Structure-activity relationship studies of a novel class of transmission blocking antimalarials targeting male gametes.

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ABSTRACT

Malaria is still a leading cause of mortality among children in the developing world, and despite the immense progress made in reducing the global burden, further efforts are needed if eradication is to be achieved. In this context, targeting transmission is widely recognized as a necessary intervention towards that goal. After carrying out a screen to discover new transmission-blocking agents, herein we report our medicinal chemistry efforts to study the potential of the most robust hit, DDD01035881, as a male-gamete targeted compound. We reveal key structural features for the activity of this series and identify analogues with greater potency and improved metabolic

stability. We believe this study lays the groundwork for further development of this series as a transmission blocking agent.

INTRODUCTION

Malaria is one of the leading causes of infant mortality in the developing world, with nearly half a million children dying each year. It is caused by a eukaryotic protozoan parasite from the genus *Plasmodium*, of which *P. falciparum* is the most lethal. The parasite is transmitted to humans by the bite of a female *Anopheles* mosquito.[1] Upon transmission, parasites invade hepatocytes and replicate, eventually being released into the bloodstream. The released parasites then invade erythrocytes to replicate asexually through a 48 h cycle during which all symptoms of the disease arise. A small percentage (0.2-1%) of parasites commit to sexual development, likely sequestered in the bone marrow, where they further develop through five morphological stages (Figure 1).[2,3] Mature, stage V, male and female gametocytes are then released into the blood stream where they remain relatively dormant, until being taken up by a mosquito during a subsequent blood meal, instigating host to vector transmission. Following feeding, gametocytes in the blood bolus become activated in the mosquito midgut, with male forms developing through a rapid 15-20-minute process of DNA replication and endomitosis to form 8 flagellated male gametes (a process termed exflagellation). Females in parallel round up and emerge from the infected red blood cell membrane. Fusion between gametes occurs within 24 hours, generating a motile zygote (called an ookinete), which traverses the midgut lining to eventually form an oocyst on the midgut wall. The oocyst goes through rounds of meiosis generating haploid parasite invasive forms, called sporozoites, which migrate to the mosquito salivary glands, ready to infect the next human, and therefore are responsible for the vector to host transmission of the disease.[4]

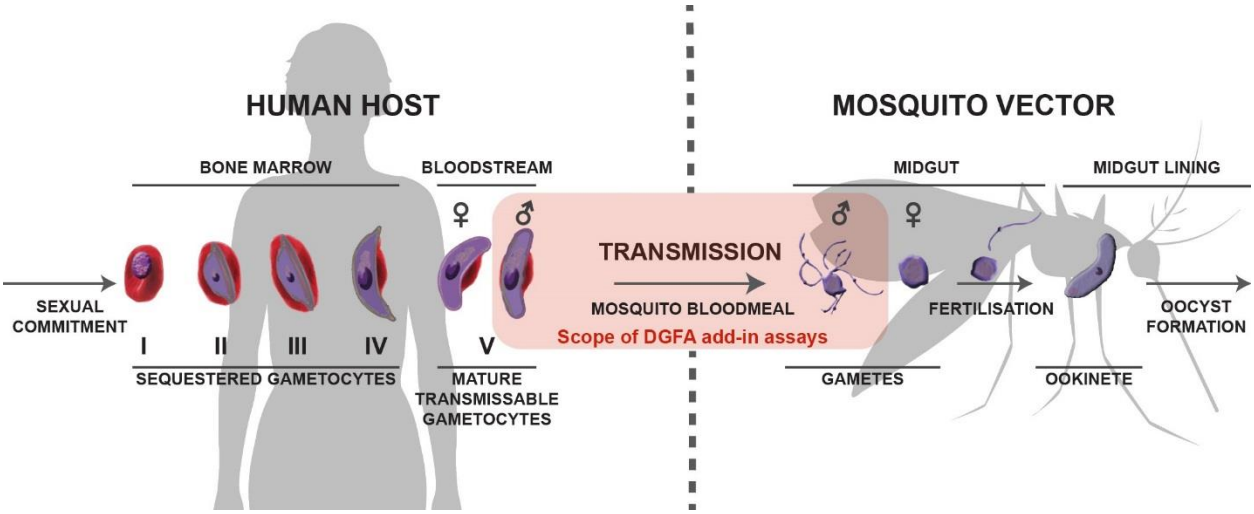


Figure 1. Host to vector transmission of *Plasmodium*. Following the commitment to sexual differentiation, gametocytes mature over five distinct morphological stages (I-V), maintaining quiescence from stages I-IV. Upon reaching maturation, stage V gametocytes withdraw from sequestration, entering the human bloodstream ready for transmission. In the event of a mosquito blood meal, male and female gametocytes rapidly transform into either 8 flagellated male microgametes or a single female macrogamete in the mosquito midgut. The fertilisation of haploid male and female gametes commences the onwards progression of the parasite lifecycle. Zygotes (ookinetes) traverse the mosquito midgut lining, leading to the eventual formation and migration of sporozoites to the salivary glands. The *in vitro* DGFA add-in (pink box) measures male gametocyte viability as the rate of exflagellation, or male gamete formation.

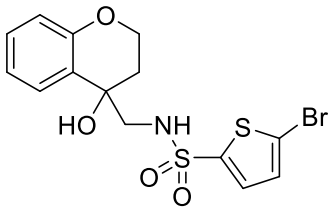
Immense progress has been made from 2000 to 2015 in the reduction of the global malaria burden,[5] thanks to the implementation of artemisinin combination therapies to reduce parasite numbers, together with the use of insecticide treated bed nets (ITNs) and indoor residual spraying (IRS) targeting the transmission of disease.[6] However, the emergence of resistance (both to insecticides and frontline chemotherapeutics, including artemisinin and related compounds) threatens the gains made.[7,8] If further progress is to be achieved towards eventual eradication of malaria, new drugs with new modes of action, including those able to stop disease transmission, will be needed.[9,10] Transmission is a particularly attractive target for chemotherapeutic intervention since it represents a key parasite population bottleneck, compared with asexual stages, with only tens of sexual stage parasites responsible for transmission.[11] Due to the low numbers of sexual stage parasites at a given time, and the fact that they are non-replicating stages, the

development of resistance to transmission-blocking drugs is predicted to be less likely. Additionally, the blockade of transmission provides a means to limit the spread of the expanding artemisinin drug-resistant strains.[10]

Over the last decade a large amount of research has been devoted to the development of biochemical assays for the identification of compounds that target parasite transmission.[12] While these efforts have provided new assays amenable to high-throughput screening (HTS), most of them only assess gametocyte viability; in contrast to the standard membrane feeding assay (SMFA),[13] which evaluates the effectiveness of potential transmission-blocking drugs *in vivo* by studying changes in the numbers of oocysts in the mosquito midgut. Despite being considered the gold standard, and efforts to increase its throughput,[14] the SMFA remains a costly and low-throughput method, making it unsuitable for large scale compound identification campaigns. To address this challenge, a dual gamete formation assay (DGFA)[15] was recently developed, which is amenable to HTS, emulating the conditions of the mosquito midgut in microtiter plate format in order to assess gametocyte development into gametes at scale. The DGFA has a sex-specific read-out that allows for the identification of compounds with dual asexual-sexual, non-differentiating sexual and sex-specific activity, enabling identification of compounds that target aspects of biology unique to male and/or female gametocytes and gametes.[16] Recently, some of us reported the use of the DGFA to screen a 70,000-compound Global Health Chemical Diversity Library (GHCDL) from the University of Dundee.[17] The study represented the first example of a HTS campaign for the discovery of transmission-blocking agents carried out on a non-biased chemical library where transmission was the primary filter.

The most robust hit identified from this screen was compound DDD01035881 (Figure 2). DDD01035881 is a fast acting, non-toxic male-gamete targeted compound with an *in vitro* EC_{50}

value of approximately 200 nM, and an *in vivo* inhibition of oocyst formation higher than 99%, as determined using the SMFA when the compound was added 30 min before the mosquito feed at 10 μM.[17] The molecular target(s) of DDD01035881 is unknown. Five analogues of DDD01035881 were reported in the initial disclosure,[17] which provided limited information on the structure activity relationships (SAR) of this series; none of which had improved characteristics over the hit. Here we report a detailed medicinal chemistry study of this chemotype, exploring its potential for usage as a male-gamete targeted compound. We reveal key structure determinants for the activity of this series and identify compounds that are more potent than DDD01035881 and have improved metabolic stability. We believe this work should enable the further progression of this series as a transmission blocking therapy.



DDD01035881

Figure 2. Structure of male-gamete targeted hit DDD01035881 identified in the GHCDL screen.[17]

RESULTS AND DISCUSSION

Taking into consideration the structure of hit compound DDD01035881 and initially reported analogues (Figure S1), we decided to perform further SAR studies in order to assess the structural requirements for transmission-blocking activity. A summary of the features explored within this study is shown Figure 3.

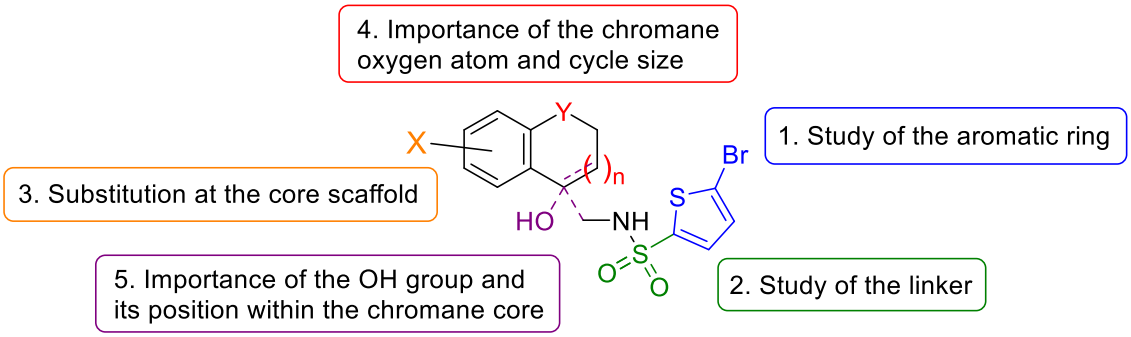
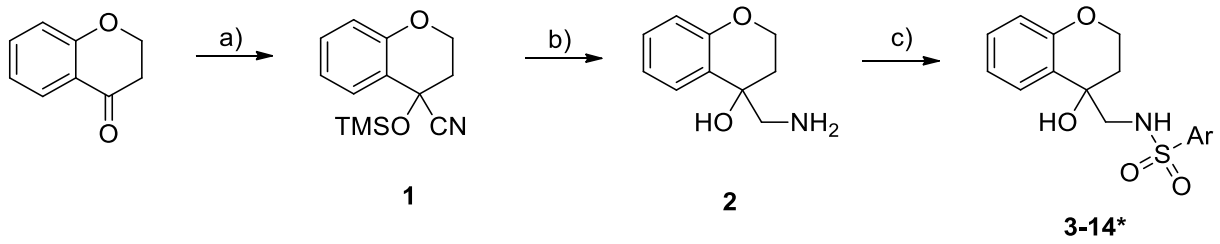


Figure 3. Structural features considered of interest for the SAR study of DDD01035881.

In order to study the effect of the changing the bromothiophene substituent, a synthetic route was developed, starting from 4-chromanone (Scheme 1). The addition of trimethylsilyl cyanide provided the protected cyanohydrin **1**, which after reduction using lithium aluminium hydride (LAH) yielded the necessary aminoalcohol **2** in quantitative yield. Treatment of amine **2** with the sulfonyl chloride of the desired aromatic substituent afforded the first series of compounds **3-14**. Compounds **3** and **4** are newly synthesised batches of DDD01035881 and DDD01028076 from the original report.[17]

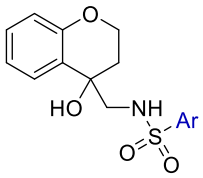


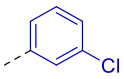
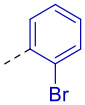
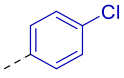
Scheme 1. Study of different aromatic substituents for the sulfonamide. Reagents and conditions: a) TMSCN, ZnI_2, DCM, rt, 16 h, quant.; b) LAH, THF, rt, 16 h, quant.; c) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 4-74%. *Ar groups can be reviewed in Table 1.

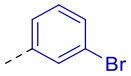
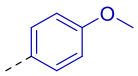
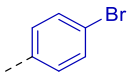
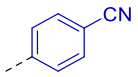
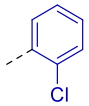
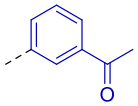
Compounds **3-14** were evaluated using the DGFA, and the results are shown in Table 1. The EC_{50} value obtained for compound **4** is in agreement with the data from the HTS, while derivative **3** shows a slight improvement when compared to the initial value,[17] which could be explained due to experimental variability inherent to the DGFA assay coupled with differences in compound

purity. Compound **5**, where the bromine atom has been moved to position 3 of the thiophene ring maintains the activity of **3**. Movement of the bromine atom within a phenyl rather than thiophene ring has more impact however. For example, changing from the *ortho*- position in **4** to *meta*- in **6** resulted in a >2.5 fold improvement in the activity, while the presence of a bromine atom at the *para*- position in **7** produced a complete loss of activity. Derivatives **8-10** containing a chlorine atom instead of a bromine atom show a similar trend. Removal of the halogen entirely does not result in a large decrease in activity (compound **11**), while introduction of an electron withdrawing group such as a ketone at the *meta*- position is not tolerated (compound **14**). In agreement with what was observed for halo- substitution, introduction of other groups at the *para*- position seems to be detrimental, regardless of their electronic properties (compounds **12** and **13**). Taken together, this data suggests there is limited space available within this region the binding pocket of the (unknown) target(s) - particularly once the ring is expanded to a six-membered ring - with the *para*-position being particularly sensitive to substitution.

Table 1. Modifications in the aromatic ring (Ar).

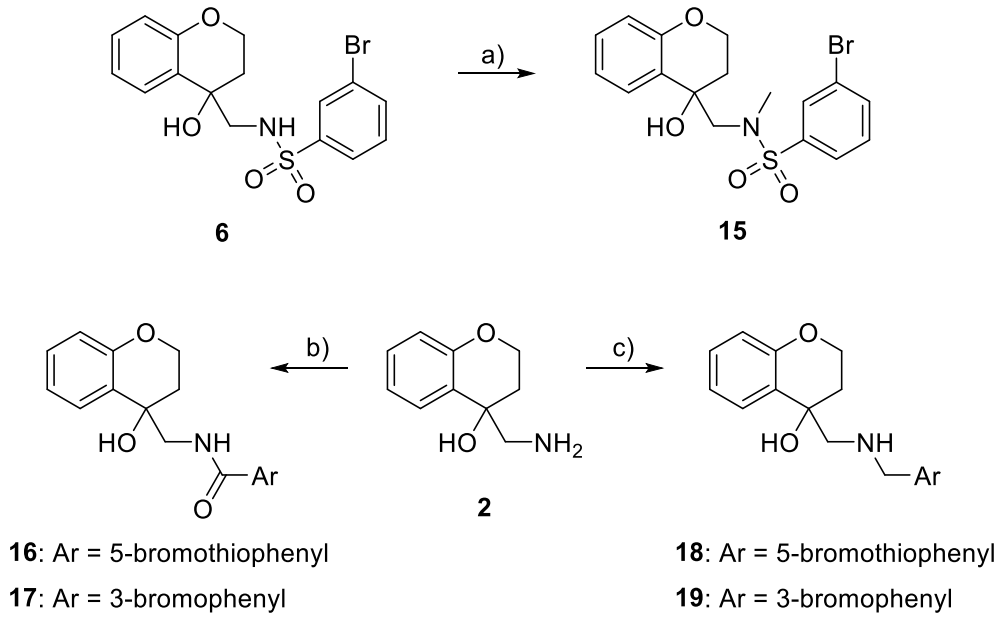


Compound	Ar	EC_{50} (nM)[a]	Compound	Ar	EC_{50} (nM)[a]
DDD01035881 **3**		292±38 (200 nM[b]) 130±30	**9**		118±27
DDD01028076 **4**		367±34 (530 nM[b]) 344±71	**10**		> 10000
5		212±91	**11**		470±21

6		128±10	**12**		> 25000
7		> 5000	**13**		> 25000
8		> 1000	**14**		> 20000

[a]Biological evaluation was carried out using the DGFA under the specific "add-in" format. Compounds were incubated at variable concentrations with fresh gametocytes, and their ability to impair exflagellation of male gametes determined. Values below 1 μM are expressed as the mean±SEM obtained from between three and eight biological replicates, each carried out in at least duplicate. [b]Value reported from initial HTS study.[17]

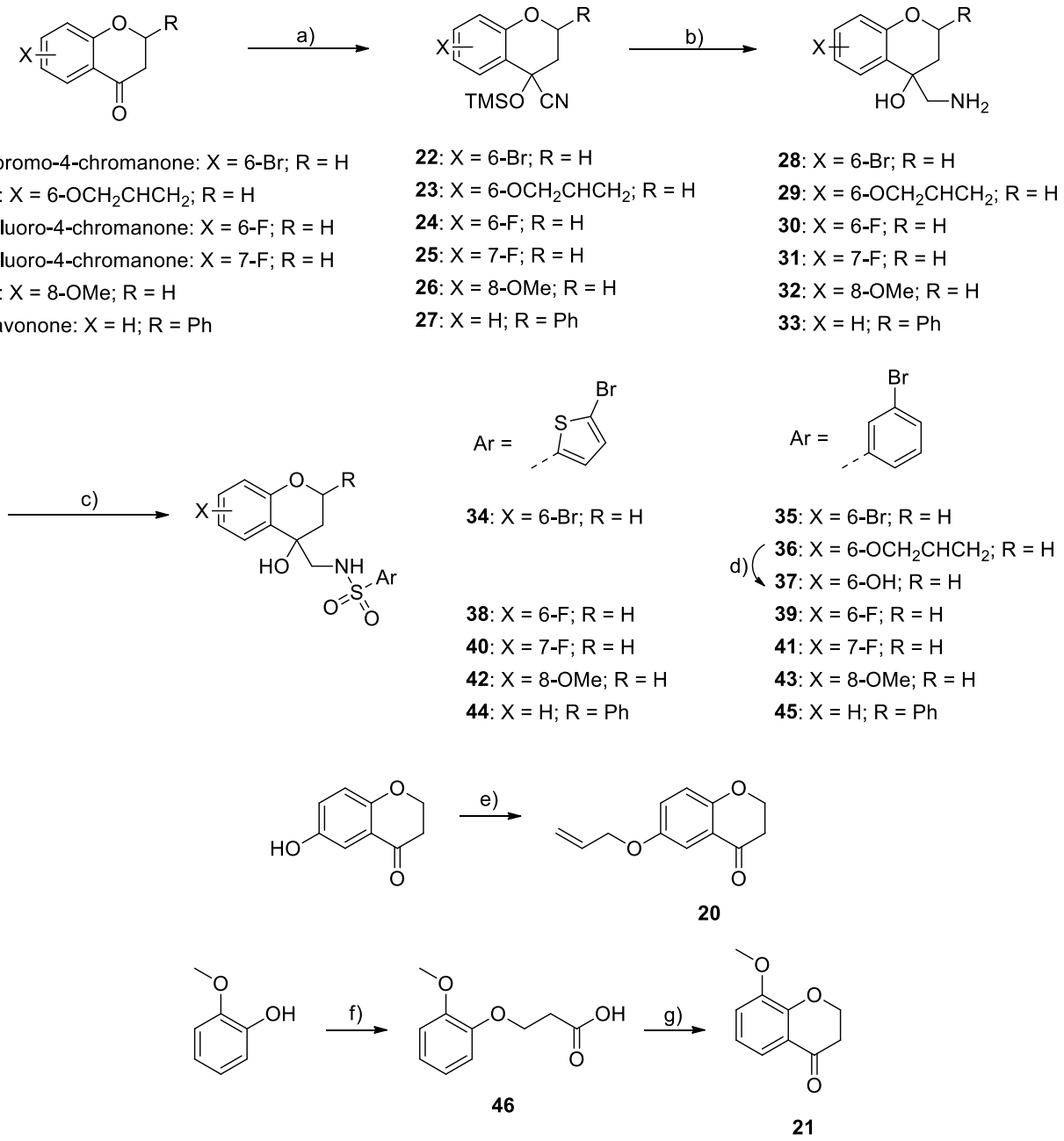
As both 5-bromothiophene and *meta*-halobenzene rings in derivatives **3**, **6** and **9** were able to produce the desired biological activity, we selected one of each for further SAR studies, specifically compounds **3** and **6** to maintain the identity of the halogen atom. To evaluate the importance of the sulfonamide linker, we synthesized derivatives **15-19**, where the sulfonamide had been either methylated or replaced by an amide or amine group (Scheme 2). Treatment of **6** with methyl iodide in the presence of potassium carbonate as base yielded methylsulfonamide **15** in good yield. Preparation of amides **16** and **17** was performed from coupling of aminoalcohol **2** to the desired carboxylic acid, in moderate yields, under standard coupling conditions of *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) in the presence of an excess of triethylamine. Amines **18** and **19** were synthesized by reductive amination of the desired aromatic aldehyde using aminoalcohol **2** as the amine source. Picoline borane complex was selected as the reducing agent[18] in the absence of acetic acid, to prevent elimination of the labile benzylic hydroxyl group.



Scheme 2. Study of the sulfonamide liker. Reagents and conditions: a) MeI, K_2CO_3, DMF, 50 ºC, 4 h, 80%; b) ArCOOH, EDC, HOBt, Et_3N, DCM/DMF, rt, 16 h, 55-68%; c) ArCHO, 2-picoline borane, MeOH, rt, 24 h, 10-50%.

All the attempted modifications to the linker resulted inactive compounds (Table S1). This highlights the importance of the sulfonamide group for activity. Interestingly, the fact that methylation of the sulfonamide in compound **15** renders loss of activity suggests that the NH group might be involved in a hydrogen-bonding interaction.

Next, we conducted a preliminary study of substitution of the chromane ring. Substituents were selected based on commercial availability of the reagents and synthetic feasibility.



6-bromo-4-chromanone: X = 6-Br; R = H
20: X = 6-OCH_2CHCH_2; R = H
6-fluoro-4-chromanone: X = 6-F; R = H
7-fluoro-4-chromanone: X = 7-F; R = H
21: X = 8-OMe; R = H
Flavonone: X = H; R = Ph

22: X = 6-Br; R = H
23: X = 6-OCH_2CHCH_2; R = H
24: X = 6-F; R = H
25: X = 7-F; R = H
26: X = 8-OMe; R = H
27: X = H; R = Ph

28: X = 6-Br; R = H
29: X = 6-OCH_2CHCH_2; R = H
30: X = 6-F; R = H
31: X = 7-F; R = H
32: X = 8-OMe; R = H
33: X = H; R = Ph

34: X = 6-Br; R = H

35: X = 6-Br; R = H
36: X = 6-OCH_2CHCH_2; R = H
37: X = 6-OH; R = H

38: X = 6-F; R = H
40: X = 7-F; R = H
42: X = 8-OMe; R = H
44: X = H; R = Ph

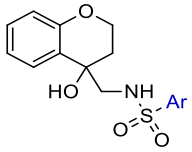
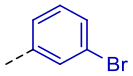
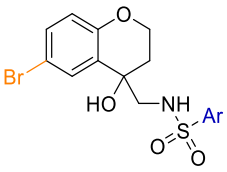
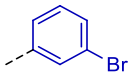
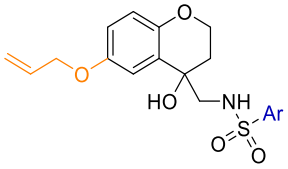
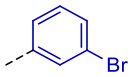
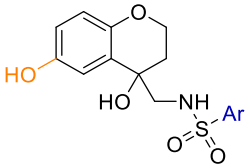
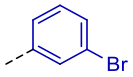
39: X = 6-F; R = H
41: X = 7-F; R = H
43: X = 8-OMe; R = H
45: X = H; R = Ph

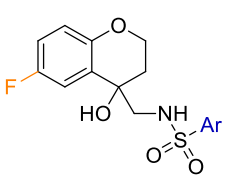
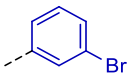
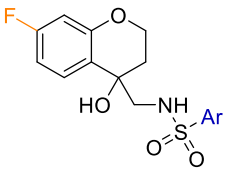
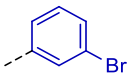
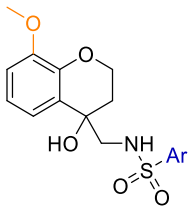
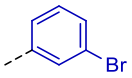
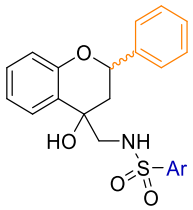
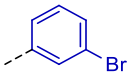
Scheme 3. Study of substitution in the core chromane scaffold. Reagents and conditions: a) TMSCN, ZnI_2, DCM, rt, 16 h, 65-91%; b) LAH, THF, rt, 16 h, 23-70%; c) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 28-90%; d) $Pd(PPh_3)_4$, K_2CO_3, MeOH, reflux, 16 h, 75%; e) allyl bromide, K_2CO_3, acetone, reflux, 16 h, 85%; f) 3-bromopropionic acid, NaH, DMF, rt, 16 h, 17%; g) Eaton's reagent, rt, 16 h, 88%.

As depicted in Scheme 3, the desired compounds were prepared from the corresponding 4-chromanones, following an identical synthetic route to that shown in Scheme 1. In the case of

compound **37** with a free phenol group, commercially available 6-hydroxy-4-chromanone was protected with allyl bromide to avoid cross reactivity. Allylated derivative **36** was biologically tested, but also used to prepare phenol **37** by removal of the allyl chain in the presence of $Pd(PPh_3)_4$ and potassium carbonate. 8-Methoxy-4-chromanone **21** was prepared from 2-methoxyphenol as previously described,[19] but changing the reagent employed for the ring-closing Friedel-Crafts acylation from polyphosphoric acid (PPA) to Eaton's reagent. The latter is preferred over PPA as it overcomes acknowledged practical issues associated with the handling of PPA such as its strong viscosity, difficulties in the reaction workup, or the need for extremely high temperatures.[20] This alteration allowed us to increase the reported yield of 50% to 88%.

Table 2. Study of substitution in the core scaffold.

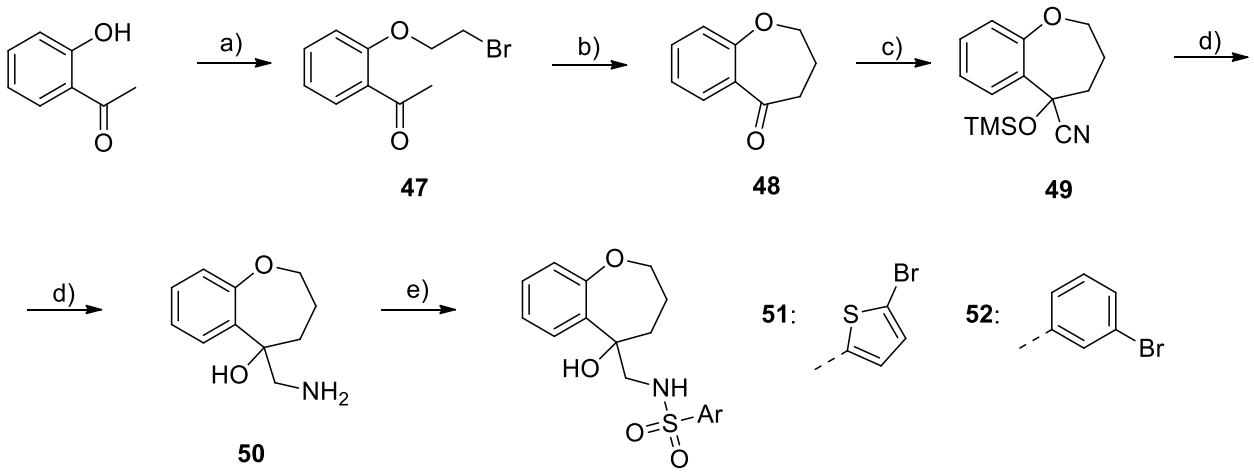
Compound	Core Scaffold	Ar	EC_{50} (nM)[a]
3			130±30
6			128±10
34			> 1000
35			785±48
36			> 25000
37			> 10000

38			196±19
39			83±13
40			364±47
41			79±18
42			> 25000
43			> 25000
44			> 25000
45			> 25000

[a]Biological evaluation was carried out using the DGFA under the specific "add-in" format. Compounds were incubated at variable concentrations with fresh gametocytes, and their ability to impair exflagellation of male gametes determined. Values below 1 µM are expressed as the mean±SEM obtained from between three and eight biological replicates, each carried out in at least duplicate.

All synthesised analogues resulted in a significant loss of activity, with the exception of fluorinated derivatives **38-41** (Table 2). Compounds **39** and **41** even show a slight improvement in potency over **6**. Once again, these results suggest the binding site of this series within the target(s) to be reasonably confined. Indeed, in contrast to other substituents, fluorine is very similar in size to hydrogen, which could explain why analogues **38-41** retain activity. It should be highlighted that fluorine is widely used within drug discovery to improve permeability by increasing lipophilicity and to address pharmacokinetic issues such as oxidative metabolism,[21] the latter being interesting in the context of this work (*vide infra*).

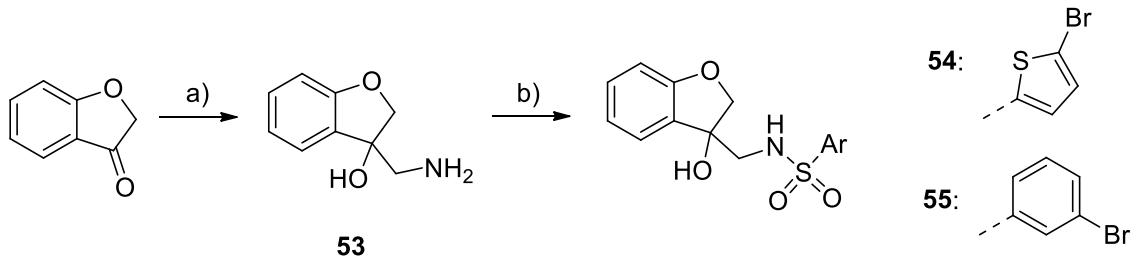
To further investigate the size constrains of the binding site, we next evaluated the outcome of modifying the size of the dihydropyran ring. Derivatives **51** and **52** with a seven-member ring, or analogues **54** and **55** containing a dihydrofuran were devised. The former analogues were synthesized from commercially available 2-hydroxyacetophenone (Scheme 4). Alkylation of the phenol with 1,2-dibromoethane, followed by enolate formation with sodium hydride and *in situ* ring closure by nucleophilic substitution of the bromine, provided the necessary ketone **48**. Treatment of **48** with trimethylsilyl cyanide, followed by reduction with LAH as described for previous analogues, yielded aminoalcohol **50**. Aminoalcohol **50** was reacted with the desired sulfonyl chlorides to afford benzoxepine derivatives **51** and **52**.



Scheme 4. Synthesis of the extended core scaffold analogues. Reagents and conditions: a) 1,2-dibromoethane, K_2CO_3, ACN, reflux, 16h, 34%; b) NaH, THF, 0 ºC to rt, 16 h, 77%; c) TMSCN, ZnI_2, DCM, rt, 16 h, 97%; d) LAH, THF, rt, 16 h, 35%; e) $ArSO_2Cl$, Et_3N, DCM, 0 ºC to rt, 16 h, 38-63%.

Preparation of dihydrofuran analogues **54** and **55** initiated from 3-coumaranone, following the same synthetic route shown for 4-chromanones. However, the typical conditions used for the formation of the cyanohydrin - trimethylsilylcyanide in the presence of catalytic zinc iodide - were unsuccessful, providing complex reactions mixtures. We speculate that lability of this scaffold to the Lewis acid was at fault and thus we attempted a different protocol that used potassium

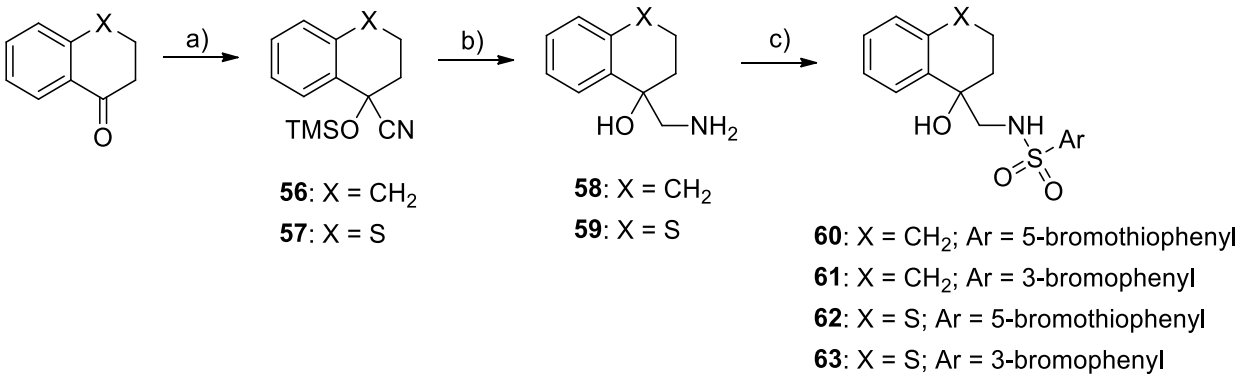
carbonate as a catalyst instead.[22] Unfortunately, these conditions also did not afford the desired cyanohydrin. Finally, the use of potassium phthalimide as catalyst in the absence of solvent provided mild enough conditions to allow for the formation of the desired cyanohydrin,[23] which was reduced immediately due to stability issues to yield aminoalcohol **53** (Scheme 5). Treatment of **53** with the corresponding sulfonyl chlorides afforded final compounds **54** and **55**.



Scheme 5. Synthesis of the reduced core scaffold analogues. Reactants and reagents: a) i) TMSCN, potassium phthalimide, rt, 16 h; ii) LAH, THF, rt, 16 h, 35% (over two steps); b) $ArSO_2Cl$, Et_3N, DCM, 0 ºC to rt, 16 h, 51-53%.

Expanding or contracting the central core resulted in a loss of activity (Table S2), being much more pronounced in the case of the seven-member ring analogues **51** and **52** (EC_{50}>25 µM *vs* 1>EC_{50}>5 µM for **54** and **55**). These results are in agreement with our previous data suggesting a small binding site within the target(s). The drop in activity observed for the smaller derivatives **54** and **55**, suggests that the geometry and size of the six-member ring is important for activity.

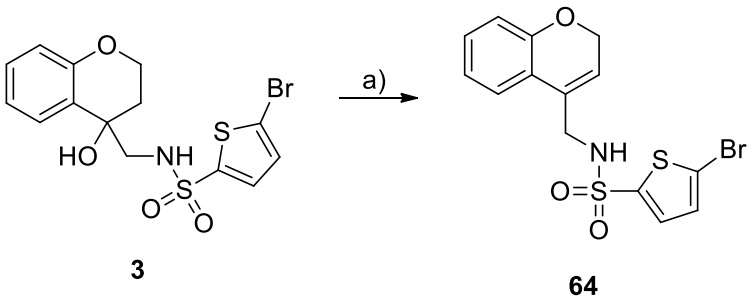
Given that alteration in ring size was not tolerated, we evaluated whether the oxygen atom within the chromane scaffold was important for activity. We therefore prepared analogues **60** and **61** with a methylene unit, and **62** and **63** with sulfur replacing the oxygen. Scheme 6 shows the synthetic route used to obtain these derivatives, which is identical to that shown previously in Scheme 1.



Scheme 6. Study of the importance of the oxygen atom. Reagents and conditions: a) TMSCN, ZnI_2, DCM, rt, 16 h, 45%-quant; b) LAH, THF, rt, 16 h, 70-91%; c) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 33-75%.

While compounds **60** and **61**, with no heteroatom at all, displayed a complete loss of activity, derivatives **62** and **63**, with a sulfur atom replacing the oxygen, showed a more moderate loss (EC_{50}>25 µM and 1>EC_{50}>5 µM, respectively, Table S3). This result is suggestive that polarity in this region of the series is important to retain activity. The loss of activity in the sulfur derivatives versus the oxygen derivatives can possibly be explained by the lower electronegativity of this element when compared to oxygen. Alternatively, it might just be that the larger size of sulfur is non-optimal.

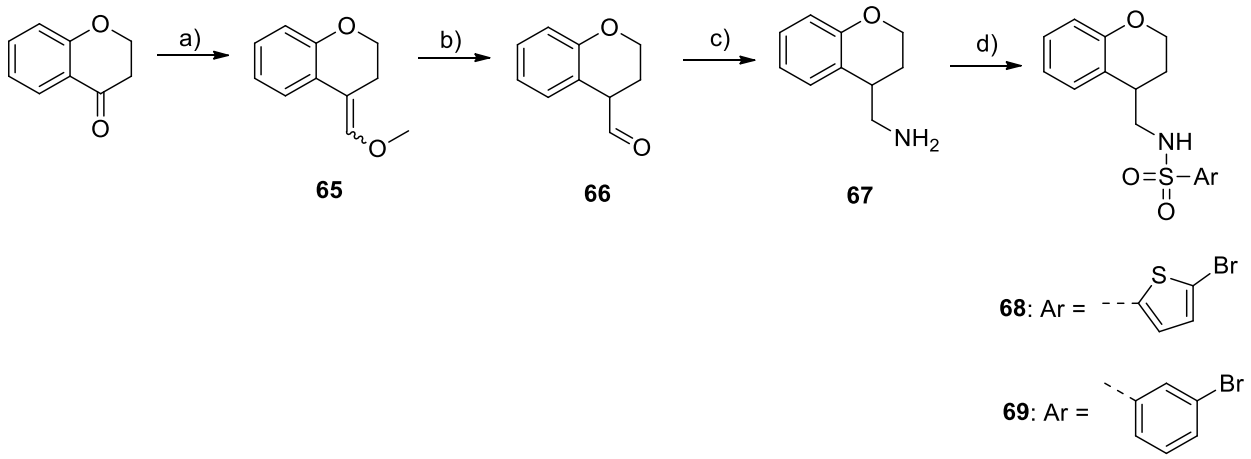
The final region of the series for exploration was the quaternary hydroxyl group. Given that this moiety is at a benzylic position could present a potential stability issue. To study this, we took compound **3** and submitted it to acidic conditions in order to get the product of the E1 elimination reaction, **64** (Scheme 7).



Scheme 7. Removal of the hydroxyl group in compound **3**. Reagents and conditions: a) $BF_3 \cdot Et_2O$, DCM, 0 ºC, 1 h, 11%.

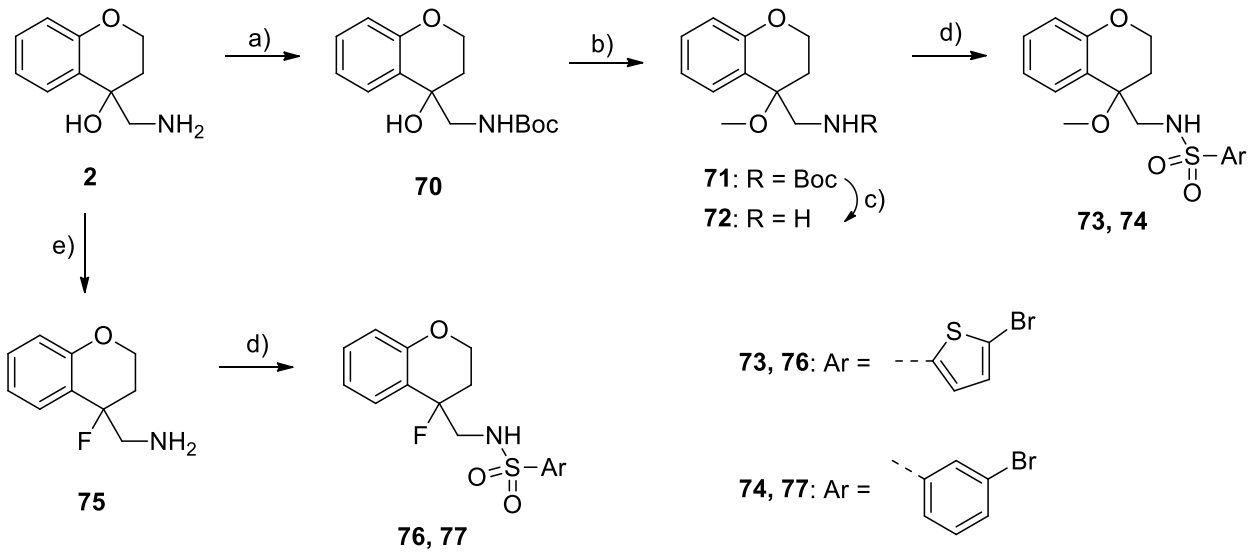
The resulting alkene was found to be completely inactive in the DGFA assay (Table 3), suggesting that the hydroxyl group is required for transmission-blocking activity. An alternative option, however, would be that the geometry of the compound imposed by the alkene is not favoured. To investigate this further, we designed the saturated dehydroxylated analogues **68** and **69**, and derivatives **73** and **74** where hydroxyl group was methylated. As a final comparator, we designed compounds **76** and **77**, where a fluorine atom replaced the hydroxyl group.

For the preparation of analogues **68** and **69**, we attempted to follow a similar strategy to the one shown in Scheme 7, followed by reduction of the alkene. Unfortunately, the yields were very low, and the conditions were not reproducible upon scale up. Therefore, we followed an alternate synthetic route (Scheme 8). Wittig reaction of 4-chromanone with methoxymethylenetriphenylphosphine, prepared *in situ* by deprotonation of the corresponding phosphonium salt with butyl lithium, yielded methyl vinyl ether **65** in good yield (86%). Cleavage of the methyl group using perchloric acid afforded aldehyde **66**, which was directly used in the next step for the formation and *in situ* reduction of the corresponding oxime, to provide amine **67**. Amine **67** was converted to **68** and **69** using the previously established chemistry.



Scheme 8. Preparation of the dehydroxylated derivatives. Reagents and conditions: a) (methoxymethyl)triphenylphosphonium chloride, BuLi, THF, -78 ºC to rt, 16 h, 86%; b) 70% $HClO_4$, Et_2O, 0 ºC to rt, 45 min, quant.; c) i) $NH_2OH{\cdot}HCl$, EtOH, rt, 45 min ii) Zn, HCl, rt, 15 min, 33%; d) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 43-68%.

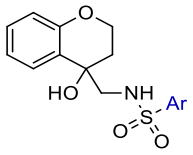
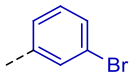
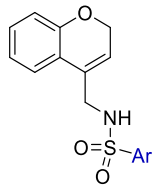
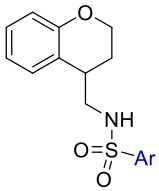
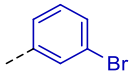
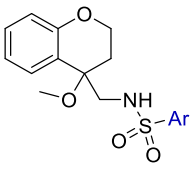
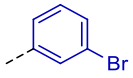
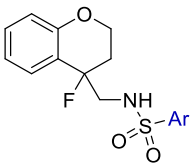
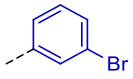
Analogues **73** and **74** were accessed from aminoalcohol **2**, by protection of the amine followed by methylation of the hydroxyl group. Cleavage of the Boc protecting group from **71** and coupling to the corresponding sulfonyl chlorides gave the final compounds **73** and **74** (Scheme 9). It is worth noting that the Boc group required removal using tetrabutylammonium fluoride (TBAF) in refluxing THF,[24] as compound **71** showed lability to commonly used acidic deprotection conditions (including TFA and HCl). Fluorinated derivatives **76** and **77**, were obtained by replacement of the hydroxyl group in **2** by a fluorine atom using diethylaminosulfur trifluoride (DAST), followed by coupling of amine **75** to the desired sulfonyl chlorides.



Scheme 9. Synthesis of alkylated and fluorinated analogues. Reagents and conditions: a) Boc_2O, Et_3N, DCM, 0 ºC to rt, 5 h, quant.; b) MeI, K^{t}OBu, THF, 0 ºC to rt, 2 h, 70%; c) 1M TBAF in THF, reflux, 16 h, 39%; d) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 44-84%; e) DAST, DCM, -78 ºC to rt, 3 h, 31%.

As shown in Table 3, the loss of activity observed for derivative **64** following elimination of the hydroxyl group does not seem to be due to the different geometry enforced by the alkene. Instead, it seems that the absence of the polar hydroxyl group is the issue, with saturated analogues **68** and **69** also giving a complete loss of biological activity. Interestingly, the methylated derivatives **73** and **74** retain comparable activity, which indicates that the hydroxyl group is not acting as a hydrogen-bond donor in the target(s). Finally, exchange of the hydroxyl group with a fluorine atom in analogues **76** and **77** gives a 7-fold decrease in activity when compared with the corresponding hydroxylated counterparts.

Table 3. Study of the importance of the hydroxyl group.

Compound	Core Scaffold	Ar	EC_{50} (nM)[a]
3			130±30
6			128±10
64			> 25000
68			> 10000
69			> 10000
73			354±22
74			149±24
76			>1000
77			945±192

[a]Biological evaluation was carried out using the DGFA under the specific "add-in" format. Compounds were incubated at variable concentrations with fresh gametocytes, and their ability to impair exflagellation of male gametes determined. Values below 1 µM are expressed as the mean±SEM obtained from between three and eight biological replicates, each carried out in at least duplicate.

As a final analysis of the importance of the hydroxyl group, we designed structurally isomeric compounds. Specifically, we elected to study compounds **78** and **79**, in which the hydroxyl group had been retained at the benzylic position but the sulfonamide moved to the adjacent carbon. We also selected derivatives **80** and **81** with both substituents moved to the adjacent carbon. The

preparation of these analogues was envisioned through a common intermediate, alkene **82**, by hydroboration-oxidation or epoxidation and ring opening, respectively (Figure 4).

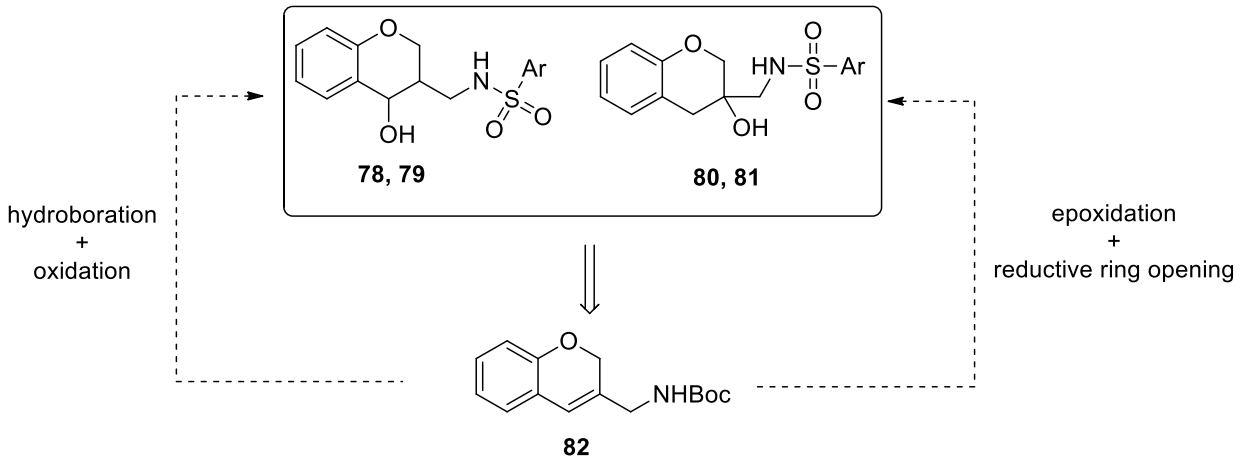
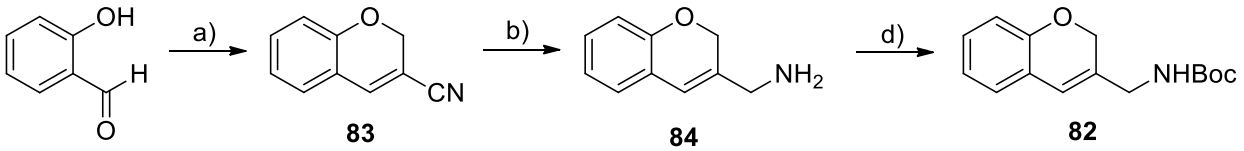


Figure 4. Schematic representation of the synthetic plan for the preparation of final compounds **78-81**.

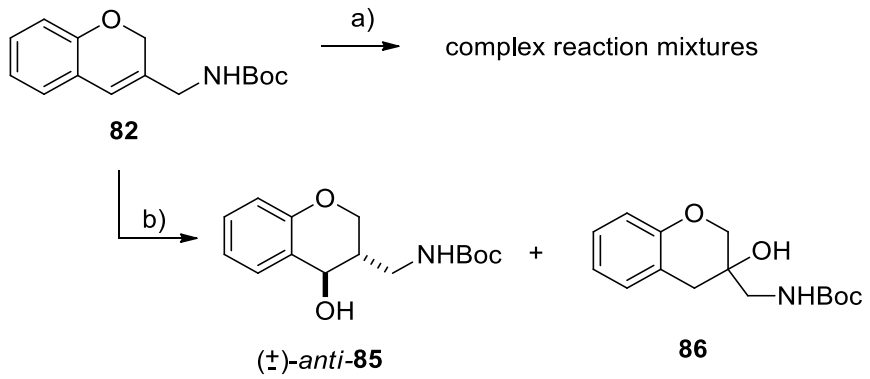
The synthesis of intermediate **82** was carried out by conjugate addition of 2-hydroxybenzaldehyde to acrylonitrile followed by an intramolecular aldol condensation[25] to yield **83** (Scheme 10). Reduction of nitrile **83** and Boc protection of the resulting amine gave product **82**.



Scheme 10. Synthesis of the necessary intermediate for the preparation of final compounds **78-81**. Reagents and conditions: a) acrylonitrile, DABCO, 90 ºC, 16 h, 74%; b) LAH, $AlCl_3$, Et_2O, 0 ºC to rt, 2 h, 56%; c) Boc_2O, Et_3N, DCM, 0 ºC to rt, 5 h, 83%.

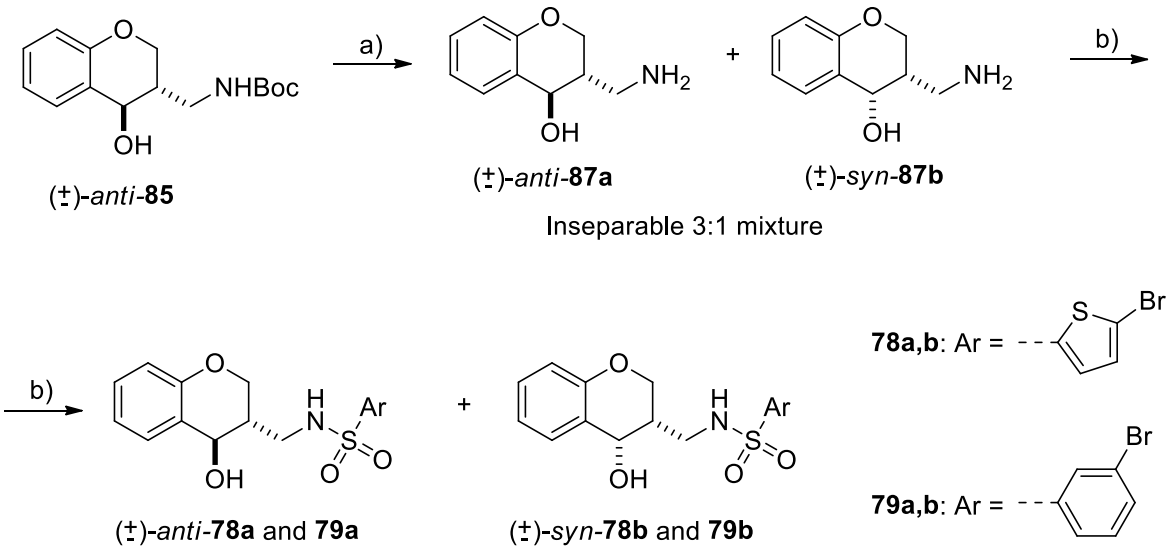
Hydroboration-oxidation of alkene **82** was attempted using standard conditions, but complex reaction mixtures were obtained (Scheme 11). Careful following of the reaction by thin layer chromatography (TLC) showed that the oxidation step using hydrogen peroxide was responsible

for the observed decomposition, while the hydroboration step appeared to occur cleanly. Therefore sodium perborate was used as an oxidant instead,[26] which, after some reaction optimization gave the desired anti-Markovnikov alcohol **85** in moderate yield (49%), showing the expected *anti*-stereochemistry as a result of the *syn*- addition of the borane to the double bond (Scheme 11). Surprisingly, the corresponding Markovnikov analogue **86** was also isolated in 27% yield. Since the latter is the product needed for the preparation of compounds **80** and **81**, we progressed **86** instead of performing the planned epoxide formation.



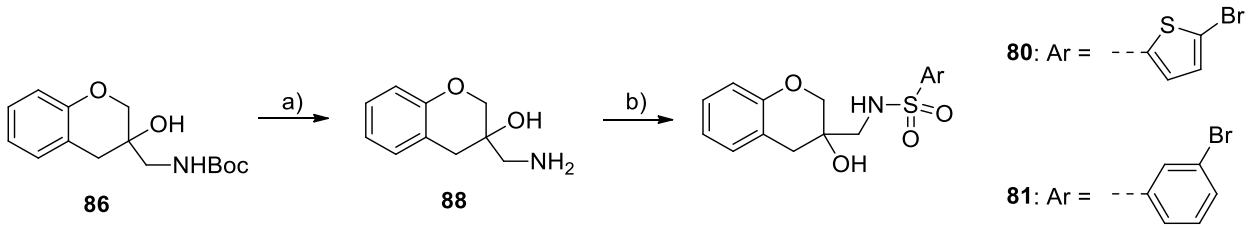
Scheme 11. Hydroboration-oxidation of **82**. Reagents and conditions: a) i) 1M BH_3·THF, 0 ºC to rt, 2 h; ii) H_2O_2, NaOH, H_2O, 0 ºC to rt, 16 h; b) i) 1M BH_3·THF, 0 ºC to rt, 2 h; ii) $NaBO_3$·$4H_2O$, H_2O, rt, 2 h, 27-49%.

Boc deprotection of compound **85** had to be optimised for reaction temperature and time in order to avoid elimination of the benzylic alcohol to return unsaturated amine **84**. However, epimerisation at the benzylic position could not be completely avoided, and the desired aminoalcohol was obtained as an inseparable 3:1 mixture of the *anti*- and *syn*- isomers **87a** and **87b** as a result (Scheme 12). The mixture was treated with the corresponding sulfonyl chlorides, and the resulting *anti*- and *syn*- isomers **78a,b** and **79a,b** could be separated by flash chromatography.



Scheme 12. Preparation of final compounds **78a,b** and **79a,b**. Reagents and conditions: a) TFA, DCM, 0 ºC, 30 min, 57%; b) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 77-93%.

With the conditions from removal of the Boc group optimised, derivatives **80** and **81** were prepared from **86** following a similar synthetic route (Scheme 13).

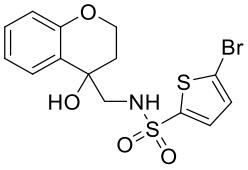
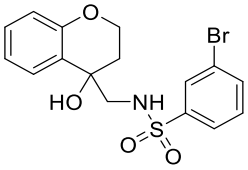
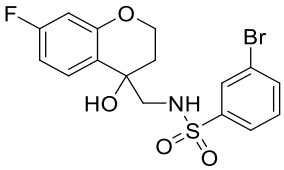
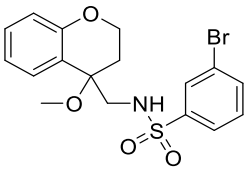


Scheme 13. Preparation of final compounds **80** and **81**. Reagents and conditions: a) TFA, DCM, 0 ºC, 30 min, 33%; b) $ArSO_2Cl$, Et_3N, DCM, rt, 16 h, 15-70%.

All six isomeric analogues were completely inactive (EC_{50}>25 µM, Table S4), verifying the importance of the positioning of these substituents in the scaffold. While the relatively tight SAR displayed by this series is a challenge for ongoing medicinal chemistry, it may point to specificity for a given target(s), rather than promiscuous activity.

Up to this point, all compounds had been tested as racemic mixtures. To establish the role of absolute stereochemistry, we performed chiral resolution on a few of the most active derivatives. We selected the initial hit DDD01035881 (**3**) together with the bromobenzene analogue **6**, one of the fluorinated compounds (**41**), and methoxylated derivative **74**. Table 4 shows the results of this analysis, which demonstrates that one enantiomer is significantly more active than the other. In all cases, the (-) isomer is the active enantiomer. This result again suggests a specific biological interaction to underpin the activity of this series and showcases compounds with a potency of 18-59 nM. While it would be ideal to assign the absolute stereochemistry of the active enantiomer, all attempts of crystallisation have been unsuccessful thus far.

Table 4. Study of the activity of the enantiomeric pairs.

Compound	Core Scaffold	EC_{50} (nM)[a]	Enantiomer	EC_{50} (nM)[a]
3		130±30	**(-)-3**	46±5
			(+)-3	>1000
6		128±10	**(-)-6**	18±3
			(+)-6	>2000
41		79±18	**(-)-41**	51±13
			(+)-41	>1000
74		149±24	**(-)-74**	59±8
			(+)-74	>2000

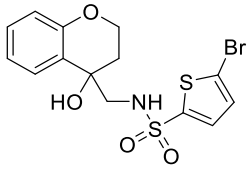
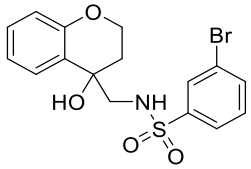
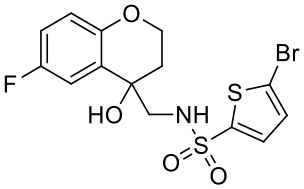
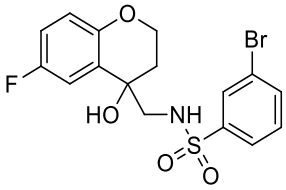
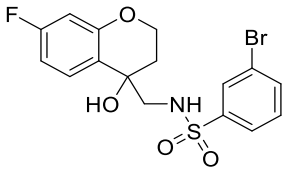
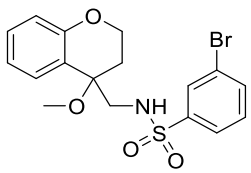
[a]Biological evaluation was carried out using the DGFA under the specific "add-in" format. Compounds were incubated at variable concentrations with fresh gametocytes, and their ability to impair exflagellation of male gametes determined. Values below 1 µM are expressed as the

mean±SEM obtained from between three and eight biological replicates, each carried out in at least duplicate.

In vivo studies carried out on the original hit DDD01035881 provided a half-life of ~90 min for this compound.[17] Taking into consideration the parasite lifecycle stage in which this scaffold intervenes, namely male gamete development in the mosquito midgut, longer circulation time would be required for the compound to be taken up by the mosquito. We hypothesised that the thiophene ring in the initial hit **3** might be one of the causes for the fast metabolism.[27] For that reason, we decided to carry out *in vitro* metabolic stability studies on the most active compounds **6**, **39, 41** and **74**, all bearing the bromobenzene ring instead. Additionally, compound **3** and its fluorinated analogue (**38**) were included for comparison. Table 5 shows the intrinsic clearance values (CL_{int}) and half-life times ($t_{1/2}$) obtained for compounds **3**, **6**, **38, 39, 41** and **74** when incubated with mouse liver microsomes. Surprisingly, changing the bromothiophene group to a bromobenzene ring does not impart metabolic stability: compound **6** is not detectable after 5 min of incubation with the microsomes, and bromobenzene derivative **39** has a reduced half-life of almost a minute when compared to its bromothiophene analogue (**38**). Compound **74** has a half-life time comparable to that of compound **3**, suggesting that the hydroxyl group is also not important for microsomal metabolism. Interestingly, fluorinated derivatives **38**, **39** and **41** show a considerable improvement in stability, with almost a 4-fold reduction in microsomal clearance for compounds **38** and **41** versus compound **3**. This result may suggest the chromane aromatic ring being a soft spot for oxidative metabolism. Oxidation of electron rich aromatic rings by cytochrome P450 (CYP450) to produce the corresponding phenol is well known, and fluorine is very commonly used to hamper such processes.[21] Oxidation normally occurs at the more electron rich positions, i.e. *ortho*- and *para*- with respect to activating substituents, being the latter the most commonly found. In the case of compound **41**, the most stable fluorinated analogue under

microsomal metabolism, the fluorine atom is at *para*- with respect to the alkyl chain and *meta*- with regard to the more activating ether substituent. Despite this, **41** shows a similar half-life than its analogue **39** where the fluorine atom is in *para*- to the ether oxygen. This may suggest that the increased microsomal stability of the fluorinated derivatives stems from general electronic tuning of the chromane ring, rather than blocking a specific metabolic soft spot on the aromatic ring.

Table 5. Metabolic stability data for compounds **3, 6, 38**, **39**, **41** and **74** in mouse microsomes.

Compound	Core Scaffold	EC_{50} (nM)[a]	CL_{int} (µL/min/mg protein)[b]	$t_{1/2}$ (min)[b]
3		130±30	1130	1.23
6		128±10	N/A[c]	N/A[c]
38		196±19	298	4.65
39		83±13	355	3.90
41		79±18	291	4.76
74		149±24	1310	1.06

[a]Biological evaluation was carried out using the DGFA under the specific "add-in" format. Compounds were incubated at variable concentrations with fresh gametocytes, and their ability to impair exflagellation of male gametes determined. Values below 1 μM are expressed as the mean±SEM obtained from between three and eight biological replicates, each carried out in at least duplicate. [b]Values expressed as the mean from two to four experiments. [c]Metabolism was too fast to determine accurate values.

The toxicity of four representative analogues against a human HepG2 cell line was evaluated as previously described.[17] No cytotoxicity was observed for any of the assayed compounds after 48 h of incubation, when compared to the drug doxorubicin, which was used as positive control (Table S5).

CONCLUSIONS

This study aimed to further explore the early medicinal chemistry of DDD01035881, the most robust hit identified from a 70,000-compound Global Health Chemical Diversity Library (GHCDL) screen using the DGFA assay.[17] The ultimate aim of this project is to further the progression of compounds that can stop the transmission of malaria. In addition to a clearer understanding of the SAR of this series, we have identified a compound (**41**) with improved metabolic stability over the original hit and have clearly defined the active enantiomer of this series. While this certainly bodes well for further optimisation: ultimately a long circulating half-live will be required in order for the optimised compound to reach its biological target in the mosquito. We note that drug delivery techniques may be another approach to extend the circulating half-life of this series. Taking advantage of the different environment found in the vector, namely the decrease in temperature to 28 ºC, temperature-controlled release from a drug delivery system may be possible; an approach more commonly exploited for hyperthermia.[28] A final approach may be to use an optimised compound from this series as part of long-lasting ITNs or IRS. It has been recently shown that the antimalarial atovaquone can interrupt the parasite lifecycle completely in

the mosquito, after exposure of the *Anopheles* female to a glass surface coated with the drug.[29] This is an exciting study which opens new avenues for the development of transmission-blocking agents through perturbing biology in the mosquito, rather than the human host.

EXPERIMENTAL SECTION

Chemistry

Unless otherwise stated, the starting materials, reagents, and solvents were purchased as high-grade commercial products from Sigma-Aldrich, Acros, Alfa-Aesar, Fluorochem, TCI, or VWR. Solvents were either purchased anhydrous or dried by passing them through activated alumina columns using a Pure Solv™ Micro 100 Liter solvent purification system. All reactions were performed under nitrogen atmosphere.

Analytical thin-layer chromatography was run on Merck silica gel plates (Kieselgel 60 F-254), with detection by UV light (λ=254 nm and 365 nm), ninhydrin or phosphomolybdic acid solutions in ethanol, or $KMnO_4$ (aqueous, aq). Products were purified by flash chromatography on glass column with silica gel type 60 (particle size 40-63 u from Fluorochem). Optical rotation [α] was measured on a Bellingham and Stanley ADP 440+ polarimeter using a LED light source (interference filter, λ=589 nm) with a 0.5 dm path length; concentrations (c) are given as g/100 mL. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 400 MHz (^{1}H, 400 MHz; ^{13}C, 101 MHz; ^{19}F, 377 MHz) instrument at room temperature (rt) at the NMR core facility at Imperial College London. Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane; coupling constants (*J*) are in hertz (Hz). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet),

qt (quintet), m (multiplet), app (apparent), and br (broad). High resolution mass spectrometry (HRMS) spectra were recorded on a Micromass Autospec Premier and Micromass LCT Premier Spectrometer in electrospray ionization (ESI) mode at Imperial College London mass spectrometry core facility. For all final compounds, purity was determined by high-performance liquid chromatography coupled to mass spectrometry (HPLC-MS) using a Waters 2767 system. Separation was achieved using a XBridge C18 (5 μm, 4.6 mm × 100 mm) column, equipped with an XBridge C18 guard column (5 μm, 4.6 mm × 20 mm). The gradient mobile phase consisted of A (95:5 H_2O/acetonitrile [ACN]) and B (5:95 H_2O/ACN) with 0.1% formic acid as solvent modifier. Purity of tested compounds was at least 95%, unless stated otherwise. Spectra were acquired in positive or negative ionization mode from 100 to 1000 m/z and in UV-mode (scan 190-700 nm). MS analysis was performed with an ESI source. Chiral resolution of selected compounds was performed by HPLC using either a Perkin Elmer Series 200 or an Agilent Thecnologies 1200 Series system. Separation was achieved using a Chiralcel® OD-H or a Chiralpack® IE-3 column, with the corresponding guard columns. The mobile phase consisted of an isocratic gradient of hexane and isopropanol.

All compound spectra are freely available at: https://doi.org/10.14469/hpc/5733

GENERAL PROCEDURES

A. Cyanohydrin formation

To a stirred solution of the corresponding ketone (1 equiv) in dry DCM (3 mL/mmol) at 0 ºC, ZnI_2 was added (0.02 equiv) followed by trimethylsylilcyanide (1.5 equiv). The resulting mixture was allowed to warm up to rt and stirred at that temperature overnight. The reaction was diluted with DCM, washed with a saturated (sat.) solution of $NaHCO_3$, dried over $MgSO_4$, filtered and

evaporated under reduced pressure. The crude product was used in the next step without further purification.

B. Cyanohydrin reduction

To a stirred solution of the corresponding cyanohydrin (1 equiv) in anhydrous THF (4 mL/mmol) at 0 ºC, a 1M solution of LAH in THF (2 equiv) was added dropwise, and the resulting mixture was allowed to warm up to rt and stirred at that temperature overnight. The reaction was cooled down to 0 ºC and worked-up according to the *Fieser*-procedure. The crude was purified by flash chromatography using the appropriate eluent to afford the corresponding aminoalcohol.

C. Sulfonamide formation

To a stirred solution of the corresponding aminoalcohol (1 equiv) in dry DCM (4 mL/mmol) at 0 °C, triethylamine (2.5 equiv) was added dropwise. Then, a solution of the desired sulfonyl chloride (1.1 equiv) in dry DCM (4 mL/mmol) was added and the reaction mixture was allowed to warm up to rt and stirred for 5 hours. Water was added and the mixture was extracted with DCM (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography using the appropriate eluent to afford the desired product.

D. Synthesis of N-((4-hydroxychroman-4-yl)methyl)amides

To a solution of the corresponding carboxylic acid (1.1 equiv), EDC (1.5 equiv), and HOBt (1.5 equiv) in dry DMF (5 mL/mmol of EDC/HOBt) at 0 °C, a solution of the corresponding aminoalcohol (1 equiv) in dry DCM (4 mL/mmol) was added followed by triethylamine (5 equiv). The mixture was stirred at 0 °C for 30 min, and then allowed to warm up to rt and stirred overnight. The reaction mixture was then diluted with DCM and washed with 5% LiCl (aq, 3x) and brine,

dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography using the appropriate eluent to afford the desired product.

E. Synthesis of N-((4-hydroxychroman-4-yl)methyl)amines

To a solution of 4-(aminomethyl)chroman-4-ol (1 equiv) in dry MeOH (15 mL/mmol), the corresponding aldehyde (1 equiv) was added and the solution was stirred for 15 min at rt, before 2-picoline borane complex (1.2 equiv) was added portion wise. After stirring for 25 h, the reaction was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography using the appropriate eluent to afford the desired product.

4-((Trimethylsilyl)oxy)chromane-4-carbonitrile (1). Following general procedure A, cyanohydrin **1** was obtained from 4-chromanone (2.00 g, 13.3 mmol) in quantitative yield (3.3 g) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.98 (td, *J* = 7.8, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.45 – 4.26 (m, 2H), 2.52 – 2.30 (m, 2H), 0.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 131.5, 128.8, 121.2, 120.9, 117.7, 65.7, 61.4, 36.4, 1.3. Spectra available at: https://doi.org/10.14469/hpc/5801

4-(Aminomethyl)chroman-4-ol (2). Following general procedure B, aminoalcohol **2** was obtained from cyanohydrin **1** (3.30 g, 13.3 mmol) in quantitative yield (2.4 g) as a pale-yellow oil. Column chromatography: DCM/7N NH_3 in MeOH, 10:0 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.83 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.30 – 4.20 (m, 2H), 3.07 (d, *J* = 13.1 Hz, 1H), 2.95 (d, *J* = 13.0 Hz, 1H), 2.12 – 2.02 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 156.2, 130.2, 127.9, 127.5, 121.6, 118., 68.7, 64.2, 51.0, 33.8. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{13}NO_2$ 180.1025, found 180.1024. Spectra available at: https://doi.org/10.14469/hpc/5802

5-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)thiophene-2-sulfonamide (3). Following general procedure C, sulfonamide **3** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 3-bromobenzenesulfonyl chloride (90 mg, 0.50 mmol) in 52% yield (105 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.20 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 7.06 (d, *J* = 3.9 Hz, 1H), 6.90 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.27 (t, *J* = 6.6 Hz, 1H, NH), 4.29 – 4.14 (m, 2H), 3.33 (d, *J* = 6.5 Hz, 2H), 2.36 (ddd, *J* = 14.1, 6.3, 3.5 Hz, 1H), 2.29 (br s, 1H, OH), 2.03 (ddd, *J* = 14.1, 8.1, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 141.5, 132.4, 130.6, 130.2, 126.4, 125.0, 121.1, 120.2, 117.5, 68.4, 63.4, 51.6, 33.0. HRMS (ESI) calcd for $[M-H]^-$ $C_{14}H_{13}NO_4S_2Br$ 401.9469, found 401.9469. Spectra available at: https://doi.org/10.14469/hpc/5803

Chiral resolution was performed on a Chiralcel® OD-H column using an isocratic gradient of hexane/isopropanol, 8:2 to yield (-)-**3** and (+)-**3**.

(+)-**3**: $[\alpha]_D^{20}$ = + 48° (*c* = 0.125, MeOH)

(-)-**3**: $[\alpha]_D^{20}$ = - 48° (*c* = 0.125, MeOH)

2-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (4). Following general procedure C, sulfonamide **4** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 2-bromobenzenesulfonyl chloride (141 mg, 0.55 mmol) in 67% yield (132 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.76 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.9 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.18 (ddd, *J* = 8.4, 7.3, 1.6 Hz, 1H), 6.88 (td, *J* = 7.8, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.55 (br t, *J* = 6.2 Hz, 1H), 4.30 – 4.15 (m, 2H), 3.20 (dd, *J* = 6.7, 3.9 Hz, 2H), 2.43 (ddd, *J* = 14.1, 6.5, 3.7 Hz, 1H), 2.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 154.7, 138.6, 135.2, 134.0, 131.7, 130.1, 128.0, 126.4, 125.0, 121.0, 119.8, 117.4, 68.3, 63.4, 51.5, 33.0. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SBr$ 395.9905, found 395.9912. Spectra available at: https://doi.org/10.14469/hpc/5804

3-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)thiophene-2-sulfonamide (5). Following general procedure C, sulfonamide **5** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 3-bromothiophene-2-sulfonyl chloride (144 mg, 0.55 mmol) in 60% yield (111 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 5.3 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.18 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.11 (d, *J* = 5.3 Hz, 1H), 6.89 (td, *J* = 7.8, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.63 (t, *J* = 6.6 Hz, 1H, NH), 4.29 – 4.13 (m, 2H), 3.31 (d, *J* = 6.7 Hz, 2H), 2.44 – 2.32 (m, 2H), 2.03 (ddd, *J* = 14.0, 8.0, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 135.8, 132.7, 131.2, 130.1, 126.4, 124.9, 121.0, 117.5, 113.4, 68.3, 63.4, 51.6, 32.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{14}H_{13}NO_4S_2Br$ 401.9469, found 401.9476. Spectra available at: https://doi.org/10.14469/hpc/5805

3-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (6). Following general procedure C, sulfonamide **6** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 3-bromobenzenesulfonyl chloride (141 mg, 0.55 mmol) in 42% yield (82 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 1.9 Hz, 1H), 7.75 (ddd, *J* = 7.9, 1.7, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.2, 1.9, 1.0 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.19 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 6.88 (td, *J* = 7.6, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.23 (dd, *J* = 8.1, 4.9 Hz, 1H, NH), 4.31 – 4.11 (m, 2H), 3.39 – 3.15 (m, 2H), 2.37 (ddd, *J* = 14.0, 6.3, 3.5 Hz, 1H), 2.31 (br s, 1H, OH), 2.02 (ddd, *J* = 14.0, 8.3, 4.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 141.9, 136.0, 130.9, 130.2, 130.0, 126.4, 125.6,

125.0, 123.4, 121.0, 117.5, 68.5, 63.5, 51.4, 32.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SBr$ 395.9905, found 395.9914. Spectra available at: https://doi.org/10.14469/hpc/5806

Chiral resolution was performed on a Chiralcel® OD-H column using an isocratic gradient of hexane/isopropanol, 8:2 to yield (-)-**6** and (+)-**6**.

(-)-**6**: $[\alpha]_D^{20}$ = - 87° (*c* = 0.53, DCM)

(+)-**6**: $[\alpha]_D^{20}$ = + 68° (*c* = 0.41, DCM)

4-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (7). Following general procedure C, sulfonamide **7** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 3-bromobenzenesulfonyl chloride (141 mg, 0.55 mmol) in 54% yield (107 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (app d, *J* = 8.8 Hz, 2H), 7.62 (app d, *J* = 8.9 Hz, 2H), 7.25 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.16 (ddd, *J* = 8.8, 7.3, 1.6 Hz, 1H), 6.84 (td, *J* = 7.7, 1.2 Hz, 1H), 6.79 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.47 (t, *J* = 6.6 Hz, 1H, NH), 4.23 – 4.08 (m, 2H), 3.32 – 3.13 (m, 2H), 2.66 (s, 1H, OH), 2.31 (ddd, *J* = 14.0, 6.3, 3.5 Hz, 1H), 1.98 (ddd, *J* = 13.8, 8.2, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 138.8, 132.6, 130.1, 128.6, 127.9, 126.4, 125.0, 121.0, 117.4, 68.4, 63.4, 51.4, 32.8. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SBr$ 395.9905, found 395.9915. Spectra available at: https://doi.org/10.14469/hpc/5807

2-Chloro-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (8). Following general procedure C, sulfonamide **8** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 2-chlorobenzenesulfonyl chloride (0.093 mL, 0.55 mmol) in 53% yield (93 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 1H), 7.58 – 7.48 (m, 2H), 7.41 (ddd, *J* = 8.5, 6.6, 2.1 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.17 (ddd, *J* = 8.6, 7.4, 1.6 Hz, 1H), 6.86 (td, *J* = 7.6, 1.0 Hz, 1H), 6.80 (dd, *J* = 8.3, 0.9 Hz, 1H), 5.53 (t, *J* =

6.6 Hz, 1H, NH), 4.28 – 4.11 (m, 2H), 3.27 – 3.11 (m, 2H), 2.43 – 2.37 (m, 2H), 2.02 (ddd, *J* = 13.8, 8.0, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 137.0, 134.0, 131.8, 131.4, 131.4, 130.1, 127.4, 126.4, 125.0, 121.0, 117.4, 68.3, 63.4, 51.5, 32.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SCl$ 352.0410, found 352.0412. Spectra available at: https://doi.org/10.14469/hpc/5808

3-Chloro-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (9). Following general procedure C, sulfonamide **9** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 3-chlorobenzenesulfonyl chloride (0.083 mL, 0.55 mmol) in 57% yield (101 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, *J* = 1.9 Hz, 1H), 7.72 (app d, *J* = 7.8 Hz, 1H), 7.56 (ddd, *J* = 8.0, 1.8, 0.9 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.19 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.13 (dd, *J* = 8.4, 4.6 Hz, 1H, NH), 4.31 – 4.13 (m, 2H), 3.38 – 3.21 (m, 2H), 2.39 (ddd, *J* = 14.0, 6.3, 3.4 Hz, 1H), 2.18 (br s, 1H, OH), 2.02 (ddd, *J* = 13.2, 8.6, 4.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 141.7, 135.6, 133.1, 130.7, 130.2, 127.2, 126.4, 125.2, 125.0, 121.0, 117.5, 68.5, 63.5, 51.5, 32.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SCl$ 352.0410, found 352.0406. Spectra available at: https://doi.org/10.14469/hpc/5809

4-Chloro-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (10). Following general procedure C, sulfonamide **10** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 4-chlorobenzenesulfonyl chloride (120 mg, 0.55 mmol) in 20% yield (28 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 2H), 7.53 – 7.46 (m, 2H), 7.29 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.20 (ddd, *J* = 8.8, 7.3, 1.6 Hz, 1H), 6.89 (td, *J* = 7.7, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.98 (dd, *J* = 8.4, 4.6 Hz, 1H), 4.30 – 4.15 (m, 2H), 3.37 – 3.21 (m, 2H), 2.39 (ddd, *J* = 14.0, 6.3, 3.5 Hz, 1H), 2.17 – 1.97 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 139.5, 138.5, 130.2, 129.7, 128.6, 126.3, 125.1, 121.1, 117.5, 68.5,

63.5, 51.5, 33.0. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SCl$ 352.0410, found 352.0405. Spectra available at: https://doi.org/10.14469/hpc/5810

***N*-((4-Hydroxychroman-4-yl)methyl)benzenesulfonamide (11).** Following general procedure C, sulfonamide **11** was obtained from aminoalcohol **2** (50 mg, 0.28 mmol) and benzenesulfonyl chloride (0.04 mL, 0.31 mmol) in 74% yield (66 mg) as a white solid. Column chromatography: DCM/1% NH_4OH in MeOH, 98:2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H), 7.63 – 7.57 (m, 1H), 7.56 – 7.50 (m, 2H), 7.29 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.20 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 6.92 – 6.86 (m, 1H), 6.83 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.86 (dd, *J* = 8.1, 4.9 Hz, 1H, NH), 4.30 – 4.14 (m, 2H), 3.37 – 3.19 (m, 2H), 2.40 (ddd, *J* = 14.0, 6.4, 3.5 Hz, 1H), 2.06 – 1.97 (m, 2H, OH, ½CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 139.9, 133.0, 130.1, 129.4, 127.1, 126.4, 125.2, 121.0, 117.5, 68.5, 63.5, 51.5, 33.0. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{16}NO_4S$ 318.0800, found 318.0806. Spectra available at: https://doi.org/10.14469/hpc/5811

***N*-((4-Hydroxychroman-4-yl)methyl)-4-methoxybenzenesulfonamide (12).** Following general procedure C, sulfonamide **12** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 4-methoxybenzenesulfonyl chloride (114 mg, 0.55 mmol) in 30% yield (52 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 2H), 7.29 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.17 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.87 (td, *J* = 7.6, 1.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.07 (t, *J* = 6.7 Hz, 1H, NH), 4.26 – 4.11 (m, 2H), 3.86 (s, 3H), 3.22 (d, *J* = 6.9 Hz, 2H), 2.39 – 2.33 (m, 2H), 2.00 (ddd, *J* = 14.0, 8.3, 4.0 Hz, 1H). MS: *m/z* (ES) 348 $[M-H]^-$. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 154.7, 131.3, 130.0, 129.3, 126.4, 125.3, 120.9, 117.4, 114.5, 68.4, 63.5, 55.8, 51.5, 33.0. HRMS (ESI) calcd for $[M-H]^-$ $C_{17}H_{18}NO_5S$ 348.0906, found 348.0910. Spectra available at: https://doi.org/10.14469/hpc/5812

4-Cyano-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (13). Following general procedure C, sulfonamide **13** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 4-cyanobenzenesulfonyl chloride (112 mg, 0.55 mmol) in 65% yield (111 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.30 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.20 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.51 (dd, *J* = 8.4, 4.5 Hz, 1H, NH), 4.34 – 4.14 (m, 2H), 3.44 – 3.18 (m, 2H), 2.51 (s, 1H, OH), 2.37 (ddd, *J* = 14.0, 6.1, 3.4 Hz, 1H), 2.04 (ddd, *J* = 13.3, 8.6, 4.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 144.3, 133.2, 130.2, 127.7, 126.3, 124.9, 121.0, 117.5, 117.4, 116.6, 68.5, 63.4, 51.5, 32.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{17}H_{15}N_2O_4S$ 343.0753, found 343.0748. Spectra available at: https://doi.org/10.14469/hpc/5813

3-Acetyl-*N*-((4-hydroxychroman-4-yl)methyl)benzenesulfonamide (14). Following general procedure C, sulfonamide **14** was obtained from aminoalcohol **2** (71 mg, 0.40 mmol) and 3-acetylbenzenesulfonyl chloride (120 mg, 0.50 mmol) in 4% yield (6.3 mg) as a white solid. Column chromatography: hexane/EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (t, *J* = 1.8 Hz, 1H), 8.16 (app d, *J* = 7.8 Hz, 1H), 8.03 (app d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.19 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 6.88 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.04 (dd, *J* = 8.7, 4.4 Hz, 1H, NH), 4.34 – 4.15 (m, 2H), 3.40 – 3.16 (m, 2H), 2.65 (s, 3H), 2.41 (ddd, *J* = 14.0, 6.2, 3.5 Hz, 1H), 2.04 (ddd, *J* = 13.4, 8.1, 4.4 Hz, 1H), 1.61 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 154.7, 141.0, 138.1, 132.3, 131.2, 130.2, 129.9, 126.8, 126.3, 125.0, 121.0, 117.5, 68.5, 63.5, 51.5, 33.0, 26.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{18}H_{18}NO_5S$ 360.0906, found 360.0887. Spectra available at: https://doi.org/10.14469/hpc/5814

3-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)-*N*-methyl benzenesulfonamide (15). To a stirred suspension of sulfonamide **6** (40 mg, 0.10 mmol) and K_2CO_3 (48 mg, 0.35 mmol) in DMF (1.5 mL), methyl iodide (14 μL, 0.20 mmol) was added dropwise and the solution heated to 50 °C for 4 h. The mixture was diluted with EtOAc, washed with water (3x) and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography (hexane/EtOAc, 3:1) to afford methylated sulfonamide **15** as a pale brown oil (36 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, *J* = 1.8 Hz, 1H), 7.72 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.68 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.20 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 6.91 (ddd, *J* = 7.7, 7.3, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.37 – 4.26 (m, 2H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.11 (dd, *J* = 14.5, 0.7 Hz, 1H), 2.94 (s, 3H), 2.57 (ddd, *J* = 14.0, 5.5, 3.1 Hz, 1H), 2.33 (s, 1H, OH), 2.10 (dddd, *J* = 13.9, 9.4, 4.4, 0.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 139.3, 136.0, 130.8, 130.3, 129.9, 126.7, 126.2, 126.0, 123.4, 120.9, 117.4, 70.0, 63.8, 58.6, 38.3, 33.2. HRMS, found 456.0117 ($C_{18}H_{19}NO_6S^{79}Br$, [M-OH + HCO_2H]$^+$, requires 456.0116). Spectra available at: https://doi.org/10.14469/hpc/5815

5-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)thiophene-2-carboxamide (16). Following general procedure D, amide **16** was obtained from aminoalcohol **2** (80 mg, 0.45 mmol) and 5-bromo-2-thiophenecarboxylic acid (104 mg, 0.55 mmol) in 55% yield (81 mg) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.48 (m, 2H), 7.19 – 7.12 (m, 2H), 6.91 (td, *J* = 7.8, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.35 – 4.18 (m, 2H), 3.84 (d, *J* = 14.0 Hz, 1H), 3.62 (d, *J* = 14.0 Hz, 1H), 2.12 (ddd, *J* = 14.0, 6.4, 3.2 Hz, 1H), 2.00 (m, ddd, *J* = 13.2, 9.1, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 163.7, 155.9, 141.8, 132.3, 130.2 130.1, 128.2, 127.6, 121.55, 119.2, 117.8, 70.0, 64.6, 49.6, 49.4, 49.2, 49.0, 48.8, 34.2. HRMS (ESI) calcd for [M-H]$^-$ $C_{15}H_{13}NO_3SBr$ 365.9756, found 365.9771. Spectra available at: https://doi.org/10.14469/hpc/5822

3-Bromo-*N*-((4-hydroxychroman-4-yl)methyl)benzamide (17). Following general procedure D, amide **17** was obtained from aminoalcohol **2** (134 mg, 0.75 mmol) and 3-bromobenzoic acid (165 mg, 0.82 mmol) in 68% yield (184 mg) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.99 (app s, 1H), 7.78 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.69 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.20 – 7.11 (m, 1H), 6.91 (dd, *J* = 10.7, 4.4 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.23 (ddd, *J* = 10.5, 6.5, 3.7 Hz, 1H), 3.88 (d, *J* = 13.9 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 2.14 (ddd, *J* = 14.0, 6.5, 3.1 Hz, 1H), 2.02 (ddd, *J* = 13.2, 9.1, 4.0 Hz, 1H).^{13}C NMR (101 MHz, MeOD) δ 169.2, 155.9, 137.7, 135.6, 131.5, 131.4, 130.2, 128.2, 127.6, 127.2, 123.5, 121.5, 117.8, 70.0, 64.6, 49.8, 34.3. HRMS (ESI) calcd for $[M-H]^-$ $C_{17}H_{15}NO_3Br$ 360.0235, found 360.0229. Spectra available at: https://doi.org/10.14469/hpc/5823

4-((((5-Bromothiophen-2-yl)methyl)amino)methyl)chroman-4-ol (18). Following general procedure E, amine **18** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 5-bromothiophene-2-carbaldehyde (0.06 mL, 0.50 mmol) in 50% yield (89 mg) as a colourless oil. ^{1}H NMR (400 MHz, MeOD) δ 7.41 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.16 – 7.09 (m, 1H), 6.94 – 6.85 (m, 2H), 6.75 (dd, *J* = 11.2, 2.5 Hz, 2H), 4.25 – 4.13 (m, 2H), 3.94, 3.90 (ABq, J_{AB} = 14.4 Hz, 2H), 2.92 (s, 2H), 2.36 (ddd, *J* = 13.9, 7.4, 4.2 Hz, 1H), 1.96 (ddd, *J* = 14.0, 6.7, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 156.2, 147.6, 130.7, 130.0, 128.0, 127.9, 126.8, 121.5, 117.8, 111.7, 69.1, 64.3, 58.5, 49.6, 34.7. HRMS (ESI) calcd for $[M-H]^-$ $C_{15}H_{17}NO_2SBr$ 354.0163, found 354.0164. Spectra available at: https://doi.org/10.14469/hpc/5824

4-(((3-Bromobenzyl)amino)methyl)chroman-4-ol (19). Following general procedure E, amine **19** was obtained from aminoalcohol **2** (90 mg, 0.50 mmol) and 3-bromobenzaldehyde (0.06 mL, 0.50 mmol) in 10% yield (18 mg) as a colourless oil. ^{1}H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.44 – 7.35 (m, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.16 – 7.10 (m, 1H), 6.88

(td, *J* = 7.8, 0.9 Hz, 1H), 6.75 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.27 – 4.11 (m, 2H), 3.80, 3.75 (ABq, *J* = 13.7 Hz, 2H), 2.94 – 2.82 (m, 2H), 2.36 (ddd, *J* = 14.0, 7.6, 4.1 Hz, 1H), 1.96 (ddd, *J* = 14.0, 6.8, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 156.2, 144.0, 132.3, 131.2, 131.1, 130.0, 128.2, 128.0, 127.9, 123.4, 121.5, 117.8, 69.1, 64.3, 58.7, 54.2, 34.8. HRMS (ESI) calcd for $[M-H]^-$ $C_{17}H_{19}NO_2Br$ 348.0599, found 348.0606. Spectra available at: https://doi.org/10.14469/hpc/5825

6-(Allyloxy)chroman-4-one (20). To a suspension of 6-hydroxy-4-chromanone (0.83 g, 5.1 mmol) and K_2CO_3 (1.1 g, 7.6 mmol) in acetone (30 mL), allyl bromide (0.48 mL, 5.1 mmol) was added dropwise and the reaction was refluxed for 24 h. The resulting mixture was diluted with EtOAc and washed with sat. NH_4Cl (3x). The combined aq. layers were extracted with EtOAc (2x). Combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc, 9:1) to provide ketone **20** as a colourless oil (880 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 3.2 Hz, 1H), 7.03 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 5.97 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.35 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.45 – 4.40 (m, 4H), 2.72 – 2.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 156.5, 152.8, 132.9, 125.5, 121.0, 119.1, 117.7, 108.6, 69.2, 67.0, 37.6. HRMS (ESI) calcd for $[M+H]^+$ $C_{12}H_{13}O_3$ 205.0859, found 205.0860. Spectra available at: https://doi.org/10.14469/hpc/5826

8-Methoxychroman-4-one (21). Eaton's reagent (15 mL) was added dropwise to a flask containing carboxylic acid **46** (600 mg, 3.10 mmol) and the mixture was stirred at rt overnight. The reaction was quenched with sat. $NaHCO_3$, and the resulting mixture extracted with DCM (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide chromanone **21** as a yellow powder (480 mg, 88% yield). The spectroscopic data corresponds with those previously reported.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.98

(t, *J* = 8.0 Hz, 1H), 4.72 – 4.53 (m, 2H), 3.93 (s, 3H), 2.93 – 2.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 152.0, 149.0, 122.1, 120.9, 118.5, 116.8, 77.5, 77.2, 76.8, 67.8, 56.4, 37.8. HRMS (ESI) calculated for $[M+H]^+$ $C_{10}H_{10}O_3$ 179.0708, found 179.0715. Spectra available at: https://doi.org/10.14469/hpc/5827

6-Bromo-4-((trimethylsilyl)oxy)chromane-4-carbonitrile (22). Following general procedure A, cyanohydrin **22** was obtained from 6-bromo-4-chromanone (454 mg, 2 mmol) in 96% yield (626 mg) as an orange oil which was used in the next step without further purification. ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 2.4 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.44 – 4.24 (m, 2H), 2.47 (ddd, *J* = 13.1, 8.7, 4.4 Hz, 1H), 2.38 (ddd, *J* = 13.9, 5.5, 3.4 Hz, 1H), 0.21 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 154.3, 135.3, 131.9, 124.5, 121.7, 120.9, 113.3, 66.7, 62.9, 36.9, 1.2. Spectra available at: https://doi.org/10.14469/hpc/5828

6-Fluoro-4-((trimethylsilyl)oxy)chromane-4-carbonitrile (24). Following general procedure A, cyanohydrin **24** was obtained from 6-fluorochroman-4-one (500 mg, 3.00 mmol) in 90% yield (718 mg) as a yellow oil, and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.6, 3.1 Hz, 1H), 6.99 (ddd, *J* = 9.1, 7.8, 3.1 Hz, 1H), 6.80 (dd, *J* = 9.1, 4.6 Hz, 1H), 4.38 – 4.27 (m, 2H), 2.43 (ddd, *J* = 13.6, 8.0, 4.5 Hz, 1H), 2.35 (ddd, *J* = 13.8, 5.7, 3.7 Hz, 1H), 0.23 (s, 9H). Spectra available at: https://doi.org/10.14469/hpc/6020

7-Fluoro-4-((trimethylsilyl)oxy)chromane-4-carbonitrile (25). Following general procedure A, cyanohydrin **25** was obtained from 7-fluorochroman-4-one (390 mg, 2.4 mmol) in 65% yield (405 mg) as a colourless oil. Column chromatography: hexane/DCM, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.7, 6.2 Hz, 1H), 6.71 (ddd, *J* = 8.7, 8.0, 2.6 Hz, 1H), 6.56 (dd, *J* = 10.0, 2.6 Hz, 1H), 4.40 – 4.28 (m, 2H), 2.46 – 2.32 (m, 2H), 0.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3 (d, *J* = 249.0 Hz), 155.0 (d, *J* = 12.7 Hz), 130.3 (d, *J* = 10.4 Hz), 120.9, 117.3 (d, *J* = 2.9 Hz),

108.6 (d, *J* = 22.4 Hz), 104.6 (d, *J* = 24.8 Hz), 65.2, 61.8, 36.2, 1.3. Spectra available at: https://doi.org/10.14469/hpc/5829

8-Methoxy-4-((trimethylsilyl)oxy)chromane-4-carbonitrile (26). Following general procedure A, cyanohydrin **26** was obtained from chromanone **21** (460 mg, 2.6 mmol) in 91% yield (652 mg) and was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.94 (t, *J* = 7.9 Hz, 1H), 6.89 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.48 (ddd, *J* = 11.5, 4.8, 4.0 Hz, 1H), 4.40 (ddd, *J* = 11.5, 9.8, 3.2 Hz, 1H), 3.88 (s, 3H), 2.48 – 2.36 (m, 2H), 0.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 143.4, 121.4, 121.1, 120.5, 120.4, 112.6, 65.5, 61.9, 56.2, 36.3, 1.3. Spectra available at: https://doi.org/10.14469/hpc/5830

2-Phenyl-4-((trimethylsilyl)oxy)chromane-4-carbonitrile (27). Following general procedure A, cyanohydrin **27** was obtained from flavonone (500 mg, 2.23 mmol) in 12% yield (90 mg) as a light yellow oil, which and was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.50 – 7.38 (m, 5H), 7.29 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.92 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.40 (dd, *J* = 12.1, 1.7 Hz, 1H), 2.67 (dd, *J* = 13.4, 1.8 Hz, 1H), 2.49 (dd, *J* = 13.4, 12.2 Hz, 1H), 0.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 139.1, 131.1, 129.0, 128.9, 127.6, 126.4, 122.6, 121.8, 121.4, 117.6, 75.9, 67.1, 43.9, 1.5. Spectra available at: https://doi.org/10.14469/hpc/5831

4-(Aminomethyl)-6-bromochroman-4-ol (28). Following general procedure B, aminoalcohol **28** was obtained from cyanohydrin **22** (652 mg, 2 mmol) in 23% yield (115 mg) as a colourless oil. Column chromatography: DCM/7N NH_3 in MeOH, 98:2. ^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 2.5 Hz, 1H), 7.27 (dt, *J* = 7.1, 3.6 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 4.31 – 4.17 (m, 2H), 2.94, 2.90 (ABq, J_{AB} = 13.6 Hz, 2H), 2.23 (ddd, *J* = 14.1, 6.6, 3.6 Hz, 1H), 1.98 (ddd, *J* = 14.0, 8.1, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 155.2, 132.8, 130.7, 130.7, 119.9, 113.3, 69.3, 64.6, 51.5,

33.0. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{13}NO_2Br$ 258.0130, found 258.0134. Spectra available at: https://doi.org/10.14469/hpc/5832

6-(Allyloxy)-4-(aminomethyl)chroman-4-ol (29). Following general procedures A and B, aminoalcohol **29** was obtained from ketone **20** (640 mg, 3.0 mmol) in 70% yield over two steps (630 mg). Column chromatography: DCM/7N NH_3 in MeOH, 10:0 to 9:1. ^{1}H NMR (400 MHz, MeOD) δ 7.00 (d, *J* = 2.9 Hz, 1H), 6.77 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.70 (d, *J* = 8.9 Hz, 1H), 6.04 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1H), 5.38 (app dq, *J* = 17.3, 1.6 Hz, 1H), 5.23 (app dq, *J* = 10.7, 1.4 Hz, 1H), 4.48 (dt, *J* = 5.1, 1.4 Hz, 2H), 4.20 – 4.11 (m, 2H), 2.90 (q, *J* = 13.6 Hz, 2H), 2.18 (ddd, *J* = 14.0, 7.0, 4.0 Hz, 1H), 1.94 (ddd, *J* = 14.0, 7.1, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 153.9, 150.3, 135.2, 128.4, 118.5, 117.39, 117.35 113.5, 70.4, 69.6, 64.2, 51.8, 33.8. HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_{18}NO_3$ 236.1282, found 236.1287. Spectra available at: https://doi.org/10.14469/hpc/5833

4-(Aminomethyl)-6-fluorochroman-4-ol (30). Following general procedure B, aminoalcohol **30** was obtained from cyanohydrin **24** (718 mg, 2.70 mmol) in 48% yield (253 mg) as a yellow solid. Column chromatography: DCM/10% NH_4OH in MeOH, 8:2. ^{1}H NMR (400 MHz, MeOD) δ 7.15 (dd, *J* = 9.6, 3.1 Hz, 1H), 6.90 (ddd, *J* = 9.0, 8.0, 3.1 Hz, 1H), 6.77 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.25 – 4.15 (m, 2H), 2.95 (d, *J* = 13.5 Hz, 1H), 2.89 (d, *J* = 13.6 Hz, 1H), 2.21 (ddd, *J* = 14.1, 6.6, 3.9 Hz, 1H), 1.97 (ddd, *J* = 14.0, 7.5, 4.4 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 156. 9 (d, *J* = 236.6 Hz), 128.0 (d, *J* = 6.2 Hz), 117.6 (d, *J* = 7.8 Hz), 115.3 (d, *J* = 23.6 Hz), 112.4 (d, *J* = 23.6 Hz), 67.9, 63.1, 50.1, 31.9. Spectra available at: https://doi.org/10.14469/hpc/6021

4-(Aminomethyl)-7-fluorochroman-4-ol (31). Following general procedure B, aminoalcohol **31** was obtained from cyanohydrin **25** (400 mg, 1.5 mmol) in 27% yield (80 mg) as a yellow oil. Column chromatography: DCM/7N NH_3 in MeOH, 99:1 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.37 (dd, *J* = 8.7, 6.6 Hz, 1H), 6.64 (ddd, *J* = 8.4, 2.6 Hz, 1H), 6.53 (dd, *J* = 10.2, 2.6 Hz, 1H), 4.31 – 4.18 (m, 2H), 3.02 (d, *J* = 13.0 Hz, 1H), 2.92 (d, *J* = 13.0 Hz, 1H), 2.04 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, *J* = 245.8 Hz), 156.2 (d, *J* = 12.2 Hz), 128.2 (d, *J* = 10.1 Hz), 122.4 (d, *J* = 2.4 Hz), 108.2 (d, *J* = 21.8 Hz), 104.0 (d, *J* = 24.2 Hz), 67.5, 63.9, 50.8, 33.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{12}FNO_2$ 198.0930, found 198.0930. Spectra available at: https://doi.org/10.14469/hpc/5834

4-(Aminomethyl)-8-methoxychroman-4-ol (32). Following general procedure B, aminoalcohol **32** was obtained from cyanohydrin **26** (600 mg, 2.2 mmol) in 34% yield (154 mg) as a white powder. Column chromatography: DCM/7N NH_3 in MeOH, 95:5 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.89 (t, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.4 Hz, 1H), 4.40 – 4.27 (m, 2H), 3.87 (s, 3H), 3.07 (d, *J* = 13.1 Hz, 1H), 2.94 (d, *J* = 13.1 Hz, 1H), 2.14 – 2.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 144.5, 127.0, 120.3, 118.3, 110.7, 67.9, 63.9, 56.1, 50.9, 33.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{11}H_{15}NO_3$ 210.1130, found 210.1126. Spectra available at: https://doi.org/10.14469/hpc/5835

4-(Aminomethyl)-2-phenylchroman-4-ol (33). Following general procedure B, aminoalcohol **33** was obtained from cyanohydrin **27** (85 mg, 0.26 mmol) in 61% yield (41 mg) as a white solid after trituration of the crude with diethylether. ^{1}H NMR (400 MHz, MeOD) δ 7.49 – 7.45 (m, 3H), 7.40 – 7.36 (m, 2H), 7.31 (ddd, *J* = 7.2, 3.6, 1.3 Hz, 1H), 7.18 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 6.95 (td, *J* = 7.7, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.15 (dd, *J* = 12.6, 1.9 Hz, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 3.08 (d, *J* = 13.5 Hz, 1H), 2.40 (dd, *J* = 13.9, 2.2 Hz, 1H), 2.17 (ddd, *J* = 13.7, 12.7, 0.8 Hz, 1H), 1.93 (s, 2H, NH_2). ^{13}C NMR (101 MHz, MeOD) δ 154.7, 140.9, 129.8, 129.0, 128.6, 127.0, 126.7, 126.5, 121.3, 117.1, 76.4, 68.9, 50.0, 40.1. HRMS (ESI) calcd for $[M+H]^+$ $C_{16}H_{18}NO_2$ 256.1338, found 256.1339. Spectra available at: https://doi.org/10.14469/hpc/5836

5-Bromo-*N*-((6-bromo-4-hydroxychroman-4-yl)methyl)thiophene-2-sulfonamide (34). Following general procedure C, sulfonamide **34** was obtained from aminoalcohol **28** (26 mg, 0.10 mmol) and 5-bromothiophene-2-sulfonyl chloride (40 mg, 1.5 mmol) in 83% yield (40 mg) as a white solid. Column chromatography: petroleum ether/Et_2O, 1:2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.5 Hz, 1H), 7.37 (d, *J* = 4.0 Hz, 1H), 7.25 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.16 (d, *J* = 4.0 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 4.29 – 4.15 (m, 2H), 3.31 (ddd, *J* = 9.4, 8.0, 7.6 Hz, 3H), 3.18 (d, *J* = 13.4 Hz, 1H), 2.31 (ddd, *J* = 14.1, 6.0, 3.8 Hz, 1H), 1.96 (ddd, *J* = 13.4, 8.3, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 144.2, 133.1, 132.0, 131.1, 129.6, 120.0, 119.9, 113.4, 68.6, 64.6, 52.7, 33.5. HRMS (ESI) calcd for $[M-H]^-$ $C_{14}H_{12}NO_4SBr_2$ 479.8574, found 479.8586. Spectra available at: https://doi.org/10.14469/hpc/5837

3-Bromo-*N*-((6-bromo-4-hydroxychroman-4-yl)methyl)benzenesulfonamide (35). Following general procedure C, sulfonamide **35** was obtained from aminoalcohol **28** (26 mg, 0.10 mmol) and 3-bromobenzenesulfonyl chloride (31 mg, 0.12 mmol) in 90% yield (43 mg) as a white solid. Column chromatography: petroleum ether/Et_2O, 1:2. ^1H NMR (400 MHz, MeOD) δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.80 (app ddd, *J* = 7.8, 1.4, 1.0 Hz, 1H), 7.76 (app ddd, *J* = 8.1, 1.8, 0.9 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.22 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 4.25 – 4.17 (m, 2H), 3.27 (d, *J* = 13.4 Hz, 1H), 3.11 (d, *J* = 13.4 Hz, 1H), 2.36 – 2.28 (m, 1H), 1.99 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 155.2, 144.2, 136.5, 133.1, 132.0, 131.0, 130.6, 129.6, 126.6, 123.8, 119.8, 113.3, 68.7, 64.5, 52.5, 33.4. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{14}NO_4SBr_2$ 473.9010, found 473.9025. Spectra available at: https://doi.org/10.14469/hpc/5838

***N*-((6-(Allyloxy)-4-hydroxychroman-4-yl)methyl)-3-bromobenzenesulfonamide (36).** Following general procedure C, sulfonamide **36** was obtained from aminoalcohol **29** (540 mg, 2.3 mmol) and 3-bromobenzenesulfonyl chloride (980 mg, 3.4 mmol) 53% yield (558 mg). Column

chromatography: hexane/EtOAc, 7:3. ^{1}H NMR (400 MHz, DMSO) δ 7.97 (t, *J* = 1.7 Hz, 1H), 7.88 (br s, 1H, OH), 7.84 (ddd, *J* = 8.0, 1.8, 0.9 Hz, 1H), 7.80 (ddd, *J* = 7.8, 1.4, 0.8 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 3.0 Hz, 1H), 6.75 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.69 (d, *J* = 8.9 Hz, 1H), 6.00 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1H), 5.39 – 5.33 (m, 2H, NH, ½CH_2=), 5.21 (dq, *J* = 10.5, 1.6 Hz, 1H), 4.49 – 4.40 (m, 2H), 4.13 – 4.06 (m, 2H), 3.13 (d, *J* = 13.3 Hz, 1H), 2.97 (d, *J* = 13.2 Hz, 1H), 2.19 (ddd, *J* = 13.8, 6.4, 3.6 Hz, 1H), 1.82 (ddd, *J* = 12.1, 7.5, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 151.7, 148.2, 142.9, 135.1, 134.1, 131.3, 128.9, 127.3, 125.5, 122.0, 117.0, 116.8, 115.8, 112.9, 68.6, 67.1, 62.6, 51.1, 32.4. HRMS (ESI) calcd for [M-H]$^{-}$ $C_{19}H_{19}NO_5SBr$ 452.0167, found 454.0161. Spectra available at: https://doi.org/10.14469/hpc/5839

3-Bromo-*N*-((4,6-dihydroxychroman-4-yl)methyl)benzene-sulfonamide (37). To a solution of compound **36** (530 mg, 1.2 mmol) in MeOH (20 mL), $Pd(PPh_3)_4$ (135 mg, 0.3 mmol) was added and the mixture stirred for 10 min. K_2CO_3 (481 mg, 3.5 mmol) was then added and the reaction was refluxed for 16 h. The resulting solution was concentrated *in vacuo*, taken up in DCM, washed with H_2O (3x), extracted with DCM (2x), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc, 1:1) to yield phenol **37** as a white solid (356 mg, 75%). ^{1}H NMR (400 MHz, DMSO) δ 8.84 (s, 1H, OH), 7.98 (t, *J* = 1.8 Hz, 1H), 7.87 – 7.82 (m, 2H, OH, CH), 7.80 (ddd, *J* = 7.8, 1.4, 0.9 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 6.71 (t, *J* = 1.5 Hz, 1H), 6.55 (d, *J* = 1.5 Hz, 2H), 5.33 (s, 1H, NH), 4.10 – 4.00 (m, 2H), 3.04 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.88 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.16 (ddd, *J* = 13.7, 6.5, 3.2 Hz, 1H), 1.81 (ddd, *J* = 13.3, 8.2, 3.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 150.6, 146.9, 142.8, 135.2, 131.4, 129.0, 127.4, 125.6, 122.1, 116.8, 116.0, 113.1, 67.1, 62.7, 51.3, 32.5. HRMS (ESI) calcd for [M-H]$^{-}$ $C_{16}H_{15}NO_5SBr$ 411.9854, found 411.9860. Spectra available at: https://doi.org/10.14469/hpc/5840

5-Bromo-*N*-((6-fluoro-4-hydroxychroman-4-yl)methyl)thiophene-2-sulfonamide (38). Following general procedure C, sulfonamide **38** was obtained from aminoalcohol **30** (48 mg, 0.24 mmol) and 5-bromothiophene-2-sulfonyl chloride (78 mg, 0.30 mmol) in 28% yield (29 mg) as a white solid. Reverse phase column chromatography: ACN/H_2O, 5:95. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 4.0 Hz, 1H), 7.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.92 (ddd, *J* = 9.0, 7.8, 3.1 Hz, 1H), 6.79 (dd, *J* = 9.0, 4.7 Hz, 1H), 4.97 (br s, 1H, NH), 4.25-4.14 (m, 2H), 3.29 (dd, *J* = 30.8, 13.0 Hz, 2H), 2.40 (ddd, *J* = 14.1, 5.9, 3.1 Hz, 1H), 2.03-1.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (d, *J* = 239.5 Hz), 150.7, 141.5, 132.4, 130.6, 126.0 (d, *J* = 6.1 Hz), 120.3, 118.6 (d, *J* = 7.8 Hz), 117.3 (d, *J* = 23.2 Hz), 112.6 (d, *J* = 23.6 Hz), 68.6, 63.6, 51.6, 32.8. HRMS (ESI) calcd for $[M\text{-}OH+H]^+$ $C_{14}H_{12}BrFNO_3S_2$ 403.9426, found 403.9420. Spectra available at: https://doi.org/10.14469/hpc/6022

3-Bromo-*N*-((6-fluoro-4-hydroxychroman-4-yl)methyl)benzenesulfonamide (39). Following general procedure C, sulfonamide **39** was obtained from aminoalcohol **30** (49 mg, 0.25 mmol) and 3-bromobenzenesulfonyl chloride (76 mg, 0.30 mmol) in 35% yield (37 mg) as a pale-yellow solid. Reverse phase column chromatography: ACN/H_2O, 5:95. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.8 Hz, 1H), 7.77 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.73 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.01 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.91 (ddd, *J* = 9.0, 7.8, 3.1 Hz, 1H), 6.78 (dd, *J* = 9.0, 4.7 Hz, 1H), 4.99 (s, 1H), 4.32 – 4.14 (m, 2H), 3.32 (dd, *J* = 13.2, 6.8 Hz, 1H), 3.19 (d, *J* = 13.9 Hz, 1H), 2.43 (ddd, *J* = 14.0, 5.8, 3.1 Hz, 1H), 2.19 – 1.88 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (d, *J* = 239.3 Hz), 155.8, 150.6, 141.7, 136.1, 131.0, 129.9, 126.0 (d, *J* = 6.4 Hz), 125.5, 123.4, 118.5 (d, *J* = 7.8 Hz), 117.1 (d, *J* = 23.3 Hz), 112.6 (d, *J* = 23.5 Hz), 68.7, 63.6, 51.4, 32.6. HRMS (ESI) calcd for $[M\text{-}OH+H]^+$ $C_{16}H_{14}BrFNO_3S$ 397.9862, found 397.9859. Spectra available at: https://doi.org/10.14469/hpc/6023

5-Bromo-*N*-((7-fluoro-4-hydroxychroman-4-yl)methyl)thiophene-2-sulfonamide (40). Following general procedure C, sulfonamide **40** was obtained from aminoalcohol **31** (35 mg, 0.2 mmol) and 5-bromothiophene-2-sulfonyl chloride (52 mg, 0.2 mmol) in 53% yield (40 mg) as a yellow powder. Column chromatography: pentane/EtOAc, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.0 Hz, 1H), 7.31 (dd, *J* = 8.8, 6.4 Hz, 1H), 7.07 (d, *J* = 4.0 Hz, 1H), 6.63 (ddd, *J* = 8.6, 8.1, 2.6 Hz, 1H), 6.54 (dd, *J* = 10.1, 2.6 Hz, 1H), 5.12 (t, *J* = 6.5 Hz, 1H, NH), 4.30 – 4.18 (m, 2H), 3.38 – 3.25 (m, 2H), 2.37 (ddd, *J* = 14.1, 6.3, 3.4 Hz, 1H), 2.09 – 1.97 (m, 2H, OH, ½CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (d, *J* = 247.4 Hz), 156.1 (d, *J* = 12.4 Hz), 141.7, 132.4, 130.6, 127.9 (d, *J* = 10.1 Hz), 121.2 (d, *J* = 2.7 Hz), 120.3, 108.6 (d, *J* = 22.1 Hz), 104.5 (d, *J* = 24.3 Hz), 68.2, 63.9, 51.7, 33.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ -110.8 (dd, *J* = 16.3, 7.9 Hz). HRMS (ESI) calcd for $[M-H]^-$ $C_{14}H_{13}BrFNO_4S_2$ 419.9375, found 419.9368. Spectra available at: https://doi.org/10.14469/hpc/5841

3-Bromo-*N*-((7-fluoro-4-hydroxychroman-4-yl)methyl)benzenesulfonamide (41). Following general procedure C, sulfonamide **41** was obtained from aminoalcohol **31** (35 mg, 0.2 mmol) and 3-bromobenzenesulfonyl chloride (51 mg, 0.2 mmol) in 53% yield (40 mg) as a white powder. Column chromatography: pentane/EtOAc, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.76 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H), 7.72 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 8.6, 6.3 Hz, 1H), 6.61 (ddd, *J* = 8.7, 8.0, 2.6 Hz, 1H), 6.53 (dd, *J* = 10.1, 2.6 Hz, 1H), 5.10 (dd, *J* = 8.2, 4.7 Hz, 1H, NH), 4.32 – 4.17 (m, 2H), 3.32 – 3.21 (m, 2H), 2.37 (ddd, *J* = 14.1, 6.2, 3.3 Hz, 1H), 2.14 (br s, 1H, OH), 2.06 – 1.95 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (d, *J* = 247.8 Hz), 156.1 (d, *J* = 12.4 Hz), 142.0, 136.1, 130.9, 130.0, 127.9 (d, *J* = 10.1 Hz), 125.6, 123.4, 121.2 (d, *J* = 3.0 Hz), 108.5 (d, *J* = 22.2 Hz), 104.4 (d, *J* = 24.5 Hz), 68.3, 63.9, 51.5, 32.9. ^{19}F NMR (377 MHz, $CDCl_3$) δ -110.93 (dd, *J* = 16.3, 7.9 Hz). HRMS (ESI) calcd for $[M-H]^-$

$C_{16}H_{15}BrFNO_4S$ 413.9811, found 413.9820. Spectra available at: https://doi.org/10.14469/hpc/5842

Chiral resolution was performed on a Chiralpack® IE-3 column using an isocratic gradient of hexane/isopropanol, 7:3 to yield (-)-**41** and (+)-**41**.

(+)-**41**: $[\alpha]_D^{20}$ = + 74° (*c* = 0.49, $CDCl_3$)

(-)-**41**: $[\alpha]_D^{20}$ = - 82° (*c* = 0.41, $CDCl_3$)

5-Bromo-*N*-((4-hydroxy-8-methoxychroman-4-yl)methyl)thiophene-2-sulfonamide (42). Following general procedure C, sulfonamide **42** was obtained from aminoalcohol **32** (60 mg, 0.3 mmol) and 5-bromothiophene-2-sulfonyl chloride (84 mg, 0.3 mmol) in 67% yield (86 mg) as a yellow powder. Column chromatography: hexane/EtOAc, 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.0 Hz, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.89 (t, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.93 (dd, *J* = 7.2, 5.8 Hz, 1H, NH), 4.41 – 4.26 (m, 2H), 3.87 (s, 3H), 3.43 – 3.30 (m, 2H), 2.39 (ddd, *J* = 14.1, 6.6, 3.8 Hz, 1H), 2.10 – 1.98 (m, 2H, OH, ½CH_2). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.6, 144.4, 141.6, 132.4, 130.6, 125.5, 120.7, 120.2, 117.7, 111.5, 68.3, 63.8, 56.1, 51.7, 32.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{15}H_{16}BrNO_5S_2$ 431.9575, found 431.9583. Spectra available at: https://doi.org/10.14469/hpc/5843

3-Bromo-*N*-((4-hydroxy-8-methoxychroman-4-yl)methyl)benzenesulfonamide (43). Following general procedure C, sulfonamide **43** was obtained from aminoalcohol **32** (60 mg, 0.3 mmol) and 3-bromobenzenesulfonyl chloride (82 mg, 0.3 mmol) in 69% yield (86 mg) as a white powder. Column chromatography: hexane/EtOAc, 1:2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.8 Hz, 1H), 7.77 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.71 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 7.7, 1.9 Hz, 1H),

4.85 (dd, *J* = 7.2, 5.5 Hz, 1H, NH), 4.44 – 4.23 (m, 2H), 3.87 (s, 3H), 3.39 – 3.19 (m, 2H), 2.39 (ddd, *J* = 14.1, 6.6, 3.7 Hz, 1H), 2.04 (ddd, *J* = 14.0, 7.8, 4.3 Hz, 1H), 1.98 (s, 1H, OH). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.6, 144.4, 141.9, 136.0, 130.9, 130.0, 125.62, 125.56, 123.3, 120.7, 117.7, 111.5, 68.4, 63.8, 56.1, 51.5, 32.9. HRMS (ESI) calcd for [M-H]$^-$ $C_{17}H_{18}BrNO_5S$ 426.0011, found 426.0011. Spectra available at: https://doi.org/10.14469/hpc/5844

5-Bromo-*N*-((4-hydroxy-2-phenylchroman-4-yl)methyl)thiophene-2-sulfonamide (44). Following general procedure C, sulfonamide **44** was obtained from aminoalcohol **33** (18 mg, 0.07 mmol) and 5-bromothiophene-2-sulfonyl chloride (20 mg, 0.08 mmol) in 28% yield (9.6 mg) as an off-white solid. Column chromatography: DCM/1% NH_4OH in MeOH, 98:2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.44 – 7.40 (m, 3H), 7.37 – 7.33 (m, 2H), 7.27 – 7.23 (m, 1H), 7.05 (d, *J* = 4.0 Hz, 1H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.93 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.23 (dd, *J* = 12.2, 1.8 Hz, 1H), 5.19 (br s, 1H, NH), 3.58 (d, *J* = 13.4 Hz, 1H), 3.30 (dd, *J* = 13.4, 1.6 Hz, 1H), 2.81 (dd, *J* = 13.7, 2.1 Hz, 1H), 2.02 (ddd, *J* = 13.8, 12.4, 1.7 Hz, 1H), 1.87 (br s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 142.0, 140.3, 132.3, 130.6, 130.3, 128.8, 128.4, 126.5, 126.1, 125.6, 121.2, 120.1, 117.4, 76.3, 70.3, 51.8, 40.3. HRMS (ESI) calcd for [M-H]$^-$ $C_{20}H_{17}NO_4S_2Br$ 477.9782, found 477.9777. Spectra available at: https://doi.org/10.14469/hpc/5847

3-Bromo-*N*-((4-hydroxy-2-phenylchroman-4-yl)methyl)benzenesulfonamide (45). Following general procedure C, sulfonamide **45** was obtained from aminoalcohol **33** (15 mg, 0.060 mmol) and 3-bromobenzenesulfonyl chloride (16 mg, 0.064 mmol) in 12% yield (3.3 mg) as a pale yellow solid. Column chromatography: DCM/1% NH_4OH in MeOH, 98:2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 1.8 Hz, 1H), 7.79 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.70 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.44 – 7.31 (m, 5H), 7.26 – 7.21 (m, 1H), 6.98 – 6.92 (m, 2H), 5.25 (dd, *J* =

12.2, 1.7 Hz, 1H), 5.12 (br s, 1H, NH), 3.59 – 3.54 (m, 1H), 3.22 (d, *J* = 12.7 Hz, 1H), 2.84 (dd, *J* = 13.7, 2.1 Hz, 1H), 2.01 (ddd, *J* = 13.9, 12.5, 1.7 Hz, 1H), 1.85 (br s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 142.3, 140.4, 136.0, 130.9, 130.3, 129.9, 128.8, 128.3, 126.5, 126.1, 125.6, 125.5, 123.4, 121.2, 117.4, 76.3, 70.4, 51.6, 40.3. HRMS (ESI) calcd for $[M-H]^-$ $C_{22}H_{19}NO_4SBr$ 472.0218, found 472.0224. Spectra available at: https://doi.org/10.14469/hpc/5846

3-(2-Methoxyphenoxy)propanoic acid (46).[19] A solution of 2-methoxyphenol (2.7 mL, 24 mmol) in DMF (10 mL) was added dropwise to a suspension of NaH (60% suspension in mineral oil, 2.9 g, 72 mmol) in DMF (20 mL). After stirring for 1.5 hours, a solution of 3-bromopropionic acid (3.7 g, 24 mmol) in anhydrous DMF (10 mL) was added dropwise, and the solution was stirred at rt overnight. The reaction was quenched with MeOH, acidified with 1M HCl (pH~3), and extracted with EtOAc (3x). The combined organic phases were washed with 5% LiCl (2x) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was re-dissolved in EtOAc and extracted with sat. $NaHCO_3$. The aqueous layer was acidified with 1M HCl (pH 1) and the resulting precipitate was collected by filtration, washed with H_2O and dried to provide acid **46** as a white solid (824 mg, 17% yield), which was used in the next step without further purification. The spectroscopic data corresponds with those previously reported.[19] ^{1}H NMR (400 MHz $CDCl_3$) δ 6.99 – 6.89 (m, 4H), 4.31 (t, *J* = 6.5 Hz, 2H), 3.85 (s, 3H), 2.91 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 150.0, 148.0, 122.3, 121.2, 114.8, 112.4, 64.8, 56.2, 34.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{12}O_4$ 196.0736, found 196.0740. Spectra available at: https://doi.org/10.14469/hpc/5855

1-(2-(2-Bromoethoxy)phenyl)ethanone (47). To a stirred suspension of 1-(2-hydroxyphenyl)ethanone (0.5 mL, 4.2 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in ACN, 1,2-dibromoethane (4.0 mL, 41.6 mmol) was added and the mixture heated at reflux overnight. Water

was added and the mixture extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (pentane/EtOAc, 100:0 to 95:5) to provide ketone **47** as a pale yellow solid (350 mg, 34% yield). The spectroscopic data correspond with those previously reported.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.04 (td, *J* = 7.7, 0.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.41 (t app, *J* = 5.8 Hz, 2H), 3.72 (t app, *J* = 5.8 Hz, 2H), 2.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 157.4, 133.7, 130.8, 128.8, 121.7, 112.4, 68.4, 32.4, 29.0. HRMS (ESI) calcd for $[M-H]^-$ $C_{10}H_{12}O_2Br$ 243.0021, found 243.0031. Spectra available at: https://doi.org/10.14469/hpc/5856

3,4-Dihydrobenzo[*b*]oxepin-5(2*H*)-one (48). A solution of ketone **47** (350 mg, 1.43 mmol) in the minimum amount of anhydrous THF was added dropwise to a suspension of NaH (60% in mineral oil, 115 mg, 2.87 mmol) in dry THF (3.6 mL) at 0 ºC, and the resulting mixture was allowed to stir at rt overnight. The mixture was cooled down to 0 ºC and water was carefully added until no reaction was observed. The mixture was diluted with water, neutralised with 2N HCl (aq.), extracted with EtOAc (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (pentane/EtOAc, 95:5 to 85:15) to provide ketone **48** as a colourless oil (179 mg, 77% yield). The spectroscopic data correspond with those previously reported.[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.12 – 7.06 (m, 2H), 4.24 (t, *J* = 6.6 Hz, 2H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.22 (p, *J* = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 162.2, 133.9, 129.7, 129.3, 123.0, 121.0, 73.0, 40.8, 26.6. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{11}O_2$ 163.0759, found 163.0751. Spectra available at: https://doi.org/10.14469/hpc/5857

5-((Trimethylsilyl)oxy)-2,3,4,5-tetrahydrobenzo[*b*]oxepine-5-carbonitrile (49). Following general procedure A, cyanohydrin **49** was obtained from ketone **48** (150 mg, 0.92 mmol) in 97%

yield (145 mg) as a white solid. Column chromatography: pentane to pentane/EtOAc, 98:2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.29 (td, *J* = 7.6, 1.6 Hz, 1H), 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 7.04 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.19 (ddd, *J* = 9.7, 5.4, 3.6 Hz, 1H), 3.85 (ddd, *J* = 11.8, 8.7, 2.7 Hz, 1H), 2.32 – 2.12 (m, 4H), 0.22 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 158.2, 133.2, 130.6, 127.4, 124.0, 122.9, 120.5, 73.7, 72.6, 40.2, 26.9, 1.2. HRMS (ESI) calcd for $[M+ACN+Na]^+$ $C_{16}H_{22}N_2O_2SiNa$ 325.1348, found 325.1340. Spectra available at: https://doi.org/10.14469/hpc/5858

5-(Aminomethyl)-2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-ol (50). Following general procedure B, aminoalcohol **50** was obtained from cyanohydrin **49** (200 mg, 0.76 mmol) in 35% yield (52 mg). Column chromatography: 0-10% of EtOAc/EtOH 3:1 in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.18 (td, *J* = 7.6, 1.8 Hz, 1H), 7.10 (td, *J* = 7.5, 1.4 Hz, 1H), 6.97 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.38 (dtd, *J* = 12.0, 3.7, 1.3 Hz, 1H), 3.58 (td, *J* = 11.9, 1.9 Hz, 1H), 3.38 (d, *J* = 12.2 Hz, 1H), 2.85 (d, *J* = 12.2 Hz, 1H), 2.22- 2.10 (m, 1H), 2.09 – 2.03 (m, 1H), 1.95 (dd, *J* = 13.4, 3.7 Hz, 1H), 1.82 – 1.75 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$/MeOD, 9:1) δ 157.0, 137.6, 128.6, 127.4, 123.9, 122.1, 75.6, 73.0, 47.7, 37.1, 26.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{11}H_{16}NO_2$ 194.1181, found 194.1185. Spectra available at: https://doi.org/10.14469/hpc/5859

5-Bromo-*N*-((5-hydroxy-2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-yl)methyl)thiophene-2-sulfonamide (51). Following general procedure C, sulfonamide **51** was obtained from aminoalcohol **50** (25 mg, 0.13 mmol) and 5-bromothiophene-2-sulfonyl chloride (37 mg, 0.14 mmol) in 63% yield (34 mg) as a yellow solid. Column chromatography: 15-30% EtOAc/EtOH 3:1 in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1H), 7.11 (td, *J* = 7.6, 1.3 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 1H), 6.95 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.00 (dd, *J* = 7.7, 4.8 Hz, 1H, NH), 4.31 (ddd, *J* = 11.3, 3.8, 2.7 Hz, 1H),

3.67 – 3.60 (m, 2H), 3.31 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.65 (s, 1H, OH), 2.27 – 2.15 (m, 2H), 1.89 – 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 141.2, 136.7, 132.5, 130.5, 129.4, 126.8, 124.5, 122.6, 120.2, 75.8, 73.1, 49.5, 37.0, 26.5. HRMS (ESI) calcd for $[M-H]^-$ $C_{15}H_{15}BrNO_4S_2$ 415.9626, found 415.9634. Spectra available at: https://doi.org/10.14469/hpc/5860

3-Bromo-*N*-((5-hydroxy-2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-yl)methyl)benzene-sulfonamide (52). Following general procedure C, sulfonamide **52** was obtained from aminoalcohol **50** (25 mg, 0.13 mmol) and 3-bromobenzenesulfonyl chloride (36 mg, 0.14 mmol) in 38% yield (20 mg) as a white solid. Column chromatography: 15-30% EtOAc/EtOH 3:1 in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, *J* = 1.8 Hz, 1H), 7.69 (ddd, *J* = 7.9, 1.5, 1.0 Hz, 1H), 7.66 (ddd, *J* = 8.0, 1.8, 1.0 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.20 (td, *J* = 7.6, 1.7 Hz, 1H), 7.10 (td, *J* = 7.6, 1.3 Hz, 1H), 6.94 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.85 (dd, *J* = 8.1, 4.7 Hz, 1H, NH), 4.33 – 4.29 (m, 1H), 3.66 – 3.58 (m, 2H), 3.23 (dd, *J* = 12.6, 4.7 Hz, 1H), 2.61 (s, 1H, OH), 2.25 – 2.16 (m, 2H), 1.88 – 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 141.5, 136.7, 135.9, 130.8, 130.0, 129.5 126.8, 125.7, 124.4, 123.3, 122.6, 75.9, 73.1, 49.3, 37.0, 26.5. HRMS (ESI) calcd for $[M-H]^-$ $C_{17}H_{17}BrNO_4S$ 410.0062, found 410.0055. Spectra available at: https://doi.org/10.14469/hpc/5861

3-(Aminomethyl)-2,3-dihydrobenzofuran-3-ol (53). To a flask containing benzofuran-3(2*H*)-one (500 mg, 3.73 mmol) and potassium phthalimide (17 mg, 0.09 mmol), trimethylsylilcyanide (0.60 mL, 4.47 mmol) was added, and the resulting mixture was stirred at rt overnight. Water was then added, and the mixture extracted with EtOAc (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield the intermediate cyanohydrin, which due to stability issues was directly submitted to general procedure B to provide aminoalcohol **53** in 35% yield over two steps (202 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.94

(td, *J* = 7.4, 0.7 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.43 (s, 2H), 3.13 (d, *J* = 12.9 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 130.6, 129.8, 123.7, 121.1, 110.8, 81.2, 80.3, 49.3. HRMS (ESI) calcd for $[M+H]^+$ $C_9H_{12}NO_2$ 166.0868, found 166.0866. Spectra available at: https://doi.org/10.14469/hpc/5862

5-Bromo-*N*-((3-hydroxy-2,3-dihydrobenzofuran-3-yl)methyl)thiophene-2-sulfonamide (54). Following general procedure C, sulfonamide **54** was obtained from aminoalcohol **53** (50 mg, 0.30 mmol) and 5-bromothiophene-2-sulfonyl chloride (86 mg, 0.33 mmol) in 50% yield (60 mg) as a yellow solid. Column chromatography: 5-10% EtOAc/EtOH 3:1 in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 4.0 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.09 (d, *J* = 4.0 Hz, 1H), 6.95 (td, *J* = 7.5, 0.8 Hz, 1H), 6.88 (dd, *J* = 8.7, 0.9 Hz, 1H), 5.02 (t, *J* = 6.0 Hz, 1H, NH), 4.57 (d, *J* = 10.7 Hz, 1H), 4.42 (d, *J* = 10.6 Hz, 1H), 3.47 (dd, *J* = 12.6, 5.1 Hz, 1H), 3.37 (dd, *J* = 12.7, 7.2 Hz, 1H), 2.31 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 141.2, 132.7, 131.6, 130.7, 127.8, 123.8, 121.4, 120.5, 111.2, 81.1, 79.7, 50.1. HRMS (ESI) calcd for $[M-H]^-$ $C_{13}H_{11}BrNO_4S_2$ 387.9313, found 387.9320. Spectra available at: https://doi.org/10.14469/hpc/5863

3-Bromo-*N*-((3-hydroxy-2,3-dihydrobenzofuran-3-yl)methyl)benzenesulfonamide (55). Following general procedure C, sulfonamide **55** was obtained from aminoalcohol **53** (50 mg, 0.30 mmol) and 3-bromobenzenesulfonyl chloride (84 mg, 0.33 mmol) in 52% yield (60 mg) as a white solid. Column chromatography: 5-10% EtOAc/EtOH 3:1 in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (t, *J* = 1.8 Hz, 1H), 7.78 (ddd, *J* = 7.9, 1.5, 0.9 Hz, 1H), 7.73 (ddd, *J* = 8.0, 1.7, 0.9 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.93 (td, *J* = 7.6, 0.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.00 (br s, 1H, NH), 4.55 (d, *J* = 10.7 Hz, 1H), 4.40 (d, *J* = 10.7 Hz, 1H), 3.39 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.31 (dd, *J* = 12.5, 6.4 Hz, 1H), 2.36 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 141.5, 136.2, 131.6, 130.9, 130.1, 127.9, 125.7, 123.8, 123.4, 121.4, 111.2, 81.1, 79.8, 50.0.

HRMS (ESI) calcd for $[M-H]^-$ $C_{15}H_{13}BrNO_4S$ 381.9749, found 381.9753. Spectra available at: https://doi.org/10.14469/hpc/5864

1-((Trimethylsilyl)oxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (56). Following general procedure A, cyanohydrin **56** was obtained from 3,4-dihydronaphthalen-1(2H)-one (200 mg, 1.37 mmol) in quantitative yield (335 mg), and was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 1H), 7.29 – 7.24 (m, 2H), 7.13 – 7.10 (m, 1H), 2.89 – 2.77 (m, 2H), 2.34 (ddd, *J* = 12.9, 8.3, 3.3 Hz, 1H), 2.20 (ddd, *J* = 12.5, 9.2, 3.3 Hz, 1H), 2.11 – 1.92 (m, 2H), 0.21 (s, 9H). Spectra available at: https://doi.org/10.14469/hpc/5865

4-((Trimethylsilyl)oxy) thiochromane-4-carbonitrile (57). Following general procedure A, cyanohydrin **57** was obtained from thiochroman-4-one (200 mg, 1.22 mmol) in 45% yield (145 mg) as a pale-yellow oil, which and was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.15 – 7.11 (m, 2H), 3.32 (ddd, *J* = 12.8, 11.3, 3.3 Hz, 1H), 3.02 (ddd, *J* = 12.8, 6.1, 3.6 Hz, 1H), 2.64 (ddd, *J* = 13.4, 6.1, 3.3 Hz, 1H), 2.36 (ddd, *J* = 13.5, 11.3, 3.6 Hz, 1H), 0.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3, 130.8, 130.0, 129.4, 127.1, 124.4, 121.2, 68.9, 36.0, 21.1, 1.1. Spectra available at: https://doi.org/10.14469/hpc/5866

1-(Aminomethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (58). Following general procedure B, aminoalcohol **58** was obtained from cyanohydrin **56** (300 mg, 1.2 mmol) in 91% yield (195 mg) as a colourless oil. Column chromatography: DCM/1% NH_4OH in MeOH, 10:0 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.50 (m, 1H), 7.22 – 7.16 (m, 2H), 7.09 – 7.07 (m, 1H), 2.98, 2.97 (ABq, *J* = 13.4 Hz, 2H), 2.87 – 2.72 (m, 5H, OH, NH_2, CH_2), 2.08 – 2.03 (m, 1H), 1.93 – 1.72 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 137.3, 129.1, 127.8, 126.5, 126.4, 71.2, 49.6, 33.6,

29.5, 19.9. HRMS (ESI) calcd for $[M+H]^+$ $C_{11}H_{16}NO$ 178.1232, found 178.1237. Spectra available at: https://doi.org/10.14469/hpc/5867

4-(Aminomethyl)thiochroman-4-ol (59). Following general procedure B, aminoalcohol **59** was obtained from cyanohydrin **57** (130 mg, 0.55 mmol) in 70% yield (70 mg) as a white solid. Column chromatography: EtOAc/1% NH_4OH in MeOH, 99:1 to 95:5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.56 (m, 1H), 7.12 – 7.06 (m, 3H), 3.10 (dd, *J* = 12.1, 4.1 Hz, 1H), 3.03 (dt, *J* = 12.6, 4.8 Hz, 1H), 2.92, 2.96 (ABq, *J* = 12.9 Hz, 2H), 2.30 (ddd, *J* = 13.5, 5.0, 4.1 Hz, 1H), 2.22 – 2.10 (m, 2H, OH, ½CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 133.2, 127.7, 126.43, 126.37, 124.3, 70.6, 49.2, 33.2, 23.4. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{14}NOS$ 196.0796, found 196.0798. Spectra available at: https://doi.org/10.14469/hpc/5868

5-Bromo-*N*-((1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)thiophene-2-sulfonamide (60). Following general procedure C, sulfonamide **60** was obtained from aminoalcohol **58** (30 mg, 0.17 mmol) and 5-bromothiophene-2-sulfonyl chloride (49 mg, 0.19 mmol) in 39% yield (27 mg) as a yellow solid. Column chromatography: 5-10% EtOAc/EtOH 3:1 in pentane. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 1H), 7.31 (d, *J* = 3.9 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.11 – 7.09 (m, 1H), 7.04 (d, *J* = 3.9 Hz, 1H), 5.17 (dd, *J* = 8.3, 3.7 Hz, 1H, NH), 3.30 (dd, *J* = 12.7, 8.8 Hz, 1H), 3.17 (dd, *J* = 12.7, 4.0 Hz, 1H), 2.87 – 2.73 (m, 2H), 2.36 – 2.31 (m, 1H), 2.05 (br s, 1H, OH), 1.90 – 1.74 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 139.3, 137.5, 132.2, 130.5, 129.3, 128.2, 126.6, 126.4, 119.9, 72.4, 52.0, 34.2, 29.5, 20.1. HRMS (ESI) calcd for $[M-H]^-$ $C_{15}H_{15}BrNO_3S_2$ 399.9677, found 399.9669. Spectra available at: https://doi.org/10.14469/hpc/5869

3-Bromo-*N*-((1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl) benzenesulfonamide (61). Following general procedure C, sulfonamide **61** was obtained from aminoalcohol **58** (30 mg,

0.17 mmol) and 3-bromobenzenesulfonyl chloride (47 mg, 0.19 mmol) in 75% yield (50 mg) as a white solid. Column chromatography: 5-10% EtOAc/EtOH 3:1 in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (app s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.11 – 7.08 (m, 1H), 5.02 (dd, *J* = 8.5, 3.7 Hz, 1H, NH), 3.27 (dd, *J* = 12.8, 8.8 Hz, 1H), 3.10 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.36 – 2.31 (m, 1H), 1.95 (br s, 1H, OH), 1.91 – 1.69 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 139.4, 137.6, 135.8, 130.8, 130.0, 129.3, 128.2, 126.6, 126.3, 125.6, 123.3, 72.4, 51.8, 34.2, 29.5, 20.1. HRMS (ESI) calcd for [M-H]$^-$ $C_{17}H_{17}BrNO_3S$ 394.0113, found 394.0120. Spectra available at: https://doi.org/10.14469/hpc/5870

5-Bromo-*N*-((4-hydroxythiochroman-4-yl)methyl)thiophene-2-sulfonamide (62). Following general procedure C, sulfonamide **62** was obtained from aminoalcohol **59** (30 mg, 0.15 mmol) and 5-bromothiophene-2-sulfonyl chloride (44 mg, 0.17 mmol) in 43% yield (27 mg) as a yellow solid. Column chromatography: pentane/EtOAc, 7:3 to 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.17 – 7.05 (m, 3H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.06 (dd, *J* = 8.7, 3.2 Hz, 1H, NH), 3.40 (dd, *J* = 13.0, 9.1 Hz, 1H), 3.20 (td, *J* = 12.7, 3.7 Hz, 1H), 3.10 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.98 (dt, *J* = 13.1, 4.6 Hz, 1H), 2.62 (ddd, *J* = 13.4, 4.7, 3.9 Hz, 1H), 2.12 (br s, 1H, OH), 2.03 (td, *J* = 12.7, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 136.4, 133.6, 132.4, 130.6, 128.6, 126.7, 126.3, 124.7, 120.2, 71.6, 50.3, 32.7, 23.1. HRMS (ESI) calcd for [M-H]$^-$ $C_{14}H_{13}BrNO_3S_3$ 417.9241, found 417.9250. Spectra available at: https://doi.org/10.14469/hpc/5871

3-Bromo-*N*-((4-hydroxythiochroman-4-yl)methyl)benzenesulfonamide (63). Following general procedure C, sulfonamide **63** was obtained from aminoalcohol **59** (30 mg, 0.15 mmol) and 3-bromobenzenesulfonyl chloride (42 mg, 0.17 mmol) in 33% yield (23 mg) as a white solid.

Column chromatography: pentane/EtOAc, 7:3 to 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 1.8 Hz, 1H), 7.74 (ddd, *J* = 7.8, 1.5, 1.0 Hz, 1H), 7.69 (ddd, *J* = 8.0, 1.8, 0.9 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.21 – 6.94 (m, 3H), 5.03 (dd, *J* = 8.5, 3.0 Hz, 1H, NH), 3.37 (dd, *J* = 13.1, 9.1 Hz, 1H), 3.21 (td, *J* = 12.7, 3.7 Hz, 1H), 3.07 – 2.92 (m, 2H), 2.63 (ddd, *J* = 13.4, 4.8, 3.8 Hz, 1H), 2.14 (s, 1H, OH), 2.02 (td, *J* = 12.6, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 136.4, 136.0, 133.6, 130.9, 130.0, 128.6, 126.6, 126.3, 125.6, 124.6, 123.4, 71.6, 50.2, 32.6, 23.1. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}BrNO_3S_2$ 411.9677, found 411.9683. Spectra available at: https://doi.org/10.14469/hpc/5872

***N*-((2*H*-Chromen-4-yl)methyl)-5-bromothiophene-2-sulfonamide (64).** Borontrifluoride diethyletherate (0.05 mL, 0.4 mmol) was dissolved in dry DCM (1 mL) and added to a stirred solution of compound **3** (40 mg, 0.1 mmol) in dry DCM (1 mL) under N_2 at 0 °C. The reaction mixture was stirred for 1h at 0 °C. Sat. $NaHCO_3$ (aq.) was added and the mixture was diluted with DCM. The organic layer was separated and the aqueous layer was extracted with DCM (3x). The combined organic fractions were then washed with brine, dried and concentrated *in vacuo*. The crude product was purified by preparative HPLC (H_2O:ACN 50:50 to 2:98, 30 min) to give **64** as a white solid (4.3 mg, 0.011 mmol, 11%). ^{1}H NMR (400 MHz, MeOD) δ 7.37 (d, *J* = 4.0 Hz, 1H), 7.18 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.15 (d, *J* = 4.0 Hz, 1H), 7.11 (td, *J* = 7.8, 1.5 Hz, 1H), 6.87 (td, *J* = 7.6, 1.2 Hz, 1H), 6.73 (dd, *J* = 8.1, 1.0 Hz, 1H), 5.79 (t, *J* = 3.7 Hz, 1H), 4.68 (dt, *J* = 3.5, 1.3 Hz, 2H), 3.94 (dd, *J* = 2.7, 1.3 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 155.6, 133.3, 131.9, 130.8, 130.3, 124.4, 122.33, 122.26, 120.0, 116.9, 66.1, 44.9 (*two signals missing due to low quantity*). HRMS (ESI) calcd for $[M-H]^-$ $C_{14}H_{11}NO_3S_2Br$ 383.9364, found 383.9364. Spectra available at: https://doi.org/10.14469/hpc/5873

4-(Methoxymethylene)chromane (65).[32] To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (5.2 g, 15 mmol) in anhydrous THF (100 mL) at – 78, *n*BuLi (2.5 M in toluene, 6.1 mL) was added dropwise. The resulting red mixture was allowed to stir at -78 ºC for 30 min and at rt for additional 30 min. The mixture was cooled down to -78ºC before a solution of 4-chromanone (1.5 g, 10 mmol) in anhydrous THF (20 mL) was slowly added. The mixture was stirred at that temperature for 30 min and then allowed to warm up to rt and stirred overnight. The reaction mixture was poured into water, extracted with EtOAc (3x), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (pentane/EtOAc, 99:1) to provide alkene **65** in 86% yield (1.5 g) as a colourless oil containing a mixture of the *Z/E* isomers which were not assigned. ^{1}H NMR (400 MHz, $CDCl_3$, isomer 1(*1*)/isomer 2 (*2*), 3:1) δ 8.09 (dd, *J* = 7.9, 1.6 Hz, 1H$_{1}$), 7.34 – 7.32 (m, 1H$_{2}$), 7.11 – 7.02 (m, 1H$_{1}$, 1H$_{2}$), 6.90 (ddd, *J* = 8.0, 7.3, 1.3 Hz, 1H$_{1}$), 6.86 – 6.81 (m, 3H, 1H$_{1}$, 2H$_{2}$), 6.65 (t, *J* = 1.6 Hz, 1H$_{2}$), 6.03 (t, *J* = 1.2 Hz, 1H$_{1}$), 4.23 – 4.21 (m, 2H$_{1}$), 4.18 – 4.15 (m, 1H$_{2}$), 3.76 (s, 3H$_{1}$), 3.74 (s, 3H$_{2}$), 2.69 – 2.66 (m, 1H$_{2}$), 2.48 – 2.45 (m, 2H$_{1}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.61 (*2*), 153.56 (*1*), 143.8 (*1*), 141.2 (*2*), 128.9 (*1*), 127.6 (*1*), 127.1 (*2*), 121.9 (*2*), 121.4 (*2*), 120.9 (*2*), 120.5 (*1*), 117.6 (*2*), 116.6 (*1*), 109.1 (*2*), 106.0 (*1*), 67.2 (*1*), 66.0 (*2*), 60.6 (*1*), 60.3 (*2*), 28.1 (*1*), 23.0 (*2*). HRMS (FTMS) calcd for $[M+H]^+$ $C_{11}H_{13}O_2$ 177.0910, found 177.0909. Spectra available at: https://doi.org/10.14469/hpc/5880

Chromane-4-carbaldehyde (66). To a stirred solution of methyl ether **65** (760 mg, 4.31 mmol) in Et_2O (15 mL) at 0 ºC, perchloric acid (70% in water, 4.74 mL) was added dropwise and the mixture was allowed to stir at rt for 45 min. The reaction mixture was quenched with sat. $NaHCO_3$ (43 mL), and the mixture was extracted with Et_2O (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford aldehyde **66** in quantitative yield (699 mg) as a colourless oil

which was used straight away due to instability issues. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (br s, 1H), 7.23 – 7.19 (m, 2H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H), 6.89 (br d, *J* = 8.2 Hz, 1H), 4.24 (dddd, *J* = 11.2, 4.8, 3.6, 0.9 Hz, 1H), 4.00 (ddd, *J* = 11.2, 10.1, 2.6 Hz, 1H), 3.61 (t, *J* = 5.1 Hz, 1H), 2.44 (dddd, *J* = 14.0, 4.9, 4.5, 2.7 Hz, 1H), 2.10 (tddd, *J* = 10.6, 6.3, 3.6, 0.7 Hz, 1H). Spectra available at: https://doi.org/10.14469/hpc/5881

Chroman-4-ylmethanamine (67). Aldehyde **66** (699 mg, 4.31 mmol) and hydroxylamine hydrochloride salt (360 mg, 5.17 mmol) were dissolved in EtOH (3 mL) and stirred at rt for 45 min. HCl (1.5 mL, 17.2 mmol) was added dropwise followed by zinc (705 mg, 10.8 mmol), which was added portionwise. The mixture was stirred for 15 min and then carefully quenched using ammonium hydroxide (30% in water, 1.3 mL) and 8M NaOH (2 mL). The reaction mixture was extracted with DCM (2x). The combined organic layers were extracted with 1M HCl and the organic layer was discarded. The aqueous layer was basified with 8M NaOH and extracted with Et_2O (2x). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to provide amine **67** in 33% yield (229 mg) as a pale-yellow oil which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.7 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.87 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.20 – 4.18 (m, 2H), 3.07 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.92 (dd, *J* = 12.7, 8.3 Hz, 1H), 2.83 (dt, *J* = 13.5, 5.2 Hz, 1H), 2.11 – 2.05 (m, 1H), 2.03 – 1.97 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 129.2, 127.8, 123.9, 120.4, 117.1, 63.6, 47.2, 37.0, 25.1. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{14}NO$ 164.1075, found 164.1077. Spectra available at: https://doi.org/10.14469/hpc/5882

5-Bromo-*N*-(chroman-4-ylmethyl)thiophene-2-sulfonamide (68). Following general procedure C, sulfonamide **68** was obtained from amine **67** (30 mg, 0.18 mmol) and 5-bromothiophene-2-sulfonyl chloride (53 mg, 0.20 mmol) in 43% yield (30 mg) as pale-yellow oil. Column

chromatography: 5-10% of (EtOAc/EtOH, 3:1) in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.0 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.07 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.88 – 6.81 (m, 2H), 4.65 (t, *J* = 6.5 Hz, 1H, NH), 4.20 – 4.12 (m, 2H), 3.38 – 3.24 (m, 2H), 3.07 – 3.01 (m, 1H), 2.09 – 2.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 141.7, 132.4, 130.6, 128.8, 128.6, 121.4, 120.8, 120.2, 117.6, 63.2, 47.9, 33.8, 24.9. HRMS (ESI) calcd for $[M-H]^-$ $C_{14}H_{13}NO_3S_2Br$ 385.9520, found 385.9526. Spectra available at: https://doi.org/10.14469/hpc/5874

3-Bromo-*N*-(chroman-4-ylmethyl)benzenesulfonamide (69). Following general procedure C, sulfonamide **69** was obtained from amine **67** (30 mg, 0.18 mmol) and 3-bromobenzenesulfonyl chloride (51 mg, 0.20 mmol) in 68% yield (47 mg) as a colourless oil. Column chromatography: 5-10% of (EtOAc/EtOH, 3:1) in pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.8 Hz, 1H), 7.77 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.72 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.00 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.84 (ddd, *J* = 14.5, 7.8, 1.1 Hz, 2H), 4.56 (t, *J* = 6.5 Hz, 1H, NH), 4.20 – 4.10 (m, 3H), 3.31 – 3.19 (m, 3H), 3.04 – 2.98 (m, 1H), 2.11 – 1.99 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 141.9, 136.0, 130.9, 130.1, 128.8, 128.6, 125.7, 123.4, 121.5, 120.7, 117.6, 63.2, 47.7, 33.9, 24.8. HRMS (ESI) calcd for $[M-H]^-$ $C_{16}H_{15}NO_3SBr$ 379.9956, found 379.9945. Spectra available at: https://doi.org/10.14469/hpc/5875

***tert*-Butyl ((4-hydroxychroman-4-yl)methyl)carbamate (70).** To a stirred solution of aminoalcohol **2** (365 mg, 2.00 mmol) in DCM (12 mL), Et_3N (0.6 mL, 4 mmol) was added dropwise. The resulting mixture was cooled down to 0 ºC before di-*tert*-butyl dicarbonate (533 mg, 2.40 mmol) was added, and the mixture was stirred at rt for 5 h. Water was added and the mixture extracted with DCM (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford protected amine **70** in quantitative yield (559 mg) as a pale-yellow oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.19 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H), 6.94 (td, *J* = 7.7, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.93 (br s, 1H, NH), 4.29 – 4.23 (m, 2H), 3.58 – 3.47 (m, 2H), 2.90 (br s, 1H, OH), 2.18 – 2.12 (m, 1H), 2.06 – 1.99 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 154.6, 129.6, 126.7, 126.1, 120.9, 117.2, 80.1, 69.1, 63.6, 49.7, 33.3, 28.5. HRMS (ESI) calcd for $[M+ACN+Na]^+$ $C_{17}H_{24}N_2O_4Na$ 343.1634, found 343.1630. Spectra available at: https://doi.org/10.14469/hpc/5883

***tert*-Butyl ((4-methoxychroman-4-yl)methyl)carbamate (71).** Potassium *tert*-butoxide (125 mg, 1.11 mmol) was added portion wise to a flask containing anhydrous THF (3 mL) at 0 ºC under nitrogen atmosphere, followed by a solution of Boc-protected amine **70** (259 mg, 0.93 mmol) in anhydrous THF (3 mL). After stirring for 15 min at 0 ºC, iodomethane (0.09 mL, 1.40 mmol) was added and the mixture was allowed to stir at rt for 2 h. Water was slowly added and the mixture extracted with DCM (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (pentane/EtOAc, 95:5 to 9:1) to provide methyl ether **71** in 70% yield (191 mg) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 2H), 7.21 – 7.17 (m, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.96 (s, 1H), 4.30 – 4.25 (m, 2H), 3.68 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.32 (ddd, *J* = 14.1, 3.8, 1.1 Hz, 1H), 3.03 (s, 3H), 2.30 – 2.23 (m, 1H), 1.88 (dt, *J* = 13.8, 3.4 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 156.4, 129.5, 127.4, 122.4, 120.5, 117.2, 79.4, 74.4, 64.2, 50.2, 48.7, 28.5, 26.3. HRMS (ESI) calcd for $[M+ACN+Na]^+$ $C_{18}H_{26}N_2O_4Na$ 357.1790, found 357.1788. Spectra available at: https://doi.org/10.14469/hpc/5884

(4-Methoxychroman-4-yl)methanamine (72). TBAF (1M in THF, 5 mL) was added dropwise to a solution of Boc-protected amine **71** (150 mg, 0.51 mmol) in anhydrous THF (3 mL) and the resulting mixture was stirred under reflux for 24 h. The reaction mixture was diluted with DCM,

washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (DCM/10% NH_4OH in MeOH, 97:3) to provide amine **72** in 39% yield (38 mg) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.19 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 6.93 (td, *J* = 7.7, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.30 (ddd, *J* = 11.2, 6.1, 4.1 Hz, 1H), 4.21 (ddd, *J* = 11.3, 9.3, 3.2 Hz, 1H), 3.10 (d, *J* = 14.9 Hz, 1H), 3.08 (s, 3H), 2.91 (d, *J* = 13.5 Hz, 1H), 2.29 (ddd, *J* = 13.6, 9.2, 4.0 Hz, 1H), 2.05 (ddd, *J* = 13.9, 6.1, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 129.3, 127.6, 123.1, 120.4, 117.2, 74.3, 64.1, 50.8, 50.4, 27.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{11}H_{16}NO_2$ 194.1181, found 194.1187. Spectra available at: https://doi.org/10.14469/hpc/5885

5-Bromo-*N*-((4-methoxychroman-4-yl)methyl)thiophene-2-sulfonamide (73). Following general procedure C, sulfonamide **73** was obtained from amine **72** (15 mg, 0.080 mmol) and 5-bromothiophene-2-sulfonyl chloride (22 mg, 0.085 mmol) in 83% yield (27 mg) as a pale yellow solid. Column chromatography: pentane/EtOAc, 9:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 4.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.05 (t, *J* = 3.3 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.84 (dd, *J* = 8.1, 0.9 Hz, 1H), 5.10 (dd, *J* = 9.7, 2.3 Hz, 1H, NH), 4.31 (dt, *J* = 11.8, 4.3 Hz, 1H), 4.18 (td, *J* = 11.4, 2.6 Hz, 1H), 3.41 (dd, *J* = 12.7, 9.8 Hz, 1H), 3.19 (ddd, *J* = 12.7, 2.8, 1.4 Hz, 1H), 3.01 (s, 3H), 2.36 – 2.28 (m, 1H), 2.17 (ddd, *J* = 14.0, 4.3, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 141.9, 132.2, 130.5, 130.1, 127.2, 121.5, 120.8, 120.0, 117.5, 73.9, 64.1, 51.7, 50.3, 25.8. HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{15}H_{15}NO_4S_2Br$ 415.9626, found 415.9632. Spectra available at: https://doi.org/10.14469/hpc/5876

3-Bromo-*N*-((4-methoxychroman-4-yl)methyl)benzenesulfonamide (74). Following general procedure C, sulfonamide **74** was obtained from amine **72** (15 mg, 0.080 mmol) and 3-bromobenzenesulfonyl chloride (22 mg, 0.085 mmol) in 84% yield (27 mg) as a white solid.

Column chromatography: pentane/EtOAc, 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.75 (ddd, *J* = 7.9, 1.6, 1.0 Hz, 1H), 7.70 (ddd, *J* = 8.0, 1.8, 1.0 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.19 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.14 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.89 (td, *J* = 7.8, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.02 (dd, *J* = 9.7, 2.1 Hz, 1H, NH), 4.31 (dt, *J* = 11.8, 4.3 Hz, 1H), 4.18 (td, *J* = 11.5, 2.6 Hz, 1H), 3.39 (dd, *J* = 12.8, 9.9 Hz, 1H), 3.10 (ddd, *J* = 12.8, 2.6, 1.5 Hz, 1H), 3.00 (s, 3H), 2.35 – 2.27 (m, 1H), 2.18 (ddd, *J* = 14.0, 4.1, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 142.1, 135.9, 130.8, 130.0, 130.0, 127.2, 125.6, 123.3, 121.6, 120.8, 117.4, 74.1, 64.1, 51.6, 50.3, 25.6. HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{17}H_{17}NO_4SBr$ 410.0062, found 410.0070. Spectra available at: https://doi.org/10.14469/hpc/5877

Chiral resolution was performed on a Chiralpack® IE-3 column using an isocratic gradient of hexane/isopropanol, 85:25 to yield (-)-**74** and (+)-**74**.

(+)-**74**: $[\alpha]_D^{20}$ = + 70° (c = 0.37, $CDCl_3$)

(-)-**74**: $[\alpha]_D^{20}$ = - 77° (c = 0.30, $CDCl_3$)

(4-Fluorochroman-4-yl)methanamine (75). To a stirred solution of aminoalcohol **2** (356 mg, 1.99 mmol) in DCM (6 mL) at -78 ºC, DAST (0.4 mL, 2.98 mmol) was added dropwise and the resulting mixture was allowed to warm up to rt over 3h. The mixture was diluted with DCM, washed with 1M NaOH, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (DCM/1% NH_4OH in MeOH, 98:2) to afford amine **75** in 31% yield (113 mg) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.28 – 7.24 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 4.31 – 4.21 (m, 2H), 3.39 (dd, *J* = 13.9, 9.8 Hz, 1H), 3.05 (dd, *J* = 24.7, 13.9 Hz, 1H), 2.41 – 2.23 (m, 2H), 1.32 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (d, *J* = 3.2 Hz), 130.6 (d, *J* = 2.6 Hz), 127.0 (d, *J* =

2.5 Hz), 121.9 (d, *J* = 20.4 Hz), 121.0 (d, *J* = 1.9 Hz), 117.5 , 90.8 (d, *J* = 173.7 Hz), 63.1 (d, *J* = 2.7 Hz), 49.3 (d, *J* = 30.4 Hz), 31.0 (d, *J* = 21.6 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ -136.49 (tdd, *J* = 23.7, 17.5, 9.4 Hz). HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{13}NOF$ 182.0981, found 182.0974. Spectra available at: https://doi.org/10.14469/hpc/5886

5-Bromo-*N*-((4-fluorochroman-4-yl)methyl)thiophene-2-sulfonamide (76). Following general procedure C, sulfonamide **76** was obtained from amine **75** (30 mg, 0.17 mmol) and 5-bromothiophene-2-sulfonyl chloride (48 mg, 0.18 mmol) in 44% yield (30 mg) as a pale yellow solid. Column chromatography: pentane/(EtOAc/EtOH, 3:1), 95:5 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 4.0 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.85 (dd, *J* = 8.6, 4.5 Hz, 1H, NH), 4.28 – 4.21 (m, 2H), 3.64 (ddd, *J* = 13.6, 8.8, 4.6 Hz, 1H), 3.45 (ddd, *J* = 27.2, 13.7, 8.9 Hz, 1H), 2.47 – 2.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 141.5, 132.6, 131.4 (d, *J* = 2.1 Hz), 130.7, 126.6 (d, *J* = 2.6 Hz), 121.2 (d, *J* = 1.5 Hz), 120.3 (d, *J* = 34.0 Hz), 117.8, 110.1, 89.8 (d, *J* = 176.6 Hz), 63.0 (d, *J* = 3.8 Hz), 50.0 (d, *J* = 30.2 Hz), 30.8 (d, *J* = 21.4 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ -136.20 – -136.39 (m, 1F). HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{14}H_{12}NO_3S_2BrF$ 403.9426, found 403.9431. Spectra available at: https://doi.org/10.14469/hpc/5878

3-Bromo-*N*-((4-fluorochroman-4-yl)methyl)benzenesulfonamide (77). Following general procedure C, sulfonamide **77** was obtained from amine **75** (30 mg, 0.17 mmol) and 3-bromobenzenesulfonyl chloride (46 mg, 0.18 mmol) in 61% yield (40 mg) as a white solid. Column chromatography: pentane/(EtOAc/EtOH, 3:1), 95:5 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.8 Hz, 1H), 7.77 (ddd, *J* = 7.9, 1.6, 1.0 Hz, 1H), 7.73 (ddd, *J* = 8.0, 1.7, 0.9 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.30 – 7.25 (m, 4H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 4.80 (dd, *J* = 8.6, 4.4 Hz, 1H, NH), 4.28 – 4.21 (m, 2H), 3.57 (ddd, *J* = 13.6, 8.9, 4.6 Hz, 1H), 3.43

(ddd, *J* = 27.3, 13.8, 8.9 Hz, 1H), 2.51 – 2.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 141.9, 136.2, 131.4 (d, *J* = 2.4 Hz), 131.0, 130.0, 126.6 (d, *J* = 3.1 Hz), 125.6, 123.5, 121,1, 120.3 (d, *J* = 20.3 Hz), 117.8, 110.1, 89.9 (d, *J* = 176.2 Hz), 63.0 (d, *J* = 4.0 Hz), 49.8 (d, *J* = 30.1 Hz), 30.7 (d, *J* = 21.4 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ -136.60 – -136.79 (m, 1F). HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{16}H_{14}NO_3SBrF$ 397.9862, found 397.9870. Spectra available at: https://doi.org/10.14469/hpc/5879

5-Bromo-*N*-(*anti*-(4-hydroxychroman-3-yl)methyl)thiophene-2-sulfonamide (78a), and 5-bromo-*N*-(*syn*-(4-hydroxychroman-3-yl)methyl)thiophene-2-sulfonamide (78b). Following general procedure C, sulfonamides **78a** and **78b** were obtained from a 3:1 mixture of **87a** and **87b** (25 mg, 0.14 mmol) and 5-bromothiophene-2-sulfonyl chloride (40 mg, 0.15 mmol) in 86% yield (12 mg) and 88% yield (37 mg) as yellow and white solids, respectively. Column chromatography: DCM/1% NH_4OH in MeOH, 99:1 to 98:2. **78a**: ^{1}H NMR (400 MHz, MeOD) δ 7.35 (d, *J* = 4.0 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H), 6.75 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.47 (d, *J* = 4.7 Hz, 1H), 4.28 (dd, *J* = 11.3, 2.8 Hz, 1H), 4.06 (dd, *J* = 10.9, 4.9 Hz, 1H), 2.99 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.88 (dd, *J* = 13.3, 8.1 Hz, 1H), 2.14 – 2.07 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 155.4, 143.8, 133.3, 132.0, 131.4, 130.3, 124.6, 121.8, 120.1, 117.5, 66.2, 65.1, 42.9, 41.9. HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{14}H_{13}NO_4S_2Br$ 401.9469, found 401.9476. **78b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 3.9 Hz, 1H), 7.28 – 7.22 (m, 8H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.95 (td, *J* = 7.4, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.21 (t, *J* = 6.4 Hz, 1H), 4.82 (s, 1H), 4.14 – 4.07 (m, 2H), 3.32 (dt, *J* = 13.3, 7.6 Hz, 1H), 3.24 (dt, *J* = 13.3, 5.4 Hz, 1H), 2.35 – 2.27 (m, 1H), 2.09 – 2.08 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 141.5, 132.5, 130.6, 130.4, 130.1, 123.3, 121.2, 120.2, 117.3, 65.3, 63.5, 42.1, 38.1. HRMS (ESI) *m/z*

calcd for [M-H]$^-$ $C_{14}H_{13}NO_4S_2Br$ 401.9469, found 401.9473. Spectra available at: https://doi.org/10.14469/hpc/5887 (a) and https://doi.org/10.14469/hpc/5888 (b)

3-Bromo-*N*-(*anti*-(4-hydroxychroman-3-yl)methyl)benzenesulfonamide (79a), and 3-bromo-*N*-(*syn*-(4-hydroxychroman-3-yl)methyl)benzenesulfonamide (79b). Following general procedure C, sulfonamides **79a** and **79b** were obtained from a 3:1 mixture of **87a** and **87b** (25 mg, 0.14 mmol) and 3-bromobenzenesulfonyl chloride (39 mg, 0.15 mmol) in 93% yield (13 mg) and 77% yield (32 mg) as white solids. Column chromatography: DCM/1% NH_4OH in MeOH, 99:1 to 98:2. **79a**: ^{1}H NMR (400 MHz, MeOD) δ 7.96 (t, *J* = 1.8 Hz, 1H), 7.79 (ddd, *J* = 3.0, 1.8, 1.0 Hz, 1H), 7.77 (ddd, *J* = 3.0, 1.8, 0.9 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.15 (ddd, *J* = 8.6, 7.2, 1.4 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.74 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.45 (d, *J* = 4.9 Hz, 1H), 4.26 (dd, *J* = 11.3, 2.8 Hz, 1H), 4.03 (dd, *J* = 11.6, 5.0 Hz, 1H), 2.92 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.81 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.11 – 2.04 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 155.4, 143.8, 136.6, 132.1, 131.4, 130.7, 130.2, 126.8, 124.6, 123.9, 121.8, 117.4, 66.2, 65.1, 42.7, 42.1. HRMS (ESI) *m/z* calcd for [M-H]$^-$ $C_{16}H_{15}NO_4SBr$ 395.9905, found 395.9907. **79b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, *J* = 1.8 Hz, 1H), 7.81 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.72 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.28 – 7.21 (m, 8H), 6.94 (td, *J* = 7.4, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.3, 0.9 Hz, 1H), 5.12 (t, *J* = 6.6 Hz, 1H), 4.81 (t, *J* = 2.7 Hz, 1H), 4.12 – 4.05 (m, 2H), 3.27 (dt, *J* = 13.4, 7.7 Hz, 1H), 3.16 (dt, *J* = 13.3, 5.4 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.14 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 141.8, 136.0, 130.9, 130.4, 130.2, 130.1, 125.7, 123.4, 123.3, 121.1, 117.2, 65.1, 63.5, 41.8, 38.3. HRMS (ESI) *m/z* calcd for [M-H]$^-$ $C_{16}H_{15}NO_4SBr$ 395.9905, found 395.9910. Spectra available at: https://doi.org/10.14469/hpc/5889 (a) and https://doi.org/10.14469/hpc/5890 (b)

5-Bromo-*N*-((3-hydroxychroman-3-yl)methyl)thiophene-2-sulfonamide (80). Following general procedure C, sulfonamide **80** was obtained from amine **88** (15 mg, 0.08 mmol) and 5-bromothiophene-2-sulfonyl chloride (24 mg, 0.09 mmol) in 15% yield (5 mg) as a white solid. Column chromatography: DCM/1% NH_4OH in MeOH, 98:2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 4.0 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H), 7.08 (d, *J* = 4.0 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.92 (td, *J* = 7.4, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.07 (t, *J* = 6.2 Hz, 1H, NH), 4.02 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.20 – 3.11 (m, 2H), 2.88, 2.84 (ABq, *J* = 16.7 Hz, 2H), 2.65 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 132.7, 130.7, 130.6, 128.2, 121.9, 120.5, 119.1, 117.0, 110.1, 70.5, 67.8, 48.8, 36.3. HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{14}H_{13}NO_4S_2Br$ 401.9469, found 401.9473. Spectra available at: https://doi.org/10.14469/hpc/5891

3-Bromo-*N*-((3-hydroxychroman-3-yl)methyl)benzenesulfonamide (81). Following general procedure C, sulfonamide **81** was obtained from amine **88** (15 mg, 0.08 mmol) and 3-bromobenzenesulfonyl chloride (24 mg, 0.09 mmol) in 70% yield (23 mg) as a white solid. Column chromatography: DCM/1% NH_4OH in MeOH, 98:2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 1.8 Hz, 1H), 7.79 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.73 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.14 (td, *J* = 8.2, 1.7 Hz, 1H), 7.03 (d, *J* = 6.4 Hz, 1H), 6.91 (td, *J* = 7.4, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.07 (t, *J* = 6.3 Hz, 1H, NH), 4.00 (dd, *J* = 11.0, 1.1 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.09 (d, *J* = 6.4 Hz, 2H), 2.85, 2.83 (ABq, *J* = 17.1 Hz, 2H), 2.72 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 141.5, 136.1, 130.9, 130.5, 130.1, 128.1, 125.7, 123.4, 121.8, 119.1, 117.0, 70.4, 67.9, 48.7, 36.2. HRMS (ESI) *m/z* calcd for $[M-H]^-$ $C_{16}H_{15}NO_4SBr$ 395.9905, found 395.9901. Spectra available at: https://doi.org/10.14469/hpc/5892

***tert*-Butyl ((2*H*-chromen-3-yl)methyl)carbamate (82).** Following the same procedure described for the synthesis of **70**, Boc-protected amine **82** was obtained from amine **84** (1.0 g, 6.2 mmol) in 83% yield (1.35 g) as a white solid. Column chromatography: pentane/EtOAc, 95:5 to 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (td, *J* = 7.9, 1.6 Hz, 1H), 6.96 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.86 (td, *J* = 7.4, 0.9 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.29 (s, 1H), 4.73 (s, 2H), 4.66 (s, 1H, NH), 3.82 (d, *J* = 5.5 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 153.4, 131.9, 129.1, 126.6, 122.3, 121.6, 120.3, 115.6, 80.0, 66.7, 42.7, 28.5. HRMS (ESI) calcd for $[M+ACN+Na]^+$ $C_{17}H_{22}N_2O_3Na$ 325.1528, found 325.1524. Spectra available at: https://doi.org/10.14469/hpc/5893

2*H*-Chromene-3-carbonitrile (83).[25] A mixture of 2-hydroxibenzaldehyde (5.0 mL, 47 mmol), acrylonitrile (15.4 mL, 235 mmol) and DABCO (1.16 g, 10.3 mmol) was stirred at 90 ºC overnight. The resulting mixture was diluted with sat. $NaHCO_3$, extracted with DCM (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (pentane/EtOAc, 98:2) to afford nitrile **83** in 74% yield (5.46 g) as white crystals. The spectroscopic data are coincident with those reported.[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 1H), 7.18 (s, 1H), 7.10 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.82 (d, *J* = 1.4 Hz, 2H). Spectra available at: https://doi.org/10.14469/hpc/5894

(2*H*-Chromen-3-yl)methanamine (84). Following a literature procedure described for a similar product,[34] a solution of anhydrous $AlCl_3$ (1.93 g, 14.5 mmol) in dry Et_2O (19 mL) was added to a suspension of $LiAlH_4$ (549 mg, 14.5 mmol) in dry Et_2O (19 mL) at 0 ºC and under nitrogen atmosphere. After leaving the mixture to stir for 10 min, a solution of nitrile **83** (1.75 g, 11.1 mmol) in dry Et_2O (19 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was then cooled down to 0 ºC and carefully quenched with water. The pH was adjusted to 9~10 with 8M NaOH, and the resulting mixture was filtered through a pad of

celite, washing with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (2-5% of (10% NH_4OH in MeOH) in DCM) to provide amine **84** in 56% yield (1 g) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (td, *J* = 7.8, 1.7 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.86 (td, *J* = 7.4, 1.1 Hz, 1H), 6.79 (br d, *J* = 8.0 Hz, 1H), 6.34 (s, 1H), 4.76 (d, *J* = 1.0 Hz, 2H), 3.38 (s, 2H), 1.37 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 136.1, 128.7, 126.5, 122.7, 121.5, 118.2, 115.6, 67.3, 44.3. Spectra available at: https://doi.org/10.14469/hpc/5895

***tert*-Butyl (*anti*-(4-hydroxychroman-3-yl)methyl)carbamate and *tert*-butyl ((3-hydroxychroman-3-yl)methyl)carbamate (85 and 86).** To a flask charged with Boc-protected amine **82** (500 mg, 1.91 mg) at 0 ºC, borane (1M in THF, 3.8 mL) was added dropwise and the resulting mixture was stirred at rt for 2 h. Water was then added (3.8 mL) followed by sodium perborate tetrahydrate (882 mg, 5.73 mmol) and the resulting mixture was stirred at rt for 2 h. The reaction mixture was diluted with water, extracted with EtOAc (2x), washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. NMR of the reaction crude showed a mixture of the expected anti-Markovnikov product together with the Markovnikov one in a 2:1 ratio. The crude was purified by flash chromatography (5-10% of [EtOAc/EtOH, 3:1] in pentane) to provide anti-Markovnikov product **85** in 49% yield (260 mg) as a white solid, and Markovnikov product **86** in 27% yield (143 mg) as a colourless oil.

85: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.81 (br s, 1H, NH), 4.59 (d, *J* = 6.7 Hz, 1H), 4.25 (dd, *J* = 11.2, 3.0 Hz, 1H), 4.04 (dd, *J* = 11.1, 7.9 Hz, 1H), 3.38 (dd, *J* = 13.7, 6.5 Hz, 1H), 3.14 (dt, *J* = 14.5, 5.6 Hz, 1H), 2.94 (br s, 1H, OH), 2.16 (br s, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 156.9, 154.1, 129.4, 129.0, 124.2, 121.0, 116.6, 80.0, 66.2, 65.5, 41.0, 39.5, 28.5. HRMS (ESI) calcd for $[M+ACN+Na]^+$ $C_{17}H_{24}N_2O_4Na$ 343.1634, found 343.1630. Spectra available at: https://doi.org/10.14469/hpc/5896

86: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.88 (td, *J* = 7.6, 0.7 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.16 (br s, 1H, NH), 4.17 (br s, 1H, OH), 3.98 (d, *J* = 10.9 Hz, 1H), 3.86 (d, *J* = 10.9 Hz, 1H), 3.31 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.19 (dd, *J* = 14.6, 6.6 Hz, 1H), 2.82 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 153.4, 130.5, 127.8, 121.4, 120.2, 116.8, 80.6, 70.4, 68.7, 46.7, 36.4, 28.4. HRMS (ESI) calcd for $[M+ACN+Na]^+$ $C_{17}H_{24}N_2O_4Na$ 343.1634, found 343.1632. Spectra available at: https://doi.org/10.14469/hpc/5897

***Anti*-3-(Aminomethyl)chroman-4-ol (87a), and *syn*-3-(aminomethyl)chroman-4-ol (87b).** To a stirred solution of Boc-protected amine **85** (170 mg, 0.61 mmol) in DCM (3 mL) at 0 ºC, TFA (0.9 mL, 1.5 mL/mmol) was added dropwise, and the resulting mixture was stirred at that temperature for 30 min. 8M NaOH was added and the mixture was extracted with DCM (2x), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography (DCM/10% NH_4OH in MeOH, 92:8) to provide an inseparable 3:1 *anti*-/*syn*-mixture of aminoalcohols **87a** and **87b** in 57% yield (62 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) (*anti*-/*syn*-, 3:1) δ 7.47 – 7.43 (m, 2H, CH_{syn}, CH_{anti}), 7.21 – 7.15 (m, 2H, CH_{syn}, CH_{anti}), 6.97 – 6.93 (m, 2H, CH_{syn}, CH_{anti}), 6.82 – 6.79 (m, 2H, CH_{syn}, CH_{anti}), 4.98 (d, *J* = 4.0 Hz, 1H, CH_{syn}), 4.78 (d, *J* = 7.7 Hz, 1H, CH_{anti}), 4.19 – 4.14 (m, 3H, CH_{2syn}, ½CH_{2anti}), 3.89 (dd, *J* = 11.2, 9.3 Hz, 1H, ½CH_{2anti}), 3.15 – 3.03 (m, 3H, CH_{2syn}, ½CH_{2anti}), 2.70 (dd, *J* = 12.3, 9.8 Hz, 1H, ½CH_{2anti}), 2.22 – 2.16 (m, 1H, CH_{syn}), 2.10 – 2.02 (m, 1H, CH_{anti}), 1.75 (brs, 6H, OH_{syn}, NH_{2syn}, OH_{anti}, NH_{2anti}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (C_{anti}), 153.3 (C_{syn}), 129.7 (CH_{syn}), 129.3 (CH_{syn}), 129.0 (CH_{anti}), 128.0 (CH_{anti}), 125.1 (C_{anti}), 124.9 (C_{syn}), 121.0 (CH_{anti}), 120.9 (CH_{syn}),

116.5 (CH_{syn}), 116.4 (CH_{anti}), 70.0 (CH_{anti}), 66.9 (CH_{syn}), 65.8 (CH_{2syn}), 65.6 (CH_{2anti}), 43.2 (CH_{2anti}), 41.6 (CH_{anti}), 41.0 (CH_{2syn}), 38.6 (CH_{syn}). HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025, found 180.1030. Spectra available at: https://doi.org/10.14469/hpc/5898

3-(Aminomethyl)chroman-3-ol (88). Following the same procedure described for the synthesis of **87**, aminoalcohol **88** was obtained from Boc-protected amine **84** (94 mg, 0.34 mmol) in 33% yield (20 mg) as a colourless oil. Column chromatography: DCM/10% NH_4OH in MeOH, 95:5 to 92:8. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.89 (dd, *J* = 11.6, 4.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 3.94 – 3.89 (m, 2H), 2.90 (d, *J* = 16.8 Hz, 1H), 2.89 (d, *J* = 13.0 Hz, 1H), 2.74 (d, *J* = 16.4 Hz, 1H), 2.68 (d, *J* = 13.1 Hz, 1H), 1.81 (s, 3H, OH, NH_2). ^{13}C NMR (101 MHz, MeOD) δ 153.7, 130.5, 127.8, 121.3, 120.3, 116.6, 70.5, 67.7, 47.3, 36.1. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025, found 180.1024. Spectra available at: https://doi.org/10.14469/hpc/5899

Biological evaluation

In vitro P. falciparum NF54 strain culture

Asexual blood stage (ABS) *P. falciparum* NF54 strain parasites were cultured to seed gametocyte cultures as previously reported.[35] Briefly, ABS cultures were routinely maintained at 4% haematocrit with O+ human blood (NHS National Blood Service), supplemented with 10% heparin, between 0.5-5% ring stage parasitemia. Cultures were maintained at 37 °C under 3% O_2/5% CO_2/92%N_2 gas (BOC Special Gases) with complete culture medium (RPMI 1640 with 25mM HEPES (Life Technologies), 50 µg/L hypoxanthine (Sigma), 2 g/L sodium bicarbonate (Sigma) and 10% A+ human serum (Interstate Blood-Bank)). Parasitemia was monitored by thin-film smear and Giemsa staining.

Sexual stage gametocyte cultures were induced from ABS cultures at 3% ring stage parasitemia and 4% haematocrit, strictly maintaining an atmosphere of 37 °C and 3% O_2/5% CO_2/92%N_2 gas (BOC Special Gases). Gametocyte culture medium (prepared as above but supplemented with 5% A+ human serum and 5% AlbuMAX II (Life Technologies)) was changed daily without the addition of fresh erythrocytes to permit gametocyte production and maturation over a 14-day period. Maturity and parasitemia were monitored at 0, 7, and 14 days post-induction by thin smear and Giemsa staining. Gametocyte culture viability was determined 14 days post-induction by measuring the rate of exflagellation, the production of male gametes, relative to red blood cell (RBC) density. Briefly, gamete production was induced by treating a small volume of gametocyte culture with ookinete medium (RPMI 1640 with 25 mM HEPES (Life Technologies), 50 µg/L hypoxanthine (Sigma), 2 g/L sodium bicarbonate (Sigma) and 100 µM xanthurenic acid), dropping the temperature from 37 °C to rt. Exflagellation was determined by counting in a haemocytometer, as previously described.[35]

P. falciparum dual gamete formation assay (*Pf* DGFA)

The DGFA was performed as previously described[15,17] in an 'add-in' format designed for the identification of male-gamete targeted compounds. Since activity for the parent molecule DDD01035881 has been demonstrated as male specific (having limited to no activity against females), here we only focussed on the male-specific readout from the DGFA. DDD01035881 and its derivatives act immediately upon activation of male gamete formation. As such there is no requirement for preincubation with gametocyte culture prior to the assay readout. Compounds were dispensed into black flat-bottom 384-well plates (Greiner) with a HP D300 Digital Dispenser in a dose response from 40 nM to 25 µM and repeated at a targeted concentration range for

compounds showing an EC_{50} < 1000 nM. Plates were normalised to 0.25% DMSO (Honeywell) and contained 0.25% DMSO and 20 µM DDD01028076 (a male-gamete targeted hit from the HTS[17]) negative and positive controls, respectively. Gametocyte cultures demonstrating > 0.2% exflagellation were diluted to 25 million RBC per mL in gametocyte culture medium. Each well of the 384-well plate was plated with 10 µL ookinete medium and then 50 µL dilute gametocyte culture, with a total of 1.25 million cells per well, to activate the gamete formation process. Plates were immediately cooled at 4 °C for 4 minutes and incubated for a further 5 minutes at 28 °C. 10-frame time lapses (4 frames per second) of each well were then recorded in a meandering pattern across the plate with a Nikon Ti-E widefield microscope at x4 objective, 1.5x zoom, under phase contrast.

Exflagellation counts per well were determined with an automated ICY Bioimage Analysis algorithm built to recognise exflagellation centres based on pixel intensity, circularity and size of disturbances to the cell monolayer. Counts were converted to a percentage inhibition relative to positive (C1) and negative (C2) controls with the following equation:

$$\%\ Inhibition = 100 - \left(\left(\frac{test\ compound - C1}{C2 - C1}\right) X100\right)$$

The assay was performed with n ≥ 2 and n ≥ 3 technical and biological replicates, respectively, demonstrating a Z' factor ≥ 0.4. Using the % inhibition dose response, EC_{50}s were calculated in GraphPad Prism version 8 using the log(inhibitor) vs. response – variable slope (four parameters) function. Each EC_{50} was derived from a curve with an $R^2 \geq 0.95$, reported as an average of biological replicates ± standard error.

Hep G2 cytotoxicity assay

HepG2 human cells (ATCC® HB-8065™) were grown in complete culture medium (Dulbecco's Modified Eagle Medium (Sigma), 10% foetal bovine serum (Sigma), 1% L-glutamine (Sigma) and 1% Penicillin-Streptomycin solution (Sigma)) in flasks coated with 1 µg/cm^2 collagen (Gibco by Life Technologies). Cells were detached with trypsin (Gibco) and counted with FastRead slides (Immune Systems) before diluting to 2.2 x 10^5 cells per mL in culture medium. 100 µL cell suspension was plated in each well of a black 96-well plate (Greiner) coated with collagen at 1 µg/cm^2 and washed with phosphate-buffered saline (Sigma). Cells were left to grow at 37 °C and 5% CO_2 for 24 hours before treating with either 10 µM compounds or negative and positive controls, DMSO (Honeywell) and 50 µM Doxorubicin (Sigma), respectively. All wells were normalised to 0.5% DMSO and blanks of media ± Alamar Blue (Thermo Fisher), HepG2 and empty wells were included. Cells were incubated with compounds at 37 °C and 5% CO_2 for 48 hours before plating Alamar Blue and incubating for a further 2.5 h at 37 °C. Fluorescence of each well was measured using a fluorescence excitation wavelength of 560 nm and emission wavelength of 590 nm. Percentage of cytotoxicity was determined using the following equation:

$$\%\ Cytotoxicity = 100 - \left(\left(\frac{test\ compound - blank}{DMSO\ control - blank}\right) X100\right)$$

The assay was performed with n ≥ 3 biological replicates, with an average Z' factor of 0.65 for each biological replicate.

***In Vitro* Metabolic Profile**

The half-lives of lead compounds **3**, **6**, **38**, **39**, **41** and **74** in mouse microsomes were determined by Cyprotex Ltd. Briefly, microsomes (0.5 mg/mL) were incubated with the test compounds (3 μM) at 37 °C in the presence of the co-factor, NADPH, which initiates the reaction. The reaction was terminated by the addition of methanol containing an internal standard. Following centrifugation, the supernatant was analysed by LC-MS and the disappearance of test compounds was monitored over a 45 min time period. The ln peak area ratio (compound peak area/internal standard peak area) is plotted against time and the gradient of the line determined. Metabolic half-life was calculated by fitting the data to a first-order decay model, and intrinsic clearance (CL_{int}) is dependent on the half-life and concentration of protein and was calculated using that data.

ASSOCIATED CONTENT

Structure of previously reported analogues, tables with *in vitro* activity data for inactive compounds, HPLC traces of selected compounds **3**, **6**, **38, 39, 41** and **74** and cytotoxicity data of **3**, **6**, **41** and **74** in a HepG2 human cell line. Molecular formula strings are also available.

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Author Contributions

A.R.-Z. designed and synthesized compounds, analyzed the data and drafted the manuscript. S.Y. and U.S. cultured gametocytes and S.Y. carried out biological evaluation and analyzed the data. O.J.F, X.H., C.N.S., J.S. and S.S. additionally synthesized compounds. M.J.F., A.B. and J.B. conceived and oversaw the study and assisted with compound design and data analysis, with additional input from E.W.T. and M.J.D. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

ITN, Insecticide Treated Bed Net; IRS, Indoor Residual Spraying; DGFA, Dual Gamete Formation Assay; GHCDL, Global Health Chemical Diversity Library; EDC, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; DAST, diethylaminosulfur trifluoride; ACN, acetonitrile; ABS, asexual blood stage; RBC, red blood cell.

REFERENCES

1. World Health Organization. *World Malaria Report 2018*; 2018.

2. Joice, R.; Nilsson, S. K.; Montgomery, J.; Dankwa, S.; Egan, E.; Morahan, B.; Seydel, K. B.; Bertuccini, L.; Alano, P.; Williamson, K. C.; et al. Plasmodium Falciparum Transmission Stages Accumulate in the Human Bone Marrow. *Sci. Transl. Med.* **2014**, *6*, 244re5-244re5.

3. Sinden, R. E. Sexual Development of Malarial Parasites. *Adv. Parasitol.* **1983**, *22*, 153–216.

4. Aly, A. S. I.; Vaughan, A. M.; Kappe, S. H. I. Malaria Parasite Development in the Mosquito and Infection of the Mammalian Host. *Annu. Rev. Microbiol.* **2009**, *63*, 195–221.

5. World Health Organization. World Malaria Report 2015. *World Health* **2015**.

6. Bhatt, S.; Weiss, D. J.; Cameron, E.; Bisanzio, D.; Mappin, B.; Dalrymple, U.; Battle, K. E.; Moyes, C. L.; Henry, A.; Eckhoff, P. A.; et al. The Effect of Malaria Control on Plasmodium Falciparum in Africa between 2000 and 2015. *Nature* **2015**, *526*, 207–211.

7. WHO, W. H. O. Status Report on Artemisinin and ACT Resistance (April 2017). *Who/Htm/Gmp/2017.9* **2017**, No. April, 11.

8. Ashley, E. a.; Dhorda, M.; Fairhurst, R. M.; Amaratunga, C.; Lim, P.; Suon, S.; Sreng, S.; Anderson, J. M.; Mao, S.; Sam, B.; et al. Spread of Artemisinin Resistance in Plasmodium Falciparum Malaria. *N. Engl. J. Med.* **2014**, *371*, 411–423.

9. Alonso, P. L.; Djimde, A. A.; Tanner, M.; Wirth, D. F.; Whitfield, K.; Winzeler, E. A.; Steketee, R.; Hemingway, J.; Kaslow, D. C.; Rabinovich, R. N.; et al. MalERA: An Updated Research Agenda for Malaria Elimination and Eradication. *PLOS Med.* **2017**, *14*, e1002456.

10. Mazzuri, S.; Macintyre, F.; Möhrle, J. J.; Duparc, S.; Wells, T. N. C.; Kaszubska, W.; Gutteridge, W. E.; Hooft van Huijsduijnen, R.; Burrows, J. N. New Developments in Anti-Malarial Target Candidate and Product Profiles. *Malar. J.* **2017**, *16*, 1–29.

11. Angrisano, F.; Tan, Y.-H.; Sturm, A.; McFadden, G. I.; Baum, J. Malaria Parasite Colonisation of the Mosquito Midgut – Placing the Plasmodium Ookinete Centre Stage. *Int. J. Parasitol.* **2012**, *42*, 519–527.

12. Yahiya, S.; Rueda-Zubiaurre, A.; Delves, M. J.; Fuchter, M. J.; Baum, J. The Antimalarial Screening Landscape—looking beyond the Asexual Blood Stage. *Curr. Opin. Chem. Biol.* **2019**, *50*, 1–9.

13. Churcher, T. S.; Blagborough, A. M.; Delves, M.; Ramakrishnan, C.; Kapulu, M. C.; Williams, A. R.; Biswas, S.; Da, D. F.; Cohuet, A.; Sinden, R. E. Measuring the Blockade of Malaria Transmission - An Analysis of the Standard Membrane Feeding Assay. *Int. J. Parasitol.* **2012**, *42*, 1037–1044.

14. Vos, M. W.; Stone, W. J. R.; Koolen, K. M.; van Gemert, G.-J.; van Schaijk, B.; Leroy, D.; Sauerwein, R. W.; Bousema, T.; Dechering, K. J. A Semi-Automated Luminescence Based Standard Membrane Feeding Assay Identifies Novel Small Molecules That Inhibit Transmission of Malaria Parasites by Mosquitoes. *Sci. Rep.* **2016**, *5*, 18704.

15. Ruecker, A.; Mathias, D. K.; Straschil, U.; Churcher, T. S.; Dinglasan, R. R.; Leroy, D.; Sinden, R. E.; Delves, M. J. A Male and Female Gametocyte Functional Viability Assay To Identify Biologically Relevant Malaria Transmission-Blocking Drugs. *Antimicrob. Agents Chemother.* **2014**, *58*, 7292–7302.

16. Delves, M. J.; Ruecker, A.; Straschil, U.; Lelièvre, J.; Marques, S.; López-Barragán, M. J.; Herreros, E.; Sinden, R. E. Male and Female Plasmodium Falciparum Mature Gametocytes Show Different Responses to Antimalarial Drugs. *Antimicrob. Agents Chemother.* **2013**, *57*, 3268–3274.

17. Delves, M. J.; Miguel-Blanco, C.; Matthews, H.; Molina, I.; Ruecker, A.; Yahiya, S.; Straschil, U.; Abraham, M.; León, M. L.; Fischer, O. J.; et al. A High Throughput Screen for Next-Generation Leads Targeting Malaria Parasite Transmission. *Nat. Commun.* **2018**, *9*, 3805.

18. Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. One-Pot Reductive Amination of

Aldehydes and Ketones with α-Picoline-Borane in Methanol, in Water, and in Neat Conditions. *Tetrahedron* **2004**, *60*, 7899–7906.

19. Abate, C.; Niso, M.; Lacivita, E.; Mosier, P. D.; Toscano, A.; Perrone, R. Analogues of σ Receptor Ligand 1-Cyclohexyl-4-[3-(5-Methoxy-1,2,3,4-Tetrahydronaphthalen-1-Yl)Propyl]Piperazine (PB28) with Added Polar Functionality and Reduced Lipophilicity for Potential Use as Positron Emission Tomography Radiotracers. *J. Med. Chem.* **2011**, *54*, 1022–1032.

20. Eaton, P. E.; Carlson, G. R.; Lee, J. T. Phosphorus Pentoxide-Methanesulfonic Acid. Convenient Alternative to Polyphosphoric Acid. *J. Org. Chem.* **1973**, *38*, 4071–4073.

21. Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880.

22. Prakash, G. K. S.; Vaghoo, H.; Panja, C.; Surampudi, V.; Kultyshev, R.; Mathew, T.; Olah, G. Effect of Carbonates/Phosphates as Nucleophilic Catalysts in Dimethylformamide for Efficient Cyanosilylation of Aldehydes and Ketones. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3026–3030.

23. Dekamin, M. G.; Karimi, Z. Activation of Trimethylsilyl Cyanide by Potassium Phthalimide for Facile Synthesis of TMS-Protected Cyanohydrins. *J. Organomet. Chem.* **2009**, *694*, 1789–1794.

24. Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J. Y.; Coudert, G. Mild and Selective Deprotection of Carbamates with Bu 4 NF. *Tetrahedron* **2004**, *60*, 10039–10047.

25. Urruzuno, I.; Mugica, O.; Oiarbide, M.; Palomo, C. Bifunctional Brønsted Base Catalyst Enables Regio-, Diastereo-, and Enantioselective Cα-Alkylation of β-Tetralones and Related Aromatic-Ring-Fused Cycloalkanones. *Angew. Chemie Int. Ed.* **2017**, *56*, 2059–2063.

26. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. Sodium Perborate: A Mild and Convenient Reagent for Efficiently Oxidizing Organoboranes. *J. Org. Chem.* **1989**, *54*, 5930–5933.

27. Gramec, D.; Peterlin Mašič, L.; Sollner Dolenc, M. Bioactivation Potential of Thiophene-Containing Drugs. *Chem. Res. Toxicol.* **2014**, *27*, 1344–1358.

28. Bikram, M.; West, J. L. Thermo-Responsive Systems for Controlled Drug Delivery. *Expert Opin. Drug Deliv.* **2008**, *5*, 1077–1091.

29. Paton, D. G.; Childs, L. M.; Itoe, M. A.; Holmdahl, I. E.; Buckee, C. O.; Catteruccia, F. Exposing Anopheles Mosquitoes to Antimalarials Blocks Plasmodium Parasite Transmission. *Nature* **2019**, *567*, 239–243.

30. Mayekar, N. V.; Chattopadhyay, S.; Nayak, S. K. An Efficient Synthetic Strategy for Geometrically Pure Symmetrical and Unsymmetrical Hydroxystilbenes via McMurry Coupling. *Synthesis* **2003**, No. 13, 2041–2046.

31. Lloyd, D. G.; Hughes, R. B.; Zisterer, D. M.; Williams, D. C.; Fattorusso, C.; Catalanotti, B.; Campiani, G.; Meegan, M. J. Benzoxepin-Derived Estrogen Receptor Modulators: A Novel Molecular Scaffold for the Estrogen Receptor. *J. Med. Chem.* **2004**, *47*, 5612–5615.

32. Naganawa, Y.; Kawagishi, M.; Ito, J.; Nishiyama, H. Asymmetric Induction at Remote

Quaternary Centers of Cyclohexadienones by Rhodium-Catalyzed Conjugate Hydrosilylation. *Angew. Chemie Int. Ed.* **2016**, *55*, 6873–6876.

33. Tsai, J.-C.; Li, S.-R.; Chiang, M. Y.; Chen, L.-Y.; Chen, P.-Y.; Lo, Y.-F.; Wang, C.-H.; Lin, C.-N.; Wang, E.-C. Synthesis of 3-Alkoxymethylcoumarin from 3-Cyanochromene via a Novel Intermediate 2-Phenylimino-3-Alkoxymethylchromene. *J. Org. Chem.* **2009**, *74*, 8798–8801.

34. Huang, X.; Jiao, N. Brønsted Acid Mediated Nitrogenation of Propargylic Alcohols: An Efficient Approach to Alkenyl Nitriles. *Org. Biomol. Chem.* **2014**, *12*, 4324.

35. Delves, M. J.; Straschil, U.; Ruecker, A.; Miguel-Blanco, C.; Marques, S.; Baum, J.; Sinden, R. E. Routine in Vitro Culture of P. Falciparum Gametocytes to Evaluate Novel Transmission-Blocking Interventions. *Nat. Protoc.* **2016**, *11*, 1668–1680.

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