A Synthetic Study of Febrifugine and Isofebrifugine Analogues Towards Novel Drug Candidates.

The University Of Sheffield.

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1 ABSTRACT

Febrifugine and Isofebrifugine are alkaloids isolated from *Dichroa febrifuga Lour* and have been characterised to be active against malaria. However, as there is still some ambiguity surrounding isofebrifugine's structure, febrifugine has generated a greater interest in the medicinal chemistry community as a lead compound for synthesising a new wave of antimalarial drugs. For example halofuginone is the synthetic derivative of febrifugine and has recently shown higher activity against malaria than that observed for the parent alkaloid.

Through extensive work, the development of new hybrid molecules containing features associated with febrifugine were investigated. This required efficient routes towards these analogues to be devised. Indeed, the synthesis of the non-commercially available halofuginone quinazolinone was accomplished, permitting a route for the production of novel halofuginone analogues. In addition X-ray crystallisation data was obtained for the natural febrifugine analogue and its synthetic derivative epifebrifuginol.

I would like to dedicate this thesis to the loving memory of my father Major Sabelo Mbelesi.

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Firstly I would like to thank Joe for giving me this opportunity and for the constant support and encouragement you have provided for the last three years. As promised I haven't burnt down the lab yet, which is surprise with the large scale DMDO reactions I have been doing. In addition, you now owe me around 100 bagels and counting, don't worry there's no rush to gather them all now I will come and collect them when I graduate. I will also like to thank Stephen and Pan our GSK supervisors for the encouragement to perceiver whenever our chemistry was being problematic, which was more often than I would like to recall.

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4 INTRODUCTION

The Chinese plant *Dichroa febrifuga* came to prominence in the medicinal chemistry community in the mid-twentieth century, as its roots and the leaves had been used to treat ailments such as headaches and stomach cancer for centuries.[2] Tests conducted on the plant revealed that its extracts had active components towards malaria induced fevers as well as stomach cancers. Later studies revealed that the activity of these extracts was due to the alkaloids febrifugine and isofebrifugine (Figure 1). The discovery of these alkaloids spiked a great interest on the development of a synthetic pathway towards them.

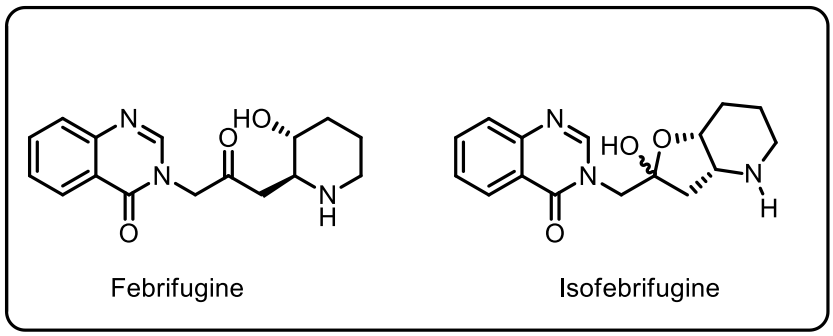
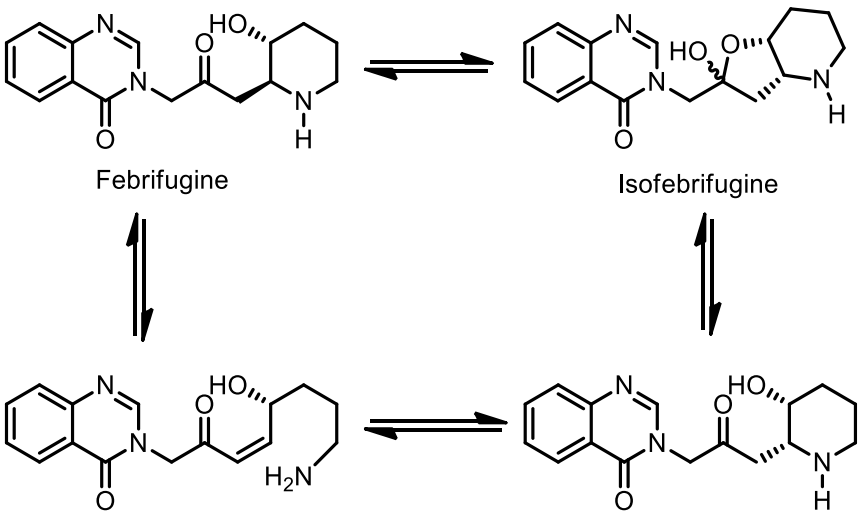


Figure 1.

However, during the attempted characterisation and synthesis of these compounds, it was found that the determination of their relative and absolute stereochemistry raised some challenges.[2] In addition, it was found that febrifugine and isofebrifugine interconverted via a retro-aza-Michael reaction (Scheme 1).[3] As a result of this isomerisation, mistakes concerning the precise structure of these alkaloids were made. However, these were later resolved following work by Kobayashi in 1999. This issue will be discussed in more detail later on.[5]



Scheme 1. The interconversion of febrifugine into isofebrifugine via a retro-aza-Michael reaction.

The aim of this thesis is to focus on the development of synthetic methods towards febrifugine analogues by the use of literature and novel methods, and to show how these analogues can be modified structurally compared to the parent febrifugine structure to meet the demands for successful drug candidates.

5 FEBRIFUGINE AND ISOFEBRIFUGINE

The alkaloids febrifugine and isofebrifugine have inspired a number of total syntheses because of their high activity for such diseases as malaria. In 1943, Koepfli *et al.* demonstrated that febrifugine possessed superior activity against malaria in comparison to pre-existing treatments.[4] During Koepfli's experiments, febrifugine extracts were shown to be active against *plasmodium gallinaceum* (the malarial parasite in poultry). It was later on discovered that febrifugine acted by impairing haemazoin formation required for the mutation of the malaria parasite.[4]

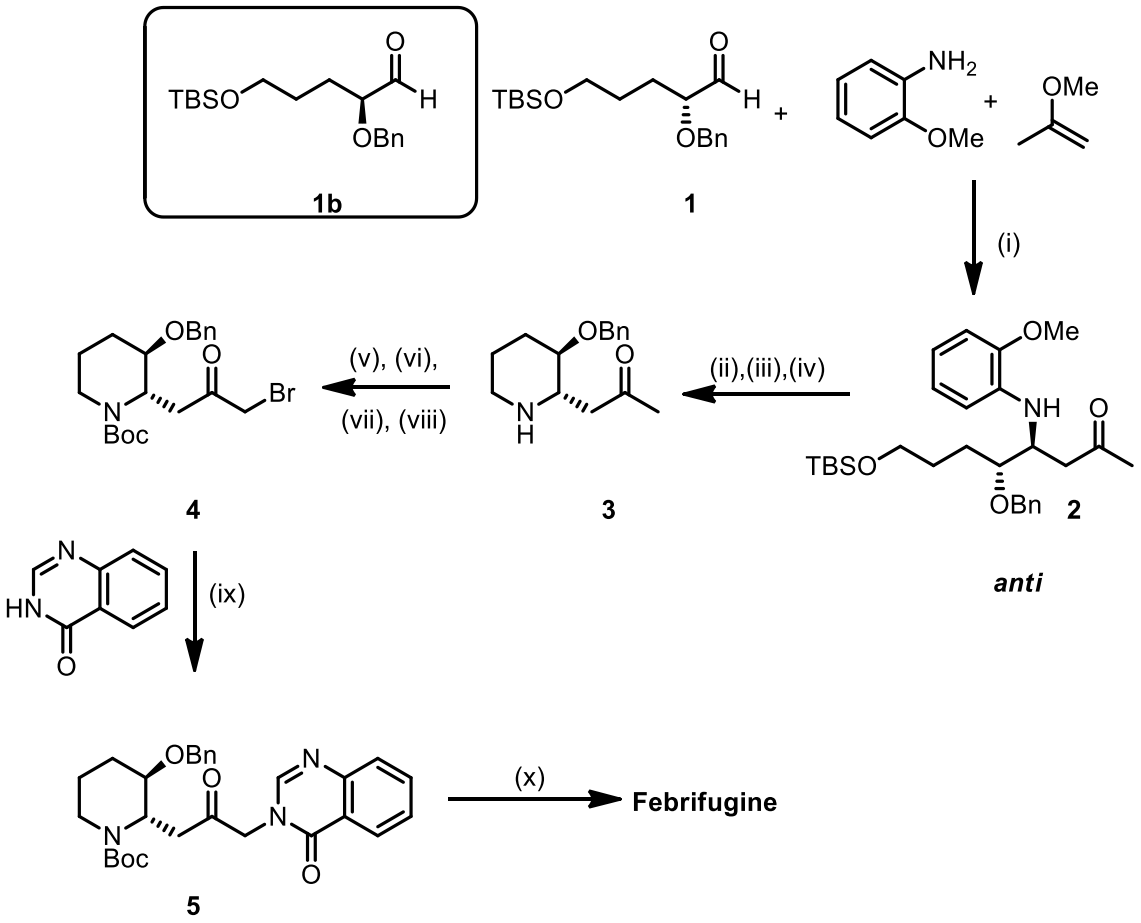
This discovery then spiked interest in the development of synthetic methods towards febrifugine, and this was to become an area of significant interest over the years. In this section some of these synthetic routes will be described.

5.1 KOBAYASHI'S ROUTE

In 1999 Kobayashi *et al.* completed the first asymmetric synthesis of febrifugine. Their approach began by controlling the two stereogenic centres of the piperidine fragment, by employing a lanthanide-catalysed three component coupling reaction between the aldehyde 1, 2-methoxyaniline and 2-methoxypropene, in aqueous media (Scheme 2).[5]

The first step was carried out in the presence of ytterbium triflate ($Yb(OTf)_3$) in aqueous THF to give the Mannich type *anti* adduct **2**. This adduct was then treated with HF to remove the TBS protecting group and this was followed by an Appel reaction resulting in spontaneous cyclisation to form an *N*-protected piperidine adduct which was readily deprotected by cerium ammonium nitrate (CAN) to give **3**.[6]

The piperidine **3** was protected as its N-Boc group and was treated with lithium hexamethyldisilazide (LHMDS) and trimethylsilyl chloride (TMSCl). The resulting silyl enol ether was then brominated to give **4**. The cross coupling reaction between the bromoketone **4** and 4-hydroxyquinazoline was carried out using potassium hydroxide to give **5** which was deprotected in 6 N HCl to produce febrifugine.



Scheme 2. Kobayashi's synthetic route to febrifugine. Reagents (i) $Yb(OTf)_3$, THF/H_2O, (ii) HF/THF, (iii) PPh_3, CBr_4/ CH_2Cl_2 , (iv) $CAN/CH_3CN/H_2O$, (v) Boc_2O, (vi) LHMDS/THF, TMSCl, (vii) $MCPBA/CH_2Cl_2$, (viii) PPh_3, CBr_4/ CH_2Cl_2 , (ix) 4-hydroxyquinazoline, KOH, (x) 6N HCl reflux

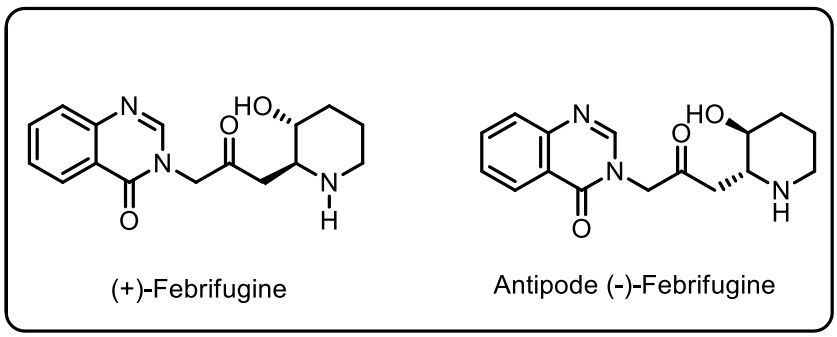


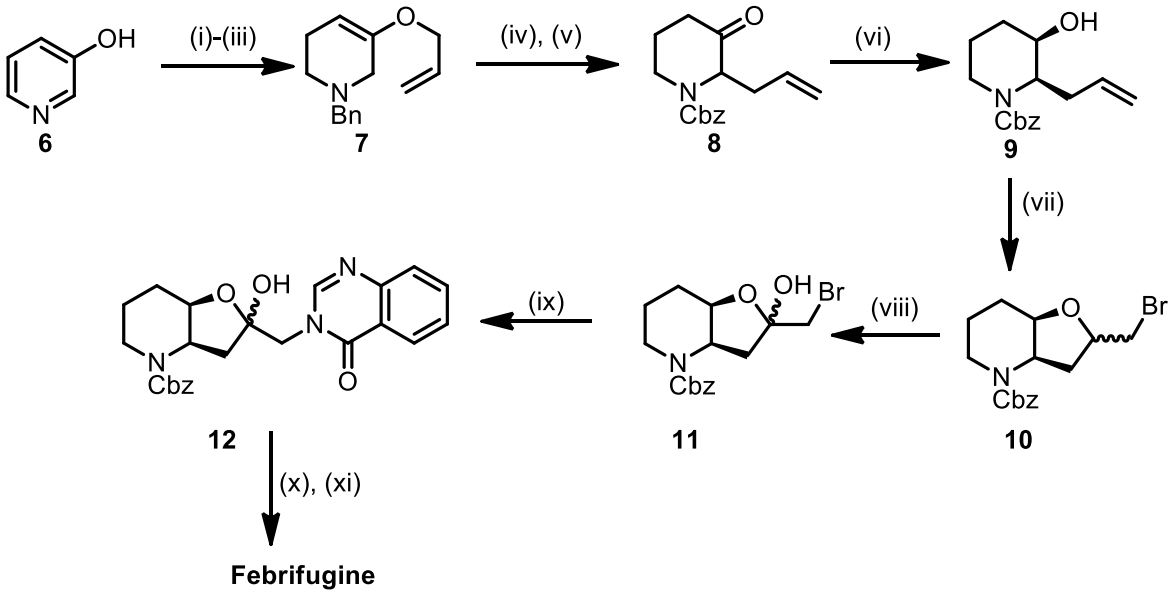
Figure 2. Shows (+)-Febrifugine and (-)-Febrifugine

Analysis of the synthetic febrifugine analogue by optical rotation revealed that the antipode of the naturally occurring (+)-febrifugine had been generated (Figure 2).[5] This drove Kobayashi to then later synthesise the naturally occurring analogue by using the chiral ester **1b.** Interestingly, the isomerisation problems encountered earlier (Scheme 1) were not met in the final products delivered by this route. This was suggested to be due to the reduced exposure of febrifugine to HCl during the removal of labile Boc protecting group.[6]

5.2 TAKEUCHI'S ROUTE

In 1999 Takeuchi *et al*. also completed their first synthetic route to (±)-febrifugine (Scheme 3), where they used the relatively cheap 3-hydroxypyridine as a starting material **6**.[7] This route consisted of the reduction of the pyridinium salt formed from the reaction between **6** and benzyl chloride to afford the 3-allyl-*N*-benzyl derivative **7**. The benzyl group was replaced by a benzyloxycarbonyl group, by treating **7** with benzyl chloroformate (CbzCl). A Lewis acid catalysed Claisen rearrangement, which took place at room temperature, gave the piperidine-3-one derivative **8**. The reduction of **8** gave **9** as the sole product, this stereoselective reduction was studied computationally by a PM3 (Parameterized model number 3) calculation.[7]

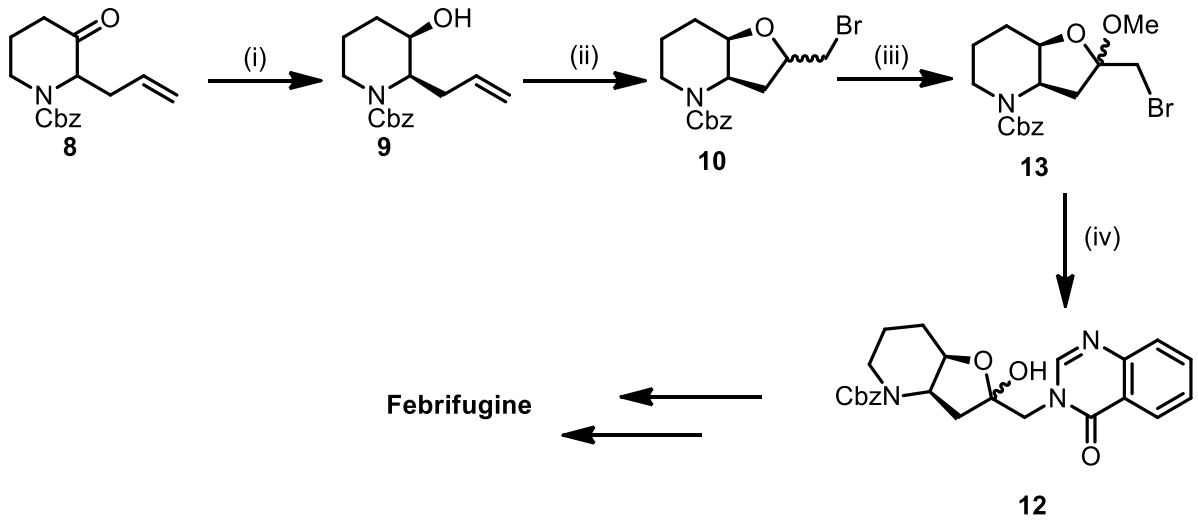
Bromination of **9** using *N*-bromosuccinimide (NBS) afforded the pyridine carboxylate **10**, this intermediate was then reacted with potassium *tert*-butoxide, followed by a bromohydrin reaction using NBS and water to produce **11**. The cross coupling reaction of the 4-hydroxyquinazoline and **11** in the presence of potassium carbonate afforded **12**, which through hydrogenolysis and isomerisation, gave the intended febrifugine structure. However, the final product was obtained in low purity, this was due to the small difference in solubility of the febrifugine product and isofebrifugine **12**.[7,8]



Scheme 3. Takeuchi's synthesis of febrifugine. Reagents: (i) BnCl; (ii) NaOMe, allylbromide; (iii) $NaBH_4$; (iv) CbzCl, Et_3N; (v) $BF_3.Et_2O$; (vi) $NaBH_4$; (vii) NBS; (viii) KOt-Bu; then NBS, H_2O; (ix) 4-hydroxy quinazoline, K_2CO_3; (x) H_2, Pd/C; (xi) EtOH, reflux;

In 2000 Takeuchi *et al.* discovered an asymmetric route to piperidine **9** via the use of baker's yeast. The yeast reduction of the 3-piperidone derivative **8** produced the chiral piperidine-3-ol intermediate **9** (Scheme 4) in a high yield and in high enatiomeric purity. This result also played a major role in determining the absolute configuration of isofebrifugine as (*2S, 3S*).[8]

Furthermore Takeuchi found that the use of the 2-methoxy derivative **13** improved the yield and reproducibility of the synthesis of Cbz protected isofebrifugine.[8]



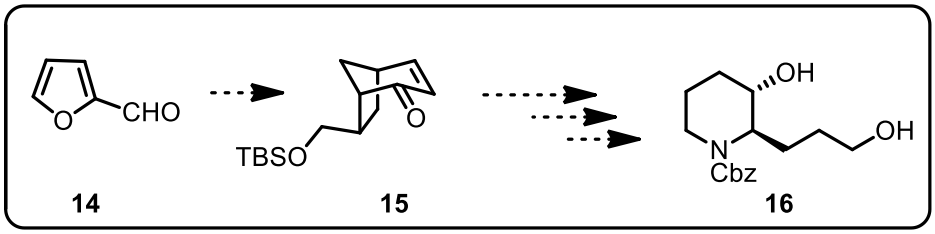
Scheme 4. Takeuchi's improved synthesis of febrifugine. Reagents: (i) Baker's Yeast, Sucrose, EtOH/H_2O, rt 24h (ii) NBS; (iii) KOt-Bu; then NBS, MeOH; (iv) 4-hydroxy quinazolinone, K_2CO_3; (v) H_2, Pd/C; (vi) EtOH, reflux;

Takeuchi and his team then examined the isomerisation of febrifugine and isofebrifugine in order to determine a method for isolating pure febrifugine analogues.[8] This study involved exposing these compounds to various solvents including toluene, DMF, pyridine, EtOH, water and 10% HCl (aq). Heating the isolated analogue **12** at 80 °C for 30 min in water resulted in the largest ratio (2:1) of febrifugine to isofebrifugine among the selected solvents. On the other hand, the epimerisation of **12** in 10% HCl was not observed under the same conditions. Based on these results, Takeuchi was able to isolate pure febrifugine as the hydrochloride salt and its analytical properties were found to be identical to those reported for the natural product.[8]

5.3 TANIGUCHI AND OGASAWARA'S ROUTE

Taniguchi and Ogasawara demonstrated an alternative method to febrifugine, where they utilised chiral building blocks to assemble these molecules with control of absolute and relative stereochemistry.[9] Their route was based on the proposal that the piperidine moiety

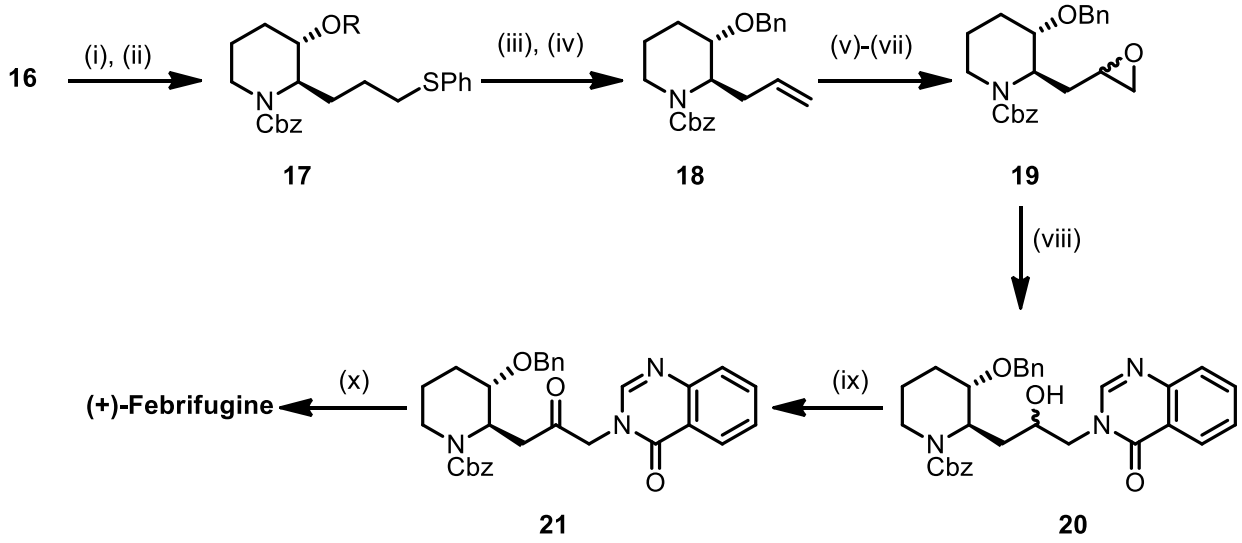
16 could be formed over several steps from an enantiomerically pure chiral building block **15**, which could in turn be prepared from furfural **14** (Scheme 5).[9]



Scheme 5.

The diol **16** was transformed regioselectively into the primary sulphide **17**, when reacted with diphenyl disulfide in pyridine in the presence of tributylphosphine (Scheme 6). After benzylation of the secondary hydroxyl functionality, the benzyl ether obtained was converted into the sulfoxide which was heated at reflux in diphenyl ether in the presence of calcium carbonate to furnish the terminal olefin **18**.

During their experimental work Taniguchi *et al.* found that the direct epoxidation of the olefin **18** with a peracid proceeded very slowly. Therefore **18** was converted into the epoxide **19** via dihydroxylation, monotosylation and base induced cyclization which in turn produced an inseparable mixture of diastereoisomers of **19**. The mixture was then reacted with the potassium salt generated from the 4-hydroxyquinazoline to furnish the secondary alcohol **20** as an inseparable mixture of diastereoisomers. This mixture was oxidised with Dess-Martin periodinane to give the protected febrifugine **21** as a single product. Heating **21** at reflux with 6 N HCl afforded (+)-febrifugine.

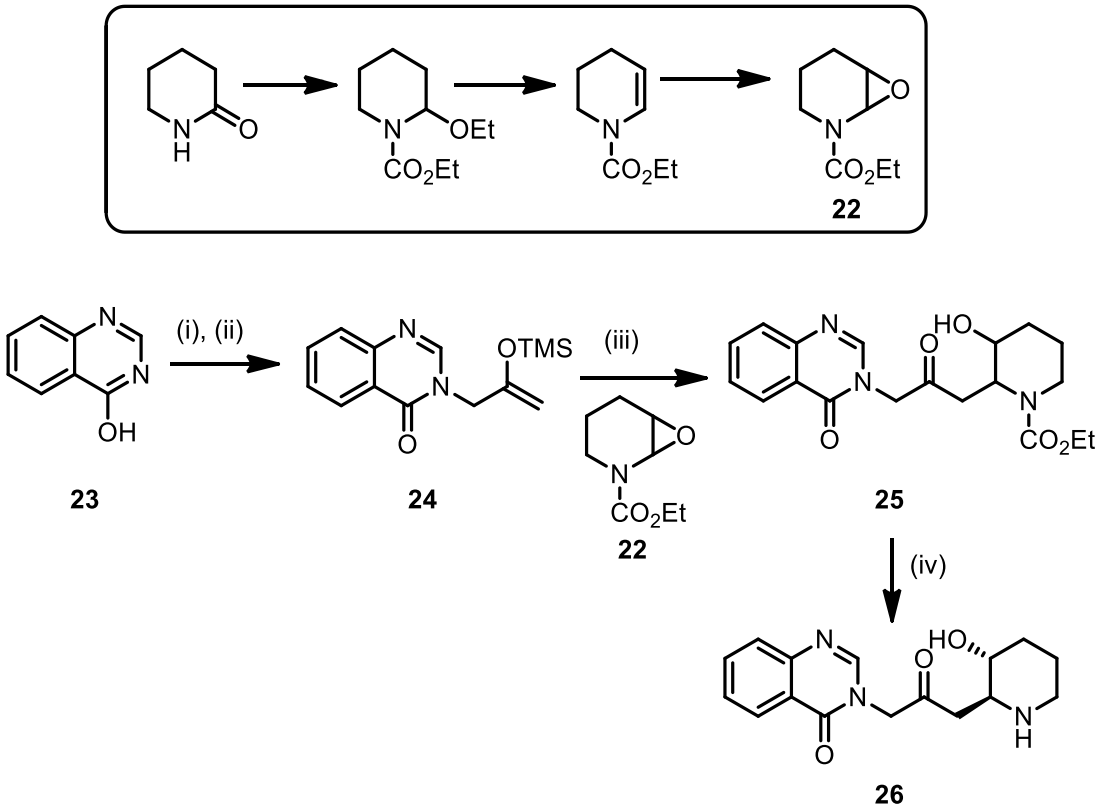


Scheme 6: Taniguchi and Ogasawara's proposed route, Reagents: (i) PhSSPh, Bu_3P, pyridine, (ii) BnBr, NaH, (iii) 30% H_2O_2, (iv) $CaCO_3$, Ph_2O reflux, (v) OsO_4 (cat.) NMO, THF, (vi) TsCl, pyridine, (vii) K_2CO_3, MeOH, (viii) KOH, 4-hydroxyquinazolinone, MeOH, (ix) Dess Martin oxidation, (x) 6N HCl

Even though Taniguchi and Ogasawara's route was successful in synthesising a pure analogue of the natural (+)-febrifugine, they were only able to obtain a yield of 11% over a total of 24 steps, hence a more efficient route would be more beneficial.[9]

5.4 Burgess' Route

Burgess *et al.* developed a synthetic route towards (+)-febrifugine analogues that employed *N*-acyl iminium ions, generated in the presence of Lewis or BrØnsted acids, for the key carbon-carbon bond construction step.[10] The *N*-acyl iminium precursor **22** (Scheme 7) was synthesised from *N*-carbethoxy-1,-2,-3,-4-tetrahydropyridine via an intermediate epoxide. The strategy was to introduce the silyl enol ether **24** which would in turn be generated by the *N*-alkylation of the 4-hydroxyquinazoline with chloroacetone and trapped by the introduction of trimethylsilyl trifluormethane sulfonate (TMSOTf) (Scheme 7)**.** [10]

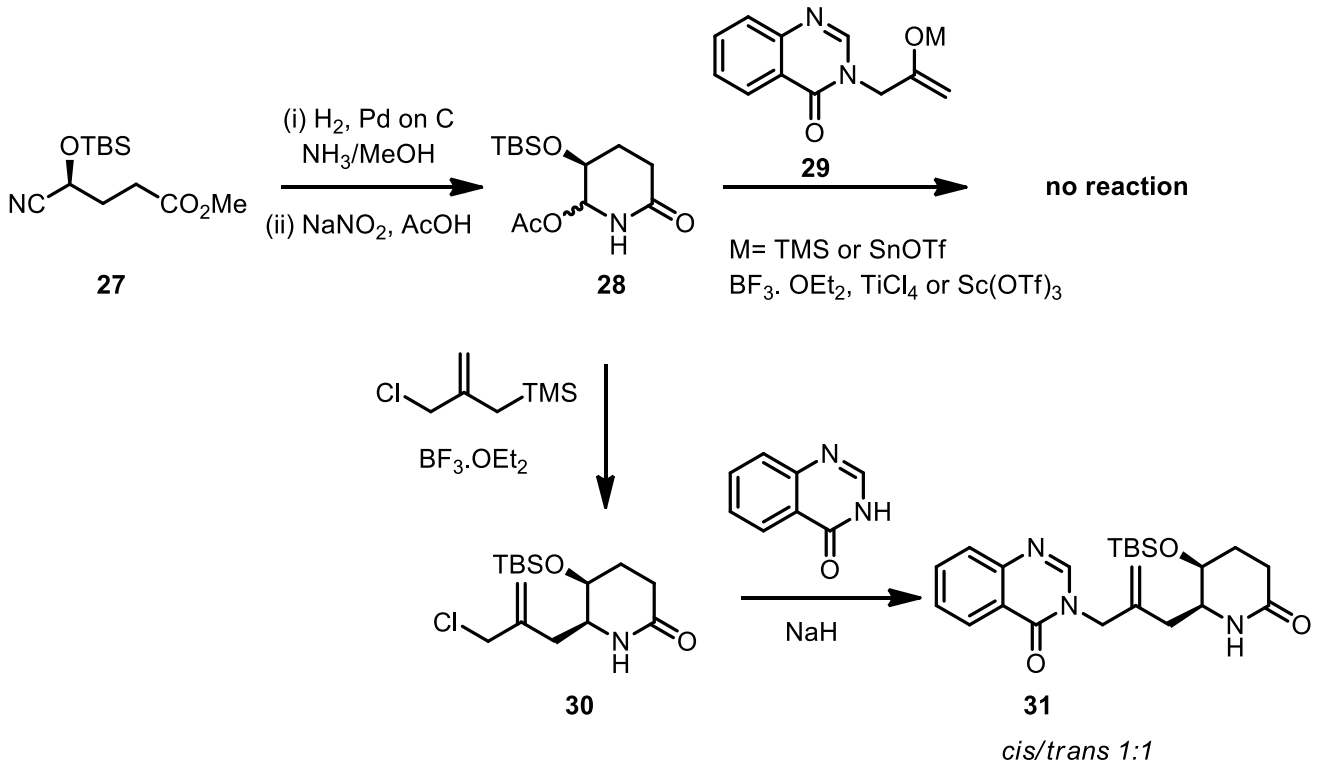


Scheme 7: Burgess' route, Reagents: (i) NaH, DMF, 0 ^{o}C then chloroacetone; (ii) TMSOTf, Hunig's Base, CH_2Cl_2, RT; (iii) $TiCl_4$, CH_2Cl_2, 0 ^{o}C; (iv) separation by flash chromatography then KOH, diethylene glycol, H_2O,reflux.

The initial coupling of the epoxide **22** and silyl enol ether **24** was accomplished by treatment with titanium tetrachloride ($TiCl_4$) to generate a mixture of separable diastereoisomers **25**. After the separation of the diastereoisomers via chromatography, potassium hydroxide was added to deprotonate the basic amine to yield the natural product analogue **26** in a 10% yield.[10]

Burgess's strategy provided a convenient method to generate (+)-febrifugine analogues. For example, the electronic effects of the 4-hydroxyquinazolinone could be explored by coupling various analogues to the piperidine epoxide. Even though the route was low yielding, Burgess's method proceeded with high stereoselectivity.

5.5 RUTJES'S ROUTE



Scheme 8: Initial approach to febrifugine devised by Rutjes *et al*.

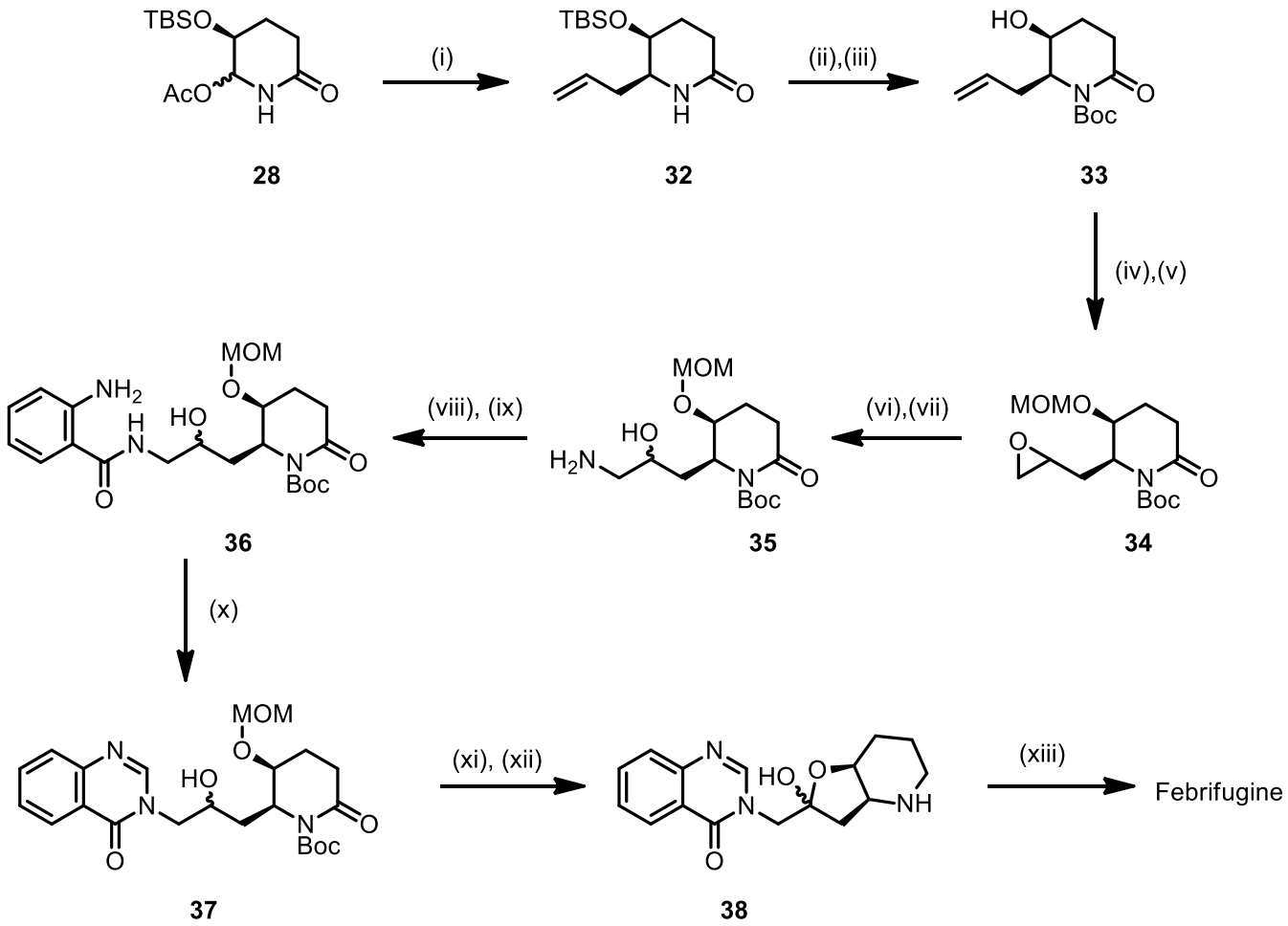
Rutjes *et al.* developed complementary chemoenzymatic approaches for the rapid construction of hydroxypiperidine scaffolds, which resulted in the enantioselective synthesis of either enantiomer of febrifugine. Their work commenced with the reductive cyclization of cyanohydrin **27** (Scheme 8), followed by diazotisation to form **28**. In their initial approach they focused on introducing the quinazoline side chain as the corresponding stannyl enol ether **29**, however their strategy was unsuccessful despite trying a variety of conditions and Lewis acids.[11]

Rutjes then anticipated that the side chain could be built in two steps, first by introducing a 2-(chloromethyl)allyl moiety to form **30**. This was then followed by the nucleophilic displacement of the chloride by the quinazoline nucleophile to form the febrifugine adduct **31** at an 81% yield.[11] However, the reduction of the lactam carbonyl proved difficult and

various methods failed to successfully lead to the selective reduction to the desired piperidine system, so this initial idea was abandoned.

The group then chose a slightly longer and more linear synthetic route which involved building the side chain to attach the piperidine moiety **28** gradually by reacting it with allyltrimethylsilane and $BF_3.OEt_2$ to give the lactam **32** as a 4.2:1 mixture of *cis/trans* isomers (Scheme 9). After chromatographic separation, the *cis*-isomer was reduced with lithium aluminium hydride ($LiAlH_4$). The newly formed amine was then protected with a Boc group and the alcohol was converted to a methoxymethyl ether (MOM) group to give **33** in a good yield. The subsequent mCPBA mediated epoxidation followed to afford **34** as a 2.5:1 mixture of diastereoisomers.[11]

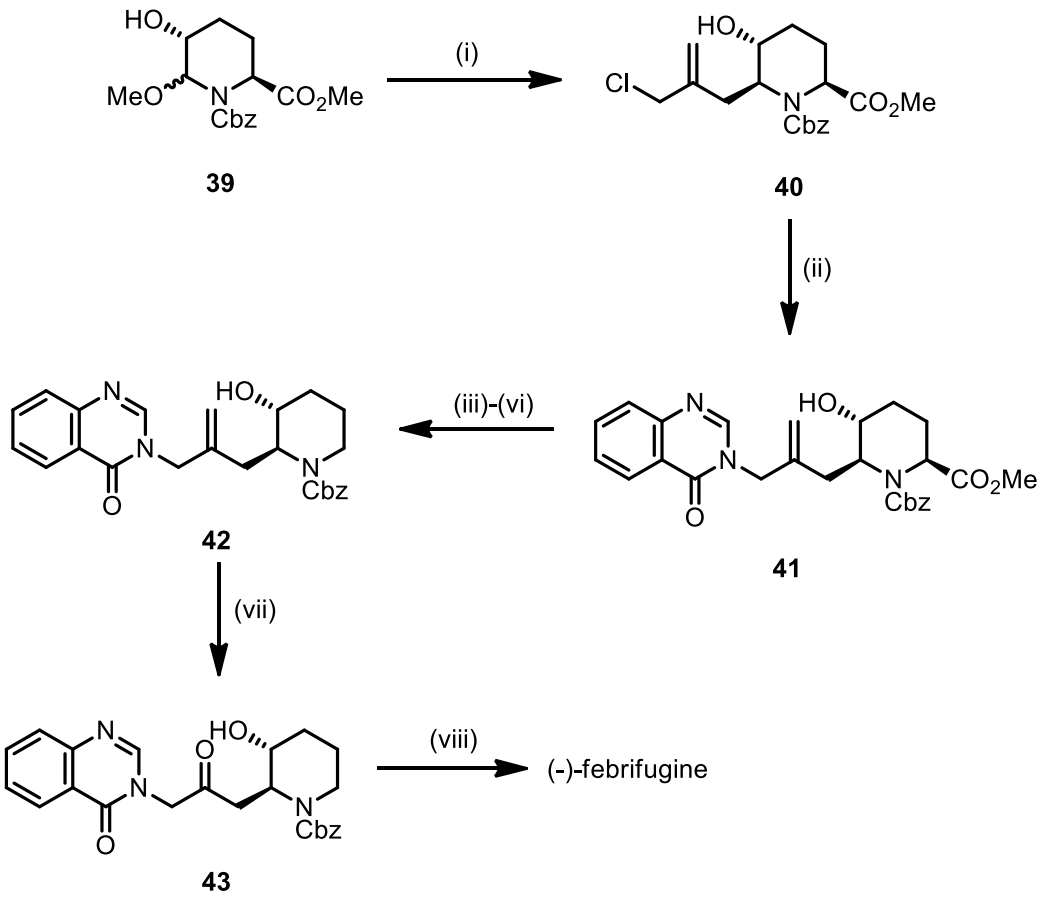
The epoxide was then opened with sodium azide, followed by Staudinger reduction to form the amine **35**. The reaction of the amine with isatotic anhydride (Et_3N, EtOAc, 40 ^oC) led to the introduction of anthranilic acid and the hydrolysis of the MOM ether afforded the desired amide **36**. The quinazolinone moiety was then formed via a condensation reaction under the influence of triethyl orthoformate ($CH(OEt)_3$) in toluene at elevated temperatures to give **37**. The final step involved Dess Martin periodinane oxidation and protecting group removal to give the isofebrifugine **38** which was isomerized in refluxing water to give the final febrifugine analogue.[11]



Scheme 9: Rutjes' synthesis of (+)-febrifugine. Reagents: (i) allytrimethylsilane, $BF_3.OEt_2$, (ii) $LiAlH_4$, THF (iii) $(Boc)_2O$, NaOH, (iv) MOMCl DiPEA, (v) mCPBA, $NaHCO_3$, (vi) NaN_3, NH_4Cl, (vii) PMe_3,NaOH, (viii) isatoic anhydride, Et_3N, EtOAc, (ix) 1M NaOH, (x) $CH(OEt)_3$, PhMe, 40 ^oC, (xi) Dess Martin , CH_2Cl_2, (xii) 10% HCl in EtOAc, (xiii) H_2O, reflux

The overall yield for this synthetic route was 2.5%, however as it utilised cheap starting materials, the route was thought to offer various possibilities for the preparation of many different synthetic analogues.[11] Recently Rutjes *et al.* have developed an alternative strategy were febrifugine is synthesised in a 32% yield in ten steps (Scheme 10). The high efficiency of this route was considered to be due to the high selectivity in the *N*-acyliminium ion reaction, which reduces the epimerization of isofebrifugine into febrifugine considerably. However, the

starting materials were not easily accessible therefore there were fewer possibilities for the synthesis of novel analogues.[12]



Scheme 10: Synthesis of (-)-febrifugine. Reagents: (i) $BF_3.OEt_2$, CH_2Cl_2 (ii) 4-Hydroxyquinazolinone, NaH (iii) NaOH,THF, H_2O (iv) *i*BuOC(O)Cl, NMM, THF, -15 ^oC (v) thiolactam, Et_3N, THF, 15 ^oC (vi) *t*BuSH, h*v*, THF, rt (vii) OsO_4, $NaIO_4$(viii) Pd/C, H_2, HCl, MeOH

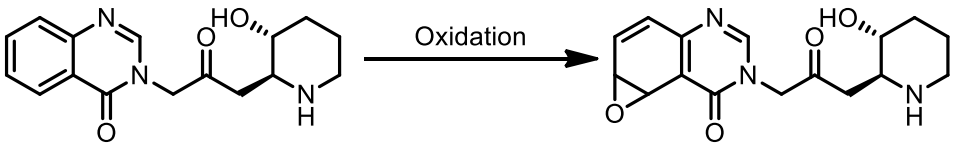
Nevertheless, this alternative route did comprise of similar steps to the preliminary synthetic route (Scheme 8). For example the *N,O*-acetal **39** was coupled to 2-(chloromethyl)allylsilane in the presence of $BF_3.OEt_2$ to afford **40**. The febrifugine skeleton **41** was then completed via the coupling reaction between **40** and the deprotonated quinazolinone intermediate. Subsequent quantitative ester saponification was achieved by sodium hydroxide, followed by a Barton decarboxylation, involving the mixed anhydride formation, coupling with thiolactam

and *t*BuSH mediated radical removal of the carboxylate producing **42**.[11,12] The oxidative cleavage of **42** with osmium tetraoxide and sodium periodate, followed by the hydrogenolysis of the Cbz-protection group yielded the final febrifugine structure.

6 FEBRIFUGINE ANALOGUES AS ANTIMALARIAL TREATMENTS

Malaria is widely regarded as the most severe protozoal disease, as it is one of the most common infectious diseases and is found in at least 100 tropical and subtropical countries. The most common strain found in humans is *plasmodium falciparum* and is known to kill on average a total of 3 million people a year.[1] Consequently, the greatest defence against malaria would be a long lasting vaccine, as there is an increasing demand for medicinal agents which will overcome the increasing number of epidemics caused by resistant strains.

Based on the early studies by Koepfli, febrifugine was initially regarded as an important breakthrough in the fight against malaria. However, side effects such as nausea, vomiting and liver toxicity have prevented its use as a potential clinical drug. Febrifugine's toxicity was proposed to be due to the metabolic oxidation of the alkaloid in the host by biomolecules such as the cytochrome P-450 enzymes. This oxidation process produces highly reactive epoxides (Scheme 11). These short lived electrophilic oxides are assumed to form covalent adducts with DNA, RNA, proteins or other biomolecules inside the host during their deactivation, resulting in genetic mutations which corresponded to the observed toxicity profile.[13]



Scheme 11. Proposed oxidation of febrifugine to the electrophillic epoxide

Consequently, in 2002 Kikuchi discovered, through antimalarial screening, that febrifugine analogues bearing a modified 4-quinazolinone ring were also active, while analogues produced through the modification of the side chain attached at the N-3 position of the quinazolinone ring were ineffective (Figure 3).[14]

Kikuchi was able to access a number of febrifugine and isofebrifugine analogues through chemical synthesis. For example **44** - **46** were synthesised in order to investigate the role of the benzene moiety and nitrogen atom of the quinazolinone ring in the molecule's bioactivity (Figure 3). The antimalarial activity of these analogues against *P.flaciparum* (FCR-3 strain) and the cytotoxicity against mouse mammary FM3A revealed moderate activity in the latter (EC_{50} = 6.0×10^{-7}, 9.0×10^{-8}, 5.0×10^{-7} and 2.1×10^{-6} M). However they showed no selectivity against *P.flaciparum* indicating the importance of the quinazolinone ring for this biological target.[14]

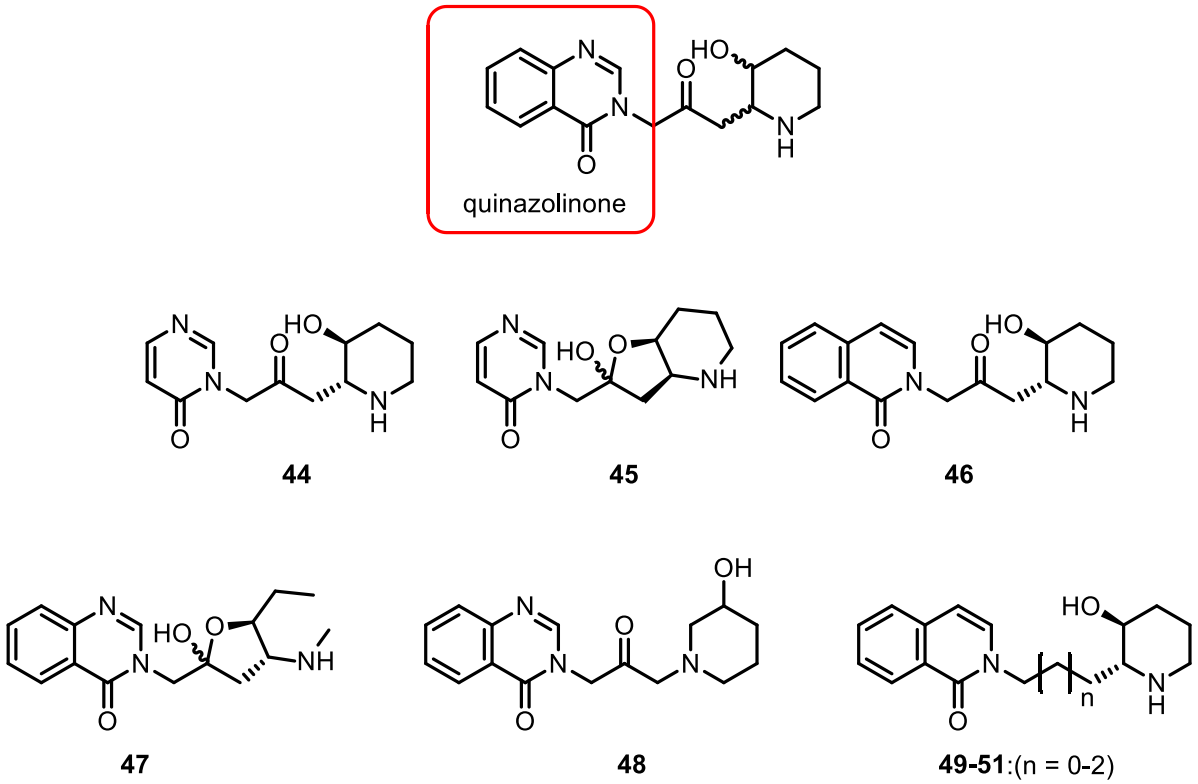


Figure 3: Kikuchi's analogues

Examination of the analogues **47** - **48** revealed how modification the piperidine ring of febrifugine resulted in a loss of activity. Kikuchi *et al.* also synthesised **49** - **51** to determine the importance of the length of the connecting linking carbon chain between the piperidine structure and quinazolinone; it was discovered that the increase in length resulted in complete loss of activity.[14]

However, Kikuchi's main intention for his work was also to examine the structure-activity relationship (SAR) studies of Takaya's bicyclic febrifugine analogues **52** and **53** (Figure 4). These analogues had exhibited excellent antimalarial activity, with high selectivity against the malarial parasite. Therefore, a large number of synthesised analogues of **52** and **53** each containing different functional groups were studied in order to develop potent chemotherapeutic drugs, for example analogues **54** and **55**.

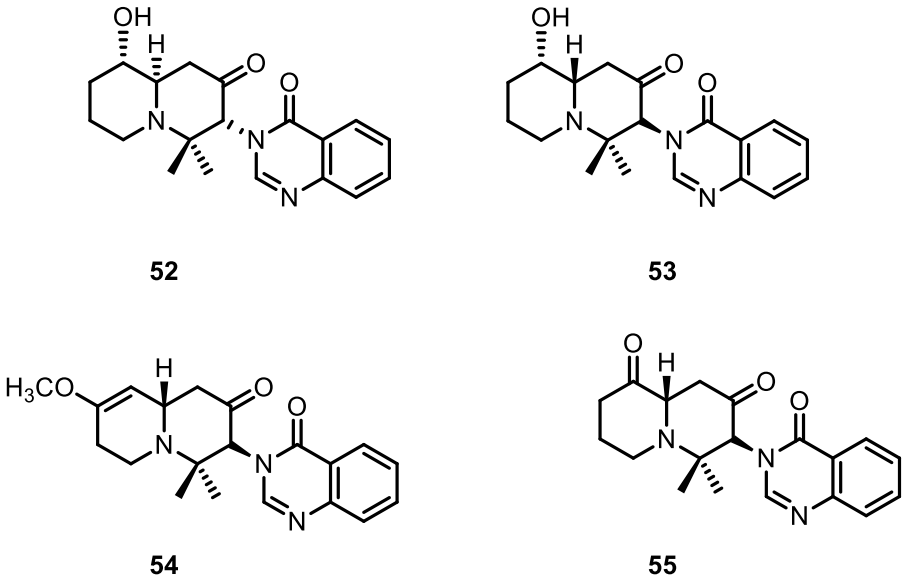


Figure 4: Kikuchi's work based on Takaya's analogues

In 2003 Hirai reported the isolation and the synthesis of the metabolic products of febrifugine (**56** and **57**) and Takaya's analogue **52** (metabolites **58** and **59**)**.** His objective was to investigate the antimalarial activity of the metabolites and their analogues in order to synthesise compounds that preserved antimalarial activity relative to their parent structures.[15]

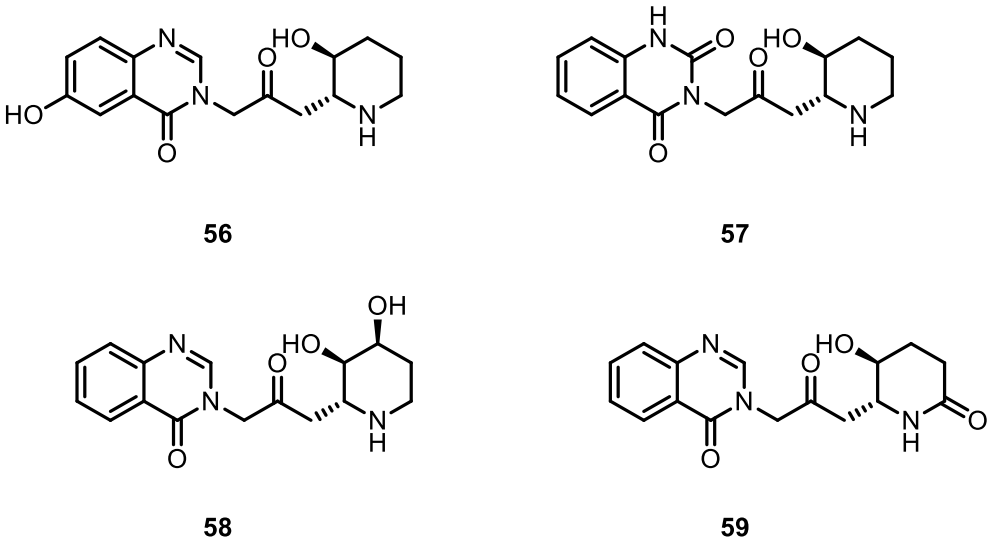
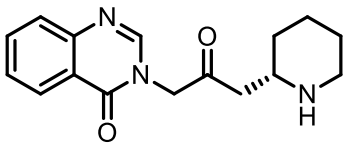


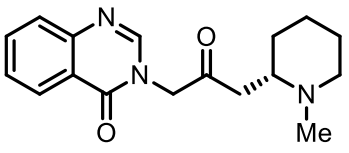
Figure 5: Hirai's metabolites

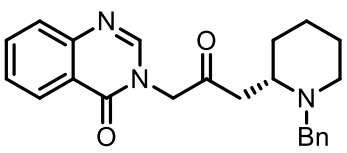
The *in vitro* antimalarial and cytotoxicity assays using the synthetic compounds demonstrated that **56** and **58** had superior activity against the *P.flaciparum* strain as compared to compounds **57** and **59**. Hirai's results suggested that the basicity of both the nitrogen atoms on the quinazolinone and piperidine structures had a crucial effect on the overall activity against malaria. Nonetheless, as no serious side effects were observed with compound **56**, this metabolite was discovered to be a promising lead compound in the development of a new type of antimalarial drugs.[15]

In 2005 Michael *et al.* focused on the synthesis of the simpler deoxyfebrifugine analogue **60** (Figure 6), even though this analogue was known to be inferior to febrifugine in *in vitro* antiplasmodial assays.[17] Michael's interest had stemmed from the fact that the deoxy analogue **60** had similar antimalarial activity to quinine, therefore a direct synthesis of deoxyfebrifugine and its analogues would provide alternative promising lead compounds for future study.[18]



60





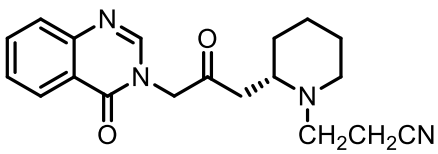


Figure 6: Deoxyfebrifugine and its synthetic derivatives

Zhu *et al.* also examined various ways of improving the biologically activity of febrifugine analogues through structural modifications.[19] Their research focused mainly on the 4-

quinazolinone moiety as it was earlier determined to be crucial for the antimalarial activity of febrifugine. The aim of their research was to prevent the oxidation of this moiety to the corresponding arene oxide by cytochrome P-450 enzymes (Scheme 11). Zhu found that the only way to make this oxidation process unfavourable was to block the C-5 or C-6 positions of the quinazolinone ring.

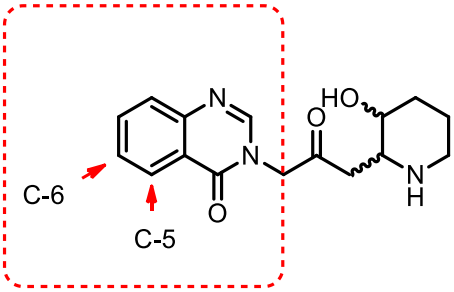


Figure 7: C-5 and C-6 positions of the quinazolinone ring

Based on this hypothesis, Zhu and his team successfully designed compounds bearing various substituents at the C-5 and C-6 positions (Figure 7) to prevent unwanted metabolic degradation.[20] Subsequently as the synthesised compounds resembled febrifugine they were expected to have the same or similar mode of action, but were also expected to be less likely to produce toxic intermediates. The synthesised compounds **61** - **66** (Figure 8) were tested *in vitro* against two *P.falciparium* malaria parasite clones W2 and D6. The W2 clone was found to be susceptible to mefloquine but resistant other antimalarial drugs such chloroquine, sulfadoxine, primethamine and quinine, whereas the D6 clone was naturally resistant to mefloquine but susceptible to the rest of the drugs.[21, 22]

The *in vitro* toxicology studies were carried out in isolated rat hepatocytes which are widely used in drug metabolism and toxicity studies.[23] Chloroquine and febrifugine were also screened in W2, D6 and rat hepatocytes as positive controls. The results revealed that

compounds **61** and **62** showed potency against both the chloroquine sensitive malarial strain (D6) and chloroquine resistant malarial strain (W2). It was also discovered that these compounds were over 100 times less toxic compared to the parent febrifugine analogue. On the other hand, compounds with electron withdrawing groups on the C-6 position or bulky substituents (**63** - **66**) had both decreased antimalarial activity and toxicity.

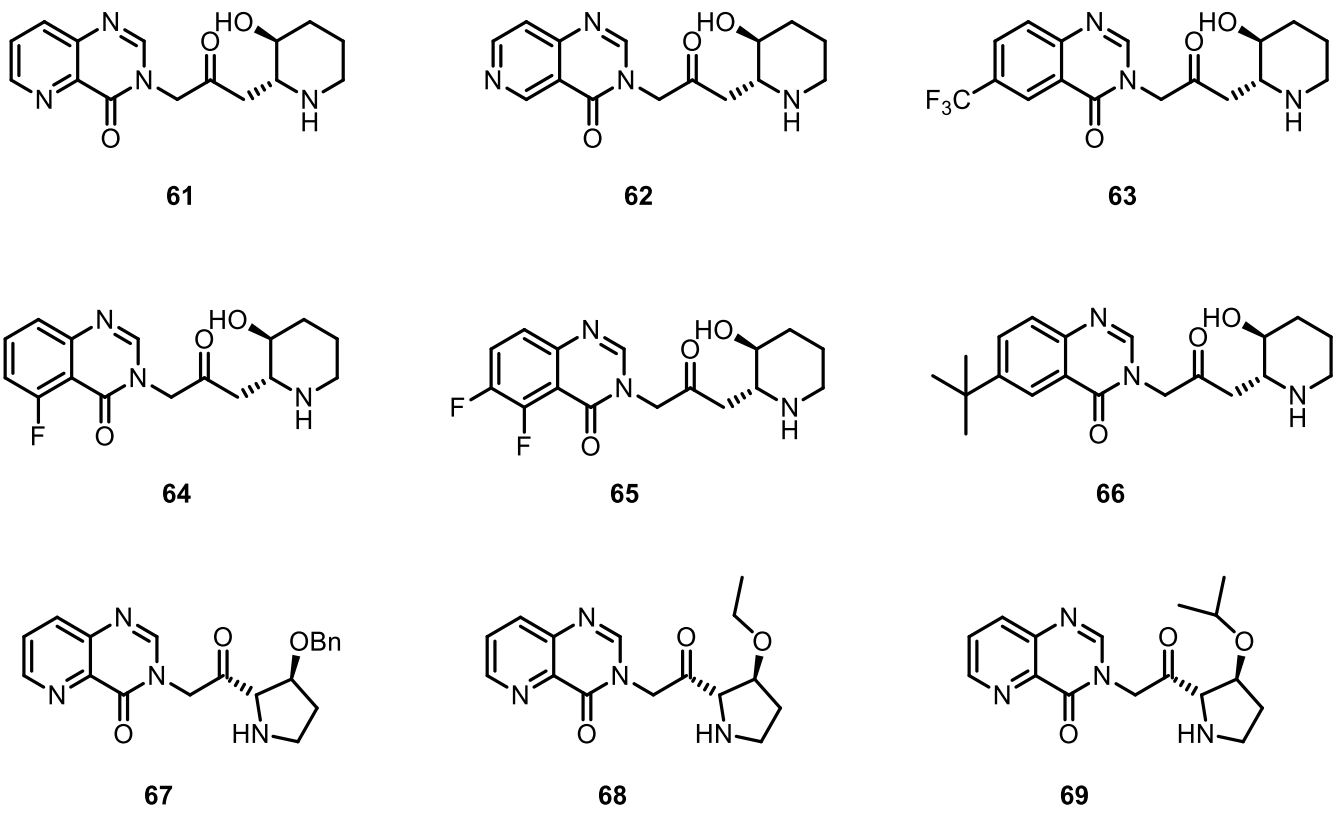


Figure 8: Zhu's analogues

In 2012 Zhu *et al.* then discovered that the original piperidine ring could be replaced by a pyrrolidine ring and that the presence of the 3'methylene group was not essential for antimalarial activity by successfully synthesising and evaluating compounds **67** - **69**. The compounds still resembled febrifugine by possessing a planar aromatic ring, a 1-amino group and C - 2', C - 3' O functionality, therefore they were still expected to exhibit a similar mode

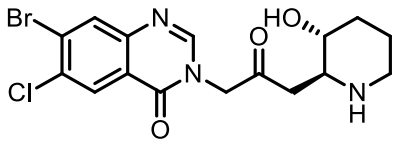
of action as the previous analogues. However, the other major difference to their structure was that they also possessed alkoxy groups on the pyrrolidine moiety, hence making them more lipophilic.[19]

The synthesised compounds **67** - **69** were also found to display superior and equally potent antimalarial activity against chloroquine sensitive and resistant malaria strains as compounds **61** - **66**. However, the antimalarial potency was found to be improved when the lipophilicity of the compound was increased. Therefore, further studies led to compounds **67** and **68** to be identified as having excellent efficacy in relevant primate models and were found to possess a wider therapeutic index than other commonly used antimalarial drugs.[19]

7 FEBRIFUGINE ANALOGUES AGAINST IPF

Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease within the group of idiopathic interstitial pneumonias. It is a distinct clinical entity occurring in adults and is limited to the lungs.[2] The disease affects approximately 5 million people globally and appears to be increasing in prevalence. Despite recent advances, IPF remains generally resistant to current drug therapies and is invariably fatal, with median survival of 3 - 5 years. Even though the current treatments for IPF, pirfenidone and nintedanib, have been proven to slow the decline of lung function, their effects on the long term prognosis of the disease are still unknown.[42] This together with the emerging evidence of different phenotypes in IPF and the lack of treatments for interstitial lung diseases other than IPF renders it an area of highly unmet therapeutic need.[2]

Recently halofuginone (Figure 9), the halogenated derivative of febrifugine, has been tested in clinical trials as a potential therapeutic towards fibrotic diseases such as IPF. This alkaloid analogue was shown to inhibit the formation of excess collagen in mouse models, by preventing differentiation of the fibroblasts to myofibroblasts.[42] As a result, a reduction in fibrosis was observed, which also improved physiological parameters such as regeneration in cirrhotic liver, cardiac and respiratory performance. Studies by Zhou have also reported how halofuginone inhibits T_H17 cell differentiation by activating the amino acid response pathway, by inhibiting human prolyl - transfer RNA synthetase (ProRS) to cause intracellular accumulation of the uncharged tRNA. This is hypothesised to decrease the submucosal infiltration of the lungs when a patient is suffering from fibrosis.[42]



Halofuginone

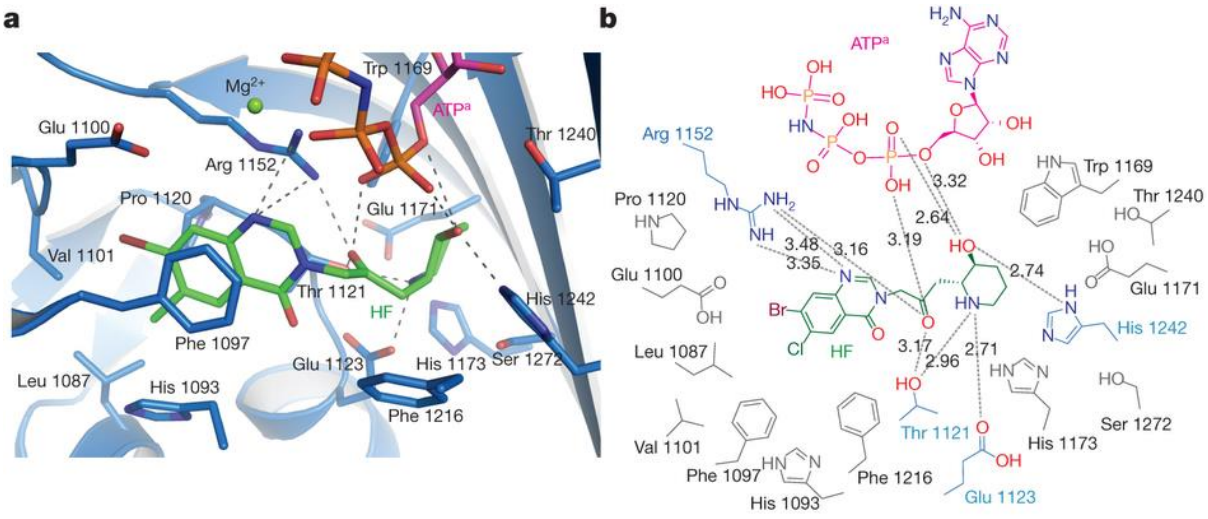


Figure 9.

Since Zhou's theory involved the presence of unhydrolysed ATP, Zhou and his team developed a binding model showing halofuginone forming extensive hydrophobic contacts and hydrogen bonding interactions with ProRS and ATP. This previously mentioned work highlights the importance in developing an efficient synthetic route towards febrifugine derivatives, as they could serve as a basis for new treatments and hopefully be possible drug candidates.

8 OUR WORK

The aim of our work was to generate an efficient route towards febrifugine analogues such as halofuginone in the hope of developing novel hybrid analogues. In order to synthesise halofuginone, a synthetic route towards its quinazolinone unit (Figure 10) had to be devised, as this compound was not commercially available at the start of the project.

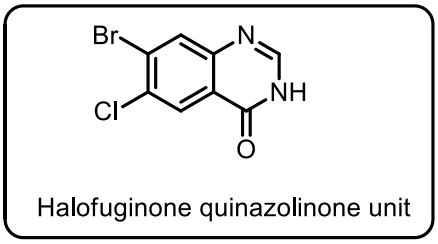


Figure 10.

The initial step was to find a literature route towards this molecule, a SciFinder Scholar search revealed that only one patented route has been reported (Figure 11). This route began with the bromination of the aromatic ring with bromine and a catalytic amount of iron chloride in *n*-butyl bromide. The oxidation of the methyl group with potassium permanganate ($KMnO_4$) then followed. The amination of the bromide using ammonium hydroxide and copper oxide

then afforded the aminated product. The reaction of the synthesised aminated product with formamide then delivered the intended quinazolinone intermediate.

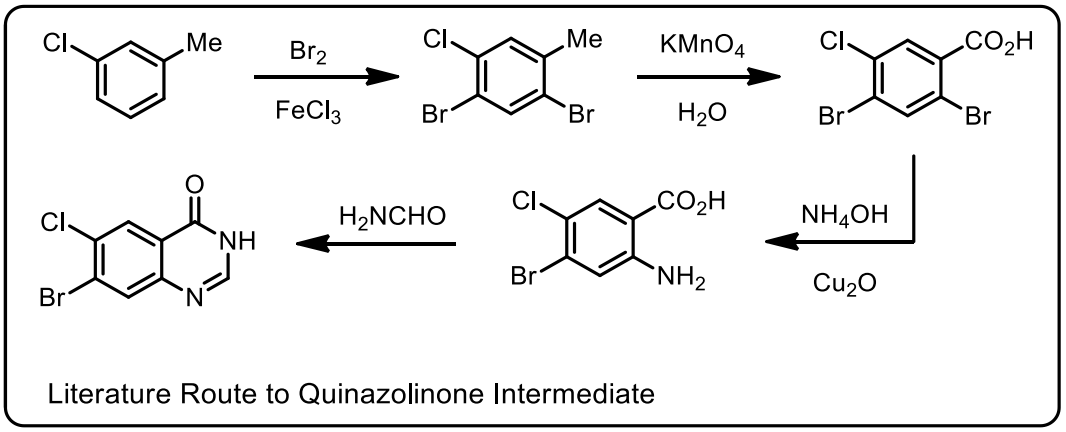
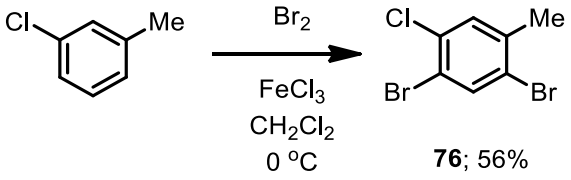


Figure 11

When we employed the reported conditions for the bromination of *m*-chlorotoluene, the intended product was obtained in a 31% yield. Interestingly, changing the solvent to the less toxic dichloromethane increased the yield to 56% (Scheme 12).



Scheme 12.

However, the subsequent permanganate mediated oxidation of the methyl group under the reported conditions proved problematic as the starting material was recovered in almost all cases (Table 1, entry 1). The ineffectiveness of this step was thought to be due to both the decomposition of the oxidant and the insolubility of the starting material.

Therefore, the use of ethyl acetate as a co-solvent and addition of the oxidant portion wise was considered, unfortunately the product was obtained in low yield (Entry 2). In addition, the use high equivalents of permanganate and employing tetra-*n*-butyl ammonium bromide

as a phase transfer catalyst also proved unsuccessful (Entry 3). Recourse to alternative conditions such as the employment of vanadium (IV) oxide sulfate ($VOSO_4$), cobalt acetate ($Co(OAc)_2$) and manganese acetate tetrahydrate ($Mn(OAc)_2.4H_2O$) catalysts also failed to promote oxidation (Entries 4, 5, 6). Consequently, the idea of brominating the methyl group and hydrolysing the resulting tribromomethyl group was investigated (Figure 12).

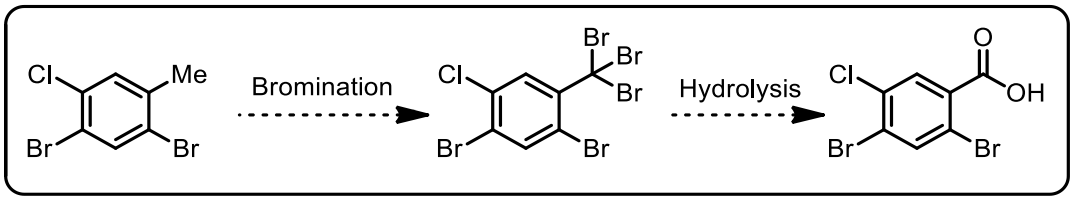
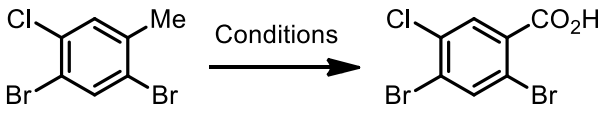


Figure 12

Reacting 4-bromo-5-chlorotoluene with NBS, azobisisobutyronitrile (AIBN) in carbon tetra chloride (CCl_4) and irradiating the mixture with a tungsten lamp without external cooling while stirring for 4 hours did not give the tribrominated product, however the dibromomethyl product was produced in a 60% yield (Table 2, entry 1). Reducing the time of irradiation to 3.5 h only resulted in a complex mixture of products being obtained.

Table 1. Permanganate mediate oxidation



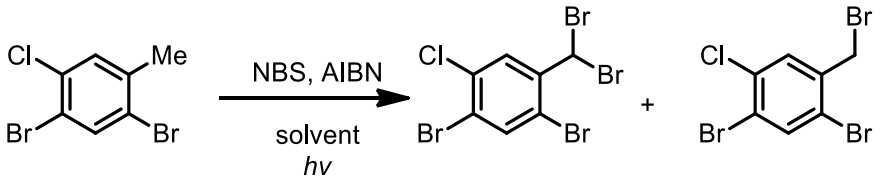
76 **77**

Entry	Conditions	Yield (%)
1	$KMnO_4$ (2 eq), H_2O, reflux, 16 h	0
2	$KMnO_4$ (8 eq), H_2O ,EtOAc , reflux, 16 h	2
3	$KMnO_4$ (20 eq), $C_{16}H_{36}BrN$ (0.6 eq), H_2O, EtOAc , reflux, 72 h	3
4	AcOH, HBr , $VOSO_4$ (3 eq), 100 °C, 20 h	0
5	$Co(OAc)_2.4H_2O$ (0.6 eq), $Mn(OAc)_2.4H_2O$ (0.2 eq), AcOH, 130 °C, 6 h	0
6	$Co(OAc)_2.4H_2O$ (1 eq), $Mn(OAc)_2.4H_2O$ (0.5 eq), AcOH, 130 °C, 6 h	0

All reactions were conducted on a 0.3 mmol scale.

As CCl_4 is a classed human carcinogen, a brief solvent screen was conducted in an effort to find a more suitable reaction medium. The use of dichloromethane afforded the product in 67% yield, however the monobrominated compound was also formed (entry 2). When a more environmentally friendly solvent such as ethyl acetate was used, the monobrominated product was observed and some starting material was recovered (entry 3).

Table 2: Optimising the reaction conditions

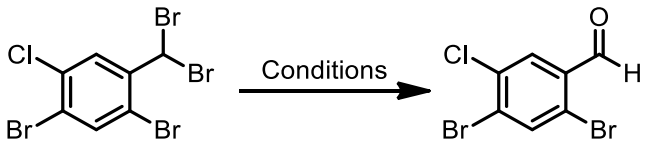


76 **78** **79**

Entry	Solvent	Time (h)	Yield (%) of 78	Yield (%) of 79
1	CCl_4	4	60	0
2	CCl_4	3.5	0	0
3	CH_2Cl_2	4	67	20
4	EtOAc	4	0	64

As dichloromethane produced the product in a good yield and was less toxic than carbon tertrachloride, the conditions listed in entry 3 of table 2 were used. With these conditions in hand the hydrolysis of the dibrominated product to form the corresponding aldehyde was investigated (Table 3).

Table 3: Hydrolysis of **78**



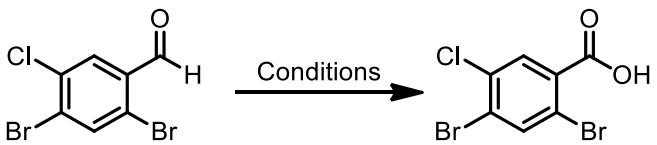
78 **80**

Entry	Solvent	Temp. °C	Time (h)	Yield (%)
1	DMSO	120	72 h	89
2	DMSO (85%), H_2O (15%)	120	16 h	90

Heating dibromide **78** in DMSO provided the product in 89% yield (entry 1, table 3). Introducing water as a co-solvent reduced the reaction time to 16 h and delivered the product in a similar yield (entry 2).

With the aldehyde **80** in hand, the oxidation step to the corresponding acid was carried out (Table 4). Oxone was used as an oxidant and it was found that increasing the equivalents of this oxidant, increased the overall yield of the product (Table 4, entries 1-3).

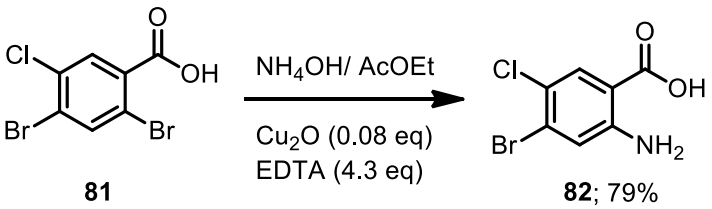
Table 4: Oxidation of the aldehyde



80 **81**

Entry	Oxidant	Solvent	Time (h)	Yield (%)
1	Oxone (1 eq)	DMF	16 h	0
2	Oxone (4 eq)	DMF	48 h	85
3	Oxone (5 eq)	DMF	48 h	91

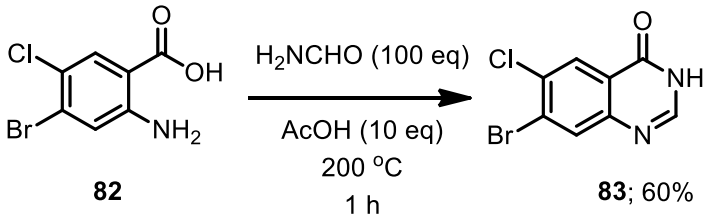
The next step was the amination of the 2,4-dibromo-5-chlorobenzoic acid to produce the aminated product. The use of ammonium hydroxide and a catalytic amount of copper oxide resulted in the product being obtained in a 79% yield (Scheme 13).



81 **82**; 79%

Scheme 13.

Finally, this product was then reacted with formamide to produce the quinazolinone intermediate in a 60% yield (Scheme 14). Having successfully synthesised the desired halofuginone quinazolinone **83**, we then turned our attention to the coupling reactions required to synthesise halofuginone and febrifugine analogues.

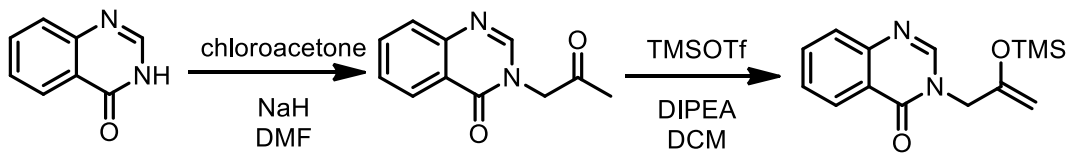


82 **83**; 60%

Scheme 14. Synthesis of the quinazolinone intermediate

9 SYNTHESIS OF FEBRIFUGINE DERIVATIVES

Before attempting to syntheses halofuginone, our preliminary goal was to synthesise a selection of febrifugine analogues using the commercially available febrifugine quinazolinone. The synthesis of these analogues would then provide a pathway to multiple derivatives, including halofuginone. Initially Burgess' method (Scheme 7) was considered as it represented a quick and straightforward coupling strategy to febrifugine.

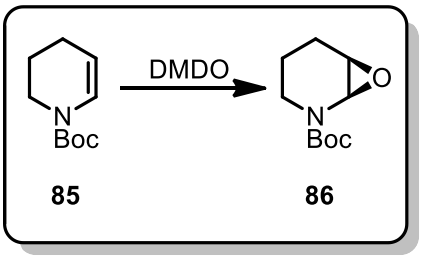


84; 93% **24**; 66%

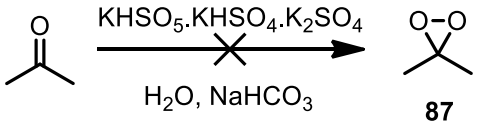
Scheme 15.

The first step in our synthetic route was to couple the quinazolinone to chloroacetone, which produced the 3-(2-oxopropyl) quinazolin-4(*3H*)-one **84** in a 93% yield (Scheme 15). This ketone was reacted with trimethylsilyl trifluoromethane sulfonate (TMSOTf) and Hünig's base (DIPEA) to produce Burgess' silyl enol ether **24** in a 66% yield, this was to be used in the next step without further purification. As the optimisation of this route was being investigated, the synthesis of the piperidine epoxide **86** was also explored. The epoxidation of the Boc protected piperidine **85** with dimethyl dioxirane (DMDO) **87** was envisioned (Scheme 16). Unfortunately, after the reaction of acetone, oxone and sodium bicarbonate it was difficult to obtain sufficient quantities of the DMDO product after distillation, hence an alternative method was devised (Scheme 16).

Initial idea:

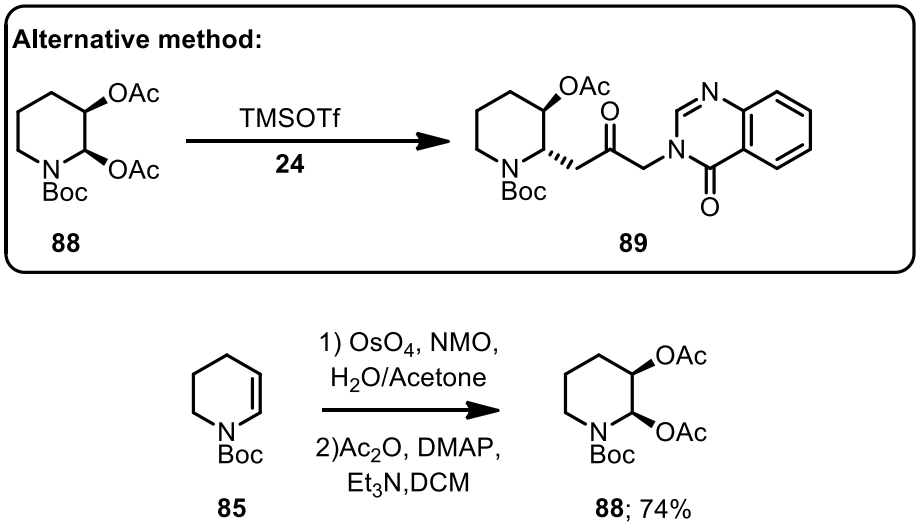


Synthesis of DMDO:



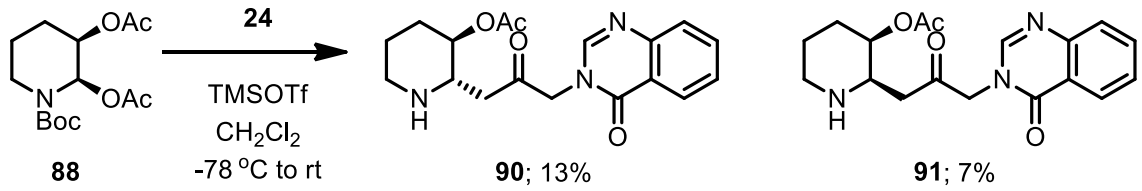
Scheme 16.

The method envisaged involved coupling the silyl enol ether **24** with a diacetate compound **88** under Lewis acidic conditions (Scheme 17). The initial step consisted of the dihydroxylation of **85** using osmium tetroxide followed by acetylation, which afforded the diacetate **88** in a 74% yield (Scheme 17).



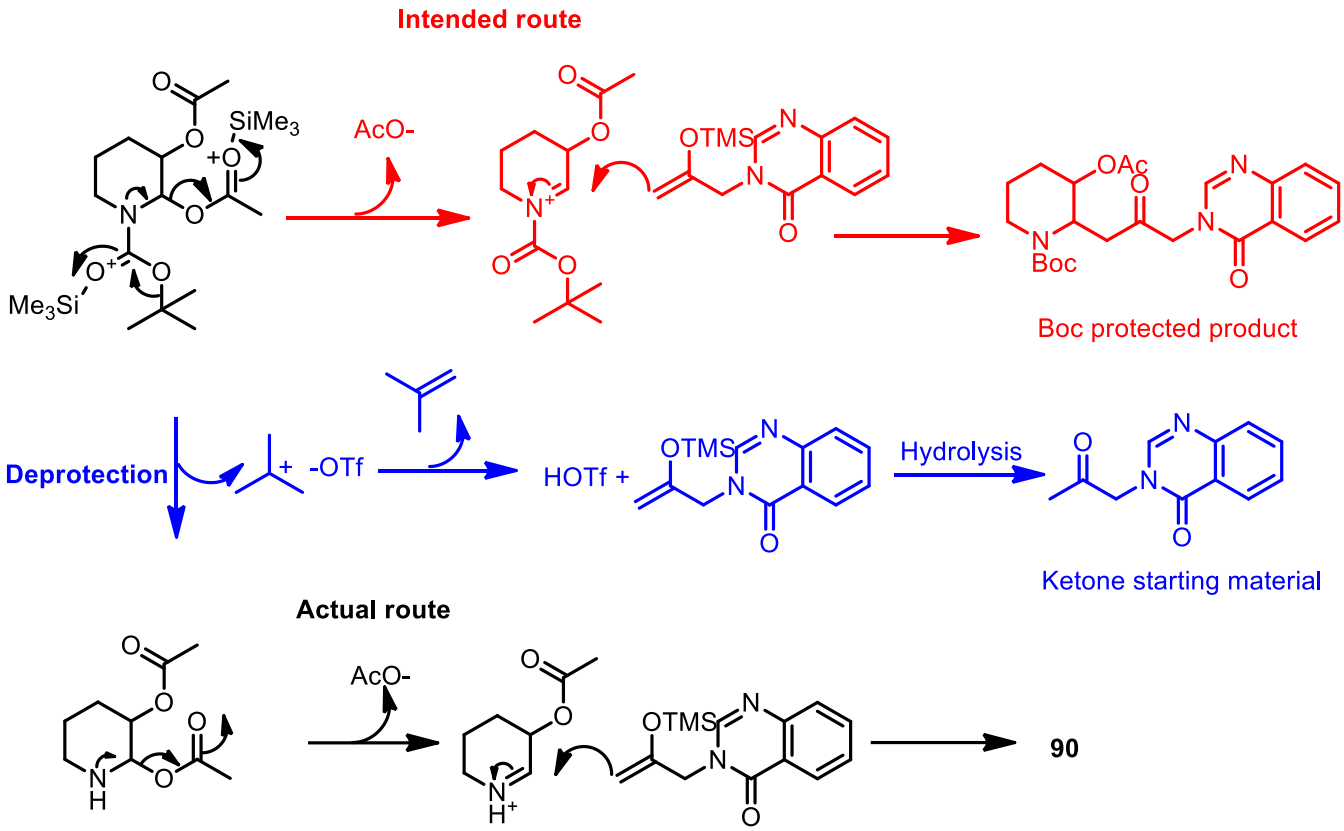
Scheme 17.

Having optimised the synthesis of the silyl enol ether **24** and diacetate piperidine **88**, we were in a position to investigate the coupling reaction. Using Burgess' conditions of introducing three equivalents of TMSOTf to **88** and then adding the silyl enol ether **24**, we were able to obtain the febrifugine analogue **90** and its corresponding diastereoisomer **91** (Scheme 18), albeit in a low yield.



Scheme 18

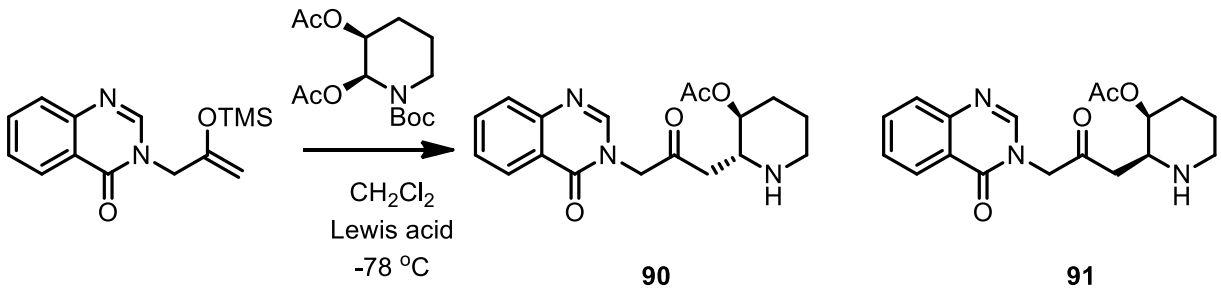
The cause of the low yield and the consequent amine deprotection was determined to be due to the use of an excess amount of the Lewis acid, which in turn coordinated to both acetate groups and the Boc carbonyl group, leading to the formation of triflic acid (Scheme 19). The acid was then proposed to react with the silyl enol ether **24** converting it back to the ketone starting material.



Scheme 19.

Therefore, a Lewis acid screen was conducted in an effort to avoid the loss of the Boc group in the hope that the protected febrifugine analogue would be obtained (Table 5). In the event, relatively weak Lewis acids ($ZnCl_2$, ZnBr, Et_2AlCl, $FeCl_3$, $Cu(CF_3SO_3)_2$, $Sc(OTf)_3$) did not afford any product, whilst the stronger promoters ($TiCl_4$, $BF_3.OEt_2$) gave the deprotected piperidine products **90** and **91** in a low yield.

Table 5: Lewis acid screen



Entry	Lewis acid	Yield (%) of 90	Yield (%) of 91
1	TMSOTf (3 eq)	13	7
2	TMSOTf (1 eq)	33	15
3	$ZnCl_2$ (1 eq)	SM recovered	-
4	$TiCl_4$ (1 eq)	25	7
5	$ZnBr_2$ (1 eq)	SM recovered	-
6	$BF_3.OEt_2$ (1 eq)	19	20
7	Et_2AlCl (1 eq)	SM recovered	-
8	$FeCl_3$ (1 eq)	SM recovered	-
9	$Cu(CF_3SO_3)_2$ (1 eq)	SM recovered	-
10	$Sc(OTf)_3$ (1 eq)	8	16

Through NMR analysis of the reaction mixture, it was found that both cis and trans products were formed. Their relative stereochemistry was determined by ^1H NMR spectroscopy using Karplus' equations. The splitting patterns for the respective isomers are shown in Figure 13. The trans isomer should exhibit large trans-diaxial coupling for the proton highlighted, while

the cis isomer should show smaller axial-equatorial coupling. In the event we assigned the compound with a broad multiplet at 4.56 ppm as product **90**, whereas compound **91** showed a narrow multiplet at 4.95 ppm.

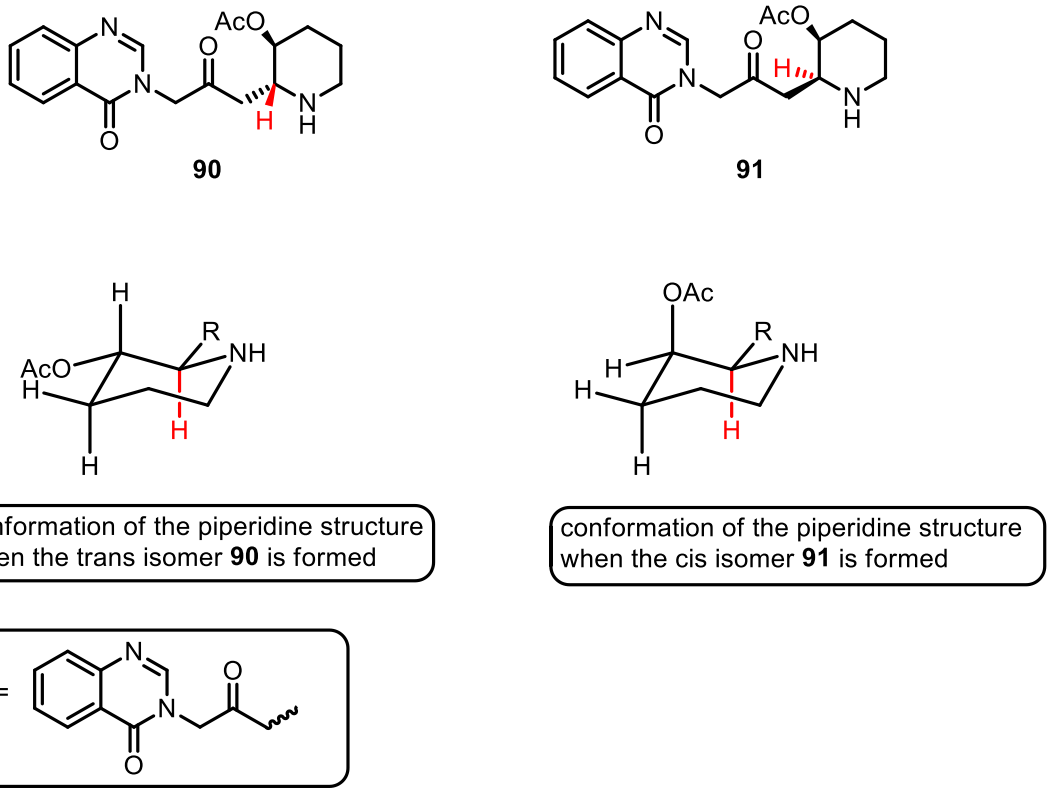
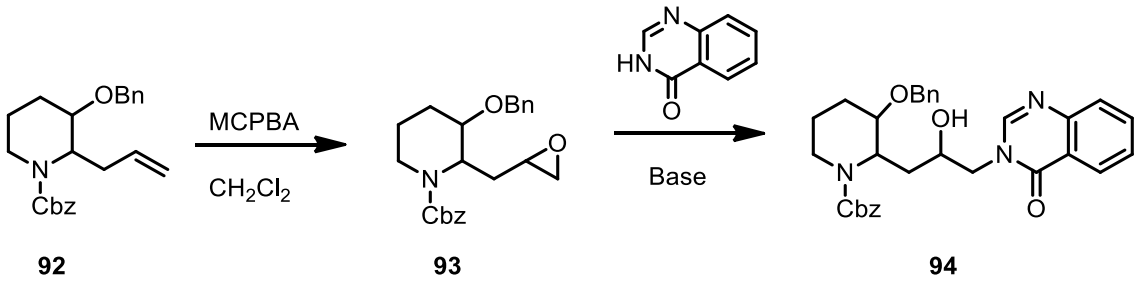


Figure 13.

The formation of both isomers could be due to product epimerisation via the retro-aza-Michael process, or an inherently unselective addition reaction. Notwithstanding these optimisation studies, the best yield obtained was 33% (Table 5, Entry 2). Considering the low yields obtained via this route, an alternative pathway was envisaged.

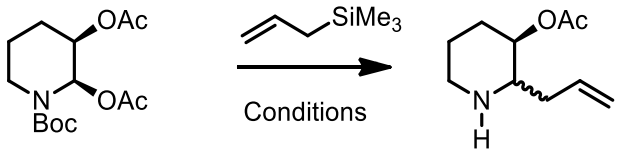
The alternative strategy to be undertaken was inspired by Zhu's method for synthesising febrifugine analogues (Scheme 20).[21,22] This route employed the epoxidation of the allylated compound **92**, followed by coupling of the corresponding epoxide **93** to the quinazolinone to form the febrifugine analogue **94**.



Scheme 20. Zhu's method

The initial step in our route was to couple the diacetate compound **88** with allyltrimethylsilane at -78 °C, using $BF_3.OEt_2$ as the Lewis acid (Table 6, entry 1). This reaction only provided the deprotected product **95** as a mixture of both cis and trans isomers in a low yield. Even when the quantity of the Lewis acid decreased to one equivalent (Table 6, entry 2), the yield was only increased by 5%, with a mixture of both cis and trans isomers once again being generated. The use of stronger Lewis acids ($TiCl_4$, TMSOTf) also afforded the product as a mixture of isomers in low yields (Table 5, Entries 3 and 4).

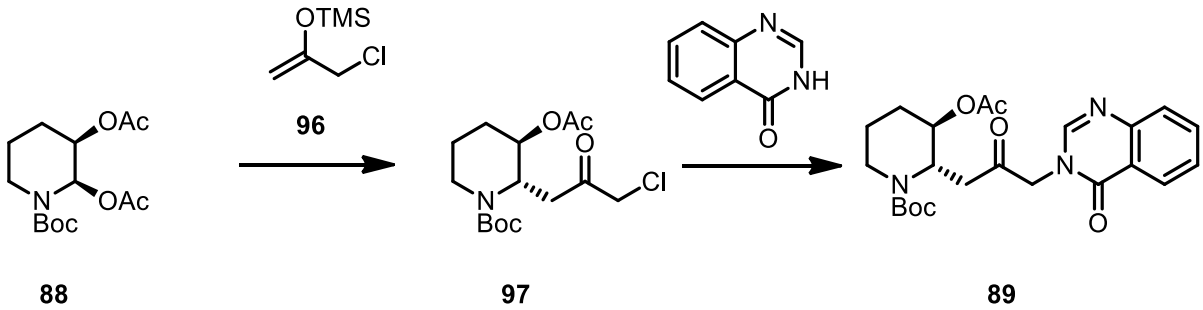
Table 6: Lewis acid promoted allylation



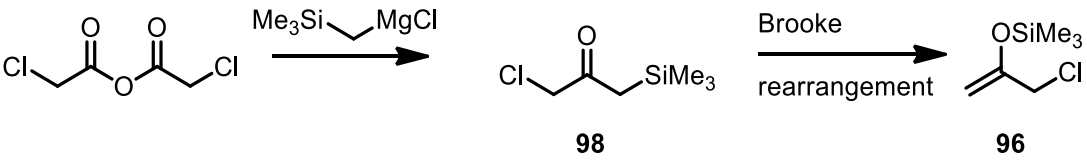
88 **95**

Entry	Conditions	Yield (%)	Cis and Trans ratio
1	$BF_3.OEt_2$ (4 eq)	5	1 : 1
2	$BF_3.OEt_2$ (1 eq)	10	1 : 1.2
3	$TiCl_4$ (4 eq)	12	1 : 1.8
4	TMSOTf (1 eq)	20	1 : 1.5

The poor yields and low stereocontrol associated with the allylation route prompted us to consider the coupling of the diacetate **88** with a chloro silyl enol ether **96** (Scheme 21). The coupled product **97** would then be reacted with the quinazoline to form the febrifugine derivative **89**. In order to accomplish this route, the silyl enol ether **96** had to be synthesised and the initial notion was to react chloroacetic anhydride with ((trimethylsilyl) methyl) magnesium chloride to form the intermediate **98**, followed by a Pd-catalysed Brooke rearrangement to afford the intended silyl enol ether **96** (Scheme 22). Table 7 summarises the results of the Grignard addition to chloroacetic anhydride.



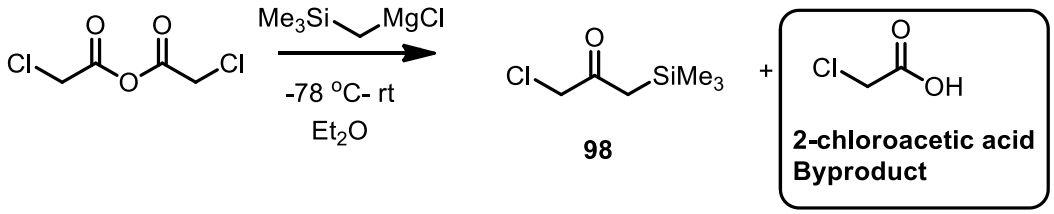
Scheme 21.



Scheme 22. Synthesis the silyl enol ether **96**

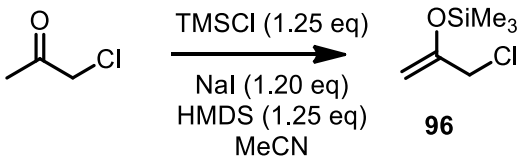
Reacting chloroacetic anhydride with one equivalent of ((trimethylsilyl) methyl) magnesium chloride for one hour returned only starting material (Table 7, entry 1), whilst using an excess of the Grignard afforded a complex mixture of products (Entry 2). Varying the time to 72 hours allowed the reaction to reach full conversion, however the yield of product obtained was low.

Table 7. Grignard addition to chloroacetate



Entry	Equivalents of Grignard	Time (h)	Yield (%)
1	1	1	0
2	3	1	Complex mixture
3	1	72	10

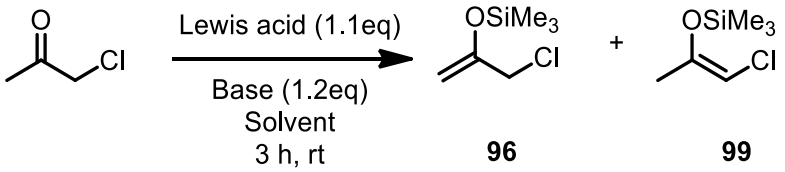
With a small amount of the product in hand, we decided to study the next step which was the Brooke rearrangement. Unfortunately, after numerous attempts the product could not be obtained. Therefore, we explored an alternative route to the chloro silyl enol ether **96** via the reaction of chloroacetone with NaI, HMDS and TMSCl (Scheme 23).



Scheme 23 : Alternative method of synthesis of chloro silyl enol ether

Deployment of literature conditions resulted in the product being produced in poor yields (Table 8, Entry 1). Consequently, an attempt to improve the yield by the use of TMSOTf instead of TMSCl was considered, as a result an increase in the yield was observed (Entry 2). Changing the solvent to dichloromethane increased the yield further to 21% (Entry 3). However, the reaction produced a mixture of **96** and **99**, and separation of the desired product from the mixture proved to be difficult. Therefore, a brief screen of hindered bases was conducted to see if the silyl enol ether **96** could be formed selectively over the by-product **99** (Entries 3, 4, 5 and 6).

Table 8.



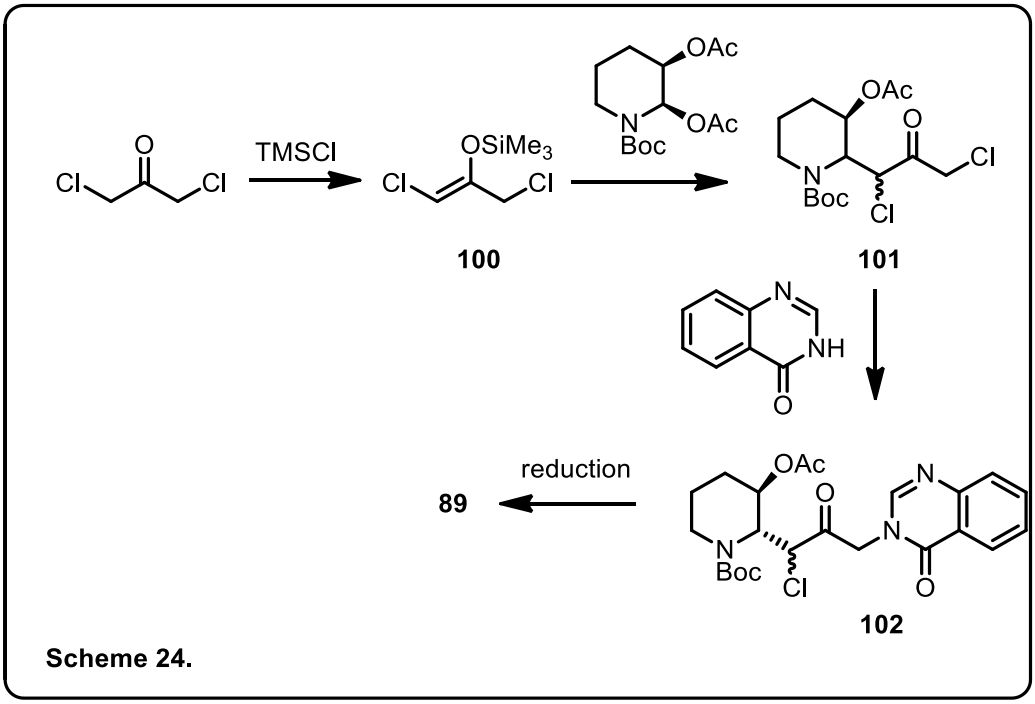
Entry	Solvent	Lewis acid	Base	Yield (%)	Ratio of 96 : 99
1	MeCN	TMSCl	LiHMDS	5	1 : 6
2	MeCN	TMSOTf	LiHMDS	10	1 : 4.5
3	CH_2Cl_2	TMSOTf	LiHMDS	21	1 : 5.4
4	CH_2Cl_2	TMSOTf	2,6 Lutidine	57	1 : 6.1
5	CH_2Cl_2	TMSOTf	DBU	24	1 : 9.1
6	CH_2Cl_2	TMSOTf	LDA	20	1 : 16

*The ratios of **95** and **98** were judged by ^{1}HNMR spectroscopy of the crude reaction mixture.*

When 2,6 lutidine was used the yield increased to 57% and a higher ratio of **99** was observed (Table 8, Entry 4). Unfortunately however, exploring other hindered bases such as DBU and LDA failed to improve selectively towards **96** (Entries 5 and 6).

Inspection of the literature highlighted that the enol ether **99** was in fact the thermodynamically more stable isomer, while **96** was formed under kinetic control. This work suggested that the selective synthesis of the kinetic enol ether was challenging, as the thermodynamic product was formed in almost every case. Therefore, the synthesis of **100** from the symmetrical 1,3-dichloropropan-2-one was then considered (Scheme 24). The initial

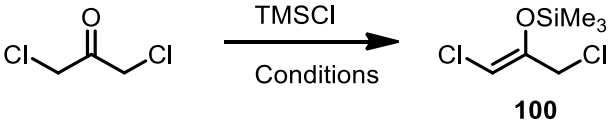
idea was that the enol ether **100** would react with the diacetate piperidine **88** to form the intermediate **101**. This intermediate would the react with the quinazolinone to form the analogue **102**, which in turn will be reduced to form the febrifugine analogue **89**.



Scheme 24.

In order to generate **100**, 1,3 dichloropropan-2-one and TMSCl were combined in the presence of triethylamine in ether; however only the starting material was recovered (Table 9, Entry 1). Changing the base to LDA showed no improvement to the reaction as the starting material was again recovered (Table 9, entries 2 and 3). This route was therefore abandoned in favour of an alternative approach.

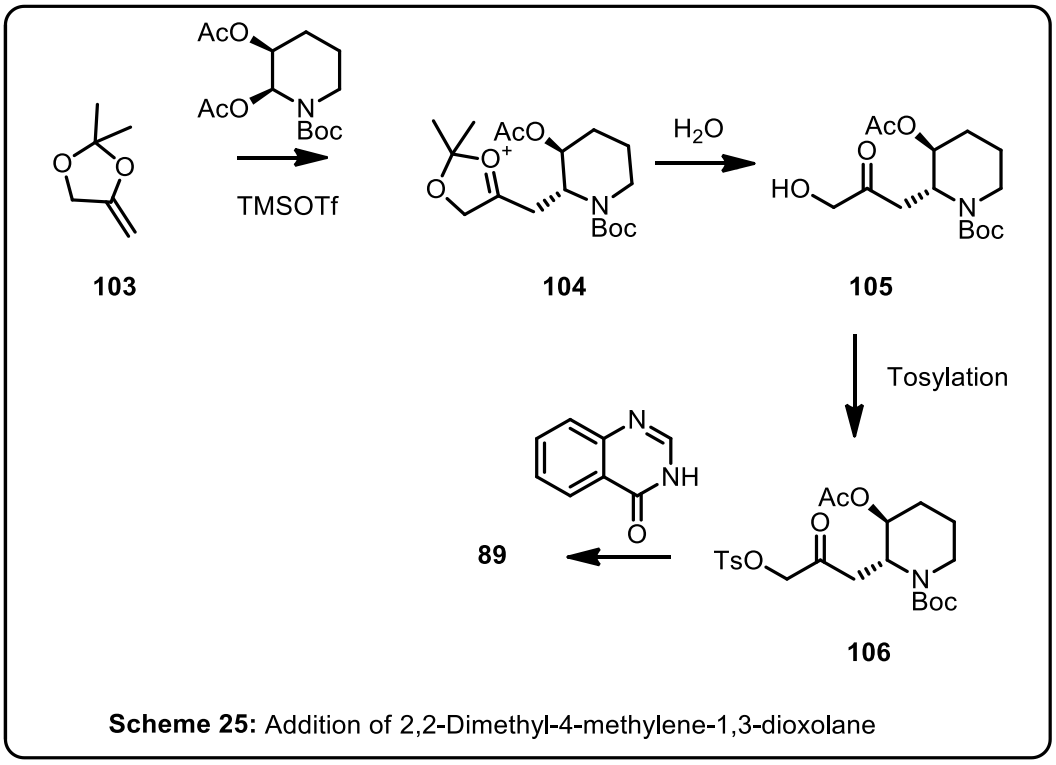
Table 9:



100

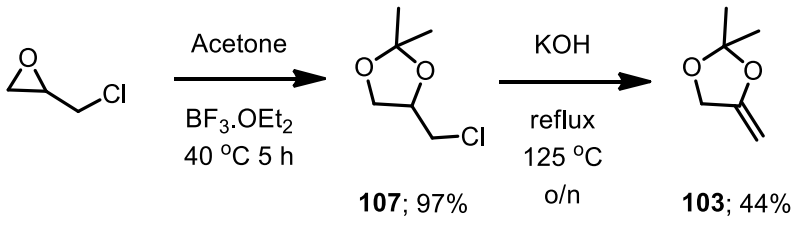
Entry	Conditions	Yield (%)
1	Et_3N (1 eq), Et_2O, 16 h	0
2	LDA (1 eq), THF, 3 h	0
3	LDA (1 eq), THF, 16 h	0

The alternative route focused on coupling 2,2-dimethyl-4-methylene-1,3-dioxolane **103** with the diacetate **88** , forming the intermediate **104** (Scheme 25). The hydrolysis of **104** would then produce piperidine analogue **105**, which through tosylation would form the analogue **106**. The plan was then to couple **106** with the febrifugine quinazolinone to form the febrifugine analogue **89**.



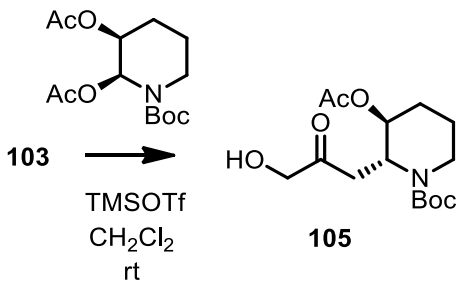
Scheme 25: Addition of 2,2-Dimethyl-4-methylene-1,3-dioxolane

The dioxolane **103** was synthesised by reacting epichlorohydrin with an excess of acetone in the presence of a Lewis acid, which afforded the intermediate **107** in a 97% yield (Scheme 26). The 4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane **107** was then reacted with KOH to produce **103** in a 44% yield.[34]



Scheme 26: Synthesis of 2,2 dimethyl-4-methylene-1,3-dioxolane

With the dioxolane **103** in hand, we investigated the key coupling reaction (Scheme 27). However, this step proved problematic as the product **105** was never obtained after numerous attempts and a complex mixture was obtained after each reaction.



Scheme 27.

As we were unable to develop an efficient route towards the febrifugine analogue **89**, we decided to target different febrifugine analogues (Figure 14). The synthesis of these analogues required the piperidine **108** to be synthesised. We hoped that the β-dicarbonyl moiety in **108** would facilitate a range of alkylation reactions.

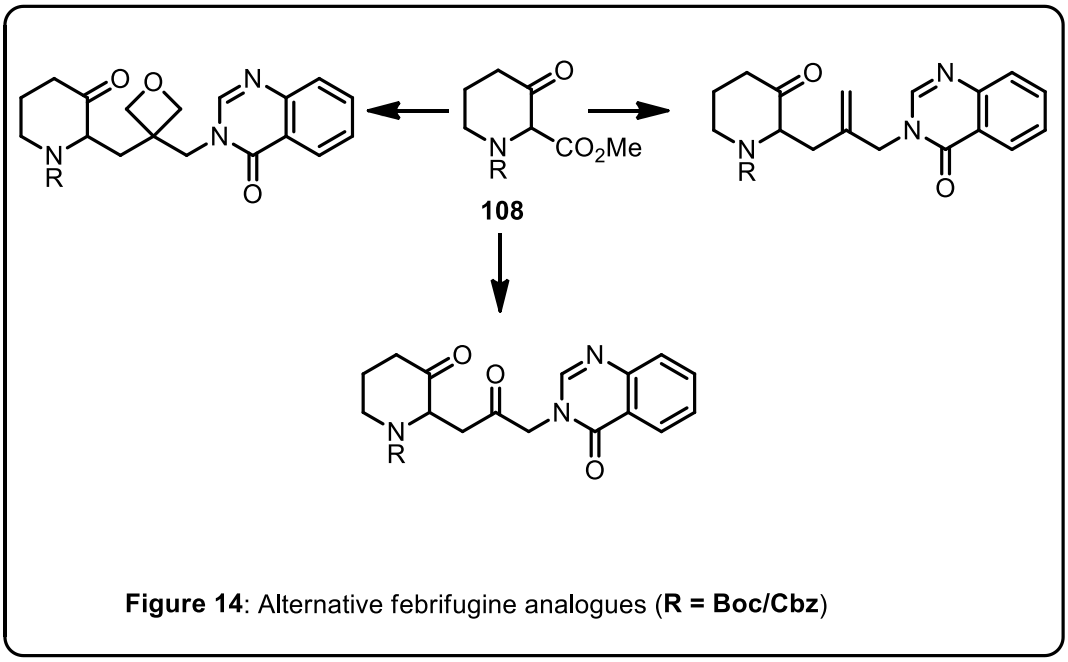
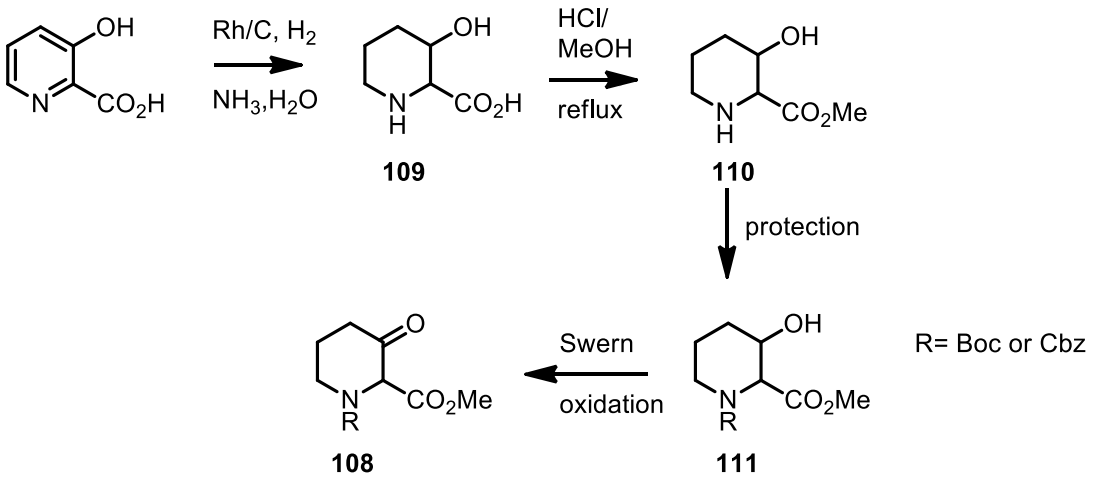


Figure 14: Alternative febrifugine analogues (**R = Boc/Cbz**)

The route envisaged for the synthesis of **108** was based on literature precedent and consisted of a hydrogenation of 3-hydroxypyridine-2-carboxylic acid to form the 3-hydroxypiperidine-2-carboxylic acid **109** (Scheme 28).[36] The next step was the esterification of **109** to form the

corresponding ester **110**. Protection of the ester with either the Boc or Cbz group followed by a Swern oxidation would then result in product **108** being produced.

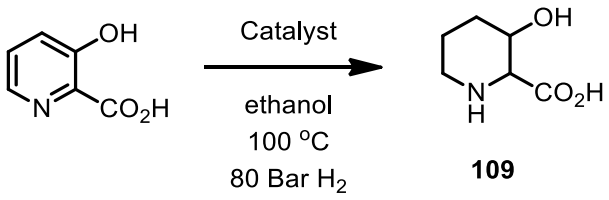


Scheme 28.

Hydrogenation of the 3-hydroxypyridine-2-carboxylic acid under the reported conditions was initially unsuccessful as the product **109** was not obtained. We believed that the use of lower hydrogen pressure (relative to literature conditions) during the reaction was responsible for this observation. Therefore, we decided to use the continuous flow hydrogenation reactor (H-cube) as this allows a range of temperatures and hydrogen pressures to be accessed.

Passing the reaction mixture through a rhodium on carbon (Rh/C) catalyst unfortunately failed to deliver product (Table 10, Entry 1). However, changing the catalyst to palladium hydroxide on carbon ($Pd(OH)_2/C$) was more successful and the product was observed (Entry 2). Nevertheless, the purification of the amino acid compound proved problematic.

Table 10:



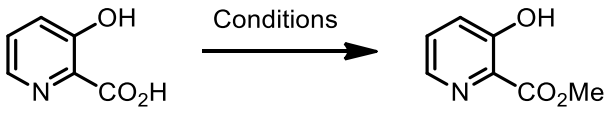
109

Entry	Catalyst	Yield (%)
1	Rh/C	0
2	$Pd(OH)_2/C$	20

Reactions run using a continuous flow hydrogenation reactor H cube. Each reaction was run under a pressure of 80 Bar of H_2 and temperature of 100 °C.

Thus the esterification of the carboxylic acid was considered prior hydrogenation to aid the purification of the piperidine product (Table 11). The reaction of the 3-hydroxypyridine-2-carboxylic acid with thionyl chloride in methanol did not yield product (Table 11, Entry 1). However, when the reaction performed in methanol with a catalytic amount of concentrated sulfuric acid, the corresponding ester **112** was produced in a 49 % yield (Entry 2).

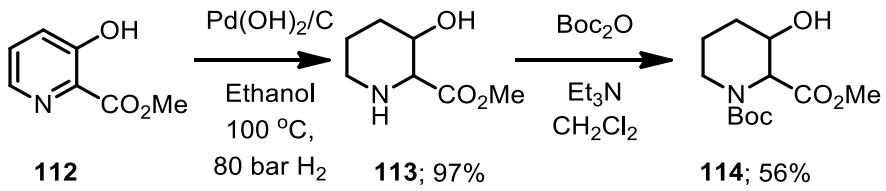
Table 11.



112

Entry	Conditions	Yield (%)
1	$SOCl_2$ (1 eq), MeOH (10 mL), rt	0
2	H_2SO_4 (0.1 eq), MeOH (10 mL), reflux	49

Hydrogenation of **112** using the H-cube reactor with a palladium hydroxide on carbon catalyst produced the heterocycle **113** in a 97 % yield (Scheme 29). The next step towards the final β-keto ester **108** was the protection of the amine in **113**. Hence, with the amine was reacted with di-*tert*-butyl dicarbonate (Boc_2O) in dichloromethane to afford the protected product **114** in a 56% yield (Scheme 29).

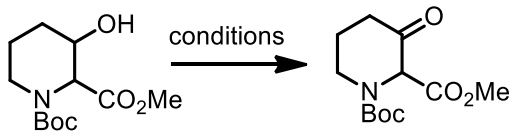


112 **113**; 97% **114**; 56%

Scheme 29.

The final Swern oxidation was attempted under literature conditions (Table 12, entry 1), unfortunately however, the product was not obtained. Thus a scope of various oxidants and conditions were examined (Table 12). Oxidants such as Jones reagent, pyridinium chlorochromate (PCC), potassium permanganate and Dess-Martin periodinane (DMP) were studied, however poor yields were obtained in each case (Table 12, Entries 3 to 8).

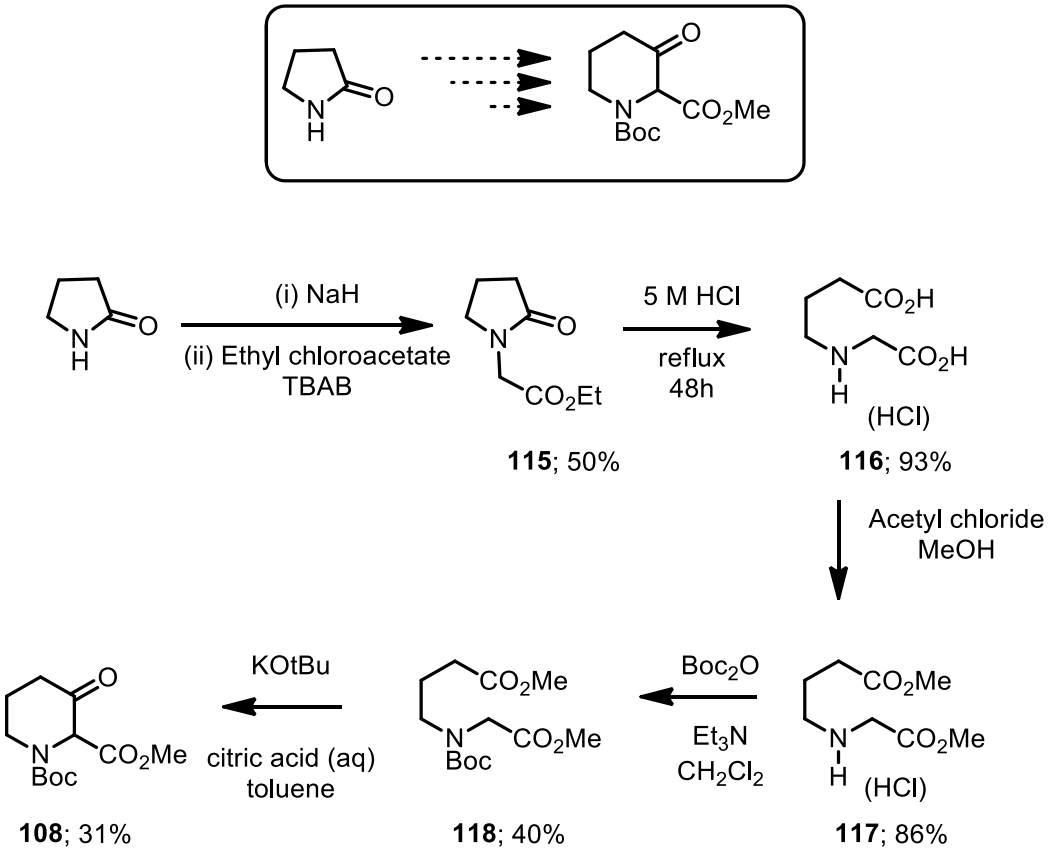
Table 12.



114 **108**

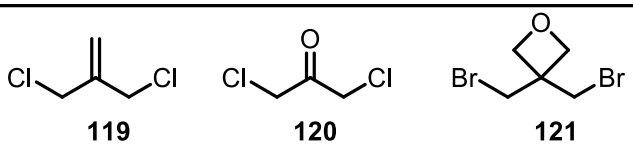
Entry	Conditions	Yield (%)
1	Oxalyl chloride (1.1 eq), DMSO (2.4 eq), Et_3N (4.5 eq), CH_2Cl_2, 16 h	0
2	Oxalyl chloride (3 eq), DMSO (2.4 eq), Et_3N (4.5 eq), CH_2Cl_2, 16 h	3
3	Jones reagent, rt, overnight	18
4	PCC (2.5 eq), florisil, CH_2Cl_2, rt, 16h	4
5	PCC (4 eq), florisil, CH_2Cl_2, rt, 16h	2
6	$KMnO_4$ (3 eq), MeCN, 16 h	0
7	$KMnO_4$ (3 eq), $BF_3.OEt_2$, MeCN, 16 h	decomposition
8	DMP (1.5 eq), CH_2Cl_2, 16 h	0

After failing to produce a significant amount of the keto ester **108**, an alternative route was employed, again based on literature precedent (Scheme 30).[38] The initial step was the reaction of pyrrolidinone with ethyl chloroacetate and sodium hydride in the presence of the phase transfer catalyst tetrabutylammonium bromide (TBAB) to form the pyrrolidinone intermediate **115** in a 50% yield. Heating **115** in 5 N HCl formed the diacid **116**, which was converted to the corresponding ester product **117** by reacting it with acetyl chloride and methanol. Protection of the free amine with di-*tert*-butyl dicarbonate (Boc_2O) afforded the diester **118** in a 40% yield. Cyclisation of **118** with potassium *tert*-butoxide (K^tOBu) produced the intended the keto ester **108** in a 31% yield.



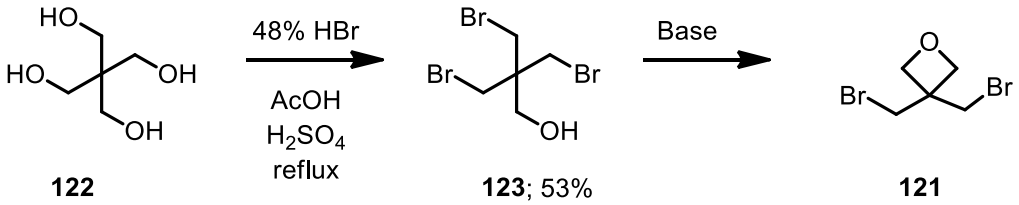
Scheme 30.

The next step in establishing routes to the analogues shown in Figure 15 was to select linkers which would allow the coupling reactions between the keto ester and the quinazoline to occur. The requisite linkers (Figure 15) were 3-chloro-2-(chloromethyl) prop-1-ene **119**, 1,3-dichloropropan-2-one **120** and 3,3-bis (bromomethyl) oxetane **121**. Both 3-chloro-2-(chloromethyl) prop-1-ene and 1,3-dichloropropan-2-on were commercially available, however the 3,3-bis (bromomethyl) oxetane was difficult to source and so this compound required further synthesis.



119 **120** **121**

Figure 15:



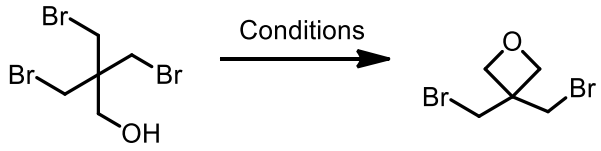
122 **123**; 53% **121**

Scheme 31: Synthesis of the 3,3-bis (bromomethyl) oxetane

The initial step was to convert the pentaerythritol **122** to the tribromide intermediate **123**, by reacting the erythritol with 48% hydrobromic acid in acetic acid and sulfuric acid (Scheme 31).[37] Through this reaction the product was obtained in a 53% yield. The intermediate **123** was then predicted to undergo cyclisation in the presence of a base to form the intended oxetane. Therefore, a brief base screen was conducted to find the optimal conditions (Table 13).

The use of sodium ethoxide and sodium *tert*-butoxide in ethanol only yielded the product in low yield (Entries 1 and 2). However, changing the base to sodium hydride and the solvent to ether increased the yield to 30% (Entry 3). Increasing the temperature resulted in a sharp increase in the yield to 84% (Entry 4). Having established the optimal conditions for the synthesis of the bromo oxetane **121**, the coupling reactions between the keto ester **108** and the selected linkers were then investigated.

Table 13: Synthesis of the 3,3-bis (bromomethyl) oxetane

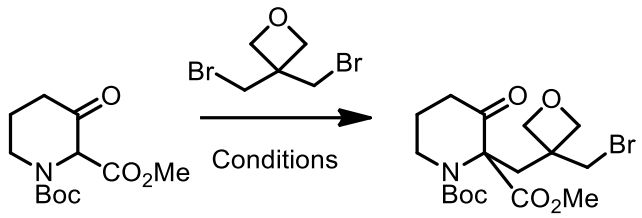


123 **121**

Entry	Conditions	Yield (%)
1	NaOEt (1.5 eq), EtOH, reflux, 2 h	4
2	NaO^{t}Bu (5 eq), EtOH, reflux, 2h	-
3	NaH (1 eq), Et_2O, rt, 16 h	30
4	NaH (1 eq), Et_2O, reflux, 16 h	84

The first reaction to be considered was the coupling of the oxetane **121** to the piperidine **108**. A range of different conditions were investigated but unfortunately no product was observed (Table 14). This result was thought to be due to the steric hindrance around the oxetanyl bromides (neopentyl effect). Thus, the oxetane was slow to undergo bimolecular nucleophilic substitution (S_N2) reaction.

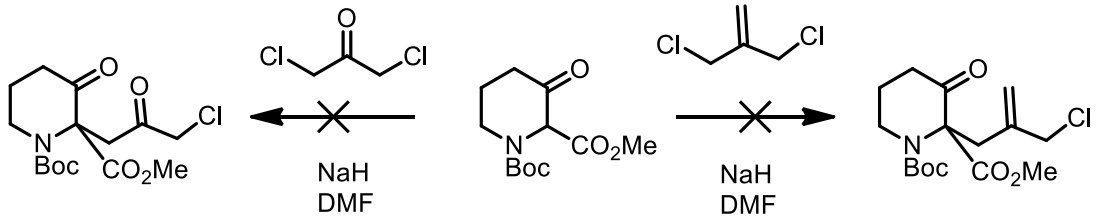
Table 14: Coupling of the 3,3-bis (bromomethyl) oxetane



108 **124**

Entry	Conditions	Yield (%)
1	NaH (1 eq), Oxetane (3 eq), DMF, rt, overnight	0
2	NaH (1 eq), Oxetane (4 eq), DMF, rt, overnight	0
3	K_2CO_3 (1 eq), Oxetane (2 eq), acetone, reflux, 12 h	0

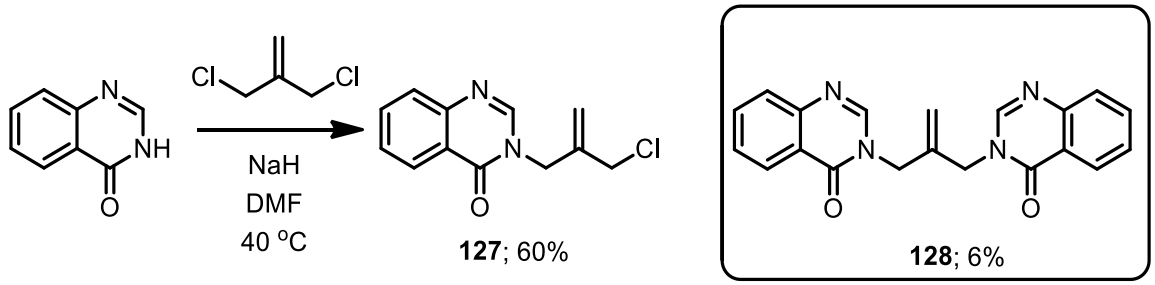
Coupling the keto ester **108** to 3-chloro-2-(chloromethyl) prop-1-ene **119** also proved unsuccessful as a complex mixture of products was obtained. A similar result was obtained when 1,3-dichloropropan-2-one **120** was coupled to the keto ester (Scheme 32).



126 **108** **125**

Scheme 32.

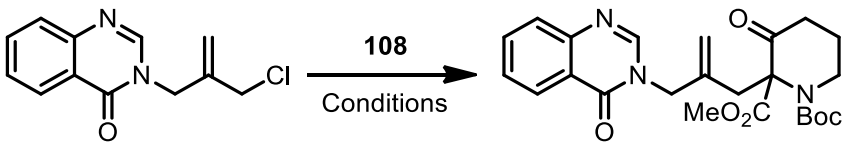
The unsuccessful coupling reactions prompted us to change the alkylating agent, in particular, moving away from the dichloride **120**. We therefore decided to couple the quinazolinone to 3-chloro-2-(chloro) methyl prop-1-ene **119** (Scheme 33). The reaction afforded the product **127** in a 60% yield. In addition, it also produced the product **128** in a 6% yield (Scheme 33).



Scheme 33.

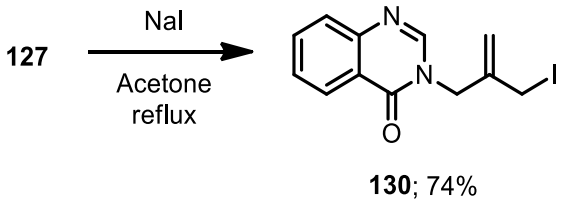
The next step was to find conditions to couple **127** to the previously synthesised keto ester **108** (Table 15). When sodium hydride was used as the base, the product **129** was not observed (Entry 1). Increasing the temperature did not improve the reaction as the starting materials were obtained (Entry 2). As a consequence, the allyl chloride was converted into the corresponding iodide via the Finkelstein reaction in the hope of improving the alkylating agent reactivity (Scheme 34).

Table 15.



127 **129**

Entry	Conditions	Yield (%)
1	NaH (1.6 eq), DMF, rt, 16 h	0
2	NaH (3 eq), DMF, 40 °C, 16 h	0

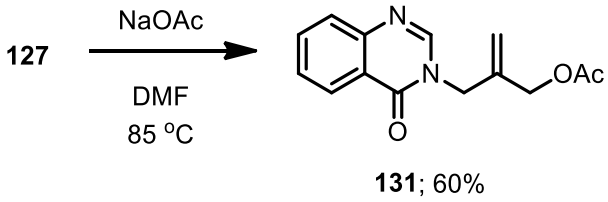


130; 74%

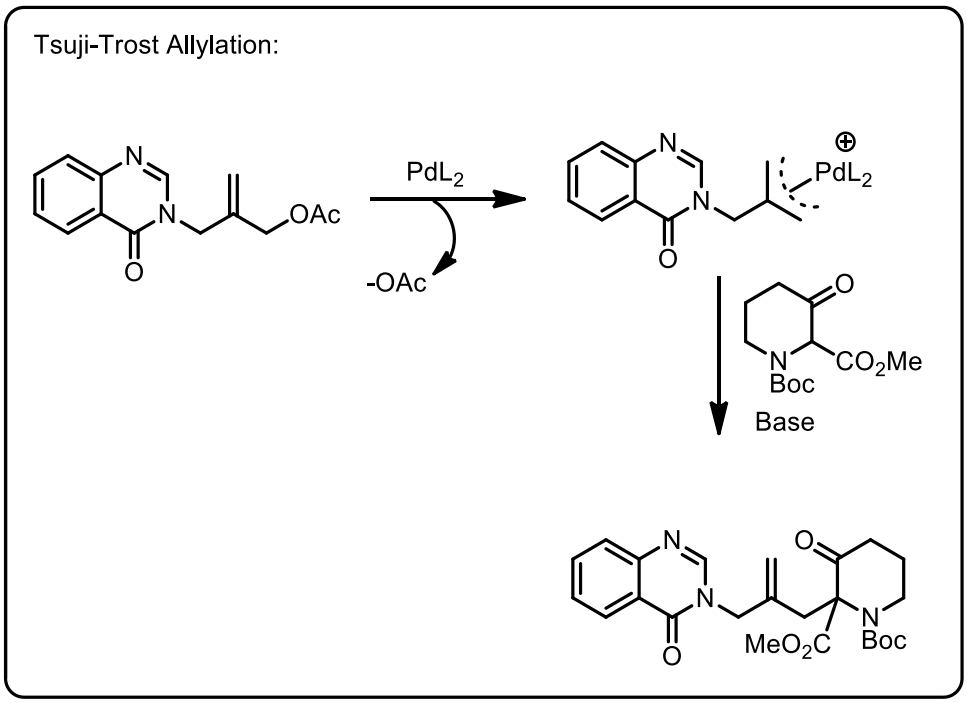
Scheme 34: Synthesis of the Finkelstein product

With the iodo product **130** in hand, conditions for the coupling reaction with **108** were examined. However, coupling the Finkelstein product with the keto ester produced a complex mixture of products and the analogue **129** was not observed. We determined that the iodo product **130** was unstable, and it underwent self-polymerisation when exposed to the open air. Therefore, the synthesis of the more stable acetate analogue **131** from the chloride **127** was considered, with the plan of carrying out the allylation under Tsuji-Trost conditions (Scheme 35).

Synthesis of the acetate product:



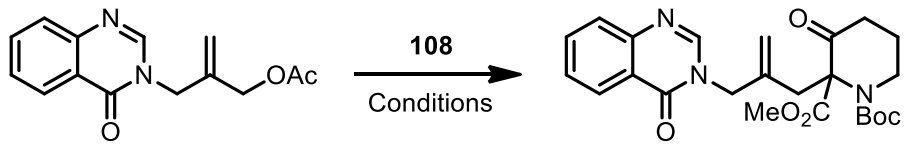
131; 60%



Scheme 35.

Reacting the chloride **127** with sodium acetate yielded the acetate product **131** in a 60% yield (Scheme 35). Employing established Tsuji-Trost conditions, the key coupling reaction was next investigated (Table 16). The use of palladium chloride with potassium carbonate in water failed to afford product (Table 16, Entry 1). Changing the catalyst to Pd $(dba)_2$ and the solvent to THF (Entry 2) also failed to generate product. Other catalysts such as palladium acetate $(Pd(OAc)_2)$ and tris(dibenzylideneacetone) dipalladium $(Pd_2(dba)_3.CHCl_3)$ were also examined, however no product was observed in these cases either. Therefore, this route was abandoned.

Table 16: Exploring Tsuji Trost conditions



131 **129**

Entry	Conditions	Yield (%)
1	$PdCl_2$ (3 mol%), TBAB (3 mol%), K_2CO_3 (1 eq), H_2O, 50 °C	0
2	$Pd(dba)_2$ (3 mol%), PPh_3 (0.5 eq), K_2CO_3, THF, 40 °C	0
3	$Pd(OAc)_2$ (5 mol%), PPh_3 (1 eq), DBU (1.5 eq), THF, reflux	0
4	$Pd_2(dba)_3.CHCl_3$ (2.5 mol%), PPh_3 (0.2 eq), NaH (1 eq), THF, rt	0

We undertook a further retrosynthetic analysis of the febrifugine scaffold and decided to break the molecule into three components in the hope of developing a convergent pathway towards the target compounds (Figure 16). As the quinazolinone was commercially available, the main aspects to focus on were the synthesis of the chiral piperidine motif and central ketone. In terms of the piperidine structure, we decided to synthesise the epoxide from benzyl 3,4-dihydropyridine-1(*2H*)-carboxylate. However, to accommodate the reactive nature of the N-acyliminium ion, neutral epoxidation conditions were targeted. This prompted us to revisit the use of DMDO as Wallace had recently developed conditions to generate DMDO in situ at neutral pH.

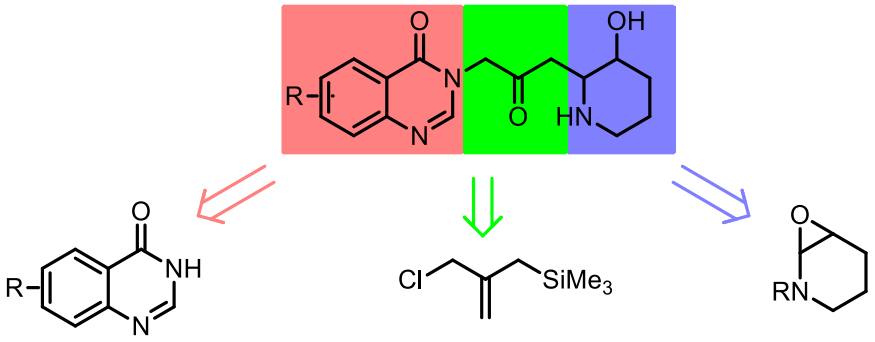
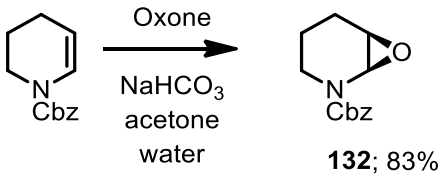


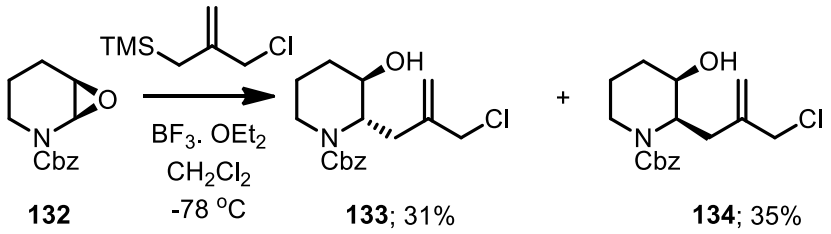
Figure 16.

Utilising Wallace's conditions of adding acetone to an aqueous solution containing potassium peroxymonosulfate (oxone) and sodium bicarbonate proved successful as the epoxide **132** was synthesised in a 83% yield (Scheme 36). The next step was to develop an alkylation approach to installing the central ketone in the febrifugine structure. This was achieved by re-examining Rutjes's route (Scheme 10) where the coupling reaction between the N,O acetal **39** and the 2-(chloromethyl) allyl silane produced the chiral piperidine **40** in a good yield.



Scheme 36

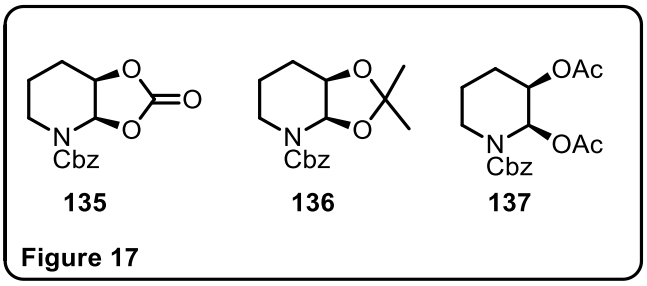
Pleasingly, adopting these conditions the reaction between the epoxide and 2-(chloromethyl)allylsilane proved to be successful in producing the trans product **133** in a 31% yield as well as the cis diastereiosomer **134** in a 35% yield (Scheme 37).



132 **133**; 31% **134**; 35%

Scheme 37

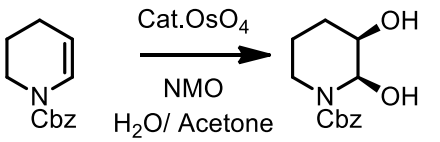
Due to the poor stereoselectivity of the reaction, alternative substrates were investigated in order to promote the selective synthesis of the trans product. The route envisaged was to introduce large groups to the piperidine motif which could favour trans-addition to the N-acyliminium ion intermediate. Therefore, the analogues shown in Figure 17 were selected for this purpose**.**



135 **136** **137**

Figure 17

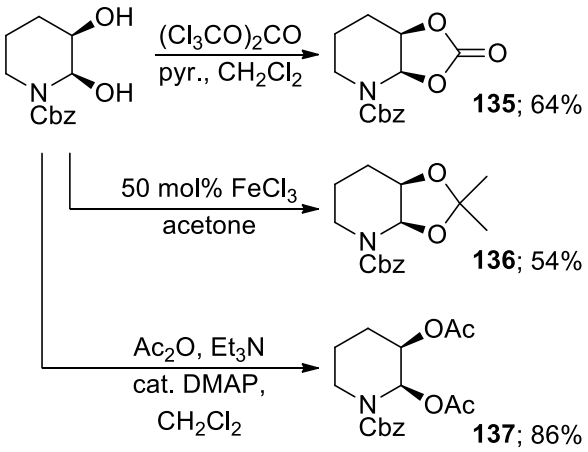
In order to synthesise the selected compounds in Figure 17, the diol **138** was targeted as a key intermediate. This was prepared using NMO and osmium tetroxide in a 68% yield (Scheme 38).



138; 68%

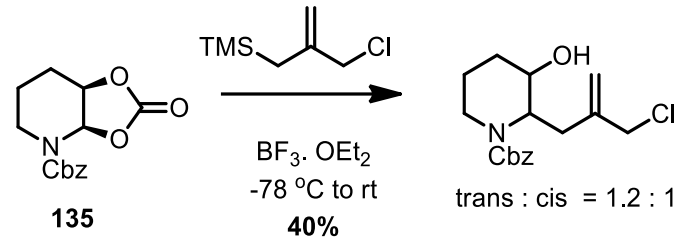
Scheme 38

Carbonate **135** was synthesised by reacting the diol **138** with triphosgene in the presence of pyridine to give the product in a 64% yield (Scheme 39). The acetal **136** was successfully formed in a 54% yield by reacting **138** with acetone in the presence of a Lewis acid catalyst. **137** was synthesised by previously established conditions mentioned earlier for the synthesis of compound **89**, were the diol **138** was reacted with acetic anhydride, triethyl amine in the presence on a nucleophilic catalyst to give the **137** in a 86% yield.

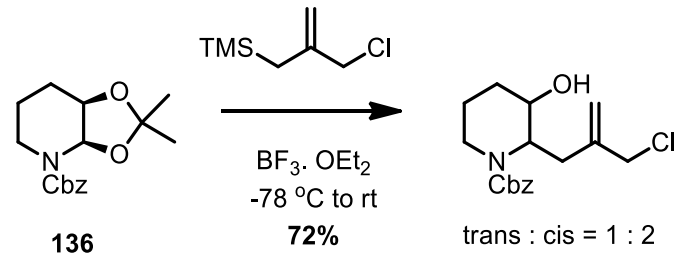


Scheme 39

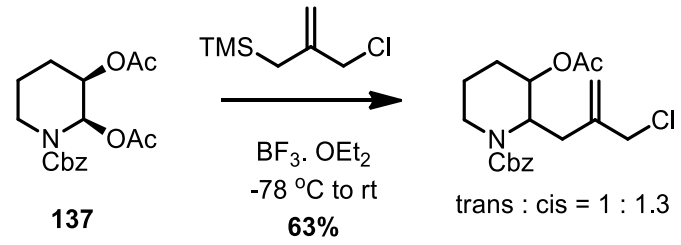
With the piperidine compounds in hand the next step was to investigate the coupling reactions with 2-(chloromethyl)allylsilane. The reaction with the carbonate **135** afforded the intended product, however this showed no selectivity as a 1.2 : 1 ratio trans to cis compounds was obtained (Scheme 40). Interestingly, the reaction of the acetal **136** with the 2-(chloromethyl)allylsilane showed slight preference towards the cis diastereoisomer, this being produced as a 1 : 2 ratio trans to cis. Finally **137** also failed to show any selectivity towards the trans product as it produced a 1 : 1.3 ratio trans to cis.



135



136



137

Scheme 40

The poor selectivities observed in the alkylation reactions was put down to the rapid equilibration of the conformers **138** and **139**, and their similar rates of nucleophilic addition (Figure 18).

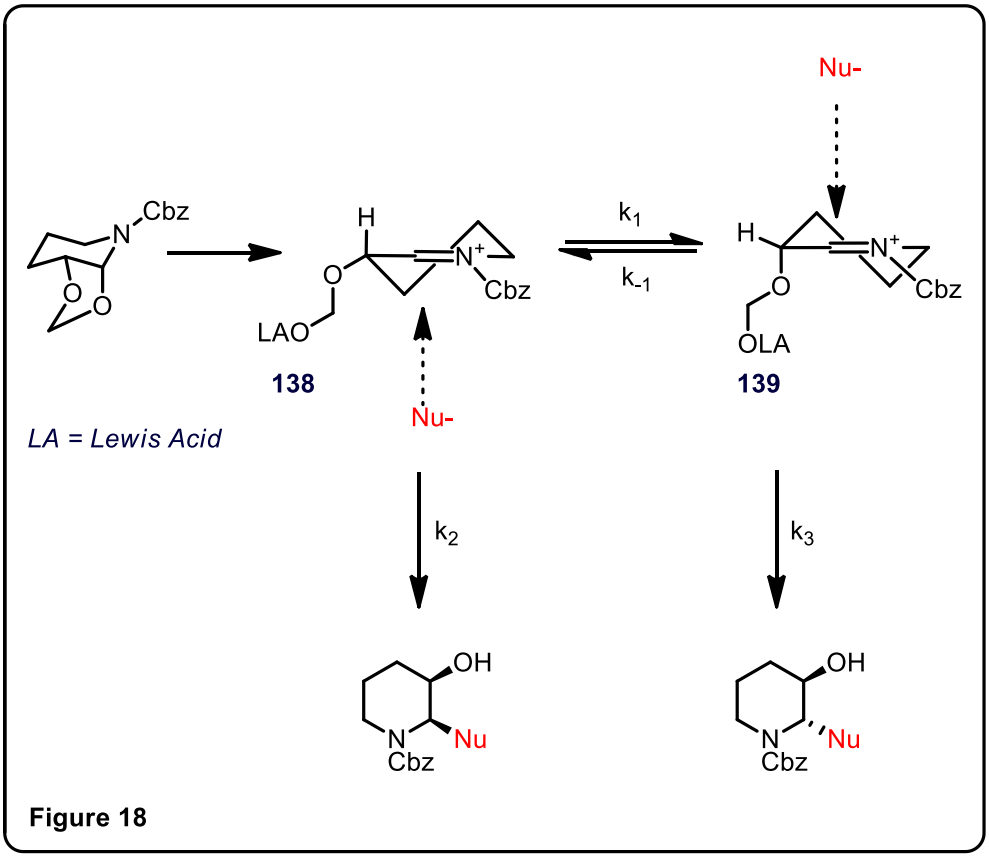
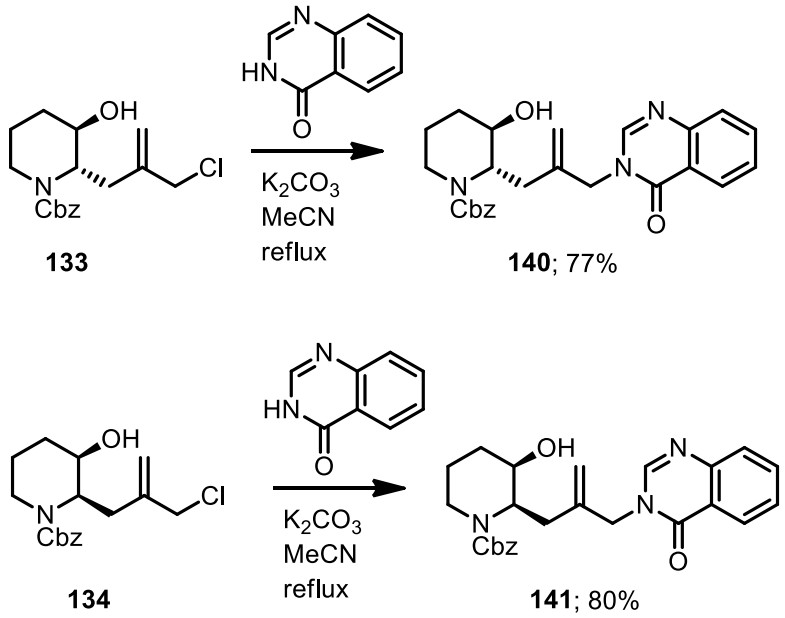


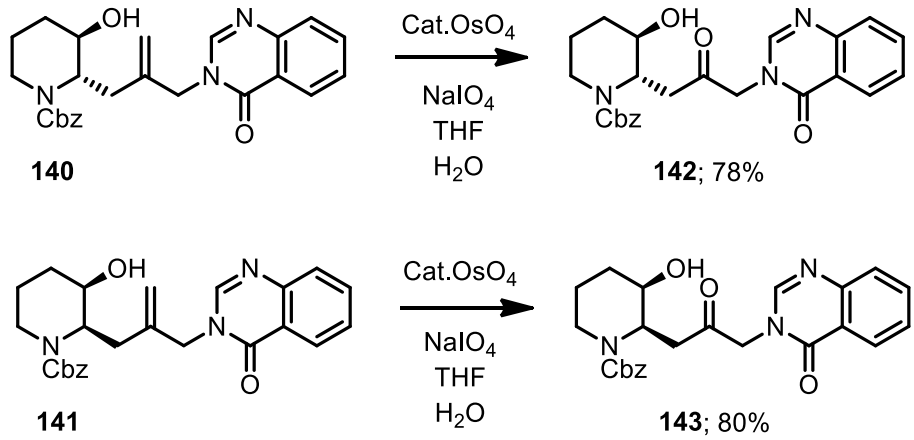
Figure 18

On the other hand, as we had successfully produced gram quantities of the both trans-alcohol **133** and cis-alcohol **134** the coupling reaction with the quinazolinone was carried out (Scheme 41). The commercial quinazolinone was reacted with the **133** in the presence of potassium carbonate to produce the analogue **140** in a 77% yield. Coupling with **134** was also successful as the cis analogue **141** was produced in a 80% yield.



Scheme 41

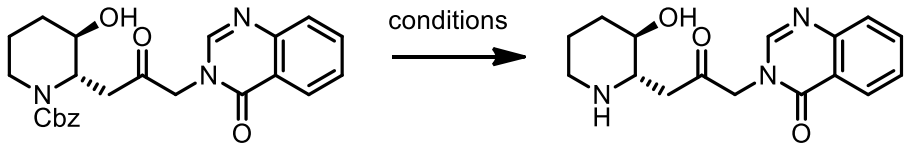
In order to produce the central ketone the oxidative cleavage of the central alkenes were investigated. Utilising Rutjes conditions, osmium tetroxide and sodium periodate in a solution of THF and water were used to successfully produce the protected febrifugine analogues **142** (78%) and **143** (80%) (Scheme 42).



Scheme 42

With the protected febrifugine analogues in hand, the next step was the removal the benzyloxy carbamate (Cbz) protecting group (Table 17). The use of boron tribromide and boron trichloride in dichloromethane failed to generate product (Entry 1 and 2). Changing the Lewis acid to trimethylsilyl iodide (TMSI) produced the febrifugine in a 20% yield (Entry 3). Whereas, subjecting **142** in neat 6 N HCl produced febrifugine **144** in a 22% yield (Entry 4).

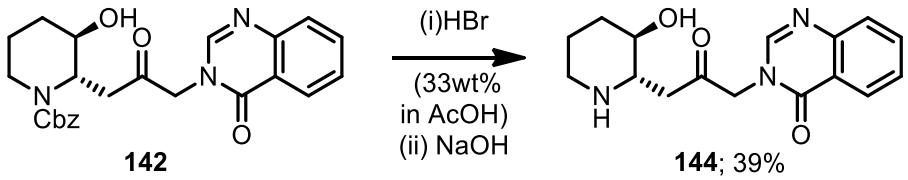
Table 17: Investigating deprotection conditions



142 **144**

Entry	Conditions	Yield (%)
1	BBr_3 (1.5 eq) , CH_2Cl_2, rt, 16 h	0
2	BCl_3 (4 eq) , CH_2Cl_2, rt, 16 h	13
3	TMSI (4 eq), CH_2Cl_2, rt, 3 h	20
4	6 N HCl, reflux, 3 h	22

We wondered if we could improve the product yield by using a stronger acid such hydrogen bromide. Therefore, using neat solution of hydrogen bromide (33 wt%) in acetic acid at 0 °C, we successfully produced the alkaloid in a 39% yield (Scheme 43). Even though the yield was moderate we found that recrystallization of the product generated fine crystals which allowed for the first X-ray crystal structure of febrifugine to be recorded. This crystal structure also confirmed the *trans*-stereochemistry of the piperidine ring (Figure 19).



Scheme 43

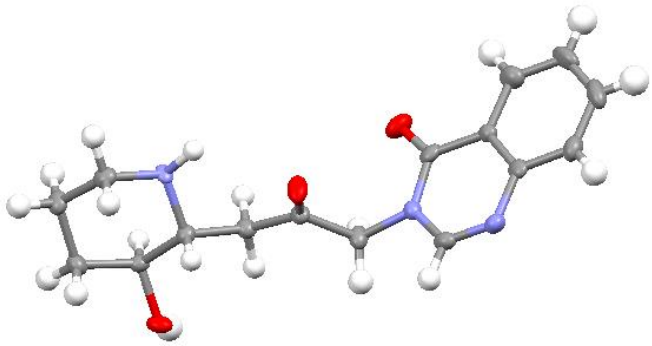
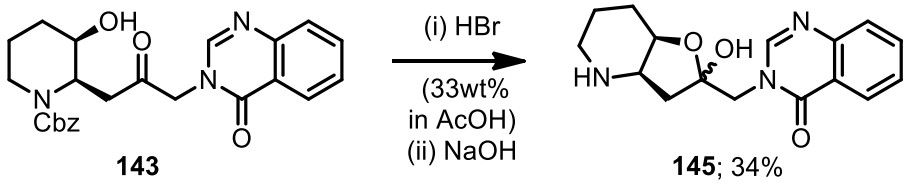


Figure 19: *First recorded X-ray crystal structure of the natural alkaloid febrifugine*.

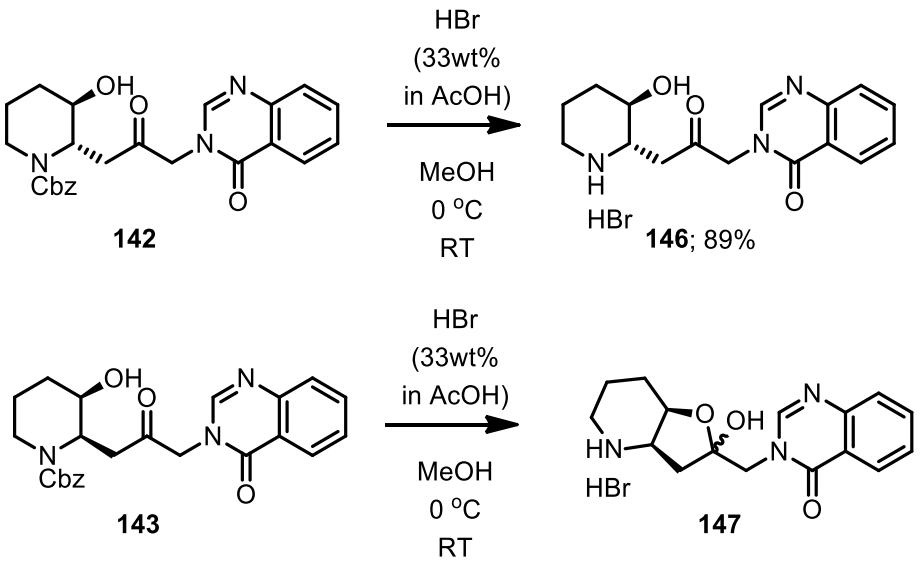
Having established that the use of a strong acid was an effective means of removing the Cbz protecting group, the deprotection of the cis analogue was also carried out and isofebrifugine **145** (34%) was produced (Scheme 44).



Scheme 44

In order to improve the yield of this step, we decided to isolate the HBr salt of the product and to consider the introduction of a solvent as a means of reducing any decomposition of starting materials that may occur due to high concentrations of acid. The protected febrifugine analogue **142** was therefore suspended in methanol and hydrogen bromide in acetic acid was added at 0 °C. This resulted in the successful formation of the hydrobromide

salt **146** in 89% yield (Scheme 45). These conditions were then repeated for the cis analogue **143** unfortunately no product was generated. Instead, it was determined that the major product was the imine **148** (Figure 20).



Scheme 45

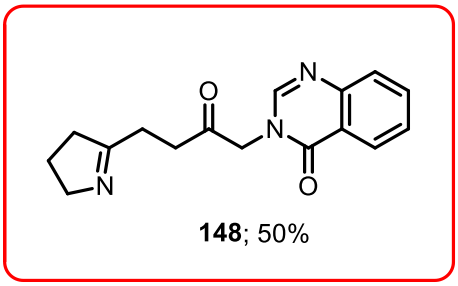
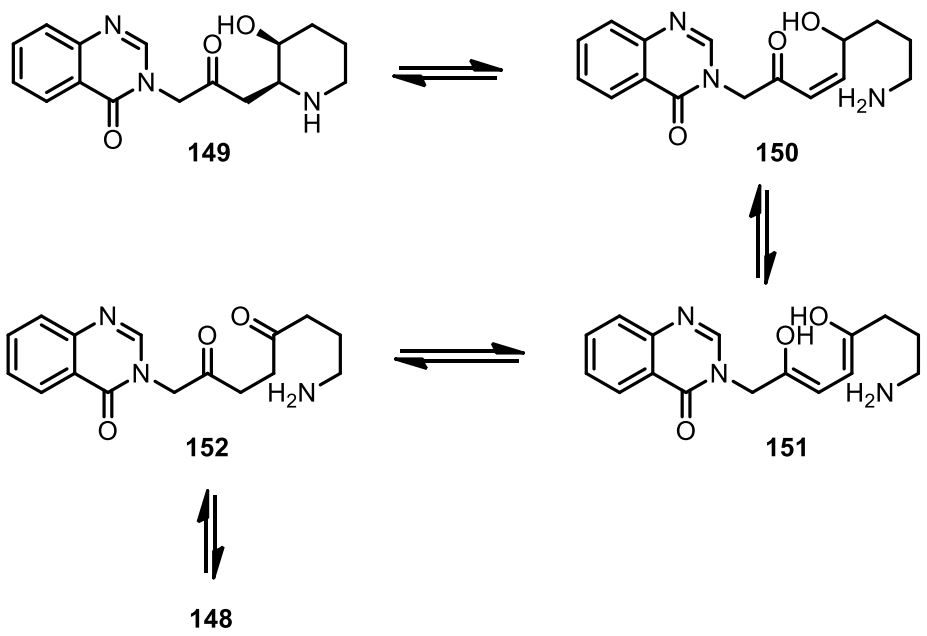


Figure 20: *By-product formed during the deprotection of the cis analogue*

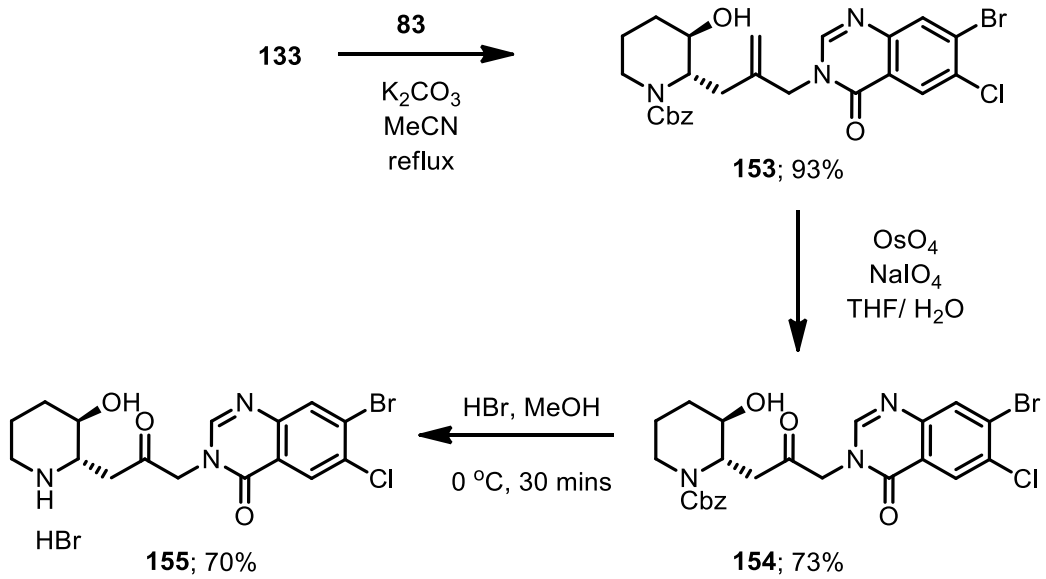
The assumption was that **148** was formed as a by-product during the epimerisation reaction of the cis analogue (Scheme 46). This result was supported by literature evidence which highlighted on how febrifugine and isoferbrifugine could interconvert via a retro-aza-Michael reaction under the influence of polar protic solvents (Scheme 1).[3,8] Therefore, as a large excess of acid is used in our reaction, we believe that the Michael intermediate **150** is in equilibrium with the dicarbonyl compound **152** via the formation of the enol **151**. The

dicarbonyl intermediate then cyclises to form **148**. Attempts to record a crystal structure of **148** failed due to the instability of the imine in both protic and aprotic solvents.



Scheme 46: *Mechanism of the formation of **148***

Having, successfully established a route to the febrifugine hydrobromide salt, the synthesis of halofuginone hydrobromide was next considered (Scheme 47). The coupling reaction between the trans **133** with our synthesised halofuginone quinazolinone **83** was well tolerated and produced the intended product **153** in an excellent yield. The oxidative cleavage using osmium tetoxide and sodium periodate produced the protected halofuginone **154** in a 73% yield and the final deprotection step produced the halofuginone hydrobromide salt **155** in a 70% yield.



Scheme 47: *Route towards halofuginone hydrobromide*

With a successful route towards febrifugine analogues, we next turned our attention to the synthesis of novel febrifugine analogues by using various quinazolinones. Our selected quinazolinones (Figure 21) were acquired from commercial sources (**158** and **159**) or obtained from previous developed Rh-catalyzed ortho-amidation cyclocondensation sequence developed in our group (**156** and **157**).[39] The quinazolinones consisted of halide-swapped analogs **156**, **157** and **159** and the quinazolinone of the tyrosine kinase inhibitor erlotinib **158**.

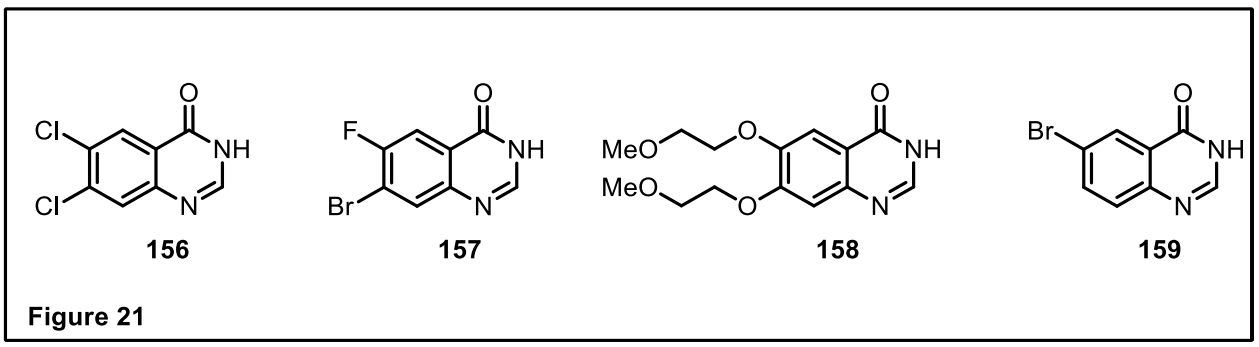
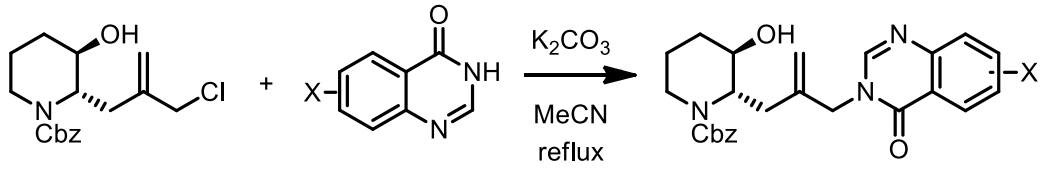
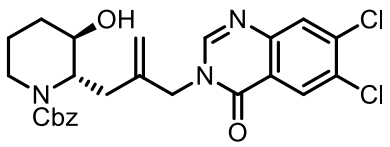
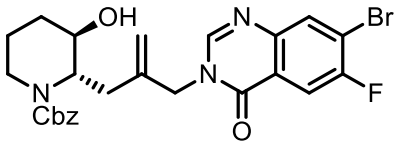
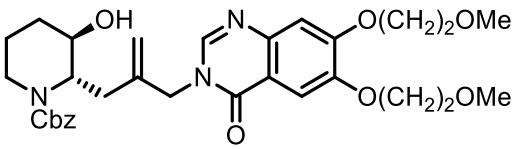
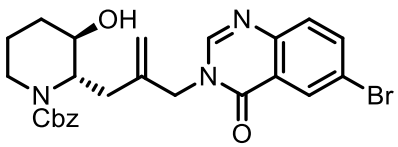


Figure 21

The coupling reactions between the different quinazolinones with the trans-piperidine **133** proceeded smoothly, thereby providing an opportunity to access unique febrifugine analogue derivatives (Table 18).

Table 18



Entry	Quinazolinone	Product	Yield (%)
1	**156**	 **160**	80
2	**157**	 **161**	85
3	**158**	 **162**	71
4	**159**	 **163**	72

Having successfully coupled the key fragments, our final objective was to confirm that intermediates **160** - **163** could be taken forward to the corresponding febrifugine derivatives. We employed an oxidative cleavage and deprotection protocol, using our modification of the Rutjes route. We were pleased to find that the analogs **164** - **167** were all isolated in good yield under these conditions as the HBr salts (Figure 22).

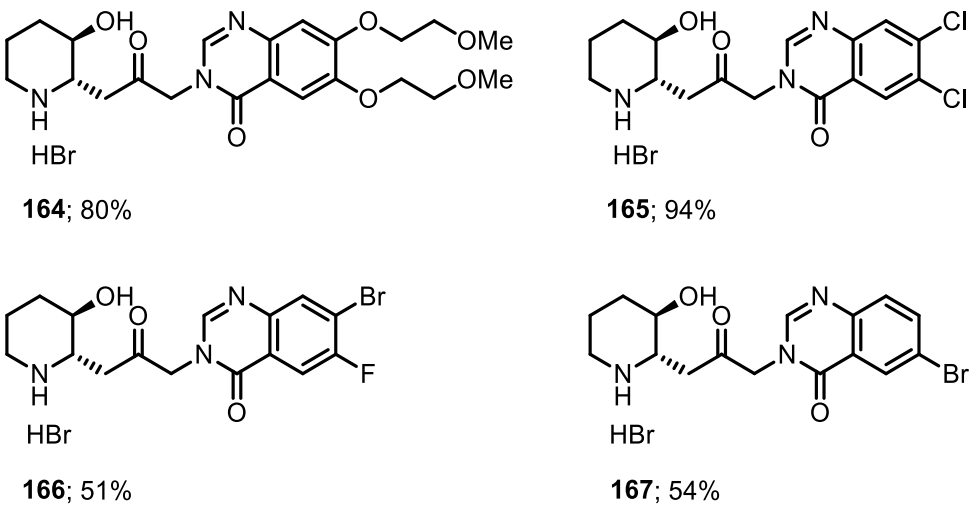


Figure 22: Showing novel febrifugine analogues

These encouraging results prompted us to further investigate other febrifugine analogues such as febrifuginol and epi-febrifuginol (Figure 23). Febrifuginol and epi-febrifuginol are synthetic analogues of febrifugine whereby the central ketone of febrifugine is converted into a hydroxyl functionality. These analogues were developed to overcome the facile interconversion of febrifugine and isofebrifugine via the retro-aza-Michael reaction (Scheme 1). Moreover, febrifuginol and epi-febrifuginol were found to exhibit superior antimalarial activity *in vitro* in comparison to chloroquine and artemisinin.[40,41] More recently, halofuginol was found to inhibit T helper 17 cells (Th17 cells), which in the future might be beneficial for autoimmunity and inflammatory diseases.[40,41]

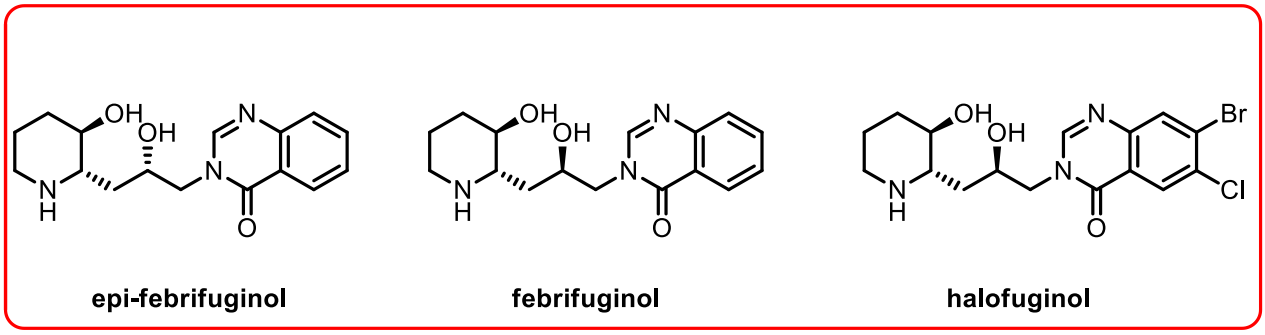
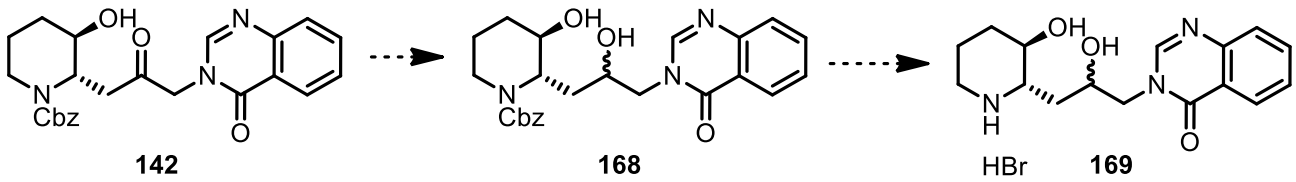


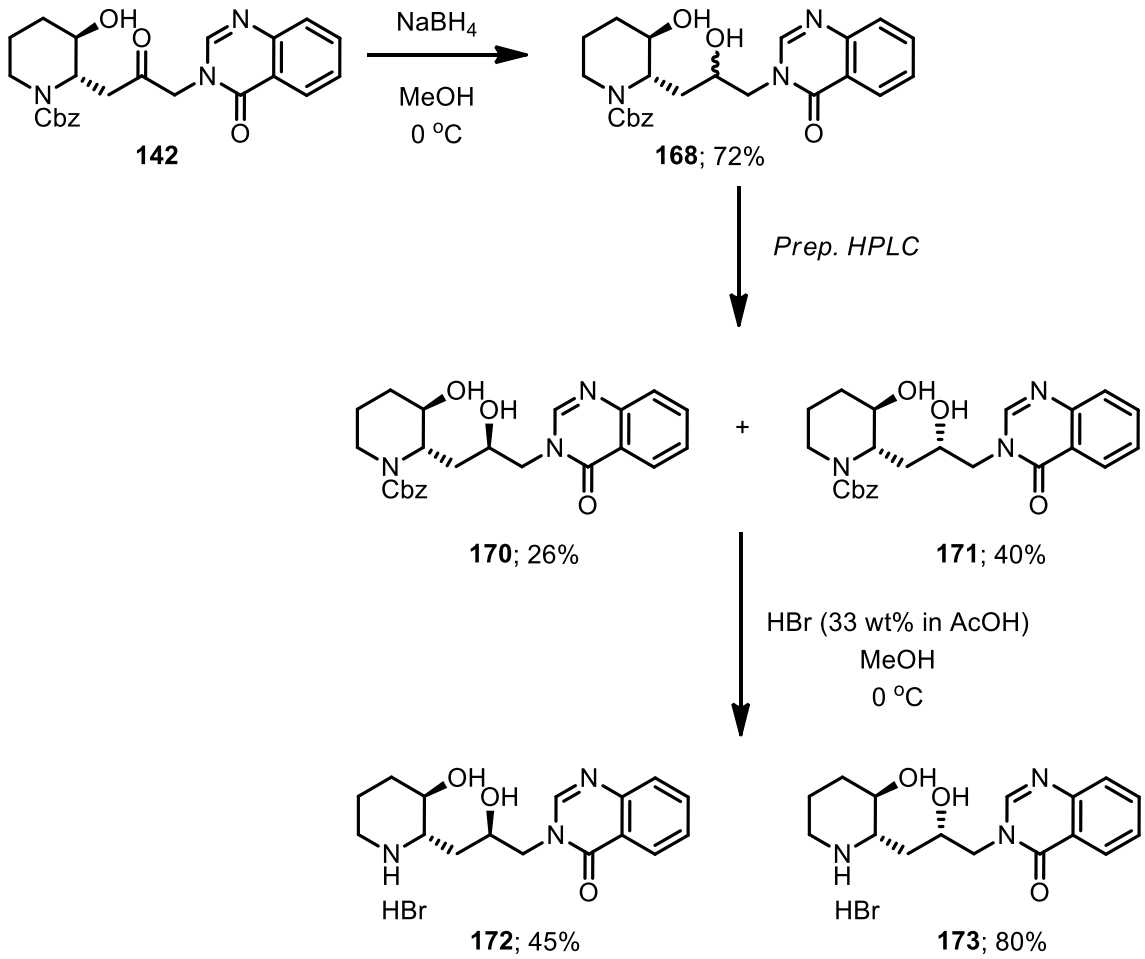
Figure 23.

Our aim was to slightly modify our already successful synthetic route towards febrifugine analogues. Primarily the protected febrifugine analogue **142** would have to be synthesised followed by the reduction of the central ketone and finally removal of the protecting group to furnish the fuginol hydrobromide salt (Scheme 48).



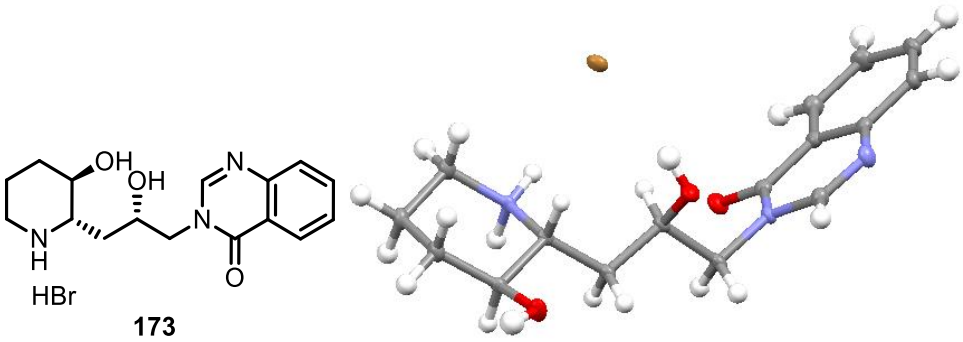
Scheme 48:

The use of sodium borohydride to reduce **142** produced the hydroxyl product as 1 : 1mixture of diastereoisomers **168** (Scheme 49). These were separated by isocratic HPLC eluting with 30% acetonitrile to 70% water to give **170** and **171**. Both diastereoisomers were subjected to the deprotection conditions which produced both the febrifuginol and epi-febrifuginol hydrobromide salts **172** and **173** in moderate to good yields.



Scheme 49:

Recrystallisation of **173** in methanol produced fine crystals which allowed for the first X-ray crystal structure of epifebrifuginol to be recorded, thereby confirming the stereochemistry of the hydroxyl group (Figure 24). The successful synthesis of the febrifuginol analogues inspired us to further alter the structure of febrifugine. Therefore, we devised a route towards analogues where the piperidine ring in febrifugine was replaced by a pyrrolidine.



173

Figure 24: *Shows X-ray crystal structure of epifebrifuginol*

10 PYRROLIDINE ANALOGUES

A literature search on similar analogues led us to work developed by Zhu, where a library of pyrrolidine analogues were synthesised in an attempt to address the toxicity associated with the natural febrifugine alkaloid (Figure 25). The synthesised pyrrolidine analogues and their six membered counterparts were tested against *P. falciparum* clones W-2, a chloroquine resistant cell line for *in vitro* efficacy.

They found that most of the analogues exhibited comparable or superior in vitro and in vivo antimalarial activity compared to febrifugine. During their acute toxicity study they discovered that compound **174** was four times less toxic compared to febrifugine. Whereas compounds **175** - **179**, where the aromatic ring has either nitrogen atom, an electron withdrawing group or a bulky group, revealed significantly reduced toxicity. Zhu's impressive results inspired us to begin our task by utilising our already developed coupling strategy.

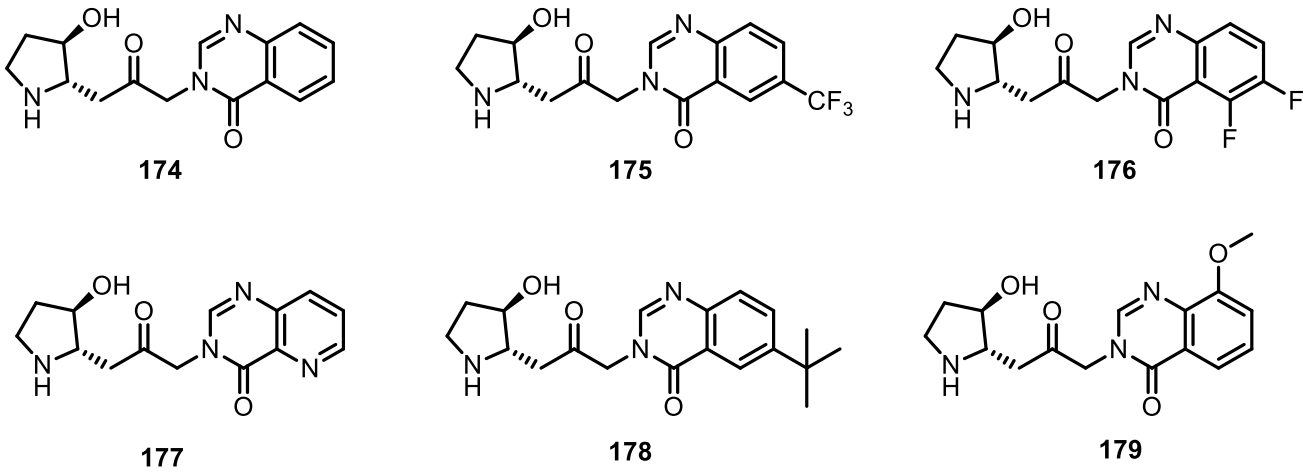
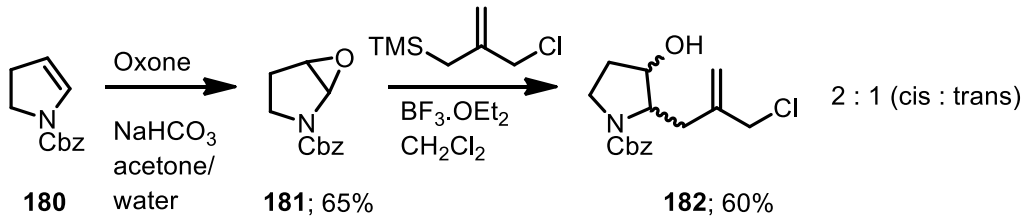


Figure 25: *Zhu's pyrrolidine analogues*

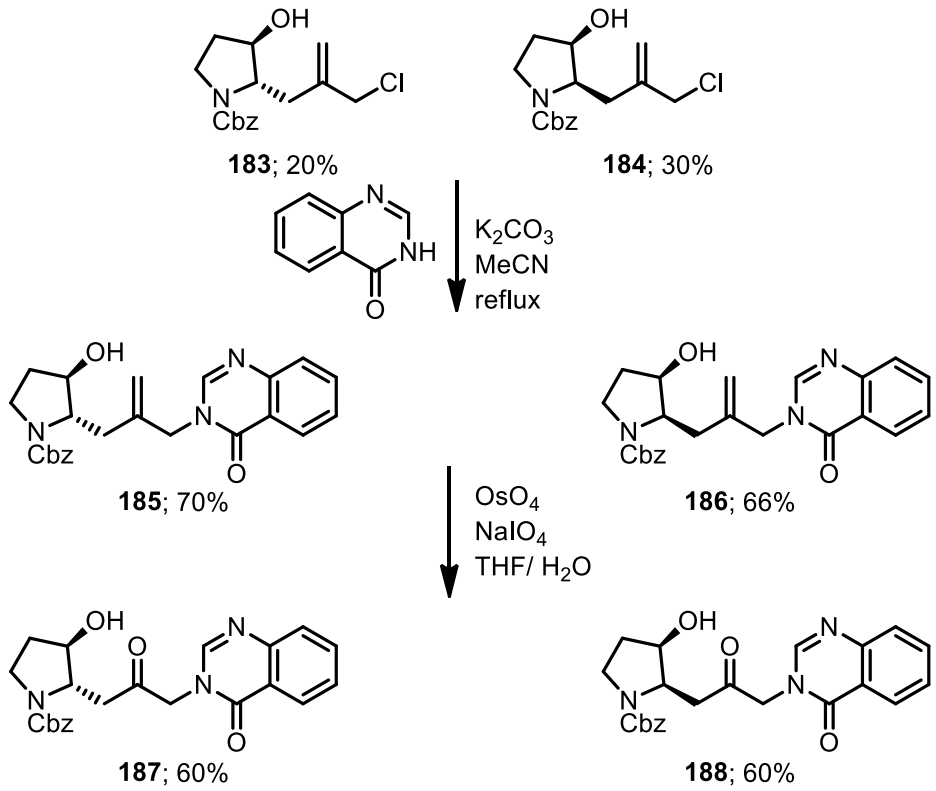
The first step was the epoxidation of the commercially available pyrrolidine **180** using Wallace's conditions. In the event, the reaction was well tolerated forming the epoxide **181** in a 65% yield (Scheme 50).The alkylation with the allyl silane produced **182** in a 60% yield as a 2 : 1 (cis : trans) mixture of diastereoisomers, which were separated via preparative HPLC eluting 40% acetonitrile to 60% water to give **183** and **184** (Scheme 51). Coupling the quinazoline component to each of the diastereoisomers proceeded smoothly producing **185** and **186** in good yields.



Scheme 50

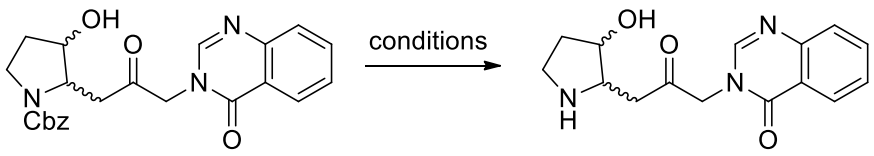
Both **185** and **186** were next subjected to the oxidative cleavage conditions and both products **187** and **188** were produced successfully in good yields. Disappointingly however, the acid deprotection step proved difficult for both diastereoisomers as the decomposition of the

starting materials was observed for each case (Table 19, entries 1 and 2). Reviewing other deprotection conditions we had come across also failed to cleanly deliver the final products (entries 3 - 5).



Scheme 51:

Table 19



Entry	Diastereoisomer	Conditions	Results
1	**187**	HBr 33wt% in AcOH (100 eq), MeOH, 0 °C	Decomposition
2	**188**	HBr 33wt% in AcOH (100 eq), MeOH, 0 °C	Decomposition
3	**187**	6N HCl	Decomposition
4	**188**	6N HCl	Decomposition
5	**187**	Pd/ C, H_2, MeOH, rt,	Complex mixture

These preliminary results suggested that our route would have to be modified to suit the sensitive nature of the pyrrolidine analogues. We also believe in order to further improve the methodology towards the 5 membered analogues, alternative protecting groups such as Boc should be used instead of the Cbz group.

11 FUTURE WORK AND CONCLUDING REMARKS

We have focused on developing strategies for the synthesis of febrifugine analogues by the use of literature and novel methods. For example, the use of Burgess' route saw the synthesis of the novel febrifugine analogue **90**, unfortunately the yields obtained via this route were low.[10] Fortunately, after some optimisation, a successful route towards febrifugine analogues was realised, as the isolation of the final analogues such as **146**, **155**, **164**, **165**, **166** and **167**

were achieved. Disappointingly, the attempts to synthesise the 5 membered analogues provide difficult as the intermediates were unstable under our deprotection conditions.

This, recent research on febrifugine analogues has set the stage for future work on these compounds towards the development of a new wave of drugs with a wide therapeutic index e.g halofuginone.[19,20] Therefore, we intend to continue with our efforts to find an efficient synthetic method towards a series of febrifugine derivatives in the hope they become lead compounds.

12 EXPERIMENTAL

12.1 GENERAL PROCEDURES AND MATERIALS

All the reagents used as received from commercial suppliers unless otherwise stated.

Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230 - 400 mesh). Thin layer chromatography (TLC) was performed on aluminium backed plates precoated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) which were developed using standard visualizing agents : UV fluorescence (254 and 366 nm), potassium permanganate/ Δ.

Melting points (m.p.) are of recrystallized materials and were recorded on Gallenkamp melting point apparatus and are uncorrected.

^{1}H NMR spectra were recorded on a Bruker AMX 400 (400 MHz) instrument supported by an Aspect 200 data system. Chemical shift (δ) are reported in ppm from tetramethylsilane with solvent resonance as the internal standard ($CHCl_3$ in $CDCl_3$: δ7.27 ppm; H_2O in D_2O : δ4.60;

DMSO in $(CD_3)_2SO$: δ2.52). Data are reported as : chemical shift, multiplicity, integration, coupling constant (Hz), and assignment.

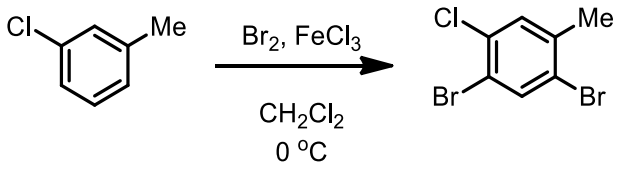
^{13}C NMR spectra were recorded using the JMOD pulse sequence on a Bruker AMX-400 with complete proton decoupling. Chemical shift are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ77.0 ppm; $(CD_3)_2SO$: δ39.7).

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.

12.2 SYNTHESIS OF HALOFUGINONE QUINAZOLINONE

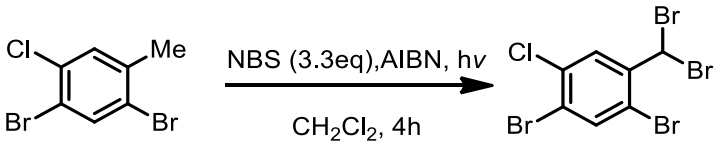
Synthesis of 4-bromo-5-chlorotoluene (76).[31]



m-Chlorotoluene (2.5 g, 19.0 mmol) was added to a solution of $FeCl_3$ (0.2 g, 1.2 mmol) in CH_2Cl_2 (50 mL) and the reaction mixture was cooled to 0 °C. Bromine (6.4 g, 40.0 mmol) was then added dropwise, whilst maintaining this temperature and the reaction was stirred for 2

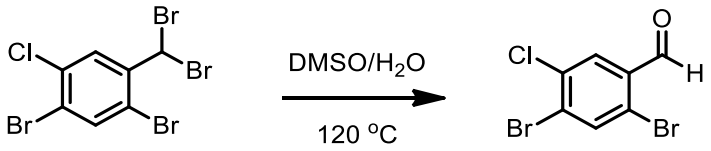
h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with $NaHCO_3$ and then dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product. Recrystallization of the crude product in petroleum ether yielded the title compound as a colourless solid (3.2 g, 71%) Mp 68 - 70 °C (lit. Mp 92 - 95 °C); δ_H (400 MHz, $CDCl_3$) 7.78 (s, 1H), 7.35 (s, 1H), 2.30 (s, 3H); δ_C (101 MHz, $CDCl_3$) 138.7, 136.3, 133.3, 131.7, 123.0, 119.8, 22.4; *m/z*(EI) 284 (100%, $[M(^{35}Cl)]^+$); 286 (58%, $[M(^{37}Cl)]^+$); HRMS, found 281.8437 ($C_7H_5\,^{35}Cl^{79}Br_2$ requires 281.8446).

Synthesis of 1,5-dibromo-2-chloro-4-(dibromomethyl)benzene (78).



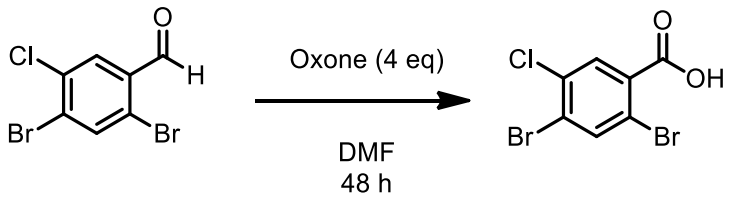
A solution of 4-bromo-5-chlorotoluene (1.0 g, 3.5 mmol), NBS (1.3 g, 11.0 mmol) and AIBN (5.0 mg, 0.01 mmol) in CH_2Cl_2 (30 mL) was irradiated with a tungsten lamp (Nikko Electron Co., Ltd., RF-110 V/500 WH) without external cooling while stirring for 4 hours. Then, succinimide was removed by filtration and aqueous sodium hydrogen sulphite was added to the filtrate. The organic layer was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed under vacuum to provide the oily crude product, which was purified by flash column chromatography eluting 0→5% AcOEt/ 40-60 petroleum ether to give a clear waxy product (0.9 g, 71%) mp 54 - 58 °C; ν_{max} (solid /cm^{-1}) 3075, 3013, 1448, 1339, 1045, 888, 640 ; δ_H (400 MHz, $CDCl_3$) 8.10 (s, 1H), 7.81 (s, 1H), 6.94 (s, 1H); δ_C (101 MHz, $CDCl_3$) 141.0, 136.6, 135.1, 132.2, 124.7, 117.6, 37.4; *m/z*(EI) 440 (5%, $[M(^{35}Cl(^{79}Br_3)^{81}Br)]^+$); 442 (10%, $[M(^{35}Cl(^{79}Br_2)(^{81}Br_2)]^+$); 363 (100%, $[M(^{35}Cl^{79}Br(^{81}Br_2)]^+$); HRMS, found 437.6673 ($[C_7H_3(^{35}Cl)(^{79}Br_4)]$ requires 437.6656).

Synthesis of 2,4-dibromo-5-chlorobenzaldehyde (80).



A solution of 1,5-dibromo-2-chloro-4-(dibromomethyl)benzene (2.2 g, 5.0 mmol) in DMSO (100 mL) and water (15 mL) was heated to 120 °C and stirred overnight. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3 × 20 mL). The extract was washed with water (2 × 20 mL), brine and then was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product purified by recrystallization from chloroform/ petroleum ether to afford the title compound as a colourless solid (1.3 g, 85%) Mp 110 - 112 °C; ν_{max} (solid /cm^{-1}) 3077, 2879, 1680, 1561; δ_H (400 MHz, $CDCl_3$) 10.25 (s, 1H), 7.99 (s, 2H); δ_C (101 MHz, $CDCl_3$) 189.5, 138.1, 135.3, 133.3, 130.6, 129.9, 124.2; *m/z* (EI) 302 (10%, $[M(^{35}Cl^{81}Br^{81}Br)]^+$), 300 (47%, $[M(^{35}Cl(^{81}Br_2)]^+$); 298 (64%, $[M(^{35}Cl^{79}Br^{81}Br)]^+$), 296 (30%, $[M(^{35}Cl(^{79}Br_2)]^+$); HRMS, found 295.8251 ($[C_7H_3O(^{35}Cl(^{79}Br_2)]$ requires 295.8239).

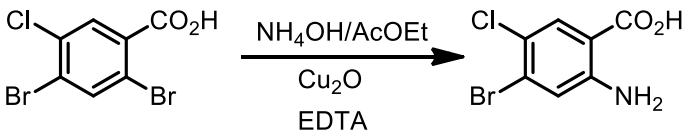
Synthesis of 2,4-dibromo-5-chlorobenzoic acid (81).[30]



Oxone (4. 0 g, 26.4 mmol) was added to a solution of 2,4-dibromo-5-chlorobenzaldehyde (2.0 g, 6.6 mmol) in DMF (20 mL) in one portion and the mixture was stirred for 48 h. 1 N HCl was added to dissolve the salts formed and the product was extracted with ethyl acetate. The

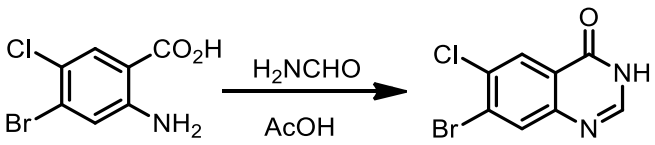
organic extracts were washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to afford the crude product. Recrystallization of the crude material in toluene afforded the title product (1.0 g, 52%) Mp 110 °C; δ_H (400 MHz, DMSO-d^6) 13.85 (s, 1H), 7.99 (s, 1H), 8.21 (s, 1H); δ_C (101 MHz, DMSO-d^6) 138.7, 136.2, 133.2, 131.6, 123.0, 119.8, 22.4.

Synthesis of 2-amino-4-bromo-5-chlorobenzoic acid (82).[31]



Copper oxide (228 mg, 1.6 mmol) was added to a solution of 4-bromo-5-chlorobenzoic acid (5.7 g, 18.0 mmol) in ammonium hydroxide (400 mL) and ethyl acetate (240 mL). The reaction was heated at reflux for 5 hours. EDTA (23.0 g, 79.0 mmol) was then added and the reaction was stirred overnight. 1 M HCl added to the solution until pH ~ 3 and the organic layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and, the resulting brown solid was recrystallized in toluene to yield the title compound as a cream solid (3.6 g, 68%) Mp 112 °C. δ_H (400 MHz, DMSO-d^6) 7.75 (s, 1H), 7.15 (s, 1H); δ_C (101 MHz, DMSO-d^6) 168.3, 151.1, 132.1, 127.3, 121.0, 117.8, 110.8; *m/z*(ESI) 253 (30%, $[M(^{37}Cl^{79}Br)]^+$); 251 (100%, $[M(^{35}Cl\ ^{79}Br)]^+$); HRMS, found 249.9272 ($C_7H_6NO^{35}Cl^{79}Br$ requires 249.9270).

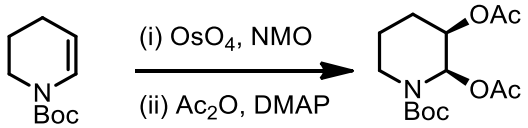
Synthesis of 7-bromo-6-chloroquinazolin-4(3*H*)-one (83).[32]



A mixture of 2-amino-4-bromo-5-chlorobenzoic acid (3.6 g, 14.0 mmol) in formamide (64.0 g, 1.4 mol) and acetic acid (8.6 g, 14.0 mmol) was heated at 200 °C for 1 hour. The reaction mixture was cooled and ice water was added. The mixture was stirred for a further 30 mins at 0 °C to allow the product to precipitate from solution. The brown precipitate was filtered, washed with water and dried under vacuum to yield the product, which was purified by recrystallization from ethanol (2.2 g, 60%) Mp 270 °C (decomp.). δ_H (400 MHz, DMSO-d^6) 12.56 (s, 1H), 8.20 (s, 1H), 8.17 (s, 1H), 8.10 (s, 1H); δ_C (101 MHz, DMSO-d^6) 159.8, 148.5, 147.6, 132.6, 131.6, 128.4, 127.1, 123.5; *m/z*(ESI) 262 (20%, $[M(^{37}Cl\ ^{81}Br)]^+$); 260 (100%, $[M(^{35}Cl\ ^{81}Br)]^+$); 258 (70%, $[M(^{35}Cl^{79}Br)]^+$); HRMS, found 258.9282 ($C_8H_5N_2O^{35}Cl^{79}Br$ requires 258.9274).

12.3 SYNTHESIS TOWARDS FEBRIFUGINE ANALOGUES

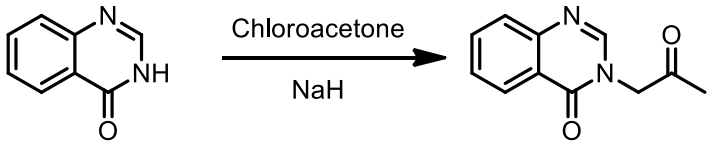
Synthesis of *tert*-butoxycarbonyl piperidine-2, 3-diyl diacetate (88).[33]



To a solution of *N*-Boc-3,4-dihydro-2*H*-pyridine (1.0 g, 5.4 mmol) in acetone (50 mL) and water (5 mL) were added two crystals of osmium tetraoxide. The reaction was then stirred at room temperature and monitored by TLC analysis. After completion, the mixture was cooled and quenched with a saturated solution of sodium metabisulfite (10 mL). Water (10 mL) was added and the product was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure to give a white solid. The solid was immediately dissolved in $CHCl_3$ and reacted with acetic anhydride (2.6 mL, 27 mmol), triethylamine (3.8 mL, 27 mmol) and DMAP (66 mg, 0.5 mmol). After stirring for one hour the mixture was

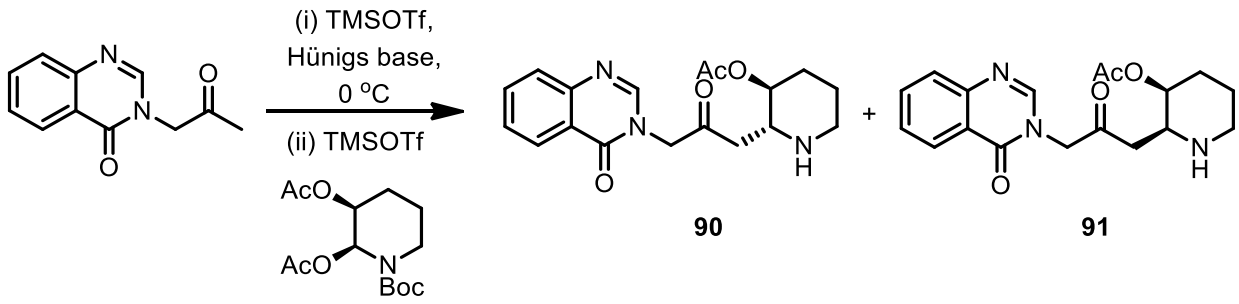
diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil (1.21 g, 73%); δ_H (400 MHz, $CDCl_3$), 6.82 (d, 1H, *J* = 6.5 Hz), 4.90 - 4.76 (m, 1H), 3.89 - 3.83 (m, 2H), 3.10 - 3.04 (m, 2H), 2.94 - 2.86 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.41 (s, 9H); δ_C (101 MHz, $CDCl_3$) 169.2, 166.3, 153.9, 81.1, 80.9, 69.5, 45.0, 28.2, 28.0, 23.7, 22.9, 22.0, 20.7, 20.3; *m/z* (ESI) 324(100%, $[M(Na)]^+$); HRMS, found 324.1431 ($C_{14}H_{23}N_6Na$ requires 324.1423).

Synthesis of 3-(2-oxopropyl) quinazolin-4(3*H*)-one (84).[10]



NaH 60% dispersion in mineral oil; (130 mg, 5.4 mmol) was added to a solution of 4-hydroxyquinazoline (500 mg, 3.4 mmol) in DMF (20 mL). The reaction was then cooled to 0 ^oC and stirred for 30 min. Chloroacetone (0.5 mL, 6.8 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. Saturated NH_4Cl was added and the product was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to afford the title a colourless solid (0.65 g, 93%); δ_H (400 MHz, $CDCl_3$) 8.29 (d, 1H, *J* = 8.0 Hz), 7.91 (s, 1H), 7.84 - 7.72 (m, 2H), 7.53 (t, 1H, *J* = 7.0 Hz), 4.78 (s, 2H), 2.39 (s, 3H); δ_C (101 MHz, $CDCl_3$) 200.0, 160.8, 148.1, 146.2, 134.5, 127.6, 127.4, 126.7, 121.8, 54.6, 29.6.

Synthesis of 2-(2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl) propyl) piperidin-3-yl (90).

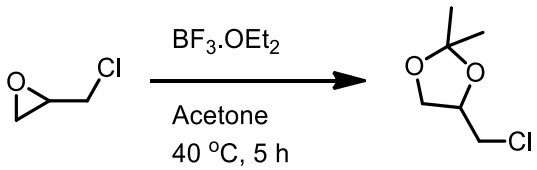


Hünigs base (100 mg, 1.0 mmol) was added to a solution of 3-(2-oxopropyl) quinazolin-4(3H)-one (100 mg, 0.5 mmol) dissolved in CH_2Cl_2 (5 mL). Trimethylsilyl trifluoromethane sulfonate (TMSOTf) (200 mg, 10.0 mmol) was then added dropwise. The mixture was stirred for 2 h, before it was added to a diethyl ether (10 mL)/ Water (10 mL) mixture. The organic layer was extracted with diethyl ether (2 × 10 mL); washed with sodium bicarbonate, brine and dried over Na_2SO_4. The solvent was removed under vacuum to afford the silyl enol ether as yellow oil (77. 0 mg, 66%). Without further purification the silyl enol ether was dissolved in CH_2Cl_2 (5mL) with the *tert*-butoxycarbonyl piperidine-2, 3-diyl diacetate (200 mg, 0.5 mmol) and the mixture was cooled to -78 °C. The TMSOTf (11 mg, 0.5 mmol) was introduced and the reaction was stirred overnight. The reaction was quenched with NH_4Cl (aq), extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was then removed under vacuum to afford the crude product, which was purified via flash column chromatography (CH_2Cl_2 : MeOH, 8 : 2) to give the title compound as a yellow oil (65 mg, 33%). ν_{max} (solid /cm^{-1}) 3088, 2671, 1766, 1713, 1671, 1612, 1239, 1160, 1029, 912; δ_H (400 MHz, $CDCl_3$) 8.25 (d, 1H, *J* = 8.0 Hz), 7.95 (s, 1H), 7.74 - 7.70 (m, 2H), 7.50 (t, 1H, *J* = 8.3 Hz), 4.92 (d, 1H, *J* = 13.0 Hz), 4.76 (d, 1H, *J* = 13.0 Hz), 4.56 - 4.50 (m, 1H), 3.15 - 3.10 (m, 2H), 2.90 (dd, 2H, *J* = 4.0 Hz and *J* = 2.0 Hz), 2.75 - 2.70 (m, 1H), 2.65 - 2.63 (m, 1H), 2.10 (s, 3H), 1.75 - 1.70 (m, 2H), 1.60 - 1.55 (m, 2H), 1.40 - 1.35 (m, 2H); δ_C (101 MHz, $CDCl_3$) 201.9, 170.4, 160.9, 148.2, 146.4, 134.5, 127.6, 127.4, 126.6, 121.7, 118.6, 72.5,

55.9, 54.6, 46.7, 45.2, 29.8, 24.4; *m/z* (ESI) 344 (100%, $[M]^+$); HRMS, found 344.1604 ($C_{18}H_{22}N_3O_4$ requires 344.1610).

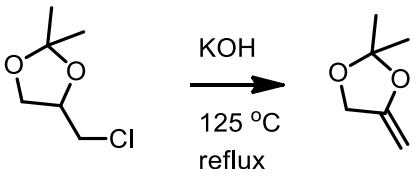
91 afforded as a Clear oil (19 mg, 11%). ν_{max} (solid /cm^{-1}) 3090, 2924, 1766, 1713, 1672, 1610, 1243,1155, 1029, 910; δ_H (400 MHz, $CDCl_3$) 8.30 (d, 1H, *J* = 7.0 Hz), 7.95 (s, 1H), 7.75 - 7.71 (m, 2H), 7.53 (t, 1H, *J* = 7.5 Hz), 4.95 - 4.92 (m, 1H), 4.88 (d, 1H, *J* = 4.0 Hz), 4.76 (d, 1H, *J* = 4.0 Hz), 3.40 - 3.35 (m, 2H), 3.15 - 3.10 (m, 2H), 2.80 - 2.70 (m, 2H), 2.20 (s, 3H), 2.00 - 1.95 (m, 2H), 1.70 - 1.65 (m, 2H); δ_C (101 MHz, $CDCl_3$) 201.8, 170.4, 161.2, 147.3, 145.0, 134.5, 128.0, 127.0, 126.6, 121.7, 118.6, 72.5, 56.2, 54.3, 46.3, 44.9, 30.8, 25.5; *m/z* (ESI) 344 (100%, $[M]^+$); HRMS, found 344.1003 ($C_{18}H_{22}N_3O_4$ requires 344.1610).

Synthesis of 4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (107).[34]



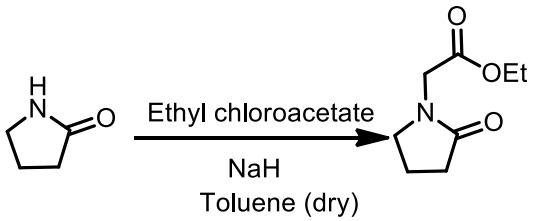
Boron trifluoride diethyl etherate (20 mg, 0.1 mmol) was added to a solution of epichlorohydrin (2.0 g, 22.0 mmol) in acetone (19 mL) at 0 °C. The reaction mixture was then stirred for 1 h allowing the mixture to reach room temperature. The reaction mixture was then heated to 40 °C and left to stir for 5 h. Removal of the solvent under reduced pressure gave the title product as a clear oil (3.3 g, 97%). δ_H (400 MHz, $CDCl_3$) 4.35 - 4.25 (m, 1H), 4.10 (dd, 1H, *J* = 6.0 Hz and *J* = 2.5 Hz), 3.86 (dd, 1H, *J* = 5.5 Hz and *J* = 2.5 Hz), 3.60 - 3.55 (m, 1H), 3.45 - 3.40 (m, 1H); δ_C (101 MHz, $CDCl_3$) 110.1, 75.3, 67.4, 44.5, 26.8, 25.2.

Synthesis of 2,2-dimethyl-4-methylene-1,3-dioxolane (103).[34]



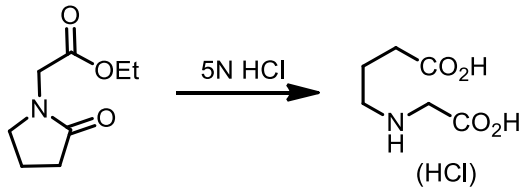
A mixture of 4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (3.3 g, 21.0 mmol) and potassium hydroxide (7.3 g, 131.0 mmol) was heated to reflux . The reaction was left to stir overnight and the product was distilled out of the crude mixture at 110 °C under reduced pressure to afford the title product as a clear oil (1.0 g, 44%). δ_H (400 MHz, $CDCl_3$) 4.49 (s, 2H), 4.26 (s, 1H), 3.83 (s, 1H), 1.44 (s, 6H); δ_C (101 MHz, $CDCl_3$) 156.1, 111.8, 77.6, 66.3, 25.0.

Synthesis of Ethyl 2-(2-oxopyrrolidin-1-yl) acetate (115).[35]



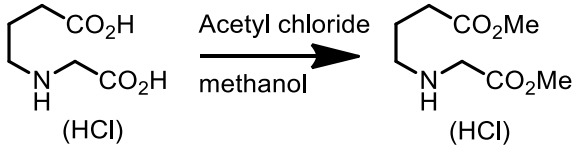
To a suspension of sodium hydride (11.3 g, 0.5 mol) in dry toluene (150 mL), 2-pyrrolidine (20.0 g, 0.2 mol) was added. The mixture was stirred at reflux for 1 h and then cooled to room temperature. Tetra-*n*-butyl ammonium bromide (7.7 g, 0.2 mol) and ethyl chloroacetate (35.8 g, 0.3 mol) were added and the mixture was stirred for a further 48 h at room temperature. The solvent was removed under reduced pressure and ether (20 mL) was added to the residue. The mixture was filtered and the solvent removed under vacuum. The product was purified by distillation under reduced pressure to provide the title compound as a colourless oil (20.5 g, 50%). δ_H (400 MHz, $CDCl_3$) 4.19 (q, 2H, *J* = 7.5 Hz), 4.05 (s, 2H), 3.50 (t, 2H, *J* = 7.0 Hz), 2.39 (t, 2H, *J* = 8.0 Hz), 2.08 - 2.02 (m, 2H), 1.28 (t, 3H, *J* = 7.5 Hz); δ_C (101 MHz, $CDCl_3$) 175.5, 168.6, 61.1, 47.4, 44.0, 30.2, 17.8, 14.0.

Synthesis of 4-((carboxymethyl) amino) butanoic acid hydrochloride (116).[35]



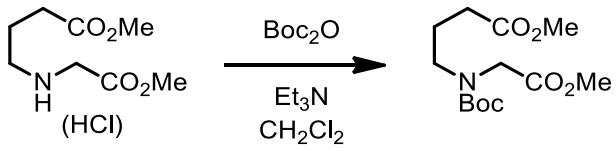
A solution of ethyl 2-(2-oxopyrrolidin-1-yl) acetate (20.4 g, 0.1 mol) in aqueous 5 M HCl (100 mL) was heated at reflux for 48 h. The mixture was then cooled and concentrated. The residue was dissolved in methanol (100 mL) and the solution then evaporated under reduced pressure to afford the product as a colourless gum (22.0 g, 93%). δ_H (400 MHz, D_2O) 4.05 (s, 2H), 3.08 - 3.02 (m, 2H,), 2.44 - 2.31 (m, 2H), 2.00 - 1.80 (m, 2H); δ_C (101 MHz, D_2O) 179.1, 171.0, 46.7, 38.6, 30.4, 21.9.

Synthesis of methyl 4-((2-methoxy-2-oxoethyl) amino) butanoate hydrochloride (117).[35]



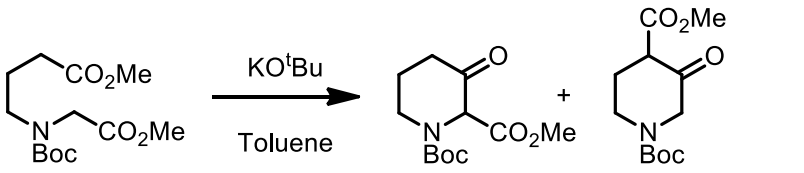
Acetyl chloride (3.6 g, 46.0 mmol) was added to methanol (30 mL) and the solution was stirred for 15 min. The mixture was transferred to a flask containing the 4-((carboxymethyl) amino) butanoic acid hydrochloride diacid (6.2 g, 32.0 mmol) and the resulting solution was heated at reflux overnight. After completion the mixture was allowed to reach room temperature and the solvent was removed under reduced pressure to afford the product as a yellow oil (6.3 g, 86%). δ_H (400 MHz, MeOD-d^4) 5.48 (s, 1H), 4.10 (s, 2H), 3.87 (s, 3H), 3.71 (s, 3H), 3.15 - 3.25 (m, 2H), 2.56 - 2.50 (m, 2H), 2.01-2.16 (m, 2H) ; δ_C (101 MHz, MeOD-d^4) 168.8, 168.1, 54.1, 53.7, 52.4, 49.9, 31.5, 23.8.

Synthesis of methyl 4-((tert-butoxycarbonyl) (2-methoxy-2-oxoethyl) amino) butanoate (118).[35]



A solution of the methyl 4-((2-methoxy-2-oxoethyl) amino) butanoate hydrochloride diester (4.0 g, 17.0 mmol) in dichloromethane (10 mL) was added to a solution of the di-tert-butyl dicarbonate (5.8 g, 26.0 mmol) in CH_2Cl_2 (30 mL) and the mixture was allowed to stir for 10 mins. Triethylamine (5.4 g, 53.0 mmol) was then added and the mixture was allowed to stir overnight. After completion the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 ×20 mL). The organic layers were combined and washed with brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product, which was purified via flash column chromatography (60 / 40, Pet.ether/ EtOAc) to afford the product as a yellow oil (2.0 g, 40 %). δ_H (400 MHz, $CDCl_3$) 3.70 (s, 2H) , 3.52 (s, 3H), 3.46 (s, 3H), 3.13 (t, 2H, *J* = 6.8 Hz), 2.15 (t, 2H, *J* = 7.3 Hz), 1.68 - 1.55 (m, 2H), 1.23 (s, 9H); δ_C (101 MHz $CDCl_3$,) 173.6, 170.4, 155.7, 79.8, 51.3, 50.9, 47.5, 39.9, 30.8, 27.9, 23.4.

Synthesis of 1-tert-butyl 2 methyl 3-oxopiperidine-1,2-dicarboxylate (108).[35]



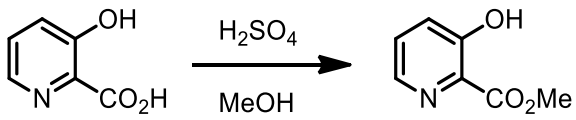
108 **Regioisomer**

To a solution of the methyl 4-((*tert*-butoxycarbonyl) (2-methoxy-2-oxoethyl) amino) butanoate (2.0 g, 7.0 mmol) in toluene (30 mL) cooled to 0 °C, potassium *tert*-butoxide (3.2 g, 28.0 mmol) was added in one portion. The mixture was stirred for 1 h and quenched with

acetic acid (10 mL), the resulting mixture was then extracted with diethyl ether (2 ×20 mL). The combined organic extracts were washed with 1 N HCl, water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product which was purified via flash column chromatography (60 / 40, Pet. ether/ EtOAc) to give the title compound as a yellow oil (0.6 g, 31%). δ_H (400 MHz, $CDCl_3$) 11.12 (s, 1H), 5.22 (s, 1H), 5.06 (s, 1H), 4.10 - 3.86 (m, 1H), 3.79 (s, 3H), 3.45 - 3.28 (m, 1H), 2.60 - 2.42 (m, 1.3H), 2.41 (t, 0.7H, *J* = 7.2 Hz), 2.08 - 1.95 (m, 1.3H), 1.90 - 1.81 (m, 0.7H), 1.49 (s, 3H), 1.44 (s, 6H); δ_C (101 MHz, $CDCl_3$) 200.0, 175.0, 170.5, 165.5, 155.0, 81.2, 66.9, 65.5, 53.0, 41.4, 40.4, 37.8, 28.1, 26.5, 22.7, 22.2 (Complexity of the NMR is due to rotamers and tautomers).

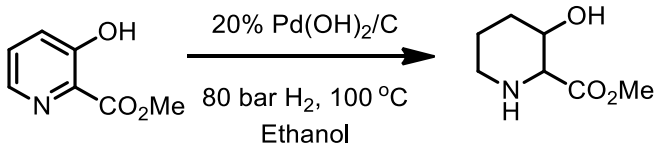
Regioisomer afforded as a clear oil (0.2 g, 10%), δ_H (400 MHz, $CDCl_3$) 1.45 (s, 9H), 2.29 (m, 2H), 3.45 (t, 2H, *J* = 5.5 Hz) , 3.75 (s, 3H), 4.01 (s, 2H), 11.95 (s, 1H) ; δ_C (101 MHz, $CDCl_3$) 172.0, 167.0, 154.5, 98.5, 96.8, 79.4, 51.6, 45.5, 41.2, 39.9, 28.3, 21.9.

Synthesis of methyl 3-hydroxypicolinate (112).



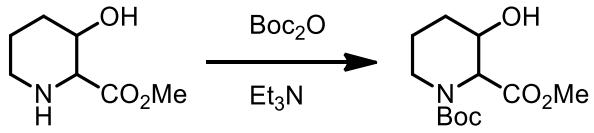
Sulfuric acid (14.1 g, 144.0 mmol) was added to a solution of 3-hydroxypyridine-2-carboxylic acid (2.0 g, 14. 4 mmol) in methanol (125 mL). The mixture was heated to reflux overnight and quenched with $NaHCO_3$. The reaction mixture was extracted with diethyl ether and the combined organic layers were washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the title product as a colourless oil (1.1 g, 49%); δ_H (400 MHz, $CDCl_3$) 10.50 (s, 1H), 8.15 (d, 2H, *J* = 1.3 Hz), 7.50 (t, 1H, *J* = 2.8 Hz), 7.45 (d, 1H, *J* = 1.3 Hz), 3.88 (s, 3H); δ_C (101 MHz, $CDCl_3$) 168.1, 155.9, 141.1, 133.6, 129.2, 125.9, 52.83.

Synthesis of methyl 3-hydroxypiperidine-2-carboxylate (113). [36]



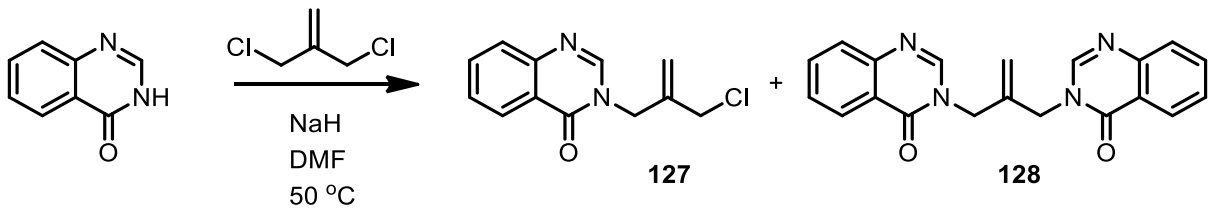
A solution of methyl 3-hydroxypicolinate (1.0 g, 7.0 mmol) in ethanol (140 mL) was introduced into a continuous flow hydrogenation reactor H-cube. The reaction mixture was subjected to 80 bars of hydrogen and was heated to 100 °C for 4 h. After completion the reacted solution was cooled down and the solvent was removed under reduced pressure to afford the title product as yellow oil (1.1 g, 97%). δ_H (400 MHz, $CDCl_3$) 3.89 - 3.84 (m, 1H), 3.60 (s, 3H), 3.40 (d, 1H, *J* = 2.5 Hz), 2.94 - 2.89 (m, 2H), 2.48 - 2.40 (m, 2H), 1.65 - 1.57 (m, 2H); δ_C (101 MHz, $CDCl_3$) 172.1, 68.6, 62.8, 51.9, 45.0, 31.1, 19.9.

Synthesis of 1-tert-butyl 2-methyl 3-hydroxypiperidine-1,2-dicarboxylate (114).[35]



Methyl 3-hydroxypiperidine 2-carboxylate (1.1 g, 6.8 mmol) was added to a solution of Boc anhydride (1.9 g, 8.8 mmol) in DCM. Triethylamine (0.9 g, 8.8 mmol) was added and the resulting solution was stirred overnight. The mixture was diluted with water and extracted with DCM. The combined organic layers were washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the oily product (1.0 g, 56%); δ_H (400 MHz, $CDCl_3$) 5.12 - 5.04 (m, 1H) , 4.96 - 4.92 (m, 1H), 4.05 - 3.95 (m, 1H), 3.80 (s, 3H), 2.80 - 2.74 (m, 1H), 2.66 - 2.54 (m, 2H), 2.00 - 1.90 (m, 2H), 1.40 (s, 9H); δ_C (101 MHz, $CDCl_3$) 172.5, 155.3, 80.5, 69.0, 61.4, 52.2, 41.4, 30.0, 28.2, 23.3.

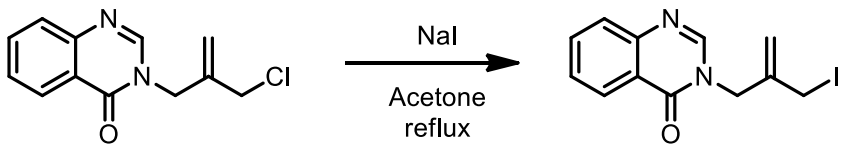
Synthesis of 3-(2-(chloromethyl) allyl) quinazoline-4(3*H*)-one (127).



4-hydroxyquinazoline (1.0 g, 7.0 mmol) was added to a solution of NaH 60% dispersion in mineral oil (0.3 g, 10.0 mmol) in DMF (50 mL). The mixture was cooled to 0 °C and left to stir for 30 mins before, 3-chloro-2-chloro-methyl propene (5.1 g, 41.0 mmol) was added dropwise. The mixture was heated to 50 °C for 4 h. After cooling to room temperature the reaction was quenched with NH_4Cl (aq) (20 mL) and the product extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with aqueous LiCl solution (5% mass/volume), brine and dried over $MgSO_4$. The solvent was removed under vacuum to afford the crude product, which was purified by recrystallization in chloroform/ petroleum ether (1/ 9) to give the title product (0.9 g, 60%). ν_{max} (solid /cm^{-1}) 3064, 2963 1661, 1606, 990, 800; δ_H (400 MHz, $CDCl_3$) 8.34 (d, 1H, *J* = 6.0 Hz), 8.09 (s, 1H), 7.85 - 7.75 (m, 2H), 7.60 - 7.50 (m, 1H), 5.41 (s, 1H), 5.15 (s, 1H), 4.78 (s, 2H), 4.15 (s, 2H); δ_C (101 MHz, $CDCl_3$) 160.7, 147.9, 146.4, 139.6, 134.3, 127.4, 127.3, 126.6, 121.9, 117.8, 47.7, 45.7; *m/z* (ESI) 235 (100%, $[M (Cl^{35}]^+$); HRMS, found 235.0647 ($C_{12}H_{12}N_2O^{35}Cl$ requires 235.0638).

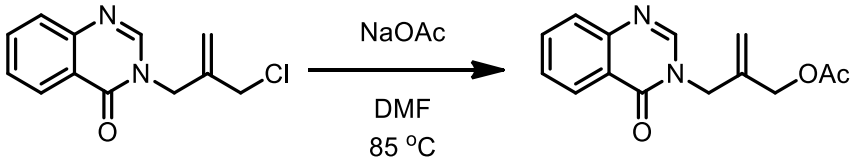
128 formed as a colourless solid (54.0 mg, 6%) Mp 198 - 199 °C. ν_{max} (solid /cm^{-1}) 3064, 2964, 1661, 1605, 989, 768; δ_H (400 MHz, $CDCl_3$) 8.32 (d, 2H, *J* = 6.0 Hz), 8.11 (s, 2H), 7.75 (m, 4H), 7.55 (m, 2H), 5.17 (s, 2H), 4.72 (s, 4H); δ_C (101 MHz, $CDCl_3$) 160.9, 148.0, 146.1, 138.9, 134.5, 127.6, 127.5, 126.8, 121.9, 116.5, 48.3; *m/z* (ESI) 345 (100%, $[M]^+$); HRMS, found 345.1353 ($C_{20}H_{17}N_4O_2$ requires 345.1352).

Synthesis of 3-(2-(iodomethyl) allyl) quinazolin-4 (3*H*)-one (130).



Sodium iodide (0.2 g, 1.5 mmol) was added to a solution of 3-(2-(chloromethyl) allyl) quinazoline-4(3*H*)-one (0.3 g, 1.3 mmol) in acetone (30 mL). The mixture was heated at reflux for 3 h. After completion (as judged by TLC analysis) the mixture was cooled to room temperature, quenched with water (10 mL) and extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with dilute sodium bisulfite, water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the product as a yellow oil (0.3 g, 69%). ν_{max} (solid)/cm^{-1}) 3063, 2921, 1661, 1605, 989, 508; δ_H (400 MHz, $CDCl_3$) 8.32 (d, 1H, *J* = 6.0 Hz), 8.09 (s, 1H), 7.83 - 7.73 (m, 2H), 7.57 - 7.51 (m, 1H), 5.48 (s, 1H), 5.03 (s, 1H), 4.81 (s, 2H), 3.97 (s, 2H); δ_C (101 MHz, $CDCl_3$) 161.0, 148.0, 146.2, 140.9, 134.4, 127.6, 127.5, 126.8, 122.0, 116.6, 48.7, 5.6. *m/z* (ES) 327 (100%, $[M(^{127}I)]^+$); HRMS, found 327.0005 ($[C_{12}H_{12}N_2O^{127}I]$ requires 326.9994).

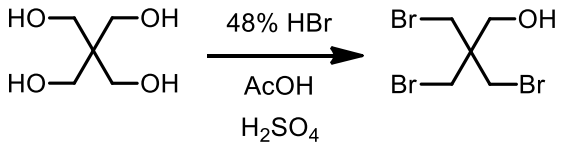
Synthesis of 2-((4-oxoquinazolin-3 (4*H*)-yl) methyl) allyl acetate (131).[37]



A solution of 3-(2-(chloromethyl) allyl) quinazoline-4(3*H*)-one (0.3 g, 1.3 mmol) and sodium acetate (0.1 g, 1.6 mmol) in DMF (30 mL) was heated at 85 °C. The reaction mixture was monitored by thin layered chromatography until completion. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were

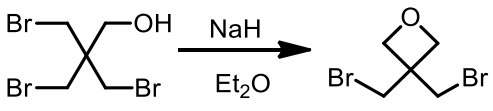
washed with aqueous LiCl (5% mass/volume), Brine and then dried over $MgSO_4$. The solvent was removed under vacuum to afford the oily product (0.23 g, 70%). δ_H (400 MHz, $CDCl_3$) 8.32 (d, 1H, *J* = 6.0 Hz), 8.09 (s, 1H), 7.82 - 7.73 (m, 2H), 7.58 - 7.51 (m, 1H), 5.48 (s, 1H), 5.20 (s, 1H), 4.79 (s, 2H), 4.76 (s, 2H), 2.03 (s, 3H); δ_C (101 MHz, $CDCl_3$) 170.3, 160.8, 147.9, 146.2, 138.5, 134.4, 127.5, 127.4, 126.8, 121.9, 117.3, 64.4, 47.8, 20.7.

Synthesis of 3-bromo-2,2-bis (bromomethyl) propan-1-ol (123).[37]



A mixture of pentaerythritol (6.0 g, 44.0 mmol) in glacial acetic acid (29.6 g, 49.0 mmol) and 48% queous HBr (8.3 g, 0.1 mol) was refluxed for 24 h. Then 48% aqueous HBr (35.2 g, 0.4 mol) and concentrated sulphuric acid (20.0 g, 0.2 mol) were added. The resulting solution was refluxed a further 24 h. After cooling to an ambient temperature, the mixture was extracted with dichloromethane. The extracts were combined, washed with water, brine and dried over anhydrous potassium carbonate. The solvent was removed under reduced pressure to afford the crude product, which in turn was subjected to flash column chromatography (Et_2O: Petroleum ether 40/60 (4:6)) to provide the colourless product (7.58 g, 53%); δ_H (400 MHz, $CDCl_3$) 3.75(s, 2H), 3.55 (s, 6H); δ_C (101 MHz, $CDCl_3$) 62.3, 44.2, 34.4.

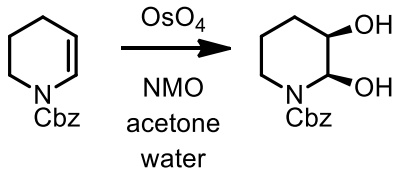
Synthesis of 3,3-bis (bromomethyl) oxetane (121).



To a solution of sodium hydride (0.1 g, 5.0 mmol) in dry diethyl ether (5 mL) 3-bromo-2,2-bis (bromomethyl) propan-1-ol (1.0 g, 3.0 mmol) was added. The reaction mixture was left to stir

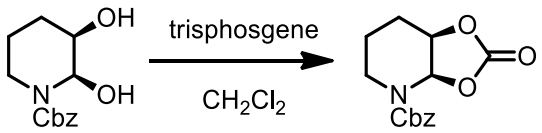
overnight and the unreacted sodium hydride was quenched by the addition of methanol. The mixture was filtered and the solvent was removed under reduced pressure to afford the oily crude product. The crude product was subjected to flash column chromatography (Et_2O: Petroleum ether 40/60 (1 : 9)) to afford the title product as a clear oil (0.2 g, 30%); δ_H (400 MHz, $CDCl_3$) 3.85 (s, 4H), 4.42 (s, 4H); δ_C (101 MHz, $CDCl_3$) 71.2, 44.9, 37.0.

Synthesis of benzyl 2,3-dihydroxypiperidine-1-carboxyalte (138). [38]



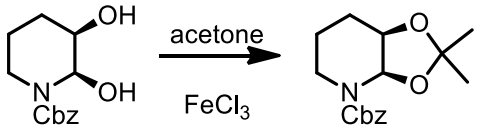
To a solution of *N*-Boc-3,4-dihydro-2*H*-pyridine (1.0 g, 5.4 mmol) in acetone (50 mL) and water (5 mL) a few crystals of osmium tetroxide were added. The reaction was stirred at room temperature and monitored by TLC analysis. After completion, the mixture was cooled and quenched with a saturated solution of sodium metabisulfite (10 mL). Water (10 mL) was added and the product was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure to give the crude product. The crude residue was purified via flash column chromatography eluting with petroleum ether : EtOAc (6 : 4) to give the title product as a yellow oil (922 mg, 68%); δ_H (400 MHz, $CDCl_3$) 7.38 - 7.34 (m, 5H), 5.75 (d, 1H, *J* = 3.5 Hz), 5.13 (s, 2H), 3.90 - 3.82 (m, 1H), 3.64 - 3.56 (m, 1H), 3.10 (dt, 1H, *J* = 12.0, 2.0 Hz), 1.86 - 1.78 (m, 1H), 1.74 - 1.66 (m, 2H), 1.56 - 1.46 (m, 1H); δ_C (101 MHz, $CDCl_3$) 156.0, 136.1, 128.5, 128.2, 127.9, 76.5, 69.0, 67.5, 36.1, 26.6, 23.5.

Synthesis of benzyl 2-oxotetrahydro-[1,3]dioxolo[4,5-*b*]pyridine-4(3*aH*)-carboxylate (135). [38]



To a solution of benzyl 2,3-dihydroxypiperidine-1-carboxyalte (200 mg, 0.8 mmol) and pyridine (251 mg, 3.2 mmol) in dichloromethane (6 mL) at 0 °C, triphosgene (259 mg, 0.8 mmol) was added. The mixture was monitored by TLC analysis whilst maintaining the temperature. After completion, diethyl ether (10 mL) was added and the crude mixture including the salts was washed with a $CuSO_4$ (satd.) solution. The layers were separated and the organic layer was washed with brine, dried over anhydrous $MgSO_4$ and removed under reduced pressure to afford the title product as a clear oil (141 mg, 64%). ν_{max} (solid /cm^{-1}) 3661, 2956, 2197, 1794, 1704, 695; δ_H (400 MHz, $CDCl_3$) 7.44 - 7.32 (m, 5H), 6.66 (d, 1H, *J* = 5.0 Hz), 5.23 - 5.15 (m, 2H), 4.95 - 4.88 (m, 1H), 3.95 - 3.70 (m, 2H), 3.45 - 3.30 (m, 1H), 2.05 - 1.99 (m, 1H), 1.89 - 1.77 (m, 2H); δ_C (101 MHz, $CDCl_3$) 157.5, 156.0, 136.3, 128.3, 128.2, 128.1, 90.8, 74.6, 67.4, 40.7, 23.4, 22.6; *m/z* (ESI) 300 (100%, $[M(Na)]^+$); HRMS, found 300.0846 ($[C_{14}H_{15}NO_5Na]$ requires 300.0842).

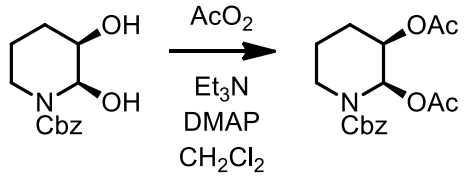
Synthesis of benzyl 2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*b*]pyridine-4(3*aH*)-carboxylate (136).



To a solution of benzyl 2,3-dihydroxypiperidine-1-carboxyalte (303 mg, 1.2 mmol) in acetone (6 mL), $FeCl_3$ (98 mg, 0.6 mmol) was added. The reaction was stirred at room temperature for 16 h. The mixture was then diluted with water (20 mL) and product extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine, dried over

anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product. The crude residue was purified via flash column chromatography eluting with petroleum ether : EtOAc (6 : 4) to give the title product (188 mg, 54%) Mp 166 - 167 °C. ν_{max} (solid /cm^{-1}) 3661, 2941, 2159, 1976, 1702, 1076, 694; δ_H (400 MHz, $CDCl_3$) 7.45 - 7.30 (m, 5H), 5.96 (d, 1H, *J* = 8.0 Hz), 5.26 - 5.10 (m, 2H), 4.12 (q, 1H, *J* = 6.0 Hz), 3.09 - 3.80 (m, 2H), 3.70 - 3.65 (m, 2H), 2.53 - 2.48 (m, 2H), 2.12 - 2.19 (m, 2H), 2.07 - 2.00 (m, 2H), 1.45 (s, 6H); δ_C (101 MHz, $CDCl_3$) 156.0, 136.5, 128.6, 128.5, 128.2, 128.1, 128.0, 111.8, 89.9, 72.5, 68.0, 42.5, 23.5, 23.3, 22.3, 21.5; *m/z* (ESI) 292 (100%, $[M]^+$); HRMS, found 292.1543 ($[C_{16}H_{21}NO_4]$ requires 292.1543).

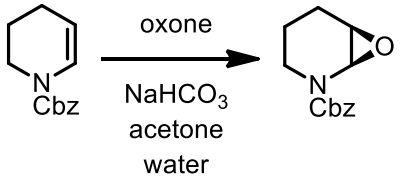
Synthesis of 1-((benzyloxy)carbonyl) piperidine-2,3-diacetate (137). [38]



To a solution of benzyl 2,3-dihydroxypiperidine-1-carboxyalte (400 mg, 1.5 mmol) in CH_2Cl_2 (10 mL), acetic anhydride (325 mg, 3.2 mmol), triethylamine (321 mg, 3.2 mmol) and DMAP (18 mg, 0.1 mmol) were added. The mixture was left to stir for 1 h then diluted with water (10 mL). The product was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The crude residue was purified via flash column chromatography eluting with petroleum ether : EtOAc (6 : 4) to give the title product (432 mg, 86%); δ_H (400 MHz, $CDCl_3$) 7.40 - 7.28 (m, 5H), 7.00 (d, 1H, *J* = 4.0 Hz), 5.21 (d, 1H, *J* = 15.0 Hz), 5.12 (d, 1H, *J* = 15.0 Hz), 4.92 - 4.85 (m, 1H), 4.00 - 3.95 (m, 1H), 3.01 (t, 1H, *J* = 14.0 Hz), 2.08 (s, 3H), 2.00

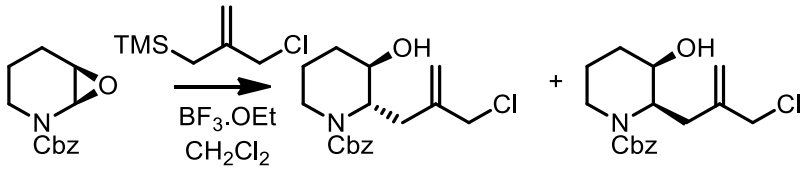
(s, 3H), 1.88 - 1.64 (m, 4H); δ_C (101 MHz, $CDCl_3$) 170.0, 169.2, 154.7, 136.0, 128.5, 128.1, 127.9, 75.3, 69.5, 67.7, 39.2, 23.8, 23.0, 20.8, 20.8.

Synthesis of benzyl 7-oxa-2-azabicyclo[4.1.0] heptane-2-carboxylate (132).



Oxone monopersulfate (45.0 g, 147.0 mmol) was added portion wise to a solution of sodium bicarbonate (60.0 g, 720.0 mmol) in water (300 mL), and the mixture was allowed to stir for 10 mins. To this solution was added acetone (240 mL) and benzyl 3,4-dihydropyridine-1(2*H*)-carboxylate (4.0 g, 18.0 mmol). The mixture was allowed to stir for 16 h at room temperature. After completion, water (100 mL) was added and the organic layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product, which was purified by flash column chromatography eluting with cyclohexane : EtOAc (2 : 8) to afford the title product as a clear oil (3.5 g, 60%) and as a 1 : 1 mixture of rotamers. ν_{max} (solid /cm^{-1}) 3375, 2947, 1673, 1255, 987; δ_H (400 MHz, $CDCl_3$) 7.37 - 7.20 (s, 5H), 5.75 (s, 0.5H), 5.60 (s, 0.5H), 5.15 (s, 2H), 4.17 - 4.11 (m, 0.5H), 3.95 - 3.85 (m, 2H), 3.65 - 3.55 (m, 0.5H), 3.24 - 3.16 (m, 1H), 3.12 - 3.04 (m, 1H), 1.57 - 1.40 (m, 2H); δ_C (101 MHz, $CDCl_3$) 157.0, 136.2, 128.5, 128.2, 128.1, 127.9, 127.8, 67.5, 67.0, 45.7, 44.7, 22.5, 22.4; *m/z* (ESI) 234 (100%, $[M]^+$); HRMS, found 234.2614 ($[C_{13}H_{15}NO_3]$ requires 234.2613).

Benzyl 2-(2-(chloromethyl) allyl)-3-hydroxypiperidine-1-carboxylate (133).



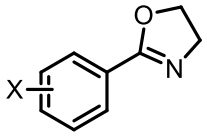
133 **134**

To a solution of benzyl 7-oxa-2-azabicyclo[4.1.0]heptane-2-carboxylate (3.5 g, 149.0 mmol) and chlorotrimethylsilane (2.9 g, 179.0 mmol) in dichloromethane (40 mL) at -78 °C, $BF_3.OEt_2$ (2.1 g, 149.0 mmol) was added. The reaction was allowed to stir overnight. $NaHCO_3$ (aq) (20 mL) was added and the reaction mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude oil which was purified by chromatography eluting with petroleum ether : EtOAc (4 : 6) to afford title product **133** as a clear oil (1.5 g, 31%) as a 1 : 1 mixture of rotamers. ν_{max} (solid /cm^{-1}) 3444, 2938, 2516, 2159, 2028, 1670, 1424 ; δ_H (400 MHz, DMSO-d^6) 7.42 - 7.30 (m, 5H), 5.16 - 5.14 (m, 1H), 5.08 - 4.98 (m, 2H), 4.80 - 4.78 (m, 1H), 4.35 - 3.95 (m, 3H), 3.90 - 3.85 (m, 1H), 3.65 - 3.55 (m, 1H), 2.97 - 2.82 (m, 1H), 2.35 - 2.25 (m, 2H), 1.80 - 1.70 (m, 2H), 1.60 - 1.55 (m, 2H), 1.35 - 1.25 (m, 1H); δ_C (101 MHz, DMSO-d^6) 155.9, 155.8, 142.4, 142.2, 137.7, 137.4, 128.8, 128.2, 128.0, 127.6, 117.6, 117.3, 66.6, 66.3, 65.9, 65.4, 55.7, 55.4, 53.2, 48.2, 47.9, 38.9, 38.6, 32.5, 26.0, 24.4, 24.1; *m/z* (ESI) 324 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 324.1374 ($[C_{17}H_{23}NO_3{}^{35}Cl_2]$ requires 324.1366).

134 clear oil (1.7 g, 35%) as a 1 : 1 mixture of rotamers. ν_{max} (solid /cm^{-1}) 3444, 2938, 2516, 2159, 2028, 1670, 1424; δ_H (400 MHz, DMSO-d^6) 7.40 - 7.29 (m, 5H), 5.12 - 4.99 (m, 4H), 4.45 - 4.40 (m, 2H), 4.30 - 4.25 (m, 1H), 4.20 - 4.15 (m, 2H), 4.05 - 3.95 (m, 1H), 3.85 - 3.75 (m, 1H), 3.65 - 3.55 (m, 1H), 2.86 - 2.74 (m, 2H), 1.66 - 1.62 (m, 2H), 1.42 - 1.30 (m, 1H); δ_C (101 MHz, DMSO-d^6) 155.2, 155.1, 142.9, 142.8, 137.6, 137.1, 128.9, 128.5, 128.1, 127.7, 117.5, 117.1,

68.2, 67.8, 66.8, 66.4, 55.4, 54.4, 53.6, 48.2, 48.0, 37.8, 37.4, 27.7, 26.8, 24.6, 24.2; *m/z* (ESI) 324 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 324.1367 ($[C_{17}H_{23}NO_3{}^{35}Cl_2]$ requires 324.1366).

General Procedure for the Synthesis of Oxazolines.

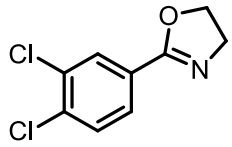


To the benzoic acid (1.0 equiv) in a round bottomed flask was added dichloromethane (0.2 M) and the mixture cooled to 0 °C using an ice/H_2O bath. Oxalyl chloride was then added (3.0 equiv), followed by a few drops of DMF. The reaction mixture was warmed to room temperature and stirred for a period of 3 h. The reaction mixture was concentrated, re-dissolved in dichloromethane (0.2 M) and cooled to 0 °C using an ice/H_2O bath. Triethylamine (3.0 equiv) was added via syringe, followed by ethanolamine (3.0 equiv), and the reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was then concentrated and the residue was purified by trituration with ethyl acetate or flash column chromatography on silica gel with petroleum ether (40/60)/ethyl acetate to afford the amide product which was used subsequently in oxazoline formation.

To the amide substrate (1.0 equiv) in a round bottomed flask was added dichloromethane (0.6 M), trimethylamine (1.9 equiv), DMAP (0.2 equiv) and *p*-toluenesulfonyl chloride (1.7 equiv). The reaction mixture was stirred for 16 h, quenched with water and the product extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was treated with methanol (0.5 M) and sodium hydroxide pellets (3.0 equiv) for a period of 2 - 3 hours. The reaction mixture was then concentrated. The residue was dissolved in dichloromethane and water and the product extracted with dichloromethane. The combined organic layers were dried over

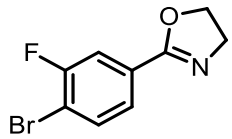
$MgSO_4$, filtered and the solvent was removed in *vacuo*. Purification by flash column chromatography on silica gel afforded the desired oxazoline substrates.

2-(3,4-Dichlorophenyl)-4,5-dihydrooxazole.



3,4-Dichlorobenzoic acid (2.0 g, 10.5 mmol) was subjected to the general reaction conditions to afford the corresponding amide (1.0 g, 44%). The corresponding oxazoline was then afforded as a colourless solid (623 mg, 63%) Mp 95 - 96 °C. ν_{max} (solid /cm^{-1}) 3082, 2983, 1647, 1241, 1071, 714; δ_H (400 MHz, $CDCl_3$) 7.99 (d, 1H, *J* = 2.0 Hz), 7.73 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.44 (d, 1H, *J* = 8.5 Hz), 4.41 (t, 2H, *J* = 9.5 Hz), 4.03 (t, 2H, *J* = 9.5 Hz); δ_C (101 MHz, $CDCl_3$) 162.8, 135.6, 132.8, 130.5, 130.1, 127.8, 127.3, 68.0, 55.1; *m/z* (ESI) 215 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 215.9977 ($[C_9H_8NO^{35}Cl_2]$ requires 215.9983).

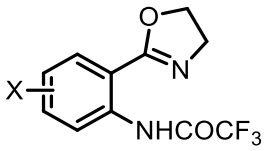
2-(4-Bromo-3-fluorophenyl)-4,5-dihydrooxazole.



4-Bromo-3-fluorobenzoic acid (2.0 g, 9.1 mmol) was subjected to the general reaction conditions to afford the corresponding amide (1.6 g, 70%). The corresponding oxazoline was then afforded as a colourless solid (1.5 g, 77%) Mp 95 - 96 °C. ν_{max} (solid /cm^{-1}) 3078, 2938, 1644, 1422, 951, 712; δ_H (400 MHz, MeOD-d^4) 7.75 (m, 2H), 7.60 (dd, 1H, *J* = 6.0 Hz, 2.0 Hz), 4.67 (t, 2H, *J* = 6.0 Hz), 4.10 (t, 2H, *J* = 6.0 Hz); δ_C (101 MHz, MeOD-d^4) 163.5, 160.0 (d, *J* = 250.0 Hz), 133.7, 129.4, 124.8, 115.0 (d, *J* = 28.0 Hz), 110.3 (d, *J* = 27.5 Hz), 68.8, 54.0; δ_F (376

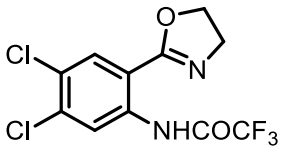
MHz, MeOD-d^4) - 108.2; *m/z* (ESI) 243 (100%, $[M(^{79}Br)]^+$); HRMS, found 243.9768 ($[C_9H_7{}^{79}BrFNO]$ requires 243.9768).

General Procedure for the C-H Amidation of Oxazoline Substrates.



Oxazoline substrate (1.2 equiv) was placed in a round bottomed flask equipped with a reflux condenser. Trifluoroacetamide (1.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %) and $PhI(OAc)_2$ (1.5 equiv) were all added sequentially and the resulting mixture dissolved in dichloromethane (0.1 M). The reaction was then heated at reflux for a period of 24 hours. After cooling to room temperature the solvent was removed in vacuo. The resulting residue was purified by flash column chromatography on silica gel eluting with dichloromethane or petroleum ether (40/60)/ethyl acetate (0 to 100% ethyl acetate) to afford to the aminated products.

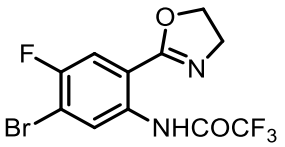
***N*-(4,5-Dichloro-2-(4,5-dihydrooxazol-2-yl)phenyl)-2,2,2-trifluoroacetamide.**



2-(3,4-Dichlorophenyl)-4,5-dihydrooxazole (617 mg, 2.8 mmol) and trifluoroacetamide (260 mg, 2.3 mmol) were subjected to the general conditions affording a colourless solid (495 mg, 64%) Mp 135 - 136 °C. ν_{max} (solid /cm^{-1}) 3117, 2887, 1711, 1145; δ_H (400 MHz, $CDCl_3$) 13.64 (s, 1H), 8.85 (s, 1H), 7.94 (s, 1H), 4.46 (t, 2H, *J* = 9.5 Hz), 4.18 (t, 2H, *J* = 9.5 Hz); δ_C (101 MHz, $CDCl_3$) 163.3, 155.8 (q, *J* = 38.5 Hz), 137.0, 136.6, 130.6, 128.2, 122.0, 115.8 (q, *J* = 288.5 Hz),

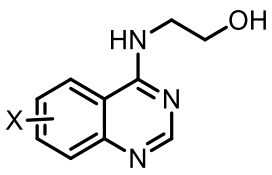
114.2, 67.1, 54.6; δ_F (376 MHz, $CDCl_3$) - 76.0; *m/z* (ESI) 326 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 326.9931 ($[C_{11}H_8N_2O_2F_3{}^{35}Cl_2]$ requires 326.9915).

N-(5-Bromo-2-(4, 5-dihydrooxazol-2-yl)-4-fluorophenyl)-2, 2, 2-trifluoroacetamide.



2-(4-Bromo-3-fluorophenyl)-4,5-dihydrooxazole (1.1 g, 4.6 mmol) and trifluoroacetamide (430 mg, 3.8 mmol) were subjected to the general conditions affording a colourless solid (690 mg, 42%) Mp 115 - 116 °C. ν_{max} (solid /cm^{-1}) 2889, 1750, 1639, 1577, 1524, 1449, 1122, 1138; δ_H (400 MHz, $CDCl_3$) 11.92 (s, 1H), 7.60 - 7.52 (m, 2H), 4.48 (t, 2H, *J* = 10.0 Hz), 4.16 (t, 2H, *J* = 10.0 Hz); δ_C (101 MHz, $CDCl_3$) 163.0, 158.1 (d, *J* = 250.0 Hz), 156.2 (q, *J* = 25.0 Hz), 139.0, 125.7, 120.9, 115.5 (d, *J* = 27.0 Hz), 114.3 (d, *J* = 26.5 Hz), 113.9 (q, *J* = 260.0 Hz), 68.8, 55.0 ; δ_F (376 MHz, $CDCl_3$) - 75.4, -108.5; *m/z* (ESI) 355 (100%, $[M(^{79}Br)]^+$); HRMS, found 355.9733 ($[C_{11}H_7N_2O_2F_4{}^{79}Br]$ requires 355.9711).

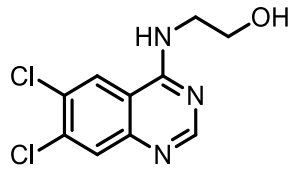
General Procedure for the Cyclization to the Quinazoline Heterocycle.



Trifluoroacetamide substrate (1.0 equiv) was dissolved in ethanol (0.1 M), NaOH pellets (20 equiv) were added and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by TLC analysis until complete conversion of the starting material was observed (typically 5 - 6 h); upon completion the solvent was removed in *vacuo*. The residue was dissolved in water and ethyl acetate, and transferred to a separating funnel. The layers

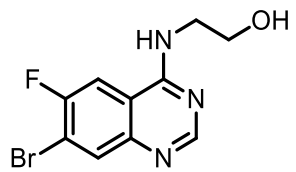
were partitioned, followed by further extraction of the aqueous layer with ethyl acetate. The combined organics were then washed with brine, followed by drying over $MgSO_4$, filtered and the solvent removed in *vacuo*. The residue was then dissolved in ethanol (0.1 M) and formamidine acetate (3.0 equiv) was added, and the mixture heated at reflux for 1 hour. After cooling to room temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography eluting with dichloromethane and methanol to afford the quinazolinone products.

2-((6, 7-Dichloroquinazolin-4-yl) amino) ethanol.



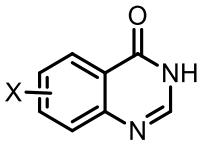
N-(4,5-Dichloro-2-(4,5-dihydrooxazol-2-yl)phenyl)-2,2,2-trifluoroacetamide (490 mg, 1.5 mmol), sodium hydroxide (1.2 g, 30.3 mmol) and formamidine acetate (470 mg, 4.5 mmol) were subjected to the general reaction conditions to afford the product as a colourless solid (283 mg, 73%) Mp 204 - 205 °C. ν_{max} (solid /cm^{-1}) 3315, 3006, 2981, 1580, 1362, 1059, 913, 873; δ_H (400 MHz, DMSO-d^6) 8.66 (s, 1H), 8.52 (br, 1H), 8.48 (s, 1H), 7.93 (s, 1H), 4.82 (br, 1H), 3.66 - 3.55 (m, 4H); δ_C (101 MHz, DMSO-d^6) 158.6, 156.5, 148.6, 135.3, 128.7, 127.7, 124.9, 114.6, 58.9, 43.3; *m/z* (ESI) 258 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 258.0198 ($[C_{10}H_9{}^{35}Cl_2N_3O]$ requires 258.0195).

2-((7-Bromo-6-fluoroquinazolin-4-yl)amino)ethanol.



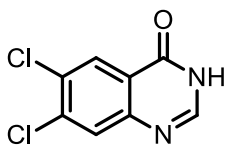
N-(5-Bromo-2-(4,5-dihydrooxazol-2-yl)-4-fluorophenyl)-2,2,2-trifluoroacetamide (670 mg, 1.9 mmol), sodium hydroxide (1.5 g, 3.8 mmol) and formamidine acetate (590 mg, 5.7 mmol) were subjected to the general reaction conditions to afford the product as a colourless solid (0.15 mg, 55%) Mp 210 - 211 °C. ν_{max} (solid /cm^{-1}) 3316, 3004, 2989, 1584, 1365, 1059, 914, 873; δ_H (400 MHz, MeOD-*d*^{4}) 8.50 (s, 1H), 7.88 (d, 1H, *J* = 7.0 Hz), 7.73 - 7.60 (m, 1H), 3.86 - 3.76 (m, 4H); δ_C (101 MHz, MeOD-*d*^{4}) 159.0, 153.5, 153.3 (d, *J* = 260. 0 Hz), 148.8, 130.1, 119.3 (d, *J* = 25.0 Hz), 112.6 (d, *J* = 25.0 Hz), 106.2, 57.9, 42.5; δ_F (376 MHz, MeOD-*d*^{4}) - 108.8; *m/z* (ESI) 285 (100%, [M(^{79}Br)]$^+$); HRMS, found 285.9983 ([$C_{10}H_9{}^{79}BrFN_3O$] requires 285.9986).

General Procedure for the Hydrolysis to the Quinazolinone Heterocycle.



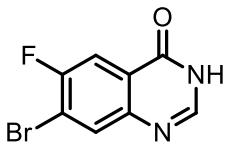
Quinazolinone substrate (1.0 equiv) was suspended in aqueous 6 M HCl in a round bottomed flask equipped with reflux condenser, and heated to 100 - 105 °C. The reaction was then allowed to cool to room temperature, then cooled to 0 °C with an ice/water bath. The reaction mixture was basified to pH 11 with 35% aqueous ammonia solution, and allowed to stir for 15 minutes. The resulting precipitate was filtered and washed with ice cold water to afford the quinazolinone products.

6,7-Dichloroquinazolin-4(3*H*)-one (156).



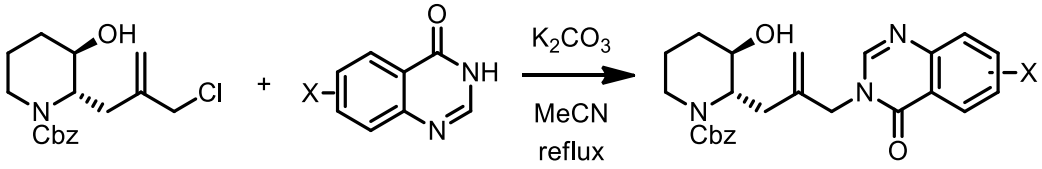
2-((6,7-Dichloroquinazolin-4-yl)amino)ethanol (181 mg, 0.7 mmol) was added to aqueous 6 M HCl (5 mL) according to the general conditions for 2 h to afford the product as a colourless solid (132 mg, 88%) Mp > 250 °C. ν_{max} (solid /cm^{-1}) 3047, 3012, 1665, 1611, 1444, 1254, 1122, 910, 866; δ_H (400 MHz, DMSO-*d*^{6}) 12.18 (s, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 7.95 (s, 1H); δ_C (101 MHz, DMSO-*d*^{6}) 159.3, 148.3, 147.3, 137.1, 129.3, 128.9, 127.2, 122.7; *m/z* (ESI) 214 (100%, [M($^{35}Cl_2$)]$^+$); HRMS, found 214.9772 ([$C_8H_4{}^{35}Cl_2N_2O$] requires 214.9773).

7-Bromo-6-fluoroquinazolin-4(3*H*)-one (157).



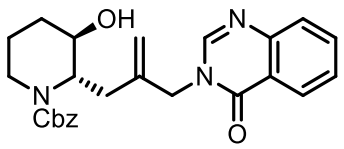
2-((7-Bromo-6-fluoroquinazolin-4-yl)amino)ethanol (100 mg, 3.6 mmol) was added to aqueous 6 M HCl (2.5 mL) according to the general conditions for 2 h to afford the product as a colourless solid (50 mg, 50%) Mp > 250 °C. ν_{max} (solid /cm^{-1}) 3316, 3004, 2989, 1584, 1365, 1059, 914, 873; δ_H (400 MHz, DMSO-*d*^{6}) 12.40 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J* = 3.0 Hz), 7.93 (d, 1H, *J* = 5.0 Hz); δ_C (101 MHz, DMSO-*d*^{6}) 160.2, 157.8 (d, *J* = 260.0 Hz), 146.7, 146.6, 132.8, 123.8, 116.5 (d, *J* = 24.0 Hz), 112.3 (d, *J* = 24.0 Hz); δ_F (376 MHz, DMSO-*d*^{6}) - 109.2; *m/z* (ESI) 285 (100%, [M(^{79}Br)]$^+$); HRMS, found 285.9983 ([$C_{10}H_9{}^{79}BrFN_3O$] requires 285.9986).

General Procedure for the Synthesis of substrates 140, 141, 153 and 160 - 163.



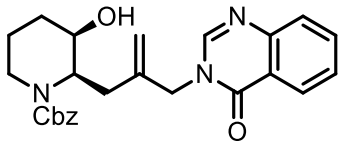
Potassium carbonate (1.5 equiv) was added to a suspension of quinazolinone (1.0 equiv) in MeCN (0.1 M) and the mixture was heated at reflux. A solution of benzyl 2-(2-(chloromethyl) allyl)-3-hydroxypyrrolidine-1-carboxylate (1.0 equiv) in MeCN (0.3 M) was added dropwise to the reaction mixture and the reaction was left to stir for 16 h. After completion, aq. NH_4Cl was added and the product extracted with ethyl acetate. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flush column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding products.

Benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (140).[11]



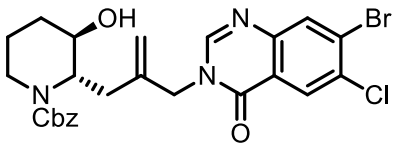
Quinazolin-4(3*H*)-one (50 mg, 0.03 mmol), K_2CO_3 (70 mg, 0.05 mmol) and **133** (110 mg, 0.03 mmol) were subjected to the general conditions for 16 h to afford the product as a yellow oil (113 mg, 77%). δ_H (400 MHz, $CDCl_3$) 8.30 - 8.26 (m, 1H), 8.10 (s, 1H), 7.80 - 7.70 (m, 2H), 7.55 - 7.45 (m, 1H), 7.40 - 7.25 (m, 5H), 5.20 - 5.05 (m, 2H), 5.00 - 4.90 (m, 1H), 4.70 - 4.60 (m, 1H), 4.50 - 4.45 (m, 1H), 4.10 - 4.05 (m, 2H), 3.95 - 3.85 (m, 1H), 2.96 - 2.85 (m, 2H), 2.60 - 2.40 (m, 2H), 2.00 - 1.90 (m, 2H), 1.85 - 1.65 (m, 1H), 1.50 - 1.35 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.3, 158.4, 148.0, 147.2, 144.1, 136.6, 134.6, 128.4, 127.9, 127.6, 127.2, 126.8, 126.4, 121.9, 114.1, 67.2, 60.4, 55.4, 49.2, 42.2, 38.8, 34.1, 21.0.

Benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (141).



Quinazolin-4(3*H*)-one (50 mg, 0.03 mmol), K_2CO_3 (70 mg, 0.05 mmol) and **134** (110 mg, 0.03 mmol) were subjected to the general conditions for 16 h to afford the product as a yellow oil (118 mg, 80%). V_{max} (solid /cm^{-1}) 3389, 2920, 1736, 1666, 1476, 1071; δ_H (400 MHz, $CDCl_3$) 8.35 - 8.25 (m, 1H), 8.10 (s, 1H), 7.80 - 7.70 (m, 2H), 7.55 - 7.45 (m, 1H), 7.40 - 7.30 (m, 5H), 5.20 - 5.05 (m, 2H), 4.95 - 4.90 (m, 1H), 4.85 - 4.70 (m, 1H), 4.45 - 4.30 (m, 1H), 4.10 - 3.90 (m, 2H), 2.90 - 2.75 (m, 1H), 2.50 - 2.38 (m, 2H), 2.34 - 2.15 (m, 2H), 1.84 - 1.78 (m, 2H), 1.76 - 1.68 (m, 1H), 1.58 - 1.44 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.3, 158.4, 148.0, 147.2, 143.8, 136.4, 134.7, 128.4, 127.7, 127.6, 127.2, 126.8, 126.4, 121.9, 114.1, 67.2, 60.4, 53.6, 49.3, 42.2, 37.7, 34.0, 21.0; *m/z* (ESI) 434 (100%, $[M]^+$); HRMS, found 434.2075 ($[C_{25}H_{27}N_3O_4]$ requires 434.2074).

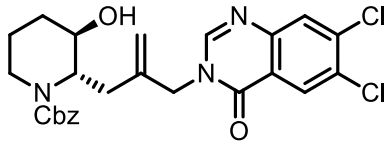
Benzyl 2-(2-((7-bromo-6-chloro-4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (153).



7-Bromo-6-chloroquinazolin-4(3*H*)-one (**83**) (50 mg, 0.2 mmol), K_2CO_3 (40 mg, 0.3 mmol) and **133** (62 mg, 0.9 mmol) were subjected to the general conditions for 16 h to afford the product as a yellow oil (98 mg, 91%). ν_{max} (solid /cm^{-1}) 3454, 2917, 1738, 1659, 1609, 1465, 1419,1231, 922; δ_H (400 MHz, $CDCl_3$) 8.30 (s, 1H), 8.10 (s, 1H), 8.00 (s, 1H), 7.36 - 7.27 (m, 5H), 5.15 - 5.05 (m, 2H), 4.90 - 4.85 (m, 2H), 4.60 - 4.55 (m, 1H), 3.90 - 3.88 (m, 2H), 3.18 - 3.08 (m, 1H), 2.98 - 2.88 (m, 2H), 2.56 - 2.48 (m, 1H), 2.32 - 2.28 (m, 2H), 2.00 - 1.90 (m, 2H), 1.85 - 1.70 (m, 2H);

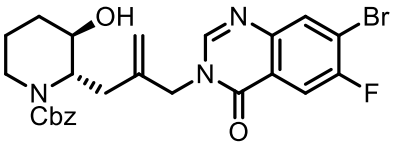
δ_C (101 MHz, $CDCl_3$) 162.5, 158.4, 155.1, 152.6, 146.7, 136.9, 129.7, 128.7, 128.3, 128.2, 128.1, 127.5, 126.0, 124.9, 111.2, 70.3, 67.4, 56.5, 49.4, 42.2, 35.4, 31.2, 23.2; *m/z* (ESI) 548 (100%, $[M(^{35}Cl^{79}Br)]^+$); HRMS, found 548.0766 ($[C_{25}H_{25}{}^{79}Br^{35}ClN_3O_4]$ requires 548.0770).

Benzyl 2-(2-((6,7-dichloro-4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (160).



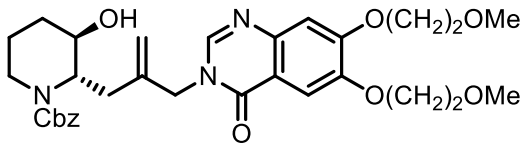
6, 7-Dichloroquinazolin-4(3*H*)-one (**156**) (20 mg, 0.1 mmol), K_2CO_3 (19 mg, 0.2 mmol) and **133** (30 mg, 0.1 mmol) were subjected to the general conditions for 16 h to afford the product as a yellow oil (30 mg, 80%). ν_{max} (solid /cm^{-1}) 3440, 2918, 2849, 1738, 1667, 1601, 1076, 695; δ_H (400 MHz, $CDCl_3$) 8.35 (s, 1H), 8.10 (s, 1H), 7.85 (s, 1H), 7.40 - 7.28 (m, 5H), 5.20 - 5.10 (m, 2H), 4.95 - 4.90 (m, 2H), 4.60 - 4.50 (m, 1H), 4.10 - 4.08 (m, 2H), 3.90 - 3.84 (m, 1H), 3.00 - 2.85 (m, 2H), 2.50 - 2.40 (m, 1H), 2.20 - 2.15 (m, 2H), 1.80 - 1.70 (m, 2H), 1.50 - 1.45 (m, 2H); δ_C (101 MHz, $CDCl_3$) 162.0, 159.4, 155.6, 152.2, 148.3, 136.5, 129.7, 129.1, 128.5, 128.1, 127.6, 127.3, 126.0, 121.4, 114.3, 70.3, 67.3, 55.4, 49.5, 38.8, 34.2, 31.9, 22.7; *m/z* (ESI) 502 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 502.1299 ($[C_{25}H_{25}{}^{35}Cl_2N_3O_4]$ requires 502.1295).

Benzyl 2-(2-((7-bromo-6-fluoro-4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (161).



7-Bromo-6-fluoroquinazolin-4(3*H*)-one (**157**) (100 mg, 0.4 mmol), K_2CO_3 (85 mg, 0.6 mmol) and **133** (132 mg, 0.4 mmol) were subjected to the general conditions for 16 h to afford the product as a yellow oil (186 mg, 85%). ν_{max} (solid /cm^{-1}) 3454, 2917, 1738, 1659, 1465, 1234, 696; δ_H (400 MHz, $CDCl_3$) 8.10 - 7.99 (m, 3H), 7.35 - 7.27 (m, 5H), 5.20 - 5.15 (m, 2H), 4.99 - 4.93 (m, 2H), 4.70 - 4.50 (m, 1H), 4.20 - 4.00 (m, 2H), 3.90 - 3.80 (m, 1H), 3.02 - 2.80 (m, 2H), 2.56 - 2.40 (m, 1H), 2.23 - 2.13 (m, 2H), 2.00 - 1.90 (m, 2H), 1.85 - 1.70 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.0, 158.7 (d, *J* = 250.0 Hz), 147.5, 145.1, 139.8, 136.5, 128.9, 128.5, 128.3 128.0, 127.6, 122.3, 117.3, 114.3 (d, *J* = 27.0 Hz), 112.7 (d, *J* = 25.0 Hz), 70.3, 67.3, 55.4, 49.5, 40.1, 38.8, 34.1, 22.7; δ_F (376 MHz, $CDCl_3$) - 106.7; *m/z* (ESI) 532 (100%, $[M(^{79}Br)]^+$); HRMS, found 532.1074 ($[C_{25}H_{25}{}^{79}BrFN_3O_4]$ requires 532.1068).

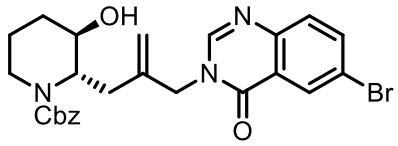
Benzyl 2-(2-((6, 7-bis(2-methyoxyethoxy)-4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (162).



6, 7-Bis(2-methoxyethoxy) quinazolin-4(3*H*)-one (**158**) (20 mg, 0.06 mmol), K_2CO_3 (14 mg, 0.10 mmol) **133** (22 mg, 0.06 mmol) were subjected to the general conditions for 16 h to afford the product as a clear oil (28 mg, 69%). ν_{max} (solid /cm^{-1}) 3386, 2928, 1666, 1607, 1496, 1271, 727; δ_H (400 MHz, $CDCl_3$) 8.05 (s, 1H), 7.65 (s, 1H), 7.40 - 7.30 (m, 5H), 7.15 (s, 1H), 5.18 - 5.12 (m, 2H), 4.97 - 4.91 (m, 1H), 4.66 - 4.63 (m, 1H), 4.30 - 4.25 (m, 4H), 3.90 - 3.80 (m, 4H), 3.48 (s, 6H), 2.98 - 2.81 (m, 2H), 2.55 - 2.45 (m, 1H), 2.42 - 2.30 (m, 2H), 2.25 - 2.15 (m, 2H), 2.00 - 1.90 (m, 2H), 1.85 - 1.70 (m, 2H), 1.50 - 1.40 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.3, 158.5, 154.8, 152.6, 148.8, 145.8, 142.3, 136.6, 128.4, 128.0, 127.7, 116.0, 109.2, 107.3, 106.9, 70.6, 70.5,

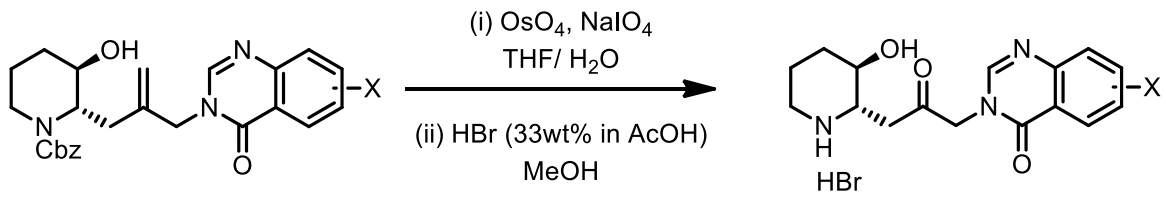
68.6, 68.5, 67.2, 59.4, 59.3, 55.5, 49.4, 49.2, 38.8, 34.1, 29.7, 22.6; *m/z* (ESI) 582 (100%, $[M]^+$); HRMS, found 582.2823 ($[C_{31}H_{39}N_3O_8]$ requires 582.2810).

Benzyl 2-(2-((6-bromo-4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (163).



6-Bromoquinazolin-4(3*H*)-one (**159**) (139 mg, 0.4 mmol), K_2CO_3 (128 mg, 0.9 mmol) and **133** (200 mg, 0.4 mmol) were subjected to the general conditions for 16 h to afford the product as a yellow oil (316 mg, 72%). ν_{max} (solid /cm^{-1}) 3434, 2934, 2860, 1669, 1608, 1256, 729; δ_H (400 MHz, $CDCl_3$) 8.40 (s, 1H), 8.10 (s, 1H), 7.80 (d, 1H, *J* = 9.0 Hz), 7.55 (d, 1H, *J* = 9.0 Hz), 7.40 - 7.20 (m, 5H), 5.20 - 5.15 (m, 2H), 4.99 - 4.93 (m, 2H), 4.70 - 4.50 (m, 1H), 4.20 - 4.00 (m, 2H), 3.90 - 3.80 (m, 1H), 3.02 - 2.80 (m, 2H), 2.56 - 2.40 (m, 1H), 2.23 - 2.13 (m, 2H), 2.00 - 1.90 (m, 2H), 1.85 - 1.70 (m, 2H); δ_C (101 MHz, $CDCl_3$) 161.1, 159.7, 147.5, 146.9, 145.6, 140.0, 137.4, 129.3, 129.2, 128.4, 127.9, 127.5, 123.3, 120.8, 114.1, 67.2, 67.0, 55.4, 49.2, 38.8, 34.1, 29.6, 21.0; *m/z* (ESI) 513 (100%, $[M(^{79}Br)]^+$); HRMS, found 513.1215 ($[C_{25}H_{26}{}^{79}BrN_3O_4]$ requires 513.1211).

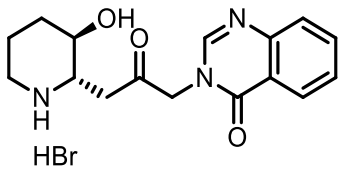
General Procedure for the Synthesis of Febrifugine Analogs 146, 155 and 164 - 167.



OsO_4 (a few crystals) was added to a suspension of benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (1.0 equiv) and $NaIO_4$ (2.0 equiv) in THF (0.1 M) and water (0.2 M), and the solution was left to stir for 16 h. After completion, a saturated solution of $Na_2S_2O_5$ was added and the organic layers were extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flash column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding ketone.

To the ketone substrate (1.0 equiv) in a round bottom flask was added methanol (0.2 M) and HBr (33 wt% in AcOH) (100.0 equiv) at 0 °C. The mixture was stirred for 30 mins and after completion the solvent was removed *in vacuo*, purification by recrystallization from ethanol afford the corresponding products.

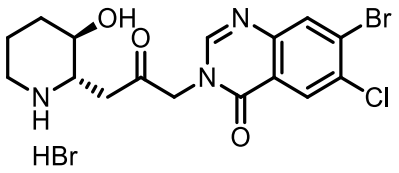
3-Hydroxypiperidin-2-yl-2-oxopropyl quinazolin-4(3*H*)-one hydrobromide (146).



140 (113 mg, 0.2 mmol) was subjected to the general conditions to afford the title product as a colourless solid (88 mg, 89%) Mp > 250 °C. ν_{max} (solid /cm^{-1}) 3329, 2924, 1704, 1660, 1507, 1028 ; δ_H (400 MHz, MeOD-d^4) 8.90 (s, 1H), 8.40 - 8.30 (m, 1H), 8.10 - 7.95 (m, 1H), 7.85 - 7.70 (m, 2H), 5.30 (d, 1H, *J* = 17.5 Hz), 5.22 (d, 1H, *J* = 17.5 Hz), 3.75 - 3.65 (m, 1H), 3.55 - 3.50 (m, 2H), 3.45 (d, 1H, *J* = 4.5 Hz), 3.05 (dd, 1H, *J* = 15.0, 4.0 Hz), 3.01 (dd, 1H, *J* = 15.0, 4.0 Hz), 2.16 - 2.04 (m, 2H), 1.88 - 1.76 (m, 1H), 1.68 - 1.60 (m, 1H); δ_C (101 MHz, MeOD-d^4) 201.1, 158.0,

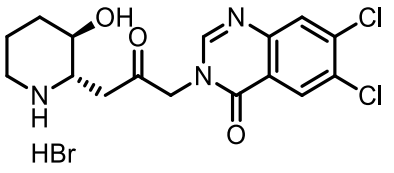
151.0, 147.4, 138.4, 136.8, 129.5, 127.5, 120.7, 66.9, 56.6, 55.2, 43.5, 39.0, 30.1, 19.9; *m/z* (ESI) 302 (100%, $[M]^+$); HRMS, found 302.3403 ($[C_{16}H_{19}N_3O_3]$ requires 302.3404).

7-Bromo-6-chloro-3-(3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4(3*H*)-one hydrobromide (155).



153 (88 mg, 0.2 mmol) was subjected to the general conditions to afford the title product as a colorless solid (55 mg, 70%) Mp > 250 °C. ν_{max} (solid /cm^{-1}) 3290, 2943, 1705, 1677, 1598, 1080; δ_H (400 MHz, MeOD-*d*^{4}) 8.32 (s, 1H), 8.22 (s, 1H), 8.12 (s, 1H), 5.11 (d, 1H, *J* = 17.5 Hz), 5.02 (d, 1H, *J* = 17.5 Hz), 3.70 - 3.60 (m, 1H), 3.55 - 3.45 (m, 2H), 3.40 (d, 1H, *J* = 5.0 Hz), 3.05 (dd, 1H, *J* = 15.0, 4.0 Hz), 3.00 (dd, 1H, *J* = 15.0, 4.0 Hz), 2.15 - 2.00 (m, 2H), 1.85 - 1.75 (m, 1H), 1.65 - 1.55 (m, 1H); δ_C (101 MHz, MeOD-*d*^{4}) 201.4, 158.0, 151.0, 147.5, 138.4, 136.8, 129.5, 127.5, 120.7, 66.8, 56.8, 54.4, 43.6, 38.4, 30.0, 20.0; *m/z* (ESI) 416 (100%, $[M(^{35}Cl^{79}Br)]^+$); HRMS, found 416.0193 ($[C_{16}H_{17}{}^{79}Br^{35}ClN_3O_3]$ requires 416.0193).

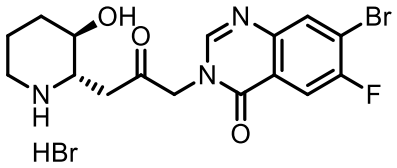
6,7-Dichloro-3-(3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4(3*H*)-one hydrobromide (165).



160 (30 mg, 0.05 mmol) was subjected to the general conditions to afford the title product as a colourless solid (24 mg, 94%) Mp > 250 °C. ν_{max} (solid /cm^{-1}) 3332, 2925, 1705, 1658, 1508 ,

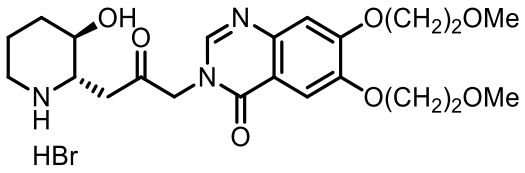
1031; δ_H (400 MHz, MeOD-*d*^{4}) 8.34 (s, 1H), 8.22 (s, 1H), 7.94 (s, 1H), 5.11 (d, 1H, *J* = 18.0 Hz), 5.02 (d, 1H, *J* = 18.0 Hz), 3.70 - 3.60 (m, 1H), 3.52 - 3.45 (m, 2H), 3.41 (d, 1H, *J* = 5.0 Hz), 3.08 (dd, 1H, *J* = 15.0, 4.0 Hz), 3.00 (dd, 1H, *J* = 15.0, 4.0 Hz), 2.15 - 2.00 (m, 2H), 1.85 - 1.75 (m, 1H), 1.67 - 1.57 (m, 1H); δ_C (101 MHz, MeOD-*d*^{4}) 201.1, 157.9, 151.0, 147.5, 138.4, 136.8, 129.5, 127.5, 120.7, 66.5, 56.7, 54.3, 43.5, 38.3, 29.9, 19.8; *m/z* (ESI) 308 (100%, $[M(^{35}Cl_2)]^+$); HRMS, found 308.2323 ($[C_{16}H_{17}{}^{35}Cl_2N_3O_3]$ requires 308.2310).

7-Bromo-6-fluoro-3-(3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4(3*H*)-one hydrobromide (166).



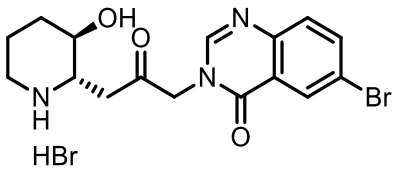
161 (69 mg, 0.1 mmol) was subjected to the general conditions to afford the title product as a grey solid (31 mg, 51%) Mp 246 - 247 °C. ν_{max} (solid /cm^{-1}) 3332, 2925, 1705, 1658, 1508, 1031; δ_H (400 MHz, DMSO-*d*^{6}) 8.25 (s, 1H), 8.19 (d, 1H, *J* = 10.0 Hz), 7.97 (d, 1H, *J* = 10.0 Hz), 5.13 (d, 1H, *J* = 18.0 Hz), 5.07 (d, 1H, *J* = 18.0 Hz), 3.55 - 3.45 (m, 1H), 3.25 - 3.20 (m, 2H), 3.15 (d, 1H, *J* = 5.0 Hz), 2.91 (dd, 1H, *J* = 15.5, 4.0 Hz), 2.87 (dd, 1H, *J* = 15.5, 4.0 Hz), 2.90 - 1.90 (m, 2H), 1.85 - 1.80 (m, 1H), 1.65 - 1.55 (m, 1H); δ_C (101 MHz, DMSO-*d*^{6}) 201.5, 159.5, 157.0 (d, *J* = 260.0 Hz), 149.2, 145.9, 133.0, 128.0, 117.0 (d, *J* = 24.0 Hz), 112.5 (d, *J* = 24.0 Hz), 67.5, 57.0, 55.0, 43.5, 43.3, 31.0, 20.5; δ_F (376 MHz, DMSO-*d*^{6}) - 108.9; *m/z* (ESI) 401 (100%, $[M(^{79}Br)]^+$); HRMS, found 401.0090 ($[C_{16}H_{17}{}^{79}BrFN_3O_3]$ requires 401.1010).

3-Hydroxypiperidin-2-yl-2-oxopropyl quinazolin-6,7-bis(2-methoxyethoxy)quinazolin-4(3*H*)-one hydrobromide (164).



162 (28 mg, 0.04 mmol) was subjected to the general conditions to afford the title product as a colourless solid (20 mg, 80%) Mp > 250 °C. ν_{max} (solid /cm^{-1}) 3346, 2926, 1659, 1604, 1382, 987; δ_H (400 MHz, MeOD-*d*^{4}) 9.20 (s, 1H), 7.70 (s, 1H), 7.27 (s, 1H), 5.33 (d, 1H, *J* = 18.0 Hz), 5.26 (d, 1H, *J* = 18.0 Hz), 4.40 - 4.30 (m, 4H), 3.90 - 3.80 (m, 4H), 3.70 - 3.60 (m, 1H), 3.52 - 3.45 (m, 2H), 3.43 (s, 6H), 3.41 (d, 1H, *J* = 5.0 Hz), 3.08 (dd, 1H, *J* = 15.0, 4.0 Hz), 3.00 (dd, 1H, *J* = 15.0, 4.0 Hz), 2.15 - 2.00 (m, 2H), 1.85 - 1.75 (m, 1H), 1.67 - 1.57 (m, 1H); δ_C (101 MHz, MeOD-*d*^{4}) 201.0, 157.5, 156.3, 150.6, 149.1, 134.9, 113.5, 107.5, 102.5, 70.5, 70.3, 69.5, 69.0, 67.0, 58.1, 58.0, 56.6, 55.2, 43.4, 39.0, 30.0, 20.0; *m/z* (ESI) 450 (100%, $[M]^+$); HRMS, found 450.2237 ($[C_{22}H_{31}N_3O_7]$ requires 450.2235).

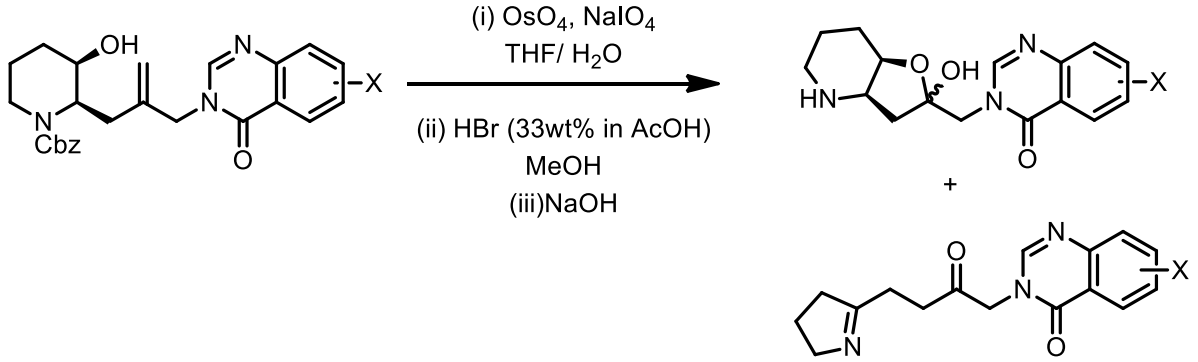
6-bromo-3-(3-(3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4(3*H*)-one hydrobromide (167).



163 (25 mg, 0.04 mmol) was subjected to the general conditions to afford the title product as a colourless solid (12 mg, 54%) Mp 221 - 222 °C. ν_{max} (solid /cm^{-1}) 3088, 2671, 1766, 1713, 1631, 784; δ_H (400 MHz, DMSO-*d*^{6}) 8.30 (s, 1H), 8.25 (s, 1H), 8.05 (d, 1H, *J* = 9.0 Hz), 7.70 (d, 1H, *J* = 9.0 Hz), 5.14 (d, 1H, *J* = 18.0 Hz), 5.08 (d, 1H, *J* = 18.0 Hz), 3.55 - 3.50 (m, 1H), 3.40 - 3.30 (m, 2H), 3.25 - 3.15 (m, 1H), 2.95 - 2.85 (m, 1H), 2.00 - 1.90 (m, 1H), 1.85 - 1.80 (m, 2H),

1.70 - 1.60 (m, 1H), 1.55 - 1.40 (m, 1H); δ_C (101 MHz, DMSO-d^6) 201.5, 159.3, 149.2, 147.4, 138.0, 130.2, 128.5, 123.3, 120.2, 67.2, 56.6, 54.8, 43.5, 43.4, 30.9, 20.6; *m/z* (ESI) 380 (100%, [M (^{79}Br)]$^+$); HRMS, found 380.0613 ([$C_{16}H_{18}{}^{79}BrN_3O_3$] requires 380.0604).

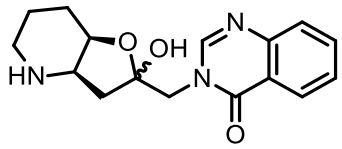
General Procedure for the Synthesis of Febrifugine Analogue 145.



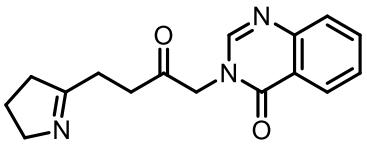
OsO_4 (a few crystals) was added to a suspension of benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate (1.0 equiv) and $NaIO_4$ (2.0 equiv) in THF (0.1 M) and water (0.2 M), and the solution was left to stir for 16 h. After completion, a saturated solution of $Na_2S_2O_5$ was added and the organic layers were extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flush column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding ketone.

To the ketone substrate (1.0 equiv) in a round bottom flask was added dichloromethane (0.2 M) and HBr (33 wt% in AcOH) (100.0 equiv) at 0 °C. The mixture was stirred for 30 mins and after completion, aq. NaOH was added and the organic layer extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product, which was purified by flash column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding products.

Hydroxyoctahydrofuro [3,2-*b*] pyridine-2-yl methyl quinazolin-4(3*H*)-one (145).[11]



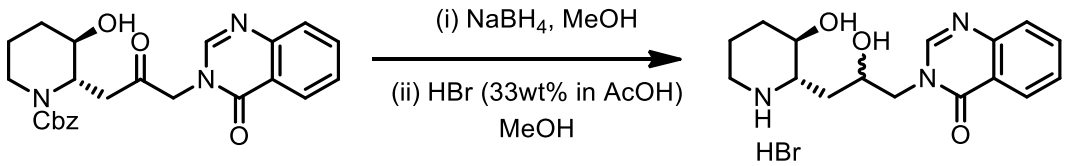
141 (118 mg, 0.3 mmol) was subjected to the general conditions to afford the title product as a yellow oil (27 mg, 34%). δ_H (400 MHz, $CDCl_3$) 8.35 - 8.25 (m, 1H), 8.10 (s, 1H), 7.80 - 7.70 (m, 2H), 7.55 - 7.45 (m, 1H), 4.39 (d, 1H, *J* = 13.9 Hz), 4.19 (d, 1H, *J* = 13.9 Hz), 3.94 - 3.91 (m, 1H), 3.34 - 3.32 (m, 1H), 3.04 - 3.05 (m, 2H), 2.56 - 2.53 (m, 1H), 2.20 - 2.05 (m, 1H), 1.90 - 1.80 (m, 2H), 1.65 - 1.55 (m, 2H), 1.50 - 1.45 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.5, 149.2, 149.1, 134.3, 132.6, 129.3, 126.9, 121.9, 105.4, 77.6, 55.7, 52.4, 49.9, 44.5, 26.7, 20.0.



148

148 obtained as a yellow oil (58 mg, 50%). ν_{max} (solid /cm^{-1}) 3072, 2974, 1722, 1676, 1646, 1354, 786; δ_H (400 MHz, $CDCl_3$) 8.35 - 8.25 (m, 1H), 7.95 (s, 1H), 7.85 - 7.70 (m, 2H), 7.55 - 7.45 (m, 1H), 5.00 (s, 2H), 3.82 - 3.76 (m, 2H), 2.98 -2.94 (m, 2H), 2.71 - 2.66 (m, 2H), 2.51 - 2.46 (m, 2H), 1.94 - 1.85 (m, 2H); δ_C (101 MHz, $CDCl_3$) 202.5, 176.6, 161.0, 148.8, 148.2, 135.0, 134.4, 127.8, 127.6, 121.9, 60.5, 54.5, 37.9, 35.7, 27.5, 22.6; *m/z* (ESI) 284 (100%, $[M]^+$); HRMS, found 284.1395 ($[C_{16}H_{17}N_3O_2]$ requires 284.1394).

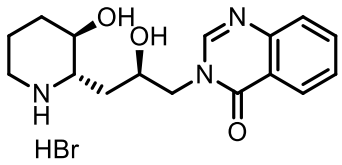
General Procedure for the Synthesis of Febrifugine Analogues 172 and 173.



$NaBH_4$ (2.0 eq) was added to a suspension of benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)-3-hydroxypiperidine-1-carboxylate **142** (1.0 equiv) in MeOH (0.1 M), and the solution was left to stir for 2 h. After completion, a saturated solution of $NaHCO_3$ was added and the organic layers were extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via isocratic preparative high performance liquid chromatography (HPLC) eluting MeCN : H_2O (3 : 7) to afford the corresponding protected febrifuginol analogues.

To each of the alcohol substrates (1.0 equiv) in a round bottom flask was added methanol (0.2 M) and HBr (33 wt% in AcOH) (100.0 equiv) at 0 °C. The mixture was stirred for 30 mins and after completion the solvent was removed *in vacuo*, purification by recrystallization from ethanol afford the corresponding products.

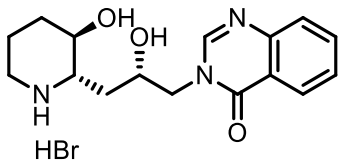
Febrifuginol hydrobromide 172.



172 colourless solid (8 mg, 45%) Mp 198 - 199 °C. ν_{max} (solid /cm^{-1}) 3294, 30.70, 2974, 1672, 1473; δ_H (400 MHz, MeOD-d^4) 9.60 (s, 1H), 8.45 (d, 1H, *J* = 8.0 Hz), 8.15 - 8.05 (m, 1H), 7.90 - 7.80 (m, 2H), 4.55 (dd, 1H, *J* = 10.0, 4.0 Hz), 4.40 - 4.32 (m, 1H), 4.10 - 4.02 (m, 1H), 3.40 - 3.30 (m, 2H), 3.25 - 3.20 (m, 1H), 3.10 - 2.95 (m, 1H), 2.50 - 2.40 (m, 2H), 2.20 - 2.00 (m, 2H), 1.85 - 1.75 (m, 1H), 1.65 - 1.55 (m, 2H); δ_C (101 MHz, MeOD-d^4) 161.2, 153.7, 151.3, 134.3, 127.9,

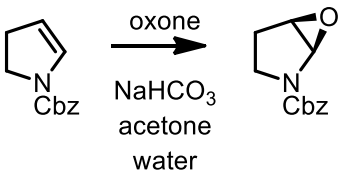
125.6, 124.2, 121.0, 73.7, 66.9, 58.4, 51.4, 45.4, 39.7, 32.0, 24.1; *m/z* (ESI) 304 (100%, $[M]^+$); HRMS, found 304.1657 ($[C_{16}H_{21}N_3O_3]$ requires 304.1656).

Epi-febrifuginol hydrobromide (173).



173 colourless solid (28 mg, 80%) Mp 200 - 201 °C . ν_{max} (solid /cm^{-1}) 3294, 30.70, 2974, 1672, 1473; δ_H (400 MHz, MeOD-d^4) 9.50 (s, 1H), 8.40 (d, 1H, *J* = 8.0 Hz), 8.10 - 8.05 (m, 1H), 7.85 - 7.80 (m, 2H), 4.51 (dd, 1H, *J* = 10.0, 4.0 Hz), 4.40 - 4.35 (m, 1H), 4.12 - 4.04 (m, 1H), 3.72 - 3.64 (m, 2H), 3.08 - 3.00 (m, 1H), 2.20 - 2.00 (m, 4H), 1.85 - 1.75 (m, 2H), 1.65 - 1.55 (m, 2H); δ_C (101 MHz, MeOD-d^4) 161.2, 153.7, 151.3, 134.3, 127.9, 125.6, 124.2, 121.0, 73.7, 66.9, 58.4, 51.4, 45.4, 39.7, 32.0, 24.1; *m/z* (ESI) 304 (100%, $[M]^+$); HRMS, found 304.1656 ($[C_{16}H_{21}N_3O_3]$ requires 304.1656).

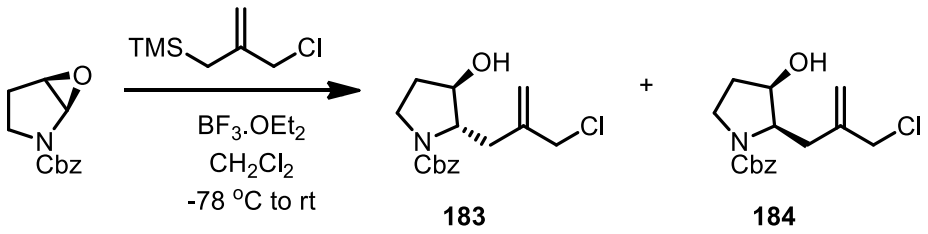
Synthesis of benzyl 6-oxa-2-azabicyclo [3.1.0]hexane-2-carboxylate (181).



Oxone monopersulfate (12.0 g, 39.3 mmol) was added portion wise to a solution of sodium bicarbonate (16.5 g, 19.6 mmol) in water (100 mL), and the mixture was allowed to stir for 10 mins. To this solution was added acetone (60 mL) and benzyl 2,3-dihydro-1*H*-pyrrole-1-carboxylate (1.0 g, 4.9 mmol). The mixture was allowed to stir for 16 h at room temperature. After completion, water (100 mL) was added and the organic layer extracted with ethyl

acetate (2 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product, which was purified by flash column chromatography eluting with cyclohexane : EtOAc (2 : 8) to afford the title product as a clear oil (0.7 g, 65%). V_{max} (solid /cm^{-1}) 3375, 2947, 1673, 1255, 987; δ_H (400 MHz, $CDCl_3$) 7.40 - 7.35 (m, 5H), 5.16 (s, 2H), 4.39 (d, 1H, *J* = 4.0 Hz), 3.63 - 3.57 (m, 1H), 3.09 - 3.02 (m, 2H), 2.29 - 2.19 (m, 2H); δ_C (101 MHz, $CDCl_3$) 156.0, 136.2, 128.6, 128.5, 128.2, 128.1, 127.9, 86.6, 67.3, 44.3, 42.8, 29.9; *m/z* (ESI) 219 (100%, $[M]^+$); HRMS, found 219.0895 ($[C_{12}H_{13}NO_3]$ requires 219.0890).

Synthesis of benzyl 2-(2-(chloromethyl)allyl)-3-hydroxypyrrolidine-1-carboxylate (183).

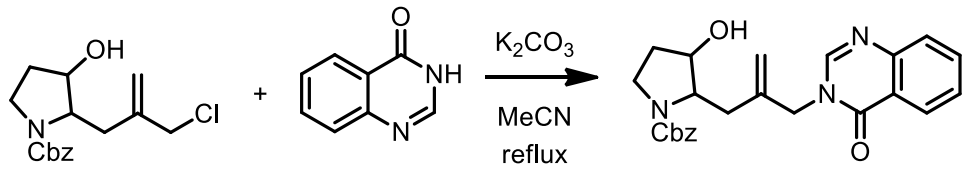


To a solution of benzyl 6-oxa-2-azabicyclo [3.1.0]hexane-2-carboxylate (476 mg, 1.7 mmol) and chlorotrimethylsilane (1.1 g, 6.8 mmol) in dichloromethane (10 mL) at -78 °C, $BF_3.OEt_2$ (242 mg, 1.7 mmol) was added. The reaction was allowed to stir overnight. $NaHCO_3$ (aq) (20 mL) was added and the reaction mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the product as a mixture of diastereoisomers which were purified via isocratic preparative high performance liquid chromatography (HPLC) eluting MeCN : H_2O (4 : 6) to afford the corresponding products. **183** as a clear oil (87 mg, 16%); ν_{max} (solid /cm^{-1}) 3444, 2938, 2516, 2159, 2028, 1670, 1424; δ_H (400 MHz, $CDCl_3$) 7.42 - 7.36 (m, 5H), 5.15 - 5.13 (m, 4H), 4.51 - 4.45 (m, 1H), 4.32 - 4.24 (m, 1H), 4.16 - 4.04 (m, 2H), 3.64 - 3.50 (m, 2H), 3.55 - 3.49 (m, 2H), 2.63 - 2.55 (m, 2H); δ_C (101 MHz, $CDCl_3$) 156.0, 148.1, 137.0, 128.3, 128.2, 128.1,

127.9, 120.7, 76.3, 67.0, 59.1, 49.7, 44.0, 37.0, 33.1; *m/z* (ESI) 310 (100%, $[M(^{35}Cl)]^+$); HRMS, found 310.1205 ($[C_{16}H_{20}NO_3{}^{35}Cl]$ requires 310.1204).

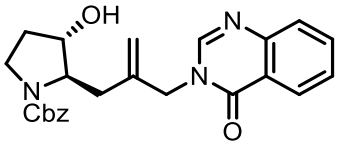
184 clear oil (42 mg, 9%). ν_{max} (solid /cm^{-1}) 3444, 2938, 2516, 2159, 2028, 1670, 1424; δ_H (400 MHz, $CDCl_3$) 7.39 - 7.32 (m, 5H), 5.24 - 5.06 (m, 4H), 4.23 - 4.19 (m, 1H), 4.06 - 4.02 (m, 1H), 3.97 - 3.90 (m, 2H), 3.72 - 3.64 (m, 2H), 3.56 - 3.52 (m, 2H), 2.60 - 2.50 (m, 2H); δ_C (101 MHz, $CDCl_3$) 155.9, 148.1, 137.1, 128.3, 128.2, 128.1, 127.9, 120.7, 76.2, 67.1, 59.0, 49.7, 44.1, 37.3, 33.3; *m/z* (ESI) 310 (100%, $[M(^{35}Cl)]^+$); HRMS, found 310.1203 ($[C_{16}H_{20}NO_3{}^{35}Cl]$ requires 310.1204).

General Procedure for the Synthesis of substrates 185 and 186.



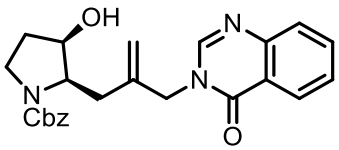
Potassium carbonate (1.5 equiv) was added to a suspension of quinazolinone (1.0 equiv) in MeCN (0.1 M) and the mixture was heated at reflux. A solution of benzyl 2-(2-(chloromethyl)allyl)-3-hydroxypyrrolidine-1-carboxylate (1.0 equiv) in MeCN (0.3 M) was added dropwise to the reaction mixture and the reaction was left to stir for 16 h. After completion, aq. NH_4Cl was added and the product extracted with ethyl acetate. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flash column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding products.

Benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl)methyl)allyl)pyrrolidine-1-carboxylate (185).



183 (42 mg, 0.1 mmol) was subjected to the general conditions to afford the title product as a yellow oil (39 mg, 70%). ν_{max} (solid /cm^{-1}) 3454, 3023, 2917, 1738, 1706, 1659, 1609, 1231; δ_H (400 MHz, $CDCl_3$) 8.30 - 8.26 (m, 1H), 8.10 (s, 1H), 7.80 - 7.70 (m, 2H), 7.55 - 7.45 (m, 1H), 7.40 - 7.25 (m, 5H), 5.20 - 5.05 (m, 2H), 5.00 - 4.90 (m, 1H), 4.70 - 4.60 (m, 1H), 4.50 - 4.45 (m, 1H), 4.10 - 4.05 (m, 2H), 3.95 - 3.85 (m, 1H), 2.60 - 2.40 (m, 2H), 2.00 - 1.90 (m, 2H), 1.50 - 1.35 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.3, 158.4, 148.0, 147.2, 144.1, 136.6, 134.6, 128.4, 127.9, 127.6, 127.2, 126.8, 126.4, 121.9, 114.1, 67.2, 60.4, 55.4, 49.2, 42.2, 38.8, 34.1; *m/z* (ESI) 420 (100%, $[M]^+$); HRMS, found 420.1920 ($[C_{24}H_{25}N_3O_4]$ requires 420.1918).

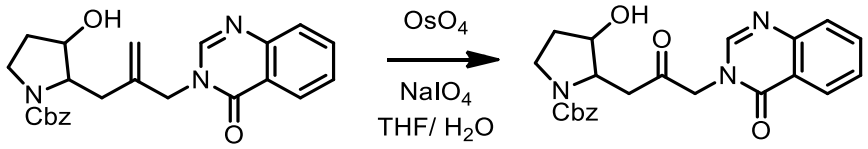
Benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl)methyl)allyl)pyrrolidine-1-carboxylate (186).



184 (87 mg, 0.3 mmol) was subjected to the general conditions to afford the title product as a yellow oil (77 mg, 66%). ν_{max} (solid /cm^{-1}) 3440, 3129, 2918, 1738, 1660, 1601, 1423; δ_H (400 MHz, $CDCl_3$) 8.29 - 8.25 (m, 1H), 8.10 (s, 1H), 7.79 - 7.70 (m, 2H), 7.53 - 7.40 (m, 1H), 7.36 - 7.25 (m, 5H), 5.18 - 5.05 (m, 2H), 5.00 - 4.89 (m, 1H), 4.65 - 4.60 (m, 1H), 4.50 - 4.45 (m, 1H), 4.10 - 4.04 (m, 2H), 3.95 - 3.85 (m, 1H), 2.63 - 2.44 (m, 2H), 2.04 - 1.94 (m, 2H), 1.50 - 1.35 (m, 2H); δ_C (101 MHz, $CDCl_3$) 160.3, 158.4, 148.0, 147.2, 144.1, 136.6, 134.6, 128.3, 127.9, 127.7,

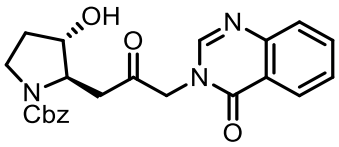
127.3, 126.8, 126.4, 121.9, 114.3, 67.1, 60.4, 55.0, 49.2, 42.2, 38.8, 33.9; *m/z* (ESI) 420 (100%, $[M]^+$); HRMS, found 420.1919 ($[C_{24}H_{25}N_3O_4]$ requires 420.1918).

General Procedure for the Synthesis of substrates 187 and 188.



OsO_4 (a few crystals) was added to a suspension of benzyl 3-hydroxy-2-(2-((4-oxoquinazolin-3(4*H*)-yl) methyl) allyl)pyrrolidine-1-carboxylate (1.0 equiv) and $NaIO_4$ (2.0 equiv) in THF (0.1 M) and water (0.2 M), and the solution was left to stir for 16 h. After completion, a saturated solution of $Na_2S_2O_5$ was added and the organic layers were extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flush column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding products.

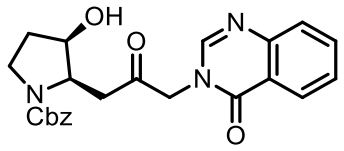
Benzyl 3-hydroxy-2-(2-oxo-3-(4-oxoquinazolin-3(*4H*)-yl)propyl)pyrrolidine-1-carboxylate (187).



185 (36 mg, 0.08 mmol) was subjected to the general conditions to afford the title product as a yellow oil (22 mg, 60%). ν_{max} (solid /cm^{-1}) 3365, 3033, 2932, 1732, 1688, 1610, 1041; δ_H (400 MHz, $CDCl_3$) 8.30 - 8.26 (m, 1H), 8.10 (s, 1H), 7.80 - 7.70 (m, 2H), 7.55 - 7.45 (m, 1H), 7.40 - 7.25 (m, 5H), 5.20 - 5.05 (m, 2H), 5.00 - 4.90 (d, 1H, *J* = 17.5 Hz), 4.70 - 4.60 (d, 1H, *J* = 17.5 Hz), 4.50 - 4.45 (m, 1H), 4.10 - 4.05 (m, 2H), 3.95 - 3.85 (m, 1H), 2.60 - 2.40 (m, 2H), 1.50 - 1.35

(m, 2H); δ_C (101 MHz, $CDCl_3$) 201.0, 160.9, 155.2, 147.7, 146.8, 136.6, 134.7, 128.7, 128.5, 128.3, 128.1, 127.8, 127.6, 126.8, 121.6, 67.0, 63.0, 54.4, 54.2, 44.6, 43.9, 31.5; *m/z* (ESI) 422 (100%, $[M]^+$); HRMS, found 422.1490 ($[C_{23}H_{23}N_3O_5]$ requires 422.1495).

Benzyl 3-hydroxy-2-(2-oxo-3-(4-oxoquinazolin-3(4H)-yl)propyl)pyrrolidine-1-carboxylate (188).



186 (77 mg, 0.1 mmol) was subjected to the general conditions to afford the title product as a yellow oil (46 mg, 60%). ν_{max} (solid /cm^{-1}) 3297, 2925, 1734, 1661, 1607, 1263; δ_H (400 MHz, $CDCl_3$) 8.29 - 8.25 (m, 1H), 8.10 (s, 1H), 7.81 - 7.72 (m, 2H), 7.55 - 7.45 (m, 1H), 7.37 - 7.25 (m, 5H), 5.20 - 5.05 (m, 2H), 5.10 - 5.05 (m, 1H), 4.89 - 4.80 (m, 1H), 4.79 - 4.75 (m, 1H), 4.50 - 4.45 (m, 2H), 3.95 - 3.85 (m, 1H), 2.60 - 2.40 (m, 2H), 1.48 - 1.38 (m, 2H); δ_C (101 MHz, $CDCl_3$) 201.1, 161.0, 155.2, 147.9, 146.7, 136.6, 134.6, 128.7, 128.5, 128.3, 128.1, 127.8, 127.5, 126.7, 121.7, 67.2, 63.0, 54.4, 54.2, 44.6, 43.9, 31.5; *m/z* (ESI) 422 (100%, $[M]^+$); HRMS, found 422.1495 ($[C_{23}H_{23}N_3O_5]$ requires 422.1495).

13 APPENDENCES

The X-ray crystallography data used to assign the stereochemistry of the compounds listed below is provided.

Compound:

- 3-(3- (3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4 (*3H*)-one (**147**).
- 3-(2-hydroxy-3- (3-hydroxypiperidin-2-yl) propyl) quinazolin-4 (*3H*)-one hydrobromide (**176**).

X-Ray crystal structure data for (147) 3-(3- (3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4 (3*H*)-one.

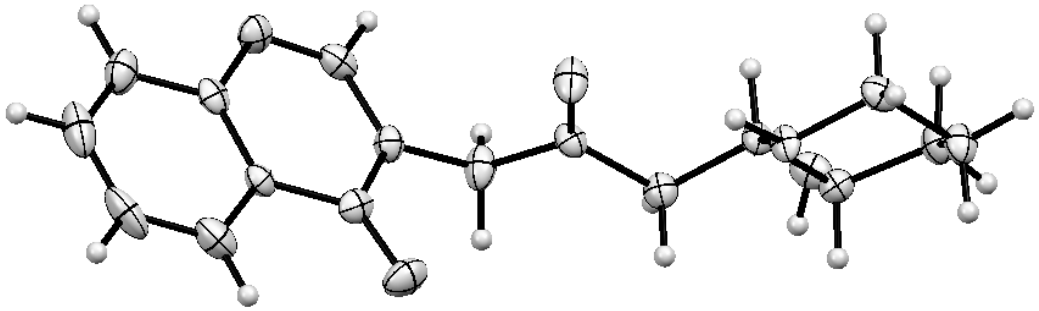


Table 1. Crystal data and structure refinement for **147**.

Identification code	ohj328_a	
Empirical formula	C16 H19 N3 O3	
Formula weight	301.34	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.2591(6) Å	α = 90°.
	b = 9.6617(5) Å	β = 90°.
	c = 30.5377(16) Å	γ = 90°.
Volume	3026.9(3) $Å^3$	
Z	8	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	0.762 mm^{-1}	
F(000)	1280	
Crystal size	0.200 x 0.080 x 0.040 mm^3	
Theta range for data collection	2.894 to 66.664°.	
Index ranges	-11<=h<=12, -11<=k<=11, -29<=l<=36	
Reflections collected	12393	
Independent reflections	2658 [R(int) = 0.1251]	
Completeness to theta = 66.664°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.82	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2658 / 0 / 200	
Goodness-of-fit on F^2	1.517	

Final R indices [I>2sigma(I)]	R1 = 0.0784, wR2 = 0.0831
R indices (all data)	R1 = 0.1345, wR2 = 0.0889
Extinction coefficient	n/a
Largest diff. peak and hole	0.276 and -0.313 e.Å^{-3}

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for ohj328_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7899(2)	6118(2)	3942(1)	33(1)
O(2)	5283(2)	6482(2)	4685(1)	31(1)
O(3)	6482(2)	10018(2)	5761(1)	26(1)
N(1)	6127(2)	7492(2)	3869(1)	21(1)
N(2)	4668(2)	7372(2)	3269(1)	25(1)
N(3)	6122(2)	6229(2)	5646(1)	19(1)
C(1)	6954(3)	6467(3)	3720(1)	22(1)
C(2)	6610(3)	5916(3)	3293(1)	19(1)
C(3)	7379(3)	4902(3)	3093(1)	33(1)
C(4)	7043(4)	4383(3)	2693(1)	39(1)
C(5)	5939(4)	4868(3)	2480(1)	39(1)
C(6)	5173(3)	5857(3)	2672(1)	31(1)
C(7)	5494(3)	6399(3)	3083(1)	21(1)
C(8)	5035(3)	7863(3)	3642(1)	24(1)
C(9)	6443(3)	8195(3)	4278(1)	27(1)
C(10)	6078(3)	7407(3)	4684(1)	21(1)
C(11)	6749(3)	7927(3)	5087(1)	23(1)
C(12)	6061(3)	7707(3)	5521(1)	20(1)
C(13)	6687(3)	8588(3)	5875(1)	20(1)
C(14)	6128(3)	8302(3)	6325(1)	26(1)
C(15)	6125(3)	6764(3)	6430(1)	26(1)
C(16)	5460(3)	5967(3)	6069(1)	25(1)

Table 9. Bond lengths [Å] and angles [°] for ohj328_a.

O(1)-C(1)	1.230(3)
O(2)-C(10)	1.210(3)
O(3)-C(13)	1.441(3)
O(3)-H(3)	0.8400
N(1)-C(8)	1.366(3)
N(1)-C(1)	1.381(3)
N(1)-C(9)	1.457(3)
N(2)-C(8)	1.288(3)
N(2)-C(7)	1.388(3)
N(3)-C(12)	1.479(3)
N(3)-C(16)	1.482(3)
N(3)-H(3N)	0.9923
C(1)-C(2)	1.453(4)
C(2)-C(7)	1.392(4)
C(2)-C(3)	1.398(4)
C(3)-C(4)	1.366(4)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.387(4)
C(4)-H(4)	0.9500
C(5)-C(6)	1.368(4)
C(5)-H(5)	0.9500
C(6)-C(7)	1.401(4)
C(6)-H(6)	0.9500
C(8)-H(8)	0.9500
C(9)-C(10)	1.503(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.498(4)
C(11)-C(12)	1.516(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.518(3)
C(12)-H(12)	1.0000
C(13)-C(14)	1.514(3)
C(13)-H(13)	1.0000
C(14)-C(15)	1.521(3)

C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.508(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900

C(13)-O(3)-H(3)	109.5
C(8)-N(1)-C(1)	121.6(2)
C(8)-N(1)-C(9)	119.7(2)
C(1)-N(1)-C(9)	118.7(3)
C(8)-N(2)-C(7)	115.6(3)
C(12)-N(3)-C(16)	111.7(2)
C(12)-N(3)-H(3N)	115.0
C(16)-N(3)-H(3N)	110.1
O(1)-C(1)-N(1)	119.9(3)
O(1)-C(1)-C(2)	125.9(3)
N(1)-C(1)-C(2)	114.2(3)
C(7)-C(2)-C(3)	119.9(3)
C(7)-C(2)-C(1)	119.4(3)
C(3)-C(2)-C(1)	120.7(3)
C(4)-C(3)-C(2)	120.3(3)
C(4)-C(3)-H(3A)	119.8
C(2)-C(3)-H(3A)	119.8
C(3)-C(4)-C(5)	120.1(3)
C(3)-C(4)-H(4)	120.0
C(5)-C(4)-H(4)	120.0
C(6)-C(5)-C(4)	120.3(3)
C(6)-C(5)-H(5)	119.8
C(4)-C(5)-H(5)	119.8
C(5)-C(6)-C(7)	120.6(3)
C(5)-C(6)-H(6)	119.7
C(7)-C(6)-H(6)	119.7
N(2)-C(7)-C(2)	122.7(3)
N(2)-C(7)-C(6)	118.5(3)
C(2)-C(7)-C(6)	118.8(3)
N(2)-C(8)-N(1)	126.3(3)

N(2)-C(8)-H(8)	116.8
N(1)-C(8)-H(8)	116.8
N(1)-C(9)-C(10)	114.5(2)
N(1)-C(9)-H(9A)	108.6
C(10)-C(9)-H(9A)	108.6
N(1)-C(9)-H(9B)	108.6
C(10)-C(9)-H(9B)	108.6
H(9A)-C(9)-H(9B)	107.6
O(2)-C(10)-C(11)	123.7(3)
O(2)-C(10)-C(9)	123.0(3)
C(11)-C(10)-C(9)	113.2(2)
C(10)-C(11)-C(12)	117.2(2)
C(10)-C(11)-H(11A)	108.0
C(12)-C(11)-H(11A)	108.0
C(10)-C(11)-H(11B)	108.0
C(12)-C(11)-H(11B)	108.0
H(11A)-C(11)-H(11B)	107.2
N(3)-C(12)-C(11)	109.9(2)
N(3)-C(12)-C(13)	109.9(2)
C(11)-C(12)-C(13)	110.3(2)
N(3)-C(12)-H(12)	108.9
C(11)-C(12)-H(12)	108.9
C(13)-C(12)-H(12)	108.9
O(3)-C(13)-C(14)	109.8(2)
O(3)-C(13)-C(12)	107.7(2)
C(14)-C(13)-C(12)	112.5(2)
O(3)-C(13)-H(13)	108.9
C(14)-C(13)-H(13)	108.9
C(12)-C(13)-H(13)	108.9
C(13)-C(14)-C(15)	111.8(2)
C(13)-C(14)-H(14A)	109.3
C(15)-C(14)-H(14A)	109.3
C(13)-C(14)-H(14B)	109.3
C(15)-C(14)-H(14B)	109.3
H(14A)-C(14)-H(14B)	107.9
C(16)-C(15)-C(14)	110.2(2)
C(16)-C(15)-H(15A)	109.6
C(14)-C(15)-H(15A)	109.6

C(16)-C(15)-H(15B)	109.6
C(14)-C(15)-H(15B)	109.6
H(15A)-C(15)-H(15B)	108.1
N(3)-C(16)-C(15)	110.1(2)
N(3)-C(16)-H(16A)	109.6
C(15)-C(16)-H(16A)	109.6
N(3)-C(16)-H(16B)	109.6
C(15)-C(16)-H(16B)	109.6
H(16A)-C(16)-H(16B)	108.2

Symmetry transformations used to generate equivalent atoms:

Table 10. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for ohj328_a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	29(1)	31(1)	38(1)	10(1)	-10(1)	0(1)
O(2)	44(1)	27(1)	23(1)	1(1)	-1(1)	-19(1)
O(3)	26(1)	15(1)	36(1)	-3(1)	5(1)	-1(1)
N(1)	26(2)	18(1)	18(1)	-1(1)	0(1)	-2(1)
N(2)	29(2)	23(1)	24(1)	4(1)	-1(1)	4(1)
N(3)	27(1)	14(1)	18(1)	-4(1)	1(1)	-8(1)
C(1)	23(2)	17(2)	25(2)	9(2)	-1(2)	-3(2)
C(2)	21(2)	17(2)	19(2)	3(1)	5(2)	0(1)
C(3)	34(2)	30(2)	34(2)	3(2)	13(2)	3(2)
C(4)	52(3)	28(2)	37(2)	-5(2)	27(2)	-1(2)
C(5)	62(3)	34(2)	22(2)	-5(2)	10(2)	-17(2)
C(6)	40(2)	30(2)	23(2)	6(2)	-4(2)	-6(2)
C(7)	27(2)	17(2)	21(2)	5(2)	7(2)	-5(2)
C(8)	25(2)	18(2)	29(2)	4(2)	7(2)	2(1)
C(9)	40(2)	23(2)	20(2)	0(2)	-2(2)	-9(1)
C(10)	24(2)	17(2)	22(2)	2(2)	4(2)	-3(2)
C(11)	26(2)	19(2)	23(2)	-1(2)	1(2)	-3(1)
C(12)	21(2)	18(2)	20(2)	1(1)	0(2)	-4(1)
C(13)	22(2)	16(2)	24(2)	0(2)	-2(2)	-1(1)
C(14)	32(2)	23(2)	22(2)	-4(2)	3(2)	-1(2)
C(15)	32(2)	25(2)	22(2)	3(2)	3(2)	-9(2)
C(16)	26(2)	21(2)	30(2)	5(2)	5(2)	-3(2)

Table 11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ohj328_a.

	x	y	z	U(eq)
H(3)	7201	10388	5700	39
H(3N)	5799	5574	5420	23
H(3A)	8139	4571	3237	39
H(4)	7567	3689	2560	47
H(5)	5714	4512	2200	47
H(6)	4416	6179	2524	37
H(8)	4495	8549	3771	29
H(9A)	5990	9100	4282	33
H(9B)	7392	8380	4284	33
H(11A)	6901	8932	5051	27
H(11B)	7614	7476	5104	27
H(12)	5127	7984	5489	24
H(13)	7645	8397	5880	24
H(14A)	5225	8660	6338	31
H(14B)	6650	8800	6547	31
H(15A)	7032	6433	6464	32
H(15B)	5662	6606	6710	32
H(16A)	5485	4965	6136	30
H(16B)	4536	6253	6049	30

Table 12. Hydrogen bonds for ohj328_a [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...N(3)#1	0.84	1.91	2.744(3)	172.3
N(3)-H(3N)...O(2)	0.99	2.47	3.069(3)	118.5
N(3)-H(3N)...O(2)#2	0.99	2.30	3.155(3)	144.0
C(8)-H(8)...O(3)#3	0.95	2.23	3.154(3)	164.2
C(9)-H(9A)...O(1)#1	0.99	2.48	3.079(3)	118.2
C(14)-H(14A)...O(1)#4	0.99	2.54	3.457(4)	153.2

Symmetry transformations used to generate equivalent atoms:
#1 -x+3/2,y+1/2,z #2 -x+1,-y+1,-z+1 #3 -x+1,-y+2,-z+1
#4 x-1/2,-y+3/2,-z+1

X-Ray crystal structure data for (176) 3-(2-hydroxy-3- (3-hydroxypiperidin-2-yl) propyl) quinazolin-4 (3*H*)-one hydrobromide.

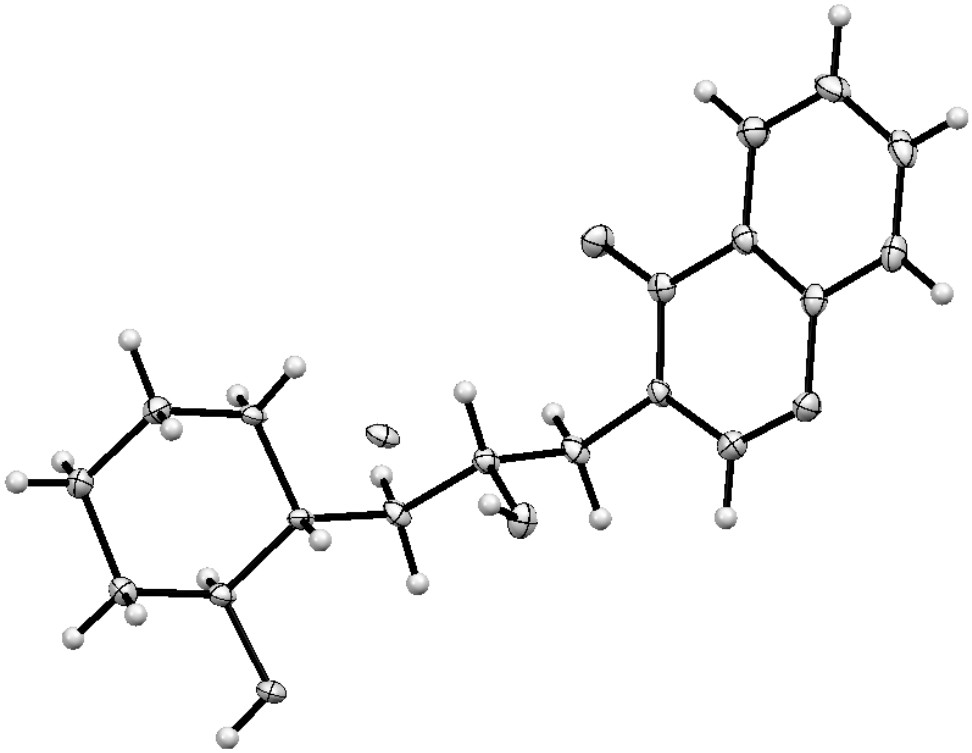


Table 1. Crystal data and structure refinement for **176**.

Identification code	ohj337_0m_a	
Empirical formula	C16 H22 Br N3 O3	
Formula weight	384.27	
Temperature	108(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.7816(2) Å	α = 99.3200(10)°.
	b = 9.6161(3) Å	β = 92.9270(10)°.
	c = 11.1044(3) Å	γ = 90.6810(10)°.
Volume	818.72(4) $Å^3$	
Z	2	
Density (calculated)	1.559 Mg/m^3	
Absorption coefficient	3.587 mm^{-1}	
F(000)	396	
Crystal size	0.200 x 0.100 x 0.080 mm^3	

Theta range for data collection	4.040 to 66.717°.
Index ranges	-9<=h<=9, -11<=k<=11, -13<=l<=13
Reflections collected	21000
Independent reflections	2869 [R(int) = 0.0422]
Completeness to theta = 66.717°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.81 and 0.58
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2869 / 0 / 210
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R1 = 0.0244, wR2 = 0.0571
R indices (all data)	R1 = 0.0269, wR2 = 0.0580
Extinction coefficient	n/a
Largest diff. peak and hole	0.347 and -0.372 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for ohj337_0m_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(01)	6764(1)	3517(1)	4293(1)	15(1)
O(1)	332(2)	6318(2)	2920(1)	19(1)
O(2)	3444(2)	2526(2)	2491(1)	18(1)
O(3)	2293(2)	-556(2)	4652(1)	18(1)
N(1)	1253(2)	4490(2)	1551(2)	13(1)
N(2)	2687(2)	4807(2)	-225(2)	18(1)
N(3)	2829(2)	3184(2)	5994(2)	13(1)
C(1)	1062(3)	5909(2)	1973(2)	14(1)
C(2)	1801(3)	6846(2)	1213(2)	15(1)
C(3)	1746(3)	8314(2)	1559(2)	20(1)
C(4)	2442(3)	9183(2)	825(2)	23(1)
C(5)	3198(3)	8594(2)	-250(2)	22(1)
C(6)	3279(3)	7162(2)	-590(2)	20(1)
C(7)	2584(3)	6258(2)	141(2)	15(1)
C(8)	2054(3)	4028(2)	483(2)	17(1)
C(9)	662(3)	3446(2)	2283(2)	15(1)
C(10)	2078(3)	3148(2)	3191(2)	13(1)
C(11)	1416(3)	2147(2)	4008(2)	14(1)
C(12)	2705(3)	1894(2)	5024(2)	12(1)
C(13)	2232(3)	617(2)	5615(2)	13(1)
C(14)	3444(3)	474(2)	6700(2)	17(1)
C(15)	3502(3)	1825(2)	7638(2)	17(1)
C(16)	4050(3)	3064(2)	7049(2)	17(1)

Table 3. Bond lengths [Å] and angles [°] for ohj337_0m_a.

O(1)-C(1)	1.231(3)
O(2)-C(10)	1.429(2)
O(2)-H(2)	0.8400
O(3)-C(13)	1.427(2)
O(3)-H(3)	0.8400
N(1)-C(8)	1.380(3)
N(1)-C(1)	1.381(3)
N(1)-C(9)	1.473(3)
N(2)-C(8)	1.282(3)
N(2)-C(7)	1.393(3)
N(3)-C(16)	1.491(3)
N(3)-C(12)	1.504(3)
N(3)-H(1BR)	0.9776
N(3)-H(1N)	0.9060
C(1)-C(2)	1.463(3)
C(2)-C(3)	1.404(3)
C(2)-C(7)	1.405(3)
C(3)-C(4)	1.382(3)
C(3)-H(3C)	0.9500
C(4)-C(5)	1.398(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.371(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.403(3)
C(6)-H(6)	0.9500
C(8)-H(8)	0.9500
C(9)-C(10)	1.517(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.528(3)
C(10)-H(10)	1.0000
C(11)-C(12)	1.522(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.532(3)
C(12)-H(12)	1.0000

C(13)-C(14)	1.517(3)
C(13)-H(13)	1.0000
C(14)-C(15)	1.526(3)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.516(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900

C(10)-O(2)-H(2)	109.5
C(13)-O(3)-H(3)	109.5
C(8)-N(1)-C(1)	121.43(17)
C(8)-N(1)-C(9)	119.04(17)
C(1)-N(1)-C(9)	119.46(17)
C(8)-N(2)-C(7)	116.37(18)
C(16)-N(3)-C(12)	114.31(16)
C(16)-N(3)-H(1BR)	108.7
C(12)-N(3)-H(1BR)	106.1
C(16)-N(3)-H(1N)	105.7
C(12)-N(3)-H(1N)	113.2
H(1BR)-N(3)-H(1N)	108.7
O(1)-C(1)-N(1)	121.33(19)
O(1)-C(1)-C(2)	124.1(2)
N(1)-C(1)-C(2)	114.52(18)
C(3)-C(2)-C(7)	120.5(2)
C(3)-C(2)-C(1)	120.39(19)
C(7)-C(2)-C(1)	119.14(19)
C(4)-C(3)-C(2)	119.5(2)
C(4)-C(3)-H(3C)	120.2
C(2)-C(3)-H(3C)	120.2
C(3)-C(4)-C(5)	119.9(2)
C(3)-C(4)-H(4)	120.1
C(5)-C(4)-H(4)	120.1
C(6)-C(5)-C(4)	121.1(2)
C(6)-C(5)-H(5)	119.4
C(4)-C(5)-H(5)	119.4

C(5)-C(6)-C(7)	120.1(2)
C(5)-C(6)-H(6)	120.0
C(7)-C(6)-H(6)	120.0
N(2)-C(7)-C(6)	118.86(19)
N(2)-C(7)-C(2)	122.24(19)
C(6)-C(7)-C(2)	118.9(2)
N(2)-C(8)-N(1)	126.3(2)
N(2)-C(8)-H(8)	116.9
N(1)-C(8)-H(8)	116.9
N(1)-C(9)-C(10)	110.76(17)
N(1)-C(9)-H(9A)	109.5
C(10)-C(9)-H(9A)	109.5
N(1)-C(9)-H(9B)	109.5
C(10)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	108.1
O(2)-C(10)-C(9)	106.61(16)
O(2)-C(10)-C(11)	110.69(16)
C(9)-C(10)-C(11)	110.45(17)
O(2)-C(10)-H(10)	109.7
C(9)-C(10)-H(10)	109.7
C(11)-C(10)-H(10)	109.7
C(12)-C(11)-C(10)	114.01(17)
C(12)-C(11)-H(11A)	108.7
C(10)-C(11)-H(11A)	108.7
C(12)-C(11)-H(11B)	108.7
C(10)-C(11)-H(11B)	108.7
H(11A)-C(11)-H(11B)	107.6
N(3)-C(12)-C(11)	109.11(16)
N(3)-C(12)-C(13)	108.91(16)
C(11)-C(12)-C(13)	113.30(17)
N(3)-C(12)-H(12)	108.5
C(11)-C(12)-H(12)	108.5
C(13)-C(12)-H(12)	108.5
O(3)-C(13)-C(14)	112.61(17)
O(3)-C(13)-C(12)	104.47(15)
C(14)-C(13)-C(12)	112.01(17)
O(3)-C(13)-H(13)	109.2
C(14)-C(13)-H(13)	109.2

C(12)-C(13)-H(13)	109.2
C(13)-C(14)-C(15)	110.77(18)
C(13)-C(14)-H(14A)	109.5
C(15)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
C(15)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	108.1
C(16)-C(15)-C(14)	110.06(17)
C(16)-C(15)-H(15A)	109.6
C(14)-C(15)-H(15A)	109.6
C(16)-C(15)-H(15B)	109.6
C(14)-C(15)-H(15B)	109.6
H(15A)-C(15)-H(15B)	108.2
N(3)-C(16)-C(15)	109.22(17)
N(3)-C(16)-H(16A)	109.8
C(15)-C(16)-H(16A)	109.8
N(3)-C(16)-H(16B)	109.8
C(15)-C(16)-H(16B)	109.8
H(16A)-C(16)-H(16B)	108.3

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for ohj337_0m_a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(01)	15(1)	9(1)	22(1)	4(1)	4(1)	0(1)
O(1)	20(1)	20(1)	18(1)	2(1)	9(1)	2(1)
O(2)	14(1)	23(1)	16(1)	4(1)	5(1)	1(1)
O(3)	30(1)	8(1)	16(1)	2(1)	1(1)	-1(1)
N(1)	14(1)	13(1)	12(1)	5(1)	3(1)	1(1)
N(2)	24(1)	17(1)	14(1)	2(1)	5(1)	1(1)
N(3)	19(1)	7(1)	15(1)	2(1)	5(1)	-1(1)
C(1)	11(1)	16(1)	15(1)	3(1)	0(1)	1(1)
C(2)	14(1)	16(1)	14(1)	4(1)	-1(1)	-1(1)
C(3)	22(1)	17(1)	20(1)	2(1)	3(1)	1(1)
C(4)	28(1)	13(1)	27(1)	6(1)	0(1)	-2(1)
C(5)	24(1)	23(1)	20(1)	11(1)	-1(1)	-7(1)
C(6)	21(1)	26(1)	12(1)	5(1)	2(1)	-3(1)
C(7)	14(1)	19(1)	13(1)	3(1)	-2(1)	-1(1)
C(8)	20(1)	16(1)	15(1)	1(1)	1(1)	1(1)
C(9)	16(1)	14(1)	17(1)	7(1)	4(1)	-2(1)
C(10)	15(1)	12(1)	14(1)	3(1)	4(1)	0(1)
C(11)	14(1)	12(1)	16(1)	6(1)	3(1)	-1(1)
C(12)	15(1)	8(1)	13(1)	1(1)	5(1)	0(1)
C(13)	17(1)	9(1)	15(1)	2(1)	4(1)	-1(1)
C(14)	22(1)	14(1)	17(1)	5(1)	2(1)	1(1)
C(15)	22(1)	16(1)	13(1)	3(1)	3(1)	2(1)
C(16)	23(1)	14(1)	14(1)	1(1)	2(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ohj337_0m_a.

	x	y	z	U(eq)
H(1BR)	1674	3326	6292	18
H(2)	4387	2717	2890	26
H(3)	2480	-1293	4949	27
H(1N)	3169	3969	5709	16
H(3C)	1233	8708	2292	23
H(4)	2407	10177	1051	27
H(5)	3665	9197	-754	26
H(6)	3806	6781	-1321	23
H(8)	2145	3038	250	20
H(9A)	313	2561	1734	18
H(9B)	-354	3807	2727	18
H(10)	2495	4052	3706	16
H(11A)	359	2538	4380	16
H(11B)	1099	1231	3495	16
H(12)	3858	1736	4673	14
H(13)	1030	715	5890	16
H(14A)	4615	270	6417	20
H(14B)	3054	-324	7086	20
H(15A)	2350	1995	7966	20
H(15B)	4326	1723	8326	20
H(16A)	4052	3942	7653	21
H(16B)	5230	2924	6764	21

Table 6. Hydrogen bonds for ohj337_0m_a [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(1BR)...O(1)#1	0.98	1.84	2.807(2)	171.3
O(2)-H(2)...Br(01)	0.84	2.39	3.2226(15)	169.5
O(3)-H(3)...Br(01)#2	0.84	2.49	3.3256(15)	175.1
N(3)-H(1N)...Br(01)#3	0.91	2.42	3.2527(17)	153.3
C(9)-H(9B)...Br(01)#4	0.99	2.95	3.852(2)	152.7
C(10)-H(10)...Br(01)#3	1.00	2.98	3.959(2)	165.8
C(11)-H(11A)...Br(01)#4	0.99	2.96	3.877(2)	153.9
C(12)-H(12)...Br(01)	1.00	2.91	3.692(2)	135.7
C(13)-H(13)...O(3)#5	1.00	2.62	3.518(3)	149.2
C(16)-H(16A)...N(2)#6	0.99	2.65	3.439(3)	137.0

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+1,-z+1 #2 -x+1,-y,-z+1 #3 -x+1,-y+1,-z+1

#4 x-1,y,z #5 -x,-y,-z+1 #6 x,y,z+1

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