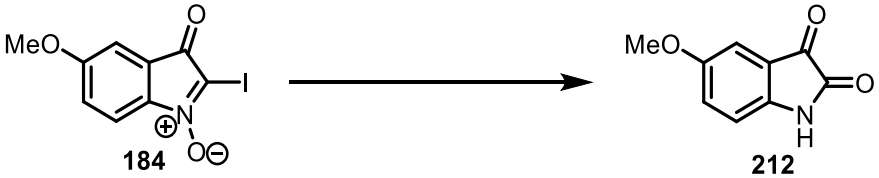
Figure 6

Using sodium thiosulfate as an alternative reducing agent was also ineffective with the reaction giving a complex mixture (Scheme 120).



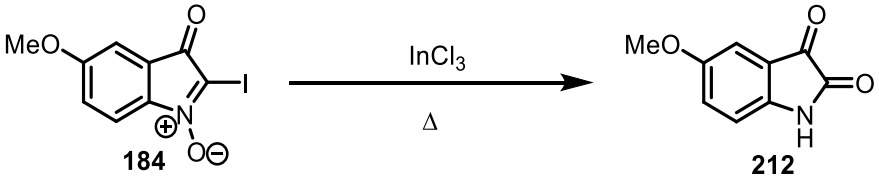
Scheme 120

A wide variety of metals were then explored for the reduction of the isatogens, in which reagents used for the deoxygenation of amine *N*-oxides were focused on. Reported conditions involving ruthenium,[117] cerium,[118] copper,[119] zinc[120] and titanium[121] were all ineffective for the required transformation (Table 19). More promising results were obtained using $Mo(CO)_6$[122] and $InCl_3$[117] in which the desired isatin was isolated in moderate yields. It was then decided to optimize the reaction conditions using $InCl_3$.



Entry	Conditions	Yield
1	$RuCl_3.xH_2O$ (1 eq.), MeCN, Δ, 24 h	0%
2	$CeCl_3.7H_2O$ (2 eq.), Zn (4 eq.), MeOH, rt, 18 h	0%
3	CuI (1 eq.), Zn (1 eq.), EtOH, Δ, 18 h	0%
4	$TiCl_4$ (1 eq.), NaI (3 eq.), MeCN, rt, 2 min.	34%
5	$Mo(CO)_6$ (1 eq.), EtOH Δ, 3 h	38%
6	$InCl_3$ (1 eq.), MeCN, Δ, 30 h	47%

Table 19

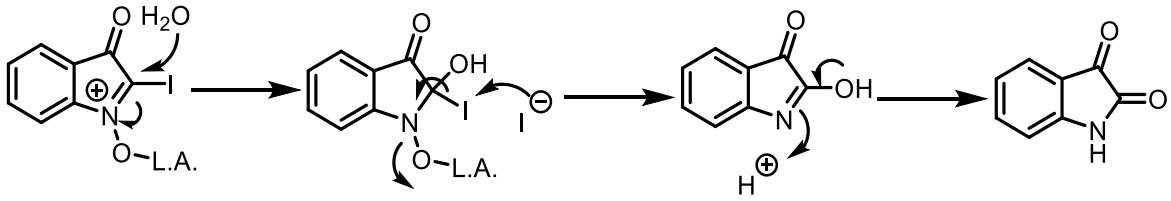


Entry	$InCl_3$	Solvent	Time	Yield
1	1 eq.	MeCN	30 h	47%
2	2 eq.	MeCN	24 h	58%
3	2 eq.	MeCN:H_2O (10:1)	18 h	73%

Table 20

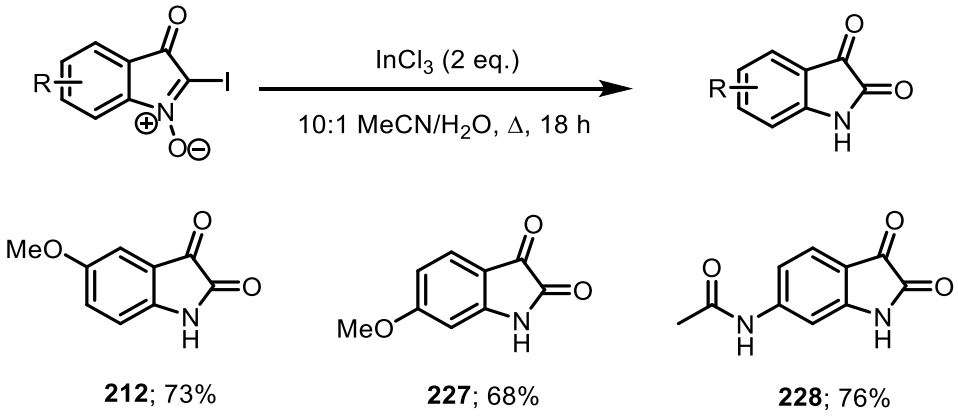
Whilst $InCl_3$ effectively transforms the iodoisatogen to isatin, it was observed that most of the starting material was still present even after heating for 30 h. Doubling the equivalents only marginally improved the yield and unconverted isatogen was still detected after 24 h. It was then envisaged that the reaction mechanism involves the initial addition of water after the coordination of the Lewis acid with the oxide (Scheme 121).

Accordingly, water was added to the reaction mixture which converted all the starting isatogen into isatin with an excellent yield of 73%.



Scheme 121

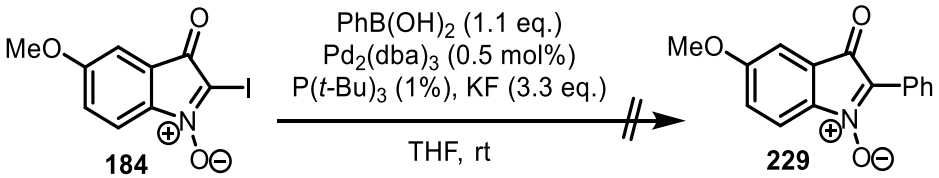
With effective conditions to reduce the isatogens to the corresponding isatin, two more examples were studied to obtain isatin analogues in good yields. Using this new strategy, a number of isatins which are either not commercially available or very expensive can be obtained in reasonable quantities. Moreover, this new approach avoids the use of expensive palladium catalyst for the cyclization to isatogens and the subsequent reduction to isatins. This efficient synthetic methodology was performed with easily accessible starting materials and relatively non-toxic reagents making it an attractive alternative to traditional methods to prepare isatins.



Scheme 122

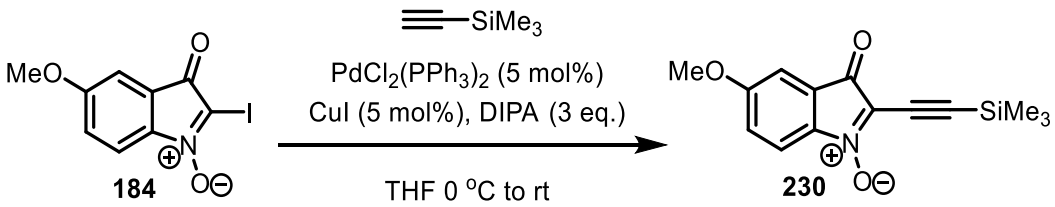
Investigations into the Functionalization of 2-Iodoisatogen

Having developed an efficient method to synthesise 2-iodoisatogens and to reduce them to the corresponding isatins, efforts were turned to functionalizing these novel substrates to access new heterocyclic products other than isatins. Specifically, we decided to concentrate efforts on elaborating the C-I bond and finding suitable nucleophiles to displace the iodide and form novel heterocyclic products. The first strategy proposed was employing Pd-catalyzed cross coupling reactions although the tendency of Pd to reduce 2-iodosatogens to isatins was an anticipated problem.



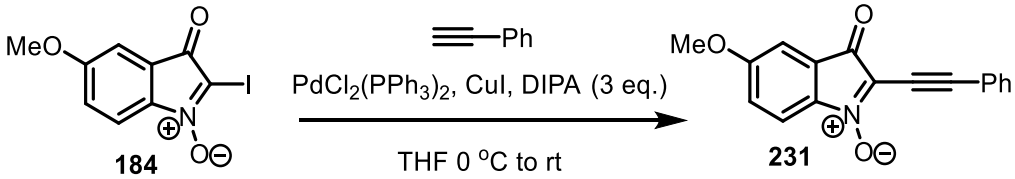
Scheme 123

In an effort to avoid this potential drawback, initial Pd-catalyzed cross coupling reactions were attempted at room temperature in order to slow down the reduction to isatin. However, it was disappointing to find that Suzuki reactions employing Fu's conditions[123] failed to give any of the desired cross-coupled products at room temperature and application of heat only led to isatin products. Nevertheless, a Sonogashira reaction was attempted at 0 °C to room temperature and pleasingly, this resulted in the desired cross-coupled product, albeit at a moderate yield of 35%. Fortunately, increasing the equivalents of the acetylene coupling partner to 3 lead to a more promising yield of 68% (Table 21). Buoyed by these encouraging results, it was decided to explore the scope of this cross-coupling reaction which was not previously reported. However, the reaction with phenylacetylene gave the expected product in a dissatisfying yield of 44% therefore further optimisation studies were performed.



Entry	TMS-acetylene	Time	Yield
1	1.5 eq.	5 h	35%
2	1.5 eq.	24 h	36%
3	2 eq.	1 h	68%

Table 21



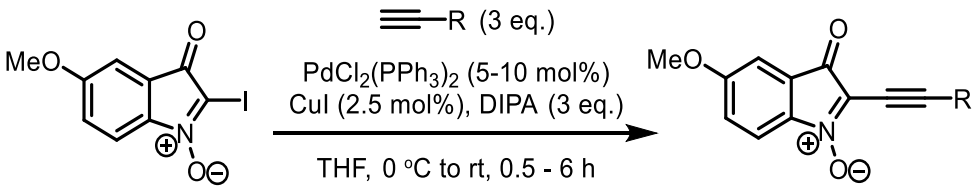
Entry	phenyl-acetylene	Pd. cat	Cu cat.	Time	Yield
1	3 eq.	5 mol%	5 mol%	1 h	44%
2	3 eq.	5 mol%	0 mol%	24 h	0%
3	3 eq.	5 mol%	5 mol%	1 h	0%
4	0 eq.	5 mol%	5 mol%	24 h	0%
5	3 eq.	10 mol%	2.5 mol%	0.5 h	51%

Table 22

As the reaction in the presence of 5 mol% of CuI led to Glaser coupled product, which is common in Sonogashira cross-coupling reactions, the copper catalyst was removed but this completely shut down the reaction (Table 22). Adding phenylacetylene portion wise to alleviate the homocoupling problem did not help either as this resulted in a complex mixture. Finally, doubling the loading of Pd catalyst to 10 mol% and decreasing the amount of Cu catalyst improved the yield to 51%.

Using other acetylene cross-coupling partners gave the desired products in moderate yields (Table 23). Interestingly, one by-product isolated in the reaction with 1-hexyne was the rearranged product **233** which was previously reported by Ibrahim (Scheme 124).[124] Even more peculiar is the result obtained in the absence of a Pd

catalyst; in this case the base employed acted as a nucleophile and added to the isatogen product (Scheme 125). Since this unusual reaction has not been previously reported, the addition of different amines were next investigated.



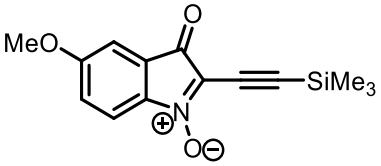
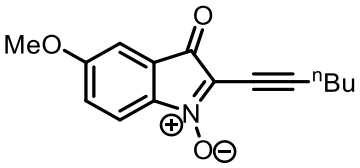
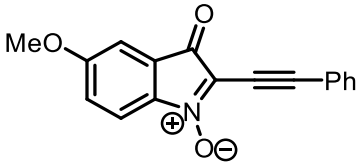
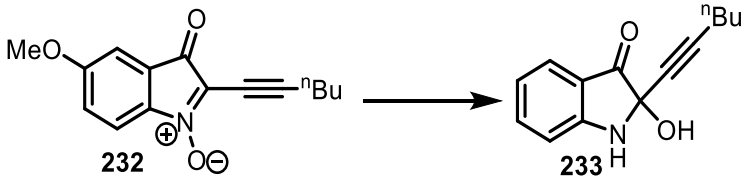
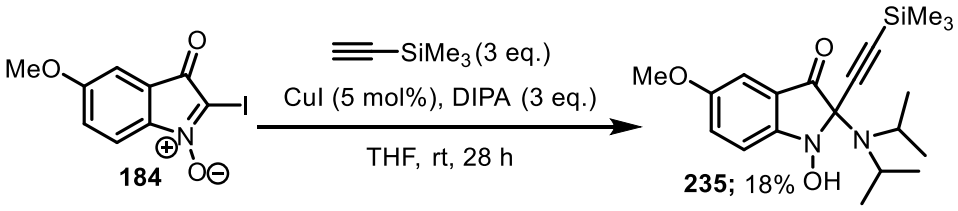
	Product	Yield		Product	Yield
230		68%	**232**		49%
231		51%			

Table 23



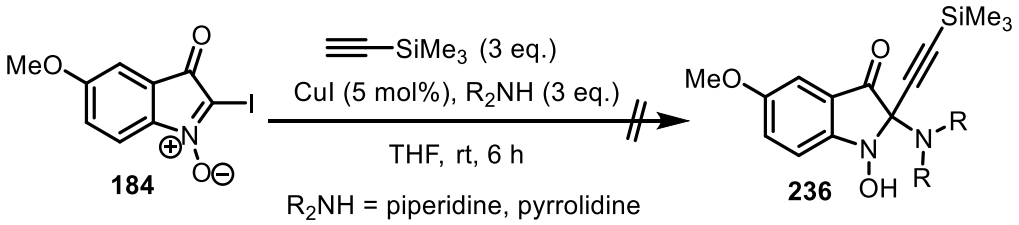
Scheme 124



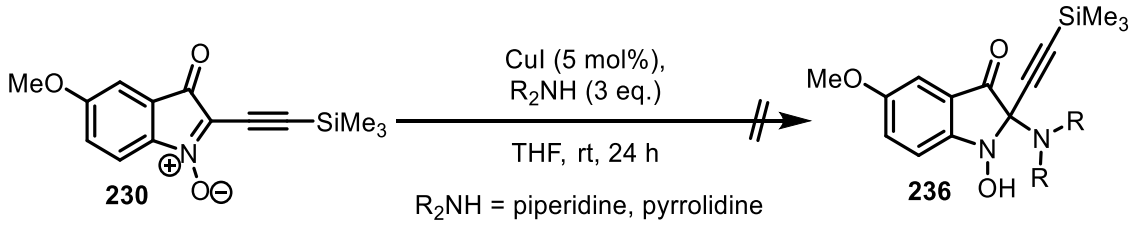
Scheme 125

Preliminary experiments focused on replacing the diisopropylamine base with piperidine and pyrrolidine, however these generated complex mixtures when 2-iodoisatogen **184** was used as the starting material. It was then speculated that the cross-coupling with the acetylene occurs first before the addition of the amine.

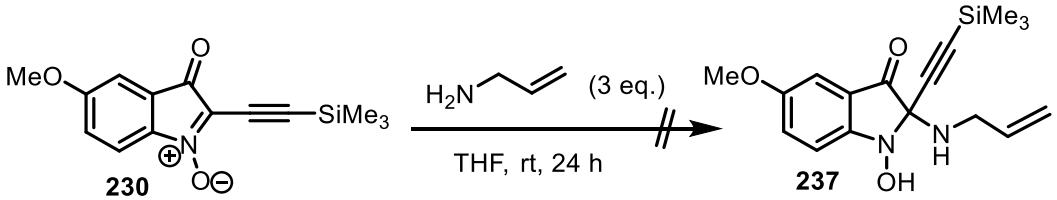
Accordingly, the 2-alkynylisatogen **230** was subjected to the reaction conditions but again, this resulted to complex mixtures (Scheme 127). Moreover, the reaction of allylamine without the presence of any copper catalyst resulted in the recovery of starting material (Scheme 128).



Scheme 126

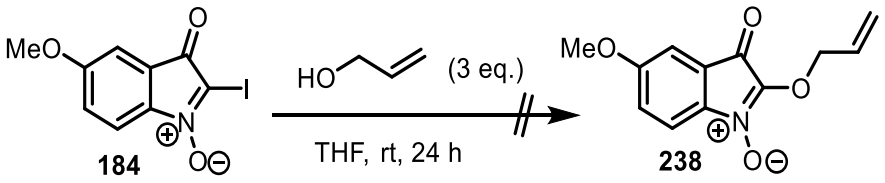


Scheme 127

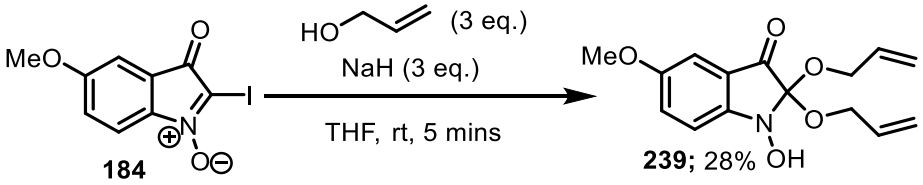


Scheme 128

With the endeavours to add amines to 2-iodoisatogens proving futile, the addition of alcohols was next investigated. Treating 2-iodoisatogen **184** with 3 equivalents of allyl alcohol led to recovery of starting material (Scheme 129). Adding sodium hydride to the reaction led to full consumption of starting material after 5 mins but only the double addition product **239** was isolated in a 28% yield (Scheme 130). In an effort to obtain only the mono-addition product, only 1 equivalent of allyl alcohol was added and the reaction was performed at 0 °C but only the double addition product was obtained in an 8% yield.

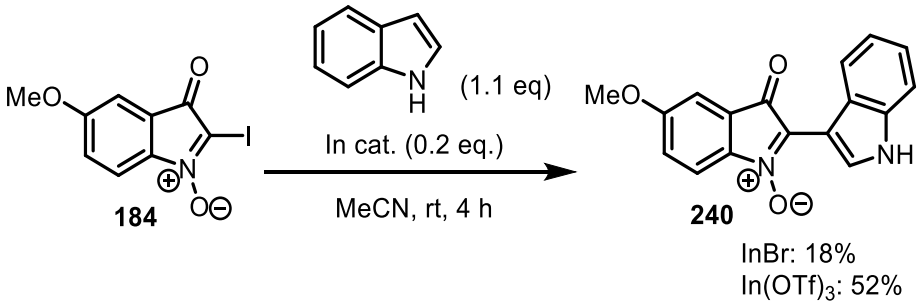


Scheme 129

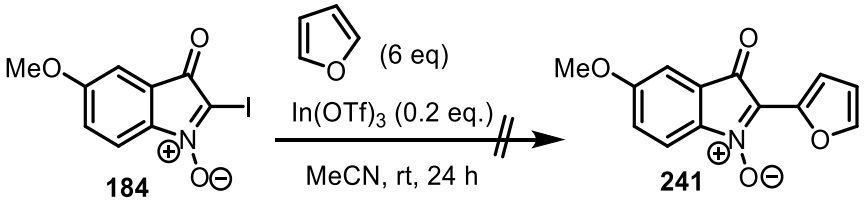


Scheme 130

Inspired by Ramana's report of adding indoles to 2-phenylisatogens in the presence of an indium catalyst,[125] the same reaction with 2-iodoisatogens was explored next. Treating isatogen **184** with 20 mol% of $InCl_3$ and 1.1 equivalents of indole gave the desired product **240** in a poor yield of 18%. Replacing the indium catalyst with $In(OTf)_3$ afforded the product in an improved yield of 52% (Scheme 131). Unfortunately, all attempts to extend the scope to other heterocycles such as furan led to no reaction (Scheme 132).

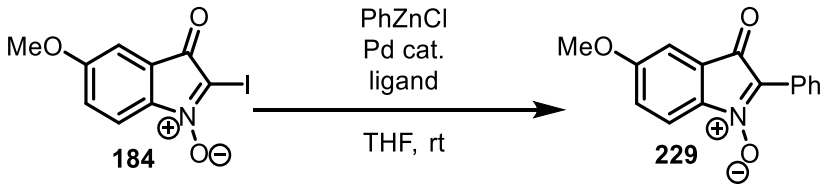


Scheme 131



Scheme 132

With the addition of various nitrogen and oxygen based nucleophiles to 2-iodoisatogens giving only moderate yields at best, focus was shifted back to Pd-catalyzed cross coupling reactions. After the success of the Sonogashira reactions, Negishi couplings were next explored in the effort to prepare 2-arylisatogens. Whilst these compounds are quite well known in the literature already, the established routes towards these intermediates incorporate the aryl group at an early stage of the synthesis. An opportunity to develop a new aryl coupling strategy with 2-iodoisatogens to obtain the corresponding 2-aryl analogues was, therefore, advantageous.

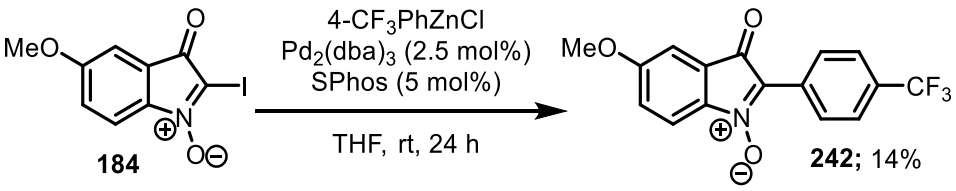


Entry	PhZnCl	Pd. cat	ligand	Time	Yield
1	3 eq.	$PdCl_2(dppf)_2$ 10 mol%	-	24 h	28%
2	3 eq.	$Pd_2(dba)_3$ 2.5 mol%	SPhos 5 mol%	4 h	45%
3	3 eq.	$Pd_2(dba)_3$ 2.5 mol%	RuPhos 5 mol%	24 h	25%
4	3 eq.	$Pd_2(dba)_3$ 2.5 mol%	XPhos 5 mol%	24 h	21%
5	5 eq.	$Pd_2(dba)_3$ 2.5 mol%	SPhos 2.5 mol%	24 h	30%
6	5 eq.*	$Pd_2(dba)_3$ 2.5 mol%	SPhos 2.5 mol%	24 h	22%

Table 24 *added portion wise

To begin the investigation for the Negishi couplings, 2-iodoisatogen **184** was treated with 3 equivalents of phenylzinc iodide in the presence of 10 mol% of $PdCl_2(dppf)_2$. The organozinc reagent was prepared in situ by the addition of zinc chloride to the corresponding aryl Grignard reagent and pre-mixing before addition to the reaction mixture. This initial reaction gave the desired 2-phenylisatogen **229** in a 28% yield with some starting material recovered. The Pd catalyst was replaced with $Pd_2(dba)_3$ and a variety of Buchwald phosphine ligands were explored. SPhos proved to be the best ligand which afforded the product in a 45% yield but some starting material was still observed. The equivalents of organozinc reagent was increased to 5 eq. but the reaction

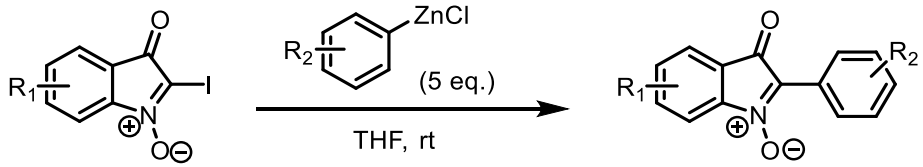
mixture started to become more complex and the product was only obtained in a 30% yield. Adding the organozinc reagent portion wise was not beneficial and only resulted in a 22% yield of desired product. It was observed that the reaction mixtures tended to be very complex with the presence of homo-coupled by-product evident in the NMR spectra of the crude mixtures.



Scheme 133

Attempts to vary the electronic properties of the arylzinc chloride coupling partner involved using *p*-trifluoromethylphenylzinc chloride but this only favoured homocoupling of the organozinc reagent (Scheme 133). Remarkably, when a control experiment was performed where the 2-iodoisatogen was treated with 5 equivalents of arylzinc chloride in the absence of Pd catalyst, the desired product was obtained in a 68% yield. Using Rieke organozinc reagent phenylzinc iodide did not yield any product whatsoever which suggests that preparing the organozinc reagent from the corresponding Grignard reagent is crucial. It is possible that excess Mg salts present in the reaction mixture aid the cross-coupling since using less than 5 equivalents of Grignard gave the product in inferior yields.

The scope of this aryl coupling was then explored by treating 2-iodoisatogen **184** with a selection of arylzinc chlorides, and these were all found to react smoothly. Electron-withdrawing and electron-donating substituents on the arylzinc chloride can be tolerated which afforded the 2-arylisatogens in good yields (Table 25). The chemistry can also be applied to the halogenated analogues of 2-iodoisatogens but the inherent instability of these compounds led to the 2-arylisatogen products in modest yields. Moreover, the 7-chloro substituted isatogen **247** was also obtained but this compound appeared to decompose quickly and efforts to isolate this compound in pure form proved unsuccessful.



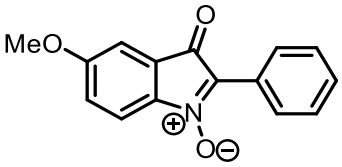
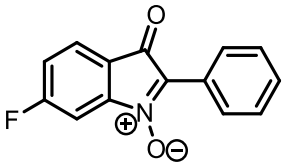
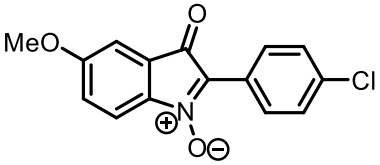
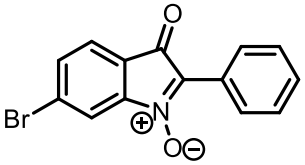
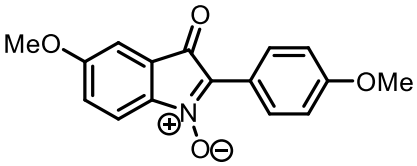
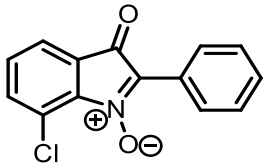
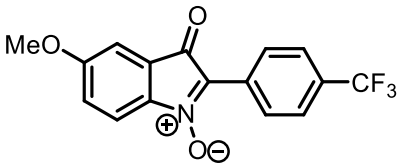
	Product	Yield		Product	Yield
229		65%	**245**		40%
243		65%	**246**		48%
244		66%	**247**		46%
242		59%			

Table 25

Finally, with the displacement of the iodide observed already, it was envisaged that 2-iodoisatogens could also be used as intermediates to prepare 2-acylidene 3-oxindoles **248** which are the isomers of the initially targeted 3-acylidene 2-oxindoles **3** (Figure 7). Whilst the synthesis and chemistry of the 2-oxindole isomers are well established, strategies to prepare the 3-oxindole counterparts are quite limited. As well as bearing useful biological properties,[126,127] these compounds have also been proven to be useful intermediates in organic synthesis.[128] For instance, these oxindoles have been used as dienophiles in a Diels-Alder strategy to generate biologically important Aristotelia alkaloids.[129]

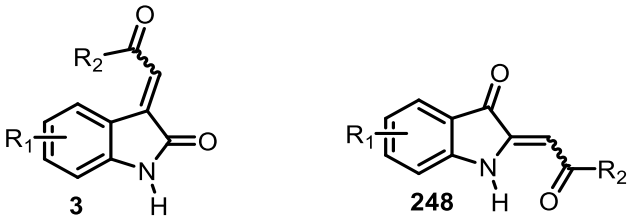
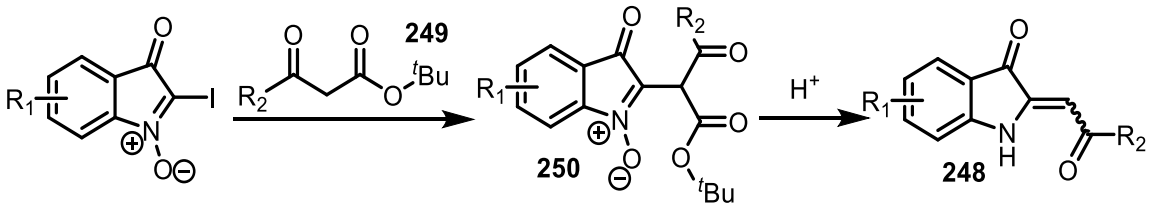


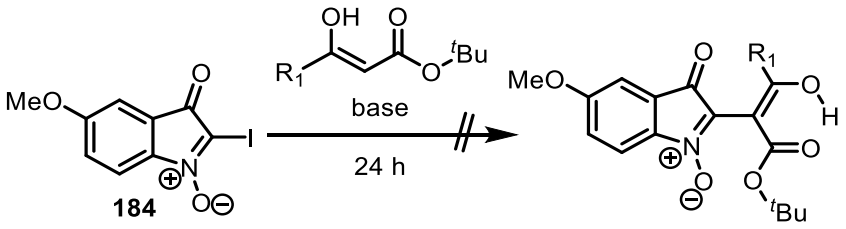
Figure 7

The initial strategy devised to prepare these 2-acylidene 3-oxindoles involved the use of α-arylacetic acid t-butyl esters. It was envisaged that displacing the iodide with dicarbonyl **249** would give intermediate **250** which could be acidified to obtain the desired oxindole (Scheme 134).



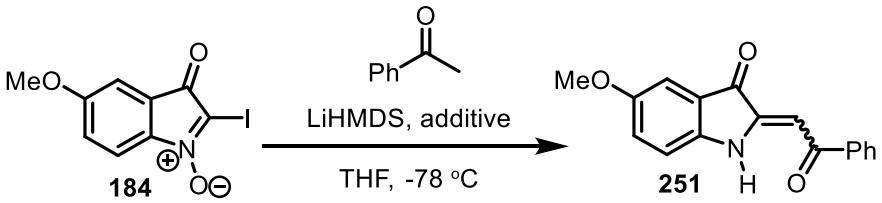
Scheme 134

Unfortunately, after trying a variety of bases to aid the reaction, the displacement proved to be difficult and no desired product was obtained (Table 26). Remarkably, both unreacted keto ester and isatogen were recovered from the reaction mixture which suggests that the deprotonation step might not be taking place due to steric hindrance from the *t*-butyl group.



Entry	R1	base	solvent	Temp.	Yield
1	phenyl	NaH (2 eq.)	THF	Δ	0%
2	4-chlorophenyl	LiHMDS (1 eq.)	THF	-78 °C to rt	0%
3	4-chlorophenyl	K_2CO_3 (1 eq.)	DMF	rt	0%

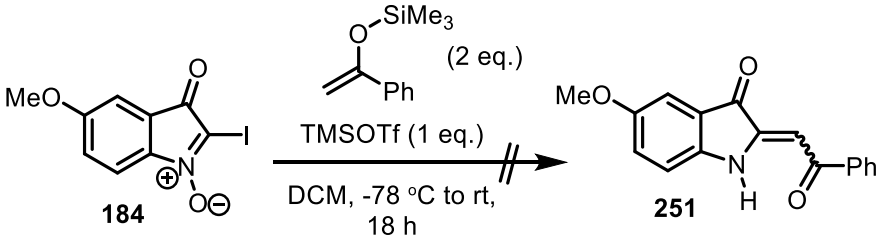
Table 26



Entry	ketone	additive	time	Yield
1	1 eq.	-	15 mins	12%
2	1 eq.	-	1 h	20%
3	1 eq.	NaI	1 h	18%
4	4 eq.	-	4 h	9%

Table 27

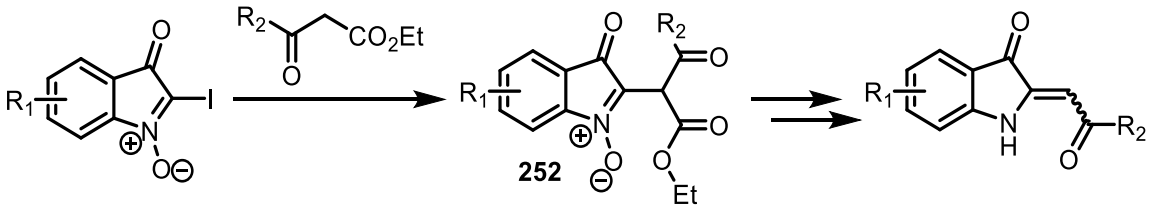
The next strategy explored is much simplified in which aryl ketones where envisaged to displace the iodide and obtain the corresponding acylidene oxindoles in one step. Accordingly, 2-iodoisatogen **184** was treated with acetophenone and sodium hydride which led to full consumption of starting material after 15 mins but only gave product **251** in a poor yield of 12% (Table 27). Changing the base to LiHMDS only marginally improved the yield and using sodium iodide as an additive to aid the displacement did not prove beneficial. Moreover, adding an excess of the ketone was ineffective and product was only generated in less than 10% yield. It was then decided to form the silyl enol ether of the ketone and react with the 2-iodoisatogen **184** in the presence of TMSOTf as the Lewis acid. This proved to be ineffective as the starting isatogen decomposed under the reaction conditions.



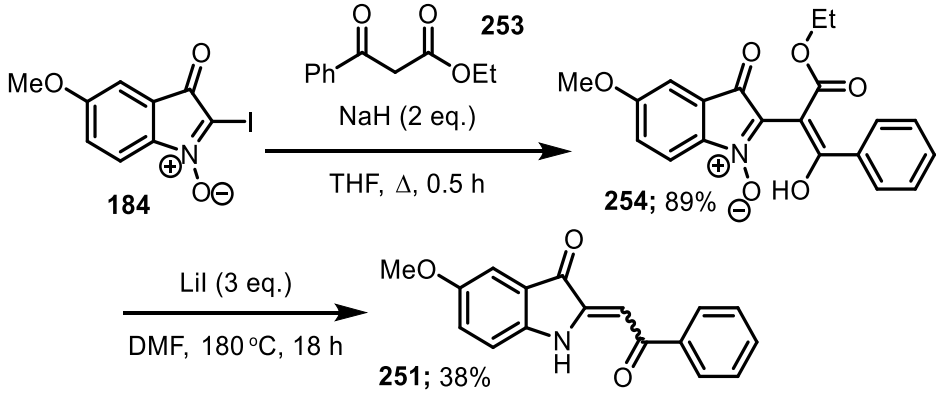
Scheme 135

We returned to the initial idea of using a β-keto ester nucleophile, but a substrate bearing a smaller ester group. Specifically, we chose to employ dicarbonyl **252**, with the

intention of performing a decarboxylation-reduction sequence to generate the desired acylidene oxindole (Scheme 136). Hence, isatogen **184** was treated with β-keto ester **253** in the presence of sodium hydride to obtain isatogen **254** in an 89% yield. Remarkably, it was discovered that upon treatment with 3 equivalents of lithium iodide at 180 °C, the isatogen underwent decarboxylation with concomitant reduction of the N-O bond to generate 2-acylidene 3-oxindole **251** (Scheme 137). Since the product was only obtained in a moderate yield of 38%, the Krapcho decarboxylation was investigated further.

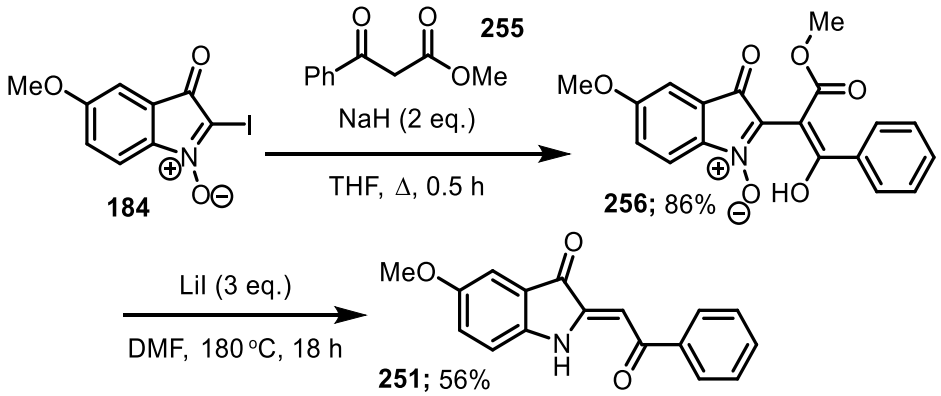


Scheme 136



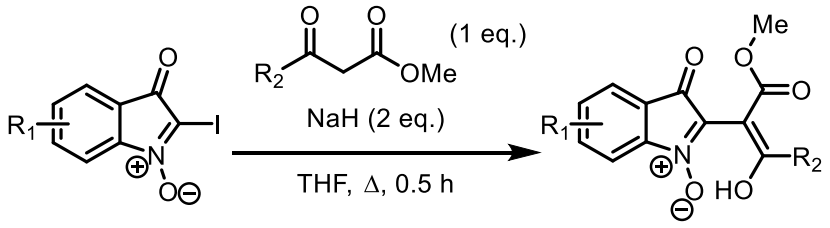
Scheme 137

Since the traditional mechanism proposed for the Krapcho decarboxylation involves an S_N2 reaction where the iodide attacks the alkyl group of the ester,[130] it was envisaged that having the less sterically hindered methyl group will aid the decarboxylation. Accordingly, β-keto ester **255** which is not easy to obtain commercially was prepared by treating the corresponding ethyl ester **253** with acid in methanol. The resulting methyl ester was reacted with isatogen **184** which gave the product **256** in an 86% yield. Pleasingly, the decarboxylation-reduction sequence proceeded to generate 2-acylidene 3-oxindole **251** in a 56% yield.



Scheme 138

The displacement reaction was then applied to different iodoisatogens and β-keto esters to obtain 3 more examples of the isatogen intermediate required for decarboxylation (Table 28). Unfortunately, applying the subsequent decarboxylation-reduction sequence with the other substrates only gave the acylidene oxindoles in modest yields (Table 29). One by-product in the crude reaction mixture which was detected by LC-MS was the deoxygenated starting material **263** that could be derived via iodide addition at the N-O bond rather than the ester C-O bond (Scheme 138). In addition, when the reaction was run over longer times, the deoxygenated compound failed to convert to the acylidene oxindole and could still be detected in the reaction mixture, which suggests that **263** is not an intermediate in the 2-acylidene 3-oxindole forming pathway. Regardless, it was necessary to find a different reagent to effect the decarboxylation but prevent the unwanted deoxygenation of the starting material.



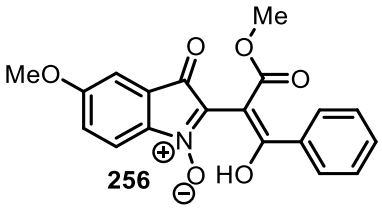
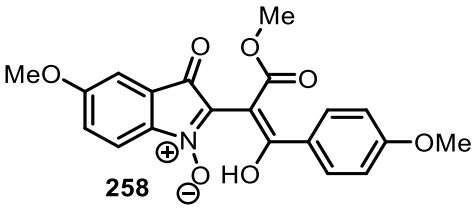
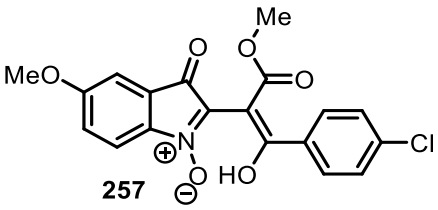
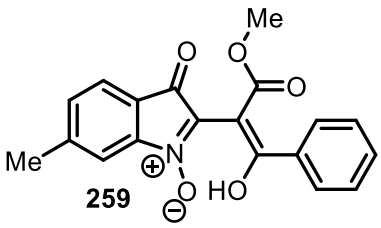
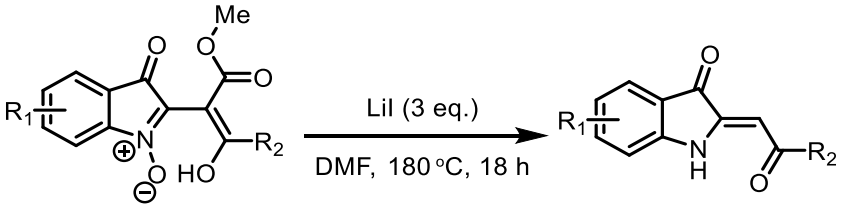
Product	Yield	Product	Yield
 **256**	86%	 **258**	87%
 **257**	88%	 **259**	75%

Table 28



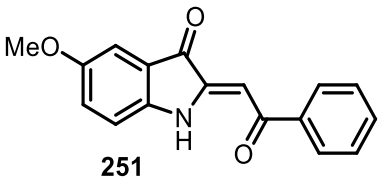
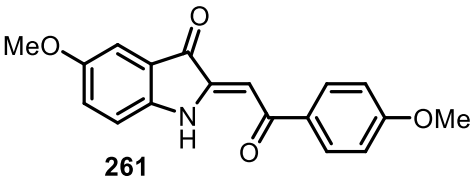
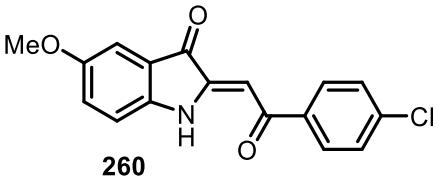
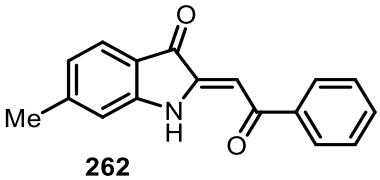
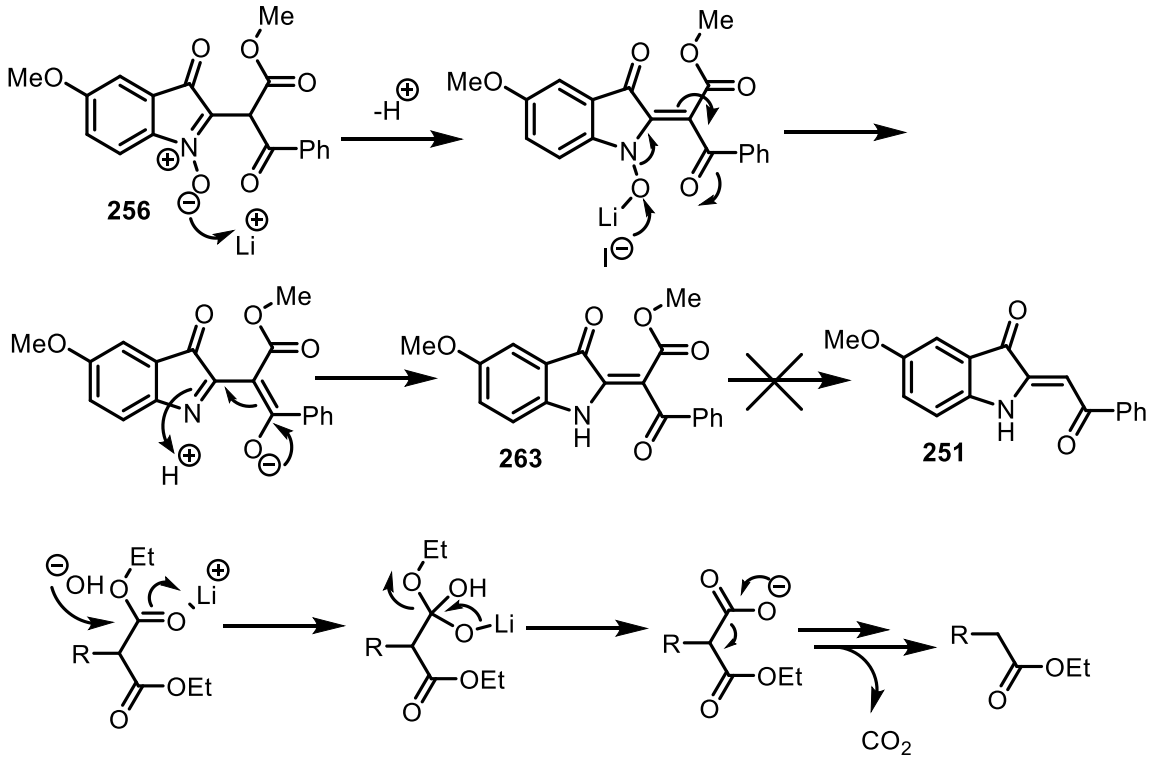
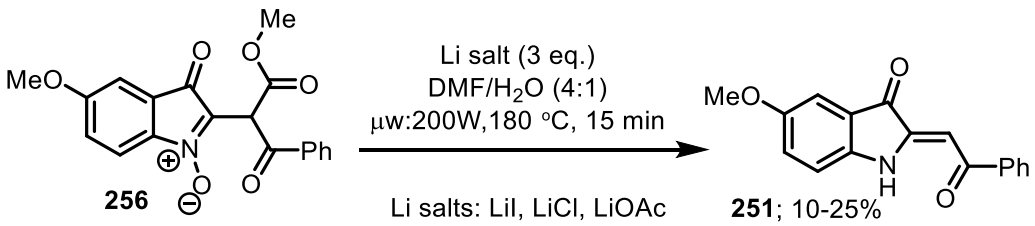
Product	Yield	Product	Yield
 **251**	56%	 **261**	24%
 **260**	47%	 **262**	40%

Table 29

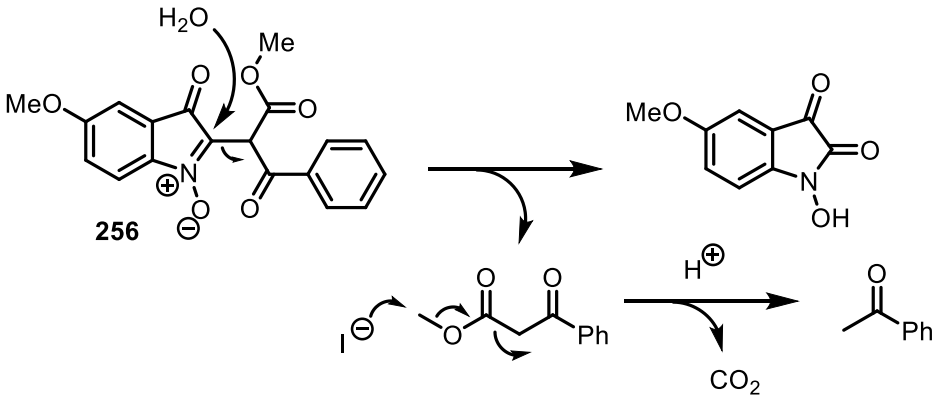


Scheme 139

Murphree reported the use of microwave conditions for the Krapcho decarboxylation of alkyl malonate derivatives.[131] A new mechanism was also proposed in which water is required to generate a hydroxide ion that can attack the carbonyl (Scheme 139). Hence, isatogen **256** was treated with a variety of lithium salts in aqueous microwave conditions. Unfortunately, the product could only be obtained in around 25% yield and the crude mixtures were always rather complex. Moreover, acetophenone was observed in the crude mixture which could arise from an isatogen **256** hydrolysis-decarboxylation pathway (Scheme 140). With these observations in mind, it was concluded that anhydrous conditions were required and conventional heating was once again considered.

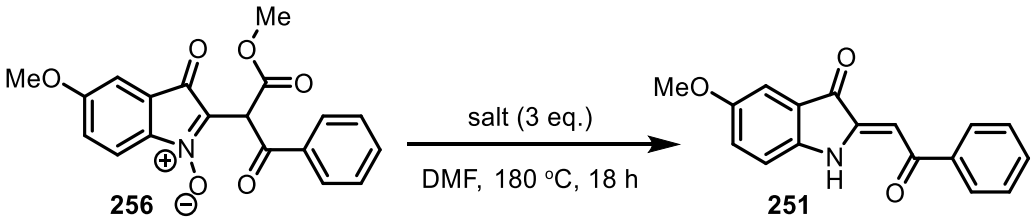


Scheme 140



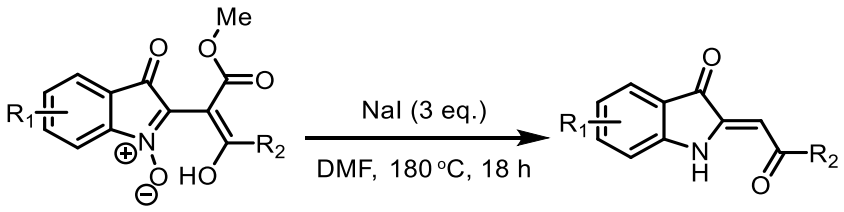
Scheme 141

We next screened a series of salt additives under anhydrous conditions. From the salts employed for the reaction, sodium iodide gave the best results providing the acylidene oxindole with a 62% yield (Table 30). Only traces of the deoxygenated starting material was observed, possibly because of the low Lewis acidity of the sodium cation. With these new conditions, the decarboxylation was applied to the other substrates to obtain 4 examples of 2-acylidene 3-oxindoles in improved yields (Table 31).



Entry	salt	Yield
1	LiI	56%
2	LiCl	44%
3	NaI	62%
4	KI	51%

Table 30



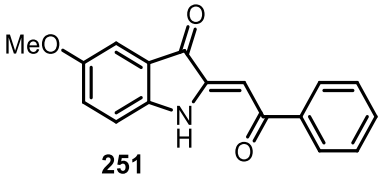
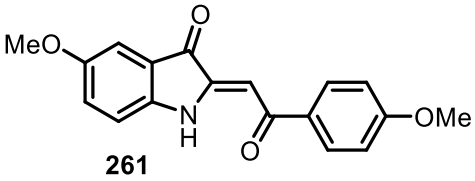
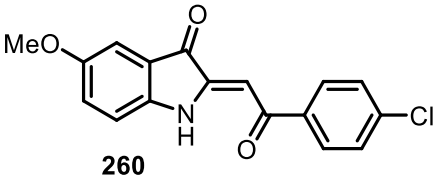
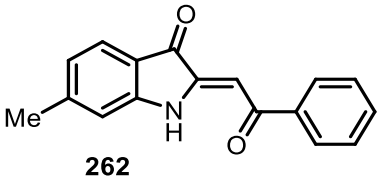
Product	Yield	Product	Yield
 **251**	62%	 **261**	40%
 **260**	64%	 **262**	59%

Table 31

The 2-acylidene 3-oxindoles were isolated as single olefin isomers and compound **262** was determined to have the *Z*-configuration by X-ray crystallography (Figure 8). By analogy, the remaining analogues were tentatively assigned as the *Z*-isomers as well. This can be attributed to the potential H-bond formed between the carbonyl and the amine proton. Moreover, with the *Z*-configuration, dipole-dipole interactions are minimized with the two carbonyl groups pointing away from each other.

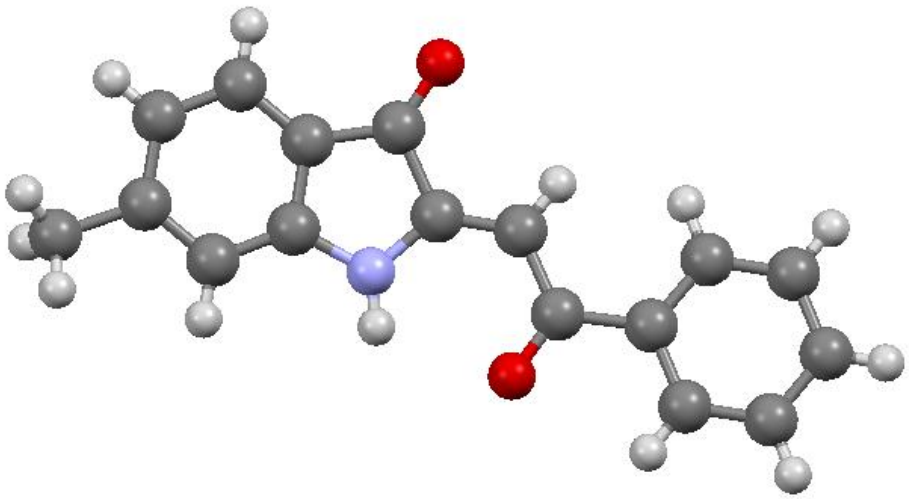


Figure 8

Conclusion

Isatogens are interesting compounds that are traditionally prepared via the cyclization of 2-nitrophenylacetylenes under acidic or basic conditions or via the oxidation of 2-substitued indoles. In this investigation, novel 2-iodoisatogens were prepared via the copper-promoted cycloisomerization of 2-nitrophenyl iodoacetylenes in moderate to excellent yields. These isatogens have been transformed to the corresponding isatin analogues effectively by treatment with indium chloride or molybdenum hexacarbonyl. This represents a cheaper and more efficient protocol to synthesise isatins without the use of toxic reagents and harsh conditions which have hampered previously reported strategies.

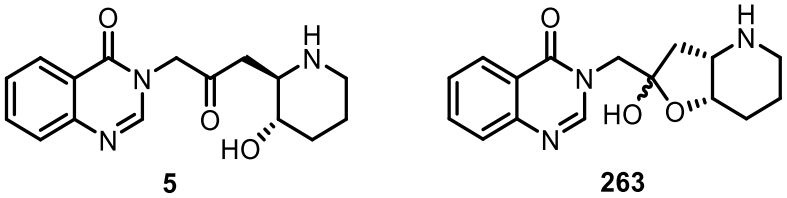
The versatility of 2-iodoisatogens has also been highlighted in which a wide range of novel nitrogen-containing heterocycles have been prepared via the elaboration of the C–I bond. Sonogashira reactions have been performed to couple 2-iodoisatogens with a variety of acetylenes to obtain novel 2-alkynylisatogens. 2-Arylisatogens were furnished via the substitution of 2-iodoisatogens with arylzinc chlorides in the absence of Pd catalyst. Notably, this provides a new aryl coupling strategy since established routes towards 2-arylisatogens incorporate the aryl group at an early stage of the synthesis.

Finally, a two-step displacement-decarboxylation sequence has been devised to prepare 3-acylidene-2-oxindoles. These intermediates are isomers of 2-acylidene-3-oxindoles which are biologically important and potential treatment for Idiopathic Pulmonary Fibrosis. Further research would be useful to determine what other transformations could be carried out on 2-iodoisatogens by exploiting the reactivity of the C–I bond. This would unlock the potential of these versatile compounds as useful intermediates in organic synthesis.

Chapter 4: Synthesis of Febrifugine Analogues

Introduction

Febrifugine **5** is an alkaloid that exists in the leaves and roots of the Chinese herb *Dichroa Febrifuga* of the Saxifragaceae family.[132] For centuries, the Chinese have been using this medicinal plant as a treatment for symptoms of fever but it wasn't until 1943 when Chou disclosed that a crude extract from the roots (*Chang Shan*) could be applied in clinical cases of tertian malaria.[133] The first reported isolation of febrifugine and the related compound isofebrifugine was in 1946 when Chou extracted two alkaloids from Chang Shan which were initially termed 'dichroine A' and 'dichroine B'.[134] Koepfli named the two alkaloids as febrifugine and isofebrifugine in 1947, after the empirical formula of dichroine B was calculated to be $C_{16}H_{19}O_3N_3$.[135]



5 **263**

Figure 9

Further progress towards elucidating the structure of febrifugine emerged in 1948 when Chou disclosed that the dichroine alkaloids were in fact isomers that interconverted under acidic and basic conditions, and with the application of heat.[136] Later that year, in a chemical degradation study, quinazolinone was isolated by Chou which was a structural motif prevalent in many reported alkaloids during the time. Accordingly, Koepfli proposed structures for febrifugine and isofebrifugine with the quinazolinone core and a hemiketal motif with different configurations at the hemiacetal carbon atom for both diastereoisomers (Figure 9).[137] However, the emergence of a new alkaloid similar to the pair of isomers in 1952 led to the proposed structures of febrifugine and isofebrifugine to be modified.

Extracts from the plant *Hydrangea umbellata* which also comes from the Saxifragaceae family were shown to have antimalarial activity after analysis in 1952.[138]

Baker, Hutchings and Williams then synthesised analogues of febrifugine and compared them to the naturally occurring substance. Hence it was concluded that febrifugine and the hydrangea alkaloid were identical and a new structure **266** was proposed which contained a hydroxy group on the piperidine and a keto linker.[139] Finally, after efforts to synthesise febrifugine and isofebrifugine by different groups such as Kobayashi[140] and Takeuchi,[141] the ambiguity surrounding their structures was finally clarified which eventually led to the verification of the structures as **5** for febrifugine and **263** for isofebrifugine (Figure 10).

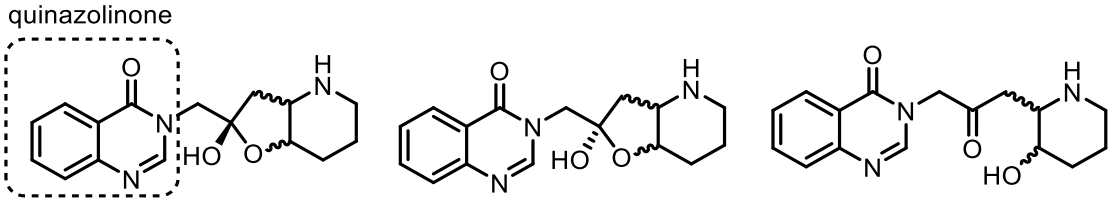


Figure 10

Whilst *Dichroa Febrifuga* has been used in East Asia to treat various ailments for over 2,000 years, the mechanism of action of the active components remained unknown. Studies in the 1970's however identified key structural features of febrifugine which are essential for its biological activity. The preparation and assessment of febrifugine analogues as potential antimalarial drugs revealed that the amino and hydroxyl group of the piperidine ring as well as the quinazolinone core were crucial for activity.[142] Moreover, the discovery that the unnatural enantiomer possessed very modest activity showed that the absolute configuration was also important.[143]

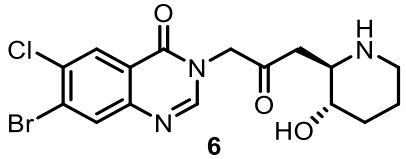


Figure 11

The emergence of halofuginone **6** in the late 1960's as a useful synthetic analogue of febrifugine led to further investigation on the mode of action of this family of

compounds. Halofuginone has been shown to be more active as an antimalarial drug than febrifugine itself and it reduces the side-effects observed in humans such as nausea and vomiting. As a result, interest in halofuginone has increased in the past few decades and it has progressed to phase 2 clinical trials as a potential cancer treatment.[144] It has also been demonstrated to be an effective antifibrotic agent among other useful biological properties.[139]

Recently, it has been established that febrifugine and halofuginone are inhibitors for the differentiation of proinflammatory TH17 cells via the activation of the amino acid response (AAR) pathway.[145] This could be triggered by the inhibition of aminoacyl-tRNA synthetases which results in the intracellular accumulation of uncharged tRNAs. The activity of aminoacyl-tRNA synthetases is crucial as they are responsible for the aminoacylation of tRNAs which entails the attachment of amino acids to specific tRNAs.[146] This particular role in protein synthesis is so vital that when it is inhibited, the viability of all cell types is suppressed and hence, cell growth is also arrested.

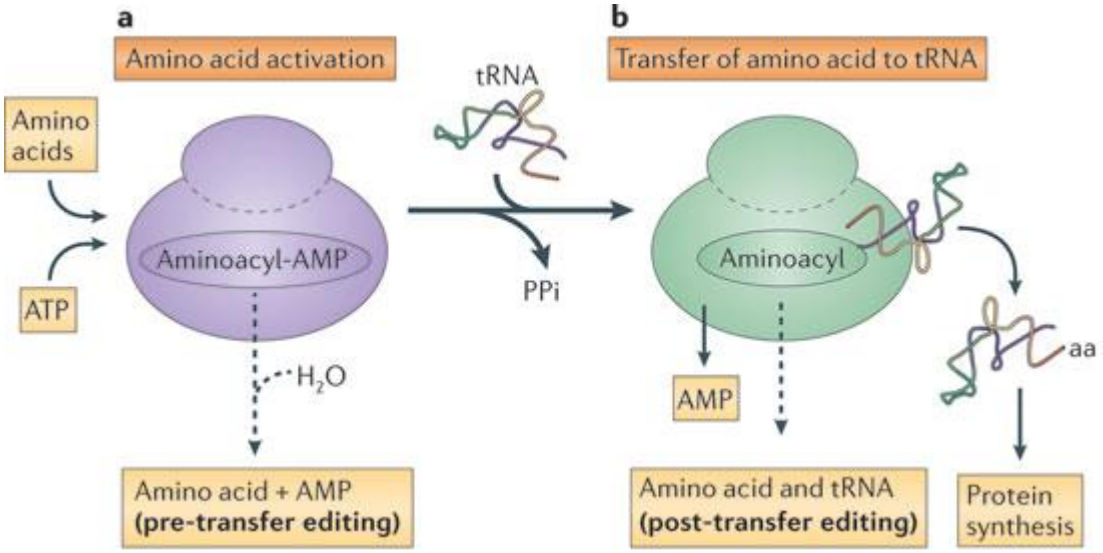


Figure 12 (Reproduced with kind permission by Nature Reviews)

Human prolyl-transfer RNA synthetase or ProRS is the specific target of febrifugine and this enzyme is responsible for the formation of aminoacyl adenylates (AA-AMP) which transfer activated amino acids to tRNAs (Figure 12).[147] This process requires ATP and regular ProRS inhibitors would mimic AA-AMP by directly occupying

the active site to block ATP and the incoming tRNA. However, it has been shown that ATP is actually essential for the binding of febrifugine/halofuginone to the active site.[148] This observation suggests that febrifugine/halofuginone are not mimics of AA-AMP and could instead be binding to ProRS via a different mechanism altogether.

To explain the inhibition of ProRS by halofuginone, a crystal structure of the binding site has been reported by Zhou and Schimmel which reveals the vital interactions between halofuginone, ProRS and ATP (Figure 13).[147] Hydrophobic stacking and hydrogen bonding interactions of ProRS and the adenosine group of ATP, in addition to the hydrogen bonding of ProRS and the ribose of ATP, allow ATP to form a cap over the binding pocket. As a consequence of these numerous interactions, the ATP sits in a bent conformation which allows the α-phosphate to form hydrogen bonds with the ketone and the hydroxy group of halofuginone. The ATP therefore orientates halofuginone to form further hydrogen bonds with the ProRS binding site. These further interactions with ProRS allow halofuginone to occupy two pockets of the binding site hence acting as a dual site inhibitor. Whilst the quinazolinone moiety blocks the pocket where tRNA normally binds, the hydroxypiperidine part of halofuginone also mimics proline and prevents the binding of proline to ProRS (Figure 14).

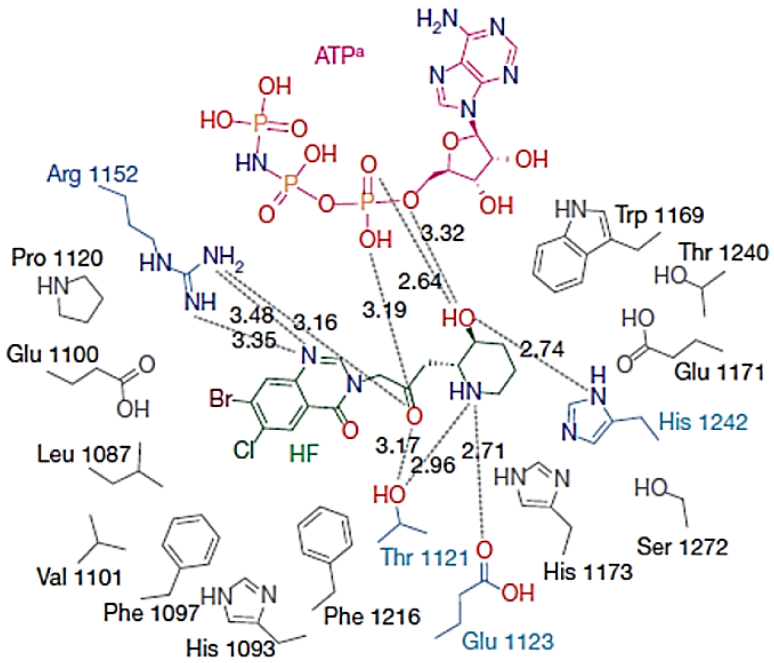


Figure 13 (Reproduced with kind permission by Zhou and Schimmel)

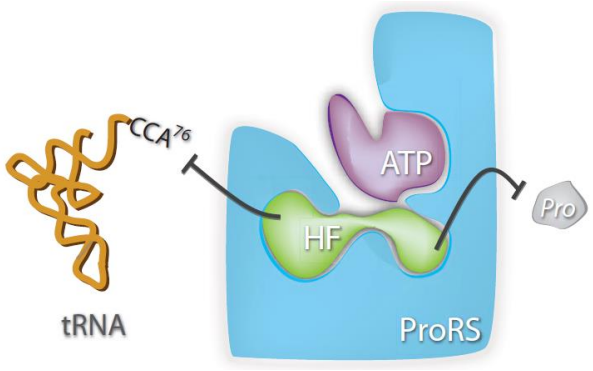


Figure 14 (Reproduced with kind permission by Zhou and Schimmel)

The reported crystal structure of the binding site showing the interactions with halofuginone suggests an analogous mode of action for febrifugine. Whilst the template used to determine the binding with halofuginone was the *Thermus thermophilus* ProRS, it has been shown that febrifugine binds similarly with *Plasmodium falciparum* ProRS which is highly similar to that of human ProRS (Figure 15).[147]

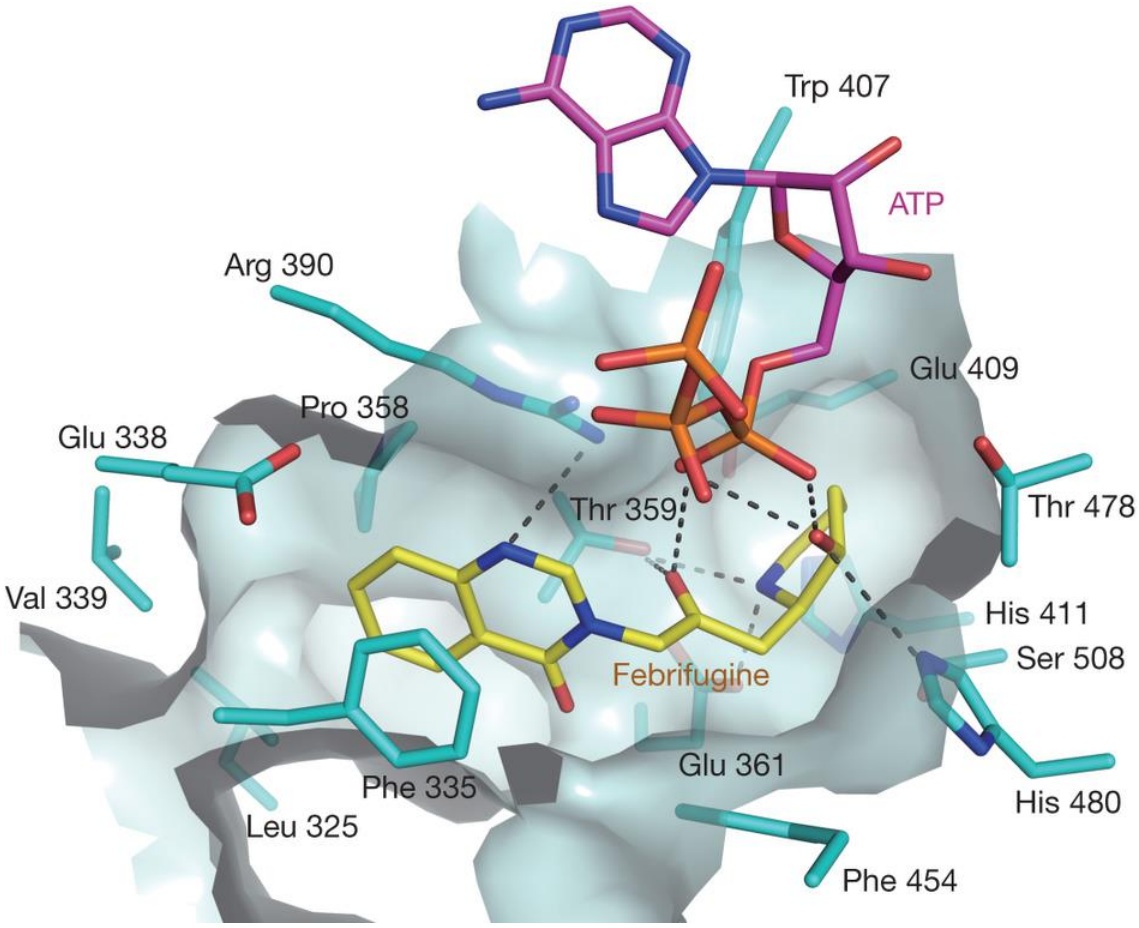


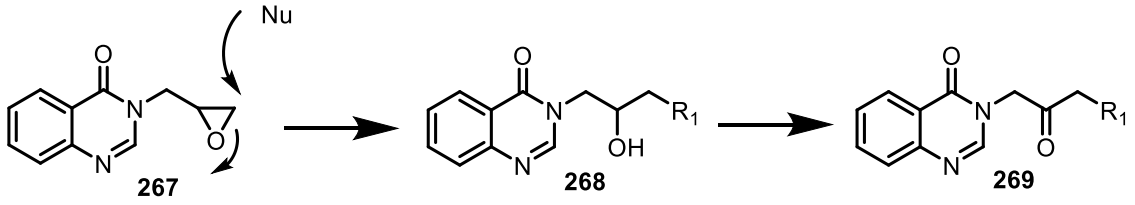
Figure 15 (Reproduced with kind permission by Zhou and Schimmel)

With the existing model as a reference, it was then possible to design febrifugine analogues for synthesis with the incentive to test them as potential therapy for IPF. The first strategy was to simplify the febrifugine structure and interrogate the binding at the southeast polar region. This entailed replacing the piperidine ring with different amine groups to introduce potential new hydrogen bonding interactions. Furthermore, the importance of the keto linker was also examined by incorporating other groups that could hydrogen-bond with the phosphate of ATP, or by varying the carbon chain length between the quinazolinone and the keto linker.

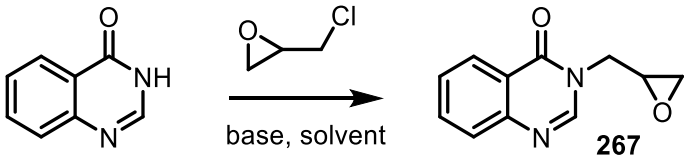
Results and Discussion

Synthesis of Quinazolinone Epoxide

Initial efforts to synthesise different analogues of febrifugine focused on exploring the binding in the southeast polar region while keeping the quinazolinone core unchanged. The early strategy to prepare the desired analogues involved the use of different nucleophiles to attack epoxide **267** regioselectively (Scheme 142). The secondary alcohol **268** could then be oxidized at a later stage to obtain the ketone **269**. Accordingly, efforts were focused on developing an efficient and scalable method to synthesise the quinazolinone epoxide starting material **267**.



Scheme 142

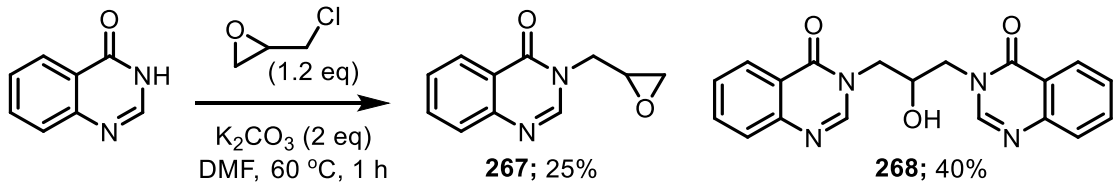


Scheme 143

Existing methods to synthesise the required epoxide involved the alkylation of quinazolinone using epichlorohydrin (Scheme 143).[149] However, the alkylating agent is employed as a solvent and removed by evaporation at the end of the reaction which is not desirable. We therefore endeavoured to find “greener conditions” which minimised the quantities of highly toxic alkylating agent. Consequently, the reaction was attempted with 2 equivalents of epichlorohydrin in the presence of a base, and a solvent screen was performed.

N,N-Dimethylformamide (DMF) was the first solvent chosen for the reaction due to its prevalent use in alkylation reactions.[150] Potassium carbonate was employed as the

base which was expected to be removed quite easily after the reaction. Using 2 equivalents of base and heating at 60 °C after 18 h resulted in complete conversion of the quinazolinone (Scheme 144). However, removal of the DMF solvent proved to be problematic and a low mass balance was observed after aqueous work-up. After recrystallization, the expected quinazolinone epoxide **267** was obtained in a 20% yield. The use of sodium hydride as an alternative base gave a complex mixture after heating at 60 °C for 18 h and none of the desired product was isolated.



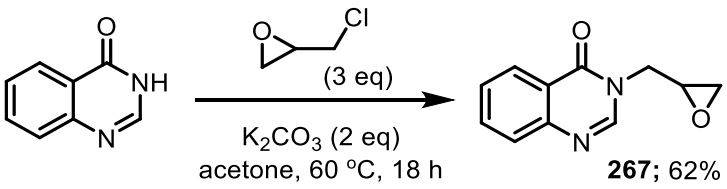
Scheme 144

Repeating the reaction with DMF as a solvent and potassium carbonate as a base on a gram scale gave the desired product in a yield of 25%. One side-product isolated was the dimer **268** resulting from the addition of the product to the starting epoxide (Scheme 144). Another identified side-product was the carbonate ester **269** derived from the reaction of the potassium carbonate base with the epoxide. A minor byproduct observed in the crude LCMS that was not isolated was the diol **270**, the result of water adding to the epoxide which highlighted the importance of ensuring anhydrous conditions for the reaction.

Figure 16

A method for the alkylation of 6,8-dibromoquinazolinone was reported which involved the use of acetone as the solvent.[150] These conditions also used potassium carbonate as the base, and were applied for the alkylation of quinazolinone (Scheme 145). Three equivalents of epichlorohydrin were employed which gave the desired

epoxide in a 62% yield after recrystallization. The reaction afforded gram quantities of material without the use of chromatography which is highly convenient. Furthermore, the acetone solvent is considered a much greener solvent than DMF which has a very high boiling point and therefore can be difficult to remove. Finally, the use of lower quantities of epichlorohydrin relative to the original procedure made this route relatively attractive.

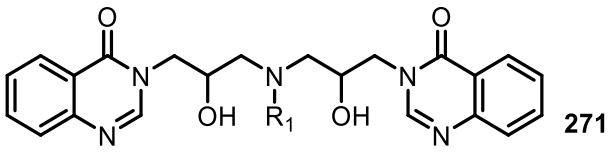


Scheme 145

Addition of Amines to the Epoxide

With the quinazolinone epoxide in hand, various nucleophiles were envisaged for the epoxide opening to afford different febrifugine analogues. Initial efforts were focused on the addition of primary amines which could mimic the piperidine part of the molecule. Accordingly, a selection of primary amines were chosen and conditions were sought to achieve the nucleophilic addition. Naturally, the use of green conditions were borne in mind when the optimisation studies began.

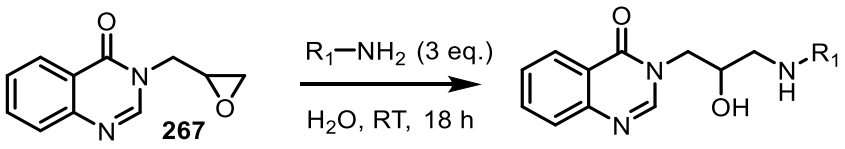
Kochetkov recently published the use of aqueous media to afford the regioselective ring opening of oxiranes with various amines to synthesise amino alcohols.[151] These conditions were applied in this investigation and a variety of aliphatic amines were chosen for the ring opening. Pleasingly, this method was successful and gave the desired amino alcohols in moderate yields. A number of these compounds precipitated from the reaction mixture and were easily isolated by filtration, hence avoiding the need for chromatography.



271

Figure 17

A side reaction observed in the epoxide opening reactions involved the addition of the secondary alcohol product to the starting material, hence affording the dimer **271** (Figure 17). It was, therefore, important to monitor the reaction in order to stop it after all the starting material has been consumed. Furthermore, in one case, the other regioisomer was also observed in which the amine had added onto the more hindered part of the epoxide. It is worth noting that the two regioisomers were difficult to separate by chromatography. In cases where chiral amines were used, diastereoisomers were generated and these were difficult to separate. Our results are summarized in Table 32.



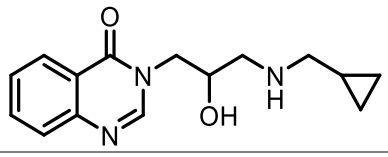
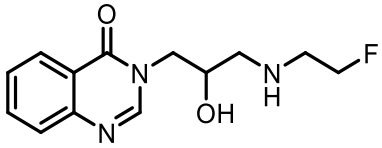
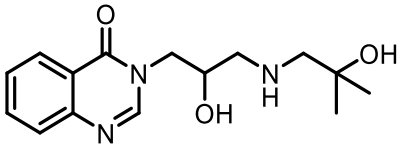
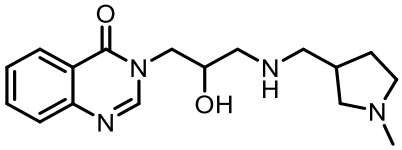
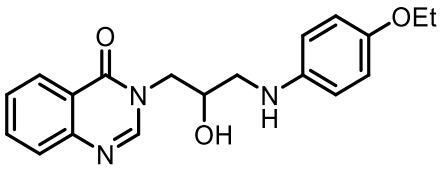
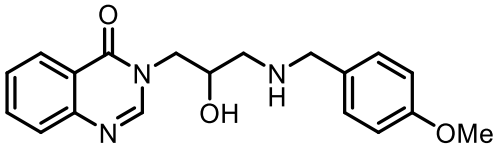
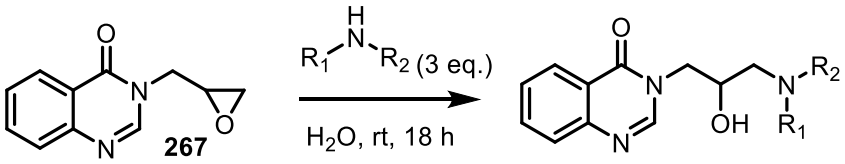
	Compound	Yield
272		53%
273		32%
274		45%
275		25%
276		20%
277		66%

Table 32

Whilst the reaction of most amines proceeded uneventfully, the reaction with the less reactive aniline proved to be more difficult and running the reaction for 18 h led to significant decomposition of starting material. Nonetheless, the desired amino alcohol **276** was still isolated albeit in a low yield of 20%.

In addition to the reaction of primary amines to the quinazolinone epoxide, the aminolysis using secondary amines was also investigated. A variety of dialkylamines were reacted with the epoxides to obtain the analogues summarized in Table 33.



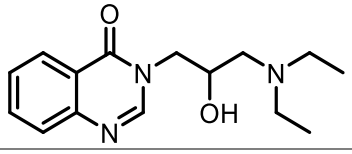
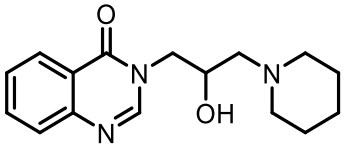
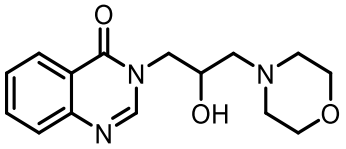
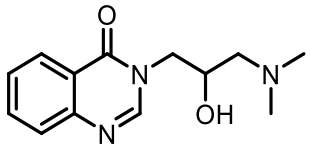
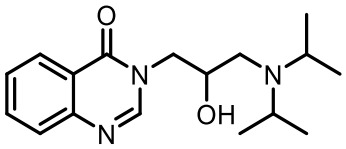
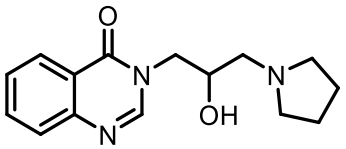
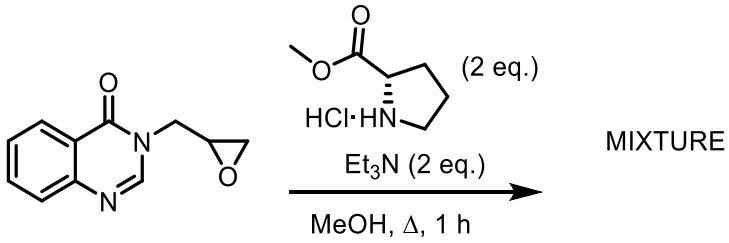
	Compound	Yield
278		72%
279		65%
280		65%
281		84%
282		65%
283		79%

Table 33

Addition of Amino Acids to the Epoxide

After the success of adding different amines to the epoxide, we then investigated whether the ring-opening would also proceed with amino acids. L-Proline was the first choice of amino acid as it was reported that proline binds to the ProRS active site as described earlier. The methyl-ester of the amino acid was used in order to avoid potential side reactions with the carboxylic acid. L-Proline methyl ester hydrochloride was reacted with the quinazolinone epoxide in the presence of base in methanol (Scheme 146). The starting material was fully consumed after 1 hour, and a mixture of the desired methyl ester product **284**, the corresponding acid **285**, as well as the resulting lactone **286** was generated (Figure 17). Instead of isolating the three products, the entire mixture was subjected to basic conditions in order to convert the mixture to acid product **285**.



Scheme 146

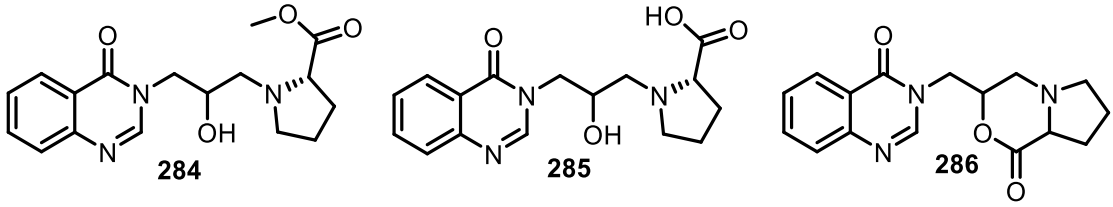
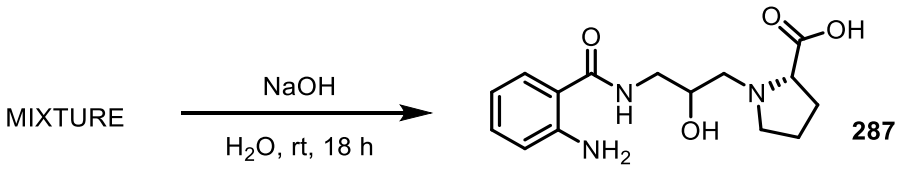


Figure 17



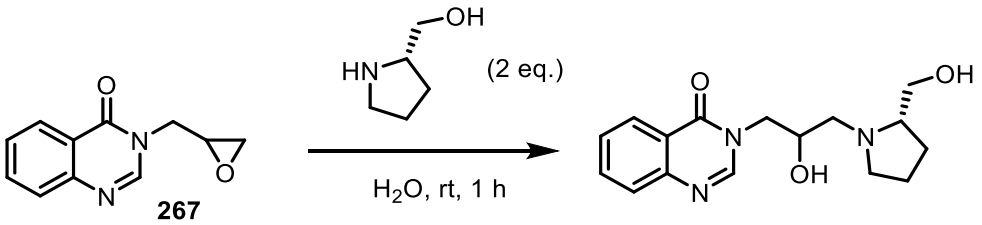
Scheme 147

After stirring the mixture in 2 M NaOH solution for 18 h at room temperature, the reaction was carefully acidified and a single product was isolated. However, the expected acid product **285** was not obtained, but instead, NMR and LCMS suggested that ring

opening of the quinazolinone core had taken place which resulted in the aniline product **287** (Scheme 147). To summarise, the addition of amino acids to the epoxide may not be as straightforward as anticipated, and none of the desired product was isolated in the case of proline. Consequently, we considered whether the corresponding amino alcohols would be more suitable nucleophiles for the ring opening of the epoxide.

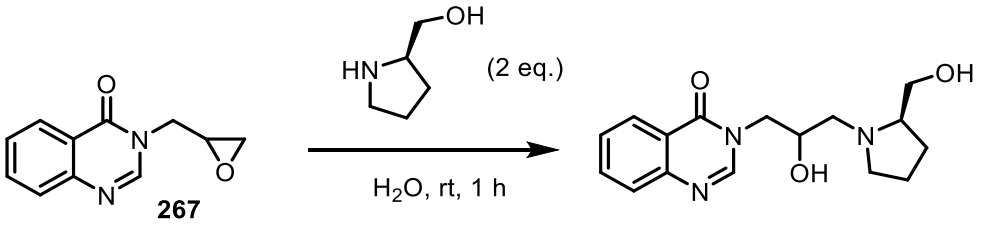
Addition of Amino Alcohols to the Epoxide

Prolinol was chosen as the next nucleophile to be used after our problematic attempts to react the corresponding amino acid. Both L- and D-prolinol were reacted with the racemic quinazolinone epoxide resulting in four different diastereoisomeric products (Scheme 148, 149). Gratifyingly, the four products were successfully separated during chromatographic purification, allowing their isolation in good yields. The optical rotations for all four products were measured to confirm the two sets of enantiomers (See Experimental).



288 (ISOMER 1): 38%
289 (ISOMER 2): 40%

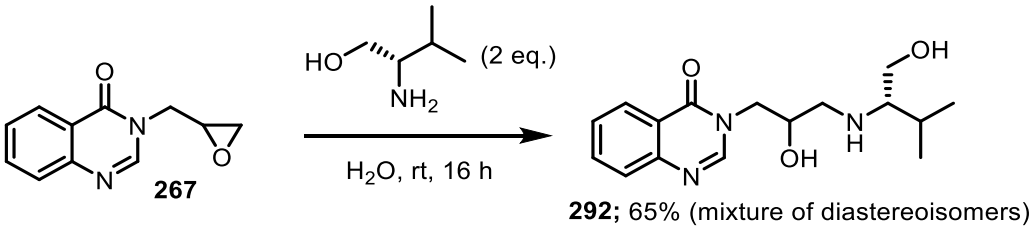
Scheme 148



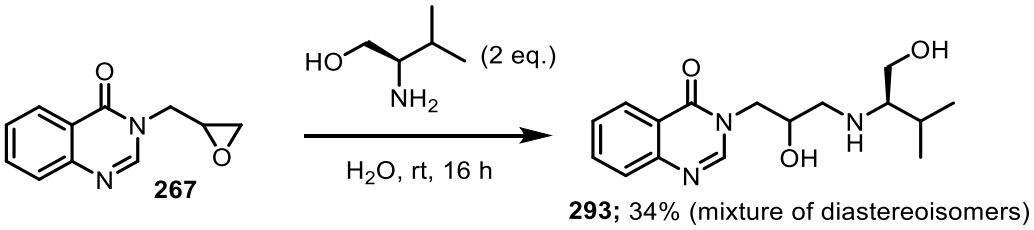
290 (ISOMER 1): 29%
291 (ISOMER 2): 36%

Scheme 149

L- and D-leucinol were also used as nucleophiles to give the expected products in moderate to good yields (Scheme 150, 151). Unfortunately, the products gave a mixture of diastereoisomers which were not successfully separated during purification.



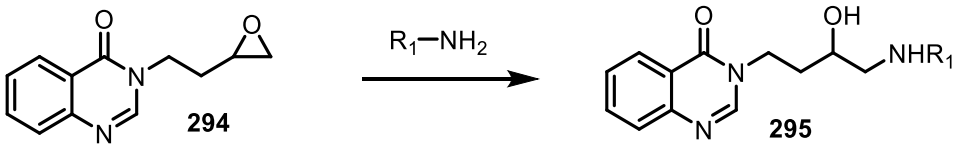
Scheme 150



Scheme 151

Synthesis of Homologues

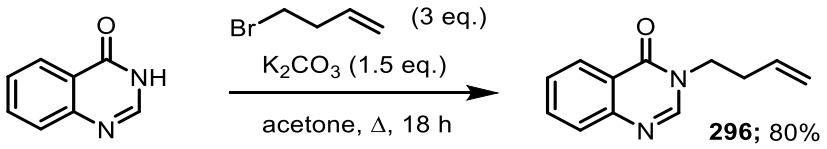
A different set of febrifugine analogues were envisaged whereby an extra methylene is introduced in between the secondary alcohol and the quinazolinone core. To synthesise these homologues, the corresponding epoxide **294** had to be generated before investigating the addition of different amines.



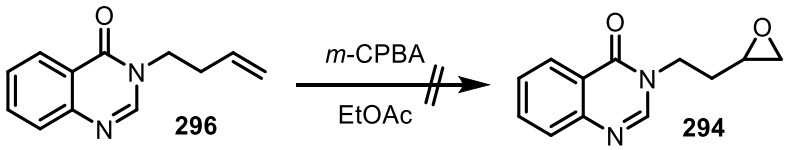
Scheme 152

The initial proposed route to the epoxide was via the alkylation of quinazolinone using 4-bromobut-1-ene followed by epoxidation. A reported competing reaction for the N-alkylation of quinazolinone is the O-alkylation[152] but gratifyingly, the N-alkylated product **296** was synthesised in an excellent yield with only traces of the by-product

observed (Scheme 153). With the desired alkene in hand, the epoxidation was attempted using *m*-CPBA and replacing the conventional dichloromethane solvent used in epoxidation reactions to a greener alternative, ethyl acetate. Surprisingly, in the presence of 2 equivalents of *m*-CPBA and running the reaction for 72 h, only traces of the expected epoxide was observed. Heating the reaction to 80 °C did not help the conversion of starting material and adding 3 more equivalents of *m*-CPBA and running for another 72 h proved unsuccessful. We therefore decided to perform the epoxidation of 4-bromobut-1-ene first before attempting the alkylation of the quinazolinone core.

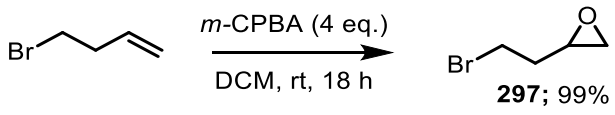


Scheme 153

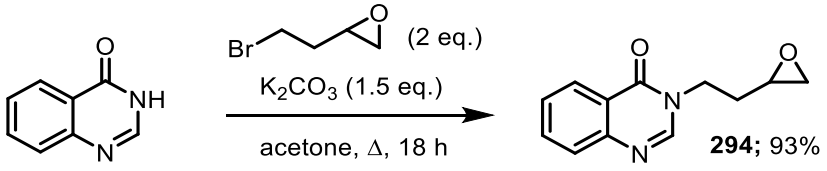


Scheme 154

Pleasingly, the epoxidation proceeded uneventfully providing the desired 2-(2-bromoethyl)oxirane **297** in a quantitative yield (Scheme 155). This bromoepoxide was then successfully coupled with the quinazolinone to give the expected product **294** in a 93% yield which was also scaled up to obtain a gram of material (Scheme 156).

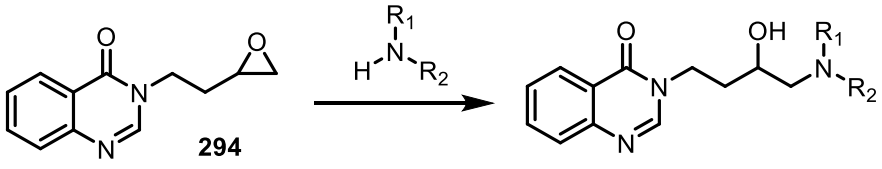


Scheme 155



Scheme 156

A number of secondary amines were then reacted with the epoxide **284** using the conditions employed for the synthesis of the earlier series of analogues. The desired amino alcohol products were obtained in generally excellent yields with only the very hindered diisopropylamine analogue **300** giving a low yield (Table 34).



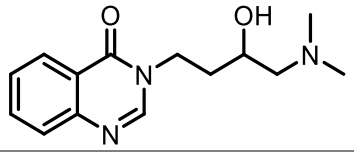
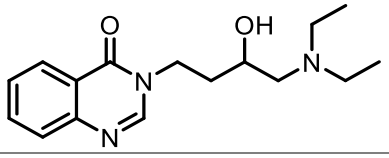
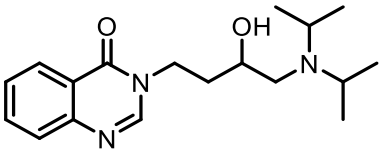
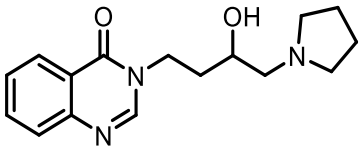
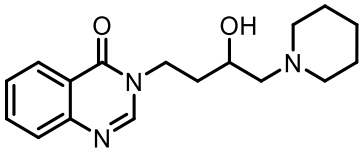
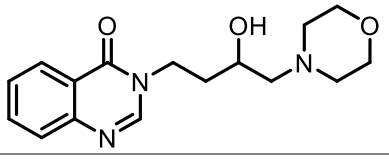
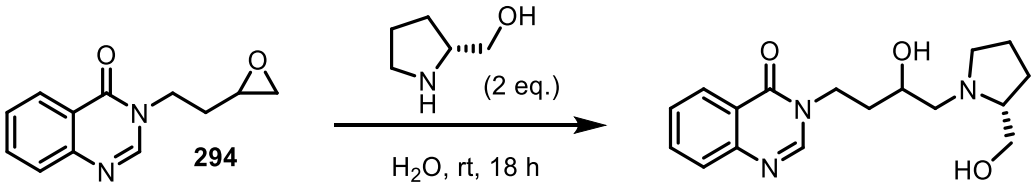
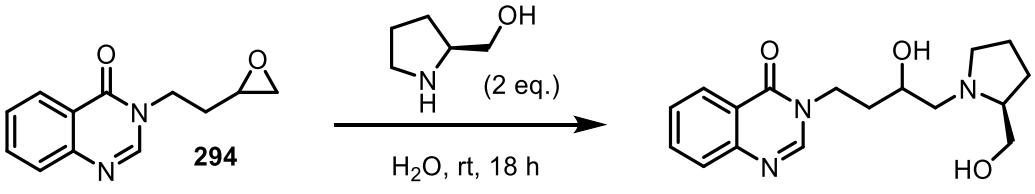
	Compound	Yield
298		65%
299		67%
300		44%
301		62%
302		74%
303		68%

Table 34

Incidentally, the reaction with both L- and D-prolinol also proceeded uneventfully and the resulting 4 diastereoisomers were successfully separated using Mass Directed Auto Preparative HPLC (Scheme 157,158). The optical rotations for all four products were measured to confirm the two sets of enantiomers (See Experimental).



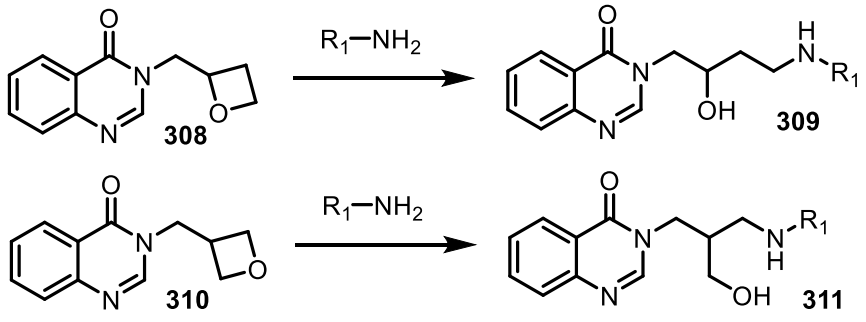
Scheme 157



Scheme 158

Addition of Amines to Oxetane

In order to access the complementary homologous series, we next targeted analogues with an extra methylene incorporated between amino group and the ketone. We envisaged that this could be achieved by a regioselective ring opening of oxetanes with amines, which has been accomplished before in the presence of different Lewis acids (Scheme 159).

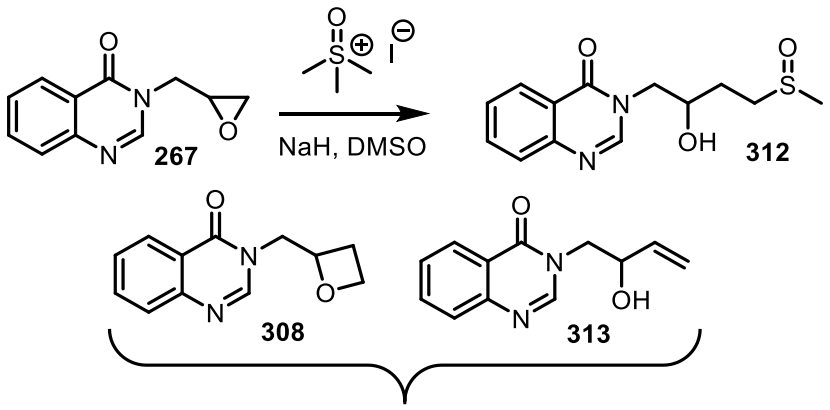


Scheme 159

To make the oxetane starting material, the alkylation of quinazolinone using a pre-formed oxetane was considered. However, these oxetanes are not readily available and are generally expensive to purchase. However, the synthesis of the corresponding quinazolinone epoxide **267** is easier and can be performed on a large scale. A way to transform this epoxide to the desired oxetane via a ring expansion was therefore

pursued. Recently, a Corey-Chaykovsky type reaction was reported in which dimethylsulfoxonium methylide was used to achieve the ring expansion of epoxides to oxetanes. This reported consecutive oxacycle ring expansion involves a high degree of regioselectivity and stereospecificity which provides a novel preparation of optically active cyclic ethers.[153] However, the reported scope did not involve epoxides appended to heterocycles.

The reaction was attempted by deprotonating dimethylsulfoxonium iodide using sodium hydride in DMSO followed by addition of the epoxide. After stirring at 60 °C for 18 h, the epoxide was fully consumed and three products were observed in the LCMS analysis (Scheme 160). The first product appeared to be the sulfoxide **312** which hadn't cyclised to the desired oxetane. The second and third products were the desired oxetane and the allylic alcohol **313** which proved to be difficult to separate via column chromatography.

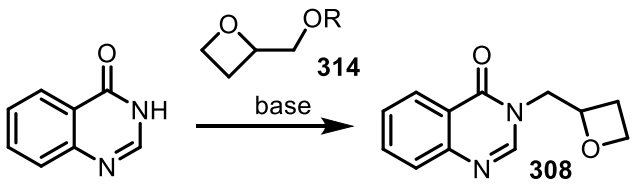


Scheme 160

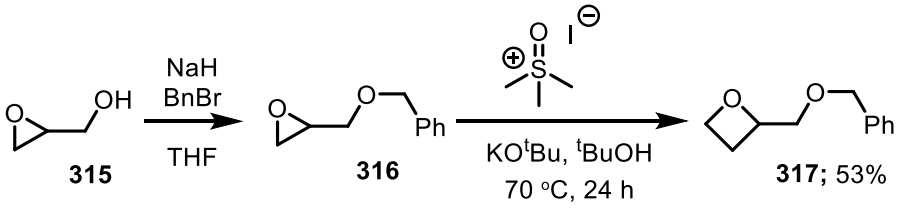
Repeating the reaction using potassium *tert*-butoxide as the base and *tert*-butanol as the solvent gave similar results in which an inseparable mixture of oxetane and alkene was obtained. Furthermore, another product observed in the NMR spectrum of the crude mixtures was the aniline resulting from ring-opening of the quinazolinone. The heterocycle core seems to be prone to ring opening under strong basic conditions as observed in previous reactions with sodium hydroxide. For this reason and the fact

that the oxetane product could not be separated from the olefin, a different approach was investigated which involved introducing the oxetane as an alkylating agent.

A new strategy was devised to make the desired quinazolinone oxetane starting material in which the oxetane **314** was prepared and then reacted with quinazolinone in an alkylation procedure (Scheme 161). We planned to prepare the oxetane via the Corey-Chaykovsky ring expansion of glycidol **315** which is a very cheap starting material.

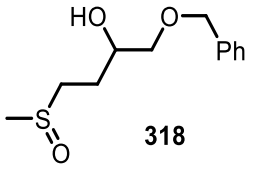


Scheme 161



Scheme 162

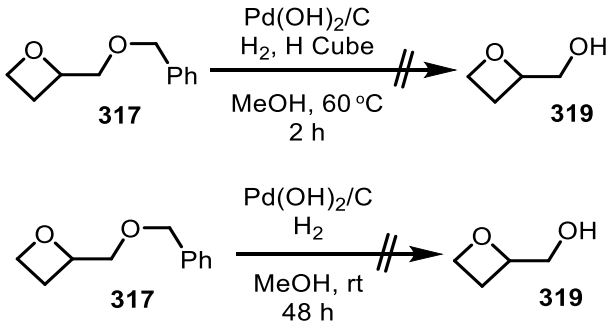
Firstly, the epoxide alcohol had to be protected, and so glycidol was reacted with benzyl bromide to afford the benzyl protected alcohol **316** in a moderate yield. The ring expansion using trimethylsulfoxonium iodide in the presence of potassium *tert*-butoxide was performed over 24 hours giving the desired oxetane **317** in a 53% yield. However, although the starting material was fully consumed after this time, the uncyclized intermediate **318** was still observed in the crude NMR spectrum (Figure 18). Related Corey-Chaykovsky reactions in literature were reported in which the reaction is performed over 3-5 days to obtain high yields.[153] Disappointingly, running the reaction over these extended times did not improve the yield for the oxetane significantly and so the reaction was stopped at 24 h to isolate the product in moderate yield.



318

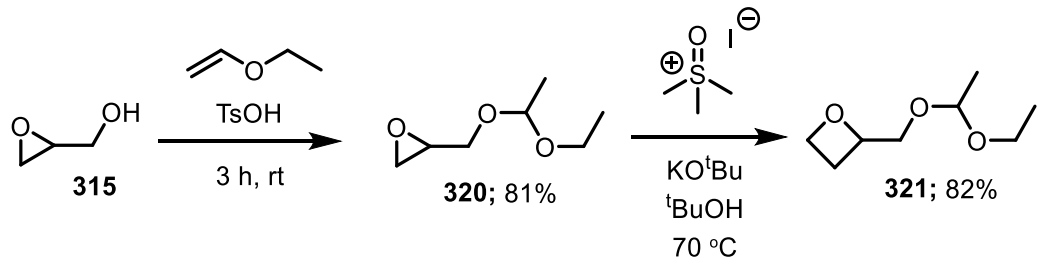
Figure 18

Efforts were then turned to the deprotection of the benzyl group to obtain the desired alcohol **319** but attempts to perform the hydrogenation using the H-cube reactor under standard conditions proved unsuccessful. Alternatively, employing a more traditional method involving the use of a hydrogen balloon did not result in debenzylation, even after 48 h (Scheme 163). Ultimately, the use of methanol or acetic acid as solvents with relatively high boiling points was also deemed to be problematic for the work-up especially with the expected high volatility of the product. For this reason, and due to the unreactive nature of the benzyl-protected alcohol under the hydrogenation conditions, a different protecting group was sought.



Scheme 163

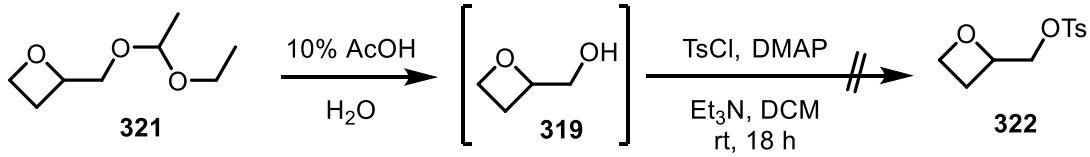
The preparation of simple oxetanes containing reactive 2-substituents was reported starting from glycidol, and also using trimethylsulfoxonium iodide as the methylene transfer agent. In this method, the alcohol was reacted with vinyl ethyl ether to afford the acetal **320**. After the ring expansion, the protecting group was removed via treatment with acid to give 2-hydroxymethyloxetane in excellent yields. This sequence was therefore applied for this investigation which gratifyingly, provided the protected alcohol **321** in an 82% yield (Scheme 164).



Scheme 164

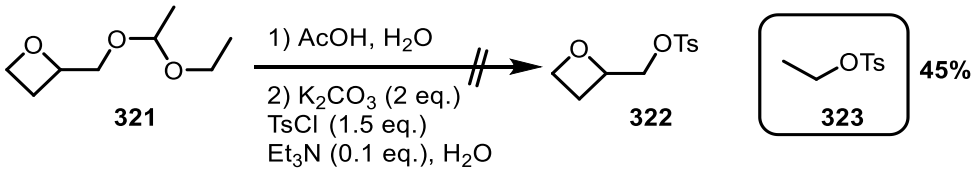
Despite the ability to prepare the desired protected alcohol in multiple grams, the acid hydrolysis step proved to be more difficult than expected. Treating the acetal **321** with 10% acetic acid in water for 18 h and then basifying afterwards resulted in poor mass balance after extraction with diethyl ether. Although the selected solvent was not ideal for efficiently extracting the product from the aqueous layer, it was anticipated that using solvents with higher boiling points such as ethyl acetate would be problematic when it came to evaporation of the extract due to the expected volatility of the product. In an attempt to omit the solvent removal stage after extraction, the solution was used directly in the subsequent tosylation step.

Attempted tosylation using crude extract



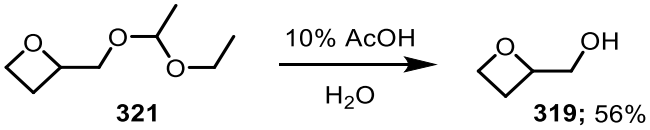
Scheme 165

Unfortunately, no product was observed after treatment of the crude extract with tosyl chloride and triethylamine in the presence of catalytic DMAP. Almost as a last resort, the extraction step was eliminated altogether and the tosylation was performed directly after basifying the reaction mixture. Unfortunately however, the main compound isolated was the tosylated alcohol **323** which arises from the initial deprotection step.



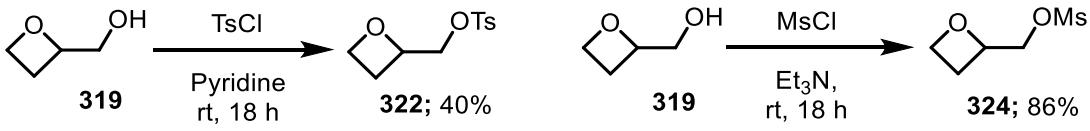
Scheme 166

To address the problem of the volatility of the product, removal of the solvent after extraction via short-path distillation was considered. After basifying the acidic reaction mixture using excess solid sodium bicarbonate, the reaction mixture was distilled to remove the ethanol by-product. The resulting residue was further basified by the addition of an excess of solid potassium carbonate and then the product was extracted with diethyl ether. Removal of the solvent via short path distillation delivered the product **319** in a 44% yield. Gratifyingly, switching the extraction solvent from diethyl ether to dichloromethane improved the yield to 56%. The reaction was also shown to be efficient on large scale with up to 5 grams of the desired alcohol obtained without reduction in yield.



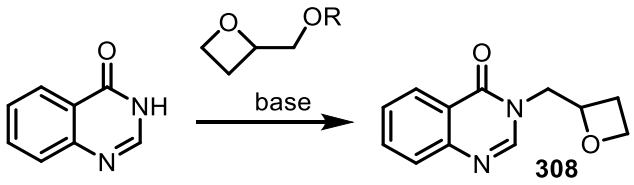
Scheme 167

With the free alcohol **319** in hand, the tosylation was performed using triethylamine as the base and in the presence of DMAP to afford the product **322** in a 40% yield (Scheme 168). Changing the base to pyridine (used neat) did not improve the yield any further. Fortunately, performing a mesylation with mesyl chloride and triethylamine gave the mesylate in an 86% yield. The change in reactivity could be attributed to the fact that the mesylation proceeds via a reactive sulphur ylide intermediate.[154]



Scheme 168

The final step to prepare the quinazolinone oxetane starting material involved the alkylation of quinazolinone using the tosylate or mesylate of the oxetane. The conditions developed in this investigation to alkylate quinazolinone with epichlorohydrin were employed in which potassium carbonate was employed as the base and with acetone as the solvent. Under these conditions, the tosylate **322** afforded the desired product in a modest yield of 56% after 18 h of reaction time. In an effort to decrease the reaction time, the temperature was increased to 120 °C with sodium hydride as the base and the solvent was changed to DMF, which solubilises the starting material better. Unfortunately, this resulted in a complex mixture with only 15% of the desired product isolated. The base was reverted back to potassium carbonate but the DMF solvent was maintained and this provided the product in better yields. Due to the inferior yields obtained when preparing the tosylate in comparison to the mesylate **324**, the latter alkylating agent was preferred. Furthermore, the crude mixture of the reaction using the mesylate tended to be cleaner (as judged by crude NMR analysis), eliminating the need to purify the product by column chromatography.



308

Entry	R	base	solvent	temp.	time	yield
1	Ts	K_2CO_3 (1.5 eq)	acetone	60 °C	18 h	55%
2	Ms	NaH (2 eq)	DMF	120 °C	2 h	15%
3	Ms	K_2CO_3 (1.5 eq)	acetone	60 °C	18 h	19%
4	Ms	K_2CO_3 (1.5 eq)	DMF	60 °C	18 h	67%

Table 35

With the quinazolinone oxetane in hand, we then investigated the ring opening of the oxetane with different amines. Firstly, a range of different Lewis acids were screened. Although the ring opening of epoxides with a variety of nucleophiles has been well studied, the corresponding reaction with oxetanes is far less investigated due to the low

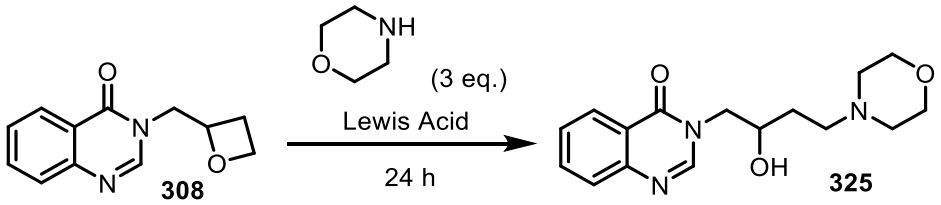
reactivity of the 4-membered cycle compared with their 3-membered counterparts. This could be attributed to the fact that there is a lower degree of strain in oxetanes although the oxygen in the ring has greater basicity.[155]

Although existing methodologies for the aminolysis of oxetanes are very limited, a number of examples exist where hard Lewis acids have been successfully employed. Papini described the use of aluminium (III) chloride to open up epoxides using aminosilanes or aminostannanes and this method was also extended for use on lactones and oxetanes.[156] Three examples of β-amino alcohols have been synthesised via the cleavage of oxetanes using catalytic $AlCl_3$. The main advantages highlighted in this method were the complete regioselectivity observed as well as the absence of competing β-elimination.

More recently, Mojtahedi reported an efficient solvent-free aminolysis of epoxides which can be applied to oxetanes as well.[157] In this method, magnesium bromide diethyl etherate was employed as the catalyst and two examples of amines were added to an unsubstituted oxetane. In addition to the solvent-less strategy, this preparation of amino alcohols is performed at room temperature with quick reaction times. It has also been reported that the catalyst can be separated from the products by simple filtration which normally obviates the need to purify by column chromatography.

Finally, Crotti disclosed the aminolysis of oxetanes using milder catalysts and avoiding the use of harsh conditions.[158] In an effort to find a more practical method to prepare γ-amino alcohols, a number of readily available metal salts were tried for the addition of primary and secondary amines to unhindered oxetanes. In their investigation, it was found that the reaction could be performed at room temperature in the presence of lithium tetrafluoroborate to give the products in moderate to good yields. However, alternative Lewis acids such as lithium perchlorate and zinc (II) triflate resulted only in unreacted starting material although both catalysts worked for the aminolysis of the corresponding epoxides.

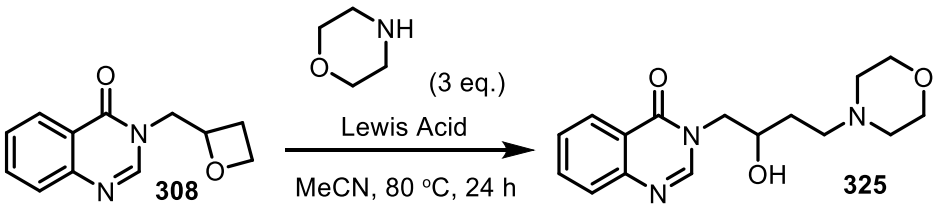
Some of these Lewis acids were employed in this investigation with morpholine as the model amine substrate. The reactions were performed at room temperature and the consumption of starting material was monitored by TLC analysis. Disappointingly, only traces of product were observed and majority of the starting material remained unreacted even after prolonged times. Warming the reaction did not help and no product was isolated after heating at 80 °C for 72 h (Table 36).



Entry	Lewis Acid	eq.	solvent	temp	result
1	$AlCl_3$	0.1	DCM	RT	RSM
2	$MgBr.OEt_2$	0.1	MeCN	RT	RSM
3	$LiBF_4$	0.5	DCM	RT	RSM
4	$LiBF_4$	0.5	DCM	40 °C	RSM
5	$LiBF_4$	0.5	MeCN	80 °C	RSM

Table 36

Whilst there are no reported methods to open up oxetanes using soft Lewis acids, the use of borderline Lewis acids has been described by Crotti as well.[158] Extraordinarily, employing rare-earth metal triflates was successful in promoting the ring opening of oxetanes. Although literature-known compounds for a long time, it wasn't until 1991 that the first use of lanthanide triflates in organic synthesis emerged.[159] These exceptional Lewis acids offer a few advantages over traditional ones which include improved stability in water. Furthermore, they are known to be recoverable after the reaction and they can be re-used without significant loss of activity.[160] Crotti exploited some of these unique lanthanide compounds, in particular ytterbium (III) triflate, neodymium (III) triflate and gadolinium (III) triflate for the aminolysis of oxetanes.

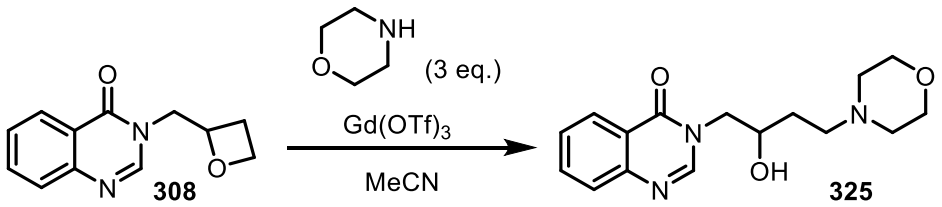


Entry	Lewis Acid	eq.	result
1	$Gd(OTf)_3$	0.5	36%
2	$Gd(OTf)_3$	1	56%
3	$Yb(OTf)_3$	1	46%
4	$Sc(OTf)_3$	1	49%

Table 37

Satisfyingly, using Crotti's conditions of 0.5 eq. of $Gd(OTf)_3$ at 80 °C in MeCN, the desired amino alcohol was obtained in a moderate yield of 36%. Some of the starting material was recovered after a reaction time of 24 h so the catalyst loading was doubled to 1 equivalent. This improved the yield to 56% but the reaction still failed to reach completion after 24 h. $Yb(OTf)_3$ also gave the product in a 46% yield while another rare-earth metal triflate, $Sc(OTf)_3$ provided the product in a slightly improved yield of 49% (Table 37).

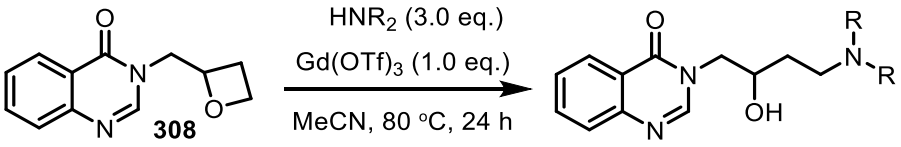
With $Gd(OTf)_3$ proving to be the most effective Lewis acid, the reaction conditions were optimized further. The catalyst loading was increased to 1.2 equivalents in the hope that the reaction would reach full conversion but starting material was still observed after 24 h. Disappointingly, running the reaction over a much more prolonged reaction time (72 h) resulted in a complex mixture which didn't lead to any desired product. In an effort to reduce the reaction time and possibly decrease the loading of the catalyst as well, microwave conditions were also attempted. Running the reaction at 80 °C under microwave irradiation for 1 h only resulted in recovered starting material with no product observable. Increasing the temperature to 120 °C and running for 10 mins resulted to full consumption of starting material but only gave 41% of the product (Table 38).



Entry	$Gd(OTf)_3$	temp	time	result
1	1.2 eq.	80 °C	72 h	Complex mixture
2	1.0 eq.	80 °C (microwave)	5 min	NO REACTION
3	1.0 eq.	80 °C (microwave)	1 h	NO REACTION
4	1.0 eq.	120 °C (microwave)	10 min	41%

Table 38

With these results in hand, the reactivity of other amines were evaluated. Diethylamine and piperidine were reacted with the oxetane using one equivalent of $Gd(OTf)_3$ and 3 equivalents of the amine. Inconveniently, the main by-product of the reaction which is the corresponding amine triflate salt which proved to be difficult to separate from the product by column chromatography. Reducing the amine equivalents to 1.2 proved to be detrimental to the reaction with no product obtained after 24 h. Performing a base wash and then an extraction with dichloromethane was unsuccessful due to the high water solubility of the amino alcohol products. After discovering that the products were not very soluble in dichloromethane, the extraction was performed with ethyl acetate and then purification by column chromatography afforded the desired products in moderate to good yields.



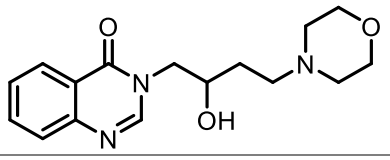
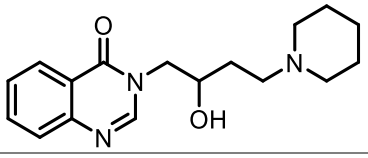
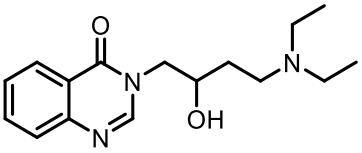
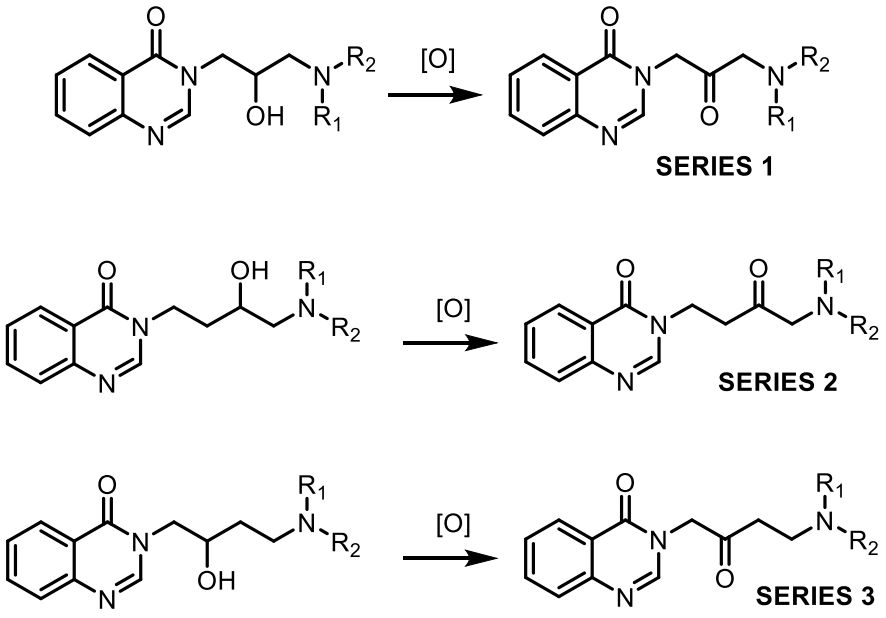
	Compound	Yield
325		56%
326		57%
327		51%

Table 39

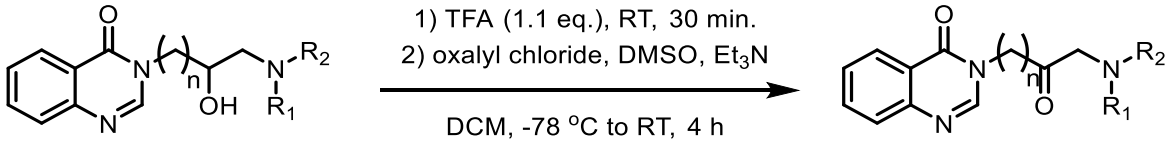
Oxidation of Amino Alcohols

With the synthesised amino alcohols in hand, we then investigated their oxidation to obtain the corresponding amino ketone analogues. An efficient oxidation method that could be applied for the amino alcohols from all the different series was sought after.



Scheme 169

The oxidation of selected amino alcohols from the first two series proceeded using Swern conditions to give the corresponding amino ketones with moderate to good yields. The amino alcohols were premixed with trifluoroacetic acid to ensure that the amine was protected as an ammonium salt in order to prevent oxidation. Unfortunately, both analogues containing the diisopropylamine unit did not react under the conditions with starting material recovered in both cases. The results are summarized in table 40.



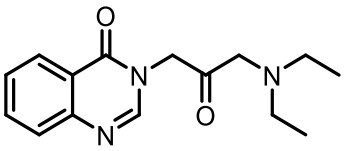
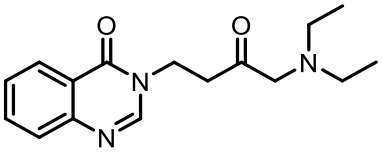
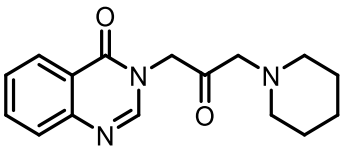
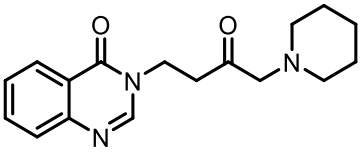
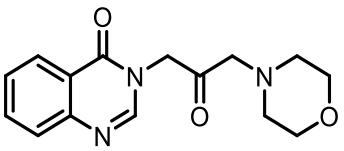
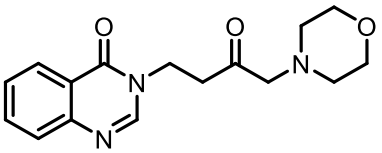
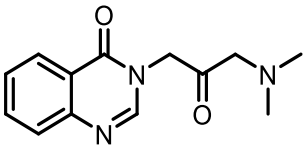
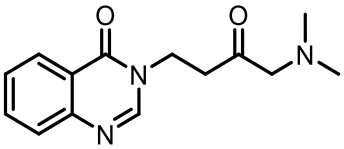
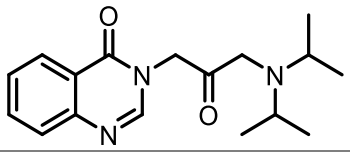
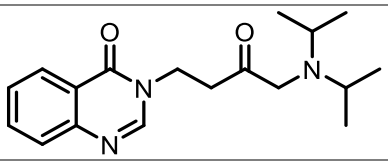
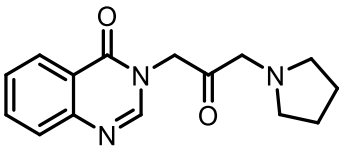
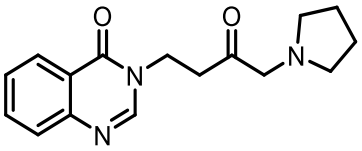
	Compound	Yield		Compound	Yield
328		78%	**334**		65%
329		86%	**335**		62%
330		84%	**336**		65%
331		44%	**337**		33%
332		0%	**338**		0%
333		34%	**339**		39%

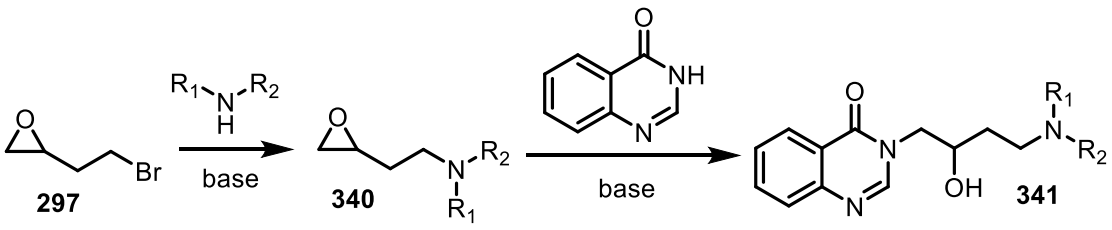
Table 40

Obtaining the ketones for the third series proved to be difficult starting from the corresponding amino alcohols since these intermediates are challenging to obtain in useful quantities. This is due to the problematic scale-up of the gadolinium-catalysed

aminolysis of the quinazolinone oxetanes in which typically ~20 mg of material is obtained. Not only are the yields for the reactions poor to moderate, the use of stoichiometric amounts of $Gd(OTf)_3$ is not practical as this reagent is expensive. Indeed, using our current conditions, obtaining 100 mg of product would require more than 1 g of gadolinium catalyst. Furthermore, the lengthy procedure to synthesise the quinazolinone oxetane starting material justified the need to develop a new strategy to obtain the required amino alcohols from the third series.

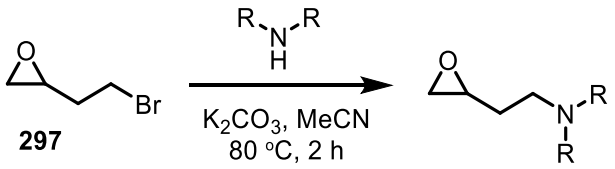
Synthesis of γ-amino alcohols

A new approach was envisioned for the synthesis of the γ-amino alcohols in which the quinazolinone is used to open up an epoxide already containing the amine moiety (Scheme 170). Bromo epoxide **297** would be employed to alkylate various amines to obtain the desired amino oxirane **340** which could be opened regioselectively by the quinazolinone with the aid of a base.



Scheme 170

Accordingly, different examples of amino oxiranes were prepared starting from 4-bromo-but-1-ene which was epoxidised with *m*-CPBA to obtain the epoxyalkyl bromide **297** in a 99% yield. Various amines were then added which remarkably reacted chemoselectively with the alkyl bromide with no observed opening of the epoxide to give the desired amino oxiranes (Table 41).



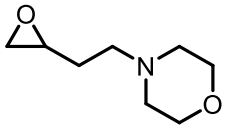
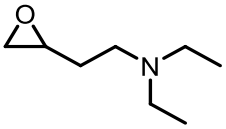
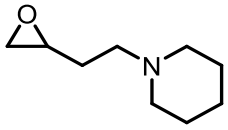
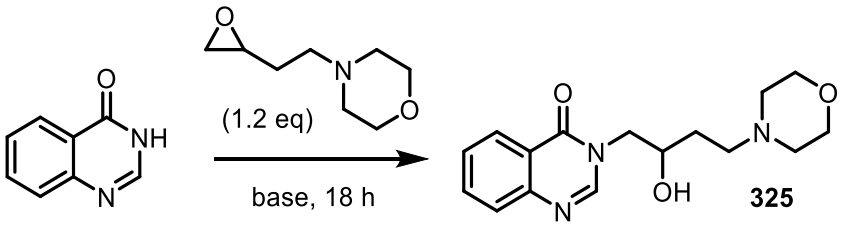
	Compound	Yield		Compound	Yield
342		65%	**344**		60%
343		68%			

Table 41



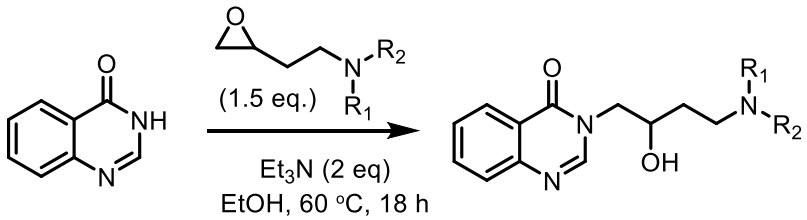
Entry	Base	Solvent	Temp.	Result
1	K_2CO_3 (1.5 eq.)	Acetone	60 °C	RSM
2	NaH (2 eq.)	DMF	80 °C	**21%**
3	NaH (5 eq.)	DMF	100 °C	**25%**
4	LiHMDS (2 eq.)	THF	0 to 70 °C	RSM
5	KHMDS (2 eq.)	THF	0 to 70 °C	RSM
6	EtMgBr (2 eq.)	THF	0 to 70 °C	RSM
7	Et_3N (2 eq.)	EtOH	60 °C	**86%**

Table 42

With the amino oxiranes in hand, the epoxide opening with quinazolinone was explored by performing a base screening with the morpholinyl epoxide as the model substrate. Amongst the bases employed, K_2CO_3, LiHMDS, KHMDS and EtMgBr were ineffective, and only starting material was recovered in all cases (Table 42). Using sodium hydride was more promising where product was obtained in a 21% yield when 2 equivalents were used at 80 °C. Increasing the temperature to 100 °C or increasing the

equivalents of sodium hydride only marginally increased the yield with most of the unreacted quinazolinone still recovered. Two previously reported aminolysis of epoxides with quinazolinones by Mai involved the use of an organic base (e.g. triethylamine, pyridine) in combination with an alcohol as a solvent (e.g. ethanol, isopropanol). Gratifyingly, performing the epoxide opening with Et_3N in EtOH gave the desired γ-amino alcohol **325** in an 86% yield.

With optimized conditions in hand, the scope of the protocol was explored by performing the reaction with the other prepared amino epoxides. Rather surprisingly, the reaction did not proceed when diethylamine or piperidine were used, with unreacted quinazolinone being recovered in both cases. A control experiment was performed in which a 1:1 mixture of morpholine and piperidine were reacted with the quinazolinone. In this case, only the morpholine product was isolated in a 23% yield with most of the quinazolinone recovered. It was then speculated if the reaction is just in the verge of proceeding and it just needs to be driven harder to completion.



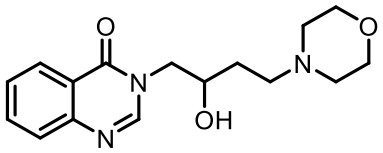
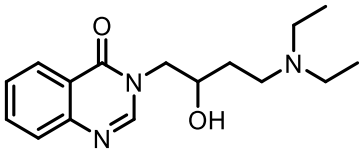
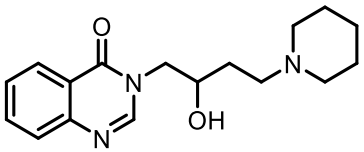
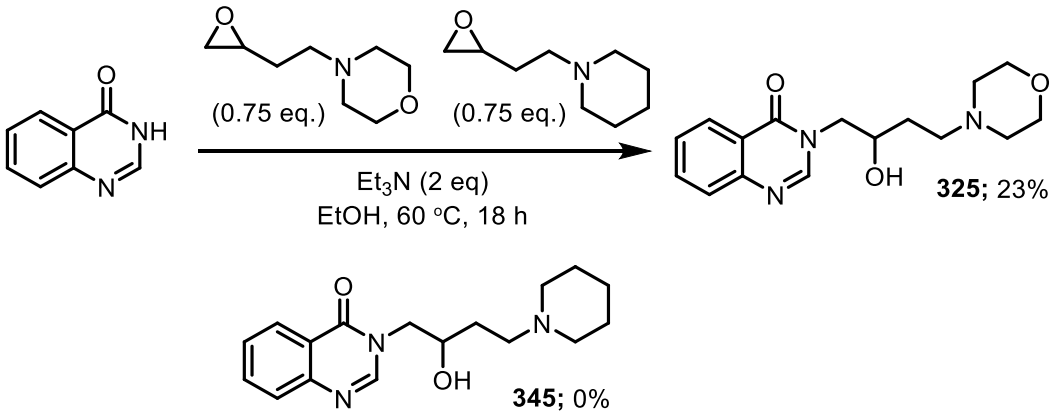
	Compound	Yield		Compound	Yield
325		86%	**346**		0%
345		0%			

Table 43

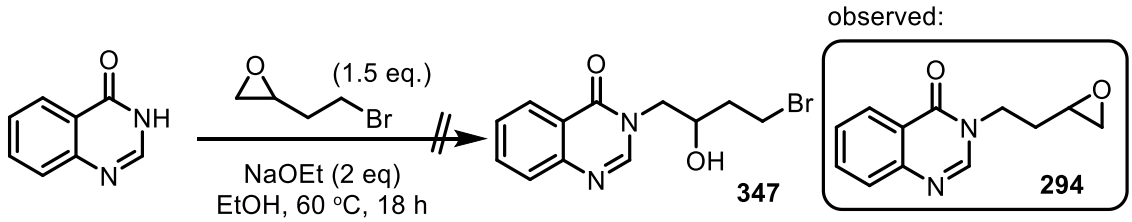


Scheme 171

Consequently, the solvent was changed to isopropanol to enable the reaction to be run at a higher temperature. Unfortunately, the epoxide opening still did not proceed using piperidine and diethylamine with unreacted quinazolinone recovered once again. One notable observation in the reaction was the failure to recover the unreacted epoxide, even though the quinazolinone was isolated afterwards. We suspected therefore that the epoxide is unstable under the reaction conditions, and so a control reaction in which the epoxide was subjected to the reaction conditions without the quinazolinone was performed. In the event, this resulted in a complex mixture which suggested that the epoxide is too reactive, possibly decomposing by polymerisation. The reaction was repeated at room temperature to address this issue but unfortunately this only resulted in a complex mixture after running the reaction for 24 h.

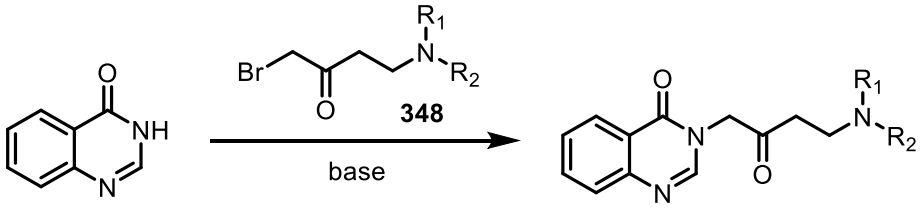
Finally, the aminolysis was attempted with the epoxyalkyl bromide **297** with the intent to do the alkylation at a later stage. This would require the quinazolinone to chemoselectively react with the oxirane ring. Studies on the reactivity of bifunctional epoxyalkyl bromides have been carried out by Cruickshank and Fishman and they reported that the alkylation is significantly affected by the choice of solvent as well as the nature of the nucleophile.[142] In theory, using a protic solvent could activate the epoxide ring hence allowing the nucleophile to open up the ring and provide hydroxy bromoalkyl derivatives. On the other hand, no solvent effects are observed with aprotic solvents hence leading the nucleophile to displace the bromide and give epoxyalkyl derivatives.

Unfortunately, attempts to perform the aminolysis of the epoxyalkyl bromide **297** with quinazolinone using NaOEt as the base and EtOH as the solvent resulted in a mixture of products, which included the undesired epoxyalkyl quinazolinone **294** (Scheme 172).

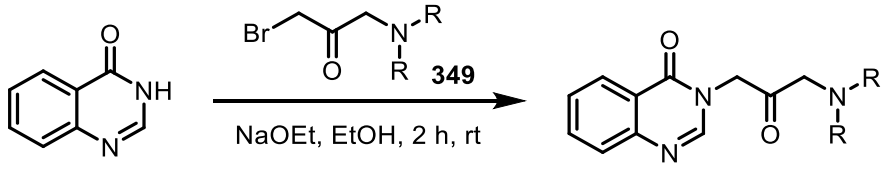


Scheme 172

A different approach was proposed which would allow the synthesis of the amino ketone without going through the corresponding γ-amino alcohols. This new strategy involved the synthesis of bromomethyl aminopropyl ketone **348** which could be used to alkylate quinazolinone and provide the desired amino ketones (Scheme 173). Magidson has previously reported the synthesis of febrifugine analogues by alkylating quinazolinone with bromomethyl aminoethyl ketone **349** in the presence of sodium ethoxide as the base (Scheme 174).[161]



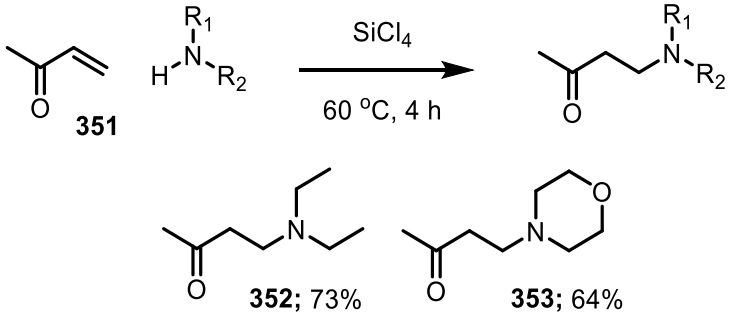
Scheme 173



Scheme 174

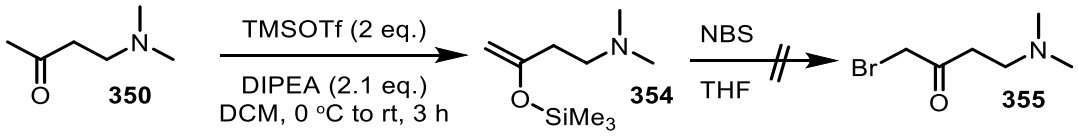
To prepare the starting bromo ketones **349**, the corresponding β-amino ketone was anticipated to be brominated on the least hindered part of the ketone. The β-amino ketone bearing the dimethyl amine substituent **350** was obtained commercially whilst two more examples were prepared using Azizi's method.[162] Accordingly, the conjugate

addition of diethylamine and morpholine to enone **351** was performed using silicon tetrachloride as the catalyst in the absence of solvent. This afforded two different β-amino ketones in excellent yields and in multi-gram amounts (Scheme 175).



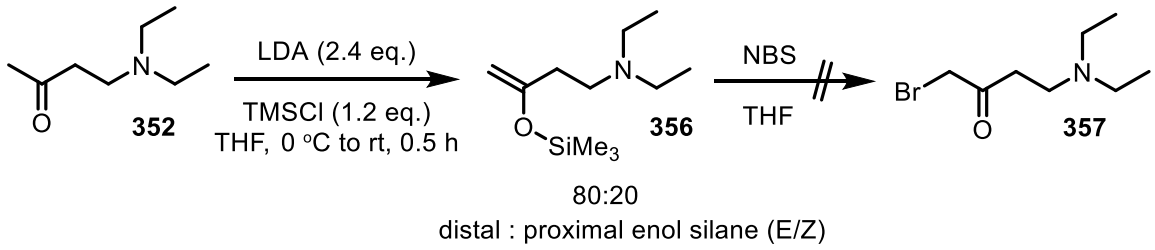
Scheme 175

With the β-amino ketones in hand, the bromination was attempted with the dimethylamine substrate. The corresponding silyl enol ether was prepared by treating the ketone with Hünig's base and TMSOTf as the Lewis acid. The silyl enol ether was used in the next step directly due to its instability and so the crude was treated with *N*-bromosuccinimide. Unfortunately, the desired bromo ketone **355** was not observed, and so we questioned whether the required silyl enol ether **354** had been made in the first place.



Scheme 176

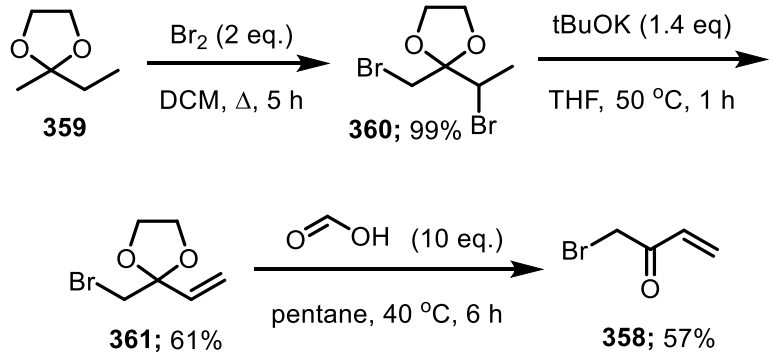
To ensure that the intermediate silyl enol ether was the active reagent, the amino ketone was changed to the diethylamine analogue since the enol silane for this substrate was already reported and the NMR data could be used for comparison. Using Pratt's optimal reaction conditions, an 8:2 mixture of distal and proximal silanes were generated, as determined by crude ^{1}H NMR spectroscopy.[163] Disappointingly, after treating the crude silanes with NBS, no desired bromo ketone was observed. It was therefore decided to change the brominating agent to diatomic bromine, and start with the ketone instead of making the silyl enol ether.



Scheme 177

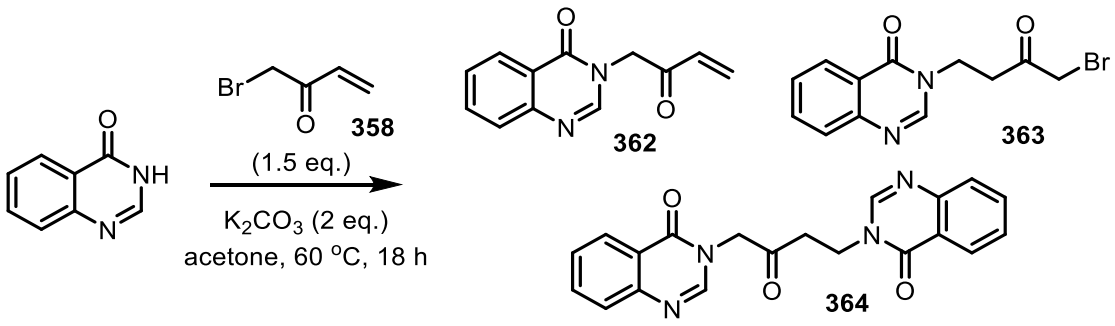
The diethylamine analogue **352** was treated with hydrobromic acid in acetic acid before the addition of bromine and heating at 60 °C for 2 h. Disappointingly, this resulted in a complex mixture in which the major identifiable product was diethylamine. This result suggested that the E1CB elimination of the amine to obtain the enone back which could decompose or further react in the reaction mixture. Furthermore, the bromo amino ketones are also prone to cyclization so it was concluded that this route was not appropriate to obtain the desired quinazolinone amino ketones.

The final strategy employed for the synthesis of the amino ketones exploited bromomethyl vinylketone **358** which could be used to alkylate quinazolinone. We envisaged that the resulting enone could then be used for the aza-Michael addition of various amines to obtain the target amino ketones without going through the corresponding amino alcohols. The preparation of 1-bromo-3-buten-2-one was reported by Carlson and starts from the commercially available protected ketone **359**.[164] Using Carlson's method, the dibrominated acetal **360** was obtained in a quantitative yield and then a dehydrobromination was performed with potassium *tert*-butoxide to obtain **361** in good yield. The deprotection step could be accomplished with formic acid either by conventional heating for 4 h or under microwave irradiation. Either way, the resulting bromomethyl vinylketone **358** must be used immediately after formation to avoid rapid polymerization.



Scheme 178

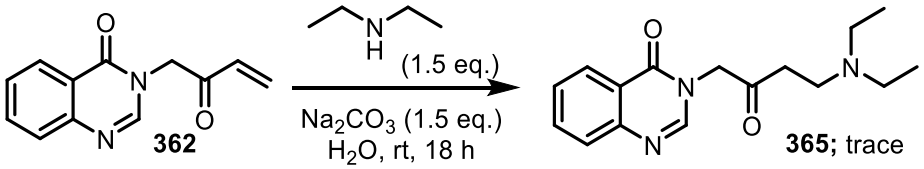
The alkylation of quinazolinone with the bromomethyl vinylketone **358** was performed with potassium carbonate as the base and acetone as the solvent. Disappointingly however, heating the reaction for 18 h gave a mixture of the desired enone **362** and the product **363** arising from the addition of the quinazolinone to the alkene. Furthermore, the dimer **364** was also observed in which the quinazolinone added to both the alkene and the bromide. Separating the mixture of products by flash column chromatography proved to be difficult and we therefore focused on addressing the lack of selectivity.



Scheme 179

We speculated that the addition of tetrabutylammonium iodide could aid the reaction by generating the more reactive iodide via an in situ Finkelstein reaction. Proust also described the addition of tosylamines to bromomethyl vinylketone at 0 °C to avoid the 1,4-addition of the nucleophile and observed only the S_N2 reaction at the bromide.[165] Using both ideas, the reaction was performed with catalytic TBAI and at 0 °C to slow down the conjugate addition. Disappointingly, the same mixture of products was still obtained after running the reaction for 24 h. A small quantity of the desired product was

isolated with minor impurities which was used for the aza-Michael addition of amines. Using Tang's conditions of sodium carbonate as the base in aqueous medium, the addition of diethylamine was attempted but only gave traces of the desired amino ketone.[166] After multiple failed attempts to develop an efficient methodology to prepare the amino ketones from the third series, we finally discontinued this aspect of our research efforts and moved on to investigate the synthesis of febrifugine analogues with different keto linkers.



Scheme 180

Synthesis of Fluorinated Analogues

Having synthesised a number of febrifugine analogues with hydroxy and keto-linkers, we decided to explore the possibility of preparing the corresponding fluorinated analogues. Although not very common in natural products, around 20% of existing pharmaceuticals on the market incorporate at least one fluorine atom and the estimate is even higher with agrochemicals.[167] This can be attributed to the significant benefits that fluorine has to offer which include improvement in important properties such as bioavailability, lipophilicity and metabolic stability. Moreover, these advantages can be exploited without too much modification in molecular geometry and shape due to the comparative sizes of hydrogen and fluorine.

Whilst the incorporation of fluorine into organic compounds is indeed highly advantageous, the task is by no means straightforward and has proven to be quite challenging in the past.[26] Firstly, issues with selectivity may arise in the presence of other functionalities which often require the introduction of the fluorine or fluorinated moiety at a much later stage in the synthesis. A more significant drawback is the use of highly toxic and hazardous reagents such as fluorine gas, hydrofluoric acid or sulfur tetrafluoride which is not ideal for large-scale synthesis in industry. Fortunately, more stable reagents that are relatively non-toxic have been developed over the years allowing for safer and more efficient protocols for fluorination reactions.

Having already obtained the amino ketone analogues from the first series, we decided to perform deoxofluorination reactions with the carbonyl groups to obtain the gem-difluorides. This transformation is traditionally carried out using sulfur tetrafluoride which is a highly toxic and corrosive gas but a safer alternative, diaminosulfurtrifluoride (DAST) **366**, is now more commonly used.[168] Unfortunately, treating amino ketone **329** with 3 equivalents of DAST led to complete recovery of starting material. Likewise, the oxygenated variant, Deoxo-Fluor **367** proved to be ineffective for the deoxofluorination.

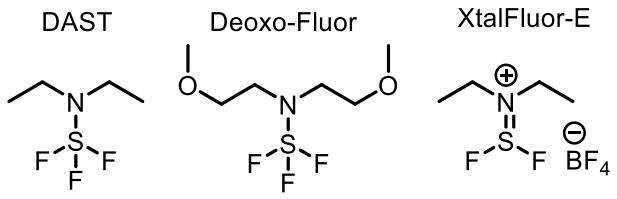
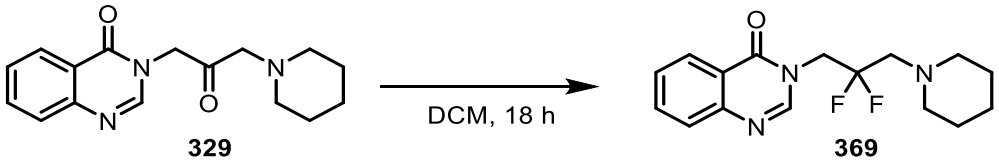


Figure 19

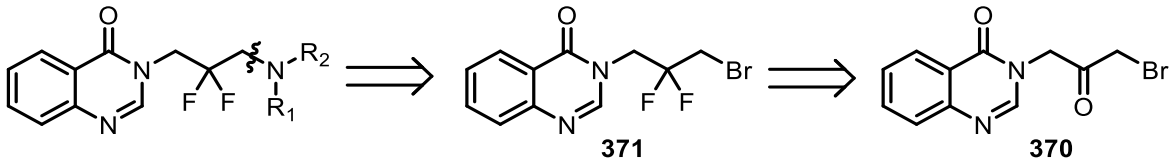
A more stable version of DAST is the aminodifluorosulfonium tetrafluoroborate salt XtalFluor-E **368** which is an easy handled crystalline solid. It is reported to have a higher decomposition temperature compared with DAST or Deoxo-Fluor and a lower exothermic heat generated which signifies greater thermal stability.[169] Disappointingly, the deoxofluorination of **329** using XtalFluor-E proved ineffective in our hands and the starting material was recovered once again. The addition of an exogenous fluoride source such as $Et_3N.HF$ or Olah's reagent (pyridine.HF) to promote the fluorination did not aid the reaction and the application of heat was also unsuccessful (Table 44).



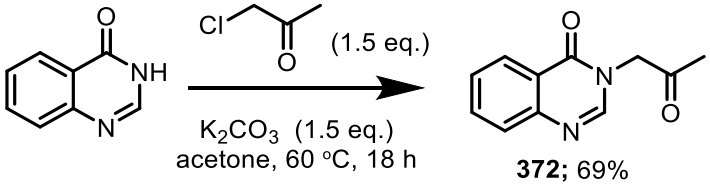
Entry	Flourinating agent	Additive	Temperature	Result
1	DAST (3 eq.)	None	-78 °C to RT	RSM
2	Deoxo-Fluor (3 eq.)	None	-78 °C to RT	RSM
3	XtalFluor-E (1.5 eq.)	None	-78 °C to RT	RSM
4	XtalFluor-E (1.5 eq.)	Pyridine.HF (1.5 eq.)	-78 °C to RT	RSM
5	XtalFluor-E (1.5 eq.)	$Et_3N.HF$ (1.5 eq.)	-78 °C to RT	RSM
6	DAST (3 eq.)	None	40 °C	RSM

Table 44

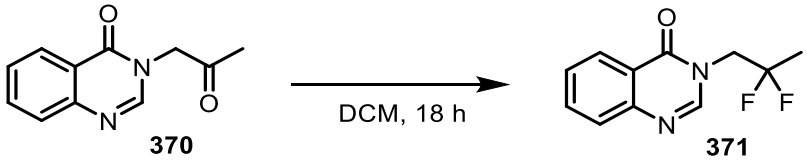
We decided to employ a new strategy which involved fluorinating α-bromoketone **370** and then introducing the amine moiety at a later stage. But before investigating the preparation of intermediate **370**, we felt it was sensible to try the fluorination of **372** which indeed is less hindered than the amino ketone **329**. Accordingly, quinazolinone was treated with chloroacetone and potassium carbonate to afford **372** which could be successfully scaled up to generate gram quantities (Scheme 182). To our disappointment, the fluorination did not proceed using various conditions (Table 45) and so we eventually decided not to attempt the preparation of α-bromoketone **370**.



Scheme 181



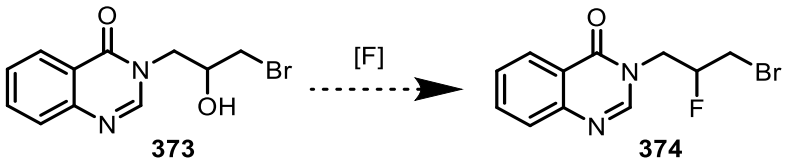
Scheme 182



Entry	Flourinating agent	Additive	Temperature	Result
1	DAST (3 eq.)	None	-78 °C to RT	RSM
2	DAST (3 eq.)	$Et_3N.HF$ (3 eq.)	-78 °C to RT	RSM
3	Deoxo-Fluor	None	-78 °C to RT	RSM
4	XtalFluor-E (1.5 eq.)	$Et_3N.HF$ (2 eq.)	40 °C	RSM

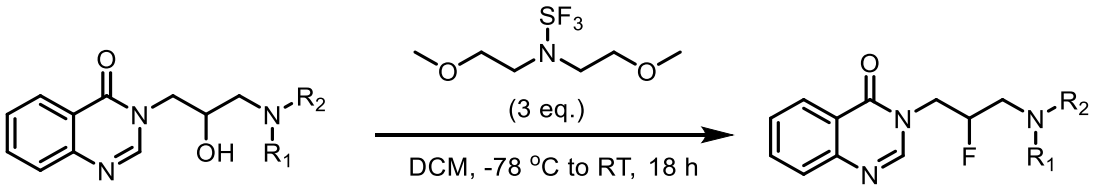
Table 45

With our unsuccessful attempts to prepare the gem-difluorinated analogues, we finally focused on the fluorination of the alcohols to obtain the mono-fluoride analogues. Initial investigation on the preparation of **374** in order to incorporate the amine moiety at a later stage showed that the fluorination of bromohydrin **373** is not feasible. Pleasingly, treating the amino alcohols with 3 equivalents of Deoxo-Fluor gave a number of the desired mono-fluorinated analogues in moderate yields (Table 46). The analogue containing the diisopropylamine unit did not react under the conditions but the analogues with the dimethylamine and pyrrolidine moieties were obtained, albeit in poor yields.



373 **374**

Scheme 183



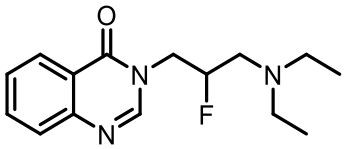
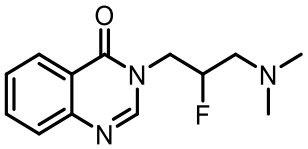
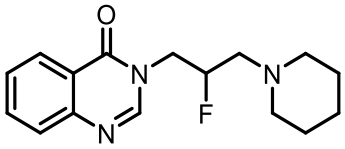
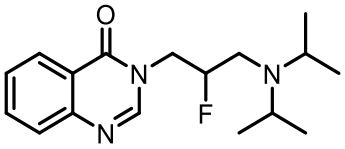
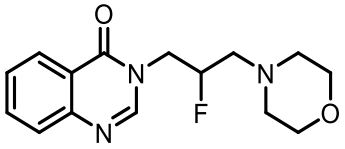
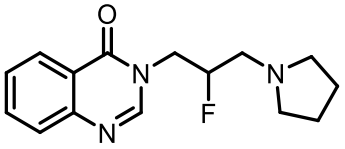
	Compound	Yield		Compound	Yield
375		54%	**378**		13%
376		55%	**379**		0%
377		49%	**380**		24%

Table 46

Conclusion

Febrifugine and the synthetic analogue halofuginone have been shown to inhibit human prolyl-transfer RNA synthetase by acting as dual site inhibitors. The quinazolinone moiety blocks the binding site of tRNA whilst the hydroxypiperidine part inhibits the binding of proline to ProRS. In this investigation, a number of febrifugine analogues have been designed and synthesised to interrogate the binding at the southeast polar region. The analogues were prepared with the incentive to test them as potential therapy for IPF.

The hydroxypiperidine moiety was replaced with different amine groups to introduce potential new hydrogen bonding interactions. This entailed opening an epoxide regioselectively with various amines as well as amino alcohols derived from amino acids. The carbon chain length between the quinazolinone and the keto linker was also varied to obtain a homologous series. This involved the aminolysis of oxetanes catalysed by rare-earth metal triflates such as gadolinium triflate.

Finally, the keto-linker was also investigated by incorporating other groups that could hydrogen-bond with ATP in the binding site. The amino alcohol analogues were successfully oxidized to obtain the corresponding amino ketones. The deoxofluorination of the ketones has been attempted to obtain the gem-difluoride analogues but was ineffective. The fluorination of the amino alcohols was successful and furnished the desired mono-fluorinated analogues.

Future Outlook

Idiopathic Pulmonary Fibrosis continues to be a disease with unsatisfied needs for treatment or effective management. At present, Pirfenidone and Nintedanib remain as the only useful therapies for patients with IPF. Understanding the polypharmacology of both agents might be key to determining their efficacy. Likewise, polypharmacology approaches could help in designing an effective treatment for IPF.

In vitro biological data from testing the synthesised isatin, isatogen and febrifugine analogues would be useful in determining which further analogues to design to improve the pharmacological properties. By identifying the polypharmacology mixtures of compounds required for activity, these could then be combined to a single molecule. The property of febrifugine as a dual site inhibitor is important to exploit to design an effective drug with multiple targets. Furthermore, it would be useful to find out the effectiveness of isatins as TG2 inhibitors and whether they could be developed as potential treatment for IPF.

Experimental

General Experimental Procedures

Unless otherwise stated, all melting points (uncorrected) were recorded directly from products after chromatography and obtained using a Gallenkamp melting point apparatus. Melting points for amorphous solids were not recorded.

All ^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or a Bruker AMX-400 (400 MHz) instrument supported by an Aspect 3000 data system. The chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$ in $CDCl_3$: δ 7.27 ppm; DMSO in $(CD_3)_2SO$: δ 2.52). Data are expressed as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, td= triplet of doublet, q = quartet, m = multiplet), coupling constant (Hz), and integration.

All ^{13}C NMR spectra were recorded using the JMOD pulse sequence on a Bruker AC-250 (62.9 MHz) or AMX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetratmethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm; $(CD_3)_2SO$: δ 39.7). Relative to $CDCl_3$ or $(CD_3)_2SO$, (+) denotes CH_3 or CH and (–) denotes CH_2 or C (or vice versa).

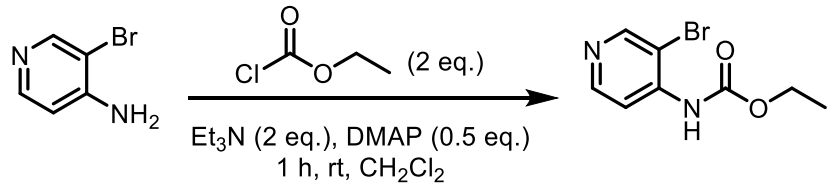
Infrared (FTIR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1}. Low resolution mass spectra (m/z) were recorded on either a Kratos MS 25 or MS 80 spectrometer supported by a DS 55 data system, operating in EI,CI or FAB mode; or a Perkin-Elmer Turbomass Benchtop GC-MS operating in either EI or CI mode,with only molecular ions (M+) and major peaks being reported with intensities quoted as percentages of the base peak. High resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES) or a MicroMass Prospec operating in either FAB, EI or CI mode.

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of nitrogen. Dichloromethane, toluene and acetonitrile were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. All reagents were used as received from commercial sources unless otherwise stated.

Petroleum ether (40-60 petroleum distillate) was distilled prior to use. Flash column chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh). Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm Merck Kieselgel 60 F_{254}) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), potassium permanganate/heat.

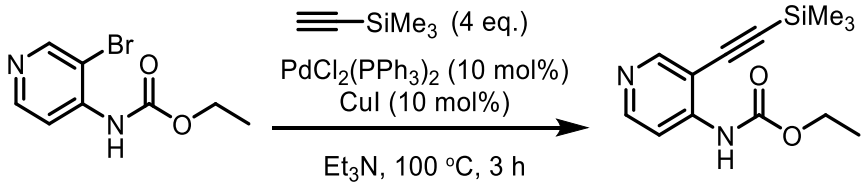
All spectral data (^{1}H NMR, ^{13}C NMR) and m.p. for compounds that have previously been described are in accordance with literature values. Silyl enol ether **354** and bromomethyl vinyl ketone **358** were found to decompose quickly after preparation therefore the ^{13}C NMR spectra were not recorded.

Synthesis of ethyl (3-bromopyridin-4-yl)carbamate (95)[80]



4-Amino-3-bromopyridine (3.00 g, 17.3 mmol, 1.0 eq.) and DMAP (1.06 g, 8.67 mmol, 0.5 eq.) were dissolved in dichloromethane (20 mL) and Et_3N (4.81 mL, 34.7 mmol, 2.0 eq.) was added. Ethyl chloroformate (2.48 mL, 26.0 mmol, 1.5 eq.) was added at 0 °C and the reaction mixture was stirred at rt under a stream of N_2 for 1 h. Water (20 mL) was added and the product extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to afford the title compound as white crystals (3.25 g, 78%). M.p. 58-60 °C (lit: 60-61.5 °C).[80] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.42 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 5.5 Hz, 1H), 7.33 (s, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5 (-), 151.6 (+), 149.5 (+), 142.9 (-), 113.2(+), 109.8 (-), 62.3 (-), 14.4 (+).

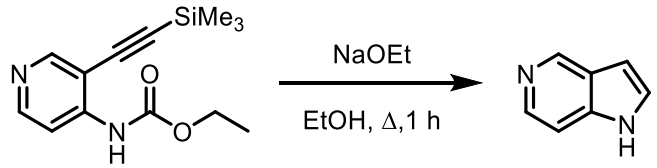
Synthesis of ethyl [3-((trimethylsilyl)ethynyl)pyridin-4-yl]carbamate (96)[80]



Copper iodide (0.230 g, 1.22 mmol, 0.1 eq.) and TMSA (6.97 mL, 49.0 mmol, 4.0 eq.) were combined in Et_3N (10 mL) and stirred at rt for 20 mins. Ethyl (3-bromopyridin-4-yl)carbamate **95** (3.00 g, 12.2 mmol, 1.0 eq.) and $PdCl_2(PPh_3)_2$ (0.86 g, 1.22 mmol, 0.1 eq.) were dissolved in Et_3N (20 mL) and then the CuI/TMSA mixture was added. The reaction mixture was stirred at 100 °C under a stream of N_2 for 3 h. Water (50 mL) was added and the product extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*.

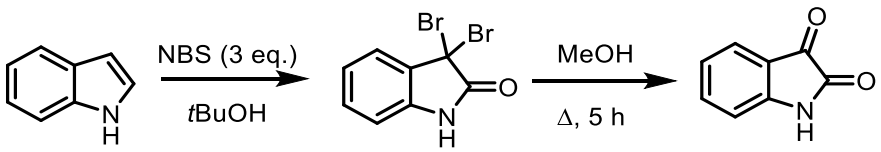
The crude product was purified by flash column chromatography (Florisil, 20% EtOAc/Petrol) to afford the title compound as a light brown solid (2.27 g, 71%). M.p. 130-132 °C (lit: 133-134 °C).[80] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.39 (d, J = 5.0 Hz, 1H), 8.06 (d, *J* = 5.0 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 0.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (+), 152.5 (-), 145.8 (-), 132.2 (-), 132.0 (+), 128.5 (+), 105.8 (-), 97.0 (-), 62.1 (-), 14.4 (+), -0.50 (+).

Synthesis of 5-azaindole (97)[80]



Sodium (0.115 g, 5 mmol) was added to absolute EtOH (10 mL) and the mixture heated at reflux until all the sodium has disappeared. Ethyl [3-((trimethylsilyl)ethynyl)pyridin-4-yl]carbamate **96** (0.150 g, 0.57 mmol, 1.0 eq.) was dissolved in the ethanolic sodium ethoxide solution and then heated at reflux for 2 h. Water (20 mL) was added and the product extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/petrol) to afford the title compound as off-white crystals (0.038 g, 56%). M.p. 110-112 °C (lit: 111.5-112.5 °C).[80] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (br s, 1H), 8.99 (s, 1H), 8.31 (d, *J* = 6.0 Hz, 1H), 7.36 (d, *J* = 6.0 Hz, 1H), 7.33 (d, *J* = 3.0 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 139.9, 139.1, 125.7, 124.8, 106.6, 101.1.

Synthesis of 1H-indole-2,3-dione (4)[59]

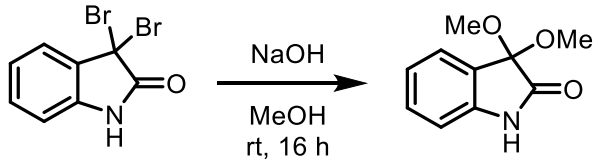


Indole (0.117 g, 1.00 mmol, 1.0 eq.) was dissolved in *tert*-butanol (20 mL) and NBS (0.534 g, 3.0 mmol, 3.0 eq.) was added portion-wise every 5 mins for 30 mins. The

reaction mixture was stirred at rt under a stream of N_2 for 3 h. The solution was concentrated at rt under high vacuum to precipitate a solid which was removed by filtration and washed with cold ether. The combined ethereal and alcoholic solution was evaporated to dryness to obtain dibromide **50** which was used in the next step without further purification.

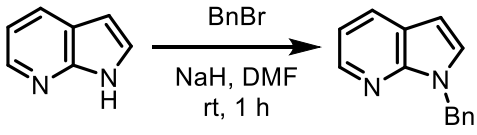
Dibromide **50** was dissolved in MeOH/H_2O (1:1, 40 mL) and the reaction mixture was heated at reflux with stirring for 5 h. The solution was cooled to rt and the solvent removed *in vacuo* to obtain the title compound as a bright orange solid (0.082 g, 56%). M.p. 200 °C (decomp) (lit: 199-200 °C).[59] ^{1}H NMR (250 MHz, DMSO) δ 11.04 (s, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.05 (app. t, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 184.5 (-), 159.5 (-), 151.0 (-), 138.5 (+), 124.9 (+), 123.0 (+), 117.8 (-), 112.4 (+).

Synthesis of 3,3-dimethoxy-1,3-dihydro-2H-indol-2-one (102)[170]



3,3-Dibromo-1,3-dihydro-2H-indol-2-one **50** (0.10 g, 0.34 mmol, 1.0 eq.) was dissolved in MeOH (10 mL) and 5 M NaOH solution (1.0 mL) was added. The reaction mixture was stirred at rt for 16 h. Anhydrous $MgSO_4$ was added before filtering and removing the solvent *in vacuo*. The product was obtained as a dark red amorphous solid (0.040 g, 61%). M.p. 80-82 °C (lit: 74.7 °C).[170] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.42 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.09 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.91 (t, *J* = 7.0 Hz, 1H), 3.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (-), 140.4 (-), 130.8 (+), 125.2 (+), 124.8 (-), 122.8 (+), 110.9 (+), 97.3 (-), 50.9 (+).

Synthesis of 1-benzyl-7-azaindole (103)[73]

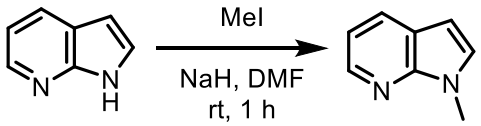


7-Azaindole (1.18 g, 10 mmol, 1.0 eq.) and NaH (0.480 g, 20 mmol, 2.0 eq.) were suspended in DMF (50 mL). The reaction mixture was stirred at rt for 30 min and then benzyl bromide (1.30 mL, 11 mmol, 1.1 eq.) was added. The reaction mixture was stirred at rt under a stream of N_2 for 1 h. Aqueous saturated NH_4Cl solution (20 mL) was added and the product was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 100 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a yellow oil (1.89 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 1.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 3.5 Hz, 1H), 7.12 (dd, *J* = 8.0, 5.0 Hz, 1H), 6.53 (d, *J* = 3.5 Hz, 1H), 5.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8 (-), 143.1 (+), 137.9 (-), 128.9 (+), 128.7 (+), 127.9 (+), 127.6 (+), 127.5 (+), 120.5 (-), 115.9 (+), 100.2 (+), 47.8 (-).

Synthesis of 1-benzyl-7-azaisatin (104)[73]

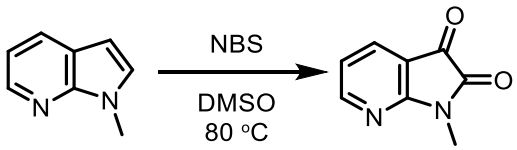
1-Benzyl-7-azaindole **103** (0.140 g, 0.67 mmol, 1.0 eq) and *N*-bromosuccinimide (0.240 g, 1.3 mmol, 2.0 eq) were dissolved in DMSO (7 mL) and then heated at 80 °C for 24 h. The reaction mixture was added to water (30 mL) and the product extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with water (3 x 50 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to afford the title compound as a yellow solid (0.055 g, 34%). M.p. 190-192 °C (lit: 187-188 °C).[73] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.83 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.52 (m, 2H), 7.40 – 7.25 (m, 3H), 7.09 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.04 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.9 (+), 163.5 (+), 158.1 (+), 155.9 (–), 135.5 (+), 132.9 (–), 128.9 (–), 128.5 (–), 128.2 (–), 119.7 (–), 112.1 (+), 42.7 (+).

Synthesis of 1-methyl-7-azaindole (105)[73]



7-Azaindole (1.18 g, 10 mmol, 1.0 eq.) and NaH (0.480 g, 20 mmol, 2.0 eq.) were suspended in DMF (50 mL). The reaction mixture was stirred at rt for 30 min and then methyl iodide (0.68 mL, 11 mmol, 1.1 eq.) was added. The reaction mixture was stirred at rt under a stream of N_2 for 1 h. Aqueous saturated NH_4Cl solution (20 mL) was added and the product was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 100 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a yellow oil (1.24 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 7.08 (dd, *J* = 8.0, 4.5 Hz, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (+), 129.0 (+), 128.7 (+), 120.5 (-), 115.5 (+), 99.3 (+), 60.4 (-), 31.3 (+).

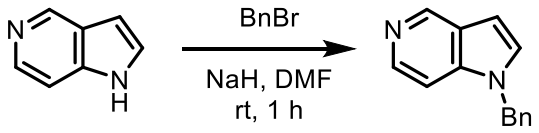
Synthesis of 1-methyl-7-azaisatin (106)[73]



1-Methyl-7-azaindole **105** (0.132 g, 1.0 mmol, 1.0 eq) and *N*-bromosuccinimide (0.356 g, 2.0 mmol, 2.0 eq) were dissolved in DMSO (10 mL) and then heated at 80 °C for 20 h. The reaction mixture was added to water (100 mL) and the product extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (3 x 100 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/petrol) to afford the title compound as a yellow-orange solid (0.038 g, 23%). M.p. 160-162 °C (lit: 160-161 °C).[73] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.84 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.11 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.36 (s, 3H). ^{13}C NMR

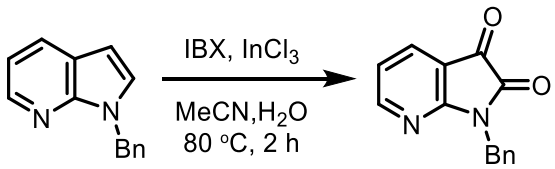
(101 MHz, $CDCl_3$) δ 181.9 (+), 163.9 (+), 158.4 (+), 155.9 (–), 132.8 (–), 119.6 (–), 112.1 (+), 25.1 (–).

Synthesis of 1-benzyl-5-azaindole (107) [171]



5-Azaindole (0.354 g, 3.0 mmol, 1.0 eq.) and NaH (0.144 g, 6.0 mmol, 2.0 eq.) were suspended in DMF (15 mL). The reaction mixture was stirred at rt for 10 min and then benzyl bromide (0.39 mL, 3.3 mmol, 1.1 eq.) was added. The reaction mixture was stirred at rt under a stream of N_2 for 1 h. Aqueous saturated NH_4Cl solution (20 mL) was added and the product was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 100 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a dark brown solid (0.350 g, 56%). M.p. 60-62 °C (lit: 61-62 °C).[171] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.31 (d, *J* = 6.0 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.22 (d, *J* = 6.0 Hz, 1H), 7.17 (d, *J* = 3.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.67 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3 (-), 144.2 (+), 137.1 (-), 128.8 (+), 127.9 (+), 127.7 (+), 126.8 (+), 124.3 (+), 118.4 (-), 116.4 (+), 100.1 (+), 47.9 (-).

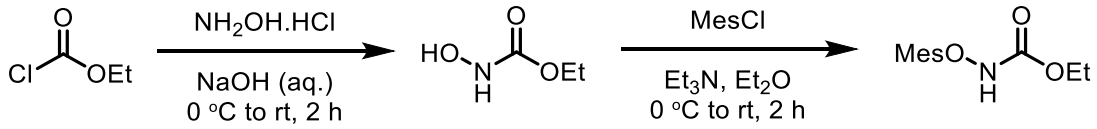
Synthesis of 1-benzyl-7-azaisatin (104) [73]



1-Benzyl-7-azaindole (0.208 g, 1.0 mmol, 1.0 eq.), 2-iodoxybenzoic acid (0.700 g, 2.5 mmol, 2.5 eq.) and $InCl_3$ (0.022 g, 0.1 mmol, 0.1 eq.) were combined in MeCN (18:2, 20 mL) and then stirred at 80 °C for 2 h. Aqueous saturated $NaHCO_3$ solution (20 mL) was added and the product extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing

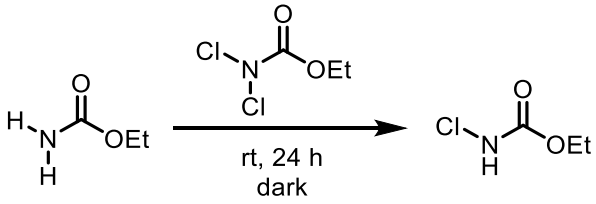
the solvent *in vacuo*. The title product was obtained as a yellow solid (0.021g, 22%). See page 149 for data.

Synthesis of ethyl (2,4,6-trimethylphenoxy)carbamate (109)[84]



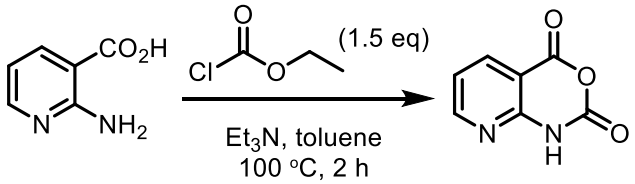
Hydroxylamine hydrochloride (3.47 g, 50 mmol, 5.0 eq.) was added to an aqueous solution of NaOH (1.5 M, 40 mL) and then cooled to 0 °C. Ethyl chloroformate (0.95 mL, 10 mmol, 1.0 eq.) was added dropwise over 5 mins and the reaction mixture was stirred at rt for 2 h. A 1 M HCl solution was added (until pH = 4) and then the product was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The residue was dissolved in diethyl ether (50 mL) and then 2-mesitylene sulfonyl chloride (2.40 g, 11 mmol, 1.1 eq.) was added. Et_3N (1.5 mL, 11 mmol, 1.1 eq.) was added dropwise at 0 °C and the reaction mixture was stirred at rt under a stream of N_2 for 2 h. H_2O (50 mL) was added and the product was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc) to afford the title compound as a white solid (1.66 g, 58%). M.p. 94-95 °C. (lit: not reported) ^{1}H NMR (400 MHz, DMSO) δ 11.47 (s, 1H), 7.14 (s, 2H), 3.97 (q, *J* = 7.0 Hz, 2H), 2.57 (s, 6H), 2.30 (s, 3H), 1.05 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.2, 144.4, 141.0, 131.8, 128.6, 62.1, 22.5, 20.7, 14.1.

Synthesis of ethyl chlorocarbamate (116)[86]



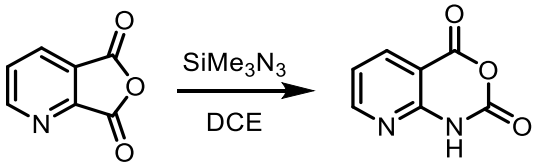
Urethane (4.57 g, 51.3 mmol, 1.0 eq.) and *N,N*-dichlorourethane (6.0 mL, 51.3 mmol, 1.0 eq.) were combined and stirred at rt in the absence of light for 18 h. The title compound was obtained as a yellow/green oil (12.6 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (-), 64.2 (-), 14.9 (+).

Synthesis of 3-azaisatoic anhydride (120) [172]



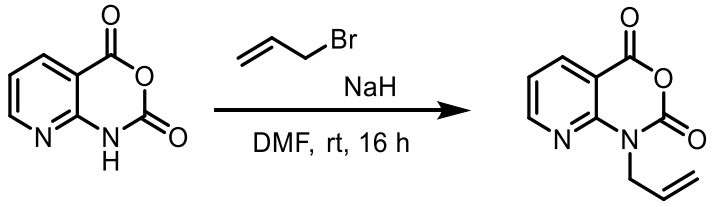
2-Aminopyridine-3-carboxylic acid (1.38 g, 10 mmol, 1.0 eq.) was suspended in toluene (20 mL) and then Et_3N (1.5 mL, 20 mmol, 2.0 eq.) was added. Ethyl chloroformate (1.43 mmol, 15 mmol, 1.5 eq.) was added dropwise and the reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to rt and the resulting precipitate removed by filtration. The crude product was triturated with EtOH to afford the title product as an off-white solid (0.394 g, 24%). M.p. 198-200 °C (lit: 195 °C).[172] ^{1}H NMR (400 MHz, d^{6}-DMSO) δ 12.30 (s, 1H), 8.66 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.32 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, d^{6}-DMSO) δ 160.0 (–), 156.4 (+), 153.5 (–), 147.5 (–), 138.8 (+), 120.3 (+), 107.2 (–).

Synthesis of 3-azaisatoic anhydride (120)[172]



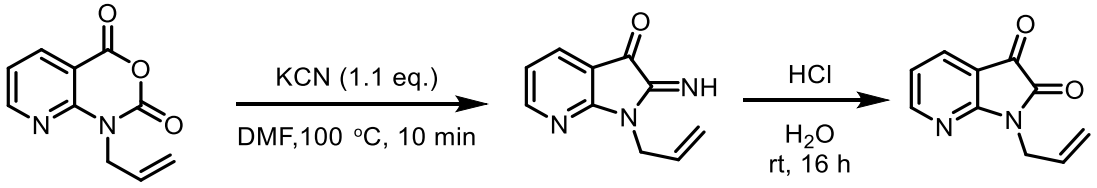
Azidotrimethylsilane (4.4 mL, 33 mmol, 1.1 eq) was added to a solution of 2,3-pyridinedicarboxylic anhydride (4.47 g, 30 mmol, 1 eq) in 1,2-dichloroethane (50 mL). The reaction mixture was stirred at 60 °C under a stream of N_2 for 2 h. The solution was cooled to rt and then EtOH (5 mL) was added and stirred for 15 mins. The resulting solid precipitate was filtered and triturated with cold EtOH to afford the title compound as an off-white solid (4.70 g, 97%). See page 153 for data.

Synthesis of *N*-allyl-3-azaisatoic anhydride (126) [88]



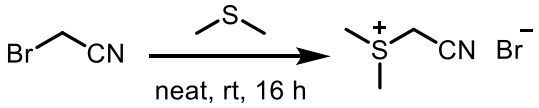
To a suspension of 3-azaisatoic anhydride **120** (0.300 g, 1.83 mmol, 1 eq) and sodium hydride (0.088 g, 3.66 mmol, 2 eq) in DMF (10 mL) was added allyl bromide (0.17 mL, 2.01 mmol, 1.1 eq) and the reaction mixture was stirred at rt under a stream of N_2 for 16 h. Ice-cold H_2O (50 mL) was added and the product was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude solid was recrystallized with DCM/petrol to afford the title compound as white crystals (0.254 g, 68%). M.p. 112-114 °C (lit: 114-117 °C).[88] ^{1}H NMR (400 MHz, d^6-DMSO) δ 8.76 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.41 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.39 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.92 (ddt, J = 17.0, 10.0, 5.0 Hz, 1H), 5.28 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.14 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.75 (dd, *J* = 5.0, 1.5 Hz, 2H). ^{13}C NMR (101 MHz, d^6-DMSO) δ 158.8 (–), 155.8 (+), 152.2 (–), 147.8 (–), 139.2 (+), 132.2 (+), 120.4 (+), 117.3 (–), 108.6 (–), 45.3 (–).

Synthesis of *N*-allyl-7-azaisatin (128) [88]



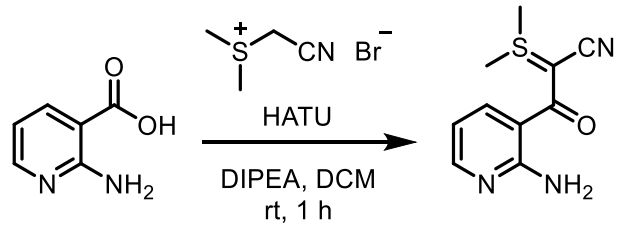
N-Allyl-3-azaisatoic anhydride **126** (0.120 g, 0.58 mmol, 1.0 eq.) was dissolved in DMF (3 mL) and a solution of KCN (0.042 g, 0.65 mmol, 1.1 eq.) in DMF (2 mL) was added. The reaction mixture was stirred at 100 °C under a stream of N_2 for 10 mins. The reaction mixture was poured onto ice-cold H_2O (100 mL) and the product extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The residue was dissolved in 2 M HCl solution (10 mL) and then stirred at rt for 16 h. Aqueous saturated $NaHCO_3$ solution (20 mL) was added and the product extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to afford the title compound as a yellow oil (0.018 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.86 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.12 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.01 – 5.91 (m, 1H), 5.39 – 5.26 (m, 2H), 4.50 (dt, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0 (-), 164.8 (-), 162.0 (-), 156.0 (+), 133.0 (+), 130.4 (+), 119.7 (+), 118.6 (-), 112.1 (-), 41.2 (-).

Synthesis of (cyanomethyl)(dimethyl)sulfonium bromide salt (91) [78]



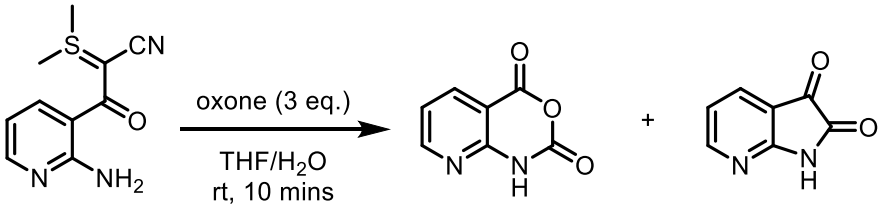
Bromoacetonitrile (0.35 mL, 5.0 mmol, 1.0 eq.) and dimethyl sulfide (0.37 mL, 5.0 mmol, 1.0 eq.) were combined and stirred at rt for 16 h. The title compound was obtained as a white solid (0.910 g, 99%). M.p. 200 °C, decomp. (lit: not reported) ^{1}H NMR (400 MHz, MeOD) δ 3.14 (s, 2H), 4.93 (s, 6H). ^{13}C NMR (101 MHz, MeOD) δ 122.0, 29.5, 25.9.

Synthesis of 3-(2-aminopyridin-3-yl)-2-(dimethyl-λ^4-sulfanylidene)-3-oxopropanenitrile (92) [78]



HATU (0.837 g, 2.2 mmol, 1.1 eq), (cyanomethyl)dimethylsulfonium bromide salt **91** (0.874 g, 4.8 mmol, 2.4 eq) and DIPEA (0.98 mL, 5.6 mmol, 2.8 eq) were added to a suspension of 2-aminonicotinic acid (0.276 g, 2.0 mmol, 1 eq) in dichloromethane (20 mL). The solution was stirred vigorously under a stream of N_2 for 1 h. A 1 M K_2CO_3 solution (20 mL) was added to the reaction mixture and the product extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, EtOAc) to afford the title compound as an off-white solid (0.354 g, 81%). M.p. 198-200 °C. (lit: not reported) ^{1}H NMR (400 MHz, d^4-MeOD) δ 8.07 – 7.91 (m, 2H), 6.67 (t, *J* = 5.0 Hz, 1H), 2.94 (s, 6H). ^{13}C NMR (101 MHz, d^6-DMSO) δ 168.1 (–), 152.8 (+), 130.1 (+), 122.2 (+), 116.5 (–), 65.5 (–), 44.4 (–), 42.5 (–), 29.7 (+).

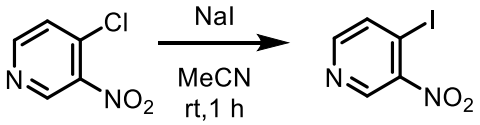
Synthesis of 3-azaisatoic anhydride and 7-azaisatin (75)[78]



3-(2-Aminopyridin-3-yl)-2-(dimethyl-λ^{4}4-sulfanylidene)-3-oxopropanenitrile **92** (0.150 g, 0.68 mmol, 1.0 eq.) was dissolved in THF/H_2O (13:6, 19 mL) and then oxone (0.581 g, 1.90 mmol, 3.0 eq.) was added. The reaction mixture was stirred at rt for 10 mins. Aqueous saturated $NaHCO_3$ solution (20 mL) was added and the product extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (20

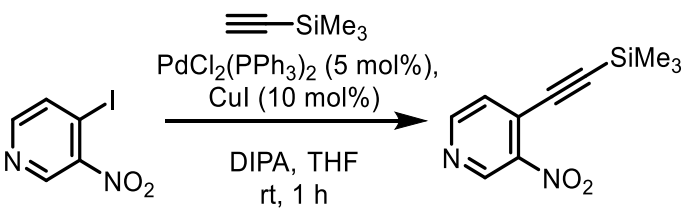
mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude solid was triturated with cold EtOH to afford 7-azaisatoic anhydride as an off-white solid (0.018 g, 16%). (See page 153 for data). The solvent from the mother liquor was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to afford 7-azaisatin as a yellow amorphous solid (0.026 g, 26%). M.p. 200 °C, decomp. (lit: 225-230 °C, decomp.).[78] ^{1}H NMR (400 MHz, DMSO) δ 11.61 (s, 1H), 8.40 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.88 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.11 (dd, *J* = 7.5, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 181.7 (-), 164.9 (-), 157.6 (-), 155.9 (+), 133.9 (+), 119.4 (+), 106.8 (-).

Synthesis of 4-iodo-3-nitropyridine (132) [173]



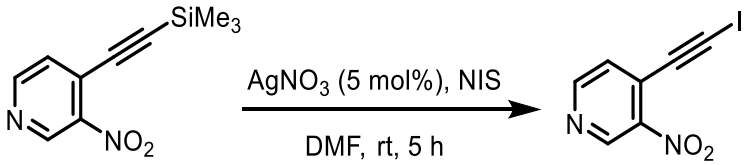
4-Chloro-3-nitropyridine (1.59 g, 10 mmol, 1 eq.) and sodium iodide (27.0 g, 180 mmol, 18 eq.) were dissolved in acetonitrile (85 mL, 0.118 M) and the reaction mixture stirred at room temperature under a stream of nitrogen for 1 h. Aqueous saturated $NaHCO_3$ (50 mL) was added to the reaction mixture and then the product extracted with ethyl acetate (3 x 50 mL). The organic phase was dried with anhydrous $MgSO_4$ before filtering and removing the solvent under reduced pressure. The title compound was obtained as a brown solid (2.46 g, 100%). M.p. 140-142 °C (lit: not reported). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.37 (d, *J* = 5.0 Hz, 1H), 8.04 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4 (-), 145.9 (-), 136.4 (-), 98.4(+), 65.1 (+).

Synthesis of 3-nitro-4-((trimethylsilyl)ethynyl)pyridine (133)



4-Iodo-3-nitropyridine **132** (5.00 g, 20.0 mmol, 1 eq.), TMSA (3.42 mL, 24.0 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.702 g, 1.00 mmol, 0.05 eq.), CuI (0.381 g, 2.00 mmol, 0.1 eq.) and DIPA (8.43 mL, 60.0 mmol, 3 eq.) were dissolved in THF (100 mL) and the reaction mixture was stirred at 0 C under a stream of nitrogen for 1 h. Aqueous saturated sodium bicarbonate solution (100 mL) was added and the product extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (20 mL) and dried with MgSO4. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a dark brown oil (3.21 g, 73%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.79 (d, *J* = 5.0 Hz, 1H), 7.55 (d, *J* = 5.0 Hz, 1H). 0.30 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0 (+), 145.9 (+), 132.0 (+), 127.9 (–), 126.3 (–), 110.8 (–), 96.8 (–), -0.5 (–). IR (FTIR, cm^{-1}) 2960, 2926, 2066, 1746, 1616, 1579, 1537, 1491, 1345, 1251, 1196, 844. HRMS calcd. mass for $C_{10}H_{12}N_2O_2Si$ ($M+H^+$) 220.0668, found 220.0660.

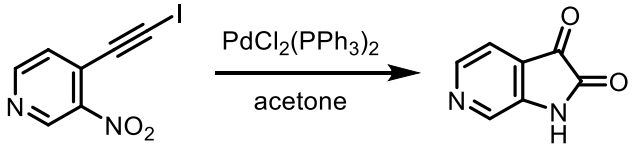
Synthesis of 4-(iodoethynyl)-3-nitropyridine (134)



3-Nitro-4-[(trimethylsilyl)ethynyl]pyridine **133** (0.500 g, 2.27 mmol, 1 eq.) and silver nitrate (0.019 g, 0.114 mmol, 0.05 eq.) were dissolved in DMF (5 mL) in a flask wrapped in aluminium foil and the reaction mixture was cooled at 0 C. A solution of *N*-iodosuccinimide (0.562 g, 2.50 mmol, 1.1 eq.) in DMF (5 mL) was added and the reaction mixture was stirred at room temperature under a stream of nitrogen for 5 h. Ice-cold water was added and the product extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with ice-cold water (50 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc/petrol) to give the title compound as a yellow solid (0.543 g, 87%). Mp 110-115 °C; ^{1}H NMR (400 MHz, d^6-DMSO) δ 9.28 (s, 1H), 8.86 (d, *J* = 5.0 Hz, 1H), 7.77 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6 (+), 153.1 (+), 146.1 (+), 126.5 (–), 91.5

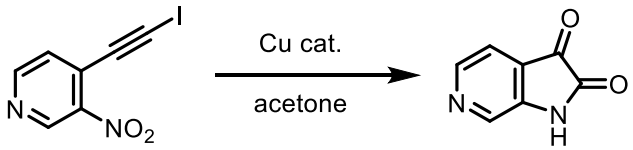
(–), 87.2 (–), 25.5 (–); IR (FTIR, cm^{-1}) 3093, 2159, 1597, 1536, 1521, 1345, 1179, 1050, 872, 847, 820, 766; HRMS calcd. mass for $C_7H_4N_2O_2{}^{127}I$ ($M+H^+$) 274.9318, found 274.9324.

Synthesis of 6-azaisatin (81) [174]



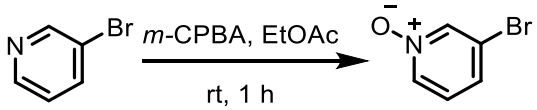
4-(Iodoethynyl)-3-nitropyridine **134** (0.100 g, 0.37 mmol. 1.0 eq.) was dissolved in acetone (10 mL) and then $PdCl_2(PPh_3)_2$ (0.013 g, 0.02 mmol, 0.05 eq.) was added. The reaction mixture was stirred at 60 °C under a stream of N_2 for 24 h. After cooling to rt, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to afford the title compound as a dark red solid (0.020 g, 36%). M.p. 200 °C (decomp).[174] ^{1}H NMR (400 MHz, DMSO) δ 9.44 (s, 1H), 9.01 (d, *J* = 5.0 Hz, 1H), 8.05 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 181.0 (-), 164.1 (-), 154.7 (+), 153.9 (-), 146.8 (+), 129.3 (+), 123.8 (-).

Synthesis of 6-azaisatin (81) [174]



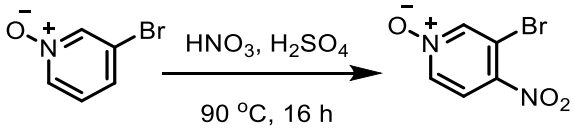
4-(Iodoethynyl)-3-nitropyridine **134** (0.120 g, 0.44 mmol. 1.0 eq.) was dissolved in acetone (10 mL) and then $PdCl_2(PPh_3)_2$ (0.088 g, 0.66 mmol, 1.5 eq.) was added. The reaction mixture was stirred at 60 °C under a stream of N_2 for 24 h. After cooling to rt, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to afford the title compound as a dark red solid (0.020 g, 31%). See above for data.

Synthesis of 3-bromopyridine 1-oxide (139)[175]



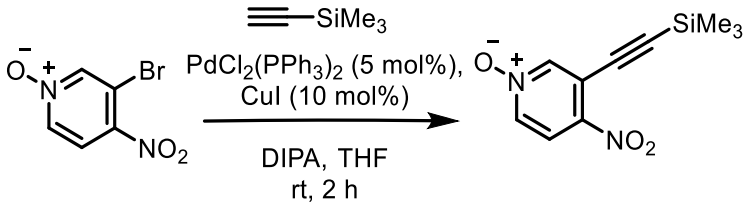
3-Bromopyridine (11.6 mL, 120 mmol, 1 eq.) was dissolved in ethyl acetate (200 mL) and *m*-CPBA (33.1 g, 192 mmol, 1.6 eq.) was added portion-wise. The reaction was stirred at ambient temperature for 1 h. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 10% MeOH/DCM) to give the title compound as a pale yellow oil (20.7 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, s), 8.11 (d, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 8.0, 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (-), 138.1 (-), 128.7(-), 126.1 (-), 120.6 (+).

Synthesis of 3-bromo-4-nitropyridine 1-oxide (140)[176]



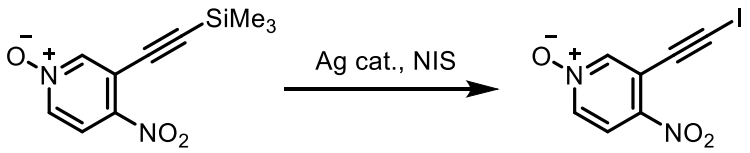
3-Bromopyridine-1-oxide **139** (10 g, 57.8 mmol, 1.0 eq.) was dissolved in conc. H_2SO_4 (15 mL). A mixture of conc. H_2SO_4 (15 mL) and HNO_3 (25 mL) was added to the solution and then stirred at 90 °C for 1 h. HNO_3 (25 mL) was added portion-wise every half an hour for 2 h and the reaction was stirred at 90 °C for 16 h. A solution of NaOH (aq. 5 M) was slowly added to the cooled reaction mixture until it was basic and then the product was extracted with DCM (3 x 100 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed at reduced pressure. The crude product was recrystallized with petrol/DCM to give the title compound as a yellow solid (5.90 g, 47%). M.p. 150-152 °C (lit: 152-153 °C).[176] ^{1}H NMR (400 MHz, DMSO-d^6) δ 8.89 (d, *J* = 2.0 Hz, 1H), 8.40 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.18 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d^6) δ 143.6 (-), 143.2 (+), 139.7 (+), 123.3 (+), 114.5 (-).

Synthesis of 4-nitro-3-[(trimethylsilyl)ethynyl] pyridine 1-oxide (141)



3-Bromo-4-nitropyridine-1-oxide **140** (1.00 g, 4.59 mmol, 1.0 eq.) $PdCl_2(PPh_3)_2$ (0.161 g, 0.230 mmol, 0.05 eq.) and copper (I) iodide (0.087 g, 0.460 mmol, 0.1 eq.) were dissolved in tetrahydrofuran (20 mL). Trimethylsilylacetylene (0.980 mL, 6.89 mmol, 1.5 eq.) and diisopropylamine (1.94 mL, 13.8 mmol, 3 eq.) were added and the reaction stirred at ambient temperature under a stream of nitrogen for 1 h. Aqueous saturated $NaHCO_3$ (20 mL) was added to the reaction mixture and the product extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a brown oil (0.758 g, 70%). ^{1}H NMR (400 MHz, DMSO-d^6) δ 8.61 (d, *J* = 2.0 Hz, 1H), 8.38 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.17 (d, *J* = 7.0 Hz, 1H), 0.27 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (+), 140.6 (+), 123.0 (+), 117.0 (-), 108.1 (-), 95.7 (-), 92.3 (-), 0.24 (+); IR (FTIR, cm^{-1}) 3103, 2960, 1605, 1596, 1527, 1341, 1251, 844. HRMS calcd for $C_{10}H_{13}N_2O_3Si$ (M + H$^+$) 237.0695, found 237.0690.

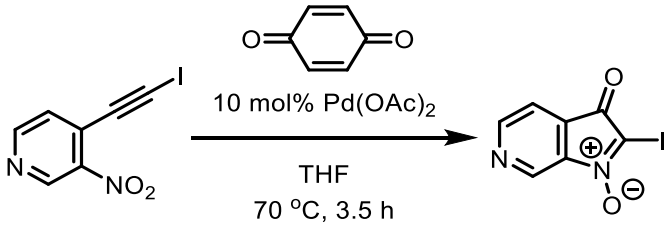
Synthesis of 3-(iodoethynyl)-4-nitropyridine 1-oxide (142)



4-Nitro-3-[(trimethylsilyl)ethynyl] pyridine 1-oxide **141** (0.300 g, 1.27 mmol, 1.0 eq.) and silver fluoride (0.161 g, 0.050 mmol, 0.05 eq.) were dissolved in DMF (5 mL) in a flask wrapped in aluminium foil. A solution of *N*-iodosuccinimide (0.286 g, 1.27 mmol, 1.0 eq.) in DMF (5 mL) was added and the reaction mixture was stirred at ambient temperature under a stream of N_2 for 5 h. The solvent was removed under reduced pressure and the

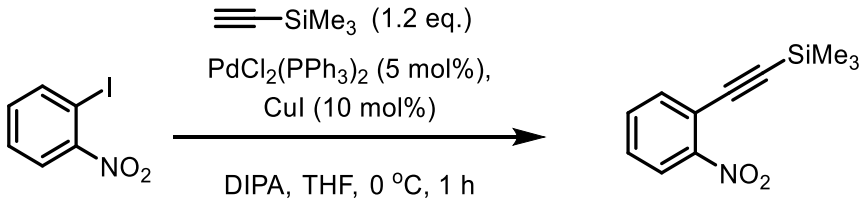
crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a yellow amorphous solid (0.240 g, 65%). ^{1}H NMR (250 MHz, DMSO-d^{6}) δ 8.63 (d, *J* = 2.0 Hz, 1H), 8.36 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.15 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 151.9 (-), 144.3 (-), 132.3 (+), 129.2 (+), 122.9 (+), 84.5 (-), 30.0 (-). IR (FTIR, cm^{-1}) 2953, 2918, 2841, 1714, 1638, 1542, 1492, 1018. HRMS calcd for $C_7H_4N_2O_3{}^{127}I$ (M + H^{+}) 290.9267, found 290.9257.

Synthesis of 2-iodo-3H-pyrrolo[2,3-c]pyridin-3-one 1-oxide (144)



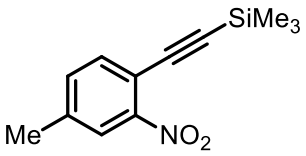
4-(Iodoethynyl)-3-nitropyridine **134** (0.050 g, 0.18 mmol, 1.0 eq.), p-benzoquinone (0.020 g, 0.18 mmol, 1.0 eq.) and $Pd(OAc)_2$ (0.004 g, 0.018 mmol, 0.1 eq.) were combined in THF (10 mL) and then stirred at 70 °C under a stream of N_2 for 3.5 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 100% EtOAc) to afford the title compound as a dark brown amorphous solid (5 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 – 9.07 (m, 2H), 7.57 (d, *J* = 4.5 Hz, 1H). IR (FTIR, cm^{-1}) 1709, 1598, 1485, 1455, 1345, 1316, 1296. HRMS calcd. mass for $C_7H_4N_2O_2{}^{127}I$ (M+H^{+}) 274.9318, found 274.9322.

General Procedure A: Synthesis of trimethyl((2-nitrophenyl)ethynyl)silane (67)[71]



1-Iodo-2-nitrobenzene (0.498 g, 2.00 mmol, 1 eq.), $PdCl_2(PPh_3)_2$ (0.070 g, 0.100 mmol, 0.05 eq.) and CuI (0.038 g, 0.2 mmol, 0.1 eq.) were dissolved in THF (10 mL). TMSA (0.342 mL, 2.40 mmol, 1.2 eq.) and DIPA (0.843 mL, 6.00 mmol, 3 eq.) were added and the reaction mixture, and the solution stirred at 0 °C under a stream of N_2 for 1 h. Aqueous saturated $NaHCO_3$ solution (10 mL) was added and the product extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a dark brown oil (0.355 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.56 (ddd, *J* =, 8.0, 8.0, 1.0 Hz, 1H), 7.50-7.40 (m,1H), 0.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 135.4, 132.9, 129.1, 124.7, 118.7, 104.1, 99.6, -0.30.

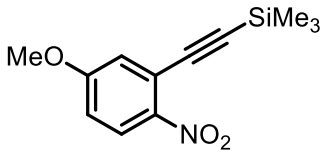
Synthesis of Trimethyl((4-methyl-2-nitrophenyl)ethynyl)silane (185)



Reaction of 1-iodo-4-methyl-2-nitrobenzene (3.16 g, 12.0 mmol, 1 eq.), TMSA (2.05 mL, 14.4 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.421 g, 0.600 mmol, 0.05 eq.), CuI (0.229 g, 1.20 mmol, 0.1 eq.) and DIPA (5.06 mL, 36.0 mmol, 3 eq.) in THF (100 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a yellow solid (2.61 g, 93%). Mp 54-56 °C (lit: 55-57 °C)[71]; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.0 Hz, 1H), 2.45 (s, 3H), 0.28 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ

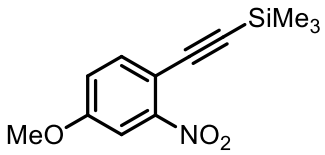
150.0 (+), 139.8 (+), 134.9 (–), 133.5 (–), 124.8 (–), 115.5 (+), 102.5 (+), 99.5 (+), 21.3 (–), -0.32 (+).

Synthesis of Trimethyl((5-methoxy-2-nitrophenyl)ethynyl)silane (182) [71]



Reaction of 2-iodo-4-methoxy-1-nitrobenzene (3.35 g, 12.0 mmol, 1 eq.), TMSA (2.05 mL, 14.4 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.421 g, 0.600 mmol, 0.05 eq.), CuI (0.229 g, 1.20 mmol, 0.1 eq.) and DIPA (5.06 mL, 36.0 mmol, 3 eq.) in THF (100 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a light-brown solid (2.86 g, 96%). Mp 64-66 °C (lit: 66-68 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 3.0 Hz, 1H), 6.93 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.91 (s, 3H), 0.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (+), 143.2 (+), 127.0 (–), 120.7 (+), 119.1 (–), 114.9 (–), 103.6 (+), 100.0 (+), 56.0 (–), -0.36 (+).

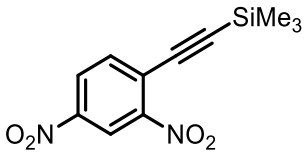
Synthesis of Trimethyl((4-methoxy-2-nitrophenyl)ethynyl)silane (186)[71]



Reaction of 1-iodo-4-methoxy-2-nitrobenzene (5.58 g, 20.0 mmol, 1 eq.), TMSA (3.42 mL, 24.0 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.702 g, 1.00 mmol, 0.05 eq.), CuI (0.381 g, 2.00 mmol, 0.1 eq.) and DIPA (8.43 mL, 60.0 mmol, 3 eq.) in THF (100 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a light-brown solid (2.86 g, 97%). Mp 68-70 °C (lit: 69-71 °C).[71] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 3.0 Hz, 1H), 7.10 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.90 (s, 3H), 0.28 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$)

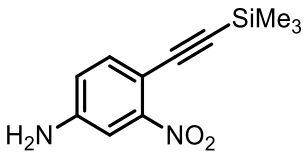
δ 159.6 (+), 151.1 (+), 136.0 (–), 119.5 (–), 110.5 (+), 109.2 (–), 101.4 (+), 99.5 (+), 56.0 (–), -0.28 (+).

Synthesis of Trimethyl((2,4-dinitrophenyl)ethynyl)silane (187)[71]



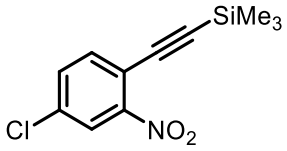
Reaction of 1-iodo-2,4-dinitrobenzene (3.53 g, 12.0 mmol, 1 eq.), TMSA (2.05 mL, 14.4 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.421 g, 0.600 mmol, 0.05 eq.), CuI (0.229 g, 1.20 mmol, 0.1 eq.) and DIPA (5.06 mL, 36.0 mmol, 3 eq.) in THF (100 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a yellow solid (2.37 g, 75%). Mp 64-66 °C (lit: 65-68 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 2.0 Hz, 1H), 8.43 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 0.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (+), 146.5 (+), 136.2 (–), 126.8 (–), 124.4 (+), 120.2 (–), 111.4 (+), 97.7 (+), -0.63 (+).

Synthesis of 3-Nitro-4-((trimethylsilyl)ethynyl)aniline (188)[177]



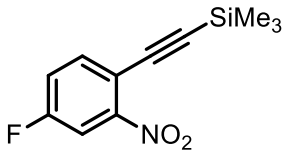
Reaction of 4-iodo-3-nitroaniline (0.500 g, 1.89 mmol, 1 eq.), TMSA (0.323 mL, 2.27 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.066 g, 0.090 mmol, 0.05 eq.), CuI (0.036 g, 0.190 mmol, 0.1 eq.) and DIPA (0.800 mL, 5.67 mmol, 3 eq.) in THF (20 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a yellow solid (0.402 g, 91%). Mp 92-94 °C (lit: 95-99 °C).[R18]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.19 (s, 2H), 0.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2 (+), 147.2 (+), 136.1 (–), 118.6 (–), 109.6 (–), 107.2 (+), 100.3 (+), 99.7 (+), -0.18 (+).

Synthesis of Trimethyl((4-chloro-2-nitrophenyl)ethynyl)silane (189)[177]



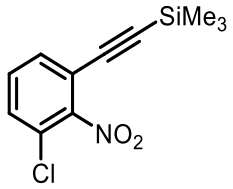
Reaction of 5-chloro-2-iodonitrobenzene (1.13 g, 4.00 mmol, 1 eq.), TMSA (0.683 mL, 4.80 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.140 g, 0.200 mmol, 0.05 eq.), CuI (0.076 g, 0.400 mmol, 0.1 eq.) and DIPA (1.67 mL, 12.0 mmol, 3 eq.) in THF (20 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a brown solid (1.01 g, 99%). Mp 45-50 °C (lit: 39-41 °C).[177] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 8.0, 2.0 Hz, 1H), 0.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (+), 136.0 (–), 134.7 (+), 132.9 (–), 124.8 (–), 116.9 (+), 105.2 (+), 98.3 (+), -0.51 (+).

Synthesis of Trimethyl((4-fluoro-2-nitrophenyl)ethynyl)silane (190)



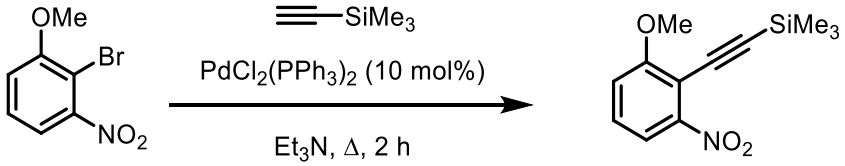
Reaction of 4-fluoro-1-iodo-2-nitrobenzene (0.541 mL, 4.00 mmol, 1 eq.), TMSA (0.683 mL, 4.80 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.140 g, 0.200 mmol, 0.05 eq.), CuI (0.076 g, 0.400 mmol, 0.1 eq.) and DIPA (1.67 mL, 12.0 mmol, 3 eq.) in THF (20 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title product as an amorphous yellow solid (0.93 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.35 – 7.27 (m, 1H), 0.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (d, J_{CF} = 253 Hz, +), 150.8 (+), 136.7 (d, J_{CF} = 8 Hz, –), 120.4 (d, J_{CF} = 21 Hz, –), 114.7 (d, J_{CF} = 4 Hz, +), 112.3 (d, J_{CF} = 27 Hz, –), 103.7 (+), 98.3 (+), -0.42 (+). IR (FTIR, cm^{-1}) 2960, 2849, 2161, 1602, 1581, 1518, 1338, 1293, 1276, 1090, 843. HRMS calcd for $C_{11}H_{12}NO_2FSi$ ($M+H^+$) 237.0621, found 237.0620.

Synthesis of Trimethyl((5-chloro-6-nitrophenyl)-ethynyl)silane (191)



Reaction of 2-chloro-6-iodonitrobenzene (2.27 g, 8.0 mmol, 1.0 eq.), TMSA (1.37 mL, 9.6 mmol, 1.2 eq.), $PdCl_2(PPh_3)_2$ (0.281 g, 0.40 mmol, 0.05 eq.), CuI (0.152 g, 0.80 mmol, 0.1 eq.) and DIPA (3.34 mL, 24.0 mmol, 3 eq.) in THF (50 mL) as described in general procedure A gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title product as an amorphous off-white solid (2.00 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 0.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5 (+), 130.5 (+), 130.4 (+), 125.2 (-), 118.1 (-), 116.9 (-), 104.0 (-), 96.2 (-), -0.56 (+). IR (FTIR, cm^{-1}) 2960, 2899, 1599, 1542, 1457, 1365, 1251, 911, 843. HRMS calcd for $C_{11}H_{13}NO_2ClSi$ ($M+H^+$) 254.0404, found 254.0415.

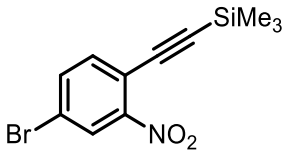
General Procedure B: Synthesis of trimethyl((2-methoxy-6-nitrophenyl)-ethynyl)silane (192)



2-Bromo-1-methoxy-3-nitrobenzene (0.500 g, 2.15 mmol, 1.0 eq) and $PdCl_2(PPh_3)_2$ (0.715 g, 0.220 mmol, 0.1 eq.) were dissolved in triethylamine (5 mL). Trimethylsilylacetylene (0.613 mL, 4.31 mmol, 2.0 eq.) was added and the reaction mixture was heated under reflux with stirring under a stream of N_2 for 2 h. Aqueous saturated $NaHCO_3$ solution (10 mL) was added and the product extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a brown solid (0.363 g, 68%). Mp 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.43 – 7.35

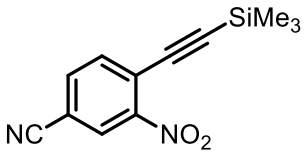
(m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.97 (s, 3H), 0.31 (s, 9H). IR (FTIR, cm^{-1}) 2963, 2899, 2841, 2157, 1532, 1472, 1350, 1275, 1250, 1055, 862, 845.

Synthesis of Trimethyl((4-bromo-2-nitrophenyl)ethynyl)silane (193)[178]



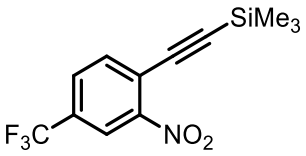
Reaction of 2,5-dibromonitrobenzene (2.00 g, 7.12 mmol, 1.0 eq.), TMSA (1.11 mL, 7.83 mmol, 1.1 eq.) and $PdCl_2(PPh_3)_2$ (0.250 g, 0.356 mmol, 0.05 eq.) in Et_3N (10 mL) as described in general procedure B gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a dark brown oil (1.92 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (+), 136.0 (–), 135.8 (–), 127.6 (–), 124.2 (+), 117.3 (+), 105.4 (+), 98.4 (+), -0.45 (–).

Synthesis of 3-Nitro-4-((trimethylsilyl)ethynyl)benzonitrile (194)[179]



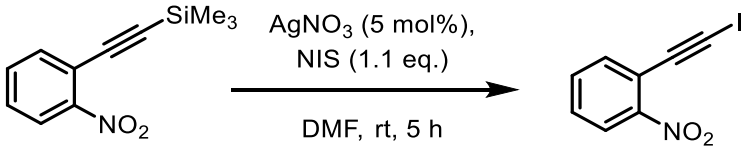
Reaction of 4-bromo-3-nitrobenzonitrile (1.00 g, 4.40 mmol, 1.0 eq.), TMSA (1.25 mL, 8.81 mmol, 2.0 eq.) and $PdCl_2(PPh_3)_2$ (0.309 g, 0.440 mmol, 0.1 eq.) in Et_3N (10 mL) as described in general procedure B gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a brown solid (0.670 g, 63%). Mp 81-82 °C (lit: 81-82 °C).[179] ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, d, *J* = 2.0 Hz), 7.85 (1H, dd, *J* = 8.0, 2.0 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 0.30 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (+), 136.0 (–), 135.3 (–), 128.2 (–), 122.8 (+), 116.3 (+), 112.5 (+), 110.3 (+), 97.8 (+), -0.61 (–).

Synthesis of Trimethyl((2-nitro-4-(trifluoromethyl)phenyl)ethynyl)silane (195)[180]



Reaction of 1-bromo-2-nitro-4-(trifluoromethyl)benzene (0.567 mL, 3.70 mmol, 1.0 eq.), TMSA (0.727 mL, 7.40 mmol, 2.0 eq.) and $PdCl_2(PPh_3)_2$ (0.260 g, 0.370 mmol, 0.1 eq.) in Et_3N (5 mL) as described in general procedure B gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a brown solid (1.25 g, 99%). Mp 70-72 °C (lit: 67-69 °C).[180] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 – 7.69 (m, 2H), 0.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (+), 135.9 (–), 130.9 (q, J_{CF} = 34 Hz, +), 129.1 (q, J_{CF} = 3 Hz, –), 121.9 (q, J_{CF} = 3 Hz, –), 121.2 (q, J_{CF} = 271 Hz, +), 107.8 (+), 98.0 (+), 87.0 (+), -0.53 (–).

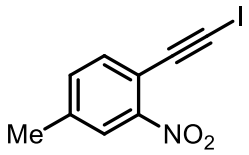
General Procedure C: Synthesis of 1-(Iodoethynyl)-2-nitrobenzene (68)[71]



Trimethyl((2-nitrophenyl)ethynyl)silane **67** (0.219 g, 1.00 mmol, 1 eq.) and silver nitrate (0.008 g, 0.050 mmol, 0.05 eq.) were dissolved in DMF (5 mL) in a flask wrapped in aluminium foil, and the reaction mixture was cooled to 0 °C. A solution of *N*-iodosuccinimide (0.247 g, 1.10 mmol, 1.1 eq.) in DMF (5 mL) was added and the reaction mixture stirred at ambient temperature under a stream of N_2 for 5 h. Ice-cold H_2O was added and the product extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with ice-cold H_2O (50 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a light-brown solid (0.218 g, 80%). Mp 66-68 °C (lit: 68-70 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.0 Hz, 1H),

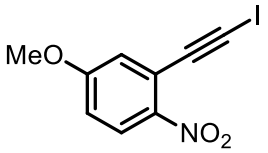
7.56 – 7.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (+), 135.9 (–), 132.9 (–), 129.1 (–), 124.6 (–), 118.6 (+), 89.0 (+), 16.8 (+).

Synthesis of 1-(Iodoethynyl)-4-methyl-2-nitrobenzene (197)[71]



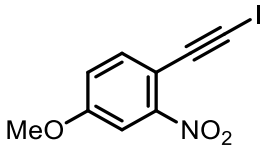
Reaction of trimethyl((4-methyl-2-nitrophenyl)ethynyl)silane **185** (0.466 g, 2.00 mmol, 1 eq.), silver nitrate (0.017 g, 0.100 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.495 g, 2.20 mmol, 1.1 eq.) in DMF (10 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a yellow solid (0.456 g, 79%). Mp 92-94 °C (lit: 94-96 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (–), 140.2 (–), 135.6 (+), 133.7 (+), 125.0 (+), 115.7 (–), 89.1 (–), 21.3 (+), 15.1 (–).

Synthesis of 2-(Iodoethynyl)-4-methoxy-1-nitrobenzene (183)[71]



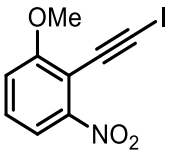
Reaction of ((5-methoxy-2-nitrophenyl)ethynyl) trimethylsilane **182** (1.00 g, 4.00 mmol, 1 eq.) silver nitrate (0.034 g, 0.200 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.994 g, 4.40 mmol, 1.1 eq.) in DMF (20 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as an orange solid (0.808 g, 67%). Mp 88-90 °C (lit: 87-88 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 3.0 Hz, 1H), 6.95 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (–), 143.3 (–), 127.1 (+), 120.8 (–), 119.9 (+), 115.2 (+), 89.6 (–), 56.1 (+), 16.7(–).

Synthesis of 4-Methoxy-2-nitro-1-(2-iodoethynyl)benzene (198)[71]



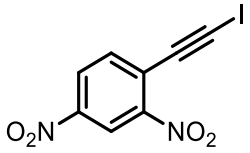
Reaction of 2-(4-methoxy-2-nitrophenyl)-1-trimethylsilylethyne **186** (0.650 g, 2.61 mmol, 1 eq.), silver nitrate (0.022 g, 0.130 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.646 g, 2.87 mmol, 1.1 eq.) in DMF (10 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a light brown solid (0.808 g, 67%). Mp 86-88 °C (lit: 89-90 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 3.0 Hz, 1H), 7.13 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (–), 151.3 (–), 136.7 (+), 119.7 (+), 110.7 (–), 109.3 (+), 88.9 (–), 56.1 (+), 13.7 (–).

Synthesis of 2-(Iodoethynyl)-1-methoxy-3-nitrobenzene (199)



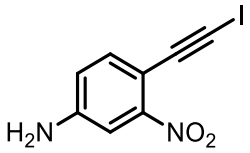
Reaction of ((2-methoxy-6-nitrophenyl)ethynyl) trimethylsilane **192** (0.310 g, 1.24 mmol, 1 eq.), silver nitrate (0.011 g, 0.060 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.308 g, 1.37 mmol, 1.1 eq.) in DMF (10 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a yellow solid (0.259 g, 69%). Mp 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.41 (app. t, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (–), 152.3 (–), 129.3 (+), 116.2 (+), 114.8 (+), 108.0 (–), 84.3 (–), 57.1 (+), 20.1 (–). IR (FTIR, cm^{-1}) 2923, 2853, 1619, 1599, 1532, 1470, 1350, 1275, 1053, 797; HRMS calcd for $C_9H_6NO_3{}^{127}I$ (MH^+) 302.9392, found 302.9394.

Synthesis of 1-(Iodoethynyl)-2,4-dinitrobenzene (200)[71]



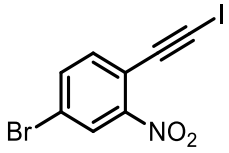
Reaction of ((2,4-dinitrophenyl)ethynyl)trimethylsilane **187** (1.06 g, 4.00 mmol, 1 eq.), silver nitrate (0.034 g, 0.200 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.990 g, 4.40 mmol, 1.1 eq.) in DMF (20 mL) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a yellow solid (1.19 g, 94%). Mp 115-118 °C (lit: 115-117 °C).[71] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.0 Hz, 1H), 8.45 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (-), 146.7 (-), 137.1 (+), 127.0 (+), 124.4 (-), 120.4 (+), 88.1 (-), 25.9 (-).

Synthesis of 4-(Iodoethynyl)-3-nitroaniline (201)



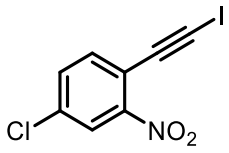
Reaction of 3-nitro-4-((trimethylsilyl)ethynyl)aniline **188** (0.350 g, 1.50 mmol, 1 eq.), silver nitrate (0.013 g, 0.080 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.370 g, 1.65 mmol, 1.1 eq.) in DMF (10 mL) as described in general procedure C gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a brown solid (0.183 g, 42%). Mp 96-98 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.15 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (–), 136.8 (+), 118.6 (+), 109.7 (+), 89.4 (–), 68.0 (–), 25.6 (–), 11.3 (–). IR (FTIR, cm^{-1}) 3323, 1615, 1557, 1516, 1346, 1311, 831. HRMS calcd for $C_8H_5N_2O_2{}^{127}I$ (MH^+) 302.9392, found 302.9394.

Synthesis of 4-Bromo-1-(iodoethynyl)-2-nitrobenzene (202)



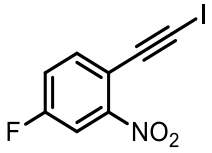
Reaction of ((4-bromo-2-nitrophenyl)ethynyl) trimethylsilane **193** (1.60 g, 5.46 mmol, 1 eq.), silver nitrate (0.046 g, 0.273 mmol, 0.05 eq.) and *N*-iodosuccinimide (1.35 g, 6.00 mmol, 1.1 eq.) in DMF (20 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a brown solid (0.805 g, 42%); Mp 87-88 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.22 (d, *J* = 2.0 Hz, 1H), 7.72 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (–), 136.8 (+), 136.0 (+), 127.8 (+), 122.6 (–), 117.5 (–), 88.2 (–), 18.7 (–); IR (FTIR, cm^{-1}) 3090, 2169, 1599, 1549, 1524, 1472, 1339, 1094, 881, 830; HRMS calcd for $C_8H_4NO_2{}^{79}Br^{127}I$ (MH^+) 288.9474, found 288.9470.

Synthesis of 4-Chloro-1-(iodoethynyl)-2-nitrobenzene (203)[71]



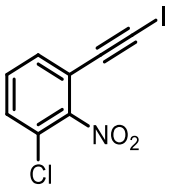
Reaction of ((4-chloro-2-nitrophenyl)ethynyl) trimethylsilane **189** (1.01 g, 4.00 mmol, 1 eq.), silver nitrate (0.034 g, 0.200 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.990 g, 4.40 mmol, 1.1 eq.) in DMF (20 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as an orange solid (0.850 g, 69%). Mp 90-92 °C (lit: 92-94 °C).[71] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.0, 2.0 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7(+), 135.1(–), 133.1(+), 127.2(–), 124.9(+), 117.1(–), 88.1(–), 18.3(–).

Synthesis of 4-Fluoro-1-(iodoethynyl)-2-nitrobenzene (204)



Reaction of ((4-fluoro-2-nitrophenyl)ethynyl) trimethylsilane **190** (1.20 g, 5.20 mmol, 1 eq.), silver nitrate (0.044 g, 0.260 mmol, 0.05 eq.) and *N*-iodosuccinimide (1.29 g, 5.72 mmol, 1.1 eq.) in DMF (20 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a yellow solid (0.820 g, 70%); Mp 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.67 (dd, *J* = 9.0, 5.0 Hz, 1H), 7.35 (ddd, *J* = 9.0, 7.0, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (d, J_{CF} = 250 Hz, –), 151.1 (–), 137.5 (d, J_{CF} = 8 Hz, +), 120.6 (d, J_{CF} = 22 Hz, +), 114.9 (d, J_{CF} = 4 Hz, –), 112.5 (d, J_{CF} = 27 Hz, +), 88.0 (–), 16.9 (–). IR (FTIR, cm^{-1}) 3096, 2164, 1580, 1530, 1490, 1345, 1270, 1200, 1129, 882, 837, 789. HRMS calcd mass for $C_8H_3NO_2F^{127}I$ ($M+H^+$) 290.9192, found 290.9199.

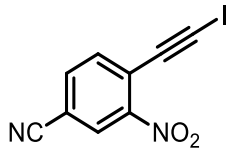
Synthesis of 5-Chloro-1-(iodoethynyl)-2-nitrobenzene (205)



Reaction of ((5-chloro-2-nitrophenyl)ethynyl) trimethylsilane **191** (2.00 g, 7.90 mmol, 1 eq.), silver nitrate (0.067 g, 0.400 mmol, 0.05 eq.) and *N*-iodosuccinimide (1.95 g, 8.70 mmol, 1.1 eq.) in DMF (50 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as an off-white solid (1.55 g, 64%). Mp 71-72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (–), 132.3 (+), 130.8 (+), 130.6 (+), 125.4 (–), 118.3 (–), 86.1 (–), 17.8 (–); IR (FTIR,

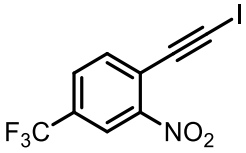
cm^{-1}) 3236, 2924, 2856, 1616, 1539, 1469, 1437, 1264, 1136, 767, 742; HRMS calcd for $C_8H_3NO_2{}^{35}Cl^{127}I$ (MH^+) 306.8897, found 306.8907.

Synthesis of 4-(Iodoethynyl)-3-nitrobenzonitrile (206)



Reaction of 3-nitro-4-((trimethylsilyl)ethynyl)benzonitrile **194** (0.550 g, 2.25 mmol, 1 eq.), silver nitrate (0.019 g, 0.110 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.558 g, 2.48 mmol, 1.1 eq.) in DMF (10 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a yellow solid (0.555 g, 83%); Mp 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.0 Hz, 1H), 7.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (+), 135.5 (+), 128.4 (+), 122.9 (–), 116.2 (–), 112.8 (–), 88.1 (–), 77.1 (–), 24.6 (–). IR (FTIR, cm^{-1}) 3091, 2925, 2854, 2275, 2237, 1614, 1430, 1351, 1200, 764; HRMS calcd for $C_9H_3N_2O_2{}^{127}I$ (MH^+) 297.9239, found 297.9249.

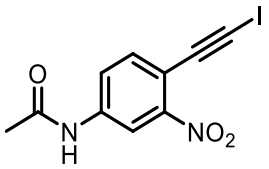
Synthesis of 1-(Iodoethynyl)-2-nitro-4-(trifluoromethyl)benzene (207)



Reaction of trimethyl((2-nitro-4-(trifluoromethyl)phenyl) ethynyl)silane **195** (1.10 g, 3.83 mmol, 1 eq.), silver nitrate (0.033 g, 0.190 mmol, 0.05 eq.) and *N*-iodosuccinimide (0.948 g, 4.21 mmol, 1.1 eq.) in DMF (20 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a brown solid (0.916 g, 70%). Mp 97-99 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.34 (d, *J* = 0.5 Hz, 1H), 7.88 – 7.84 (m, 1H), 7.81 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3 (–), 136.8 (+), 133.2 (q, J_{CF} = 35.5 Hz, –), 129.3 (q, J_{CF} = 3.0 Hz, +), 123.1 (–), 122.5 (q, J_{CF} = 286.0 Hz, –), 122.1 (q, J_{CF} = 3.0 Hz, +), 88.1 (–), 21.8 (–); IR (FTIR, cm^{-}

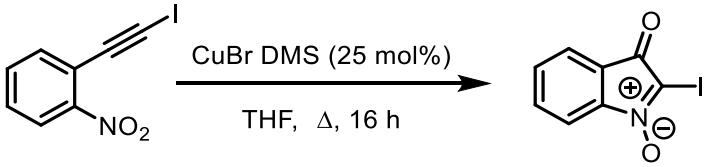
[1]) 3096, 2928, 2853, 2168, 1634, 1538, 1440, 1319, 1174, 1132, 756; HRMS calcd for $C_9H_3NO_2F_3{}^{127}I$ (MH^+) 340.9161, found 340.9177.

Synthesis of N-[4-(iodoethynyl)-3-nitrophenyl]acetamide (215)



Reaction of 3-nitro-4-((trimethylsilyl)ethynyl)acetanilide (2.20 g, 8.73 mmol, 1 eq.), silver nitrate (0.074 g, 0.440 mmol, 0.05 eq.) and *N*-iodosuccinimide (2.16 g, 9.60 mmol, 1.1 eq.) in DMF (50 mL) (5 h) as described in general procedure C gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a yellow solid (2.88 g, 78%). Mp decomp. 180 °C; ^{1}H NMR (250 MHz, DMSO) δ 10.54 (s, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (–), 146.3 (–), 140.6 (–), 136.5 (+), 123.4 (+), 114.4 (+), 111.8 (–), 88.1 (–), 25.8 (–), 24.6 (+); IR (FTIR, cm^{-1}) 3411, 1678, 1592, 1534, 1371, 1341, 1316, 1257; HRMS calcd for $C_{10}H_6N_2O_3{}^{127}I$ (MH^+) 328.9423, found 328.9438.

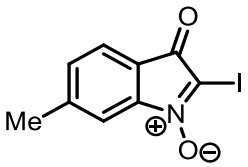
General Procedure D: Synthesis of 2-Iodo-3H-indol-3-one 1-oxide (209)



1-(Iodoethynyl)-2-nitrobenzene **68** (0.273 g, 1.00 mmol, 1.0 eq.) and copper bromide dimethyl sulphide complex (0.051g, 0.250 mmol, 0.25 eq.) were dissolved in THF (20 mL) and heated at reflux with stirring under a stream of N_2 for 16 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as an orange film (0.243 g, 89%). ^{1}H NMR (250 MHz, d^6-DMSO) δ 7.79 – 7.69 (m, 1H), 7.69 – 7.55 (m, 3H); ^{13}C NMR (101 MHz, d^6-DMSO) δ 184.8 (–), 149.0 (–), 135.4 (+), 131.7 (+), 124.4

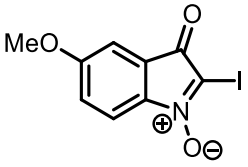
(–), 122.5 (+), 114.1 (+), 101.6 (–); IR (FTIR, cm^{-1}) 3024, 1710, 1599, 1491, 1447,1283, 1191, 1127, 760, 689, 652; HRMS calcd for $C_8H_4NO_2{}^{127}I$ (MH^+) 272.9287, found 272.9289.

Synthesis of 2-Iodo-6-methyl-3-oxo-3H-indole 1-oxide (210)



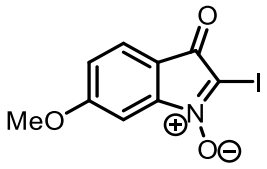
Reaction of 1-(iodoethynyl)-4-methyl-2-nitrobenzene **197** (0.287 g, 1.00 mmol, 1.0 eq.) with CuBr.DMS (0.051g, 0.250 mmol, 0.25 eq) in THF (10 mL) (2 h) as described in general procedure D gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as an orange solid (0.260 g, 91%). Mp 208-210 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.9, 149.3, 146.7, 131.3, 122.3, 121.5, 114.9, 97.3, 22.3; IR (FTIR, cm^{-1}) 3067, 2921, 2848, 718, 1596, 1501, 1466, 1300, 691; HRMS calcd for $C_9H_7NO_2{}^{127}I$ (MH^+) 287.9522, found 287.9528.

Synthesis of 2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide (184)[71]



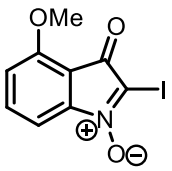
Reaction of 2-(iodoethynyl)-4-methoxy-1-nitrobenzene **183** (1.21 g, 4.00 mmol, 1.0 eq.) with CuBr.DMS (0.206 g, 1.00 mmol, 0.25 eq.) (0.5 h) in THF (50 mL) as described in general procedure D gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a bright red solid (1.20 g, 99%). Mp 175-178 °C (lit: 172-175 °C).[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9.0 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.1 (–), 162.4 (–), 142.0 (–), 125.8 (–), 117.6 (+), 115.4 (+), 109.0 (+), 94.9 (–), 56.3 (+).

Synthesis of 2-Iodo-6-methoxy-3-oxo-3H-indole 1-oxide (213)



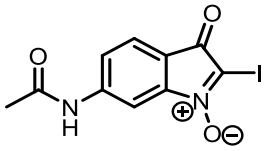
Reaction of 4-methoxy-2-nitro-1-(2-iodoethynyl)benzene **198** (0.080 g, 0.260 mmol, 1.0 eq.) with CuBr.DMS (0.014 g, 0.070 mmol, 0.25 eq.) in THF (10 mL) (1.5 h) as described in general procedure D gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a red solid (0.076 g, 95%). Mp 177-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.97 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0 (–), 165.4 (–), 151.4 (–), 124.2 (+), 116.1 (+), 114.9 (–), 101.6 (+), 98.2 (–), 56.5 (+); IR (FTIR, cm^{-1}) 2922, 2852, 1716, 1645, 1624, 1509, 1469, 1294, 1247; HRMS calcd for $C_9H_7NO_3{}^{127}I$ (MH^+) 303.9471, found 303.9479.

Synthesis of 2-Iodo-4-methoxy-3-oxo-3H-indole 1-oxide (214)



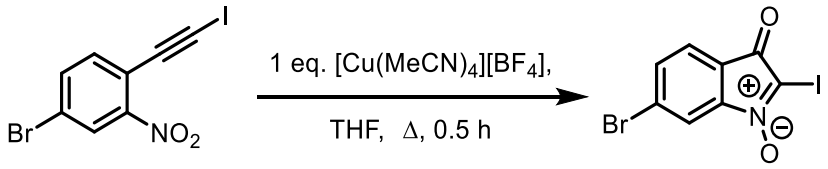
Reaction of 2-(iodoethynyl)-1-methoxy-3-nitrobenzene **199** (0.100 g, 0.330 mmol, 1.0 eq.) with CuBr.DMS (0.017 g, 0.080 mmol, 0.25 eq.) in THF (10 mL) (2 h) as described in general procedure D gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as an orange solid (0.064 g, 64%). Mp 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 1H), 7.31 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9 (–), 155.5 (–), 150.1 (–), 136.6 (+), 116.2 (+), 109.9 (–), 106.9 (+), 97.6 (–), 56.9 (+); IR (FTIR, cm^{-1}) 3082, 2934, 2844, 1712, 1591, 1499, 1474, 1435, 1292, 1171, 1043, 795, 690; HRMS calcd for $C_9H_7NO_3{}^{127}I$ (MH^+) 303.9471, found 303.9469.

Synthesis of N-(2-iodo-1-oxido-3-oxo-3H-indol-6-yl)acetamide (216)



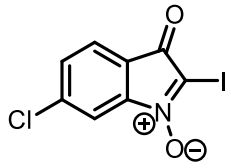
Rreaction of *N*-[4-(iodoethynyl)-3-nitrophenyl]acetamide **215** (1.12 g, 3.40 mmol, 1.0 eq.) with CuBr.DMS (0.175 g, 0.85 mmol, 0.25 eq.) in THF (50 mL) (1 h) as described in general procedure D gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a brown solid (0.851 g, 75%). Mp 240 °C (dec.). ^{1}H NMR (400 MHz, DMSO) δ 7.66 – 7.58 (m, 1H), 7.31 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, d^{6}-DMSO) δ 183.4 (+), 169.9 (+), 150.4 (+), 145.6 (+), 123.8 (+), 119.2 (+), 118.0 (–), 104.7 (+), 102.4 (–), 24.7 (+); IR (FTIR, cm^{-1}) 3355, 3071, 1716, 1680, 1594, 1540, 1504, 1469, 1343, 1300; HRMS calcd for $C_{10}H_8N_2O_3{}^{127}I$ (MH^+) 330.9580, found 330.9570.

General Procedure E: Synthesis of 2-Iodo-6-bromo-3-oxo-3H-indole 1-oxide (219)



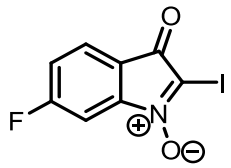
4-Bromo-1-(iodoethynyl)-2-nitrobenzene **202** (0.250 g, 0.710 mmol, 1.0 eq.) and tetrakis(acetonitrile) copper (I) tetrafluroborate (0.224 g, 0.710 mmol, 1.0 eq.) were dissolved in THF (10 mL) and heated at reflux with stirring under a stream of N_2 for 0.5 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 10% EtOAc/petrol) to give the title compound as a red film (0.161 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.5 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ; 182.1 (–), 149.2 (–), 134.3 (+), 129.2 (–), 123.3 (+), 122.7 (–), 117.9 (+), 97.8 (–). IR (FTIR, cm^{-1}) 1741, 1598, 1425, 905, 726; HRMS calcd for $C_8H_4NO_2{}^{79}Br^{127}I$ (MH^+) 351.8470, found 351.8476.

Synthesis of 2-Iodo-6-chloro-3-oxo-3H-indole 1-oxide (221)



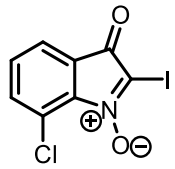
Reaction of 4-chloro-1-(iodoethynyl)-2-nitrobenzene **203** (0.100 g, 0.330 mmol, 1.0 eq.) with $Cu(MeCN)_4BF_4$ (0.102 g, 0.330 mmol, 1.0 eq.) as described in general procedure E gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as an orange film (0.059 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.9 (–), 149.5 (–), 141.2 (–), 131.2 (+), 123.2 (+), 122.2 (–), 115.2 (+), 97.9 (–). IR (FTIR, cm^{-1}) 3410, 1741, 1718, 1613, 1499, 1330, 1297, 1147, 893, 811; HRMS calcd for $C_8H_3{}^{35}ClNO_2{}^{127}I$ (MH^+) 306.8892, found 306.8888.

Synthesis of 2-Iodo-6-fluoro-3-oxo-3H-indole 1-oxide (222)



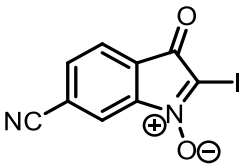
Reaction of 4-fluoro-1-(iodoethynyl)-2-nitrobenzene **204** (0.100 g, 0.340 mmol, 1.0 eq.) with $Cu(MeCN)_4BF_4$ (0.108 g, 0.340 mmol, 1.0 eq.) in THF (10 mL) (0.5 h) as described in general procedure E gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a red-orange film (0.053 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.42 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.22 (td, *J* = 8.0, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.6 (–), 166.3 (d, J_{CF} = 258 Hz, –), 150.8 (d, J_{CF} = 12 Hz, –), 124.3 (d, J_{CF} = 10 Hz, +), 120.0 (–), 117.5 (d, J_{CF} = 23 Hz, +), 103.9 (d, J_{CF} = 28 Hz, +), 98.0 (–). IR (FTIR, cm^{-1}) 3082, 1714, 1608, 1495, 1464, 1302, 1291, 1218, 829, 816, 769; HRMS calcd for $C_8H_4NO_2F^{127}I$ (MH^+) 290.9193, found 290.9199.

Synthesis of 7-Chloro-2-iodo-3H-indol-3-one 1-oxide (223)



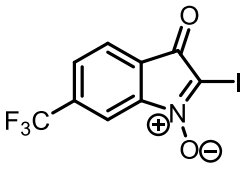
Reaction of 1-chloro-3-(iodoethynyl)-2-nitrobenzene **205** (0.308 g, 1.00 mmol, 1.0 eq.) with $Cu(MeCN)_4BF_4$ (0.315 g, 1.00 mmol, 1.0 eq.) in THF (10 mL) (0.5 h) as described in general procedure E gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a dark red film (0.169 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.58 (dd, 7.5, 1.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.5 (–), 137.7 (+), 132.2 (+), 126.7 (–), 122.3 (–), 121.0 (+), 119.8 (–), 98.2 (–). IR (FTIR, cm^{-1}) 3255, 2923, 2853, 1742, 1615, 1469, 1176, 1138, 1031, 750; HRMS calcd for $C_8H_3NO_2Cl^{127}I$ (MH^+) 306.8897, found 306.8896.

Synthesis of 2-Iodo-6-cyano-3-oxo-3H-indole 1-oxide (224)



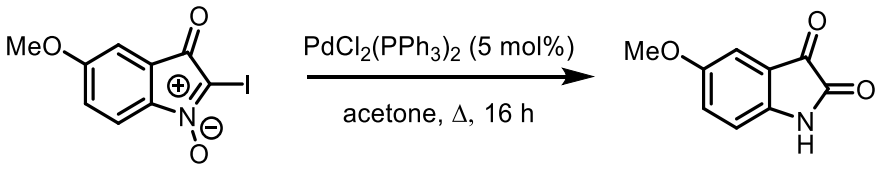
Reaction of 4-(iodoethynyl)-3-nitrobenzonitrile **206** (0.200 g, 0.670 mmol, 1.0 eq.) with $Cu(MeCN)_4BF_4$ (0.211 g, 0.670 mmol, 1.0 eq.) in THF (10 mL) (0.5 h) as described in general procedure E gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as an orange film (0.135 g, 68%). ^{1}H NMR (400 MHz, DMSO) δ 8.19 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 183.6 (–), 148.8 (–), 137.0 (+), 128.1 (–), 122.8 (+), 117.3 (–), 116.6 (+), 115.2 (–), 103.7 (–); IR (FTIR, cm^{-1}) 3082, 2923, 2852, 2239, 1704, 1626, 1496, 1461, 1297; HRMS calcd for $C_9H_3N_2O_2{}^{127}I$ (MH^+) 297.9239, found 297.9240.

Synthesis of 2-Iodo-6-trifluoromethyl-3-oxo-3H-indole 1-oxide (218)



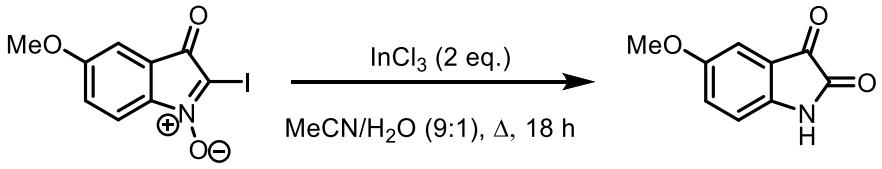
Reaction of 1-(iodoethynyl)-2-nitro-4-(trifluoromethyl)benzene **207** (0.100 g, 0.290 mmol, 1.0 eq.) with $Cu(MeCN)_4BF_4$ (0.092 g, 0.290 mmol, 1.0 eq.) in THF (10 mL) (0.5 h) as described in general procedure E gave, after work-up and chromatography (silica gel, 10% EtOAc/petrol), the title compound as a yellow-orange film (0.036 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.0 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0 (–), 148.9 (–), 136.5 (q, J_{CF} = 34.0 Hz), 128.7 (q, J_{CF} = 4.0 Hz, +), 126.7 (–), 122.6 (+), 122.5 (q, J_{CF} = 286.0 Hz, –), 111.5 (q, J_{CF} = 3.0 Hz, +), 97.9 (–); IR (FTIR, cm^{-1}) 3096, 2923, 2852, 1721, 1513, 1472, 1317, 1176, 1132, 1089, 1042, 898, 686; HRMS calcd for $C_9H_3NO_2F_3{}^{127}I$ (MH^+) 340.9161, found 340.9159.

Synthesis of 5-methoxy-1H-indole-2,3-dione (212)[71]



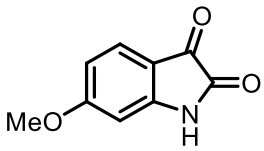
2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.100 g, 0.33 mmol, 1.0 eq.) and $PdCl_2(PPh_3)_2$ (0.012 g, 0.02 mmol, 0.05 eq.) were dissolved in acetone (10 mL). The reaction mixture was heated at reflux with stirring under a stream of N_2 for 16 h. After cooling down to rt, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to afford the title compound as a dark red solid (0.049 g, 85%). M.p. 200 °C (decomp.) (lit: 200-201 °C).[71] ^{1}H NMR (400 MHz, DMSO) δ 10.84 (br, s, 1H), 7.18 – 7.06 (m, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 184.0 (-), 159.5 (-), 155.4 (-), 144.5 (-), 124.8 (+), 118.0 (-), 113.2 (+), 108.6 (+), 55.6 (+).

General Procedure F: Synthesis of 5-methoxy-1H-indole-2,3-dione (212) [71]



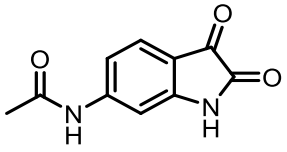
2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.50 mmol, 1.0 eq.) and $InCl_3$ (0.221 g, 1.0 mmol, 2.0 eq.) were dissolved in MeCN/H_2O (9:1, 10 mL). The reaction mixture was heated at reflux with stirring under a stream of N_2 for 18 h. Aqueous saturated NH_4Cl solution (20 mL) was added and the product extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a dark red solid (0.065 g, 73%). See above for data.

Synthesis of 6-methoxy-1H-indole-2,3-dione (227) [71]



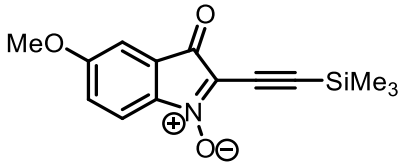
Reaction of 2-iodo-6-methoxy-3-oxo-3H-indole 1-oxide **213** (0.151 g, 0.50 mmol, 1.0 eq.) and $InCl_3$ (0.221 g, 1.0 mmol, 2.0 eq.) in MeCN/H_2O (9:1, 10 mL) as described in general procedure F gave, after work-up and chromatography (silica gel, EtOAc), the title compound as a yellow-orange solid (0.060 g, 68%). M.p. 200 °C, decomp. (lit: 229-230 °C).[71] ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 6.58 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.39 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 182.0 (-), 168.2 (-), 161.1 (-), 154.0 (-), 127.8 (+), 111.6 (-), 109.3 (+), 98.2 (+), 56.6 (+).

Synthesis of *N*-(2,3-dioxo-2,3-dihydro-1H-indol-6-yl)acetamide (228)[181]



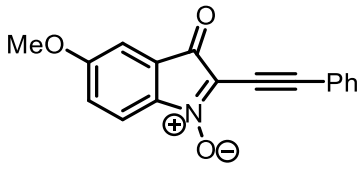
Reaction of *N*-(2-iodo-1-oxido-3-oxo-3H-indol-6-yl)acetamide **216** (0.165 g, 0.50 mmol, 1.0 eq.) and $InCl_3$ (0.221 g, 1.0 mmol, 2.0 eq.) in $MeCN/H_2O$ (9:1, 10 mL) as described in general procedure F gave, after work-up and chromatography (silica gel, EtOAc), the title compound as a brown solid (0.078 g, 76%). M.p. 200 °C, decomp. (lit: 200 °C, decomp.).[181] ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 10.52 (s, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 182.4 (-), 170.1 (-), 160.8 (-), 153.1 (-), 148.8 (-), 126.8 (+), 112.9 (-), 112.8 (+), 102.0 (+), 24.8 (+).

General Procedure G: Synthesis of 5-Methoxy-2-(trimethylsilylethynyl)-3H-indol-3-one 1-oxide (230)



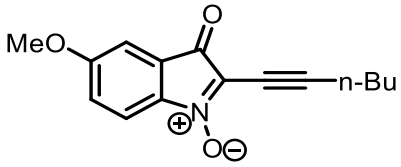
2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.500 mmol, 1.0 eq.), $PdCl_2(PPh_3)_2$ (0.018 g, 0.025 mmol, 0.05 eq.) and CuI (0.005 g, 0.025 mmol, 0.05 eq.), were dissolved in THF (10 mL). Trimethylsilylacetylene (0.214 mL,1.50 mmol, 3.0 eq.) and diisopropylamine (0.211 mL, 1.50 mmol, 3.0 eq.) were added and the reaction mixture was stirred at rt under a stream of N_2 for 0.5 h. Aqueous saturated $NaHCO_3$ solution (20 mL) was added and the product extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a dark red film (0.085 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.91 (s, 3H), 0.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5 (–), 163.3 (–), 140.0 (–), 124.4 (–), 122.8 (–), 118.4 (+), 117.8 (–), 115.6 (+), 108.3 (+), 89.2 (–), 56.2 (+), -0.45 (+). IR (FTIR, cm^{-1}) 3339, 2956, 2900, 2836, 2252, 2158, 1698, 1621, 1598, 1484, 1438, 1024, 837, 730; HRMS calcd for $C_{14}H_{16}NO_3Si$ (MH^+) 274.0899, found 274.0893.

Synthesis of 5-Methoxy-2-(phenylethynyl)-3H-indol-3-one 1-oxide (231)



Reaction of 2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.500 mmol, 1.0 eq.), $PdCl_2(PPh_3)_2$ (0.018 g, 0.025 mmol, 0.05 eq.), CuI (0.005 g, 0.025 mmol, 0.05 eq.) phenylacetylene (0.165 mL,1.50 mmol, 3.0 eq.) and diisopropylamine (0.211 mL, 1.50 mmol, 3.0 eq.) in THF (10 mL) (0.5 h) as described in general procedure G gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark purple film (0.070 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.5, 2.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.48 – 7.35 (m, 3H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6 (–), 163.1 (–), 140.3 (–), 132.1 (+), 130.0 (+), 128.5 (+), 124.6 (–), 123.2 (–), 121.4 (–), 118.4 (+), 115.6 (+), 109.3 (–), 108.5 (+), 75.7 (–), 56.3 (+). IR (FTIR, cm^{-1}) 3066, 2959, 2836, 2182, 1708, 1611, 1482, 1434, 1404, 1277, 1226, 1020, 907, 750, 727; HRMS calcd for $C_{17}H_{12}NO_3$ (MH^+) 278.0817, found 278.0830.

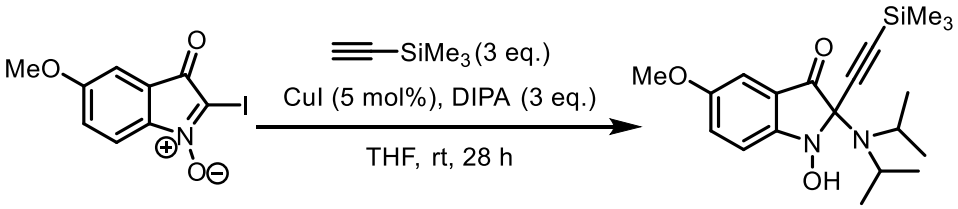
Synthesis of 2-(Hex-1-yn-1-yl)-5-methoxy-3H-indol-3-one 1-oxide (232)



Reaction of 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.500 mmol, 1.0 eq.), $PdCl_2(PPh_3)_2$ (0.018 g, 0.025 mmol, 0.05 eq.), CuI (0.005 g, 0.025 mmol, 0.05 eq.), 1-hexyne (0.172 mL,1.50 mmol, 3.0 eq.) and diisopropylamine (0.211 mL, 1.50 mmol, 3.0 eq.) in THF (10 mL) (6 h) as described in general procedure G gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark purple film (0.063 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 7.05 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.88 (s, 3H), 2.59 (t, *J* = 7.0 Hz, 2H), 1.70 –

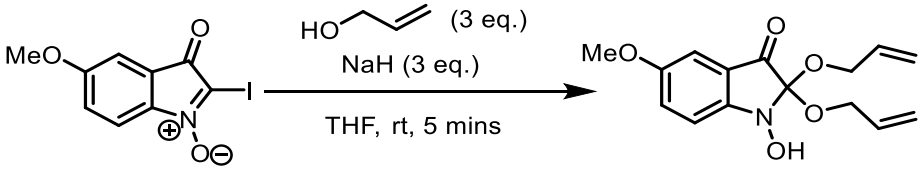
1.61 (m, 2H), 1.54 – 1.43 (m, 2H), 0.94 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0 (–), 162.9 (–), 140.1 (–), 124.4 (–), 123.4 (–), 118.2 (+), 115.4 (+), 112.6 (–), 108.4 (+), 67.2 (–), 56.2 (+), 30.1 (–), 22.0 (–), 20.3 (–), 13.6 (+). IR (FTIR, cm^{-1}) 2958, 2935, 2872, 2217, 1714, 1513, 1488, 1406, 1282, 1087, 1019, 783, 767; HRMS calcd for $C_{15}H_{15}NO_3$ (MH^+) 258.1131, found 258.1122.

Synthesis of 2-((trimethylsilyl)ethynyl)-2-[di(propan-2-yl)amino]-1-hydroxy-5-methoxy-1,2-dihydro-3H-indol-3-one (235)



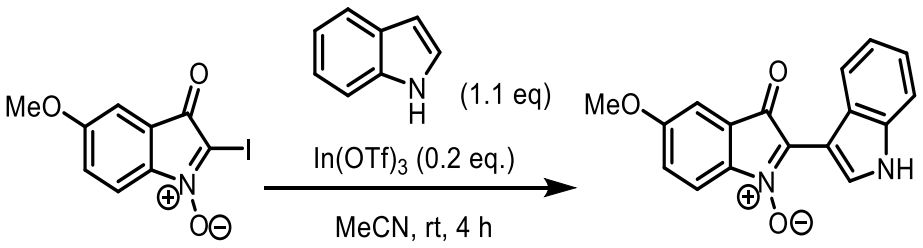
2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.500 mmol, 1.0 eq.), and CuI (0.005 g, 0.025 mmol, 0.05 eq.), were dissolved in THF (10 mL). Trimethylsilylacetylene (0.214 mL, 1.50 mmol, 3.0 eq.) and diisopropylamine (0.211 mL, 1.50 mmol, 3.0 eq.) were added and the reaction mixture was stirred at rt under a stream of N_2 for 28 h. Aqueous saturated $NaHCO_3$ solution (20 mL) was added and the product extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc/petrol) to give the title compound as a dark red film (0.034 g, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.10 (m, 2H), 6.82 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.18 (s, 1H), 4.09 – 4.01 (m, 1H), 3.80 (s, 3H), 3.54 – 3.46 (m, 1H), 1.72 (s, 1H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9 (-), 170.6 (-), 154.3 (-), 148.2 (-), 141.9 (-), 127.6 (-), 126.0 (+), 122.1 (-), 113.2 (+), 105.9 (+), 55.8 (+), 50.7 (+), 45.9 (+), 21.9 (+), 21.4 (+), 20.3 (+), 20.2 (+), -1.2 (+). IR (FTIR, cm^{-1}) 3424, 3055, 2987, 2306, 1687, 1608, 1493, 1266, 739. HRMS calcd for $C_{20}H_{31}N_2O_3Si$ (MH^+) 375.2104, found 375.2097.

Synthesis of 1-hydroxy-5-methoxy-2,2-bis(prop-2-en-1-yloxy)-1,2-dihydro-3H-indol-3-one (239)



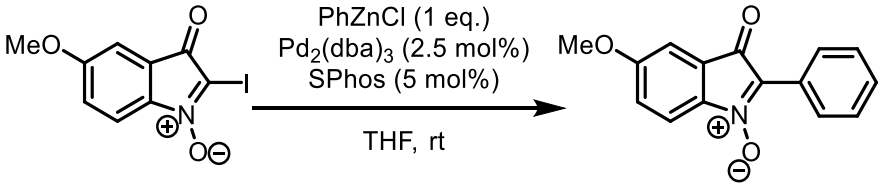
Sodium hydride (0.038 g, 1.58 mmol, 4.8 eq.) and allyl alcohol (0.068 mL, 0.99 mmol, 3.0 eq.) were combined in THF (2 mL) and the reaction mixture was stirred at rt for 10 min. 2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.100 g, 0.33 mmol, 1.0 eq.) in THF (3 mL) was added and the reaction mixture was stirred at rt under a stream of N_2 for 5 min. Aqueous saturated NH_4Cl solution (10 mL) was added and the product extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/petrol) to give the title compound as a yellow oil (0.027 g, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 8.5, 2.5 Hz 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 5.94 (ddt, *J* = 17.0, 10.0, 5.5 Hz, 2H), 5.56 (s, 1H), 5.34 (dq, *J* = 17.0, 1.5 Hz, 2H), 5.26 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 2H), 4.31 (ddd, *J* = 5.5, 2.5, 1.5 Hz, 4H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (-), 155.9 (-), 148.8 (-), 133.8 (-), 127.0 (-), 115.1 (+), 112.0 (+), 111.4 (+), 105.4 (+), 97.8 (-), 59.0 (-), 55.9 (+). IR (FTIR, cm^{-1}) 2999, 2963, 1691, 1639, 1597, 1477, 1460, 1339, 1241, 1107, 838. HRMS calcd for $C_{15}H_{17}NO_5$ (MH^+) 291.1107, found 291.1097.

Synthesis of 2-(1H-indol-3-yl)-5-methoxy-3H-indol-3-one 1-oxide (240)



2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.50 mmol, 1.0 eq.), indole (0.064 g, 0.55 mmol, 1.1 eq.) and $In(OTf)_3$ (0.056 g, 0.10 mmol, 0.20 eq.) were combined in MeCN (5 mL) and then stirred at rt under a stream of N_2 for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc) to afford the title product as dark purple amorphous solid (0.185 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.60 – 8.55 (m, 1H), 8.49 (s, 1H), 7.47 – 7.44 (m, 1H), 7.41 – 7.30 (m, 3H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (-), 158.9 (-), 136.5 (-), 136.2 (-), 131.1 (+), 126.0 (-), 124.0 (+), 123.9 (-), 123.2 (+), 122.4 (+), 121.8 (+), 121.2 (-), 120.7 (+), 111.5 (+), 110.9 (+), 110.8 (-), 56.0 (+). IR (FTIR, cm^{-1}) 3308, 2952, 2918, 2842, 1714, 1638, 1542, 1447, 1420, 1343, 1297, 1018. HRMS calcd for $C_{17}H_{13}N_2O_3$ (MH^+) 293.0926, found 293.0915.

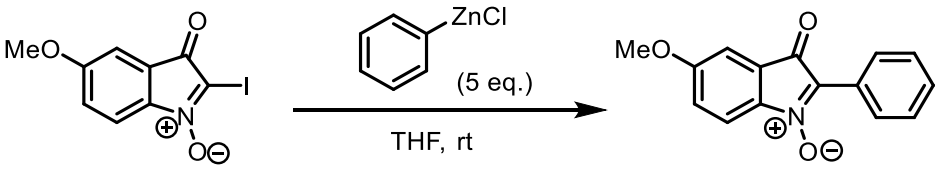
Synthesis of 5-Methoxy-2-phenyl-3H-indol-3-one 1-oxide (229)[124]



2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.50 mmol, 1.0 eq.), $Pd_2(dba)_3$ (0.011 g, 0.013 mmol, 0.025 eq.) and SPhos (0.010 g, 0.025 mmol, 0.05 eq.) were combined in THF (10 mL) and then stirred for 15 mins. PhZnCl (0.5 M in THF, 3 mL, 3.0 eq.) was added and the reaction mixture was stirred at rt under a stream of N_2 for 4 h. Aqueous saturated NH_4Cl solution (20 mL) was added and the product extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc/petrol) to give the title compound as a dark red purple solid (0.057 g, 45%). Mp 134-136 °C (lit: 135.3-135.7 °C).[108] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.56 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.43 (m, 3H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.94

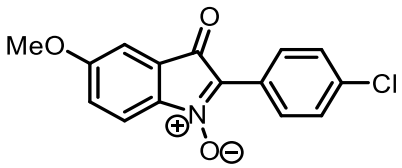
(s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7 (–), 162.5 (–), 140.7 (–), 131.8 (–), 130.4 (+), 128.5 (+), 127.5 (+), 126.1 (–), 124.6 (–), 118.3 (+), 115.5 (+), 107.9 (+), 56.2 (+).

General Procedure H: Synthesis of 5-Methoxy-2-phenyl-3H-indol-3-one 1-oxide (229) [108]



Zinc chloride (2.75 mL, 1M, 5.5 eq.) was added to a solution of phenylmagnesium bromide (0.83 mL, 3M, 5.0 eq.) in THF (10 mL) and then stirred at ambient temperature under a stream of N_2 for 15 min. The mixture was added to a solution of 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.5 mmol, 1.0 eq.) in THF (10 mL) via cannula and then stirred at ambient temperature under a stream of N_2 for 5 h. Aqueous saturated NH_4Cl solution (20 mL) was added to the reaction mixture and the product extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound as a dark red-purple solid (0.078 g, 62%). See above for data.

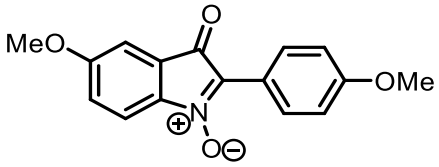
Synthesis of 2-(4-Chlorophenyl)-5-methoxy-3H-indol-3-one 1-oxide (243)[108]



Reaction of zinc chloride (2.75 mL, 1M, 5.5 eq.), 4-chlorophenylmagnesium bromide (2.5 mL, 1M, 5.0 eq.) and 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.5 mmol, 1.0 eq.) in THF (20 mL) (4 h) as described in general procedure H gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark red-

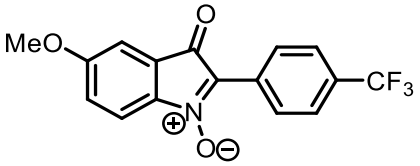
purple solid (0.093 g, 65%). Mp 192-193 °C (lit: 190.5-191.1 °C).[108] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.5, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 8.5, 2H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.5 (–), 162.6 (–), 154.4 (–), 140.7(–), 136.2 (–), 128.8 (+), 128.7 (+), 124.6 (–), 118.5 (+), 115.6 (+), 108.0 (+), 56.3 (+).

Synthesis of 5-Methoxy-2-(4-methoxyphenyl)-3H-indol-3-one 1-oxide (244)[108]



Reaction of zinc chloride (2.75 mL, 1M, 5.5 eq.), 4-methoxyphenylmagnesium bromide (5.0 mL, 0.5M, 5.0 eq.) and 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.5 mmol, 1.0 eq.) in THF (20 mL) (6 h) as described in general procedure H gave, after work-up and chromatography (silica gel, 5% EtOAc/petrol), the title compound as a dark purple solid (0.094 g, 66%). Mp 196-198 °C (lit: 196-196.8 °C).[108] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.07 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.04 – 6.98 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 187.1 (–), 162.1 (–), 161.1 (–), 153.3 (–), 140.9 (–), 129.4 (+), 124.6 (–), 119.0 (–), 118.3 (+), 115.1 (+), 114.0 (+), 107.9 (+), 56.19 (+), 55.34 (+).

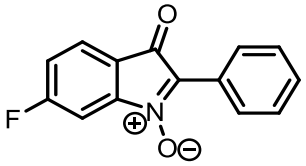
Synthesis of 5-Methoxy-2-[4-(trifluoromethyl)phenyl]-3H-indol-3-one 1-oxide (242)[108]



Reaction of zinc chloride (2.75 mL, 1M, 5.5 eq.), 4-(trifluoromethyl)benzylmagnesium bromide (2.5 mL, 1M, 5.0 eq.) and 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.151 g, 0.5 mmol, 1.0 eq.) in THF (20 mL) (6 h) as described in general procedure H gave,

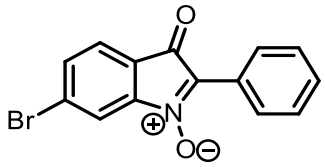
after work-up and chromatography (silica gel, 5% EtOAc/petrol), the title compound as a dark red solid (0.093 g, 59%). Mp 195-196 °C (lit: 193-198 °C).[108] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.3 (–), 162.9 (–), 140.6 (–), 130.6 (–), 129.3 (–), 127.4 (+), 125.4 (–), 125.2 (–), 124.6 (–), 122.5 (–), 118.6 (+), 115.8 (+), 108.0 (+), 56.3 (+).

Synthesis of 6-Fluoro-2-phenyl-3H-indol-3-one 1-oxide (245)



Reaction of zinc chloride (3.0 mL, 1M, 5.5 eq.), phenylmagnesium bromide (1.8 mL, 1.5M, 5.0 eq.) and 2-iodo-6-fluoro-3-oxo-3H-indole 1-oxide **222** (0.160 g, 0.55 mmol, 1.0 eq.) in THF (20 mL) (4 h) as described in general procedure H gave, after work-up and chromatography (silica gel, 5% EtOAc/petrol), the title compound as an orange film (0.053 g, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 7.5 Hz, 2H), 7.67 – 7.70 (m, 1H), 7.51 – 7.56 (m, 3H), 7.47 (d, *J* = 6.5 Hz, 1H), 7.22 – 7.78 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (–), 166.8 (d, J_{CF} = 260 Hz, –), 150.2 (d, J_{CF} = 11 Hz, –), 133.0 (–), 131.2 (+), 128.7 (+), 128.0 (+), 125.6 (–), 123.8 (d, J_{CF} = 10 Hz, +), 118.8 (–), 117.7 (d, J_{CF} = 23 Hz, +), 104.0 (d, J_{CF} = 28 Hz, +). IR (FTIR, cm^{-1}) 1718, 1612, 1523, 1493, 1381, 1227, 778; HRMS calcd for $C_{14}H_8NO_2F$ (MH^+) 242.0612, found 242.0612.

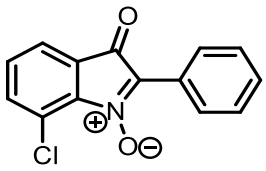
Synthesis of 6-Bromo-2-phenyl-3H-indol-3-one 1-oxide (246)



Reaction of zinc chloride (2.0 mL, 1M, 5.5 eq.), phenylmagnesium bromide (1.2 mL, 1.5M, 5.0 eq.) and 2-iodo-6-bromo-3-oxo-3H-indole 1-oxide **219** (0.130 g, 0.37 mmol,

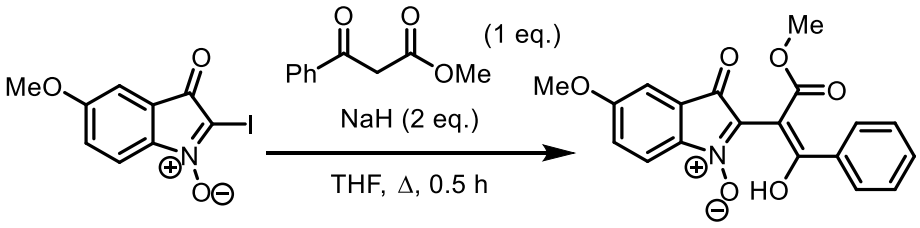
1.0 eq.) in THF (20 mL) (4 h) as described in general procedure H gave, after work-up and chromatography (silica gel, 5% EtOAc/petrol), the title compound as an orange film (0.051 g, 48%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.64 (m, 2H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.74 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.57 – 7.51 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8 (–), 161.8 (–), 148.5 (–), 134.2 (+), 131.1 (+), 129.2 (–), 128.6 (+), 127.9 (+), 125.6 (–), 122.7 (+), 121.6 (–), 118.1 (+). IR (FTIR, cm^{-1}) 1716, 1595, 1478, 1445, 1378, 1085, 894, 778; HRMS calcd for $C_{14}H_8NO_2{}^{79}Br$ (MH^+) 301.9811, found 301.9809.

Synthesis of 7-Chloro-2-phenyl-3H-indol-3-one 1-oxide (247)



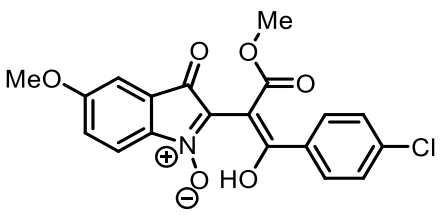
Reaction of zinc chloride (3.1 mL, 1M, 5.5 eq.), phenylmagnesium bromide (1.8 mL, 1M, 5.0 eq.) and 2-iodo-7-chloro-3-oxo-3H-indole 1-oxide **223** (0.170 g, 0.55 mmol, 1.0 eq.) in THF (20 mL) (4 h) as described in general procedure H gave, after work-up and chromatography (silica gel, 5% EtOAc/petrol), the title compound as a dark red oil (0.068 g, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.23 (m, 6H), 6.99 – 6.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 138.1, 136.4, 132.0, 131.0, 128.7, 128.1, 127.8, 127.4, 123.8, 120.4, 120.1. IR (FTIR, cm^{-1}) 1710, 1613, 1487, 1447, 1127, 739, 699; HRMS calcd for $C_{14}H_8NO_2Cl$ (MH^+) 258.0316, found 258.0319.

General procedure I: Synthesis of methyl 2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxo-3-phenylpropanoate (256)



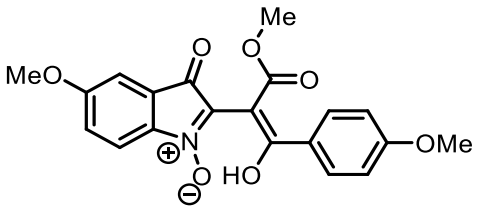
Sodium hydride (0.076 g, 3.20 mmol, 3.2 eq.) was suspended in THF (5 mL) and then methyl benzoyl acetate (0.189 mL, 1.20 mmol, 1.2 eq.) was added. The mixture was heated at reflux for 10 mins after which a solution of 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.303 g, 1.00 mmol, 1.0 eq.) in THF (15 mL) was added. The reaction mixture was stirred at reflux under a stream of N_2 for 0.5 h. Aqueous saturated NH_4Cl solution (20 mL) was added and the product extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to give the title compound (as an inseparable mixture of tautomers) as a dark red solid (0.303 g, 86%). Mp 125-126 °C. Data reported only for the major tautomer (enol form): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.70 (s, 1H), 7.50 – 7.45 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.5 (–), 177.5 (–), 171.4 (–), 162.5 (–), 140.0 (–), 134.4 (–), 132.9 (–), 131.4 (+), 128.6 (+), 127.0 (+), 124.9 (–), 117.7 (+), 115.5 (+), 108.1 (+), 87.7 (–), 56.2 (+), 52.6 (+). IR (FTIR, cm^{-1}) 2952, 2840, 1709, 1640, 1605, 1522, 1481, 1433, 1353, 1279, 1140, 777; HRMS calcd for $C_{19}H_{16}NO_6$ (MH^+) 354.0978, found 354.0985.

Synthesis of methyl 3-(4-chlorophenyl)-2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxopropanoate (257)



Reaction of sodium hydride (0.076 g, 3.20 mmol, 3.2 eq.), 3-(4-chlorophenyl)-3-oxo-propionic acid methyl ester (0.255 g, 1.20 mmol, 1.2 eq.) and 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.303 g, 1.00 mmol, 1.0 eq.) in THF (20 mL) (0.5 h) as described in general procedure I gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound (as an inseparable mixture of tautomers) as a dark red amorphous solid (0.339 g, 88%). Data reported only for the major tautomer (enol form): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.69 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.31 – 7.26 (m, 2H), 7.06 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (–), 176.1 (–), 171.3 (–), 162.6 (–), 139.9 (–), 137.6 (–), 132.8 (–), 132.5 (–), 128.9 (+), 128.4 (+), 124.8 (–), 117.9 (+), 115.6 (+), 108.2 (+), 88.0 (–), 56.2 (+), 52.7 (+). IR (FTIR, cm^{-1}) 2917, 2849, 1707, 1605, 1521, 1484, 1280, 1229, 1089, 838; HRMS calcd for $C_{19}H_{15}NO_6{}^{35}Cl$ (MH^+) 388.0588, found 388.0607.

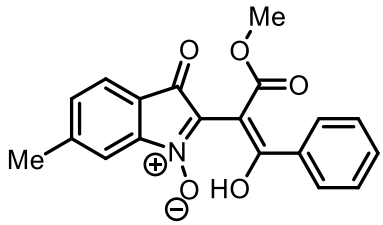
Synthesis of methyl 3-(4-methoxyphenyl)-2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxopropanoate (258)



Reaction of sodium hydride (0.076 g, 3.20 mmol, 3.2 eq.), 3-(4-methoxyphenyl)-3-oxo-propionic acid methyl ester (0.250 g, 1.20 mmol, 1.2 eq.) and 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide **184** (0.303 g, 1.00 mmol, 1.0 eq.) in THF (20 mL) (0.5 h) as described in general procedure I gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound (as an inseparable mixture of tautomers) as a dark red amorphous solid (0.339 g, 87%). Data reported only for the major tautomer (enol form): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.73 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.07 – 7.03 (m, 2H), 6.83 – 6.78 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6 (-), 177.2 (-), 171.5 (-), 164.2 (-), 162.5 (-), 162.1 (-), 140.0 (-), 128.9 (+), 126.8 (-), 124.9 (-), 117.7 (+), 114.2 (+), 113.9 (+), 108.12 (+), 86.4

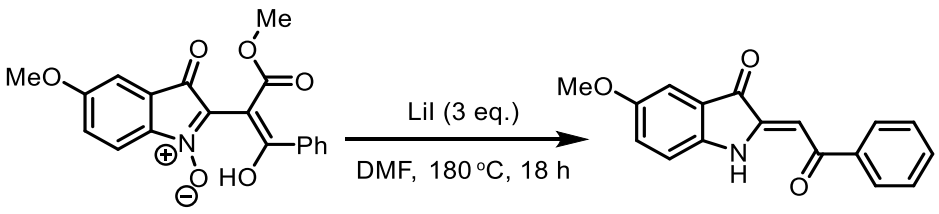
(-), 56.2 (+), 55.3 (+), 52.44 (+). IR (FTIR, cm^{-1}) 2952, 2843, 1744, 1710, 1683, 1560, 1507, 1485, 1436, 1257, 1170, 1022, 838; HRMS calcd for $C_{20}H_{18}NO_7$ (MH^+) 384.1083, found 384.1075.

Synthesis of methyl 2-(6-methyl-1-oxido-3-oxo-3H-indol-2-yl)-3-oxo-3-phenylpropanoate (259)



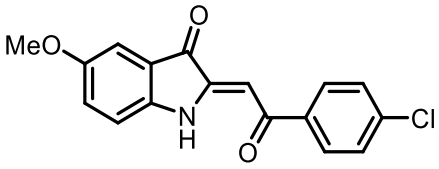
Reaction of sodium hydride (0.076 g, 3.20 mmol, 3.2 eq), methyl benzoylacetate (0.190 mL, 1.20 mmol, 1.2 eq.) and 2-iodo-6-methyl-3-oxo-3H-indole 1-oxide **210** (0.287 g, 1.00 mmol, 1.0 eq.) in THF (20 mL) (0.5 h) as described in general procedure I gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound (as an inseparable mixture of tautomers) as an orange solid (0.253 g, 75%). Mp 108-110 °C. Data reported only for the major tautomer (enol form): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.71 (s, 1H), 7.48 – 7.46 (m, 2H), 7.42 (s, 1H), 7.39 – 7.37 (m, 2H), 7.32 – 7.26 (m, 3H), 3.80 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (–), 177.6 (–), 171.3 (–), 147.6 (–), 146.4 (–), 134.4 (–), 133.7 (–), 131.5 (+), 131.4 (+), 128.6 (+), 127.0 (+), 121.7 (+), 120.6 (–), 115.1 (+), 87.7 (–), 52.5 (+), 22.3 (+). IR (FTIR, cm^{-1}) 3056, 2959, 2856, 1709, 1595, 1528, 1447, 1352, 1266, 1142, 698; HRMS calcd for $C_{19}H_{16}NO_5$ (MH^+) 338.1028, found 338.1022.

General procedure J: Synthesis of 5-Methoxy-2-(2-oxo-2-phenylethylidene)-1,2-dihydro-3H-indol-3-one (251)



Methyl 2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxo-3-phenylpropanoate **256** (0.140 g, 0.400 mmol, 1.0 eq.) and lithium iodide (0.162 g, 1.20 mmol, 3 eq.) were dissolved in *N*,*N*-dimethylformamide (10 mL) and then heated at 180 °C with stirring under a stream of N_2 for 18 h. The reaction mixture was poured onto ice-cold H_2O (100 mL) and the product was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (50 mL) and then dried with $MgSO_4$ before removing the solvent under pressure. The crude product was purified by flash column chromatography (Florisil, 20% EtOAc/petrol) to give the title compound as a dark purple solid (0.062 g, 56%). Mp 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.09 – 8.05 (m, 2H), 7.66 – 7.57 (m, 1H), 7.56 – 7.48 (m, 2H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.93 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4 (–), 188.7 (–), 155.5 (–), 147.7 (–), 145.3 (–), 138.4 (–), 132.9 (+), 128.7 (+), 127.9 (+), 125.4 (+), 120.4 (–), 112.9 (+), 108.1 (+), 94.9 (+), 55.9 (+).; IR (FTIR, cm^{-1}) 3341, 2162, 2029, 1708, 1645, 1623, 1604, 1314, 1230, 1130, 825, 750, 698; HRMS calcd for $C_{17}H_{14}NO_3$ (MH^+) 280.0974, found 280.0975.

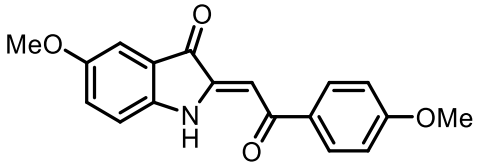
Synthesis of 2-[2-(4-Chlorophenyl)-2-oxoethylidene]-5-methoxy-1,2-dihydro-3H-indol-3-one (260)



Reaction of methyl 3-(4-chlorophenyl)-2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxopropanoate **257** (0.180 g, 0.47 mmol, 1.0 eq.) and lithium iodide (0.187 g, 1.40 mmol, 3 eq.) in DMF (10 mL) as described in general procedure J gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark purple solid (0.069 g, 47%). Mp 205-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.85 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0 (–), 188.5 (–), 155.6 (–), 147.6 (–), 145.6 (–), 139.3 (–), 136.7 (–), 129.3 (+), 129.0

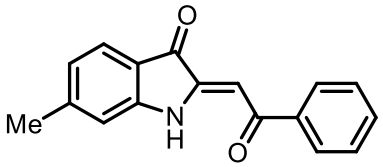
(+), 125.5 (+), 120.4 (–), 113.0 (+), 108.2 (+), 94.3 (+), 55.9 (+); IR (FTIR, cm^{-1}) 2923, 2852, 1702, 1647, 1592, 1497, 1466, 1318, 1130; HRMS calcd for $C_{17}H_{13}NO_3{}^{35}Cl$ (MH^+) 314.0584, found 314.0579.

Synthesis of 2-[2-(4-methoxyphenyl)-2-oxoethylidene]-5-methoxy-1,2-dihydro-3H-indol-3-one (261)



Reaction of methyl 2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-(4-methoxyphenyl)-3-oxopropanoate **258** (0.180 g, 0.47 mmol, 1.0 eq.) and lithium iodide (0.189 g, 1.41 mmol, 3 eq.) in DMF (10 mL) as described in general procedure J gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark red oil (0.035 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.05 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 2.5 Hz, 1H), 7.11 (dd, J = 9.0, 2.5 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.88 (s, 1H), 3.91 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9 (-), 188.8 (-), 163.6 (-), 155.3 (-), 147.9 (-), 145.1 (-), 132.3 (+), 131.5 (-), 130.2 (+), 125.5 (+), 120.4 (-), 113.9 (+), 113.7 (+), 112.9 (+), 108.0 (+), 95.1 (+), 55.9 (+), 55.5 (+) ; IR (FTIR) 2917, 2849, 1667, 1597, 1488, 1437, 1252, 1166, 1137, 1023; HRMS calcd for $C_{18}H_{16}NO_4$ ($M+H^+$) 310.1072, found 310.1079.

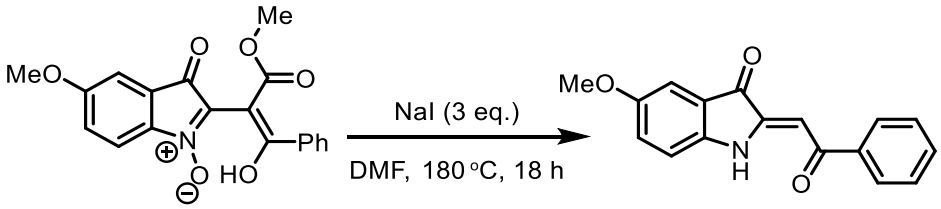
Synthesis of 6-methyl-2-(2-oxo-2-phenylethylidene)-1,2-dihydro-3H-indol-3-one (262)



Reaction of methyl 2-(6-methyl-1-oxido-3-oxo-3H-indol-2-yl)-3-oxo-3-phenylpropanoate **259** (0.100 g, 0.30 mmol, 1.0 eq.) and lithium iodide (0.119 g, 0.89 mmol, 3.0 eq.) in DMF

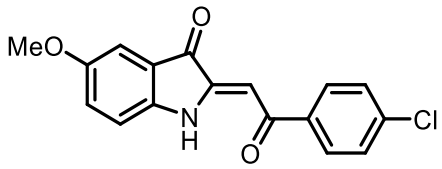
(10 mL) as described in general procedure J gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark red solid (0.032 g, 40%). Mp 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$ δ 10.06 (s, 1H), 8.14 – 8.02 (m, 2H), 7.66 – 7.58 (m, 2H), 7.55 – 7.45 (m, 2H), 6.94 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6 (–), 187.8 (–), 153.6 (–), 149.5 (–), 145.4 (–), 138.4 (–), 133.0 (+), 128.7 (+), 128.0 (+), 125.5 (+), 123.4 (+), 117.9 (–), 112.5 (+), 94.9 (+), 22.6 (+); IR (FTIR, cm^{-1}) 3330, 2921, 2852, 1709, 1650, 1619, 1560, 1453, 1308, 1289, 1234, 752, 690; HRMS calcd for $C_{17}H_{14}NO_2$ (MH^+) 264.1025, found 264.1030.

General Procedure K: Synthesis of 5-Methoxy-2-(2-oxo-2-phenylethylidene)-1,2-dihydro-3H-indol-3-one (251)



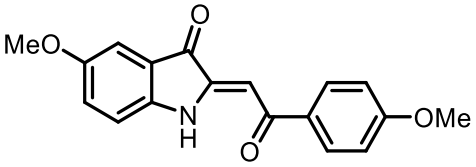
Methyl 2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxo-3-phenylpropanoate **256** (0.140 g, 0.400 mmol, 1.0 eq.) and sodium iodide (0.180 g, 1.20 mmol, 3 eq.) were dissolved in *N*,*N*-dimethylformamide (10 mL) and then heated at 180 °C with stirring under a stream of N_2 for 18 h. The reaction mixture was poured onto ice-cold H_2O (100 mL) and the product was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (50 mL) and then dried with $MgSO_4$ before removing the solvent under pressure. The crude product was purified by flash column chromatography (Florisil, 20% EtOAc/petrol) to give the title compound as a dark purple solid (0.069 g, 62%). See page 196 for data.

Synthesis of 2-[2-(4-Chlorophenyl)-2-oxoethylidene]-5-methoxy-1,2-dihydro-3H-indol-3-one (260)



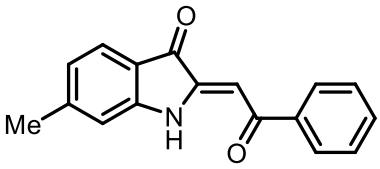
Reaction of methyl 3-(4-chlorophenyl)-2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-oxopropanoate **257** (0.135 g, 0.350 mmol, 1.0 eq.) and sodium iodide (0.157 g, 1.05 mmol, 3.0 eq.) in DMF (5 mL) as described in general procedure K gave, after work-up and chromatography (Florisil, 20% EtOAc/petrol), the title compound as a dark purple solid (0.070 g, 64%). See page 197 for data.

Synthesis of 2-[2-(4-methoxyphenyl)-2-oxoethylidene]-5-methoxy-1,2-dihydro-3H-indol-3-one (261)



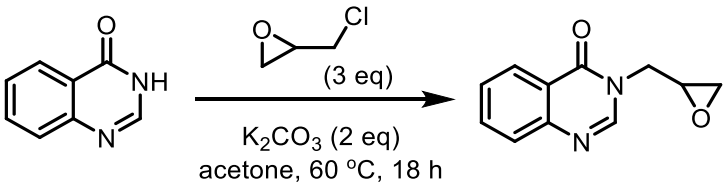
Reaction of methyl 2-(5-methoxy-1-oxido-3-oxo-3H-indol-2-yl)-3-(4-methoxyphenyl)-3-oxopropanoate **258** (0.130 g, 0.34 mmol, 1.0 eq.) and sodium iodide (0.153 g, 1.02 mmol, 3 eq.) in DMF (5 mL) as described in general procedure K gave, after work-up and chromatography (silica gel, 20% EtOAc/petrol), the title compound as a dark red oil (0.044 g, 42%). See page 197 for data.

Synthesis of 6-methyl-2-(2-oxo-2-phenylethylidene)-1,2-dihydro-3H-indol-3-one (262)



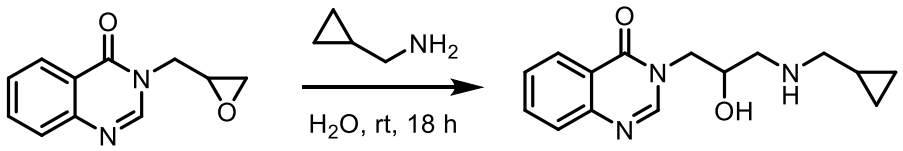
Reaction of methyl 2-(6-methyl-1-oxido-3-oxo-3H-indol-2-yl)-3-oxo-3-phenylpropanoate **259** (0.169 g, 0.500 mmol, 1.0 eq.) and sodium iodide (0.225 g, 1.50 mmol, 3.0 eq.) in DMF (5 mL) as described in general procedure K gave, after work-up and chromatography (Florisil, 20% EtOAc/petrol), the title compound as a red solid (0.078 g, 59%). See page 198 for data.

Synthesis of 3-(Oxiran-2-ylmethyl)quinazolin-4(3H)-one (267)[182]



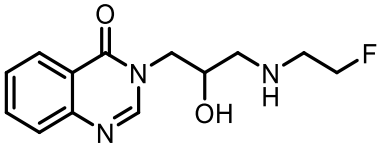
Quinazolin-4(3H)-one (1.461 g, 10 mmol) and potassium carbonate (4.15 g, 30.0 mmol) were suspended in acetone (50 mL) and then 2-(chloromethyl)oxirane (2.352 mL, 30.0 mmol) was added. The reaction mixture was heated at reflux with stirring under a stream of nitrogen for 18 h. The reaction mixture was cooled down and filtered and the solid washed with DCM (3 x 15 mL). The combined extracts were evaporated *in vacuo* and the residue dissolved in DCM (50 mL), washed with water (2 x 25 mL) and then dried with sodium sulfate before filtering and removing the solvent *in vacuo*. The crude product was recrystallized with DCM/hexane to afford the title compound as a white solid (1.25 g, 62%). M.p. 80-82 °C (lit: 82-84 °C).[182] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.06 (s, 1H), 7.83 – 7.73 (m, 2H), 7.54 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.59 (dd, *J* = 14.5, 3.0 Hz, 1H), 3.88 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.39 (ddt, *J* = 6.0, 3.0, 2.5 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.63 (dd, *J* = 4.5, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (-), 148.2 (-), 146.5 (+), 134.5 (+), 127.7 (+), 127.4 (+), 126.7 (+), 121.9 (-), 49.7 (+), 47.7 (-), 45.5 (-). IR (FTIR, cm^{-1}) 3054, 2986, 1665, 1615, 1471, 1372, 954, 860, 772. HRMS calcd for $C_{11}H_{11}N_2O_2$ (MH^+) 203.0821, found 203.0822.

General Procedure L: Synthesis of 3-(3-((Cyclopropylmethyl)amino)-2-hydroxypropyl)quinazolin-4(3H)-one (272)



3-(Oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.051 g, 0.25 mmol, 1.0 eq.) was suspended in water (1 mL) and then cyclopropylmethanamine (0.043 mL, 0.50 mmol, 2.0 eq.) was added. The reaction mixture was stirred at 20 °C for 18 h. Water (20 mL) was added to the reaction mixture and the product extracted with EtOAc (3 x 20 mL). The organic phase was dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The residue was dissolved in DMSO:MeOH (1:1, 1 mL) and purified by Mass Directed Auto Preparative HPLC to afford the title compound as a colourless oil (0.036 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H), 7.77 – 7.70 (m, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.43 (m, 1H), 4.30 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.81 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.87 (dd, *J* = 12.0, 3.5 Hz, 1H), 2.61 (dd, *J* = 12.0, 8.5 Hz, 1H), 2.54 – 2.40 (m, 2H), 0.88 – 0.86 (m, 1H), 0.43 (app q, *J* = 5.0 Hz, 2H), 0.08 (app q, *J* = 5.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 148.2, 147.6, 134.3, 127.5, 127.1, 126.6, 121.9, 67.9, 54.6, 51.9, 50.1, 11.0, 3.4, 3.3. IR (FTIR, cm^{-1}) 3362, 2921, 2853, 1652, 1611, 1475, 1376, 1327, 1106, 773, 697. HRMS calcd for $C_{15}H_{19}N_3O_2$ (MH^+) 274.1550, found 274.1546.

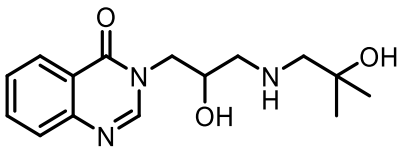
Synthesis of 3-(3-((2-Fluoroethyl)amino)-2-hydroxypropyl)quinazolin-4(3H)-one (273)



Reaction of oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.051 g, 0.25 mmol, 1.0 eq.), 2-fluoroethanamine hydrochloride (100 mg, 1.0 mmol, 2.0 eq.) and triethylamine (0.139 mL, 1.0 mmol, 2.0 eq.) in water (0.5 mL) as described in general procedure L gave, after

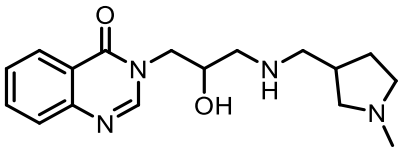
work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a white solid (0.042 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.18 (m, 1H), 8.15 (s, 1H), 7.71 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 2H), 7.65 – 7.60 (m, 1H), 7.45 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.52 (dt, *J* = 47.0, 4.5 Hz, 2H), 4.37 – 4.27 (m, 1H), 4.10 – 4.05 (m, 1H), 3.84 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.98 – 2.88 (m, 3H), 2.65 (dd, *J* = 12.0, 8.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 147.9, 147.6, 134.3, 127.3, 127.2, 126.5, 121.7, 83.2 (d, *J* = 166.7 Hz), 68.0, 52.1, 50.3, 49.4 (d, *J* = 19.2 Hz). IR (FTIR, cm^{-1}) 3346, 2900, 1729, 1612, 1662, 1475, 1375, 1324, 774, 698. HRMS calcd for $C_{13}H_{16}N_3O_2F$ (MH^+) 266.1299, found 266.1298.

Synthesis of 3-(2-Hydroxy-3-((2-hydroxy-2-methylpropyl)amino)propyl) quinazolin-4(3H)-one (274)



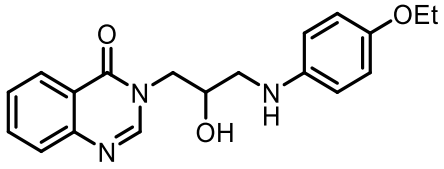
Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.051 g, 0.25 mmol, 1.0 eq.) and 1-amino-2-methylpropan-2-ol (0.048 mL, 0.50 mmol, 2.0 eq.) in water (0.5 mL) as described in general procedure L gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.033 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.5 Hz, 1H), 8.17 (s, 1H), 7.78 – 7.74 (m, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.47 (m, 1H), 4.32 (dd, *J* = 13.5, 3.0 Hz, 1H), 4.10 – 4.06 (m, 1H), 3.88 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.90 (dd, *J* = 12.0, 3.5 Hz, 1H), 2.66 (d, *J* = 12.0 Hz, 1H), 2.63 (dd, *J* = 12.0, 8.5 Hz, 1H), 2.57 (d, *J* = 12.0 Hz, 1H), 1.22 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 148.0, 147.5, 134.3, 127.4, 127.2, 126.6, 121.8, 70.1, 68.4, 60.3, 53.1, 50.4, 27.5, 27.4. IR (FTIR, cm^{-1}) 3343, 2922, 2853, 1660, 1612, 1475, 1377, 1324, 1167, 1110, 773, 699. HRMS calcd for $C_{15}H_{21}N_3O_3$ (MH^+) 292.1656, found 292.1654.

Synthesis of 3-(2-Hydroxy-3-(((1-methylpyrrolidin-3-yl)methyl)amino)propyl) quinazolin-4(3H)-one (275)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.051 g, 0.25 mmol) and (1-methylpyrrolidin-3-yl)methanamine (0.062 mL, 0.500 mmol) in water (0.5 mL) as described in general procedure L gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.020 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.28 (m, 1H), 8.19 (s, 1H), 7.77 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 4.32 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.88 (ddd, *J* = 13.5, 7.0, 2.5 Hz, 1H), 2.87 (dd, *J* = 12.0, 8.5 Hz, 1H), 2.72 – 2.41 (m, 7H), 2.33 (s, 3H), 2.27 – 2.20 (m, 1H), 2.05 – 1.94 (m, 1H), 1.52 – 1.42 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 148.2, 147.6, 134.3, 127.5, 127.1, 126.7, 121.9, 68.0, 67.8, 60.9, 56.0, 54.7, 52.3, 50.0, 42.2, 38.4, 29.5. IR (FTIR, cm^{-1}) 3340, 2920, 1660, 1615, 1475, 1370, 1170, 1110, 770, 699. HRMS calcd for $C_{17}H_{25}N_4O_2$ (MH^+) 317.1978, found 317.1978.

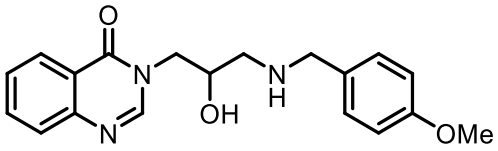
Synthesis of 3-(3-((4-Ethoxyphenyl)amino)-2-hydroxypropyl)quinazolin-4(3H)-one (276)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.051 g, 0.25 mmol) and 4-ethoxyaniline (0.064 mL, 0.50 mmol) in water (0.5 mL) as described in general procedure L gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a white solid (0.017 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.06 (s, 1H), 7.74 – 7.65 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.39 (m, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 4.33 (dd, *J* = 13.5, 3.0 Hz,

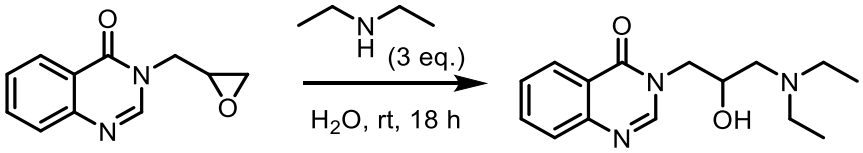
1H), 4.30 – 4.22 (m, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 3.88 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.33 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.15 (dd, *J* = 13.0, 7.0 Hz, 1H), 1.39 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 152.1, 147.7, 147.4, 141.9, 134.4, 127.3, 127.2, 126.5, 121.6, 115.9, 115.0, 68.3, 64.1, 50.7, 48.6, 15.0. IR (FTIR, cm^{-1}) 3282, 2982, 2925, 2865, 1670, 1610, 1514, 1475, 1367, 1236, 1102, 1058, 772, 697. HRMS calcd for $C_{19}H_{21}N_3O_3$ (MH^+) 340.1656, found 340.1649.

Synthesis of 3-(2-Hydroxy-3-((4-methoxybenzyl)amino)propyl)quinazolin-4(3H)-one (277)



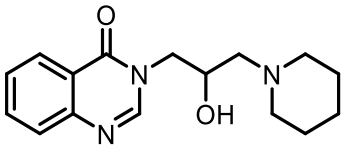
Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.051 g, 0.25 mmol) and (4-methoxyphenyl)methanamine (0.065 mL, 0.50 mmol) in water (0.5 mL) as described in general procedure L gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a white film (0.056 g, 66%). 1H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.29 (m, 1H), 8.18 (s, 1H), 7.81 – 7.71 (m, 2H), 7.52 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.90 – 6.85 (m, 2H), 4.32 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.89 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.82 (s, 3H), 3.80 – 3.71 (m, 2H), 2.89 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.61 (dd, *J* = 12.0, 5.0 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 158.8, 148.2, 147.5, 134.3, 131.9, 129.3, 127.5, 127.2, 126.7, 122.0, 113.9, 68.2, 55.3, 53.1, 51.5, 50.0. IR (FTIR, cm^{-1}) 3260, 2887, 1676, 1608, 1515, 1371, 1253, 1032, 830, 775, 698. HRMS calcd for $C_{19}H_{21}N_3O_3$ (MH^+) 340.1656, found 340.1656.

General Procedure M: Synthesis of 3-[3-(diethylamino)-2-hydroxypropyl] quinazolin-4(3H)-one (278)



3-(Oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.404 g, 2.0 mmol, 1.0 eq.) was dissolved in water (5 mL) and then diethylamine (0.62 mL, 6.0 mmol, 3.0 eq.) was added. The reaction mixture was stirred at rt for 18 h. Water (20 mL) added to the reaction mixture and the product extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% MeOH/DCM) to afford the title compound as a colourless oil (0.394 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.19 (s, 1H), 7.73 – 7.68 (m, 1H), 7.68 – 7.64 (m, 1H), 7.44 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.33 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.69 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.66 – 2.46 (m, 5H), 2.32 (dd, *J* = 12.0, 10.0 Hz, 1H), 0.98 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (-), 148.2 (-), 147.7 (+), 134.1 (+), 127.4 (+), 127.0 (+), 126.6 (+), 121.9 (-), 65.8 (+), 56.4 (-), 50.1 (-), 47.1 (-), 11.8 (+). IR (FTIR, cm^{-1}) 3383, 2969, 2820, 1673, 1612, 1562, 1475, 1377, 1324, 1293, 1058, 774, 698. HRMS calcd for $C_{15}H_{21}N_3O_2$ (MH^+) 276.1707, found 276.1706.

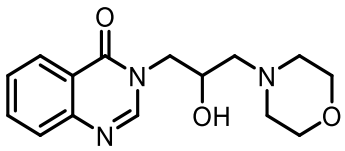
Synthesis of 3-[2-hydroxy-3-(piperidin-1-yl)propyl]quinazolin-4(3H)-one (279)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.404 g, 2.0 mmol, 1.0 eq.) and piperidine (0.60 mL, 6.0 mmol, 3.0 eq.) in water (5 mL) as described in general procedure M gave, after work-up and purification by flash column chromatography (silica gel, 10% MeOH/DCM), the title compound as a white film (0.370 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.19 (m, 1H), 8.17 (s, 1H), 7.72 – 7.66 (m, 1H), 7.66 – 7.62 (m,

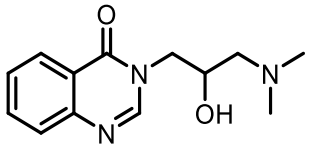
1H), 7.43 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.30 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.69 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.40 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.27 – 2.21 (m, 3H), 1.55 – 1.40 (m, 4H), 1.37 – 1.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (-), 148.1 (-), 147.8 (+), 134.1 (+), 127.4 (+), 127.0 (+), 126.6 (+), 121.9 (-), 65.1 (+), 61.7 (-), 54.7 (-), 50.1 (-), 26.0 (-), 24.1 (-). IR (FTIR, cm^{-1}) 3366, 2930, 2857, 2800, 1667, 1610, 1562, 1474, 1373, 1323, 1293, 1107, 772, 697. HRMS calcd for $C_{16}H_{21}N_3O_2$ (MH^+) 288.1707, found 288.1704.

Synthesis of 3-[2-hydroxy-3-(morpholin-4-yl)propyl]quinazolin-4(3H)-one (280)



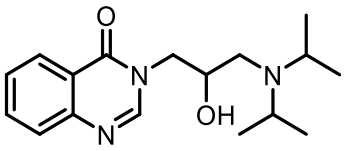
Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.506 g, 2.5 mmol, 1.0 eq.) and morpholine (0.65 mL, 7.5 mmol, 3.0 eq.) in water (5 mL) as described in general procedure M gave, after work-up and purification by flash column chromatography (silica gel, 10% MeOH/DCM), the title compound as a colourless oil (0.468 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.23 (s, 1H), 7.79 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.76 – 7.73 (m, 1H), 7.53 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.36 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.15 – 4.09 (m, 1H), 3.88 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.78 – 3.65 (m, 5H), 2.71 – 2.61 (m, 2H), 2.56 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.49 – 2.40 (m, 2H), 2.34 (dd, *J* = 12.0, 10.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (-), 148.2 (-), 147.7 (+), 134.4 (+), 127.5 (+), 127.2 (+), 127.0 (+), 121.9 (-), 67.0 (-), 65.1 (+), 61.3 (-), 53.6(-), 49.8 (-). IR (FTIR, cm^{-1}) 3390, 2924, 2857, 2813, 1667, 1611, 1562, 1475, 1375, 1114, 867, 774, 732, 697. HRMS calcd for $C_{15}H_{19}N_3O_3$ (MH^+) 290.1499, found 290.1497.

Synthesis of 3-[3-(dimethylamino)-2-hydroxypropyl]quinazolin-4(3H)-one (281)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.404 g, 2.0 mmol, 1.0 eq.) and dimethylamine (0.40 mL, 6.0 mmol, 3.0 eq.) in water (5 mL) as described in general procedure M gave, after work-up and purification by flash column chromatography (silica gel, 10% MeOH/DCM), the title compound as a pale yellow oil (0.417 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.21 (s, 1H), 7.75 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.34 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.77 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.38 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.32 (dd, *J* = 12.0, 10.0 Hz, 1H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (-), 148.2 (-), 147.8 (+), 134.3 (+), 127.5 (+), 127.1 (+), 126.7 (+), 121.9 (-), 66.0 (+), 62.2 (-), 50.0 (-), 45.5 (+). IR (FTIR, cm^{-1}) 3340, 2942, 2827, 2776, 1667, 1610, 1564, 1474, 1373, 1323, 1231, 1106, 1035, 870, 773. HRMS calcd for $C_{13}H_{17}N_3O_2$ (MH^+) 248.1394, found 248.1392.

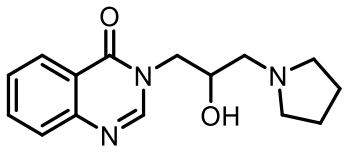
Synthesis of 3-(3-[di(propan-2-yl)amino]-2-hydroxypropyl)quinazolin-4(3H)-one (282)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.404 g, 2.0 mmol, 1.0 eq.) and diisopropylamine (0.85 mL, 6.0 mmol, 3.0 eq.) in water (5 mL) as described in general procedure M gave, after work-up and purification by flash column chromatography (silica gel, 10% MeOH/DCM), the title compound as a pale yellow oil (0.392 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.25 (s, 1H), 7.78 – 7.74 (m, 1H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.41 (dd, *J* = 13.5, 2.5 Hz, 1H), 3.66 (dd, *J* = 13.5, 7.5 Hz, 1H), 3.39 – 3.35 (m, 1H), 3.06 – 3.00 (m, 2H), 2.72 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.28 (dd, *J* = 13.0, 10.0 Hz, 1H), 1.02 (d, *J* = 6.5 Hz, 6H), 1.00 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (-), 148.1 (-), 147.7 (+), 134.2 (+), 127.5 (+), 127.0 (+), 126.6 (+), 121.8 (-), 65.4 (+), 50.3 (-), 48.3 (+), 47.4 (-), 19.4 (+). IR (FTIR, cm^{-1}) 3340, 2965, 2865, 1669, 1609, 1560, 1474, 1365,

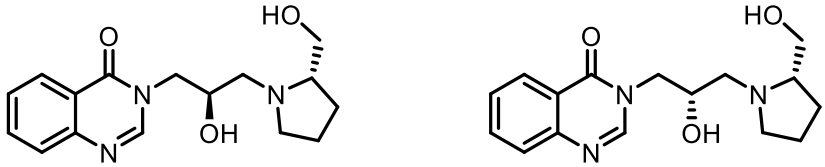
1322, 1180, 1163, 1107, 772, 733, 696. HRMS calcd for $C_{17}H_{25}N_3O_2$ (MH^+) 304.2020, found 304.2023.

Synthesis of 3-[2-hydroxy-3-(pyrrolidin-1-yl)propyl]quinazolin-4(3H)-one (283)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.404 g, 2.0 mmol, 1.0 eq.) and pyrrolidine (0.49 mL, 6.0 mmol, 3.0 eq.) in water (5 mL) as described in general procedure M gave, after work-up and purification by flash column chromatography (silica gel, 10% MeOH/DCM), the title compound as a pale yellow oil (0.431 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.74 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.48 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.35 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.78 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.69 – 2.56 (m, 3H), 2.53 – 2.45 (m, 3H), 1.76 – 1.71 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (-), 148.1 (-), 147.9 (+), 134.3 (+), 127.4 (+), 127.1 (+), 126.6 (+), 121.9 (-), 67.0 (+), 59.0 (-), 54.1 (-), 50.1 (-), 23.6 (-). IR (FTIR, cm^{-1}) 3318, 2957, 2793, 1671, 1611, 1564, 1475, 1374, 1324, 1296, 1169, 1107, 774, 698. HRMS calcd for $C_{15}H_{19}N_3O_2$ (MH^+) 274.1550, found 274.1554.

General Procedure N: Synthesis of 3-((R)-2-Hydroxy-3-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)propyl)quinazolin-4(3H)-one AND 3-((S)-2-Hydroxy-3-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)propyl)quinazolin-4(3H)-one (288/289)



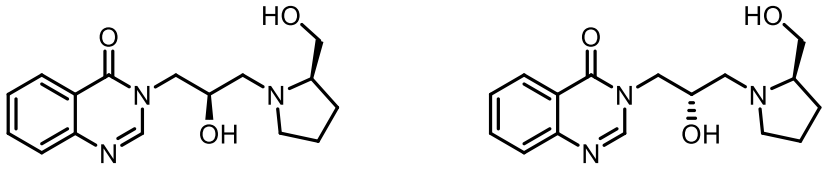
3-(Oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (50.6 mg, 0.25 mmol) was suspended in water (0.5 mL) and then (S)-pyrrolidin-2-ylmethanol (0.049 mL, 0.500 mmol) was added.

The reaction mixture was stirred at 20 °C for 1 hr. The reaction mixture was diluted with water (10 mL) and the product extracted with EtOAc (3 x 10 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The residue was dissolved in 50:50 (MeOH:DMSO, 2 mL) and then purified by Mass Directed Auto Preparative HPLC to afford the two title compounds as colourless oils.

Isomer 1 (0.029 g, 38 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.15 (s, 1H), 7.69 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.41 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.45 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.15 – 4.09 (m, 1H), 3.67 (dd, *J* = 13.5, 8.0 Hz, 1H), 3.58 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.44 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.21 (dt, *J* = 9.0, 5.0, 1H), 2.90 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.75 (td, *J* = 9.0, 5.0 Hz, 1H), 2.61 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.51 – 2.45 (m, 1H), 1.95 – 1.83 (m, 1H), 1.80 – 1.70 (m, 2H), 1.68 – 1.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 147.9, 147.8, 134.3, 127.2, 127.1, 126.5, 121.7, 68.4, 65.9, 64.0, 59.4, 56.4, 51.2, 27.4, 24.0. IR (FTIR, cm^{-1}) 3362, 2948, 2925, 2870, 2820, 1661, 1612, 1560, 1475, 1371, 1324, 1071, 773, 732, 698. HRMS calcd for $C_{16}H_{21}N_3O_3$ (MH^+) 304.1656, found 304.1651. $[\alpha]^{25}_D$ = -128 (c = 0.95, MeOH)

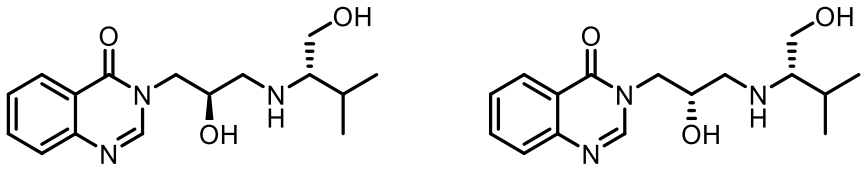
Isomer 2 (0.030 g, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.18 (s, 1H), 7.72 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 – 7.43 (m, 1H), 4.33 (dd, *J* = 13.5, 2.5 Hz, 1H), 4.09 – 4.05 (m, 1H), 3.71 (dd, *J* = 13.5, 7.5 Hz, 1H), 3.57 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.43 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.17 (dt, *J* = 9.0, 5.0 Hz, 1H), 2.77 (dd, *J* = 12.5, 3.0 Hz, 1H), 2.71 (td, *J* = 9.0, 5.0 Hz, 1H), 2.59 (dd, *J* = 12.5, 3.0 Hz, 1H), 2.40 – 2.28 (m, 1H), 1.92 – 1.82 (m, 1H), 1.80 – 1.60 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 148.0, 147.8, 134.3, 127.3, 127.1, 126.6, 121.8, 67.6, 65.5, 63.7, 59.0, 54.7, 50.2, 27.2, 23.7. IR (FTIR, cm^{-1}) 3351, 2952, 2870, 1661, 1562, 1475, 1376, 1327, 1217, 1106, 1027, 867, 746, 700, 666. HRMS calcd for $C_{16}H_{21}N_3O_3$ (MH^+) 304.1656, found 304.1653. $[\alpha]^{25}_D$ = +68 (c = 1.11, MeOH)

Synthesis of 3-((R)-2-Hydroxy-3-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)propyl)quinazolin-4(3H)-one AND 3-((S)-2-Hydroxy-3-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)propyl)quinazolin-4(3H)-one (290/291)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (50.6 mg, 0.25 mmol) and (R)-pyrrolidin-2-ylmethanol (0.049 mL, 0.500 mmol) in water (0.5 mL) as described in general procedure N gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the two title compounds as colourless oils. See page 209 for data.

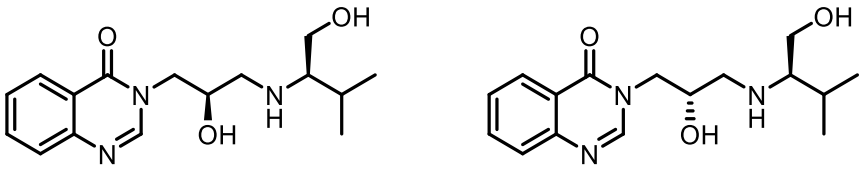
Synthesis of 3-((R)-2-Hydroxy-3-(((S)-1-hydroxy-3-methylbutan-2-yl)amino)propyl)quinazolin-4(3H)-one AND 3-((S)-2-Hydroxy-3-(((S)-1-hydroxy-3-methylbutan-2-yl)amino)propyl)quinazolin-4(3H)-one (292)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.071 g, 0.35 mmol) and (S)-2-amino-3-methylbutan-1-ol (0.108 g, 1.05 mmol) in water (1 mL) as described in general procedure N gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the two title compounds as an inseparable mixture of colourless oils (0.069 g, 64%). (Data reported for 1:1 mixture.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 4H), 7.70 – 7.64 (m, 2H), 7.60 – 7.57 (m, 2H), 7.44 – 7.38 (m, 2H), 4.28 (dd, *J* = 13.5, 2.5 Hz, 2H), 4.13 – 4.07 (m, 2H), 3.84 – 3.76 (m, 4H), 3.65 (ddd, *J* = 11.0, 3.5, 2.0 Hz, 2H), 3.43 (dt, *J* = 11.0, 7.5 Hz, 2H), 2.96 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.87 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.71 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.63 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.47 – 2.40 (m, 2H), 1.82 – 1.76 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 6H), 0.87 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 161.5, 147.8, 134.3, 127.2, 127.1, 126.5, 121.6, 68.3, 68.1, 65.1, 64.9,

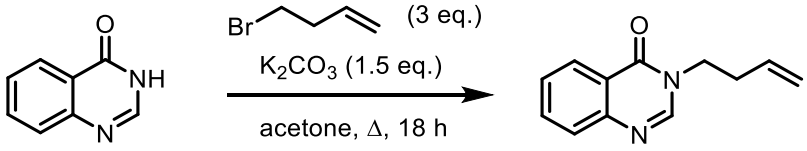
61.1, 60.9, 50.4, 50.3, 28.9, 28.8, 19.4, 19.3, 18.3, 18.2. IR (FTIR, cm^{-1}) 3328, 2963, 1666, 1611, 1475, 1372, 1323, 1217, 1106, 1049, 749, 696, 666. HRMS calcd for $C_{16}H_{23}N_3O_3$ (MH^+) 306.1812, found 306.1810.

Synthesis of 3-((R)-2-Hydroxy-3-(((R)-1-hydroxy-3-methylbutan-2-yl)amino)propyl)quinazolin-4(3H)-one AND 3-((S)-2-Hydroxy-3-(((R)-1-hydroxy-3-methylbutan-2-yl)amino)propyl)quinazolin-4(3H)-one (293)



Reaction of 3-(oxiran-2-ylmethyl)quinazolin-4(3H)-one **267** (0.071 g, 0.35 mmol) and (S)-2-amino-3-methylbutan-1-ol (0.108 g, 1.05 mmol) in water (1 mL) as described in general procedure N gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the two title compounds as an inseparable mixture of colourless oils (0.036 g, 34%). See page 210 for data.

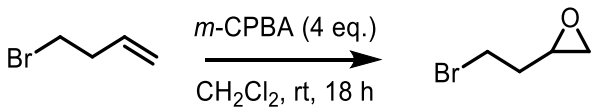
Synthesis of 3-(But-3-en-1-yl)-2,3-dihydroquinazolin-4(1H)-one (296)[152]



Quinazolin-4(3H)-one (0.585 g, 4 mmol) and potassium carbonate (0.829 g, 6 mmol) were suspended in acetone (50 mL) and then 4-bromobut-1-ene (1.21 mL, 12.0 mmol) was added. The reaction mixture was heated at reflux with stirring under a stream of nitrogen for 18 h. The reaction mixture was cooled down and filtered and the solid was washed with DCM (3 x 20 mL). The combined extracts were evaporated *in vacuo* and the residue dissolved in DCM (50 mL), washed with water (2 x 25 mL) and then dried with sodium sulfate before filtering and removing the solvent *in vacuo*. The crude product was recrystallized with DCM/hexane to afford the title compound as a white solid (0.638 g, 80%). M.p 59-61 °C (lit: 58-58.5 °C).[152] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.30 (m,

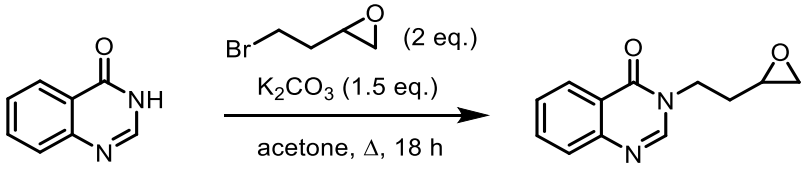
1H), 8.01 (s, 1H), 7.86 – 7.68 (m, 2H), 7.59 – 7.46 (m, 1H), 5.84 (m, 1H), 5.17 – 5.04 (m, 2H), 4.09 (t, J = 7.0 Hz, 2H), 2.66 – 2.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 148.2, 146.6, 134.2, 133.5, 127.5, 127.2, 126.7, 122.2, 118.7, 46.4, 33.4.

Synthesis of 2-(2-Bromoethyl)oxirane (297)[142]



4-Bromobut-1-ene (1.02 mL, 10 mmol) was dissolved in dichloromethane (50 mL) and then *m*-CPBA (6.90 g, 40 mmol) was added portionwise. The reaction mixture was stirred at rt for 18 h. 10% Aqueous sodium thiosulfate solution (100 mL) was added to remove excess *m*-CPBA and then the product extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (5 x 50 mL) and then brine (100 mL). The organic phase was dried with sodium sulfate before filtering and removing the solvent *in vacuo*. The title compound was obtained as a colourless oil (1.5 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (dd, *J* = 7.5, 6.0 Hz, 2H), 3.14 – 3.06 (m, 1H), 2.85 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.60 (dd, *J* = 5.0, 2.5 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.11 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 50.7 (+), 47.1 (-), 35.7 (-), 29.0 (-).

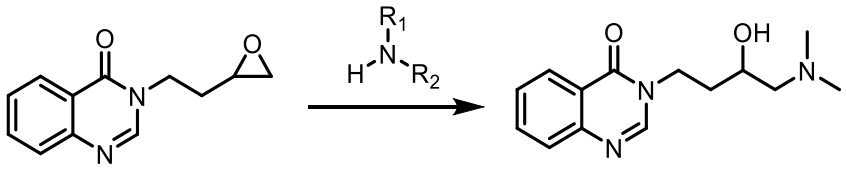
Synthesis of 3-(2-(Oxiran-2-yl)ethyl)quinazolin-4(3H)-one (294)[142]



Quinazolin-4(3H)-one (0.731 g, 5 mmol) and potassium carbonate (1.04 g, 7.5 mmol) were suspended in acetone (25 mL) and then 2-(2-bromoethyl)oxirane **297** (1.51 g, 10.0 mmol) was added. The reaction mixture was heated at reflux with stirring under a stream of nitrogen for 18 h. The reaction mixture was cooled down and filtered and the solid washed with DCM (3 x 15 mL). The combined extracts were evaporated *in vacuo* and

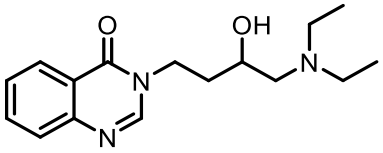
the residue dissolved in DCM (50 mL), washed with water (2 x 25 mL) and then dried with sodium sulfate before filtering and removing the solvent *in vacuo*. The crude product was recrystallized with DCM/hexane to afford the title compound as a white solid (1.01 g, 93%). M.p. 86-88 °C (lit: 88-89 °C).[142] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.28 (m, 1H), 8.09 (s, 1H), 7.85 – 7.68 (m, 2H), 7.61 – 7.48 (m, 1H), 4.32 – 4.12 (m, 2H), 3.03 (m, 1H), 2.82 (dd, J = 5.0, 2.5 Hz, 1H), 2.53 (dd, J = 5.0, 2.5 Hz, 1H), 2.38 – 2.21 (m, 1H), 1.93 – 1.72 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 148.2, 146.4, 134.3, 127.6, 127.4, 126.7, 122.2, 49.5, 46.9, 44.4, 32.0.

General Procedure O: Synthesis of 3-(4-(Dimethylamino)-3-hydroxybutyl)quinazolin-4(3H)-one (298)



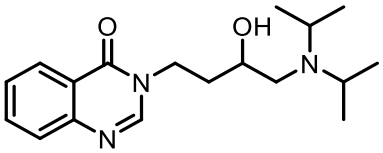
3-(2-(Oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.054 g, 0.25 mmol) was suspended in water (1 mL) and then dimethylamine (0.051 mL, 0.75 mmol) was added. The reaction mixture was stirred at room temp. for 18 h and then the solvent was removed *in vacuo*. The residue was dissolved in 50:50 (MeOH:DMSO, 1 mL) and then purified by Mass Directed Auto Preparative HPLC to afford the title compound as a colourless oil (0.045 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.16 (s, 1H), 7.74 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.24 (ddd, *J* = 13.0, 7.5, 5.0 Hz, 1H), 4.15 (ddd, *J* = 13.0, 7.5, 5.0 Hz, 1H), 3.70 (tt, *J* = 10.0, 3.0 Hz, 1H), 2.52 (dd, *J* = 12.0, 10.0 Hz, 1H), 2.38 (s, 6H), 2.35 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.75 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 148.2, 147.1, 134.2, 127.5, 127.1, 126.5, 122.1, 64.9, 63.6, 45.1, 44.1, 33.7. IR (FTIR, cm^{-1}). 3358, 1668, 1611, 1475, 1376, 1323, 1292, 1167, 1106, 776, 753, 700. HRMS calcd for $C_{14}H_{19}N_3O_2$ (MH^+) 262.1550, found 262.1551.

Synthesis of 3-(4-(Diethylamino)-3-hydroxybutyl)quinazolin-4(3H)-one (299)



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.054 g, 0.25 mmol) and diethylamine (0.078 mL, 0.75 mmol) in water (1 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.051 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.16 (s, 1H), 7.73 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.28 – 4.22 (m, 1H), 4.19 – 4.10 (m, 1H), 3.70 (tt, *J* = 10.0, 3.0 Hz, 1H), 2.72 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.62 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.51 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.44 (dd, *J* = 13.0, 10.0 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.71 – 1.63 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 148.2, 147.2, 134.1, 127.5, 127.1, 126.5, 122.1, 63.5, 59.1, 47.3, 44.2, 33.7, 11.1. IR (FTIR, cm^{-1}). HRMS calcd for $C_{16}H_{23}N_3O_2$ (MH^+) 290.1790, found 290.1791.

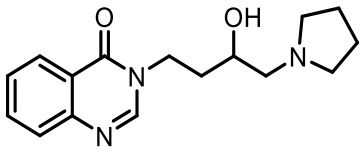
Synthesis of 3-(4-(Diisopropylamino)-3-hydroxybutyl)quinazolin-4(3H)-one (300)



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.054 g, 0.25 mmol) and diisopropylamine (0.106 mL, 0.75 mmol) in water (1 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.037 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.16 (s, 1H), 7.75 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.29 – 4.13 (m, 2H), 4.09 – 4.03 (m, 1H), 3.50 (hept, *J* = 6.5 Hz, 2H), 2.88 (dd, *J* = 13.0, 10.0 Hz, 1H), 2.76 (dd, *J* = 13.0, 2.0 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.83 – 1.71 (m, 1H), 1.33 (d, *J* = 6.5 Hz, 6H), 1.30 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 148.3, 147.1, 134.2, 127.6,

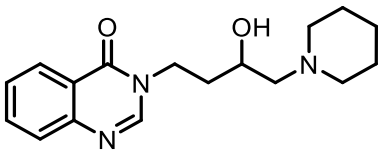
127.1, 126.4, 122.0, 63.9, 54.8, 54.3, 44.3, 33.7, 18.4. IR (FTIR, cm^{-1}) 3351, 2967, 1669, 1609, 1473, 1367, 1348, 1323, 1160, 775, 755, 699. HRMS calcd for $C_{18}H_{27}N_3O_2$ (MH^+) 318.2176, found 318.2176.

Synthesis of 3-(3-Hydroxy-4-(pyrrolidin-1-yl)butyl)quinazolin-4(3H)-one (301)



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.054 g, 0.25 mmol) and pyrrolidine (0.061 mL, 0.75 mmol) in water (1 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.047 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.14 (s, 1H), 7.72 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.46 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.22 (ddd, *J* = 13.0, 7.0, 5.0 Hz, 1H), 4.13 (ddd, *J* = 13.0, 7.0, 5.0 Hz, 1H), 3.80 (tt, *J* = 10.0, 3.0 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.82 – 2.73 (m, 3H), 2.54 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.91 – 1.78 (m, 4H), 1.77 – 1.66 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 148.2, 147.1, 134.1, 127.5, 127.1, 126.4, 122.0, 64.5, 61.9, 54.3, 44.0, 33.8, 23.3. IR (FTIR, cm^{-1}) 3328, 2960, 2804, 1660, 1610, 1475, 1325, 1372, 1325, 1160, 883, 774, 698. HRMS calcd for $C_{16}H_{21}N_3O_2$ (MH^+) 288.1707, found 288.1704.

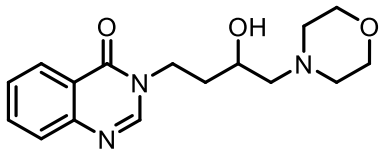
Synthesis of 3-(3-Hydroxy-4-(piperidin-1-yl)butyl)quinazolin-4(3H)-one (302)



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.054 g, 0.25 mmol) and piperidine (0.074 mL, 0.75 mmol) in water (1 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.059 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* =

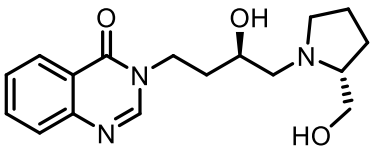
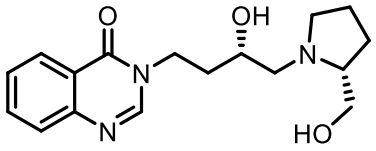
8.0, 1.5 Hz, 1H), 8.14 (s, 1H), 7.71 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.46 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.27 – 4.19 (m, 1H), 4.16 – 4.07 (m, 1H), 3.94 (tt, *J* = 10.0, 3.0 Hz, 1H), 2.93 – 2.79 (m, 4H), 2.78 – 2.70 (m, 1H), 2.59 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.08 – 1.94 (m, 1H), 1.85 – 1.65 (m, 6H), 1.60 – 1.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 148.2, 147.1, 134.2, 127.5, 127.1, 126.4, 122.0, 63.7, 62.5, 54.6, 43.9, 33.7, 23.7, 22.7. IR (FTIR, cm^{-1}) 3335, 2934, 2853, 2796, 1669, 1610, 1474, 1373, 1324, 1159, 1119, 775, 699. HRMS calcd for $C_{17}H_{23}N_3O_2$ (MH^+) 302.1863, found 302.1860.

Synthesis of 3-(3-hydroxy-4-morpholinobutyl)quinazolin-4(3H)-one (303)



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.054 g, 0.25 mmol) and morpholine (0.064 mL, 0.75 mmol) in water (1 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the title compound as a colourless oil (0.054 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.15 (s, 1H), 7.73 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.28 – 4.19 (m, 1H), 4.18 – 4.09 (m, 1H), 3.77 (tt, *J* = 10.0, 3.0 Hz, 1H), 3.74 – 3.66 (m, 4H), 2.77 – 2.65 (m, 2H), 2.59 – 2.49 (m, 2H), 2.49 – 2.39 (m, 2H), 2.07 – 1.94 (m, 1H), 1.76 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 148.1, 147.1, 134.2, 127.4, 127.2, 126.5, 122.0, 66.2, 64.2, 62.9, 53.5, 44.0, 33.7. IR (FTIR, cm^{-1}) 3404, 2925, 2857, 2811, 1667, 1610, 1474, 1373, 1324, 1294, 1115, 865, 699, 775. HRMS calcd for $C_{16}H_{21}N_3O_3$ (MH^+) 304.1686, found 304.1685.

Synthesis of 3-((R)-3-hydroxy-4-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)butyl)quinazolin-4(3H)-one AND 3-((S)-3-hydroxy-4-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)butyl)quinazolin-4(3H)-one (304/305)

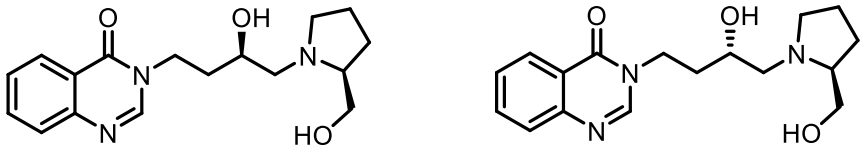



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.070 g, 0.32 mmol) and (R)-pyrrolidin-2-ylmethanol (0.063 mL, 0.65 mmol) in water (0.5 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the two title compounds as colourless oils.

Isomer 1 (0.042 g, 41 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.15 (s, 1H), 7.76 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.20 – 4.11 (m, 1H), 3.81 (tt, *J* = 10.0, 3.0 Hz, 1H), 3.59 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.47 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.20 (dt, *J* = 10.0, 5.0 Hz, 1H), 2.88 (td, *J* = 10.0, 5.0 Hz, 1H), 2.81 – 2.76 (m, 1H), 2.63 – 2.51 (m, 2H), 2.07 – 1.99 (m, 1H), 1.94 – 1.71 (m, 4H), 1.69 – 1.61 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 148.1, 146.9, 134.3, 127.4, 127.3, 126.6, 121.9, 66.5, 65.5, 63.7, 61.9, 56.7, 43.9, 34.4, 27.3, 24.0. IR (FTIR, cm^{-1}) 3381, 2922, 1667, 1612, 1475, 1377, 1323, 1296, 1160, 1068, 777, 699. HRMS calcd for $C_{17}H_{23}N_3O_3$ (MH^+) 318.1812, found 318.1807. $[\alpha]^{25}_D$ = +38 (c = 1.20, MeOH)

Isomer 2 (0.040 g, 39 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.18 (s, 1H), 7.75 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.23 – 4.17 (m, 2H), 3.81 (tt, *J* =10.0, 3.0 Hz, 1H), 3.68 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.56 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.30 (dt, *J* = 10.0, 5.0 Hz, 1H), 2.93 – 2.85 (m, 2H), 2.52 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.39 (dd, *J* = 13.0, 10.0 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.95 – 1.88 (m, 1H), 1.84 – 1.70 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 148.2, 147.1, 134.2, 127.4, 127.2, 126.5, 122.0, 66.7, 65.3, 63.0, 61.9, 54.8, 44.0, 33.7, 27.0, 23.6. IR (FTIR, cm^{-1}) 3351, 2925, 1670, 1612, 1475, 1375, 1261, 1159, 1102, 768, 750, 699. HRMS calcd for $C_{17}H_{23}N_3O_3$ (MH^+) 318.1812, found 318.1810. $[\alpha]^{25}_D$ = -6.3 (c = 0.80, MeOH)

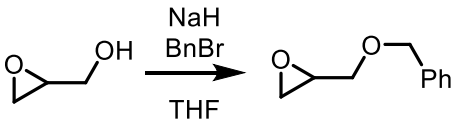
Synthesis of 3-((R)-3-hydroxy-4-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)butyl)quinazolin-4(3H)-one AND 3-((S)-3-hydroxy-4-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)butyl)quinazolin-4(3H)-one (306/307)



Reaction of 3-(2-(oxiran-2-yl)ethyl)quinazolin-4(3H)-one **294** (0.070 g, 0.32 mmol) and (S)-pyrrolidin-2-ylmethanol (0.063 mL, 0.65 mmol) in water (0.5 mL) as described in general procedure O gave, after work-up and purification by Mass Directed Auto Preparative HPLC, the two title compounds as colourless oils.

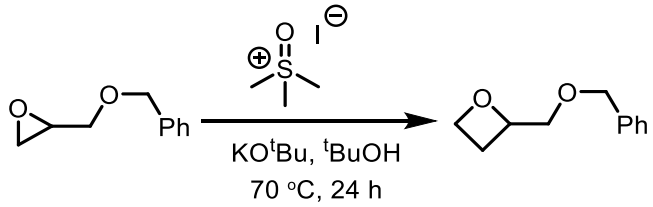
Isomer 1 (0.037 g, 36%). Isomer 2 (0.036 g, 35%). See page 217 for data.

Synthesis of 2-[(benzyloxy)methyl]oxirane (316)[183]



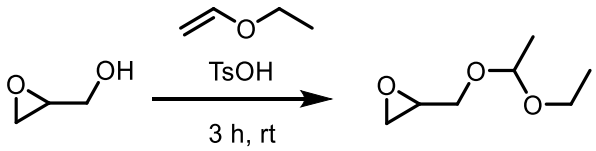
Glycidol (1.11 g, 15 mmol, 1.0 eq.) was added to a suspension of sodium hydride (0.720 g, 30 mmol, 2.0 eq.) in THF (5 mL) dropwise at 0 °C for 15 mins. Benzyl bromide (2.0 mL, 16.5 mmol, 1.1 eq.) was added and the reaction mixture was stirred at rt under a stream of N_2 for 4 h. Water (20 mL) was added to the reaction mixture and the product extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petrol) to afford the title compound as a yellow oil (0.892 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 3H), 7.36 – 7.29 (m, 2H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 3.79 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.47 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.24 – 3.20 (m, 1H), 2.83 (t, *J* = 5.0 Hz, 1H), 2.65 (dd, *J* = 5.0, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9 (-), 128.4 (+), 128.3 (+), 127.8 (+), 73.3 (-), 70.8 (-), 50.9 (+), 44.3 (-).

Synthesis of 2-[(benzyloxy)methyl]oxetane (317)[184]



Potassium *tert*-butoxide (0.260 g, 2.2 mmol, 2.0 eq.) and trimethylsulfoxonium iodide (0.510 g, 2.2 mmol, 2.0 eq.) were suspended in *tert*-butanol (5 mL) and the reaction mixture was stirred at 70 °C for 1 h. 2-[(Benzyloxy)methyl]oxirane **316** (0.190 g, 1.1 mmol, 1.0 eq.) in *tert*-butanol (5 mL) was added dropwise and the reaction mixture was stirred at 70 °C for 24 h. After cooling down to rt, the solvent was removed *in vacuo*. The residue was diluted with water (20 mL) and then the product was extracted with hexane (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a colourless oil (0.095 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 5.04 – 4.97 (m, 1H), 4.73 – 4.66 (m, 2H), 4.64 – 4.57 (m, 2H), 3.68 – 3.65 (m, 2H), 2.75 – 2.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0 (-), 128.2 (+), 127.4 (+), 127.3 (+), 80.7 (+), 73.7 (-), 72.8 (-), 67.8 (-), 23.6 (-).

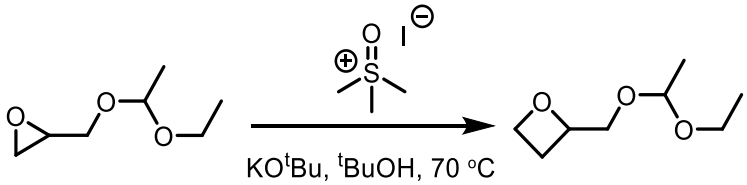
Synthesis of 2-[(1-ethoxyethoxy)methyl]oxirane (320)[185]



Glycidol (9 mL, 135 mmol, 1.0 eq.) was dissolved in ethyl vinyl ether (52 mL, 540 mmol, 4.0 eq.) and then *p*-toluenesulfonic acid (0.257 g, 1.35 mmol, 0.01 eq.) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 3 h. Aqueous saturated $NaHCO_3$ solution (50 mL) was added and then the product was extracted with diethyl ether (2 x 50 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a pale yellow oil (16.0 g, 81%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 – 4.75 (m, 1H), 3.70 – 3.63 (m, 1H),

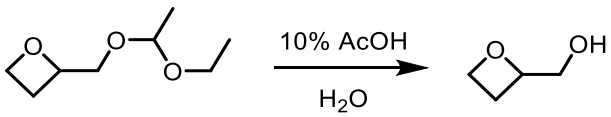
3.58 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.54 – 3.47 (m, 1H), 3.44 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.20 – 3.14 (m, 1H), 2.83 (ddd, *J* = 5.0, 4.0, 1.0 Hz, 1H), 2.65 (ddd, *J* = 14.5, 5.0, 2.5 Hz, 1H), 1.34 (d, *J* = 6.0, Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 99.7 (+), 65.7 (-), 60.9 (-), 50.9 (+), 44.6 (-), 19.7 (+), 15.2 (+).

Synthesis of 2-[(1-ethoxyethoxy)methyl]oxetane (321)[185]



Potassium *tert*-butoxide (26.9 g, 240 mmol, 2.0 eq.) and trimethylsulfoxonium iodide (52.8 g, 240 mmol, 2.0 eq.) were suspended in *tert*-butanol (120 mL) and the reaction mixture was stirred at 70 °C for 1 h. 2-[(1-Ethoxyethoxy)methyl]oxirane **320** (17.5 g, 120 mmol, 1.0 eq.) in *tert*-butanol (120 mL) was added dropwise and the reaction mixture was stirred at 70 °C for 24 h. After cooling down to rt, the solvent was removed *in vacuo*. The residue was diluted with water (20 mL) and then the product was extracted with hexane (3 x 100 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a colourless oil (15.8 g, 82%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 – 4.87 (m, 1H), 4.80 – 4.76 (m, 1H), 4.67 – 4.60 (m, 1H), 4.57 – 4.51 (m, 1H), 3.73 – 3.56 (m, 4H), 2.69 – 2.44 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 99.9 (+), 81.0 (+), 68.9 (-), 68.0 (-), 60.9 (-), 31.2 (+), 23.8 (-), 15.3 (+).

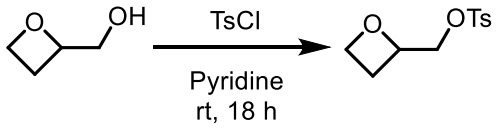
Synthesis of oxetan-2-ylmethanol (319)[185]



2-[(1-Ethoxyethoxy)methyl]oxetane **321** (5.0 g, 31.2 mmol, 1.0 eq.) was dissolved in 10% acetic acid in water (25 mL) and the reaction mixture was stirred at ambient temperature for 2 h. $NaHCO_3$ (3.75 g) was added and the mixture was distilled to remove ethanol.

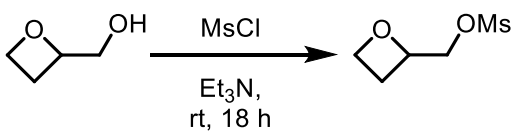
The residual solution was cooled to rt and then solid K_2CO_3 was added until it was saturated. The product was extracted with dichloromethane (3 x 30 mL) and then dried with $MgSO_4$ before filtering. The solvent was removed via short-path distillation to afford the title product as a yellow oil (1.55 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 – 4.90 (m, 1H), 4.70 (ddd, *J* = 8.5, 7.5, 6.0 Hz, 1H), 4.54 (dt, *J* = 8.5, 6.0 Hz, 1H), 3.76 (dd, *J* = 12.5, 4.0 Hz, 1H), 3.64 (dd, *J* = 12.5, 4.0 Hz, 1H), 2.70 – 2.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.7 (+), 69.0 (-), 65.4 (-), 22.6 (-).

Synthesis of oxetan-2-ylmethyl 4-methylbenzenesulfonate (322)[185]



Tosyl chloride (2.6 g, 13.7 mmol, 1.1 eq.) was dissolved in pyridine (3 mL) and the solution cooled to 0 °C. Oxetan-2-ylmethanol **319** (1.1 g, 12.5 mmol, 1.0 eq.) in pyridine (2.5 mL) was added dropwise and the reaction mixture was stirred at ambient temperature for 18 h. Water (20 mL) was added and the product was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 10% H_2SO_4 solution (3 x 30 mL) and then brine (30 mL) and dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a pale yellow oil (1.24 g, 40%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.98 – 4.91 (m, 1H), 4.66 – 4.59 (m, 1H), 4.56 – 4.50 (m, 1H), 4.17 (d, *J* = 4.0 Hz, 2H), 2.78 – 2.68 (m, 1H), 2.64 – 2.54 (m, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (-), 133.0 (-), 130.0 (+), 128.0 (+), 78.7 (+), 72.1 (-), 69.0 (-), 23.5 (-), 21.8 (+).

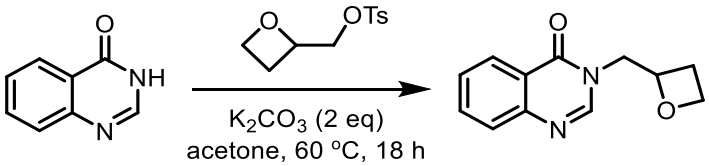
Synthesis of oxetan-2-ylmethyl methanesulfonate (324)[186]



Oxetan-2-ylmethanol **319** (0.500 g, 5.68 mmol, 1.0 eq.) was dissolved in dichloromethane 20 mL) and then triethylamine (2.4 mL, 17.0 mmol, 3.0 eq.) and mesyl

chloride (0.53 mL, 6.82 mmol, 1.2 eq.) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to ambient temperature for 18 h. Water (20 mL) was added and the product was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title product was obtained as a yellow oil (0.801 g, 86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 – 5.02 (m, 1H), 4.73 – 4.68 (m, 1H), 4.64 – 4.57 (m, 1H), 4.38 (d, *J* = 4.0 Hz, 2H), 3.13 (s, 3H), 2.83 – 2.74 (m, 1H), 2.70 – 2.60 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 78.9 (+), 72.0 (-), 68.9 (-), 37.7 (+), 23.2 (-).

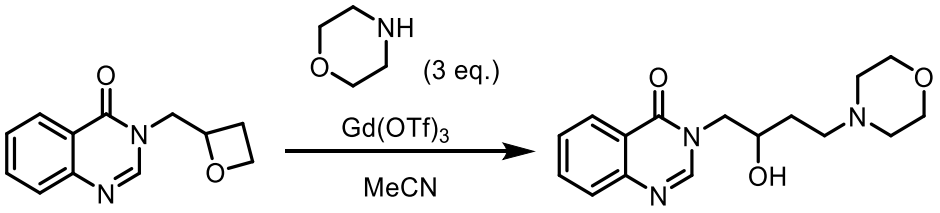
Synthesis of 3-(oxetan-2-ylmethyl)quinazolin-4(3H)-one (308)



Quinazolinone (0.146 g, 1.00 mmol, 1.0 eq) and potassium carbonate (0.207 g, 1.50 mmol, 1.5 eq.) were suspended in acetone (10 mL) and then heated at reflux for 0.5 h. 2-(Tosyloxymethyl)oxetane **322** (0.347 g, 1.40 mmol, 1.4 eq) was added and the reaction mixture was stirred at reflux under a stream of N_2 for 18 h. The reaction mixture was cooled down and then filtered. The solid was washed with dichloromethane (2 x 20 mL) and then added to the initial filtrate. The combined solution was evaporated to dryness and the residue dissolved in dichloromethane (20 mL). The solution was washed with water (3 x 20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, EtOAc) to afford the title compound as a pale yellow oil (0.119 g, 55%). ^{1}H NMR (400 MHz, DMSO) δ 8.36 (s, 1H), 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.85 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.70 (d, *J* = 8.0, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.50 (dd, *J* = 14.0, 7.0 Hz, 1H), 4.42 – 4.29 (m, 2H), 4.23 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.74 – 2.63 (m, 1H), 2.48 – 2.38 (m, 1H).^{13}C NMR (101 MHz, DMSO) δ 160.8 (-),

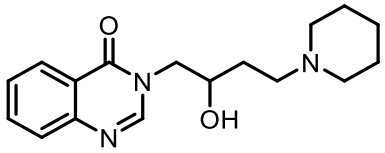
148.9 (+), 148.4 (-), 134.9 (+), 127.7 (+), 127.5 (+), 126.6 (+), 121.9 (-), 79.1 (+), 68.2 (-), 50.5 (-), 24.6 (-). IR (FTIR, cm^{-1}) 2957, 2859, 1720, 1612, 1475, 1354, 1175, 946, 777. HRMS calcd for $C_{12}H_{12}N_2O_2$ (MH^+) 217.0972, found 217.0968.

General Procedure P: Synthesis of 3-[2-hydroxy-4-(morpholin-4-yl)butyl] quinazolin-4(3H)-one (325)



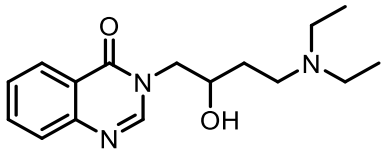
3-(Oxetan-2-ylmethyl)quinazolin-4(3H)-one **308** (0.044 g, 0.20 mmol, 1.0 eq) and gadolinium triflate (0.123 g, 0.20 mmol, 1.0 eq) were dissolved in acetonitrile (2 mL) and then morpholine (0.05 mL, 0.60 mmol, 3 eq.) was added. The reaction mixture was heated at reflux under a stream of N_2 for 24 h. The reaction mixture was added to water (10 mL) and the product extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% methanol/dichloromethane) to afford the title compound as a pale yellow oil (0.034 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.76 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.30 (dd, *J* = 13.5, 3.0 Hz, 1H), 4.24 – 4.16 (m, 1H), 3.79 (dd, *J* = 13.5, 7.5 Hz, 1H), 3.74 – 3.64 (m, 4H), 2.74 – 2.60 (m, 4H), 2.45 – 2.35 (m, 2H), 1.78 – 1.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (-), 148.2 (-), 147.7 (+), 134.2 (+), 127.7 (+), 127.5 (+), 126.7 (+), 122.0 (-), 71.7 (+), 66.8 (-), 57.9 (-), 53.6 (-), 51.9 (-), 28.4 (-). IR (FTIR, cm^{-1}) 2957, 2859, 1666, 1613, 1475, 1380, 1115, 914, 776. HRMS calcd for $C_{16}H_{22}N_3O_3$ (MH^+) 304.1661, found 304.1671.

Synthesis of 3-[2-hydroxy-4-(piperidin-1-yl)butyl]quinazolin-4(3H)-one (326)



Reaction of 3-(oxetan-2-ylmethyl)quinazolin-4(3H)-one **308** (0.108 g, 0.50 mmol, 1.0 eq), gadolinium triflate (0.302 g, 0.50 mmol, 1.0 eq) and piperidine (0.15 mL, 1.5 mmol, 3 eq.) in acetonitrile (2 mL) as described in General Procedure P gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.086 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.19 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.69 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.43 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.23 (dd, *J* = 13.0, 3.0 Hz, 1H), 4.20 – 4.15 (m, 1H), 3.86 (dd, *J* = 13.0, 7.5 Hz, 1H), 3.21 – 3.16 (m, 1H), 3.08 – 2.91 (m, 3H), 2.80 – 2.70 (m, 2H), 1.89 – 1.63 (m, 8H). ^{13}C NMR (101 MHz, DMSO) δ 161.0 (-), 149.1 (+), 148.5 (-), 134.8 (+), 127.6 (+), 127.4 (+), 126.5 (+), 122.1 (-), 119.5 (-), 66.1 (+), 54.0 (-), 52.7 (-), 52.2 (-), 29.0 (-), 23.1 (-), 21.8 (-). IR (FTIR, cm^{-1}) 3442, 2956, 1669, 1612, 1475, 1283, 1244, 1224, 1153, 1029, 778, 638. HRMS calcd for $C_{17}H_{23}N_3O_2$ (MH^+) 302.1863, found 302.1864.

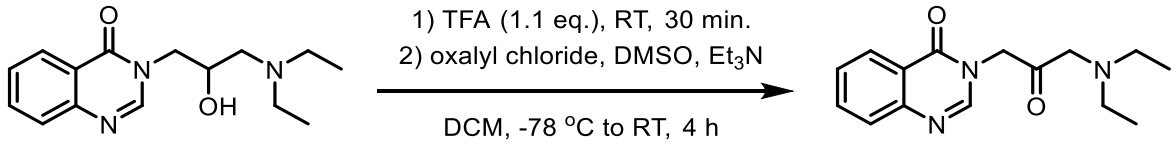
Synthesis of 3-[4-(diethylamino)-2-hydroxybutyl]quinazolin-4(3H)-one (327)



Reaction of 3-(oxetan-2-ylmethyl)quinazolin-4(3H)-one **308** (0.108 g, 0.50 mmol, 1.0 eq), gadolinium triflate (0.302 g, 0.50 mmol, 1.0 eq) and diethylamine (0.16 mL, 1.5 mmol, 3 eq.) in acetonitrile (2 mL) as described in General Procedure P gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a brown oil (0.074 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.22 (s, 1H), 7.75 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.27 (dd, *J* = 13.5, 3.0 Hz, 1H), 4.22 (ddd, *J* = 10.5, 7.0,

3.0 Hz, 1H), 3.90 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.97 – 2.89 (m, 3H), 2.79 – 2.72 (m, 2H), 1.84 – 1.77 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (-), 148.3 (-), 147.7 (+), 134.2 (+), 127.5 (+), 127.1 (+), 126.6 (+), 121.9 (-), 70.1 (+), 52.0 (-), 51.6 (-), 47.1 (-), 29.0 (-), 10.2 (+). IR (FTIR, cm^{-1}) 3411, 2922, 1661, 1613, 1476, 1243, 1225, 1163, 1029, 775, 698, 637. HRMS calcd for $C_{16}H_{23}N_3O_2$ (MH^+) 290.1863, found 290.1863.

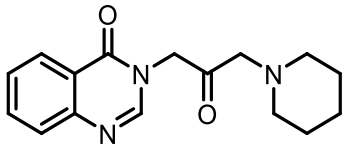
General Procedure Q: Synthesis of 3-[3-(diethylamino)-2-oxopropyl]quinazolin-4(3H)-one (328)



Trifluoroacetic acid (0.15 mL, 1.98 mmol, 1.1 eq) was added to a solution of 3-[3-(diethylamino)-2-hydroxypropyl]quinazolin-4(3H)-one **278** (0.495 g, 1.80 mmol, 1.0 eq) in dichloromethane (5 mL) and then stirred for 30 min. Oxalyl chloride (0.19 mL, 2.16 mmol, 1.2 eq) was dissolved in dichloromethane (5 mL) and then dimethyl sulfoxide (0.32 mL, 4.50 mmol, 2.5 eq) in dichloromethane (8 mL) was added at -78 °C. The solution was stirred for 2 mins after which, the amino alcohol/TFA solution was added. The reaction mixture was stirred at -78 °C under a stream of N_2 for 1 h. Triethylamine (1.1 mL, 7.56 mmol, 4.2 eq) was added and the reaction mixture was allowed to warm to rt and stirred for 4 h. Aqueous saturated $NaHCO_3$ solution (20 mL) was added to the reaction mixture and the product extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% methanol/dichloromethane) to afford the title compound as a yellow oil (0.383 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.91 (s, 1H), 7.79 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.99 (s, 2H), 3.39 (s, 2H), 2.65 (q, *J* =

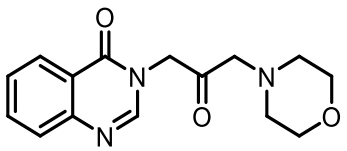
7.0 Hz, 4H), 1.12 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8 (-), 161.1 (-), 148.3 (-), 146.6 (+), 134.5 (+), 127.6 (+), 127.4 (+), 126.7 (+), 121.9 (-), 62.5 (-), 53.3 (-), 48.6 (-), 12.1 (+). IR (FTIR, cm^{-1}) 2924, 2853, 1735, 1661, 1610, 1566, 1474, 1371, 1324, 1295, 772, 753, 664. HRMS calcd for $C_{15}H_{19}N_3O_2$ (MH^+) 274.1550, found 274.1550.

Synthesis of 3-[2-oxo-3-(piperidin-1-yl)propyl]quinazolin-4(3H)-one (329)



Reaction of 3-[2-hydroxy-3-(piperidin-1-yl)propyl]quinazolin-4(3H)-one **279** (0.517 g, 1.80 mmol, 1.0 eq), trifluoroacetic acid (0.15 mL, 1.98 mmol, 1.1 eq), oxalyl chloride (0.19 mL, 2.16 mmol, 1.2 eq), dimethyl sulfoxide (0.32 mL, 4.50 mmol, 2.5 eq) and triethylamine (1.1 mL, 7.56 mmol, 4.2 eq) in dichloromethane (18 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a yellow-orange oil (0.479 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.5, Hz, 1H), 7.91 (s, 1H), 7.82 – 7.73 (m, 2H), 7.53 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H), 4.97 (s, 2H), 3.29 (s, 2H), 2.56 – 2.45 (m, 4H), 1.66 (m, 4H), 1.54 – 1.41 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8 (-), 161.1 (-), 148.3 (-), 146.6 (+), 134.5 (+), 127.6 (+), 127.4 (+), 126.7 (+), 121.9 (-), 67.5 (-), 55.3 (-), 53.3 (-), 25.9 (-), 23.7 (-). IR (FTIR, cm^{-1}) 2933, 1735, 1675, 1612, 1475, 1364, 1324, 776. HRMS calcd for $C_{16}H_{19}N_3O_2$ (MH^+) 286.1550, found 286.1549.

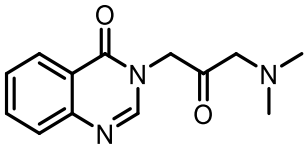
Synthesis of 3-[3-(morpholin-4-yl)-2-oxopropyl]quinazolin-4(3H)-one (330)



Reaction of 3-[2-hydroxy-3-(morpholin-4-yl)propyl]quinazolin-4(3H)-one **280** (0.376 g, 1.30 mmol, 1.0 eq), trifluoroacetic acid (0.11 mL, 1.43 mmol, 1.1 eq), oxalyl chloride (0.13

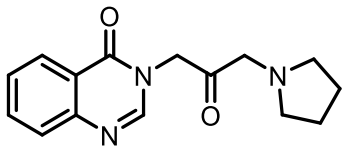
mL, 1.56 mmol, 1.2 eq), dimethyl sulfoxide (0.23 mL, 3.25 mmol, 2.5 eq) and triethylamine (0.76 mL, 5.46 mmol, 4.2 eq) in dichloromethane (18 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a yellow oil (0.310 g, 84%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.92 (s, 1H), 7.80 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.94 (s, 2H), 3.81 – 3.77 (m, 4H), 3.37 (s, 2H), 2.62 – 2.59 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (-), 161.0 (-), 148.2 (-), 146.4 (+), 134.6 (+), 127.7 (+), 127.5 (+), 126.7 (+), 121.8 (-), 66.8 (-), 61.3 (-), 53.6 (-), 49.8 (-). IR (FTIR, cm^{-1}) 2923, 2852, 1735, 1672, 1612, 1564, 1474, 1363, 1324, 1296, 1115, 776, 698. HRMS calcd for $C_{15}H_{17}N_3O_3$ (MH^+) 288.1343, found 288.1338.

Synthesis of 3-[3-(dimethylamino)-2-oxopropyl]quinazolin-4(3H)-one (331)



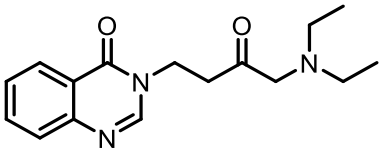
Reaction of 3-[3-(dimethylamino)-2-hydroxypropyl]quinazolin-4(3H)-one **281** (0.300 g, 1.20 mmol, 1.0 eq), trifluoroacetic acid (0.10 mL, 1.32 mmol, 1.1 eq), oxalyl chloride (0.12 mL, 1.44 mmol, 1.2 eq), dimethyl sulfoxide (0.21 mL, 3.00 mmol, 2.5 eq) and triethylamine (0.70 mL, 5.04 mmol, 4.2 eq) in dichloromethane (18 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.129 g, 44%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.92 (s, 1H), 7.76 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.93 (s, 2H), 3.51 (s, 2H), 2.65 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0 (-), 161.0 (-), 148.2 (-), 146.4 (+), 134.6 (+), 127.7 (+), 127.5 (+), 126.7 (+), 121.8 (-), 61.3 (-), 53.6 (-), 44.8 (+). IR (FTIR, cm^{-1}) 2979, 1737, 1671, 1610, 1562, 1473, 1369, 1324, 1295, 1169, 879, 775, 699. HRMS calcd for $C_{13}H_{15}N_3O_2$ (MH^+) 246.1237, found 246.1238.

Synthesis of 3-[2-oxo-3-(pyrrolidin-1-yl)propyl]quinazolin-4(3H)-one (333)



Reaction of 3-[2-hydroxy-3-(pyrrolidin-1-yl)propyl]quinazolin-4(3H)-one **283** (0.328 g, 1.20 mmol, 1.0 eq), trifluoroacetic acid (0.10 mL, 1.32 mmol, 1.1 eq), oxalyl chloride (0.12 mL, 1.44 mmol, 1.2 eq), dimethyl sulfoxide (0.21 mL, 3.00 mmol, 2.5 eq) and triethylamine (0.70 mL, 5.04 mmol, 4.2 eq) in dichloromethane (18 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.112 g, 34%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.94 (s, 1H), 7.80 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.94 (s, 2H), 3.45 (s, 2H), 3.17 – 3.11 (m, 4H), 1.37 – 1.33 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4 (-), 162.8 (-), 148.8 (-), 143.9 (+), 134.8 (+), 127.6 (+), 127.3 (+), 126.4 (+), 122.6 (-), 63.1 (-), 53.1 (-), 45.7 (-), 24.8 (-). IR (FTIR, cm^{-1}) 2994, 1744, 1670, 1612, 1475, 1201, 1180, 1134, 906, 724, 699. HRMS calcd for $C_{15}H_{17}N_3O_2$ (MH^+) 272.1394, found 272.1396.

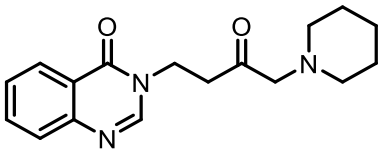
Synthesis of 3-(5-ethyl-3-oxoheptyl)quinazolin-4(3H)-one (334)



Reaction of 3-(4-(diethylamino)-3-hydroxybutyl)quinazolin-4(3H)-one **299** (0.181 g, 0.63 mmol, 1.0 eq), trifluoroacetic acid (0.05 mL, 0.69 mmol, 1.1 eq), oxalyl chloride (0.06 mL, 0.76 mmol, 1.2 eq), dimethyl sulfoxide (0.11 mL, 1.58 mmol, 2.5 eq) and triethylamine (0.37 mL, 2.65 mmol, 4.2 eq) in dichloromethane (12 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.118 g, 65%) ^{1}H NMR (400

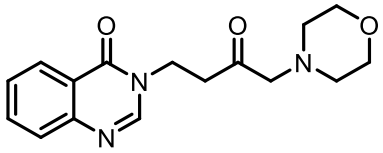
MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.24 (s, 1H), 7.76 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.25 (t, *J* = 6.0 Hz, 2H), 3.18 (s, 2H), 3.14 (t, *J* = 6.0 Hz, 2H), 2.50 (q, *J* = 7.0 Hz, 4H), 0.97 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2 (-), 161.3 (-), 148.1 (-), 147.5 (+), 134.2 (+), 127.4 (+), 127.2 (+),126.5 (+), 122.0 (-), 63.6 (-), 48.2 (-), 42.3 (-), 38.4 (-), 11.5 (+). IR (FTIR, cm^{-1}) 2987, 2933, 1722, 1664, 1609, 1563, 1473, 1373, 1323, 1157, 773, 732, 697. HRMS calcd for $C_{16}H_{21}N_3O_2$ (MH^+) 288.1707, found 288.1709.

Synthesis of 3-[3-oxo-4-(piperidin-1-yl)butyl]quinazolin-4(3H)-one (335)



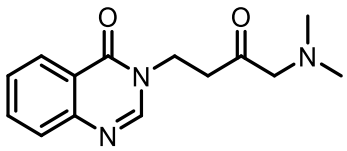
Reaction of 3-(3-hydroxy-4-(piperidin-1-yl)butyl)quinazolin-4(3H)-one **302** (0.207 g, 0.69 mmol, 1.0 eq), trifluoroacetic acid (0.06 mL, 0.76 mmol, 1.1 eq), oxalyl chloride (0.07 mL, 0.83 mmol, 1.2 eq), dimethyl sulfoxide (0.12 mL, 1.73 mmol, 2.5 eq) and triethylamine (0.40 mL, 2.90 mmol, 4.2 eq) in dichloromethane (12 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.128 g, 62%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.24 (s, 1H), 7.76 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.25 (t, *J* = 6.0 Hz, 2H), 3.13 – 3.09 (m, 4H), 2.37 – 2.30 (m, 4H), 1.58 – 1.52 (m, 4H), 1.42 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (-), 161.3 (-), 148.2 (-), 147.5 (+), 134.2 (+), 127.5 (+), 127.2 (+), 126.5 (+), 122.0 (-), 68.6 (-), 54.9 (-), 42.3 (-), 38.5 (-), 25.7 (-), 23.7 (-). IR (FTIR, cm^{-1}) 2964, 1705, 1662, 1612, 1590, 1472, 1383, 1201, 1182, 1133, 721, 699. HRMS calcd for $C_{16}H_{21}N_3O_2$ (MH^+) 288.1707, found 288.1709.

Synthesis of 3-[4-(morpholin-4-yl)-3-oxobutyl]quinazolin-4(3H)-one (336)



Reaction of 3-(3-hydroxy-4-morpholinobutyl)quinazolin-4(3H)-one **303** (0.250 g, 0.82 mmol, 1.0 eq), trifluoroacetic acid (0.07 mL, 0.90 mmol, 1.1 eq), oxalyl chloride (0.08 mL, 0.98 mmol, 1.2 eq), dimethyl sulfoxide (0.15 mL, 2.05 mmol, 2.5 eq) and triethylamine (0.48 mL, 3.44 mmol, 4.2 eq) in dichloromethane (12 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.160 g, 65%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.19 (s, 1H), 7.72 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.46 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.65 – 3.62 (m, 4H), 3.12 (s, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 2.42 – 2.37 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4 (-), 161.2 (-), 148.1 (-), 147.4 (+), 134.3 (+), 127.5 (+), 127.2 (+), 126.3 (+), 121.9 (-), 67.8 (-), 66.6 (-), 53.7 (-), 42.3 (-), 38.5 (-). IR (FTIR, cm^{-1}) 2972, 2861, 2811, 1719, 1669, 1610, 1562, 1473, 1378, 1265, 1115, 776, 731, 699. HRMS calcd for $C_{16}H_{19}N_3O_3$ (MH^+) 302.1499, found 302.1497.

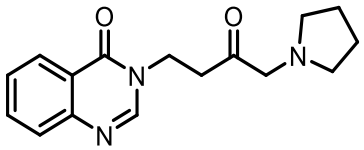
Synthesis of 3-[4-(dimethylamino)-3-oxobutyl]quinazolin-4(3H)-one (337)



Reaction of 3-(4-(dimethylamino)-3-hydroxybutyl)quinazolin-4(3H)-one **298** (0.138 g, 0.52 mmol, 1.0 eq), trifluoroacetic acid (0.04 mL, 0.57 mmol, 1.1 eq), oxalyl chloride (0.05 mL, 0.62 mmol, 1.2 eq), dimethyl sulfoxide (0.09 mL, 1.30 mmol, 2.5 eq) and triethylamine (0.30 mL, 2.18 mmol, 4.2 eq) in dichloromethane (12 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.044 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.76 (ddd, *J* = 8.0, 7.0, 1.5

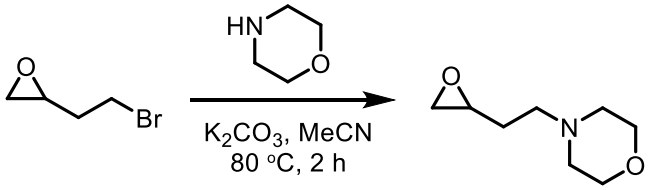
Hz, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.25 (t, *J* = 6.0 Hz, 2H), 3.16 (s, 2H), 3.08 (t, *J* = 6.0 Hz, 2H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6 (-), 161.3 (-), 148.1 (-), 147.4 (+), 134.3 (+), 127.5 (+), 127.2 (+), 126.5 (+), 121.9 (-), 68.6 (-), 43.4 (-), 38.5 (-), 8.5 (+). IR (FTIR, cm^{-1}) 2993, 2690, 1719, 1669, 1612, 1565, 1383, 1200, 1178, 1128, 799, 776, 720, 699. HRMS calcd for $C_{14}H_{17}N_3O_2$ (MH^+) 260.1394, found 260.1391.

Synthesis of 3-[3-oxo-4-(pyrrolidin-1-yl)butyl]quinazolin-4(3H)-one (339)



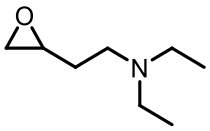
Reaction of 3-(3-hydroxy-4-(pyrrolidin-1-yl)butyl)quinazolin-4(3H)-one **301** (0.156 g, 0.54 mmol, 1.0 eq), trifluoroacetic acid (0.05 mL, 0.59 mmol, 1.1 eq), oxalyl chloride (0.06 mL, 0.65 mmol, 1.2 eq), dimethyl sulfoxide (0.10 mL, 1.35 mmol, 2.5 eq) and triethylamine (0.31 mL, 2.27 mmol, 4.2 eq) in dichloromethane (12 mL) for 4 h as described in General Procedure Q gave, after work-up and chromatography (silica gel, 10% MeOH, dichloromethane), the title compound as a pale yellow oil (0.112 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.25 (s, 1H), 7.77 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 2H), 3.37 (s, 2H), 3.10 (t, *J* = 6.0 Hz, 2H), 2.63 – 2.53 (m, 4H), 1.85 – 1.74 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (-), 161.3 (-), 148.2 (-), 147.4 (+), 134.3 (+), 127.6 (+), 127.2 (+), 126.4 (+), 122.0 (-), 65.3 (-), 54.3 (-), 42.3 (-), 38.5 (-), 23.7 (-). IR (FTIR, cm^{-1}) 2954, 2865, 1719, 1667, 1610, 1474, 1372, 1265, 775, 731, 698. HRMS calcd for $C_{16}H_{19}N_3O_2$ (MH^+) 286.1550, found 286.1550.

General Procedure R: Synthesis of 4-[2-(oxiran-2-yl)ethyl]morpholine (342)[187]



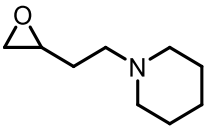
Potassium carbonate (0.341 g, 2.47 mmol, 1.3 eq.) was added to a solution of 2-(4-bromoethyl)oxirane **297** (0.287 g, 1.90 mmol, 1 eq.) in acetonitrile (10 mL). Morpholine (0.16 mL, 1.90 mmol, 1 eq.) was added and the reaction mixture was stirred at 80 °C under a stream of N_2 for 2 h. Water (20 mL) was added and then the product was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*, giving the title compound as a pale yellow oil (0.212 g, 71%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 – 3.66 (m, 4H), 3.02 – 2.93 (m, 1H), 2.78 (dd, J = 4.5, 4.5 Hz, 1H), 2.56 – 2.44 (m, 7H), 1.86 – 1.75 (m, 1H), 1.62- 1.70 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ, 66.9 (-), 55.4 (-), 53.7 (-), 50.8 (+), 47.1 (-), 29.8 (-).

Synthesis of *N,N*-diethyl-2-(oxiran-2-yl)ethanamine (344)



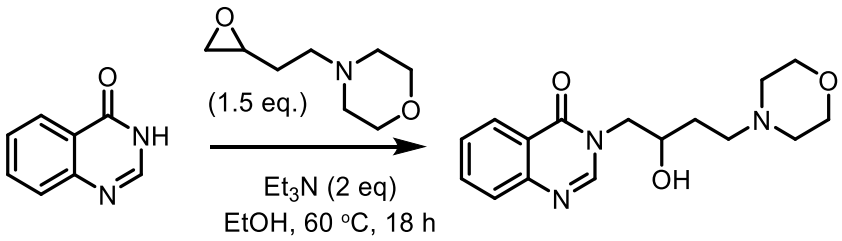
Reaction of 2-(4-bromoethyl)oxirane **297** (0.453 g, 3.00 mmol, 1 eq.), potassium carbonate (0.539 g, 3.90 mmol, 1.3 eq.) and diethylamine (0.26 mL, 3.00 mmol, 1 eq.) in acetonitrile (20 mL) as described in General Procedure R gave, after work-up, the title compound as a pale yellow oil (0.258 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 – 2.96 (m, 1H), 2.80 – 2.77 (m, 1H), 2.65 – 2.59 (m, 3H), 2.55 (q, *J* = 7.0 Hz, 4H), 1.81 – 1.70 (m, 1H), 1.70 – 1.59 (m, 1H), 1.05 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.2 (+), 49.4 (-), 47.2 (-), 46.9 (-), 30.4 (-), 11.8 (+). IR (FTIR, cm^{-1}) 2925, 1720, 1575, 1467, 1428, 1281, 1255, 1128, 1085, 1073. HRMS calcd for $C_8H_{17}NO$ (MH^+) 144.1383, found 144.1382.

Synthesis of 1-[2-(oxiran-2-yl)ethyl]piperidine (343)



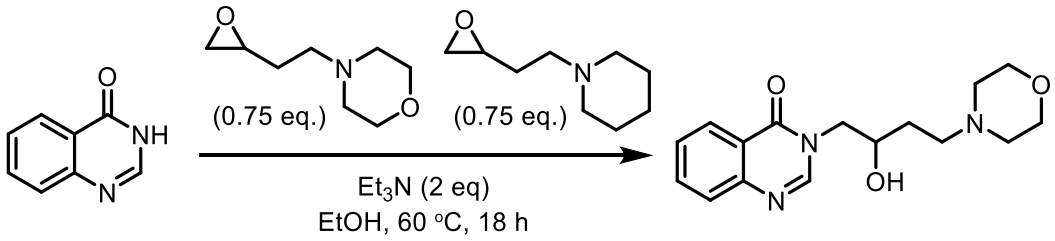
Reaction of 2-(4-bromoethyl)oxirane **297** (0.453 g, 3.00 mmol, 1 eq.), potassium carbonate (0.539 g, 3.90 mmol, 1.3 eq.) and piperidine (0.30 mL, 3.00 mmol, 1 eq.) in acetonitrile (20 mL) as described in General Procedure R gave, after work-up, the title compound as a pale yellow oil (0.316 g, 68%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 – 2.95 (m, 1H), 2.80 – 2.76 (m, 1H), 2.53 – 2.47 (m, 3H), 2.45 – 2.35 (m, 4H), 1.84 – 1.67 (m, 2H), 1.64 – 1.54 (m, 4H), 1.51 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.7 (-), 54.6 (-), 51.1 (+), 47.1 (-), 30.2 (-), 25.8 (-), 24.4 (-). IR (FTIR, cm^{-1}) 2930, 2853, 2807, 1647, 1443, 1376, 1351, 1273, 1118, 1038, 863. HRMS calcd for $C_9H_{17}NO$ (MH^+) 157.1415, found 157.1416.

Synthesis of 3-[2-hydroxy-4-(morpholin-4-yl)butyl]quinazolin-4(3H)-one (325)



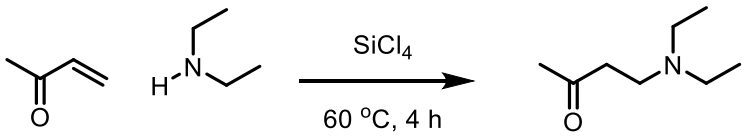
Quinazolinone (0.073 g, 0.50 mmol, 1 eq.) was dissolved in EtOH (3 mL) and then 4'-(4-(oxiran-2-yl)ethyl)morpholine **342** (0.095 g, 0.6 mmol, 1.2 eq.) in EtOH (2 mL) was added. Triethylamine (0.14 mL, 1 mmol, 2 eq.) was added and the reaction mixture was heated at 60 °C under a stream of N_2 for 18 h. The reaction mixture was cooled down to room temperature and then the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5% methanol/dichloromethane) to afford the title compound as a pale yellow oil (0.130 g, 86%). See page 224 for data.

Synthesis of 3-[2-hydroxy-4-(morpholin-4-yl)butyl]quinazolin-4(3H)-one (325)



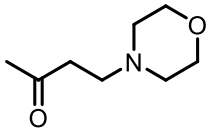
Quinazolinone (0.078 g, 0.53 mmol, 1 eq.) was dissolved in EtOH (3 mL) and then a mixture of 4'-(4-(oxiran-2-yl)ethyl)morpholine **342** (0.063 g, 0.4 mmol, 0.75 eq.) and 4'-(4-(oxiran-2-yl)ethyl)piperidine **343** (0.062 g, 0.4 mmol, 0.75 eq.) in EtOH (2 mL) was added. Triethylamine (0.15 mL, 1.07 mmol, 2 eq.) was added and the reaction mixture was heated at 60 °C under a stream of N_2 for 18 h. The reaction mixture was cooled down to room temperature and then the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5% methanol/dichloromethane) to afford the title compound as a pale yellow oil (0.036 g, 23%). See page 224 for data.

General Procedure S: Synthesis of 4-(diethylamino)butan-2-one (352)[162]



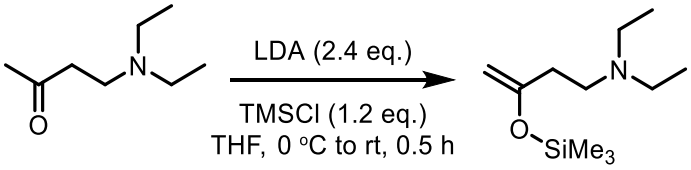
Silicon tetrachloride (0.12 mL, 1.0 mmol, 0.02 eq.) was added to a mixture of methyl vinyl ketone (4.2 mL, 50 mmol, 1.0 eq.) and diethylamine (5.4 mL, 52 mmol, 1.04 eq.) at 0 °C. The reaction mixture was stirred at 60 °C under a stream of N_2 for 4 h. Water was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ before filtering and removing the solvent *in vacuo.* The title compound was obtained as a dark red oil (5.2 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.45 (q, *J* = 7.0 Hz, 4H), 2.11 (s, 3H), 0.96 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5 (-), 47.3 (-), 46.8 (-), 41.4 (-), 30.2 (+), 11.6 (+).

Synthesis of 4-(morpholin-4-yl)butan-2-one (353)[162]



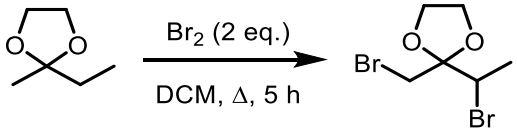
Reaction of silicon tetrachloride (0.12 mL, 1.0 mmol, 0.02 eq.), methyl vinyl ketone (4.2 mL, 50 mmol, 1.0 eq.) and morpholine (4.5 mL, 52 mmol, 1.04 eq.) as described in General Procedure S gave, after work-up, the title compound as a yellow-orange oil (5.0 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 – 3.57 (m, 4H), 2.57 – 2.55 (m, 4H), 2.40 – 2.33 (m, 4H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (-), 66.9 (-), 53.5 (-), 53.1 (-), 40.9 (-), 30.1 (+).

Synthesis of *N,N*-diethyl-3-[(trimethylsilyl)oxy]- 3-buten-1-amine (354)[163]



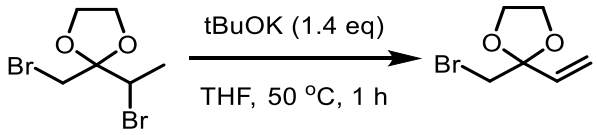
LDA (2.4 mmol) was prepared by adding n-BuLi (2.5 M in hexanes, 0.96 mL) to a solution of diisopropylamine (0.37 mL) in THF (5 mL) at -78 °C for 5 min then allowing to warm to 0 C for 5 mins. Chlorotrimethylsilane (0.15 mL, 1.2 mmol, 1.2 eq.) was added at -78 C then 4-(diethylamino)butan-2-one (0.143 g, 1.0 mmol, 1.0 eq.) in THF (1 mL) was added. The reaction mixture was stirred at -78 °C under a stream of N_2 for 0.5 h. Aqueous saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) were added and the product was extracted with pentane (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 before filtering and removing the solvent *in vacuo.* The title compound was obtained as a yellow oil (0.210 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 1H), 4.08 (s, 1H) 2.71 – 2.61 (m, 2H), 2.55 (q, *J* = 7.0 Hz, 4H), 2.23 – 2.15 (m, 2H), 1.06 (t, *J* = 7.0 Hz, 6H), 0.23 (s, 9H).

Synthesis of 2-(1-bromoethyl)-2-(bromomethyl)-1,3-dioxolane (360)[164]



2-Ethyl-2-methyl-1,3-dioxolane **359** (11.6 g, 100 mmol, 1.0 eq.) was dissolved in dichloromethane (100 mL) and then bromine (10. 3 mL, 200 mmol, 2.0 eq.) was added dropwise over 20 mins. The reaction mixture was stirred at reflux under a stream of N_2 for 5 h. Ice-cold H_2O (200 mL) was added and sodium bisulfite was added until the yellow colour of unreacted bromine had disappeared. The organic phase was separated and washed with ice-cold H_2O (200 mL) and aqueous saturated $NaHCO_3$ solution (200 mL). The organic phase was dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title compound was obtained as a pale yellow oil (2.7 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (q, *J* = 7.0 Hz, 1H), 4.23 – 4.14 (m, 4H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.60 (d, *J* = 11.0 Hz, 1H), 1.73 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 108.6 (-), 69.1 (-), 67.1 (-), 50.0 (+), 34.4 (-), 20.2 (+).

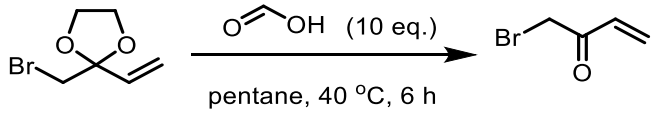
Synthesis of 2-(bromomethyl)-2-ethenyl-1,3-dioxolane (361)[164]



Potassium *tert*-butoxide (1.02 g, 9.1 mmol, 1.4 eq.) was suspended in THF (8 mL) and then 2-(1-bromoethyl)-2-(bromomethyl)-1,3-dioxolane **360** (1.78 g, 6.5 mmol, 1.0 eq.) in THF (2 mL) was added dropwise over 10 mins. The reaction mixture was stirred at 50 °C under a stream of N_2 for 1 h. The reaction mixture was cooled to rt and the solvent was removed to reveal a brown residue. Water (30 mL) was added and the product was extracted with diethyl ether (3 x 20 mL). The organic phase was washed with brine (10 mL) and then dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The title compound was obtained as a yellow oil (0.765 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.0, 10.0 Hz, 1H), 5.55 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.31 (dd, *J* = 10.0, 1.5

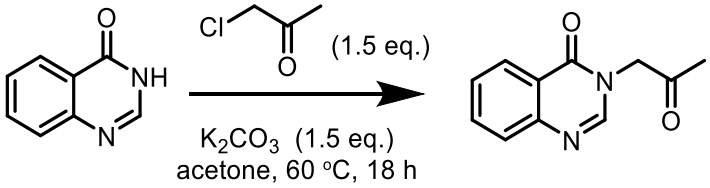
Hz, 1H), 4.13 – 4.10 (m, 2H), 4.00 – 3.97 (m, 2H), 3.50 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9 (+), 117.8 (-), 106.1 (-), 66.6 (-), 36.3 (-).

Synthesis of 1-bromobut-3-en-2-one (358)[164]



2-(Bromomethyl)-2-ethenyl-1,3-dioxolane **361** (0.772 g, 4.0 mmol, 1.0 eq.) was dissolved in pentane (4 mL) and then formic acid (1.5 mL, 40 mmol, 10 eq.) was added. The reaction mixture was stirred at 40 °C under a stream of N_2 for 6 h. Water (20 mL) was added and the product was extracted with pentane (3 x10 mL). MgO_2 (5 mg) and hydroquinone (5 mg) were added to the organic phase before removing the solvent *in vacuo*. The title compound was obtained as a pale yellow oil (0.337 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.40 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.97 (dd, *J* = 10.5, 1.0 Hz, 1H), 4.06 (s, 2H).

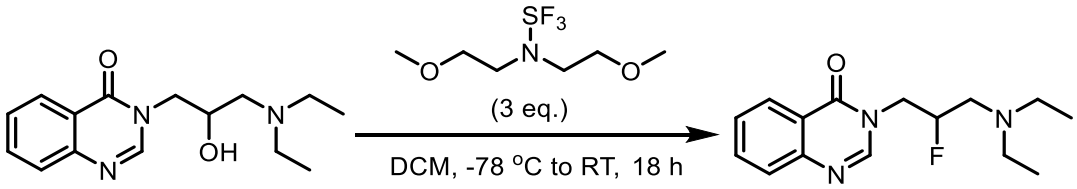
Synthesis of 3-(2-oxopropyl)quinazolin-4(3*H*)-one (372)[188]



Quinazolinone (1.46 g, 10 mmol, 1.0 eq.) and potassium carbonate (2.07 g, 15 mmol, 1.5 eq.) were suspended in acetone (100 mL) and then chloroacetone (1.2 mL, 15 mmol, 1.5 eq.) was added. The reaction mixture was heated at reflux with stirring under a stream of N_2 for 18 h. The reaction mixture was cooled down to rt and then filtered under vacuum. The solid was washed with dichloromethane (3 x 20 mL) and then added to the initial filtrate. The solvent was removed *in vacuo* to reveal the crude product which was recrystallized with EtOH to obtain the title product as an off-white solid (1.40 g, 69%). M.p. 158 – 160 °C (lit: 158 °C).[188] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.90 (s, 1H), 7.81 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55

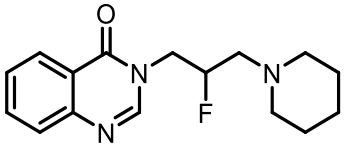
(ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 4.82 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (-), 160.9 (-), 148.1 (-), 146.2 (+), 134.6 (+), 127.6 (+), 127.5 (+), 126.8 (+), 121.9 (-), 54.7 (-), 27.5 (+).

General Procedure T: Synthesis of 3-[3-(diethylamino)-2-fluoropropyl]quinazolin-4(3H)-one (375)



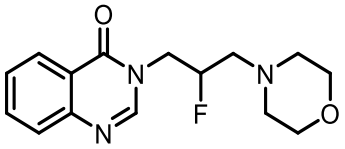
3-[3-(Diethylamino)-2-hydroxypropyl]quinazolin-4(3H)-one **278** (0.80 g, 0.28 mmol, 1.0 eq.) was dissolved in dichloromethane (0.5 mL) and then Deoxo-Fluor (0.36 mL, 50% in THF, 0.84 mmol, 3.0 eq.) was added dropwise at -78 °C. The reaction mixture was allowed to warm to rt and stirred under a stream of N_2 for 18 h. Aqueous saturated $NaHCO_3$ solution (10 mL) was added and the product extracted with dichloromethane (3 x 10 mL). The organic phase was dried with $MgSO_4$ before filtering and removing the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5% MeOH, dichloromethane) to afford the title compound as a pale yellow oil (0.044 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.09 (s, 1H), 7.80 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.07 – 4.85 (m, 1H), 4.66 (ddd, *J* = 32.0, 14.5, 2.5 Hz, 1H), 3.90 (ddd, *J* = 15.0, 14.5, 8.5 Hz, 1H), 2.80 (dd, *J* = 20.0, 5.0 Hz, 2H), 2.70 – 2.56 (m, 4H), 1.07 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (-), 148.2 (-), 147.0 (+), 134.4 (+), 127.6 (+), 127.3 (+), 126.7 (+), 122.0 (-), 90.5 (d, J_{CF} = 173.7 Hz, +), 54.4 (d, J_{CF} = 21.2 Hz, -), 49.4 (d, J_{CF} = 20.2 Hz, -), 47.9 (-), 11.9 (+). ^{19}F NMR (377 MHz, $CDCl_3$) δ -188. 7. IR (FTIR, cm^{-1}) 2966, 2934, 2820, 1670, 1609, 1564, 1473, 1368, 1322, 1293, 1035, 837, 773, 697. HRMS calcd for $C_{15}H_{20}FN_3O$ (MH^+) 278.1663, found 278.1663.

Synthesis of 3-[2-fluoro-3-(piperidin-1-yl)propyl]quinazolin-4(3H)-one (376)



Reaction of 3-[2-hydroxy-3-(piperidin-1-yl)propyl]quinazolin-4(3H)-one **279** (0.100 g, 0.36 mmol, 1.0 eq.) and Deoxo-Fluor (0.46 mL, 50% in THF, 1.1 mmol, 3.0 eq.) in dichloromethane (1 mL) for 18 h as described in General Procedure T gave, after work-up and chromatography (silica gel, 5% MeOH, dichloromethane), the title compound as a yellow oil (0.063 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.11 (s, 1H), 7.79 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.16 – 4.89 (m, 1H), 4.60 (ddd, *J* = 30.0, 14.5, 3.0 Hz, 1H), 3.97 (ddd, *J* = 16.0, 14.5, 8.0 Hz, 1H), 2.68 (dd, *J* = 22.0, 5.0 Hz, 2H), 2.57 – 2.41 (m, 4H), 1.67 – 1.36 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (-), 148.2 (-), 147.0 (+), 134.4 (+), 127.6 (+), 127.3 (+), 126.7 (+), 122.0 (-), 89.7 (d, J_{CF} = 174.7 Hz, +), 60.0 (d, J_{CF} = 21.2 Hz, -), 55.3 (-), 49.1 (d, J_{CF} = 22.2 Hz, -), 26.0 (-), 24.0 (-).^{19}F NMR (377 MHz, $CDCl_3$) δ -187.3. IR (FTIR, cm^{-1}) 2966, 2934, 2820, 1670, 1610, 1564, 1474, 1370, 1323, 1293, 1036, 844, 774, 733, 697. HRMS calcd for $C_{16}H_{20}FN_3O$ (MH^+) 290.1663, found 290.1665.

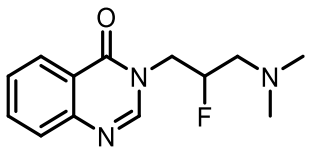
Synthesis of 3-[2-fluoro-3-(morpholin-4-yl)propyl]quinazolin-4(3H)-one (377)



Reaction of 3-[2-hydroxy-3-(morpholin-4-yl)propyl]quinazolin-4(3H)-one **280** (0.087 g, 0.30 mmol, 1.0 eq.) and Deoxo-Fluor (0.39 mL, 50% in THF, 0.9 mmol, 3.0 eq.) in dichloromethane (3 mL) for 18 h as described in General Procedure T gave, after work-up and chromatography (silica gel, 5% MeOH, dichloromethane), the title compound as a light brown oil (0.063 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.08 (s, 1H), 7.78 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53

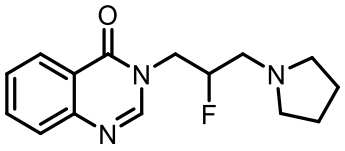
(ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.13 – 4.92 (m, 1H), 4.58 (ddd, *J* = 30.0, 14.5, 3.0 Hz, 1H), 4.00 (ddd, *J* = 16.0, 14.5, 8.0 Hz, 1H), 3.75 – 3.64 (m, 4H), 2.72 (dd, *J* = 22.0, 5.0, Hz, 2H), 2.63 – 2.51 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (-), 148.1 (-), 146.9 (+), 134.4 (+), 127.6 (+), 127.4 (+), 126.6 (+), 121.9 (-), 89.7 (d, J_{CF} = 174.7 Hz, +), 66.9 (-), 59.6 (d, J_{CF} = 20.2 Hz, -), 54.3 (-), 49.0 (d, J_{CF} = 21.2 Hz, -). ^{19}F NMR (377 MHz, $CDCl_3$) δ -187.8. IR (FTIR, cm^{-1}) 2952, 2858, 2816, 1668, 1610, 1564, 1474, 1368, 1322, 1293, 1115, 1007, 909, 774, 727, 697. HRMS calcd for $C_{15}H_{18}FN_3O_2$ (MH^+) 292.1456, found 292.1455.

Synthesis of 3-[3-(dimethylamino)-2-fluoropropyl]quinazolin-4(3H)-one (378)



Reaction of 3-[3-(dimethylamino)-2-hydroxypropyl]quinazolin-4(3H)-one **281** (0.074 g, 0.30 mmol, 1.0 eq.) and Deoxo-Fluor (0.39 mL, 50% in THF, 0.9 mmol, 3.0 eq.) in dichloromethane (3 mL) for 18 h as described in General Procedure T gave, after work-up and chromatography (silica gel, 5% MeOH, dichloromethane), the title compound as a pale yellow oil (0.010 g, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.09 (s, 1H), 7.80 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.08 – 4.89 (m, 1H), 4.60 (ddd, *J* = 30.0, 14.5, 3.0 Hz, 1H), 3.95 (ddd, *J* = 16.0, 14.5, 8.0 Hz, 1H), 2.71 – 2.62 (m, 2H), 2.35 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (-), 147.9 (+), 147.8 (-), 134.4 (+), 127.2 (+), 127.1 (+), 126.6 (+), 121.7 (-), 89.6 (d, J_{CF} = 174.7 Hz, +), 60.2 (d, J_{CF} = 20.2 Hz, -), 49.9 (d, J_{CF} = 21.2 Hz, -), 45.5 (+).^{19}F NMR (377 MHz, $CDCl_3$) δ -188.4. IR (FTIR, cm^{-1}) 2944, 2830, 2770, 1672, 1611, 1564, 1474, 1363, 1323, 1294, 1104, 1035, 776, 730, 697. HRMS calcd for $C_{13}H_{16}FN_3O$ (MH^+) 250.1350, found 250.1351.

Synthesis of 3-[2-fluoro-3-(pyrrolidin-1-yl)propyl]quinazolin-4(3*H*)-one (380)



Reaction of 3-[2-hydroxy-3-(pyrrolidin-1-yl)propyl]quinazolin-4(3H)-one **283** (0.082 g, 0.30 mmol, 1.0 eq.) and Deoxo-Fluor (0.39 mL, 50% in THF, 0.9 mmol, 3.0 eq.) in dichloromethane (3 mL) for 18 h as described in General Procedure T gave, after work-up and chromatography (silica gel, 5% MeOH, dichloromethane), the title compound as a pale yellow oil (0.020 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.10 (s, 1H), 7.79 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.09 – 4.91 (m, 1H), 4.60 (ddd, *J* = 30.0, 14.5, 3.0 Hz, 1H), 4.00 (ddd, *J* = 16.0, 14.5, 8.0 Hz, 1H), 2.84 (dd, *J* = 22.0, 5.0 Hz, 2H), 2.71 – 2.55 (m, 4H), 1.86 – 1.72 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (-), 151.8 (-), 147.5 (+), 134.6 (+), 127.7 (+), 127.4 (+), 126.7 (+), 118.3 (-), 90.8 (d, J_{CF} = 174.7 Hz, +), 63.4 (d, J_{CF} = 21.2 Hz, -), 56.3 (d, J_{CF} = 22.2 Hz, -), 54.9 (-), 23.6 (-). ^{19}F NMR (377 MHz, $CDCl_3$) δ -188.4. IR (FTIR, cm^{-1}) 2941, 1670, 1612, 1540, 1475, 1375, 1323, 1264, 1107, 776, 731, 699. HRMS calcd for $C_{15}H_{18}FN_3O$ (MH^+) 276.1507, found 276.1507.

References

(1) *Am. J. Respir. Crit. Care Med.,* **2000,** *161*, 646.

(2) Raghu, G.; Collard, H. R.; Egan, J. J.; Martinez, F. J.; Behr, J.; Brown, K. K.; Colby, T. V.; Cordier, J.-F.; Flaherty, K. R.; Lasky, J. A.et al., *Am. J. Respir. Crit. Care Med.,* **2011,** *183*, 788.

(3) Ahluwalia, N.; Shea, B. S.; Tager, A. M., *Am. J. Respir. Crit. Care Med.,* **2014,** *190*, 867.

(4) O'Connell, O. J.; Kennedy, M. P.; Henry, M. T., *Advances in Therapy,* **2011,** *28*, 986.

(5) *N. Engl. J. Med.,* **2014,** *370*, 2093.

(6) Noth, I.; Anstrom, K. J.; Calvert, S. B.; de Andrade, J.; Flaherty, K. R.; Glazer, C.; Kaner, R. J.; Olman, M. A., *Am. J. Respir. Crit. Care Med.,* **2012,** *186*, 88.

(7) King, T. E.; Behr, J.; Brown, K. K.; du Bois, R. M.; Lancaster, L.; de Andrade, J. A.; Stähler, G.; Leconte, I.; Roux, S.; Raghu, G., *Am. J. Respir. Crit. Care Med.,* **2008,** *177*, 75.

(8) *N. Engl. J. Med.,* **2010,** *363*, 620.

(9) Daniels, C. E.; Lasky, J. A.; Limper, A. H.; Mieras, K.; Gabor, E.; Schroeder, D. R., *Am. J. Respir. Crit. Care Med.,* **2010,** *181*, 604.

(10) Hilberg, F.; Roth, G. J.; Krssak, M.; Kautschitsch, S.; Sommergruber, W.; Tontsch-Grunt, U.; Garin-Chesa, P.; Bader, G.; Zoephel, A.; Quant, J.et al., *Cancer Research,* **2008,** *68*, 4774.

(11) Roth, G.; Heckel, A.; Colbatzky, F.; Handschuh, S.; Kley, J.; Lehmann-Lintz, T.; Lotz, R.; Tontsch-Grunt, U.; Walter, R.; Hilberg, F., *J. Med. Chem. ,* **2009,** *52*, 4466.

(12) Mazzei, M. E.; Richeldi, L.; Collard, H. R., *Ther. Adv. Respir. Dis.,* **2015,** *9*, 121.

(13) Kakugawa, T.; Mukae, H.; Hayashi, T.; Ishii, H.; Abe, K.; Fujii, T.; Oku, H.; Miyazaki, M.; Kadota, J.; Kohno, S., *Eur. Respir. J.,* **2004,** *24*, 57.

(14) Taniguchi, H.; Ebina, M.; Kondoh, Y.; Ogura, T.; Azuma, A.; Suga, M.; Taguchi, Y.; Takahashi, H.; Nakata, K.; Sato, A.et al., *Eur. Respir. J.,* **2010,** *35*, 821.

(15) Noble, P. W.; Albera, C.; Bradford, W. Z.; Costabel, U.; Glassberg, M. K.; Kardatzke, D.; King Jr, T. E.; Lancaster, L.; Sahn, S. A.; Szwarcberg, J.et al., *The Lancet,* **2011,** *377*, 1760.

(16) King, T. E.; Bradford, W. Z.; Castro-Bernardini, S.; Fagan, E. A.; Glaspole, I.; Glassberg, M. K.; Gorina, E.; Hopkins, P. M.; Kardatzke, D.; Lancaster, L.et al., *N. Engl. J. Med.,* **2014,** *370*, 2083.

(17) Klock, C.; Jin, X.; Choi, K.; Khosla, C.; Madrid, P.; Spencer, A.; Raimundo, B.; Lanza, G.; Griffin, J., *Bioorg. Med. Chem. Lett. ,* **2011,** *21*, 2692.

(18) Wang, Z.; Griffin, M., *Amino acids,* **2012,** *42*, 939.
(19) Erdmann, O. L., *J. Prakt. Chem.,* **1840,** *19*, 321.
(20) Laurent, A., *Annales de Chimie et de Physique,* **1840,** *3*, 393.
(21) Silva, J. F. M. d.; Garden, S. J.; Pinto, A. C., *J. Braz. Chem. Soc.,* **2001,** *12*, 273.
(22) Sumpter, W. C., *Chem. Rev.,* **1944,** *34*, 393.
(23) Gou, Y.; Chen, F., *Zhongcaoyao* **1986,** *7*, 8.
(24) Yoshikawa, M.; Murakami, T.; Kishi, A.; Sakurama, T.; Nomura, M.; Matsuda, H.; Kubo, M., *Chem. Pharm. Bull. ,* **1998**, 886.
(25) Bergman, J.; Lindström, J.-O.; Tilstam, U., *Tetrahedron,* **1985,** *41*, 2879.
(26) Kapadia, G. J.; Shukla, Y. N.; Basak, S. P.; Sokoloski, E. A.; Fales, H. M., *Tetrahedron,* **1980,** *36*, 2441.
(27) Grafe, U.; Radics, L., *J. Antibiotics,* **1986,** *39*, 162.
(28) Breinholt, J.; Demuth, H.; Heide, M.; Jensen, G.; Moller, I.; Nielsen, R.; Olsen, C.; Rosendahl, C., *Acta Chem. Scand.,* **1996,** *50*, 443.
(29) Wei, L.; Wang, Q.; Liu, X., *Yaowu Fenxi Zazhi,* **1982,** *2*, 288.
(30) d'Ischia, M.; Palumbo, A.; Prota, G., *Tetrahedron,* **1988,** *44*, 6441.
(31) Medvedev, A.; Buneeva, O.; Glover, V., *Biologics: Targets & Therapy,* **2007,** *1*, 151.
(32) Kekulé, A., *Ber.,* **1869,** *2*, 748.
(33) Baeyer, A., *Ber.,* **1878,** *11*, 1228.
(34) Claisen, L.; Shadwell, J., *Ber.,* **1879,** *12*, 350.
(35) Forrer, C., *Ber.,* **1884,** *17*, 975.
(36) Sandmeyer, T., *Zeitschrift fuer Farben- und Textil-Chemie,* **1903,** *2*, 129.
(37) Reissert, A., *Ber.,* **1904,** *37*, 3708.
(38) Bauer, R., *Ber.,* **1907,** *40*, 2650.
(39) Heller, G., *Ber.,* **1906,** *39*, 2334.
(40) Burton, H.; Stoves, J. L., *J. Chem. Soc.,* **1937**, 402.
(41) Fetscher, C. A.; Bogert, M. T., *J. Org. Chem. ,* **1939,** *04*, 71.
(42) Sandmeyer, T., *Helv. Chim. Acta* **1919**, 234.
(43) Garden, S.; Torres, J.; Ferriera, A.; Silva, R.; Pinto, A., *Tetrahedron Lett.,* **1997,** *38*, 1501.
(44) Jnaneswara, G.; Bedekar, A.; Deshpande, V., *Synth. Commun. ,* **1999,** *29*, 3627.
(45) Lackey, K.; Besterman, J.; Fletcher, W.; Leitner, P.; Morton, B.; Sternbach, D., *J. Med. Chem.,* **1995,** *38*, 906.
(46) Prinz, W.; Kayle, A.; Levy, P., *J. Chem. Res. (S),* **1978**, 116.
(47) Varma, R.; Singh, A., *Indian J. Chem. Sect. B* **1990,** *29*, 578.
(48) Kearney, T.; Harris, P.; Jackson, A.; Joule, J., *Synthesis* **1992,** *8*, 769.
(49) Gandy, R.; Hill, M., *Chem. Ber.,* **1988,** *24*, 336.

(50) Gilchrist, T., *Chem. Soc. Rev. ,* **1983,** *12*, 53.

(51) Francotte, E.; Merenyi, R.; Vandenbulcke, B.; Viehe, H., *Helv. Chim. Acta* **1981,** *64*, 1208.

(52) Stolle, R., *J. Prakt. Chem. ,* **1922,** *106*, 137.

(53) Loloiu, G.; Maior, O., *Rev. Roum. Chim. ,* **1997,** *42*, 67.

(54) Fukuda, Y.; Itoh, Y.; Nakatani, K.; Terashima, S., *Tetrahedron* **1994,** *50*, 2793.

(55) Lopes, W.; Silva, G.; Sequiera, L.; Pereira, A., *J. Braz. Chem. Soc. ,* **1993,** *4*, 34.

(56) Welstead, W.; Moran, H.; Stauffer, H.; Turnbull, L.; Sancilio, L., *J. Med. Chem. ,* **1979,** *22*, 1074.

(57) Bonnefoy, J.; Martinet, J., *Compt. Rend. ,* **1921,** *172*, 220.

(58) Taylor, A., *J. Chem. Res. (S)* **1980**, 347.

(59) Gassman, P.; Cue, B.; Luh, T., *J. Org. Chem. ,* **1977,** *42*, 1344.

(60) Parrick, J.; Yahya, A., *J. Chem. Soc. Perkin Trans. 1,* **1989,** *11*, 2009.

(61) Noland, W.; Rieke, R., *J. Org. Chem. ,* **1962,** *27*, 2250.

(62) Gribble, G.; Liu, Y., *Org. Prep. Proc. Int. ,* **2001,** *33*, 615.

(63) Khan, F.; Prabhudas, B.; Dash, J.; Sahu, N., *J. Am. Chem. Soc. ,* **2001,** *122*, 9558.

(64) Gribble, G.; Allison, B.; Conway, S.; Saulnier, M., *Org. Prep. Proc. Int. ,* **1992,** *24*, 649.

(65) Beauchard, A.; Laborie, H.; Rouillard, H., *Bioorg. Med. Chem. ,* **2009,** *17*, 6257.

(66) Yadav, J.; Reddy, B.; Reddy, C.; Krishna, A., *Synthesis* **2007,** *5*, 693.

(67) Mamun, H.; Foysal, M.; Mahabab, M.; Amin, A., *J. Sci. Res. ,* **2010,** *2*, 322.

(68) Raj, V.; Shaikh, T.; Sudalai, A., *Acta Chim. Slov. ,* **2010,** *57*, 466.

(69) Rogness, D.; Larock, R., *J. Org. Chem. ,* **2011,** *76*, 4980.

(70) Zhao, J.; Larock, R., *J. Org. Chem. ,* **2007,** *72*, 583.

(71) Söderberg, B.; Gorugantula, S.; Howerton, C.; Petersen, J.; Dantale, S., *Tetrahedron* **2009,** *65*, 7357.

(72) Robinson, R.; Donahue, K., *J. Org. Chem. ,* **1991,** *56*, 4805.

(73) Tatsugi, J.; Zhiwei, T.; Izawa, Y., *Arkivoc,* **2001,** *1*, 67.

(74) Kritsanida, M.; Magiatis, P.; Skaltsounis, A.; Peng, Y.; Li, P.; Wennogle, L., *J. Nat. Prod.,* **2009,** *20*, 542.

(75) Cheng, X.; Merz, K.; Vatter, S.; Christ, J.; Wolfl, S.; Eisenbrand, G., *Bioorg. Med. Chem. ,* **2014,** *22*, 247.

(76) Rivalle, C.; Bisagni, E., *J. Heterocyclic. Chem. ,* **1997,** *34*, 441.

(77) Valiante, N. **2004,** WO 2004064759

(78) Lollar, C.; Krenek, K.; Bruemmer, K.; Lippert, A., *Org. Biomol. Chem. ,* **2014,** *12*, 406.

(79) Varela-Fernández, A.; Varela, J.; Saá, C., *Adv. Synth. Catal. ,* **2011,** *353*, 1933.

(80) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H., *Chem. Pharm. Bull. ,* **1987,** *35*, 1823.

(81) Zou, H.; Zhang, L.; Ouyang, J.; Giulianotti, M.; Yu, Y., *Eur. J. Med. Chem. ,* **2011,** *46*, 5970.

(82) Rombouts, F.; Franken, D.; Martinez-Lamenca, C.; Braeken, M. Z., C.; Chen, J.; Trabanco, A., *Tetrahedron. Lett. ,* **2010,** *51*, 4815.

(83) Yang, D.; Zhang, C., *J. Org. Chem. ,* **2001,** *66*, 4814.

(84) Ng, K.; Ng, F.; Yu, W., *Chem. Commun. ,* **2012,** *48*, 11680.

(85) Ng, F.; Zhou, Z.; Yu, W., *Chem. Eur. J. ,* **2014,** *20*, 4474.

(86) Czapf, S.; Gottlieb, H.; Whitfield, G.; Swern, D., *J. Org. Chem. ,* **1973,** *38*, 2555.

(87) Kolbe, H., *J. Prakt. Chem.,* **1884,** *30*, 84.

(88) Coppola, G.; Fraser, J.; Hardtmann, G.; Shapiro, M., *J. Heterocyclic Chem. ,* **1985,** *22*, 193.

(89) Reissenweber, G.; Mangold, D., *Angew. Chem. Int. Ed. Engl.,* **1980,** *92*, 196.

(90) Adepu, R.; Sunke, R.; Meda, C. L. T.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Deora, G. S.; Parsa, K. V. L.; Pal, M., *Chem. Commun.,* **2013,** *49*, 190.

(91) Nelson, A. C.; Kalinowski, E. S.; Czerniecki, N. J.; Jacobson, T. L.; Grundt, P., *Org. Biomol. Chem.,* **2013,** *11*, 7455.

(92) Karramkam, M.; Hinnen, F.; F., V.; Dolle, F., *J. Label. Compd. Radiopharm. ,* **2003,** *46*, 979.

(93) Renard, J.; Arslan, D.; Garbacki, N.; Pirotte, B.; de Laval, X., *J. Med. Chem.,* **2009,** *52*, 5864.

(94) Asao, N.; Sato, K.; Yamamoto, Y., *Tetrahedron Lett.,* **2003,** *44*, 5675.

(95) Baeyer, A., *Ber.,* **1881,** *14*, 1741.

(96) Preston, P.; Tennant, G., *Chem. Rev.,* **1972,** *72*, 627.

(97) Bond, C.; Hooper, M., *J. Chem. Soc.,* **1969,** *1*, 2453.

(98) Ruggli, P.; Zaeslin, H.; Grand, R., *Helv. Chim. Acta,* **1938,** *21*, 33.

(99) Pfeiffer, P., *Justus Liebigs Ann. Chem.,* **1916,** *411*, 72.

(100) Krohnke, F.; Vogt, I., *Chem. Ber.,* **1952,** *85*, 376.

(101) Patterson, D.; Wibberley, D., *J. Chem. Soc.,* **1965**, 1706.

(102) Chien, C.; Takanami, T.; Kawasaki, T.; Sakamoto, M., *Chem. Pharm. Bull.,* **1985,** *33*, 1843.

(103) Slatt, J.; Bergman, J., *Tetrahedron,* **2002,** *58*, 9187.

(104) Bristow, T.; Foster, H.; Hooper, M., *J. C. S. Chem. Comm.,* **1974**, 677.

(105) Bond, C.; Hooper, M., *Communications,* **1974**, 443.

(106) Rosen, G.; Tsai, P.; Barth, E.; Dorey, G.; Casara, P.; Spedding, M.; Halpern, H., *J. Org. Chem. ,* **2000,** *65*, 4460.

(107) Cikotiene, I.; Pudziuveleyte, E.; Brukstus, A., *J. Heterocyclic Chem.,* **2008,** *45*, 1615.

(108) Nepveu, F.; Kim, S.; Boyer, J.; Chatriant, O.; Ibrahim, H.; Reybier, K.; Monje, M.; Chevalley, S.; Perio, P.; Lajoie, B.et al., *J. Med. Chem. ,* **2010,** *53*, 699.

(109) Marien, N.; Brigou, B.; Pinter, B.; De Proft, F.; Verniest, G., *Org. Lett.,* **2015,** *17*, 270.

(110) Ramana, C.; Patel, P.; Vanka, K.; Miao, B.; Degterev, A., *Eur. J. Org. Chem. ,* **2010**, 5955.

(111) DeRoy, P.; Surprenant, S.; Bertrand-Laperle, M.; Yoakim, C., *Org. Lett.,* **2007,** *9*, 2741.

(112) Huisgen, R., *Angew. Chem. Int. Ed. ,* **1963,** *75*, 604.

(113) Li, X.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H., *Organometallics,* **2005,** *24*, 3066.

(114) Luettke, W.; Klessinger, M., *Chem. Ber.,* **1964,** *97*, 2342.

(115) Guengerich, F.; Sorrells, J.; Schmitt, S.; Krauser, J.; Aryal, P.; Meijer, L., *J. Med. Chem. ,* **2004,** *47*, 3236.

(116) Russell, G.; Kaupp, G., *J. Am. Chem. Soc. ,* **1969,** *91*, 3851.

(117) Illias, M.; Barman, D.; Prajapati, D.; Sandhu, J., *Tetrahedron Lett. ,* **2002,** *43*, 1877.

(118) Yoo, B.; Jung, H.; Kim, S.; Ahn, Y.; Choi, J., *Bull. Korean Chem. Soc. ,* **2013,** *34*, 359.

(119) Singh, S.; Reddy, M.; Mangle, M.; Ganesh, K., *Tetrahedron,* **2007,** *63*, 126.

(120) Dutta, D.; Konwar, D., *J. Chem. Res.,* **1998**, 266.

(121) Balicki, R., *Chem. Ber. ,* **1990,** *123*, 647.

(122) Yoo, B.; Choi, J.; Yoon, C., *Tetrahderon Lett. ,* **2006,** *47*, 125.

(123) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C., *J. Am. Chem. Soc.,* **2002,** *124*, 13662.

(124) Ibrahim, H.; Pantaleo, A.; Turrini, F.; Arese, P.; Nallet, J.-P.; Nepveu, F., *Med. Chem. Comm.,* **2011,** *2*, 860.

(125) Kumar, C. V. S.; Puranik, V. G.; Ramana, C. V., *Chem. Eur. J.,* **2012,** *18*, 9601.

(126) Gein, V.; Tatarinov, V.; Rassudikhina, N.; Vakhrin, M.; Voronina, E., *J. Pharm. Chem. ,* **2011,** *45*, 231.

(127) Zhang, P.; Bierer, D., *J. Nat. Prod. ,* **2000,** *63*, 643.

(128) Gein, V.; Demeneva, A.; Rassudikhina, N.; Vakhrin, M., *Russian J. Org. Chem. ,* **2006,** *42*, 617.

(129) Merour, J.; Chichereau, L.; Desarbre, E.; Gadonneix, P., *Synthesis,* **1996,** *1*, 519.

(130) Poon, P.; Banerjee, A.; Laya, M., *J. Chem. Res. ,* **2011**, 67.

(131) Mason, J.; Murphree, S., *Synlett. ,* **2013,** *24*, 1391.

(132) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., *J. Am. Chem. Soc.,* **1947,** *69*, 1837.
(133) Jang, C. S.; Chou, T., *Nat. Med. J. Chin. ,* **1943,** *29*, 137.
(134) Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Chou, T. C., *Science* **1946,** *103*, 59.
(135) Chou, T. Q.; Jang, C. S.; Fu, F. Y.; Kao, Y. S.; Huang, K. C., *Chin. M. J. ,* **1947,** *65*, 189.
(136) Chou, T. Q.; Fu, F. Y.; Kao, Y. S., *J. Am. Chem. Soc. ,* **1948,** *70*, 1765.
(137) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., *J. Am. Chem. Soc. ,* **1949,** *71*, 1048.
(138) Ablondi, F.; Gordon, S.; Morton, J.; Williams, J. H., *J. Org. Chem. ,* **1952,** *17*, 14.
(139) McLaughlin, N. P.; Evans, P.; Pines, M., *Bioorg. Med. Chem.,* **2014,** *22*, 1993.
(140) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H. S.; Wataya, Y., *J. Org. Chem.,* **1999,** *64*, 6833.
(141) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T., *Synthesis* **1999**, 1814.
(142) Fishman, M.; Cruickshank, P. A., *J. Med. Chem. ,* **1970,** *13*, 155.
(143) Hewitt, R. L.; Wallace, W. S.; Gill, E. R.; Williams, J. H., *Am. J. Trop. Med. Hyg.,* **1952,** *1*, 768.
(144) de Jonge, M. J.; Dumez, H.; Verweij, J.; Yarkoni, S.; Snyder, D.; Lacombe, D.; Marréaud, S.; Yamaguchi, T.; Punt, C. J.; van Oosterom, A., *Eur. J. Cancer* **2006,** *42*, 1768.
(145) Son, J.; Lee, E. H.; Park, M.; Kim, J. H.; Kim, J.; Kim, S.; Jeon, Y. H.; Hwang, K. Y., *Acta Crystallographica Section D,* **2013,** *69*, 2136.
(146) Schimmel, P., *Annu. Rev. Biochem.,* **1984,** *56*, 125.
(147) Zhou, H.; Sun, L.; Yang, X.-L.; Schimmel, P., *Nature,* **2013,** *494*, 121
(148) Keller, T. L.; Zocco, D.; Sundrud, M. S.; Hendrick, M.; Edenius, M.; Yum, J.; Kim, Y.-J.; Lee, H.-K.; Cortese, J. F.; Wirth, D. F.et al., *Nat Chem Biol,* **2012,** *8*, 311.
(149) Roubinek, F.; Vavrina, J.; Budesinsky, Z., *Collect. Czech. Chem. Commun.,* **1982,** *47*, 630.
(150) Vishnoi, S. P.; Patnaik, G. K.; Shoeb, A.; Srimal, R. C. **1997,**
(151) Talybov, A.; Mamedbeyli, E.; Abbasov, V.; Abdullayev, Y.; Kochetkov, K., *Green and Sustainable Chemistry,* **2013,** *3*, 31.
(152) Kaneko, C.; Kasai, K.; Katagiri, N.; Chiba, T., *Chem. Pharm. Bull.,* **1986,** *34*, 3672.
(153) Butova, E. D.; Barabash, A. V.; Petrova, A. A.; Kleiner, C. M.; Schreiner, P. R.; Fokin, A. A., *J. Org. Chem. ,* **2010,** *75*, 6229.
(154) Morita, J.-i.; Nakatsuji, H.; Misaki, T.; Tanabe, Y., *Green Chemistry,* **2005,** *7*, 711.
(155) Searles, S.; Gregory, V., *J. Am. Chem. Soc.,* **1954,** *76*, 1789.
(156) Papini, A.; Ricci, A.; Taddei, M.; Seconi, G.; Dembech, P., *J. Chem. Soc. Perkin Trans 1,* **1984**, 2261.

(157) Mojtahedi, M. M.; Saeed Abaee, M.; Hamidi, V., *Catal. Commun.,* **2007,** *8*, 1671.
(158) Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M., *Tetrahedron Lett.,* **1994,** *35*, 7089.
(159) Kobayashi, S., *Chem. Lett.,* **1991**, 2187.
(160) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W., *Chem. Rev.,* **2002,** *102*, 2227.
(161) Magidson, O.; Lu, Y., *Zhurnal Obshchei Khimii,* **1959,** *29*, 2843.
(162) Azizi, N.; Baghi, R.; Ghafuri, H.; Bolourtchian, M.; Hashemi, M., *Synlett,* **2010,** *2010*, 379.
(163) Pratt, N. E.; Albizati, K. F., *J. Org. Chem.,* **1990,** *55*, 770.
(164) Carlson, R.; Descomps, A.; Mekonnen, A.; Westerlund, A.; Havelkova, M., *Synth. Commun.,* **2011,** *41*, 2939.
(165) Proust, N.; Preston, A. J.; Paquette, L. A., *Heterocylces,* **2009,** *77*, 163.
(166) Tang, X.-J.; Yan, Z.-L.; Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-Q., *Tetrahedron Lett.,* **2013,** *54*, 2669.
(167) Thayer, A., *Chemical and Engineering News,* **2006,** *84*, 15.
(168) Singh, R.; Shreeve, J., *Synthesis,* **2002,** *17*, 2561.
(169) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A., *Org. Lett.,* **2009,** *11*, 5050.
(170) Duo, X.; Yao, W.; Jiang, C.; Lu, Y., *Chem. Commun.,* **2014,** *50*, 11354.
(171) Mahadevan, I.; Rasmussen, M., *Tetrahedron,* **1993,** *49*, 7337.
(172) Sonnenburg, R.; Neda, I.; Fischer, A.; Jones, P.; Schmutler, R., *Chem. Ber. ,* **1995,** *22*, 193.
(173) Burger, M.; Ding, Y.; Han, W.; Lindvall, M.; Nishiguchi, G.; Rico, A.; Smith, A.; Tanner, H.; Wan, L. **2012,**
(174) Yu, K.; Civiello, R.; Combrink, K.; Gulgeze, H.; Sin, N.; Wang, X.; Meanwell, N.; Venables, B.; Zhang, Y.; Pearce, B.et al. **2002,** WO 2002062290
(175) Wagman, A.; Moser, H. **2010,** WO 2010030811
(176) Kim, J.; Yoon, S.; Yoon, Y.; Lee, H.; Kim, D.; Cha, M.; Park, Y.; Ahn, B.; Kang, H. **2007,** WO 2007001139
(177) Maya, F.; Flatt, A.; Stewart, M.; Shen, D.; Tour, J., *Chem. Mater. ,* **2004,** *16*, 2987.
(178) Blaszczyk, A.; Chadim, M.; Von Hanisch, C.; Mayor, M., *Eur. J. Org. Chem. ,* **2006,** *17*, 3809.
(179) Patrick, D., *J. Med. Chem.,* **2007,** *50*, 2468.
(180) Tischler, A.; Lanza, T., *Tetrahedron Lett. ,* **1986,** *27*, 1563.
(181) Giovannini, E.; Portmann, P., *Helv. Chim. Acta,* **1948,** *31*, 1381.
(182) Baker, B.; Querry, M.; Kadish, A.; Williams, J., *J. Org. Chem. ,* **1952,** *17*, 35.
(183) Riss, P.; Rosch, F., *Org. Biomol. Chem. ,* **2008,** *6*, 4567

(184) Rintjema, J.; Guo, W.; Martin, E.; Escudero-Adan, E.; Kleij, A., *Chem. Eur. J. ,* **2015,** *21*, 10754.

(185) Fitton, A.; Hill, J.; Jane, D.; Millar, R., *Synthesis* **1987,** *12*, 1140.

(186) Amans, D.; Bamborough, P.; Barker, M.; Bit, R.; Brown, J.; Campbell, M.; Garton, N.; Lindon, M.; Shipley, T.; Theodoulou, N.et al. **2014,** WO 2014140077

(187) Araujo, N.; Ferreira Da Silva, A.; Qing, Y.; Lufino, M.; Russell, A.; Small, B.; Wade-Martins, R.; Wynne, G. **2015,** WO 2015004485

(188) Ranganathan, D.; Farooqui, F., *Tetrahedron Lett. ,* **1984,** *25*, 5701.

Appendix

Table 1. Crystal data and structure refinement for zhu1_0m.

Identification code	zhu1_0m	
Empirical formula	C17 H13 N O2	
Formula weight	263.28	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 5.5472(3) Å	a= 90°.
	b = 30.6096(15) Å	b= 93.921(3)°.
	c = 7.4225(3) Å	g = 90°.
Volume	1257.37(10) $Å^3$	
Z	4	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	0.737 mm^{-1}	
F(000)	552	
Crystal size	0.190 x 0.100 x 0.020 mm^3	
Theta range for data collection	2.887 to 66.752°.	
Index ranges	-6<=h<=6, -36<=k<=36, -8<=l<=8	
Reflections collected	15694	
Independent reflections	2226 [R(int) = 0.1016]	
Completeness to theta = 67.679°	97.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.6178	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2226 / 0 / 182	
Goodness-of-fit on F^2	1.163	
Final R indices [I>2sigma(I)]	R1 = 0.0706, wR2 = 0.1753	
R indices (all data)	R1 = 0.1047, wR2 = 0.1905	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.330 and -0.267 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for zhu1_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8357(5)	7468(1)	9646(3)	26(1)
O(2)	1200(5)	6651(1)	6544(4)	30(1)
N(1)	2912(6)	7502(1)	7016(4)	22(1)
C(1)	4727(7)	7256(1)	7856(5)	22(1)
C(2)	6544(7)	7578(1)	8734(5)	22(1)
C(3)	5563(7)	8009(1)	8298(5)	22(1)
C(4)	3334(7)	7948(1)	7284(5)	22(1)
C(5)	1909(7)	8300(1)	6754(5)	23(1)
C(6)	2701(7)	8718(1)	7220(5)	24(1)
C(7)	4948(7)	8778(1)	8193(5)	25(1)
C(8)	6377(7)	8426(1)	8736(5)	23(1)
C(9)	1162(8)	9115(1)	6726(5)	28(1)
C(10)	4971(7)	6823(1)	7973(5)	22(1)
C(11)	3142(7)	6516(1)	7262(5)	23(1)
C(12)	3589(7)	6037(1)	7398(5)	24(1)
C(13)	5742(8)	5858(2)	8155(6)	32(1)
C(14)	6046(9)	5412(2)	8252(7)	39(1)
C(15)	4233(9)	5131(2)	7610(6)	40(1)
C(16)	2089(9)	5306(2)	6845(6)	37(1)
C(17)	1759(8)	5750(1)	6738(5)	30(1)

Table 3. Bond lengths [Å] and angles [°] for zhu1_0m.

O(1)-C(2)	1.222(5)
O(2)-C(11)	1.239(5)
N(1)-C(1)	1.372(5)
N(1)-C(4)	1.395(5)
N(1)-H(1)	0.8800
C(1)-C(10)	1.336(6)
C(1)-C(2)	1.524(5)
C(2)-C(3)	1.455(6)
C(3)-C(8)	1.383(6)
C(3)-C(4)	1.415(5)
C(4)-C(5)	1.379(6)
C(5)-C(6)	1.390(6)
C(5)-H(5)	0.9500
C(6)-C(7)	1.409(5)
C(6)-C(9)	1.515(6)
C(7)-C(8)	1.382(6)
C(7)-H(7)	0.9500
C(8)-H(8)	0.9500
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.455(5)
C(10)-H(10)	0.9500
C(11)-C(12)	1.488(6)
C(12)-C(13)	1.397(6)
C(12)-C(17)	1.405(6)
C(13)-C(14)	1.378(6)
C(13)-H(13)	0.9500
C(14)-C(15)	1.382(7)
C(14)-H(14)	0.9500
C(15)-C(16)	1.389(7)
C(15)-H(15)	0.9500
C(16)-C(17)	1.375(6)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500

C(1)-N(1)-C(4)	111.1(3)
C(1)-N(1)-H(1)	124.4

C(4)-N(1)-H(1)	124.4
C(10)-C(1)-N(1)	130.0(4)
C(10)-C(1)-C(2)	123.6(3)
N(1)-C(1)-C(2)	106.4(3)
O(1)-C(2)-C(3)	131.0(4)
O(1)-C(2)-C(1)	123.5(4)
C(3)-C(2)-C(1)	105.4(3)
C(8)-C(3)-C(4)	120.5(4)
C(8)-C(3)-C(2)	132.2(3)
C(4)-C(3)-C(2)	107.3(3)
C(5)-C(4)-N(1)	129.5(3)
C(5)-C(4)-C(3)	120.7(4)
N(1)-C(4)-C(3)	109.8(3)
C(4)-C(5)-C(6)	119.0(4)
C(4)-C(5)-H(5)	120.5
C(6)-C(5)-H(5)	120.5
C(5)-C(6)-C(7)	120.1(4)
C(5)-C(6)-C(9)	121.0(4)
C(7)-C(6)-C(9)	119.0(4)
C(8)-C(7)-C(6)	121.2(4)
C(8)-C(7)-H(7)	119.4
C(6)-C(7)-H(7)	119.4
C(7)-C(8)-C(3)	118.6(4)
C(7)-C(8)-H(8)	120.7
C(3)-C(8)-H(8)	120.7
C(6)-C(9)-H(9A)	109.5
C(6)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(6)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(1)-C(10)-C(11)	123.5(4)
C(1)-C(10)-H(10)	118.2
C(11)-C(10)-H(10)	118.2
O(2)-C(11)-C(10)	120.4(4)
O(2)-C(11)-C(12)	119.5(4)
C(10)-C(11)-C(12)	120.1(3)
C(13)-C(12)-C(17)	118.1(4)
C(13)-C(12)-C(11)	123.2(4)
C(17)-C(12)-C(11)	118.6(4)

C(14)-C(13)-C(12)	120.6(4)
C(14)-C(13)-H(13)	119.7
C(12)-C(13)-H(13)	119.7
C(13)-C(14)-C(15)	121.0(4)
C(13)-C(14)-H(14)	119.5
C(15)-C(14)-H(14)	119.5
C(14)-C(15)-C(16)	119.0(5)
C(14)-C(15)-H(15)	120.5
C(16)-C(15)-H(15)	120.5
C(17)-C(16)-C(15)	120.7(4)
C(17)-C(16)-H(16)	119.7
C(15)-C(16)-H(16)	119.7
C(16)-C(17)-C(12)	120.6(4)
C(16)-C(17)-H(17)	119.7
C(12)-C(17)-H(17)	119.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for zhu1_0m. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(2)	39(2)	17(1)	-1(1)	-5(1)	1(1)
O(2)	24(2)	38(2)	27(2)	-3(1)	-8(1)	0(1)
N(1)	15(2)	32(2)	16(2)	1(1)	-4(1)	1(1)
C(1)	17(2)	37(3)	11(2)	-1(2)	0(1)	-1(2)
C(2)	20(2)	36(2)	10(2)	-1(2)	1(2)	-1(2)
C(3)	20(2)	35(2)	11(2)	2(2)	2(1)	0(2)
C(4)	21(2)	34(2)	9(2)	-1(2)	2(1)	-2(2)
C(5)	21(2)	34(2)	15(2)	1(2)	2(2)	2(2)
C(6)	21(2)	40(3)	11(2)	2(2)	2(2)	1(2)
C(7)	27(2)	31(2)	17(2)	1(2)	2(2)	-1(2)
C(8)	19(2)	37(3)	12(2)	-2(2)	1(2)	-2(2)
C(9)	23(2)	38(3)	21(2)	2(2)	-3(2)	3(2)
C(10)	16(2)	35(3)	16(2)	0(2)	-2(2)	-2(2)
C(11)	15(2)	44(3)	10(2)	-1(2)	0(1)	-1(2)
C(12)	22(2)	37(2)	12(2)	-1(2)	1(2)	-4(2)
C(13)	28(2)	36(3)	32(2)	1(2)	-2(2)	-3(2)
C(14)	31(3)	37(3)	48(3)	2(2)	0(2)	5(2)
C(15)	51(3)	34(3)	36(3)	-3(2)	1(2)	0(2)
C(16)	47(3)	42(3)	22(2)	-4(2)	-3(2)	-13(2)
C(17)	31(3)	40(3)	18(2)	0(2)	-4(2)	-6(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for zhu1_0m.

	x	y	z	U(eq)
H(1)	1647	7393	6391	26
H(5)	408	8258	6081	28
H(7)	5490	9066	8482	30
H(8)	7886	8469	9397	27
H(9A)	1697	9246	5616	41
H(9B)	1329	9329	7708	41
H(9C)	-534	9026	6534	41
H(10)	6416	6708	8552	27
H(13)	7007	6046	8608	39
H(14)	7524	5295	8767	47
H(15)	4449	4824	7692	48
H(16)	837	5116	6389	45
H(17)	281	5864	6214	36

Table 6. Hydrogen bonds for zhu1_0m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#1	0.88	2.21	2.980(4)	146.5
N(1)-H(1)...O(2)	0.88	2.29	2.787(4)	115.8

Symmetry transformations used to generate equivalent atoms:
#1 x-1,-y+3/2,z-1/2