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Maiden, T.M.M., Mbelesi, N., Procopiou, P.A. et al. (2018) A convergent strategy towards febrifugine and related compounds. Organic and Biomolecular Chemistry, 16 (22). pp. 4159-4169. ISSN: 1477-0520

https://doi.org/10.1039/c8ob00935j

Journal Name

ARTICLE

A Convergent Strategy to Febrifugine and Related Compounds

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

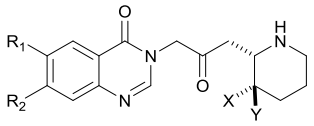
www.rsc.org/

We report a modular five step synthetic route to the febrifugines that employs 2-(chloromethyl)allyl-trimethylsilane as a conjuctive reagent for the coupling of the piperidine and quinazolinone groups. We also demonstrate the application of a recent Rh-catalyzed quinazolinone synthesis for the facile generation of febrifugine analogs.

Introduction

Quinazolinones are an important class of heterocycles in organic chemistry, and they are found in many natural products and biologically active compounds.[1] Most methods of generating these compounds rely on the availability of anthranilic acids and related systems.[2] Recently however, we have reported a directed amidation strategy for the synthesis of quinazolinones, which allows a broad range of these compounds to become available from simple (and often commercial) carboxylic acids.[3]

Amongst the many important quinazolinone-containing compounds found in nature and medicinal chemistry, the febrifugine family of alkaloids together with their synthetic analog halofuginone, have attracted considerable interest (Figure 1).[4] Febrifugine, isolated from the roots of *Dichroa febrifuga* plant and Hydrangea, has powerful antimalarial properties against *Plasmodium falciparum*, however, because of side-effects, such as severe vomiting and hepatotoxicity, is not used clinically. The synthetic analog halofuginone lactate is used as an antiparasitic agent in veterinary medicine for the treatment of neonatal dairy calves preventing infection with cryptosporidium and in poultry against coccidiosis.[5] Furthermore, halofuginone inhibits the development of human Th17 cells and collagen type 1 gene expression and has the potential to be used for the treatment of scleroderma, cancer, restinosis, autoimmune disorders and fibrotic diseases.[6] Halofuginone hydrobromide (tempostatin™) has been tested in Phase 1 clinical studies to assess dose-limiting toxicities, the maximum tolerated dose and human pharmacokinetics.[7] Observed side-effects included nausea, vomiting and fatigue, and the recommended maximum dose for further studies was determined to be 0.5 mg/day. Other analogues of febrfugine and halofuginone, devoid of toxicity and side-effects are therefore required for further exploitation and development of new medicines.



R_1/R_2=H, X=H, Y=OH: Febrifugine
R_1/R_2=H, X=OH, Y=H: Isofebrifugine
R_1=Cl, R_2=Br, X=H, Y=OH: Halofuginone

Figure 1. Febrifugine and related analogs.

Despite the attractive biological applications which the febrifugine family offer, only limited SAR has been investigated.[8] We sought to develop a modular route to the febrifugine family and synthesize biologically relevant analogs by utilizing our *C-H* amidation cyclocondensation sequence.

With respect to febrifugine, Ogasawara prepared this compound through the synthesis of a 2-allyl piperidin-3-ol derivative that allows the final compound to be delivered after alkene epoxidation, quinazolinone addition, oxidation level adjustment and protecting group manipulation.[9] This route has the advantage of introducing the quinazolinone at a late-stage thereby providing a means for acquiring SAR at this position. On the other hand, several steps are required before the key piperidine intermediate is made available.

In an effort to devise a convergent route to this class of compounds and explore SAR, we were attracted to the approaches of Burgess and Rutjes. Burgess had employed a tetrahydropyridine oxide that allowed the quinazolinone containing ketone fragment to be introduced in one step.[10] Rutjes however had devised an elegant allylsilane conjunctive

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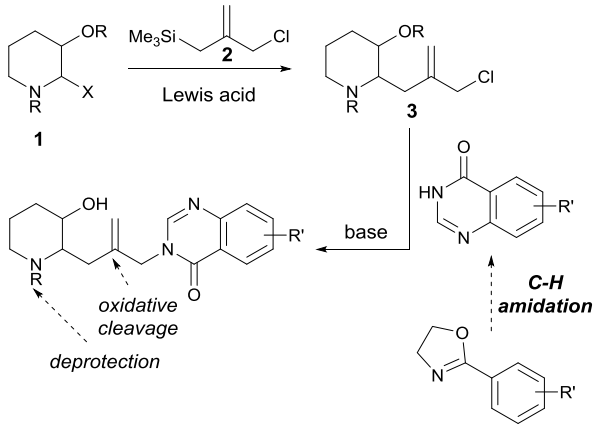
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

reagent **2** that offered a highly convergent approach to a late-stage lactam analog of febrifugine.[11] We envisaged that combining these strategies could offer a rapid and convergent method for the synthesis of febrifugine and its analogs that included the option of exploiting our *C-H* amidation methodology for the late-stage introduction of a range of bespoke quinazolinones. Our strategy is summarized in Scheme 1.

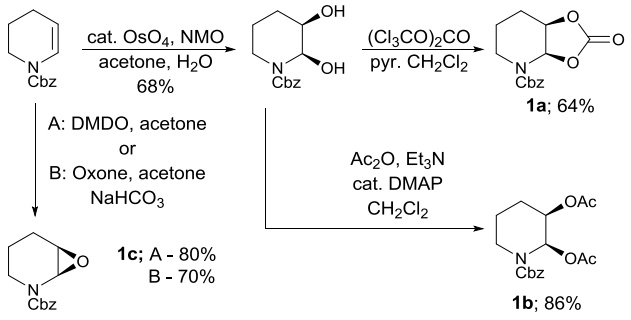
Results and Discussion

Our first task was to develop a scalable method for the coupling of Rutjes' conjunctive reagent **2** to the piperidine ring of the target compound series. We therefore investigated the synthesis of functionalized piperidines **1a-c**, all of which represented potential precursors to the first key intermediate



Scheme 1. Convergent route to febrifugine analogs.

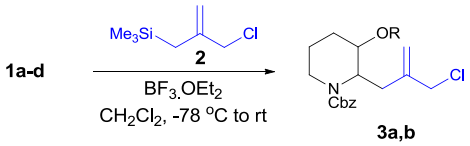
3 (Scheme 2). Accordingly, commercial Cbz-protected tetrahydropyridine was subjected to dihydroxylation followed by functionalization of the diol moiety as a carbonate and diester[12] **1a,b** in synthetically useful overall yields. In addition, we prepared epoxide **1c**. Our preliminary method for epoxidation employed freshly prepared DMDO (method A) but the in situ generation of this reagent (method B) proved to be more practical and allowed gram quantities of substrate to be accessed more conveniently.



Scheme 2. Synthesis of functionalized piperidines.

Aminals **1a-c** provided a platform to explore the efficiency and stereoselectivity of the allylation reaction using conjunctive reagent **2**, and our results are summarized in Table 1. Carbonate **1a** provided piperidine **3a** in modest yield and with a marginal preference for the *trans*-diastereomer. Diester **1b** and epoxide **1c** performed similarly and provided compounds **3a,b** with low *cis*/*trans*-selectivity. As low selectivities were observed in every case, we decided to use the route that employed **1c** as this encompassed only a two-step sequence. Moreover, as *cis*/*trans*-**3a** were separable by chromatography this procedure allowed gram quantities of each intermediate to be prepared for subsequent transformation to the target compounds.

Table 1 Coupling reaction of allylsilane **2** with piperidines **1a-d**

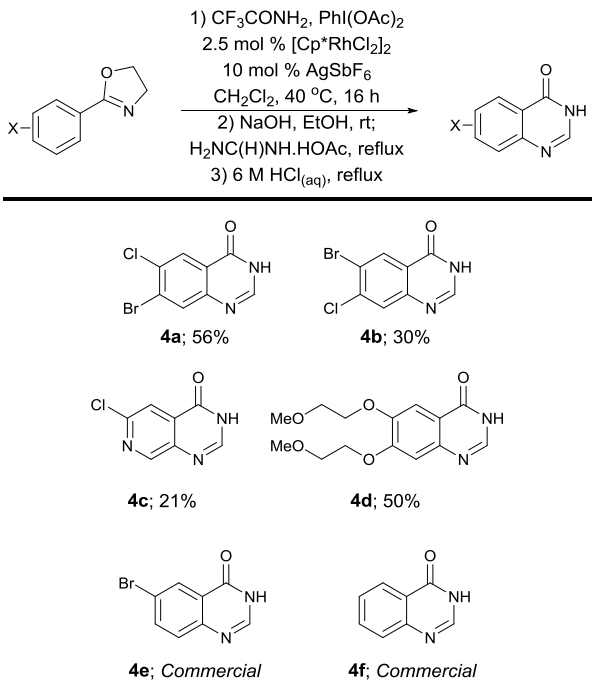


Entry[a]	Piperidine	R	Yield (*trans:cis*)[b]
1	**1a**	H; **3a**	40% (1.2:1)
2[c]	**1b**	Ac; **3b**	63% (1:1.3)
3	**1c**	H; **3a**	66% (1:1.1)

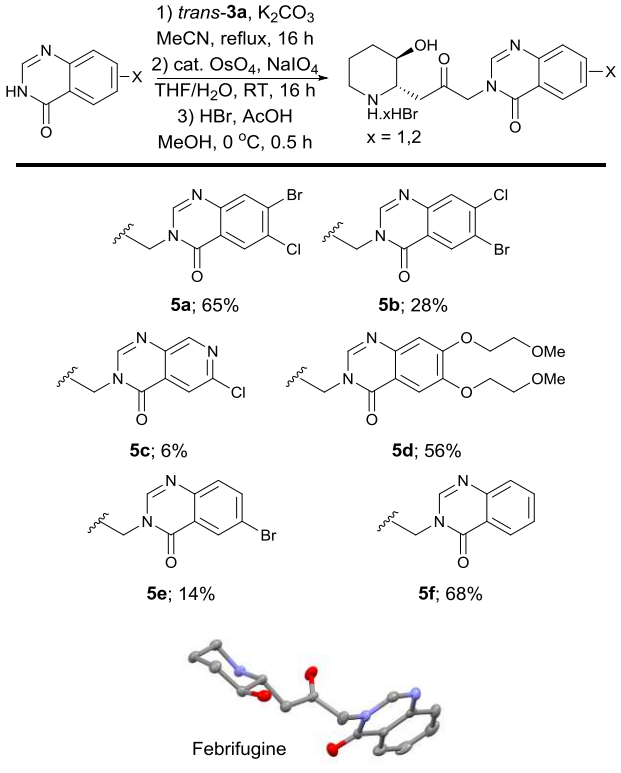
[a]Reaction conditions: **1a-d**, **2** (1.2 equiv), $BF_3.OEt_2$ (2 equiv) in CH_2Cl_2 stirred at -78 °C under N_2 for 1 h and warmed to rt overnight. [b]Isolated yields of purified compounds. [c]1 Equiv $BF_3.OEt_2$ used in this case.

We next turned our attention to the introduction of the quinazolinones, with a view to using our recently developed Rh-catalyzed ortho-amidation cyclocondensation sequence.[3(a),(b)] Employing this methodology, we were able to readily prepare a range of functionalized quinazolinones. Halofuginone quinazolinone **4a**, its corresponding isomer **4b**, aza-quinazolinone **4c** and the quinazolinone of the tyrosine kinase inhibitor, **4d**. The required quinazolinones for the febrifugine analog **4f** and the *mono*-Br **4e** were acquired from a commercial source (Scheme 3).

With quinazolinones **4a-f** in hand, we next explored the coupling of these heterocycles with the *trans*-piperidine **3a**. In the event, the couplings took place smoothly in all cases to deliver a family of fully coupled febrifugine analogs (Scheme 4). Having successfully coupled the key fragments, our final objective was to confirm that intermediates **5a-f** could be taken forward to the corresponding febrifugine derivatives.

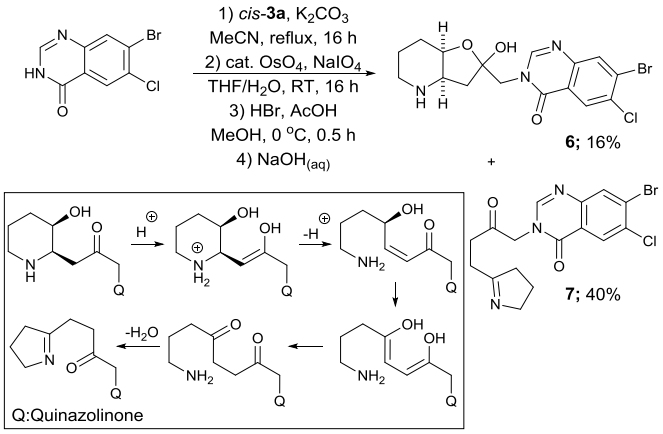


Scheme 3. Synthesis of quinazolinones by directed *CH*-amidation.



Scheme 4. Synthesis of febrifugine and analogs.

We employed an oxidative cleavage and deprotection protocol, using a modification of the method described by Rutjes.[11] We were pleased to find that halofuginone *trans*-**5a**, febrifugine *trans*-**5f** and analogs *trans*-**5b-e** were all isolated in good yield under these conditions as the HBr salts. Moreover, isolation of the free base of *trans*-**5f** followed by recrystallization from CH_2Cl_2/petroleum ether allowed us to record the first reported X-ray crystal structure of febrifugine, thereby unambiguously confirming the *trans*-stereochemistry of the piperidine ring.[13]



Scheme 5. Investigation towards the synthesis of the iso-febrifugines.

We next turned our attention to the synthesis of the corresponding *cis*-analogs of the febrifugines, but found these transformations to be less straightforward (Scheme 5). Specifically, while *cis*-**6** (iso-halofuginone) could be prepared and isolated as the free base, albeit in low yield, the corresponding derivatives derived from other quinazolinones could not be isolated cleanly by this process. Indeed, evidence for the instability of these products under acid was uncovered during the attempted syntheses of *cis*-**6**. Specifically, we were able to isolate imine **7** as major by-products in this case, and the compound structure was assigned by NMR spectroscopy and mass spectrometry, and by comparison to literature data of a similar compound.[14] We believe that this side reaction is initiated by an acid catalyzed β-amino elimination, as this pathway has been invoked as a mechanism for *cis*/*trans* isomerization in the febrifugines. Furthermore, and as shown in Scheme 5, enolization of the ring-opened product can provide a 1,4-diketone that undergoes condensation to the observed imine **7**.

As we had developed a convergent strategy for the preparation of biologically relevant *trans*-febrifugine analogs, especially those that contained halogenated quinazolinone fragments, we wanted to demonstrate that this chemistry could offer the opportunity for directed analog synthesis. Specifically, we were intrigued by a recent report by Zhou who employed crystallography to show how halofuginone binds and inhibits ATP-dependent, human prolyl tRNA synthetase (ProRS).[15] We were especially drawn to the presence of the glutamic acid 1100 residue which was in close proximity to the bound quinazolinone, and were interested in the introduction of a basic moiety such as an aminomethyl group to increase the binding affinity of these compounds. We envisaged that

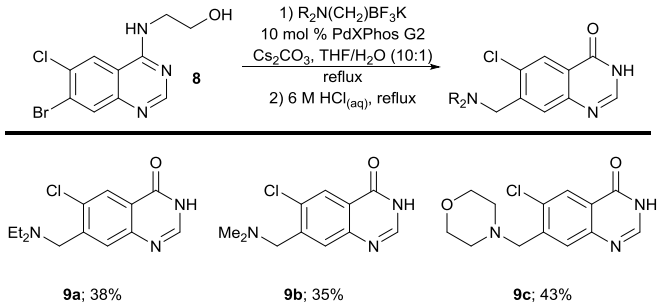
quinazolinone **4a** would offer convenient access to these compounds.

Accordingly, we designed a route to a selection of amino-methyl functionalized febrifugine analogs. Our strategy for introduction of the aminomethyl motif was underpinned by cross-coupling of Molander's potassium amino-methyl trifluoroborate salts.[16] In the event, coupling aminomethyl-borate salts to quinazolinone **4a** proceeded in low yield, and we attributed this to low solubility of the coupling partners. Gratifyingly, we found that employing the quinazolinone precursors derived from our C-H amidation chemistry satisfactorily addressed this problem. Specifically, aminoquinazoline **8** offered improved conversion and isolated yields of cross-coupled products. Subsequent hydrolysis allowed access to a range of amino-methyl functionalized quinazolinones **9a**-**c** (Scheme 6).

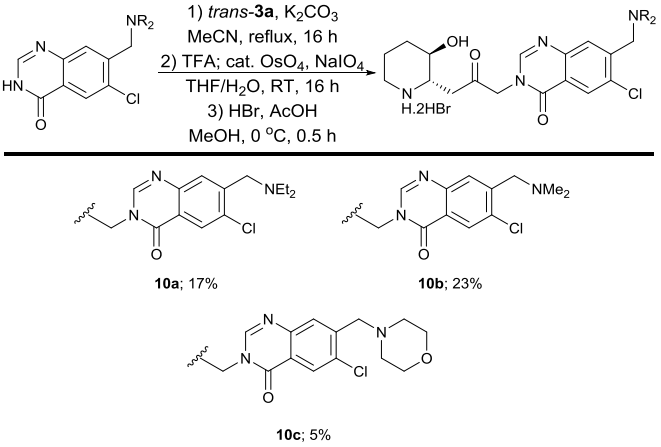
With the required quinazolinones in hand, the aminomethyl functionalized analogs were smoothly progressed through to the final compounds *trans*-**10a-c** as HBr salts (Scheme 7). Biological evaluation of the amino-methyl and halogenated analogs is ongoing and will be reported in due course.

Conclusions

We have developed a modular route to the febrifugines that delivers these compounds in a 5 step sequence. This synthesis route offers significant scope for analog preparation, as demonstrated by the synthesis of amino-methyl derivatives, and in this regard, we highlight the potential of a recent catalytic quinazolinone synthesis for the diversification of these compounds.



Scheme 6. Synthesis of amino-methyl functionalized quinazolinones.



Scheme 7. Synthesis of amino-methyl febrifugine analogs.

Experimental

Compounds 1b,[10] 4a,[3(a)] 4c,[3(a)] 4d,[3(b)] Et- and morpholineaminomethyl potassium trifluoroborates[16] were synthesized according to literature procedures.

Benzyl 2,3-dihydroxypiperidine-1-carboxylate.[10] 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 a few crystals of osmium tetroxide. The reaction was stirred at room temperature and monitored by TLC analysis. After completion, the mixture was cooled and quenched with an aqueous 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 $MgSO_4$. 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 compound (922 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.34 (5H, m), 5.75 (1H, d, *J* = 3.5 Hz), 5.13 (2H, s), 3.90 - 3.82 (1H, m), 3.64 - 3.56 (1H, m), 3.10 (1H, dt, *J* = 12.0, 2.0 Hz), 1.86 - 1.78 (1H, m), 1.74 - 1.66 (2H, m), 1.56 - 1.46 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 136.1, 128.5, 128.2, 127.9, 76.5, 69.0, 67.5, 36.1, 26.6, 23.5.

Benzyl 2-oxotetrahydro-[1,3]dioxolo[4,5-*b*]pyridine-4(3*aH*)-carboxylate (1a). To a solution of benzyl 2,3-dihydroxypiperidine-1-carboxylate (200 mg, 0.79 mmol) and pyridine (251 mg, 3.18 mmol) in dichloromethane (6 mL) at 0 °C was added triphosgene (259 mg, 0.87 mmol). The reaction was stirred at ice/water bath temperature for 6 h. After completion, diethyl ether (10 mL) was added and the crude mixture was washed with saturated aqueous $CuSO_4$. The organic extract was washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure to afford **1a** as a clear oil (141 mg, 64%); ^{1}H NMR (400 MHz, DMSO-d^6): δ 7.53 - 7.19 (5H, m), 6.64 (1H, d, *J* = 8.0 Hz), 5.19 (2H, s), 5.11 – 5.05 (1H, m), 3.66 – 3.55 (2H, m), 1.83 – 1.71 (3H, m), 1.68 – 1.57

(1H, m); ^{13}C NMR (101 MHz, DMSO-*d*^{6}): δ 154.8, 153.7, 136.4, 128.9, 128.6, 128.2, 128.0, 82.5, 73.3, 67.8, 23.9, 16.0; FTIR: ν_{max} 2956 (w), 1794 (s), 1704 (s), 695 (s); HRMS calculated for $C_{14}H_{15}NO_5$ (ES^+)(+Na^+): 300.0842. Found: 300.0846.

Benzyl 7-oxa-2-azabicyclo[4.1.0] heptane-2-carboxylate (1c). 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 $MgSO_4$ 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 **1c** as a clear oil (3.5 g, 83%) and as a 1 : 1 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (5H, s), 5.75 (0.5H, s), 5.60 (0.5H, s), 5.15 (2H, s), 4.17 - 4.11 (0.5H, m), 3.95 - 3.85 (2H, m), 3.65 - 3.55 (0.5H, m), 3.24 - 3.16 (1H, m), 3.12 - 3.04 (1H, m), 1.57 - 1.40 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 156.9, 136.2, 128.5, 128.2, 128.1, 128.0, 127.96, 127.90, 78.2, 69.0, 67.5, 67.0, 60.3, 38.5, 26.7, 25.0, 23.5, 21.0, 18.4, 14.2; FTIR: ν_{max} 3375 (w), 2947 (w), 1673 (s), 1255 (s), 987 (s); HRMS calculated for $C_{13}H_{15}NO_3$ (ES^+)(+H^+): 234.2613. Found: 234.2614.

Benzyl 2-(2-chloromethyl)allyl)-3-methylpiperidine-1-carboxylate (*trans*- and *cis*-3a). 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. Aqueous $NaHCO_3$ (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 *trans*-**3a** as a clear oil (1.5 g, 31%), and *cis*-**3a** as a clear oil (1.7 g, 35 %). *trans*-**3a** (1 : 1 mixture of rotamers): ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 7.42 - 7.30 (5H, m), 5.16 - 5.14 (1H, m), 5.08 - 4.98 (2H, m), 4.80 - 4.78 (1H, m), 4.35 - 3.95 (3H, m), 3.90 - 3.85 (1H, m), 3.65 - 3.55 (1H, m), 2.97 - 2.82 (1H, m), 2.35 - 2.25 (2H, m), 1.80 - 1.70 (2H, m), 1.60 - 1.55 (2H, m), 1.35 - 1.25 (1H, m); ^{13}C NMR (101 MHz, DMSO-*d*^{6}): δ 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; FTIR: ν_{max} 3444 (w), 2938 (w), 1670 (s), 1424 (s); HRMS calculated for $C_{17}H_{23}NO_3{}^{35}Cl_2$ (ES^+)(+H^+): 324.1366. Found: 324.1374. *cis*-**3a** (1 : 1 mixture of rotamers): ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 7.40 - 7.29 (5H, m), 5.12 - 4.99 (4H, m), 4.45 - 4.40 (2H, m), 4.30 - 4.25 (1H, m), 4.20 - 4.15 (2H, m), 4.05 - 3.95 (1H, m), 3.85 - 3.75 (1H, m), 3.65 - 3.55 (1H, m), 2.86 - 2.74 (2H, m), 1.66 - 1.62 (2H, m), 1.42 - 1.30 (1H, m); ^{13}C NMR (101 MHz, DMSO-*d*^{6}): δ 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; FTIR: ν_{max} 3444 (w), 2938 (w), 1670 (s), 1424 (s); HRMS calculated for $C_{17}H_{23}NO_3{}^{35}Cl_2$ (ES^+)(+H^+): 324.1366. Found: 324.1367.

Synthesis of 4-chloro-3-bromo-N-(2-hydroxyethyl)benzamide. To a stirred solution of 4-chloro-3-bromo benzoic acid (5.0 g, 21 mmol) in MeCN (35 mL) was added CDI (3.79 g, 23.4 mmol). The reaction mixture was allowed to stir for a period of 2 hours at room temperature before ethanol (2.45 g, 53.1 mmol) was added *via* syringe. The reaction was then stirred overnight at room temperature, before diluting with dichloromethane and transferring to a separating funnel. The organic phase was then subsequently washed with a saturated solution of $NaHCO_3$ (aq.) and deionised water. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the crude ester product. To a dried round bottomed flask was added the crude ester product (5.00 g, 18.8 mmol) and heated to 55 °C with stirring. Upon reaching the desired temperature ethanolamine (1.72 g, 28.2 mmol) was added slowly *via* syringe and the reaction was stirred for 3 h before cooling to room temperature, and stirring for a further 18 hours. The crude reaction mixture was then purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (1% MeOH to 20% MeOH) to afford the amide product as a colourless solid (3.37 g, 64%). M.p.: 166 – 167 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}); δ 8.63 (1H, t, *J* = 5.5 Hz), 8.23 (1H, d, *J* = 2.0 Hz), 7.86 (1H, dd, *J* = 8.5, 2.0 Hz), 7.73 (1H, d, *J* = 8.5 Hz), 4.74 (1H, t, *J* = 5.5 Hz), 3.55 – 3.47 (2H, m), 3.35 – 3.29 (2H, m – peak overlapped with residual H_2O); ^{13}C NMR (100.6 MHz, DMSO-*d*^{6}); δ 163.9, 135.9, 134.9, 132.4, 130.5, 128.1, 121.5, 59.5, 42.3 FTIR: ν_{max} (neat) 3289 (m), 1641 (m), 1550 (m), 1466 (m), 1328 (m), 1248 (m), 1057 (s), 1023 (m), 751 (m); HRMS calculated for $C_9H_{10}{}^{81}Br^{35}ClNO_2$ (ES^+)(+H^+): 279.9516. Found: 279.9554.

Synthesis of 2-(4-chloro-3-bromophenyl)-4,5-dihydrooxazole. To a dried round bottomed flask was added 4-chloro-3-bromo-N-(2-hydroxyethyl)benzamide (3.00 g, 10.8 mmol) and dry dichloromethane (18 mL). With stirring NEt_3 (2.07 g, 20.5 mmol) was then added, followed by DMAP (263 mg, 2.15 mmol) and *p*-TsCl (3.49 g, 18.3 mmol). The reaction mixture was allowed to stir at room temperature overnight, before being diluted with dichloromethane and water. The mixture was then transferred to a separating funnel and the layers partitioned. The aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude residue was dissolved in MeOH (22 mL) and NaOH pellets (1.29 g, 32.3 mmol) were added in one portion. The reaction mixture was stirred at room temperature for 2 h before removing the solvent *in vacuo*. The residue was dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane and ethyl acetate. The combined organic layers were dried

over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline product as a colourless solid (2.26 g, 81%). M.p.: 75 – 76 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.12 (1H, d, *J* = 2.0 Hz), 7.73 (1H, dd, *J* = 8.5, 2.0 Hz), 7.41 (1H, d, *J* = 8.5 Hz), 4.37 (2H, t, *J* = 9.5 Hz), 3.99 (2H, t, *J* = 9.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 162.9, 137.8, 133.6, 130.6, 128.3, 128.1, 122.8, 68.3, 55.4; FTIR: ν_{max} (neat) 2973 (w), 1650 (m), 1466 (m), 1372 (m), 1261 (m), 1238 (m), 1067 (s), 1016 (m); HRMS calculated for $C_9H_8{}^{81}Br^{35}ClNO$ (ES^+)($+H^+$): 261.9450. Found: 261.9451.

Synthesis of N-(4-bromo-5-chloro-2-(4,5-dihydrooxazol-2-yl)phenyl)-2,2,2-trifluoroacetamide. To a dried round bottomed flask equipped with a stirrer bar and reflux condenser was added 2-(4-chloro-3-bromophenyl)-4,5-dihydrooxazole (3.50 g, 13.4 mmol), $[RhCp^*Cl_2]_2$ (69 mg, 0.13 mmol, 1 mol %), $AgSbF_6$ (154 mg, 0.520 mmol, 4 mol %), $PhI(OAc)_2$ (5.41 g, 16.8 mmol) and trifluoroacetamide (1.27 g, 11.2 mmol). The system was evacuated and refilled with nitrogen (3 times), followed by the addition of dry dichloromethane *via* syringe (110 mL). The reaction mixture was stirred at reflux (40 – 45 °C) for 24 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) followed by dichloromethane to afford the aminated product as a colourless solid (2.29 g, 46%). M.p.: 109 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 13.63 (1H, s), 8.86 (1H, s), 8.11 (1H, s), 4.46 (2H, t, *J* = 9.5 Hz), 4.18 (2H, t, *J* = 9.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 155.9 (q, *J* = 38.5 Hz), 163.2, 139.0, 137.2, 133.9, 121.9, 117.5, 115.8 (q, *J* = 288.5 Hz), 114.3, 67.1, 54.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; FTIR: ν_{max}/ cm^{-1} (neat) 2990 (w), 1711 (m), 1607 (m), 1523 (m), 1261 (s), 1147 (s), 1073 (s); HRMS calculated for $C_{11}H_8{}^{81}Br^{35}ClF_3N_2O_2$ (ES^+)($+H^+$): 372.9382. Found: 372.9385.

Synthesis of 2-((6-bromo-7-chloroquinazolin-4-yl)amino)ethanol. *N*-(4-Bromo-5-chloro-2-(4,5-dihydrooxazol-2-yl)phenyl)-2,2,2-trifluoroacetamide (2.29 g, 6.16 mmol) was dissolved in ethanol (62 mL), NaOH pellets (4.93 g, 123 mmol) 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; 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 anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was then dissolved in ethanol (60 mL) and formamidine acetate (1.88 g, 18.1 mmol) 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 on silica gel eluting with dichloromethane and methanol (0 to 15% methanol) to afford the quinazoline product as a colourless solid (1.32 g, 73%). M.p.: 220 – 221 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}); δ 8.79 (1H, s), 8.54 (1H, app. d, *J* = 5.0 Hz), 8.47 (1H, s), 7.90 (1H, s), 4.82 (1H, t, *J* = 5.0 Hz), 3.65 – 3.53 (4H, m); ^{13}C NMR (100.6 MHz, DMSO-*d*^{6}); δ 158.5, 156.5, 149.0, 137.0, 128.4, 128.3, 117.8, 115.0, 58.9, 43.5; FTIR: ν_{max} (neat) 3285 (w), 2986 (w), 1684 (m), 1587 (s), 1543 (m), 1442 (m), 1412 (m), 1059 (s); HRMS calculated for $C_{10}H_{10}{}^{81}Br^{35}ClN_3O$ (ES^+)($+H^+$): 303.9668. Found: 303.9666.

Synthesis of 6-bromo-7-chloroquinazolin-4(3*H*)-one (4b). 2-((6-bromo-7-chloroquinazolin-4-yl)amino)ethanol (258 mg, 0.852 mmol) was suspended in 6 M HCl aq. (6.5 mL) in a round bottomed flask equipped with reflux condenser, and heated to 100 – 105 °C for a period of 2 hours. The reaction was then allowed to cool to room temperature, and further cooled to 0 °C with an ice/water bath. The reaction mixture was basified to pH 11 with aqueous NaOH solution (10% w/v) and allowed to stir for 15 minutes. The colourless precipitate was collected by vacuum filtration, washing with a little ice cold water. The precipitate was then dried further to afford the quinazolinone product as a colourless solid (202 mg, 91%). M.p.: > 250 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}); δ 8.35 (1H, s), 8.20 (1H, s), 7.94 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-*d*^{6}); δ 159.1, 148.5, 147.4, 138.9, 130.6, 128.5, 122.8, 119.4; FTIR: ν_{max}/ cm^{-1} (neat) 3043 (w), 3006 (w), 1721 (m), 1660 (s), 1610 (s), 1442 (s), 1254 (s), 899 (s); HRMS calculated for $C_8H_5{}^{81}Br^{35}ClN_2O$ (ES^+)($+H^+$): 260.9246. Found: 260.9252.

***General Procedure for the Synthesis of febrifugine analogs*.** Potassium carbonate (1.5 eq.) was added to a suspension of quinazolinone (1.0 eq.) 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 eq.) in MeCN (0.3 M) was added dropwise to the reaction mixture and the reaction was left to stir for 16 h. After completion, aqueous NH_4Cl was added and the product was extracted with ethyl acetate. The organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flash column chromatography eluting with CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding alkene intermediates, which were subjected to the subsequent step following ^{1}H NMR analysis (see SI). OsO_4 (few crystals) was added to a suspension of the alkene substrate (1.0 eq.) and $NaIO_4$ (2.0 eq.) in THF (0.1 M) and water (0.2 M), and the solution was left to stir for 16 h. After completion, a saturated aqueous solution of $Na_2S_2O_5$ was added, transferred to a separating funnel and 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 with CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding ketone.

Trans substrates: To the ketone substrate (1.0 eq.) in a round bottom flask was added methanol (0.2 M) and HBr (33 wt% in AcOH) (100 eq.) 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.

Cis substrates: To the ketone substrate (1.0 eq.) in a round bottom flask was added dichloromethane (0.2 M) and HBr (33 wt% in AcOH) (100 eq.) at 0 °C. The mixture was stirred for 30 mins and after completion, aqueous NaOH was added, transferred to a separating funnel and 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 a crude residue, which was purified by flash column chromatography eluting CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding products.

***trans*-7-Bromo-6-chloro-3-(3-(3-hydroxypiperidine-2-yl)-2-oxopropyl)quinazolin-4(3*H*)-one hydrobromide (*trans*-5a).** 7-Bromo-6-chloroquinazolin-4(3*H*)-one **(4a)** (50 mg, 0.19 mmol), K_2CO_3 (40 mg, 0.28 mmol) and *trans*-**3a** (62 mg, 0.92 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a yellow oil (98 mg, 93%). *trans*-Alkene intermediate (88 mg, 0.16 mmol) was subjected to the general conditions to afford *trans*-**5a** as a colorless solid (55 mg, 70%). M.p.: > 250 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 8.32 (1H, s), 8.22 (1H, s), 8.12 (1H, s), 5.11 (1H, d, *J* = 17.5 Hz), 5.02 (1H, d, *J* = 17.5 Hz), 3.70 - 3.60 (1H, m), 3.55 - 3.45 (2H, m), 3.40 (1H, d, *J* = 5.0 Hz), 3.05 (1H, dd, *J* = 15.0, 4.0 Hz), 3.00 (1H, dd, *J* = 15.0, 4.0 Hz), 2.15 - 2.00 (2H, m), 1.85 - 1.75 (1H, m), 1.65 - 1.55 (1H, m); ^{13}C NMR (101 MHz, MeOD-d^4) δ 202.2, 161.0, 150.5, 148.4, 134.6, 133.5, 129.5, 128.4, 123.2, 68.2, 58.1, 55.8, 44.9, 39.9, 31.5, 21.4; FTIR: ν_{max} 3290 (w), 2943 (w), 1715 (m), 1677 (s), 1598 (s), 1080 (s); HRMS calculated for $C_{16}H_{17}{}^{79}Br^{35}ClN_3O_3$ (ES^+)($+H^+$): 416.0193. Found: 416.0193.

***trans*-6-Bromo-7-chloro-3-(3-(3-hydroxypiperidine-2-yl)-2-oxopropyl)quinazolin-4(3*H*)-one hydrobromide (*trans*-5b).** 6-Bromo-7-chloroquinazolin-4(3*H*)-one **(4b)** (77 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol) and *trans*-**3a** (96 mg, 0.30 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a yellow oil (145 mg, 89%). *trans*-Alkene intermediate (102 mg, 0.186 mmol) was subjected to the general conditions to afford *trans*-ketone intermediate as a colorless oil (64 mg, 64%). *trans*-Ketone intermediate (60 mg, 0.11 mmol) was subjected to the general conditions to afford *trans*-**5b** as a colorless solid (27 mg, 50%). M.p.: 240 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.38 (1H, s), 8.29 (1H, s), 8.03 (1H, s), 5.57 (1H, d, J = 5.5 Hz), 5.12 (1H, d, J = 18.0 Hz), 5.06 (1H, d, J = 18.0 Hz), 3.56 – 3.42 (1H, m), 3.27 – 3.11 (3H, m), 2.90 (2H, dd, J = 17.5, 6.0 Hz), 1.98 – 1.88 (1H, m), 1.86 – 1.76 (1H, m), 1.70 – 1.54 (1H, m), 1.52 – 1.40 (1H, m); ^{13}C NMR (100.6 MHz, DMSO-d^6): δ 200.8, 158.5, 149.8, 147.9, 139.4, 130.8, 128.8, 121.5, 120.1, 66.8, 56.1, 54.4, 43.0, 30.5, 20.2 – one peak not resolved due to overlap with DMSO-d^6; FTIR: ν_{max}/ cm^{-1} (neat) 2924 (w), 1724 (w), 1673 (s), 1606 (s), 1442 (s), 1358 (s), 1090 (s), 1070 (s); HRMS calculated for $C_{16}H_{18}{}^{81}Br^{35}ClN_3O_3$ (ES^+)($+H^+$): 416.0193. Found: 416.0200.

***trans*-6-Chloro-3-(3-(3-hydroxypiperidin-2-yl)-2-oxopropyl)pyrido[3,4-d]pyrimidin-4(3*H*)-one dihydrobromide (*trans*-5c).** 6-Chloropyrido[3,4-d]pyrimidin-4(3*H*)-one **(4c)** (100 mg, 0.550 mmol), K_2CO_3 (114 mg, 0.826 mmol) and *trans*-**3a** (178 mg, 0.55 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a colourless oil (144 mg, 56%). *trans*-Alkene intermediate (140 mg, 0.298 mmol) was subjected to the general conditions to afford *trans*-ketone intermediate as a colorless oil (43 mg, 31%). *trans*-Ketone intermediate (40 mg, 0.085 mmol) was subjected to the general conditions to afford *trans*-**5c** as a colorless amorphous solid (15 mg, 36%). ^{1}H NMR (400 MHz, DMSO-d^6): δ 9.00 (1H, s), 8.35 (1H, s), 8.04 (1H, s), 5.57 (1H, d, J = 5.5 Hz), 5.15 (1H, d, J = 18.0 Hz), 5.09 (1H, d, J = 18.0 Hz), 3.55 – 3.42 (1H, m), 3.30 – 3.11 (2H, m), 2.97 – 2.81 (2H, m), 1.98 – 1.86 (1H, m), 1.89 – 1.75 (1H, m), 1.69 – 1.54 (1H, m), 1.52 – 1.37 (1H, m); ^{13}C NMR (100.6 MHz, DMSO-d^6): δ 200.6, 158.2, 151.3, 150.1, 146.9, 141.9, 129.1, 118.6, 66.8, 56.1, 54.6, 43.0, 30.5, 20.2 – one peak not resolved due to overlap with DMSO-d^6; FTIR: ν_{max} (neat) 2936 (w), 1738 (m), 1694 (s), 1600 (s), 1436 (s), 1372 (s), 1288 (m), 1073 (s); HRMS calculated for $C_{15}H_{18}{}^{35}ClN_4O_3$ (ES^+)($+H^+$): 337.1062. Found: 337.1063.

***trans*-3-(3-(3-Hydroxypiperidin-2-yl)-2-oxopropyl)-6,7-bis(2-methoxyethoxy)quinazolin-4(3*H*)-one hydrobromide (*trans*-5d).** 6,7-Bis(2-methoxyethoxy) quinazolin-4(3*H*)-one **(4d)** (20 mg, 0.06 mmol), K_2CO_3 (14 mg, 0.10 mmol) and *trans*-**3a** (22 mg, 0.06 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a colourless oil (28 mg, 71%). *trans*-Alkene intermediate (28 mg, 0.04 mmol) was subjected to the general conditions to afford *trans*-**5d** as a colorless solid (20 mg, 80%). M.p.: > 250 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 9.20 (1H, s), 7.70 (1H, s), 7.27 (1H, s), 5.33 (1H, d, *J* = 18.0 Hz), 5.26 (1H, d, *J* = 18.0 Hz), 4.40 - 4.30 (4H, m), 3.90 - 3.80 (4H, m), 3.70 - 3.60 (1H, m), 3.52 - 3.45 (2H, m), 3.43 (6H, s), 3.41 (1H, d, *J* = 5.0 Hz), 3.08 (1H, dd, *J* = 15.0, 4.0 Hz), 3.00 (1H, dd, *J* = 15.0, 4.0 Hz), 2.15 - 2.00 (2H, m), 1.85 - 1.75 (1H, m), 1.67 - 1.57 (1H, m); ^{13}C NMR (101 MHz, MeOD-d^4): δ 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; FTIR: ν_{max} 3346 (w), 2926 (w), 1659 (s), 1705 (s), 1604 (s), 1382 (s), 987 (s); HRMS calculated for $C_{22}H_{31}N_3O_7$ (ES^+)($+H^+$): 450.2235. Found: 450.2237.

***trans*-6-Bromo-3-(3-(3-hydroxypiperidin-2-yl)-2-oxopropyl)quinazolin-4(3*H*)-one hydrobromide (*trans*-5e).** 6-Bromoquinazolin-4(3*H*)-one **(4e)** (139 mg, 0.618 mmol), K_2CO_3 (128 mg, 0.928 mmol) and *trans*-**3a** (200 mg, 0.618 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a colourless oil (229 mg, 72%). *trans*-Alkene intermediate (229 mg, 0.447 mmol) was subjected to the general conditions to afford *trans*-ketone intermediate as a colorless oil (140 mg, 61%). *trans*-Ketone intermediate (100 mg, 0.085 mmol) was subjected to the general conditions to afford *trans*-**5e** as a colorless solid (30 mg, 33%). M.p.: 221 - 222 °C; ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.69 (2H, s), 8.28 (1H, s), 8.23 (1H, d, J = 2.5 Hz), 8.03 (1H, dd, J

= 8.5, 2.5 Hz), 7.73 – 7.66 (1H, m), 5.13 (1H, d, J = 18.0 Hz), 5.08 (1H, d, J = 18.0 Hz), 3.56 – 3.47 (1H, m), 3.39 – 3.29 (1H, m), 3.24 (1H, dd, J = 17.5, 5.5 Hz), 3.17 (1H, d, J = 12.5 Hz), 2.92 (2H, dd, J = 17.5, 6.0 Hz), 1.98 – 1.90 (1H, m), 1.87 – 1.77 (1H, m), 1.70 – 1.58 (1H, m), 1.53 – 1.40 (1H, m); ^{13}C NMR (101 MHz, DMSO-d^6): δ 200.9, 158.9, 148.5, 146.9, 137.5, 129.8, 128.1, 122.9, 119.8, 66.7, 56.1, 54.4, 43.0, 39.4, 30.5, 20.1; FTIR: ν_{max} 3088 (w), 2671 (w), 1713 (m), 1631 (w), 1522 (m), 1099 (m); HRMS calculated for $C_{16}H_{19}{}^{79}BrN_3O_3$ (ES+)(+H+): 380.0604. Found: 380.0613.

3-(3-(3-Hydroxypiperidin-2-yl)-2-oxopropyl)quinazolin-4(3*H*)-one hydrobromide (*trans*-5f). Quinazolin-4(3*H*)-one **(4f)** (50 mg, 0.03 mmol), K_2CO_3 (70 mg, 0.05 mmol) and *trans*-**3a** (110 mg, 0.03 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a yellow oil (113 mg, 77%). *trans*-Alkene intermediate (113 mg, 0.26 mmol) was subjected to the general conditions to afford *trans*-**5f** as a colorless solid (88 mg, 89%). M.p.: > 250 °C; ^{1}H NMR (400 MHz, MeOD-*d*^{4}): δ 8.90 (1H, s), 8.40 - 8.30 (1H, m), 8.10 - 7.95 (1H, m), 7.85 - 7.70 (2H, m), 5.30 (1H, d, *J* = 17.5 Hz), 5.22 (1H, d, *J* = 17.5 Hz), 3.75 - 3.65 (1H, m), 3.55 - 3.50 (2H, m), 3.45 (1H, d, *J* = 4.5 Hz), 3.05 (1H, dd, *J* = 15.0, 4.0 Hz), 3.01 (1H, dd, *J* = 15.0, 4.0 Hz), 2.16 - 2.04 (2H, m), 1.88 - 1.76 (1H, m), 1.68 - 1.60 (1H, m); ^{13}C NMR (101 MHz, MeOD-*d*^{4}): δ 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; FTIR: ν_{max} 3329 (w), 2924 (w), 1704 (s), 1660 (s), 1507 (s), 1028 (s); HRMS calculated for $C_{16}H_{19}N_3O_3$ (ES^+)($+H^+$): 302.3404. Found: 302.3403.

***cis*-7-Bromo-6-chloro-3-((6-hydroxyoctahydro-1H-cyclopenta[b]pyridine-6-yl)methyl)quinazolin-4(3*H*)-one (*cis*-6) and 7-bromo-6-chloro-3-(4-(3,4-dihydro-2H-pyrrol-5-yl)-2-oxobutyl)quinazolin-4(3*H*)-one (7).** 7-Bromo-6-chloroquinazolin-4(3*H*)-one **(4a)** (50 mg, 0.19 mmol), K_2CO_3 (40 mg, 0.28 mmol) and *cis*-**3a** (62 mg, 0.92 mmol) were subjected to the general conditions for 16 h to afford the *cis*-alkene intermediate as a colourless oil (88 mg, 85%). *cis*-Alkene intermediate (88 mg, 0.16 mmol) was subjected to the general conditions to afford *cis*-**6** as a colorless solid (10 mg, 16%) and **7** as a colorless oil (25 mg, 40%). *cis*-**6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (1H, s), 8.30 (1H, s), 8.03 (1H, s), 4.39 (1H, d, *J* = 14.0 Hz), 4.19 (1H, d, *J* = 14.0 Hz), 3.94 - 3.91 (1H, m), 3.34 - 3.32 (1H, m), 3.04 - 3.05 (2H, m), 2.56 - 2.53 (1H, m), 2.20 - 2.05 (1H, m), 1.90 - 1.80 (2H, m), 1.65 - 1.55 (2H, m), 1.50 - 1.45 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.2, 149.5, 147.2, 133.4, 132.8, 129.5, 128.0, 122.1, 105.3, 78.0, 55.8, 50.3, 44.6, 43.6, 26.9, 20.2; FTIR: ν_{max} 3294 (w), 2944 (w), 1672 (s), 1609 (s), 1473 (s); HRMS calculated for $C_{16}H_{17}{}^{79}Br^{35}ClN_3O_3$ (ES^+)($+H^+$): 416.1504. Found: 416.1495. **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (1H, s), 8.02 (1H, s), 7.87 (1H, s), 4.97 (2H, s), 3.87 – 3.69 (2H, m), 2.88 (2H, t, J = 6.5 Hz), 2.67 (2H, t, J = 6.5 Hz), 2.46 (2H, t, J = 8.0 Hz), 2.01 – 1.80 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 176.7, 159.7, 148.0, 147.3, 133.7, 132.8, 129.6, 127.8, 122.1, 60.6, 54.7, 38.0, 35.8, 27.9, 22.9; FTIR: ν_{max} 2918 (w), 1722 (w), 1676 (s), 1608 (s), 1447 (s), 1354 (s); HRMS calculated for $C_{16}H_{16}{}^{79}Br^{37}ClN_3O_2$ (ES^+)($+H^+$): 398.0087. Found: 398.0085.

Potassium N,N-dimethyltrifluoroboratomethylamine. Potassium bromomethyltrifluoroborate (1.00 g, 4.98 mmol) was added to neat dimethylamine in THF (20 mL) at RT, heated at 80 °C for 30 minutes and then concentrated in vacuo. The product was dissolved in a solution of acetone (150 mL) and K_2CO_3 (689 mg, 4.98 mmol) and stirred for 30 minutes. The insoluble salts were filtered off, and the filtrate was concentrated in vacuo. The crude solid was dissolved in a minimal amount of hot acetone, and diethyl ether was added dropwise leading to precipitation of the product. The product was then filtered and collected and dried under vacuum. The product was afforded as a colourless solid (320 mg, 39%). M.p.: 65 – 66 °C; ^{1}H NMR (400 MHz, DMSO-d^6): δ 2.63 (6H, s), 1.98 – 1.88 (2H, m); ^{13}C NMR (100.6 MHz, DMSO-d^6): δ 52.0 (br), 45.2; ^{19}F NMR (376.5 MHz, DMSO-d^6): δ – 138.5; ^{11}B (128.4 MHz, DMSO-d^6): δ 2.5; FTIR: ν_{max} (neat) 3215 (w), 1483 (w), 1463 (w), 1256 (m), 1023 (s), 952 (s); HRMS calculated for $C_3H_8{}^{11}BF_3N$ (M^-): 126.0707. Found: 126.0713.

General procedure for synthesis of amino methyl quinazolinones (9a – c). Step 1: To a round bottomed flask equipped with a reflux condenser was added quinazoline (1.0 eq.), aminomethyl-BF_3K (1.1 eq.), Cs_2CO_3 (3.0 eq.) and PdXPhosG2 (10 mol %). The reaction vessel was evacuated and refilled with N_2 (3 cycles). The degassed solvent mixture THF/H_2O (10:1) was then added *via* syringe, and the reaction was heated at reflux for 16 hours. The reaction was then cooled to room temperature, and transferred to a larger round bottomed flask, rinsing with dichloromethane and methanol. The solvent was then removed *in vacuo* to afford the crude residue. The crude reaction mixture was purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0 to 20% methanol) to afford the corresponding products. Step 2: The purified Suzuki product was then suspended in 6 M HCl aq. (100 eq.) in a round bottomed flask equipped with reflux condenser, and heated to 100 – 105 °C for a period of 2 hours. The reaction was then allowed to cool to room temperature, and further cooled to 0 °C with an ice/water bath. The reaction mixture was basified to pH 11 with aqueous NaOH solution (10% w/v) and allowed to stir for 15 minutes. The reaction mixture was then concentrated to remove H_2O. The reaction mixture was then dry loaded onto silica and purified by flash column chromatography, eluting with dichloromethane and 10% methanol to afford the quinazolinone product.

6-Chloro-7-((diethylamino)methyl)quinazoline-4(3*H*)-one (9a). Step 1: Following the general procedure, using 2-((7-bromo-6-chloroquinazolin-4-yl)amino)ethanol (300 mg, 0.992 mmol), potassium *N*,*N*-diethyltrifluoroboratomethylamine (210 mg, 1.09 mmol), Cs_2CO_3 (970 mg, 2.97 mmol), PdXPhosG2 (78 mg, 10 mol %, 0.099 mmol) and THF/H_2O (10:1, 4 mL) the product was afforded as a cream solid (166 mg, 54%). M.p.: 62 – 63 °C; ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.44 (1H, s), 8.43 (1H,

s), 8.39 – 8.26 (1H, m), 7.80 (1H, s), 4.88 – 4.76 (1H, m), 3.71 (2H, s), 3.65 – 3.52 (4H, m), 2.56 (4H, q, J = 7.0 Hz), 1.01 (6H, t, J = 7.0 Hz); ^{13}C NMR (100.6 MHz, DMSO-d^6): δ 158.7, 155.5, 147.9, 142.3, 130.0, 128.6, 123.0, 114.6, 59.1, 54.5, 46.8, 43.4, 11.8; FTIR: v_{max} (neat) 3302 (m), 2973 (w), 1587 (m), 1547 (m), 1416 (m), 1278 (m), 1067 (m), 748 (s); HRMS calculated for $C_{15}H_{22}{}^{35}ClN_4O$ (ES^+)($+H^+$): 309.1477. Found: 309.1484. Step 2: Following the general procedure, using 2-((6-chloro-7-((diethylamino)methyl)quinazoline-4-yl)amino)ethanol (100 mg, 0.323 mmol) and 6 M HCl aq. (2.5 mL) the product was afforded as a beige solid (60 mg, 70%). M.p.: 139 – 140 °C; ^{1}H NMR (400 MHz, MeOD-*d*^{4}): δ 8.10 (1H, s), 8.08 (1H, s), 7.91 (1H, s), 3.80 (2H, s), 2.65 (4H, q, *J* = 7.0 Hz), 1.10 (6H, t, *J* = 7.0 Hz); ^{13}C NMR (100.6 MHz, MeOD-*d*^{4}): δ 162.1, 148.4, 146.9, 146.1, 133.8, 129.7, 127.3, 123.5, 56.0, 48.6, 12.1; FTIR: v_{max} (neat) 2970 (w), 1698 (s), 1613 (s) 1432 (m), 1379 (m), 1258 (s), 922 (s), 751 (s); HRMS calculated for $C_{13}H_{17}{}^{35}ClN_3O$ (ES^+)($+H^+$): 266.1055. Found: 266.1055.

6-Chloro-7-((dimethylamino)methyl)quinazoline-4(3*H*)-one (9b). Step 1: Following the general procedure, using 2-((7-bromo-6-chloroquinazolin-4-yl)amino)ethanol (200 mg, 0.661 mmol), potassium N,N-dimethyltrifluoroboratomethylamine (120 mg, 0.727 mmol), Cs_2CO_3 (645 mg, 1.98 mmol), PdXPhosG2 (52 mg, 10 mol %, 0.066 mmol) and THF/H_2O (10:1, 2.6 mL) the product was afforded as a yellow amorphous solid (126 mg, 68%). ^{1}H NMR (400 MHz, MeOD-d^4): δ 8.44 (1H, s), 8.27 (1H, s), 7.79 (1H, s), 3.82 (2H, t, J = 5.5 Hz), 3.79 – 3.68 (4H, m), 2.37 (6H, s); ^{13}C NMR (100.6 MHz, MeOD-d^4): δ 160.8, 156.6, 148.3, 142.3, 133.3, 130.1, 124.3, 116.5, 61.5, 61.2, 45.6, 44.8; FTIR: v_{max} (neat) 3436 (w), 2986 (w), 1590 (w), 1274 (m), 1261 (m); HRMS calculated for $C_{13}H_{18}{}^{35}ClN_4O$ (ES^+)($+H^+$): 281.1164. Found: 281.1162. Step 2: Following the general procedure, using 2-((6-chloro-7-((dimethylamino)methyl)quinazoline-4-yl)amino)ethanol (121 mg, 0.431 mmol) and 6 M HCl aq. (3.4 mL) the product was afforded as a colourless solid (53 mg, 52%). M.p.: 161 – 162 °C; ^{1}H NMR (400 MHz, MeOD-*d*^{4}): δ 8.15 (1H, s), 8.08 (1H, s), 7.80 (1H, s), 3.70 (2H, s), 2.34 (6H, s); ^{13}C NMR (100.6 MHz, MeOD-*d*^{4}): δ 162.1, 148.5, 147.0, 144.3, 134.3, 130.4, 127.5, 123.9, 61.4, 45.7; FTIR: v_{max} (neat) 2973 (w), 1691 (m), 1614 (m), 1258 (m), 902 (m), 764 (s); HRMS calculated for $C_{11}H_{13}{}^{35}ClN_3O$ (ES^+)($+H^+$): 238.0742. Found: 238.0750.

6-Chloro-7-((morpholinomethyl)methyl)quinazoline-4(3*H*)-one (9c). Step 1: Following the general procedure, using 2-((7-bromo-6-chloroquinazolin-4-yl)amino)ethanol (200 mg, 0.661 mmol), potassium 4-trifluoroboratomethyl-morpholine (140 mg, 0.727 mmol), Cs_2CO_3 (645 mg, 1.98 mmol), PdXPhosG2 (52 mg, 10 mol %, 0.066 mmol) and THF/H_2O (10:1, 2.6 mL) the product was afforded as a colourless solid (161 mg, 76%). M.p.: 76 – 77 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 8.41 (1H, s), 8.20 (1H, s), 7.83 (1H, s), 3.82 (2H, t, J = 5.5 Hz), 3.77 – 3.69 (8H, m), 2.62 – 2.54 (4H, m); ^{13}C NMR (100.6 MHz, MeOD-d^4): δ 160.8, 156.4, 148.3, 142.5, 133.1, 129.2, 124.1, 116.2, 68.0, 61.2, 60.7, 54.8, 44.8; FTIR: v_{max} (neat) 3319 (m), 3120 (m), 2926 (m), 2832 (m), 1587 (s), 1543 (s), 1429 (s), 1409 (s), 1332 (s), 1117 (s), 1060 (s), 862 (s); HRMS calculated for $C_{15}H_{20}{}^{35}ClN_4O_2$ (ES^+)($+H^+$): 323.1269. Found: 323.1276. Step 2: Following the general procedure, using 2-((6-chloro-7-(morpholinomethyl)quinazoline-4-yl)amino)ethanol (128 mg, 0.397 mmol) and 6 M HCl aq. (3.0 mL) the product was afforded as a colourless solid (63 mg, 57%).M.p.: 187 – 188 °C; ^{1}H NMR (400 MHz, DMSO-d^6): δ 12.37 (1H, s), 8.11 (1H, s), 8.05 (1H, s), 7.78 (1H, s), 3.67 (2H, s), 3.64 – 3.58 (4H, m), 2.49 – 2.46 (4H, m); ^{13}C NMR (100.6 MHz, DMSO-d^6): δ 159.6, 147.4, 146.0, 142.1, 131.4, 128.9, 125.8, 122.5, 66.2, 59.0, 53.3; FTIR: v_{max} (neat) 3020 (m), 2963 (m), 1698 (s), 1674 (s), 1607 (s), 1426 (m), 1258 (m), 1114 (s), 865 (m); HRMS calculated for $C_{13}H_{15}{}^{35}ClN_3O_2$ (ES^+)($+H^+$): 280.0847. Found: 280.0851.

General Procedure for the Synthesis of aminomethyl halofuginone analogs (10a-c). Potassium carbonate (1.5 eq.) was added to a suspension of quinazolinone (1.0 eq.) 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 eq.) in MeCN (0.3 M) was added dropwise to the reaction mixture and the reaction was left to stir for 16 h. After completion, aqueous NH_4Cl was added and the product was extracted with ethyl acetate. The organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude product. The crude residue was purified via flash column chromatography eluting with CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding alkene intermediates, which were subjected to the subsequent step following ^{1}H NMR analysis (see SI). Alkene substrate (1.0 eq.) and TFA (1.1 eq.) in THF (0.1 M) and water (0.2 M) were stirred for 30 minutes prior to the addition of OsO_4 (few crystals) and $NaIO_4$ (2.0 eq.). The solution was left to stir at RT for 16 h. After completion, a saturated aqueous solution of $Na_2S_2O_5$ was added, transferred to a separating funnel and 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 with CH_2Cl_2 : MeOH (8 : 2) to afford the corresponding ketone. To the ketone substrate (1.0 eq.) in a round bottom flask was added methanol (0.2 M) and HBr (33 wt% in AcOH) (100 eq.) 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.

***trans*-6-Chloro-7-((diethylamino)methyl)-3-(3-(3-hydroxypiperidin-2-yl)-2-oxopropyl)quinazoline-4(3*H*)-one dihydrobromide (*trans*-10a).** 6-Chloro-7-((diethylamino)methyl)quinazoline-4(3*H*)-one **(9a)** (55 mg, 0.21 mmol), K_2CO_3 (43 mg, 0.31 mmol) and *trans*-**3a** (69 mg, 0.21 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a colorless oil (97 mg, 84%). *trans*-Alkene intermediate (111 mg, 0.200 mmol) was subjected to the general conditions to afford *trans*-ketone intermediate as a colorless oil (65 mg, 58%). *trans*-Ketone intermediate (49 mg, 0.088 mmol) was subjected to the

general conditions to afford *trans*-**10a** as a colorless solid (18 mg, 35%). M.p.: 178 – 179 °C; ^{1}H NMR (400 MHz, DMSO-d^{6}): δ 8.32 (1H, s), 8.22 (1H, s), 8.19 (1H, s), 5.16 (1H, d, J = 18.0 Hz), 5.11 (1H, d, J = 18.0 Hz), 4.62 (2H, d, J = 5.5 Hz), 3.56 – 3.31 (peak not fully resolved due to overlap with residual H_2O), 3.29 – 3.13 (6H, m), 2.92 (2H, dd, J = 17.5 Hz, 6.0 Hz), 1.97 – 1.88 (1H, m), 1.87 – 1.78 (1H, m), 1.70 – 1.56 (1H, m), 1.50 – 1.39 (1H, m), 1.29 (6H, t, J = 7.0 Hz); ^{13}C NMR (100.6 MHz, DMSO-d^{6}): δ 201.1, 159.1, 149.7, 147.0, 135.3, 133.2, 133.0, 127.2, 123.7, 67.4, 56.6, 55.0, 52.6, 47.5, 43.4, 31.0, 20.6, 9.0 – one peak not resolved due to overlap with DMSO-d^{6}; FTIR: ν_{max} (neat) 3387 (s), 2943 (m), 1733 (s), 1677 (s), 1605 (s), 1472 (s), 1397 (s), 1363 (s), 1080 (m); HRMS calculated for $C_{21}H_{30}{}^{35}ClN_4O_3$ (ES^+)($+H^+$): 421.2001. Found: 421.2009.

***trans*-6-Chloro-7-((dimethylamino)methyl)-3-(3-(3-hydroxypiperidin-2-yl)-2-oxopropyl)quinazoline-4(3*H*)-one dihydrobromide (*trans*-10b).** 6-Chloro-7-((dimethylamino)methyl)quinazoline-4(3*H*)-one **(9b)** (51 mg, 0.21 mmol), K_2CO_3 (43 mg, 0.31 mmol) and *trans*-**3a** (69 mg, 0.21 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a colorless oil (83 mg, 74%). *trans*-Alkene intermediate (81 mg, 0.15 mmol) was subjected to the general conditions to afford *trans*-ketone intermediate as a colorless oil (59 mg, 73%). *trans*-Ketone intermediate (54 mg, 0.10 mmol) was subjected to the general conditions to afford *trans*-**10b** as a pale orange solid (24 mg, 43%). M.p.: 221 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d^{6}): δ 8.33 (1H, s), 8.21 (1H, s), 8.18 (1H, s), 5.16 (1H, d, J = 18.5 Hz), 5.11 (1H, d, J = 18.5 Hz), 4.64 (2H, app s), 3.58 – 3.49 (1H, m), 3.25 (1H, d, J = 6.0 Hz), 3.47 – 3.31 (peak not fully resolved due to overlap with residual H_2O), 3.22 – 3.13 (2H, m), 2.98 – 2.84 (8H, m), 1.97 – 1.90 (1H, m), 1.87 – 1.78 (1H, m), 1.71 – 1.59 (1H, m), 1.52 – 1.40 (1H, m); ^{13}C NMR (100.6 MHz, DMSO-d^{6}): δ 200.6, 158.7, 149.2, 146.6, 134.8, 132.6, 132.4, 126.7, 123.2, 66.9, 56.3, 56.2, 54.5, 43.0, 42.6, 30.5, 20.2 – one peak not resolved due to overlap with DMSO-d^{6}; FTIR: ν_{max} (neat) 3299 (w), 3011 (w), 2924 (w), 1720 (m), 1678 (s), 1610 (m), 1472 (m), 1325 (m), 1278 (m), 1093 (m); HRMS calculated for $C_{19}H_{26}{}^{35}ClN_4O_3$ (ES^+)($+H^+$): 393.1688. Found: 393.1699.

***trans*-6-Chloro-3-(3-(3-hydroxypiperidin-2-yl)-2-oxopropyl)-7-(morpholinomethyl)quinazoline-4-(3*H*)-one dihydrobromide (*trans*-10c).** 6-Chloro-7-((morpholinomethyl)methyl)quinazoline-4(3*H*)-one **(9c)** (50 mg, 0.18 mmol), K_2CO_3 (25 mg, 0.27 mmol) and *trans*-**3a** (58 mg, 0.18 mmol) were subjected to the general conditions for 16 h to afford the *trans*-alkene intermediate as a colorless oil (70 mg, 69%). *trans*-Alkene intermediate (76 mg, 0.13 mmol) was subjected to the general conditions to afford *trans*-ketone intermediate as a colorless oil (52 mg, 68%). *trans*-Ketone intermediate (47 mg, 0.082 mmol) was subjected to the general conditions to afford *trans*-**10c** as a pale orange solid (5 mg, 10%). M.p.: 58 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d^{6}): δ 8.30 (1H, s), 8.20 (2H, br), 5.14 (1H, d, J = 18.0 Hz), 5.09 (1H, d, J = 18.0 Hz), 4.68 (2H, app s), 3.96 (2H, app s), 3.72 (2H, app s), 3.56 – 3.26 (peaks not fully resolved due to overlap with residual H_2O), 3.27 – 3.09 (3H, m), 2.90 (2H, dd, J = 17.5, 6.0 Hz), 1.98 – 1.88 (1H, m), 1.88 – 1.76 (1H, m), 1.70 – 1.53 (1H, m), 1.54 – 1.37 (1H, m); ^{13}C NMR (100.6 MHz, DMSO-d^{6}): δ 200.6, 158.7, 149.2, 146.5, 133.8, 133.2, 132.8, 126.6, 123.3, 66.9, 63.2, 56.2, 55.9, 54.5, 51.5, 43.0, 30.6, 20.2 – one peak not resolved due to overlap with DMSO-d^{6}; FTIR: ν_{max} (neat) 3011 (w), 2984 (w), 1677 (m), 1610 (m), 1278 (s), 1258 (s); HRMS calculated for $C_{21}H_{28}{}^{35}ClN_4O_4$ (ES^+)($+H^+$): 435.1794. Found: 435.1807.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge GlaxoSmithKline and the EPSRC for financial support.

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