The Optimisation of a Series of 2,3-Dihydrobenzofurans as Highly Potent, Second Bromodomain (BD2) Selective, Bromo and Extra Terminal Domain (BET) Inhibitors.

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Abstract

Herein, a series of 2,3-dihydrobenzofurans have been developed as highly potent Bromo and Extra Terminal domain (BET) inhibitors with 1000-fold selectivity for the second bromodomain (BD2) over the first bromodomain (BD1). Investment in the development of two orthogonal synthetic routes delivered inhibitors that were potent and selective, but had raised

in vitro clearance and sub-optimal solubility. Insertion of a quaternary centre into the 2,3-dihydrobenzofuran core blocked a key site of metabolism and improved solubility. This led to the development of inhibitor **71** (GSK852); a potent, 1000-fold selective, highly soluble compound with good *in vivo* rat and dog pharmacokinetics.

Introduction

The Bromo and Extra Terminal domain (BET) family consists of 4 proteins (BRD2, BRD3, BRD4 and BRDT), each of which contain two bromodomains, named the first bromodomain (N-terminus, BD1) and second bromodomain (C-terminus, BD2) respectively.[1] Pan-BET inhibitors, which inhibit equipotently all 8 BET bromodomains, are well-established in drug discovery, with the therapeutic potential to treat a range of diseases. In particular, a significant amount of research has been directed towards both oncology and immunoinflammation indications with a number of assets in oncology clinical trials.[2-19] However, a number of dose-limiting clinical findings have been linked to pan-BET inhibition.[20] A logical next step is to design selective BET inhibitors, which target a subset of the bromodomains, to assess if efficacy and toxicity can be teased apart. The respective sequences and structures of the BD1 and BD2 domains are well conserved throughout the BET family and this makes the search for isoform selective inhibitors challenging. Whilst the sequence homology between BD1 and BD2 is also similar, there are a number of differences which have already been exploited to achieve domain selectivity. Recent research has shown that the phenotype of pan-BD2 selective BET inhibitors (interacting equipotently with all BD2 bromodomains) is differentiated from their pan-BET counterparts: BD2 inhibitors retain efficacy in immunoinflammation and show differentiated anti-proliferative effects in a sub-set of cancer cell lines.[21-26] Therefore, there is significant interest in developing potent and

selective inhibitors of BD2 to further probe the mechanism of action and ultimately to progress into clinical trials. Reports of BD2 selective compounds are indeed beginning to appear in the literature. For example, RVX-208 and RVX-297 (**1**, Fig. 1) which were originally developed as Apo-A1 upregulators and later found to be BD2 biased inhibitors, maintained immune relevant efficacy.[24-25, 27-28] AbbVie have recently disclosed ABBV-744 (**2**) as a BD2 selective BET inhibitor which has entered the clinic for the treatment of acute myeloid leukemia and castrate-resistant prostate cancer.[29-30] Additionally, work by our group has recently disclosed tetrahydroquinoxaline **3**, GSK046 (**4**), and GSK620 (**5**) as >100-fold selective BD2 BET inhibitors.[31-35]

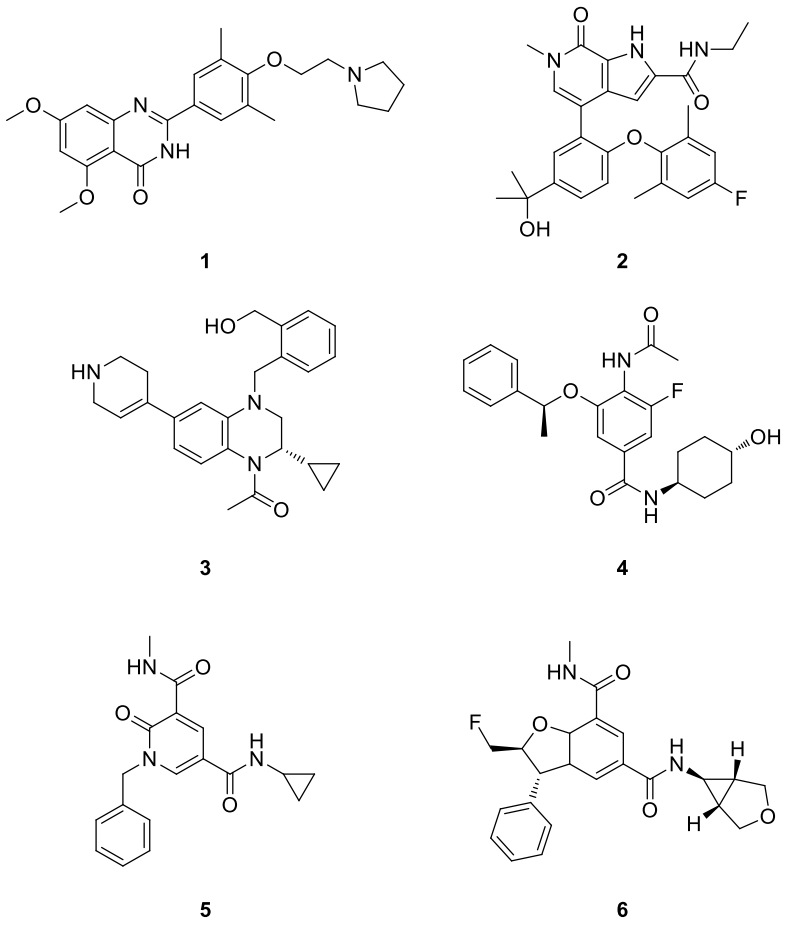


Figure 1. BD2 domain selective BET inhibitors.

Subsequently, we disclosed 2,3-dihydrobenzofuran (DBF) **6** (GSK973, Figure 1), which constrained the previous pyridone example **5** to achieve high domain selectivity of >1000 fold (Table 1).[35-36] Here, conformational restriction of the phenyl group provides an entropically more favourable interaction with BD2 due to the loss of potential free energy states of this group in solution, leading to an improvement in both potency and selectivity.[37] The edge-to-face interaction of the phenyl group with both the WPF shelf and the BD2 specific His433 (BRD2 BD2 numbering), together with a bidentate interaction with Asn429, which is engaged by the carbonyl of the methyl amide KAc mimetic and the NH of the other amide group, is believed to drive the high BD2 potency observed (Figure 2).[1, 38-39] Indeed, **6** showed excellent potency against BRD4 BD2 (pIC_{50} = 7.8) and weak potency against BRD4 BD1 (pIC_{50} = 4.6). This >1000-fold selectivity, was recapitulated against the other BET family members.

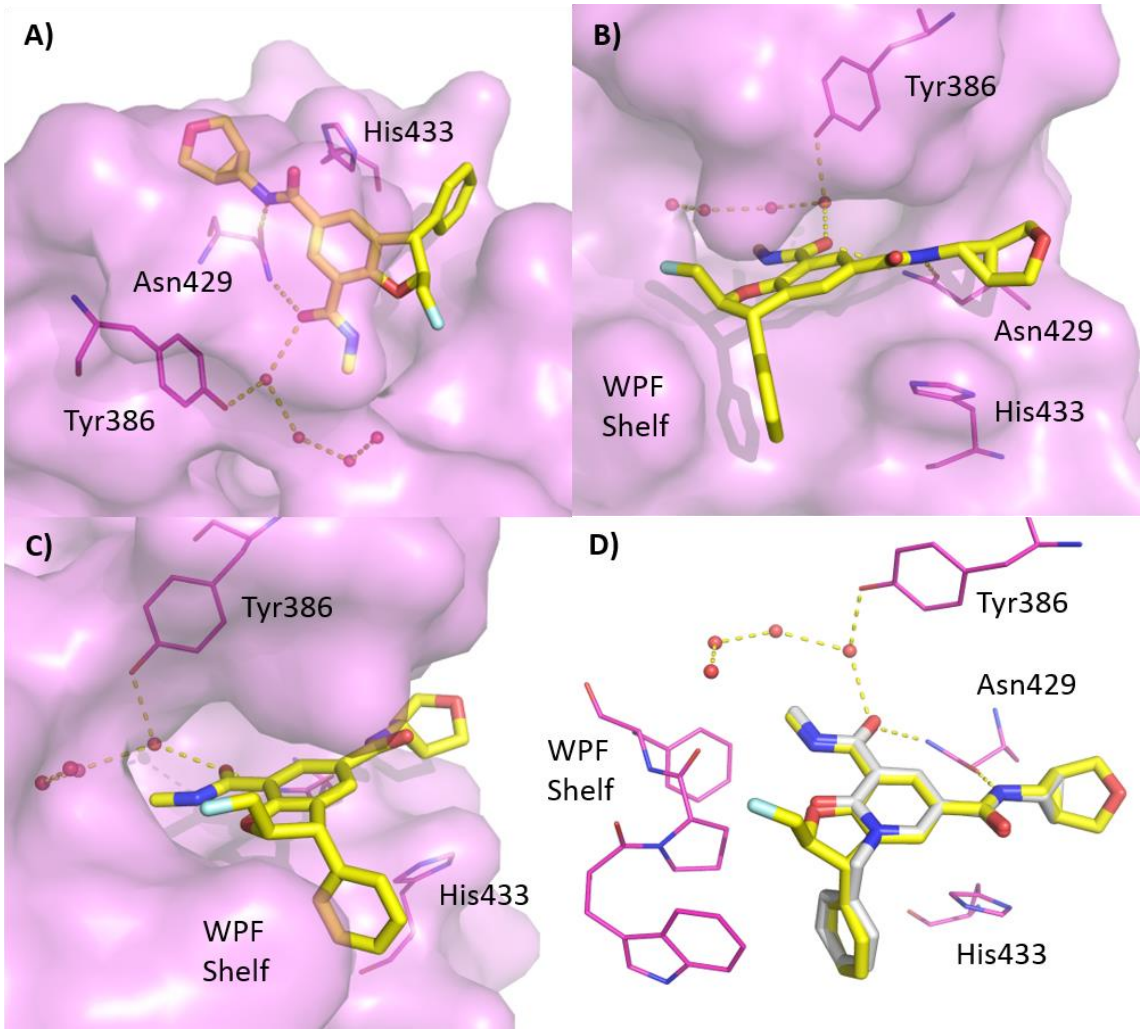
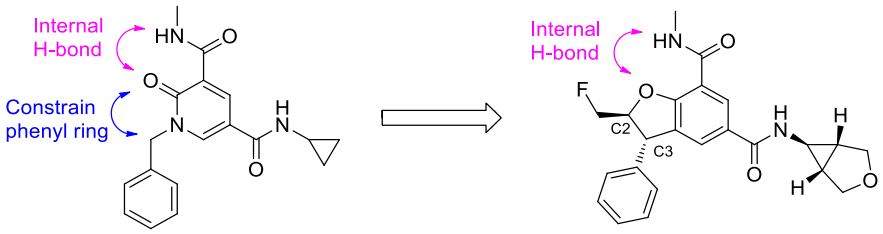


Figure 2. Crystal structure of DBF **6** (yellow, PDB 6z8p) in BRD2 BD2 (pale pink) showing key interactions with the protein from different angles. An overlay with pyridone **5** (grey, PDB 6zb1) is shown for reference. The key residues are present (magenta) and the H-bonding interactions are shown by yellow dotted lines. Water molecules are visible as red spheres. A-C) DBF **6** makes a bidentate interaction with Asn429 and place a phenyl ring between the BD2 specific His433 and the WPF shelf. D) The two inhibitors, **5** and **6**, are shown to exhibit significant overlap.

Whilst **6** displayed excellent potency and selectivity, the DBF series had an inherently more lipophilic core compared to **5**, meaning that even with a more polar amide group, the ChromLogD of **6** was higher than **5** (3.6 *vs.* 3.1, Table 1). SAR also showed that DBF

compounds such as **6** were constrained to a narrow physicochemical range (ChromLogD = 3.0 – 4.0).[40-42] Analogues of **6** which were of higher lipophilicity suffered from poor rodent PK, whilst lower lipophilicity negatively impacted permeability and oral bioavailability. DBF **6** did improve the poor solubility of pyridone **5** by Charged Aerosol Detection (CAD, ≥206 *vs.* 87 μg mL^{-1}) but this was not recapitulated in the more relevant Fasted State Simulated Intestinal Fluid (FaSSIF, 25 *vs.* 80 μg mL^{-1}) assays, which made progression into development more challenging.[43] Additionally, DBF **6** metabolic stability in the rat hepatocyte assay was inferior to that of pyridone **5** (1.8 *vs.* 1.0 mL min^{-1} g^{-1}). The aim of this work was to develop compounds that maintained the exquisite potency and selectivity of our previous work but had improved solubility (FaSSIF >100 μg mL^{-1}) and a good *in vivo* PK. An IVC of <1.0 mL min^{-1} g^{-1} was generally considered desirable for progression in to *in vivo* PK studies.

Table 1. Conformational Restriction of the Phenyl group to give the 2,3-dihydrobenzofuran series.



	5	**6**
BRD4 BD1 pIC_{50} (n) / BD2 pIC_{50} (n)	7.1(16) / 4.8(14)	7.8 (20) / 4.6(19)[a]
Selectivity (fold)	200	1600
ChromLogD @ pH 7.4	3.1	3.6

CAD solubility (μg mL^{-1})	87	≥206
FaSSIF solubility (μg mL^{-1})	25	80
In vitro clearance (IVC), rat hepatocytes (mL min^{-1} g^{-1})	1.0	1.8

[a]also tested <4.3 (n=7)

One limitation to the scope of previous SAR for this series was the synthetic tractability of changing the pendent *C3* aryl substituent. There was the potential that replacement with heteroaromatics would enable more analogues to occupy the desired physico-chemical space. Additionally, the removal of the *C2* substituent from the DBF core had not been investigated. This potentially offered a method to reduce lipophilicity and molecular weight whilst reducing the synthetic complexity and allowing the preparation of a wider variety of shelf substituents. However, to achieve this goal a new synthetic strategy was needed.

Results and Discussion

Retrosynthetically, two routes to synthesise the DBF core were envisioned which would allow for late stage functionalisation of both the shelf and amide vector in turn (Figure 3). Previous chemistry towards **6** had utilised a Claisen rearrangement-epoxidation ring-closure which mandated installation of a CH_2OH group at the *C2* position, which could be further modified (to Me or CH_2F) but not deleted.[36] To overcome this, hydroboration of vinyl phenol **9** and subsequent Mitsunobu ring-closure of alcohol **8** was considered. The R^2 amide could then be varied at a late stage. Alternatively, a complementary route from key intermediate **11** was proposed. This relied on a Sonogashira-cyclisation reaction to form benzofuran **12**. Bromination of the core would insert a useful synthetic handle, where the desired shelf groups could be installed prior to hydrogenation to form the final DBFs. This second approach would

allow for late stage variation of R^1, which had been synthetically problematic in the earlier synthesis of analogues of **6** (*vide supra*).

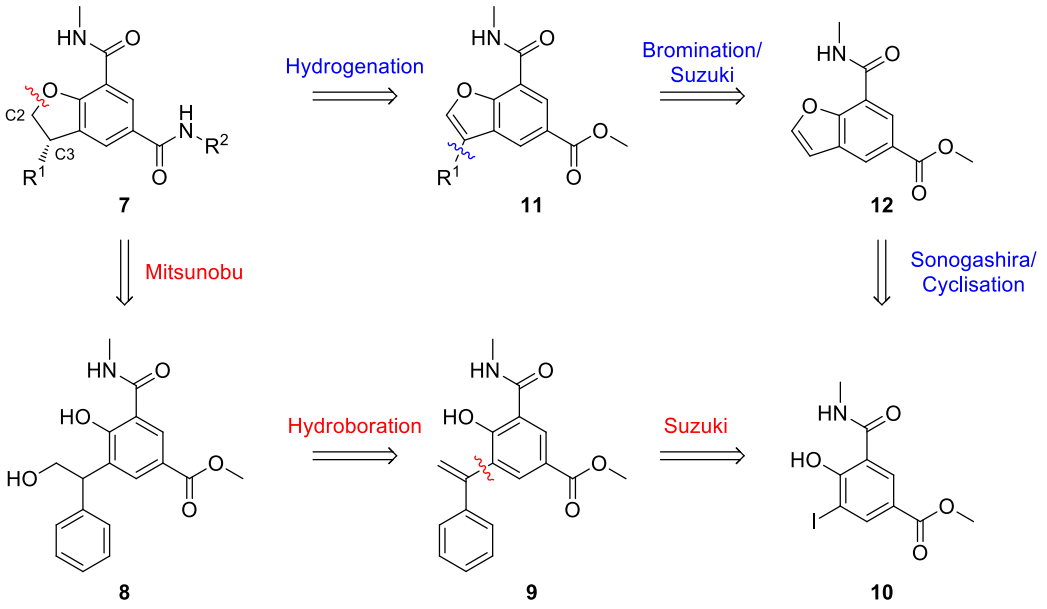
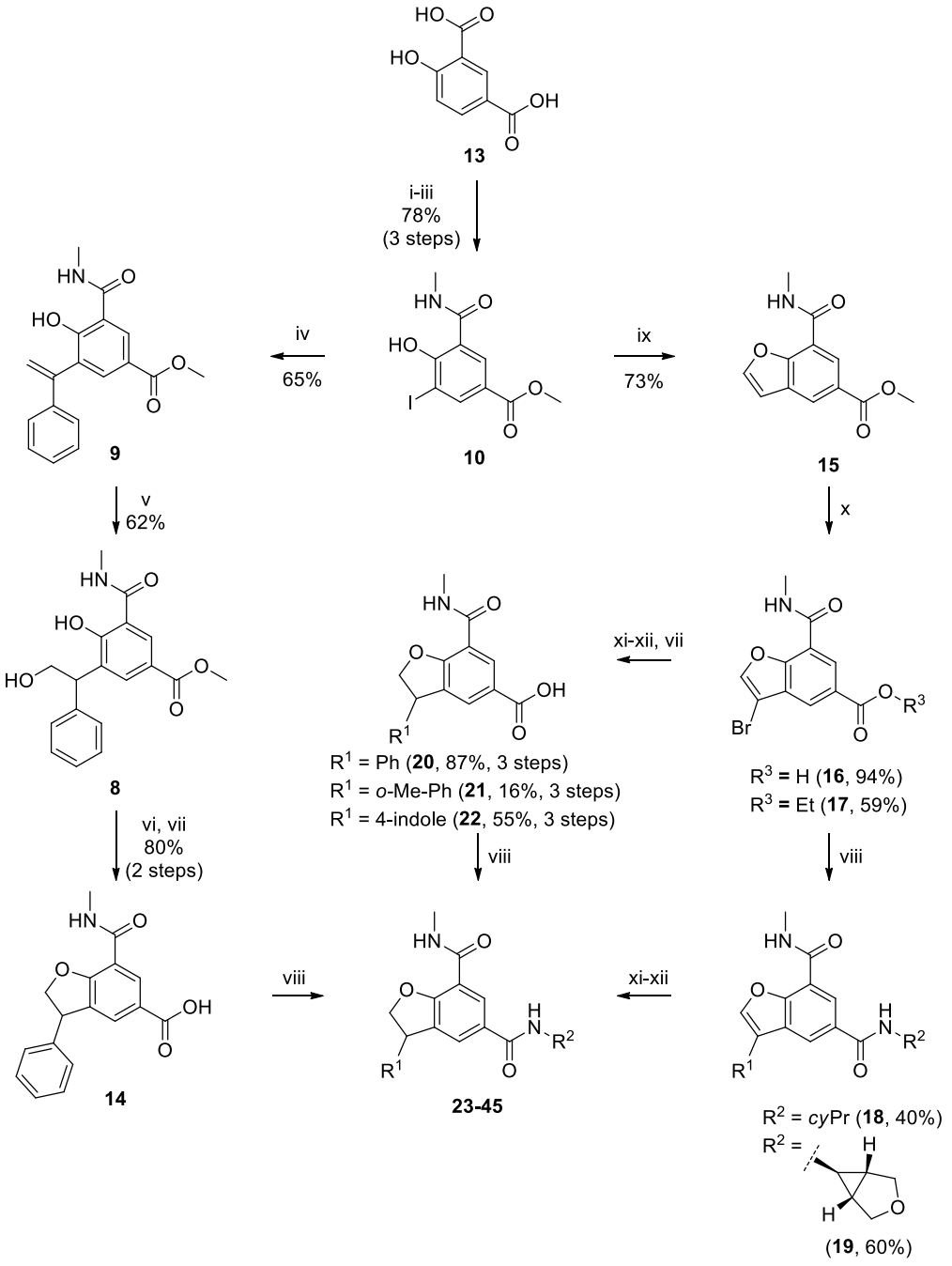


Figure 3. Retrosynthetic approach to the *C2=H* DBF series.

Firstly, the common phenol intermediate **10** was synthesised starting from 4-hydroxyisophthalic acid **13** (Scheme 1). This was first esterified using thionyl chloride in methanol. Subsequently, a regioselective amine substitution using dimethylamine was facilitated by intramolecular hydrogen bonding of the *ortho*-ester substituent. Iodination then gave intermediate **10** (83% over 3 steps). This was coupled to 1-phenylvinylboronic acid to afford alkene **9** using a PEPPSI *i*Pr pre-catalyst under Suzuki conditions in 65% yield.[44] Hydroboration of styrene **9** using borane led to a 1.8:1.0 mixture of regioisomers, whilst more hindered reagents (e.g. 9-BBN) were unable to affect the transformation. Thexylborane gave the highest regioselectivity of 4.8:1.0. The regioisomers could be readily separated at this stage providing the desired alcohol **8** in 62% yield.[45] Exposure of **8** to Mitsunobu conditions followed by ester hydrolysis under basic conditions gave DBF **14**.[46] The carboxylic acid could be used in a range of amide couplings to give the desired products **23–27** (Table 2).

Alternatively, to access 3-bromobenzofurans **18–19** as precursors to R^1 diversification, intermediate phenol **10** was reacted using Sonogashira conditions with TMS acetylene, which, after TBAF deprotection afforded benzofuran **15**. In order to brominate at the 3-position, benzofuran **15** was reacted with bromine to afford the dibromide intermediate. KOH in EtOH then facilitated the selective elimination of the bromide from the 2-position to afford 3-bromobenzofuran **16** in a yield of 98% after ester hydrolysis. A shorter reaction time led to ethyl ester **17**. Amides **18** and **19** were prepared from **16** in 40% and 60% yields respectively using HATU as a coupling agent. The shelf substituents were introduced using a Suzuki coupling of the commercially available boronic acids with bromides **18–19**. Subsequent hydrogenation of the benzofuran, using a highly activated Pd/C 424 catalyst, gave DBFs **33–45**.[47] Alternatively, C3 substituents could be installed prior to the R^2 amide group to give carboxylic acids **20–21** after acid hydrolysis. These were then coupled to the desired amines to afford DBFs **28–32**. Where desirable, the single enantiomers were accessed *via* chromatography of the final products, **(*rac*)-23–(*rac*)-27** and **(*rac*)-39–(*rac*)-45**, using a chiral stationary phase. Alternatively, the two enantiomers of **14** could be separated by chromatography using a chiral stationary phase and carried through the subsequent step to afford the desired products. Unless otherwise stated, all compound data is for a single enantiomer. The absolute configuration of the most potent enantiomer was assigned as (*S*) at the C3 position in accordance with available crystallographic evidence of **(*S*)-44** (Figure 4).

Scheme 1. Synthesis of DBFs **23-45** *via* either a hydroboration/Mitsunobu or Sonogashira/hydrogenation sequence.



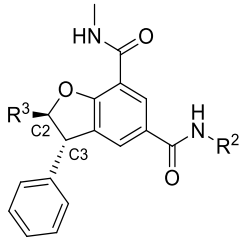
Reagents and conditions: i) $SOCl_2$, MeOH, reflux, 6 h, 92%; ii) $MeNH_2$, water/THF, rt, 16 h, 98%; iii) NIS, CH_2Cl_2, rt, 2 h, 87%; iv) 1-Phenylvinylboronic acid (2.0 eq), PEPPSI-*i*Pr, K_3PO_4, dioxane/water, 70 °C, 2 h, 65%.; v) Thexylborane (0.66 M in THF, 2.0 eq), THF, 0 °C, 16 h, *then* NaOH, H_2O_2, rt, 4 h, 62% (4.8:1.0 ratio of regioisomers); vi) PPh_3 (1.2 eq), DIAD (1.2 eq), THF, rt, 16 h, 81%; vii) LiOH (2.0 eq), THF, water, 50 °C, 2 h, 99% viii) HATU (1.2

eq), DIPEA (3 eq), amine (1.4 eq), DMF, rt, 2 h, 39–97%; ix) TMS acetylene (2.2 eq.), $PdCl_2(PPh_3)_2$ (10 mol%), CuI (5 mol%), TEA (3 eq.), DMF, 80 °C, 16 h; *then* TBAF (2 M in THF), rt, 2 h, 87%; x) Br_2 (2 eq), CH_2Cl_2 (50 mL), rt, 2 h *then* KOH (2 eq), EtOH (50 mL), 40 °C, 24 h, 94%; %; xi) boronic acid (1.2 eq), Pd Cat (10 mol%), K_3PO_4 (3 eq), 1,4-dioxane/water, 40 °C, 2 h, 25–99%; xii) Pd/C type 424 (10 mol%), EtOH, H_2, rt, 16 h, 25–63%.

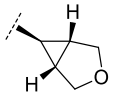
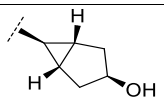
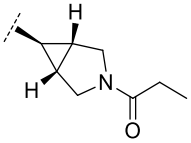
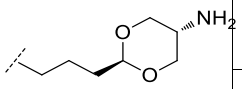
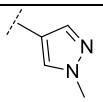
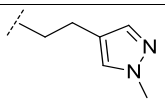
To understand the effect of removing the *C2* group a range of R^2 amides were prepared. The unsubstituted phenyl group was fixed as R^1 and the data compared with previously published DBF inhibitors bearing a *C2=CH₂F* substituent (Table 2).[36] Overall, potency and selectivity was generally maintained in all examples (**6, (*S*)-23–(*S*)-27** and **46–49**) and an average ChromLogD reduction of 0.2 log units was observed. The cyclopropyl amides **(*S*)-25** and **48** had similar profiles but **(*S*)-25** had improved CAD solubility (≥141 *vs.* 8 μg mL^{-1}).[48-50] This trend was also observed with the methyl cyclopropyl analogues **(*S,S,S*)-26** and **49** which also displayed similar potencies and increased solubility with the loss of the *CH₂F* group (≥76 from 7 μg mL^{-1}). Cyclopropyl amide **(*S*)-25** also had an encouraging rat hepatocyte *in vitro* clearance value of 2.0 mL min^{-1} g^{-1}, akin to that of the preferred DBF **6** and was therefore progressed for further profiling which will be discussed subsequently. The 3-oxobicyclo[3.1.0]hexan-6-amide (of **(*S*)-27**), which was the optimal substituent in the previous DBF template (see compound **6**), was also well tolerated in the *C2=H* series with high BD2 potency (pIC_{50} = 7.9) and >1000-fold selectivity over BD1: Inhibitor **(*S*)-27** was in a good physicochemical space (ChromLogD = 3.3) and was soluble (≥143 μg mL^{-1}). Unfortunately, DBF **(*S*)-27** had raised rat hepatocyte clearance (8.6 mL min^{-1} g^{-1}) compared to its *CH₂F* matched pair. Given the bicyclic amide provided an excellent balance of physicochemical properties and potency, further new analogues were designed using this framework that had

not been previously prepared in the *C2=CH₂F* series. Bicyclic alcohol **28** (for synthesis see Supporting Information, Scheme S1) was highly potent at BD2 (pIC_{50} = 7.9) resulting in 2000-fold selectivity over BD1. It was soluble (≥124 μg mL^{-1}) and had reduced hepatocyte clearance in rat (3.3 mL min^{-1} g^{-1}) relative to **(*S*)-27**, albeit this was still higher than **6** and **(*S*)-25**. Ethyl amide **29** also showed high potency and selectivity for BD2, but poor rat hepatocyte stability. The previously reported *trans*-1,3-dioxan-5-amide was well tolerated in both series (**30** and **50**) with a high potency against BD2 in both series and was 630-fold selective over BD1.[51] Furthermore, it showed good solubility (>153 μg mL^{-1}) but was not progressed due to a lower ChromLogD which had previously correlated with poor bioavailability.[52] Small heterocycles were also well tolerated, pyrazole **31** was highly potent, but unfortunately had raised rat hepatocyte turnover. Whereas, alkyl-linked pyrazole **32** was 0.5–1.0 log units less potent than the other examples. Overall removing the *CH₂F* group was not detrimental to BD2 potency or selectivity and did somewhat decrease the lipophilicity of the compounds. The *C2=H* analogues had similar or improved CAD solubility but unfortunately did not lower the rat *in vitro* clearance.

Table 2. Profile of *C2=H vs. C2=CH₂F* inhibitors and investigation of the amide SAR.



	R^3	R^2	BRD4 BD2(n) / BD1(n) pIC_{50}	Selectivity (fold)	Chrom LogD	CLND Solubility (μg mL^{-1})	Rat hepatocytes

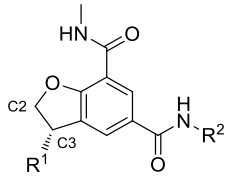
					@ pH 7.4		(mL min^{-1} g^{-1})
46	CH_2F	H	6.9(2) / 4.7(2)	160	2.9	≥128	-
23	H		7.2(3) / 5.0(2)	160	2.7	≥144[a]	-
47	CH_2F	Me	7.5(3) / 4.9(2)	400	3.3	≥149	3.0
24	H		7.7(2) / 5.2(2)	320	3.2	≥130[a]	-
48	CH_2F		7.6(3) / <3.3(2)[b]	>20000	3.9	8	3.2
25	H		7.7(10) / 4.8(10)	800	3.6	≥190	2.0
49	CH_2F		8.0(3) / 5.0(1)[c]	1000	4.5	7	-
26	H		8.0(2) / 4.8(2)	1600	4.5	≥76	-
6	CH_2F		7.8(20) / 4.6(19)[d]	1600	3.6	≥206[a]	1.8
27	H		7.8(8) / 4.8(8)	1000	3.3	≥165	8.6
28	H		7.9(3) / 4.6(2)	2000	2.9	≥124[a]	3.3
29	H		8.0(3) / 4.9(3)	1300	3.4	≥163	6.8
50	CH_2F		7.6(3) / 4.8(3)	630	2.9	174	1.1
30	H		7.8(2) / 5.0(2)	630	2.6	≥ 153 [a]	-
31	H		8.3(4) / 5.3(4)	1000	3.5	≥189	20.1
32	H		7.1(3) / <4.3(3)	630	3.2	≥78	-

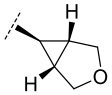
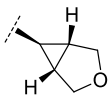
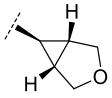
[a]CAD solubility; [b]Also tested <4.3 (n = 4); [c]Also tested <4.3 (n = 2); [d]Also tested <4.3 (n = 1);

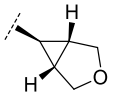
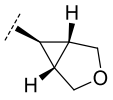
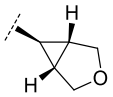
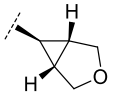
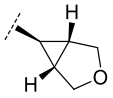
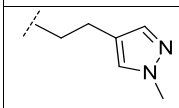
Having established that the *CH_2F* group was not essential for activity, the SAR of the shelf substituent was examined next. The BD2 selectivity of the DBF series is believed to be partly driven by an edge-to-face π-stacking between the BD2 specific His433 (see Figure 2) and the phenyl ring. Therefore, replacement of this substituent with a non-aromatic substituent should lead to a decrease in activity at BD2. However, given the potential positive impact on lipophilicity and solubility, it was important to confirm this hypothesis. The predicted decrease in potency was observed. Tetrahydropyran (THP) **33** was 10-fold less potent than the analogous phenyl **(*S*)-27**. Additionally, electron-deficient pyridyl substituents (**34–36**) were poorly tolerated with all three regioisomers showing similar potency to THP **33**. This is likely driven by the addition of polarity into an essentially hydrophobic binding pocket, although the electronics of the aryl ring may also be important**.** As an aromatic substituent appeared critical for BD2 potency and consequently selectivity, the effect of substitution on the aromatic ring was explored. The electron rich *o*-methoxyphenyl group was prepared with both the cPr and bicyclic ether amides (**37–38**). Whilst both **37** and **38** were well tolerated (BD2 pIC_{50} ≥7.3), they were less selective against BD1. Both 3- and 4- fluoro substituents were designed to further probe the electronics of the ring and understand their suitability as potential blockers of metabolism (*via* aryl-hydroxylation). Both regioisomers prepared as the cyclopropyl amides were well tolerated (**(*S*)-39** and **(*S*)-40,** pIC_{50} ≥7.5). Upon switching to the bicyclic-ether amide for the 4-F derivative **(*S*)-41**, potency and selectivity were similar, but solubility improved (176 μg mL^{-1}). Despite the ability to block potential metabolic sites on the aromatic ring, all 3 compounds showed raised hepatocyte clearance in rat, suggesting that oxidation of the aromatic ring was not a key driver of rat metabolism. Next, the effect of *ortho* substitution was investigated. DBF **(*S*)-42** maintained potency at BD2 but was only 500-fold selective over BD1. Previous SAR had shown that indole substituents capable of interacting with the WPF

shelf were highly potent at BD2.[53,34] This was believed to be due to the extended biaryl pi-system generating more optimal edge-to-face interactions with tryptophan (Trp370) and histidine (His433) residues (Figure 4), whilst the indole *NH* was also shown, by crystallography, to make a through water mediated interaction with an aspartic acid residue (Asp434) in accord with the previously reported binding mode of GSK549.[34] This SAR tracked well as indoles **(*S*)-43–(*S*)-45** had excellent BD2 potency (pIC_{50} >7.8). Moreover, all three examples showed a good selectivity profile and kinetic solubility. Due to the promising profile of these compounds, they were progressed to determine their metabolic stability. Unfortunately, none of the compounds were stable in rat hepatocytes with values >4.6 mL min^{-1} g^{-1} despite being in an acceptable LogD range suggesting the indole had introduced an additional metabolic weakness.

Table 3. Exploration of shelf group SAR.



	R¹	**R²**	**BRD4 BD2(n) / BD1 (n) pIC_{50}**	**Selectivity (fold)**	**Chrom LogD**	**CLND Solubility (µg mL^{-1})**	**IVC rat hepatocytes (mL min^{-1} g^{-1})**
33	4-THP		6.6(3) / 4.7(3)	80	2.1	≥177	-
34	2-pyridyl[a]		6.7(3) / <4.3(3)	>250	1.6	≥158	-
35	3-Pyridyl[a]		6.6(3) / 4.8(1)[b]	60	1.4	≥104	-

36	4-pyridyl[a]		6.8(2) / 4.8(1)[c]	100	1.3	≥184	-
37	3-OMe-Ph[a]		7.3(3) / 4.7(3)	400	3.8	≥161	-
38			7.5(3) / 4.6(3)	790	3.2	≥186	-
39	3-F-Ph		7.6(5) / 4.8(5)	630	3.7	≥175	10.0
40	4-F-Ph		7.5(4) / 4.7(4)	630	3.8	40	6.1
41			7.7(3) / 4.8(3)	790	3.6	≥176	14.8
42	2-Me-Ph		7.6(3) / 4.9(3)	500	4.0	≥103	30.9
43	6-indole		8.1(2) / 5.0(2)	1300	3.5	≥142	4.6
44			8.2(8) / 5.3(8)	790	3.1	≥171	3.6
45			7.8(3) / 4.7(3)	1300	3.2	≥200	16.3

[a]Tested as a racemic mixture; [b]Also tested <4.3 (n = 2); [c]Also tested <4.3 (n = 1).

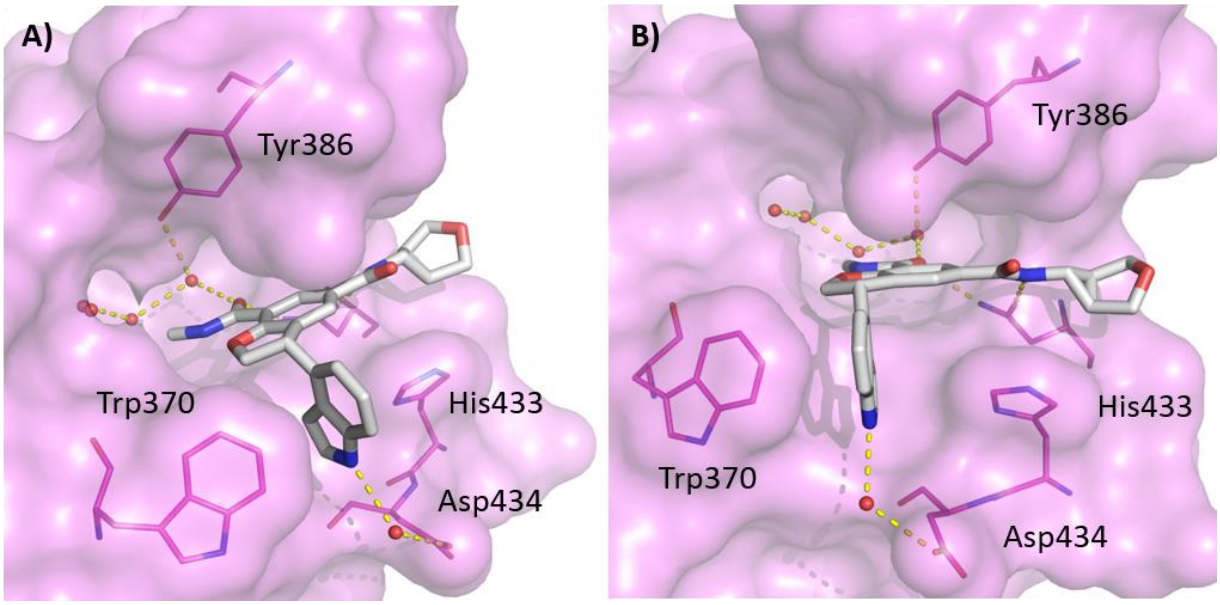


Figure 4. Crystal structure of DBF **(*S*)-44** (grey, PDB7OE8) in BRD2 BD2 (pale pink). The key residues are present (magenta) and the H-bonding interactions are shown by yellow dotted lines. Water molecules are visible as red spheres. A-B) DBF **(*S*)-44** makes a bidentate interaction with Asn429 and place the indole ring between the BD2 specific His433 where is makes a through water interaction to Asp434.

The data shown in Tables 2 and 3 revealed that whilst the desired potency and selectivity profile could be achieved with this template, none of the compounds tested showed the desired in vitro metabolic stability ($\leq$ 1.0 mL min^{-1} g^{-1}) in the rat hepatocyte assay. In order to aid rational design, an *in silico* Metasite prediction was used to identify possible metabolic liabilities of the template (Figure 5).[54] This suggested that the methyl amide warhead would be the most readily metabolised. However, as other series with close structural similarity (same R^1 and R^2 amides) had demonstrated good PK, it was hypothesised that this was in fact more metabolically stable than predicted.[33-34, 36] Moreover, previous SAR had shown that the methylamine was critical for potency and it was indeed the case in this series (data not shown) so this was considered non-replaceable. The bicyclic amide was also predicted to be metabolically labile. However, a range of structurally diverse amides all showed raised

hepatocyte clearance suggesting that *O*-dealkylation was not the issue. This pointed towards the DBF core as the main site of metabolism, with aromatisation to the benzofuran a likely culprit. This is consistent with **6** *vs*. **(*S*)-27** data where between the matched pairs the IVC increases from 1.8 to 8.6 mL min^{-1} g^{-1} despite both molecules having similar ChromLogD. If true, it is possible that the increased steric hindrance of the CH_2F helps to block oxidation to the benzofuran. Therefore, a strategy was envisioned which inserted a quaternary centre into the molecule at the 3-position to stop aromatisation/cleavage of the DBF ring and potentially lead to a more metabolically stable compound.[55] Additionally, the increased sp^3 character, and 3D structure may give rise to higher solubility.[55-56] To meet this aim and provide an opportunity to tune lipophilicity, three compounds with methyl, ethyl and CH_2OH quaternary centres were designed.

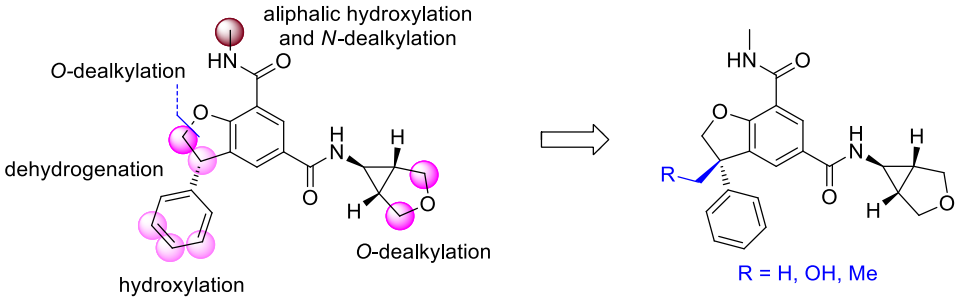
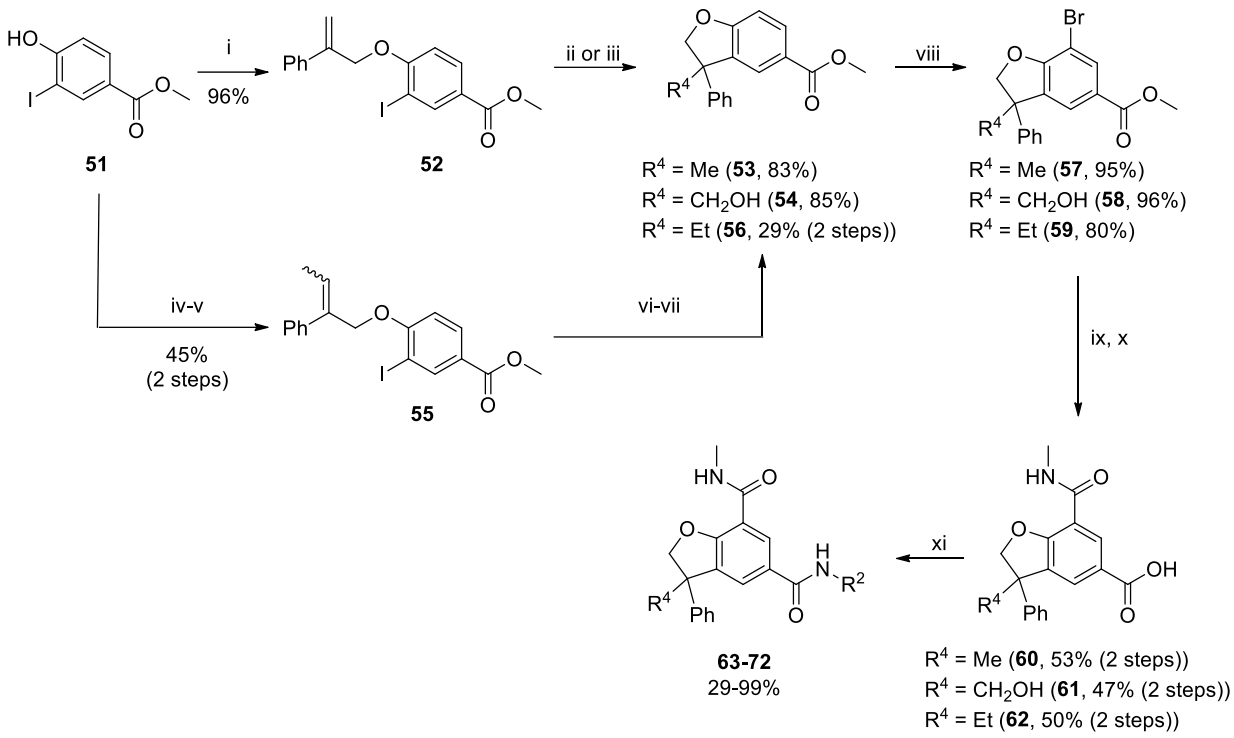


Fig. 5. *In silico* Metasite prediction of **(*S*)-27** highlighted potential metabolic liabilities. Potential liabilities are showed by pink spheres where the darker spheres highlight areas which are predicted to be more prone to oxidation.

The synthesis of the quaternary DBF core proceeded in accordance with scheme 3. Starting from phenol **51**, alkylation using (3-bromoprop-1-en-2-yl)benzene gave ether **52** in 96% yield. A Pd catalysed reductive Heck-cyclisation procedure was envisioned to install the methyl quaternary centre. Pleasingly, the conditions first published by Trost *et al.* in their total synthesis of Furaquinocin A, B, and E, which used formic acid as a terminal reductant, inserted

the methyl quaternary centre in 83% yield.[57-60] Interestingly, this reaction failed when attempted with the *ortho* methylamide group present. The formation of **53** ($R^4 = CH_3$) is driven by reduction of the corresponding palladium species ($R^4 = CH_2PdX$) by the formic acid. There was literature precedent for the diversion of this palladium species into an alternative catalytic cycle. Of particular interest was the separate work of Vachhani and Lautens which installed a pendant boronic ester moiety after palladium-mediated cyclisation into alkenes.[61-62] This strategy proved effective on the DBF template using an XPhos Pd G2 catalyst, and the resulting boronic ester could be oxidised *in situ* to afford alcohol **54** in 85% yield. In order to insert an ethyl quaternary centre, an alternative strategy was employed. Alkylation of phenol **51** with 2-bromoacetophenone and subsequent Wittig olefination of the ketone with ethyltriphenylphosphosium bromide gave alkene **55**. This was cyclised using a (non-reductive) Heck reaction to afford a pendant vinyl group which could be hydrogenated in 95% yield to give the ethyl quaternary centre (**56**). All three of the intermediates were then regioselectively brominated to give bromides **57–59** in up to 96% yield. A palladium-catalysed amino carbonylation reaction was then used to install the methyl amide warhead, using cobalt carbonyl as the carbon monoxide source.[63] A base mediated hydrolysis followed by an amidation using HATU as the coupling agent afforded the desired quaternary DBFs **63–72** in yields of 29–99%. The single enantiomers of **63-72** were accessed *via* the enantiopure esters which were prepared by chromatography using a chiral stationary phase and processed through the subsequent steps to afford the desired products.

Scheme 3. Synthetic strategy for the synthesis of a dihydrobenzofuran quaternary centre.



Reagents and conditions: i) (3-bromoprop-1-en-2-yl)benzene (2 eq), K_2CO_3 (3 eq), acetone, 80 °C, 1 h, 96%; ii) R^4 = Me: $PdCl_2(MeCN)_2$, PMP, HCO_2H, DMF, 50 °C, 83%; iii) R^1 = OH: Pd Xphos G2, bispinacolatodiboron, KOAc, EtOH, 100 °C, mw, 4 h *then* NaOH, H_2O_2 (38% *w/w* in water), rt, 1 h, 85%; iv) 2-bromoacetophenone (1 eq), K_2CO_3 (3 eq), acetone, 80 °C, 2.5 h, 74%; v) Ethyltriphenylphosphosium bromide (2 eq), *t*BuOK (2 eq), THF, rt, 1.5 h, 86%; vi) Ag_2CO_3 (2.0 eq), PPh_3 (0.8 eq), $Pd(OAc)_2$ (0.1 eq), 80 °C, 48 h, 30%; vi) Pd/C, H_2, EtOH, 3 h, 95%; vii) Br_2, CH_2Cl_2, rt, 4 h, 80–96%; viii) $MeNH_2$.HCl, $Pd(OAc)_2$, Xantphos, DMAP, $Co_2(CO)_8$, 1,4-dioxane, 100 °C, mw, 4 h, 50–70%; x) LiOH (2 eq), THF/water (1:1), 50 °C, 2 h, 72–94% xi) *amine*, HATU, DIPEA, CH_2Cl_2, rt, 2 h, 29–99%.

To investigate the impact of incorporating the quaternary stereocentres, examples with the bicyclic ether amide at R^2 were evaluated and compared to previous *C2=H* analogues (Table 4) . Pleasingly, the three quaternary derivatives **63**-**65** were potent ($pIC_{50} \geq 7.5$) albeit with a slight reduction in selectivity (630-fold, 320-fold, and 400-fold for the methyl, ethyl and CH_2OH quaternary centres respectively) relative to **(*S*)-27** (1000-fold).

An X-ray crystal structure of **63** was solved and is shown in Figure 6. The crystal structure of **63** was compared to **6** and **(*S*)-44** (Figure 6 (D)). All three compounds were shown to overlay well, which rationalises the observed SAR. Whereas in **6** the *CH_2F* group points into the ZA channel, the methyl substituent points away from it between Trp457 and an overhanging lipophilic region. As discussed previously, the phenyl ring then sits between the WPF shelf and the BD2 specific His433, driving selectivity for BD2. The two amide groups make a dual interaction with the conserved Asn429. The carbonyl group of the methyl amide also makes a second, water mediated, interaction to the conserved Tyr386 residue.

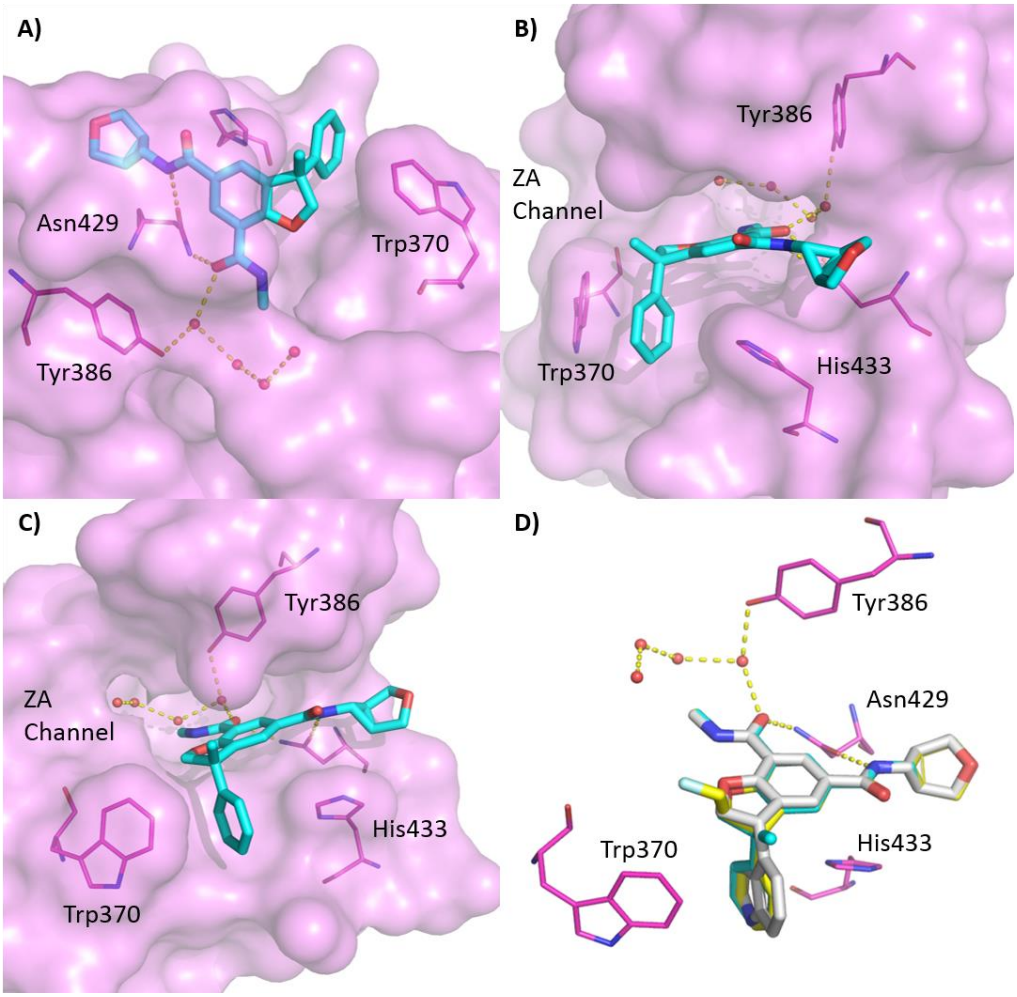
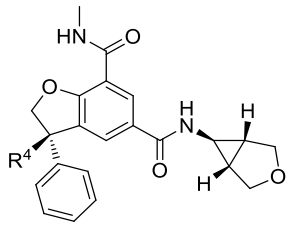


Fig. 6. X-ray crystallography of **63** (teal) in BRD2 BD2 (pink, PDB7oe9). Key residues are shown as magenta lines, H-bonds as dashed yellow lines and waters as red spheres. DBF **63** makes a through water interaction with Tyr386 and a bidentate H-bonding interaction to Asn429. The phenyl C3 group is then placed between the BD2 specific His433 and Trp370 of the WPF shelf. The C3 methyl occupies a lipophilic area adjacent to the WPF shelf. DBF **6** (yellow, PDB6z8p) and DBF **(*S*)-44** (silver, PDB7oe8) are shown for comparison (bottom right) and a high degree of overlay is observed.

Of the initial quaternary compounds, **63** and **64** were in good physicochemical space, with the ethyl (**65**) derivative, expectedly, showing an increased ChromLogD over the methyl analogue. The primary alcohol offered a 1.0 log unit reduction *vs.* **(*S*)-27**. All three compounds showed good CAD solubility (≥147 μg mL^{-1}) and were therefore progressed to determine their thermodynamic solubility using a FaSSIF solubility assay.[64] Unfortunately, **65** had sub-optimal FaSSIF solubility (<100 μg mL^{-1}), which was worse than previous analogue **(*S*)-27** and didn't offer any other advantage to the other analogues in terms of potency, so was not profiled further or incorporated in subsequent analogues. It remained important to assess the metabolic stability of **63** and **64** bearing the quaternary centre. In line with our hypothesis, both were significantly more stable in rat hepatocytes than the analogous compound **(*S*)-27**. This gave us belief that installation of the quaternary stereocentre had indeed blocked a likely mechanism of metabolism, at least in rat. The lower IVC of **63** meant that it was progressed to *in vivo* studies, discussed subsequently (Table 6). In order to optimise FaSSIF solubility, the amide vector was re-examined.

Table 4. Exploration of the effect of a quaternary centre at the 3-position of the DBF.



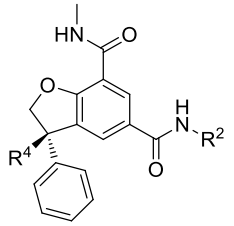
	R^4	BRD 4 BD2(n)/BD1 (n) pIC_{50}	Selectivity (fold)	Chrom LogD	Solubility CAD/ FaSSIF ($\mu g\ mL^{-1}$)	IVC rat hepatocytes ($mL\ min^{-1}\ g^{-1}$)
27	H	7.8(8) / 4.8(8)	1000	3.3	≥165[a] / 836 >1000	8.6
63	Me	7.5(8) / 4.7(8)	63	3.7	≥147 / 84,80	1.2
64	CH_2OH	7.5(6) / 4.7(7)	630	2.4	≥202 / -	1.4
65	Et	7.5(3) / 5.0(3)	320	4.2	≥152 / 93	-

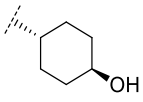
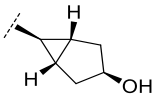
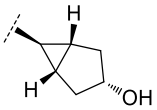
[a]CLND solubility;

As shown earlier, a range of amides were well tolerated in the DBF series. Therefore, the most desirable analogues, which were predicted to be potent and in the desired physico-chemical space (ChromLogD ≤4.0), were synthesised with a quaternary stereocentre. As in previous examples, the C5 methyl amide (**66**) did not provide the desired profile and was only 63-fold selective. The C5 cyclopropyl amide **67** was potent and selective (BD2 pIC_{50} = 7.3, 630-fold selective) and soluble (FaSSIF = 585 $\mu g\ mL^{-1}$), but the increased ChromLogD (4.0)

was believed to contribute to the raised rat IVC (6.7 mL min^{-1} g^{-1}). The methyl cyclopropyl **68** was also potent against BD2 (pIC_{50} = 7.6) but had poor FaSSIF solubility (88 μg mL^{-1}). Additionally, the high ChromLogD (4.7) meant that progression to IVC studies was not warranted. In order to move **68** analogues into more polar physicochemical space, the CH_2OH analogue was prepared. DBF **69** was 1000-fold selective over BD1 (pIC_{50} = 7.6) and offered the expected reduction in ChromLogD. The additional H-bond donor in **69**, likely contributes to the high kinetic and FaSSIF solubility (>1000 μg mL^{-1}). The rat hepatocyte clearance showed improvements (*c.f.* Tables 2 and 3) and **69** was therefore progressed to *in vivo* studies (*vide infra*). As the additional hydrogen bond donor in **69** had proved beneficial to the FaSSIF solubility, cyclohexanol **70** (analogous to **4**, Figure 1) and bicyclic alcohols **71** and **72**, which had been well tolerated amongst the earlier examples (Table 2) were synthesised with a quaternary methyl stereocentre. The cyclohexanol derivative **70** had sub-optimal activity at BD2 (BRD4 BD2 pIC_{50} = 6.4). However, the constrained analogue **71** showed 1000-fold selectivity for the second bromodomain of BRD4 (pIC_{50} = 7.7). A ChromLogD of 3.3 put this compound in an excellent physicochemical space, and this, together with the polar OH function, was consistent with the observed high solubility (FaSSIF > 1000 μg mL^{-1}). DBF **71** was progressed into IVC studies and was shown to have good stability in rat hepatocytes (1.0 mL min^{-1} g^{-1}). Due to this exciting profile, **71** was taken forward for evaluation of its *in vivo* PK profile, alongside the other lead examples (Table 6). Interestingly, the diastereomer **72** had a comparable profile to **71** but raised IVC (6.4 mL min^{-1} g^{-1}).

Table 5. Optimisation of the amide vector with a quaternary DBF.



	R^4	R^2	BRD4 BD2/BD1 pIC_{50} Selectivity	Selectivity	Chrom LogD	Solubility CAD/ FaSSIF (μg mL^{-1})	IVC rat hepatocytes (mL min^{-1} g^{-1})
66	Me	Me	7.1(4) / 5 .3(4)	60	3.4	≥132 / -	-
67			7.3(4) / 4.5(4) 630x	630	4.0	≥138 / 585	6.7
68			7.6(4) / 4.7(4)	790	4.7	3 / 88	-
69	CH_2OH		7.6(6) / 4.6(7)	1000	3.3	≥229 / >1000	2.7
70			6.5(4) / <4.3(4)	>160	3.3	≥161 / ≥ 1000	-
71			7.9(10) / 4.8(10)	1300	3.3	≥209 / >1000	1.0
72			8.0(2) / 4.7(2)	2000	3.7	≥151 / 539	6.4

Previous BD2 inhibitors have shown efficacy in cell and human whole blood (WB) assays.[33-34, 36] Following stimulation with lipopolysaccharide (LPS) of PBMC cells or human whole blood aliquots pretreated with BD2 inhibitors, inhibition of the resultant release of monocyte chemoattractant protein 1 (MCP-1 / CCL2) was evaluated. DBFs **(*S*)-25**, **63**, **69** and **71** were selected due to their low IVC and maintenance of >500 fold BD2 selectivity. As discussed, **69** and **71** in particular also had excellent solubility. Pleasingly, all four showed

efficacy in both the phenotypic LPS stimulated PBMC and WB assays indicating excellent cell permeability and target engagement (Table 6).[65] Therefore, the *in vivo* PK of these examples was assessed. Pleasingly, for **(*S*)-25**, low clearance in hepatocytes translated into a low *in vivo* blood clearance (CL_b) of 34 mL min^{-1} kg^{-1}. However, the unbound clearance ($CL_{b,ub}$) was raised (723 mL min^{-1} kg^{-1}) suggesting that the apparent low total clearance is a function of high protein binding. DBF **63** had a moderate blood clearance of 61 mL min^{-1} kg^{-1} (77% of the liver blood flow), however, the $CL_{b,ub}$ was 274 mL min^{-1} kg^{-1}, which was significantly lower than for **(*S*)-25**. DBF **63** had good oral bioavailability of 54% but due to a sub-optimal FaSSIF solubility was not progressed further. Despite a slightly raised IVC (2.7 mL min^{-1} g^{-1}) relative to the other examples progressed, DBF **69** was investigated *in vivo*. **69** had a moderate clearance of 60 mL min^{-1} kg^{-1}, and an unbound clearance of 340 mL min^{-1} kg^{-1} in the rat. An acceptable clearance and good permeability led to an oral bioavailability of 38%. However, the raised dog IVC (1.0 mL min^{-1} g^{-1}), in combination with sub-optimal solubility, meant this analogue was not investigated further. With **71**, a moderate blood clearance of 55 mL min^{-1} kg^{-1} was observed in the rat, equating to 69% LBF, but with a moderate unbound clearance of 260 mL min-1 kg-1. Good oral bioavailability in the rat (32%) and low dog hepatocyte clearance, made it a suitable candidate for progression into dog *in vivo* PK studies. Pleasingly, DBF **71** had a low clearance in dog (CL_b = 5 mL min^{-1} kg^{-1}, $CL_{b,ub}$ = 24 mL min^{-1} kg^{-1}) and was 64% orally bioavailable. By virtue of its encouraging pharmacokinetics and solubility, **71** (GSK852) has shown a clear improvement to the profile of **6** (GSK973).

Table 6. Further profiling of the lead DBFs **(*S*)-25**, **63**, **69**, and **71**.

	25	**63**	**69**	**71**
BRD4 BD2 pIC_{50} (n) / BD1 pIC_{50} (n)	7.7(10) / 4.8(10)	7.5(8) / 4.7(8)	7.6(6) / 4.6(7)	7.9(10) / 4.8(10)

Selectivity (fold)		790	630	1000	1260
BRD4 BD2 LE / LLE_{AT}		0.42 / 0.40	0.35 / 0.36	0.37 / 0.39	0.36 / 0.40
PBMC pIC_{50}		7.7	8.1	-	7.7
WB MCP-1 pIC_{50}		7.0	6.8	7.0	7.8
CAD Solubility (μg mL^{-1})		≥ 190[a]	≥ 144	≥ 229	≥ 209
FaSSIF Solubility (μg mL^{-1})		28	82	>1000	>1000
IVC hepatocytes (mL min^{-1} g^{-1})	Rat	2.0	1.2	2.7	1.0
	Dog	<0.7	<0.7	1.0	<0.7
	Human	<0.5	<0.5	<0.5	<0.5
Rat IV PK	CL_b / $CL_{b,ub}$ (mL min^{-1} kg^{-1})	34 / 723	61 / 274	60 / 340	55 / 260
	%LBF	43	77	60	69
	V_{ss} (L kg^{-1})	0.6	1.6	1.2	2.3
	$t_{1/2}$ (h)	0.3	0.3	0.3	0.7
Rat Oral PK	Fpo (%)	47	54	38	32
	CL_b / $CL_{b,ub}$ (mL min^{-1} kg^{-1})	-	-	-	5 / 24
	%LBF	-	-	-	8
Dog IV PK	V_{ss} (L kg^{-1})	-	-	-	0.9
	$T_{1/2}$ (h)	-	-	-	2.9
Dog Oral PK	Fpo (%)	-	-	-	64

[a]CLND solubility.

Subsequently, **71** was submitted the DiscoverX BROMO*scan* panel of 36 bromodomains to investigate, both its domain selectivity in an orthogonal assay (Table 7), and its wider

bromodomain selectivity (Figure 7 and Table S3, Supporting Information) Pleasingly, **71** maintained excellent potency at all 4 BD2 isoforms and showed >3100-fold selectivity over each respective BD1 domain. This was concordant with further in house TR-FRET data for BRD2, 3 and T which showed improved BD2 potency (pIC_{50} >8.0) and >2500-fold selectivity for these isoforms. Additionally, **71** showed excellent selectivity over the non-BET bromodomains and maintained 1000-fold selectivity over the closest non-BET off-target (TAF1(2), pK_d = 6.0).

Table 7. BET family Selectivity data for **71**.

	TR-FRET pIC_{50}	Sel. (fold)	BROMO*scan* pK_d	Sel. (fold)
BRD2 BD1	4.6	2500	5.0	4200
BRD2 BD2	8.0		8.6	
BRD3 BD1	4.5	5000	5.4	3100
BRD3 BD2	8.2		8.9	
BRD4 BD1	4.8	1000	5.5	3100
BRD4 BD2	7.9		9.0	
BRDT BD1	4.7	2500	4.8	10000
BRDT BD2	8.1		8.8	

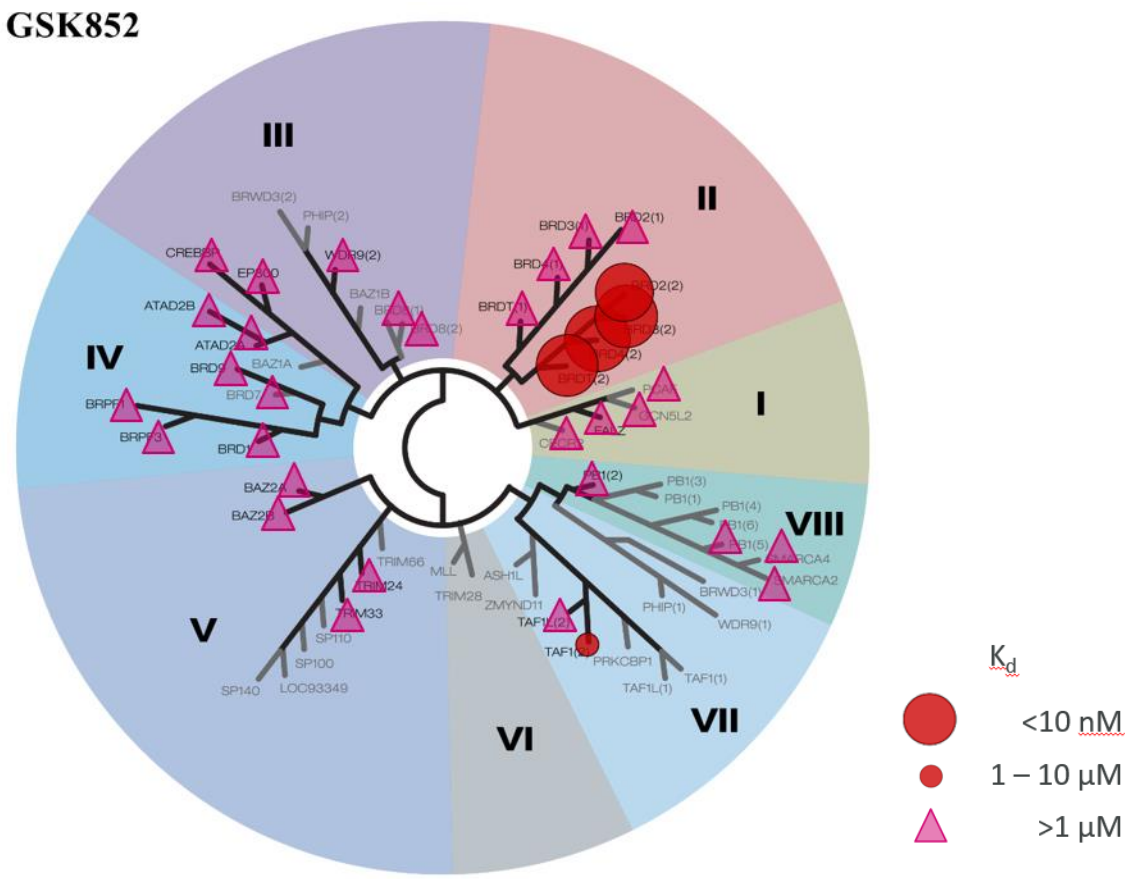


Figure 7. BROMO*scan* TREEspot for **71** (GSK852).

Conclusion

In summary, herein we have demonstrated that a stepwise assessment of the functionality attached to an initially (rat) metabolically unstable DBF core, as well as careful control of the lipophilicity of new compounds, has led to the generation of significant improvements in both solubility and rat PK. Of particular importance was the insertion of a quaternary carbon on the DBF core which improved upon the low rat hepatocyte clearance and poor solubility of the initial substrates. Importantly, we believe this approach was only achieved by investing in synthetic route optimisation to facilitate the preparation of complex

targets. This has culminated in **71** (GSK852) a highly selective, soluble and *in vivo* capable BD2 tool compound.

EXPERIMENTAL SECTION

General Experimental

The purity of all biologically tested compounds was >95% as determined by LCMS analysis. Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen in heat- or oven-dried glassware and using anhydrous solvent. Solvents and reagents were purchased from commercial suppliers and used as received. Reactions were monitored by thin layer chromatography (TLC) or liquid chromatography-mass spectroscopy (LCMS). TLC was carried out on glass- or aluminium-backed 60 silica plates coated with UV_{254} fluorescent indicator. Spots were visualized using UV light (254 or 365 nm) or alkaline $KMnO_4$ solution, followed by gentle heating. Flash column chromatography was carried out using Biotage SP4 or Isolera One apparatus with SNAP silica cartridges. NMR spectra were recorded at ambient temperature (unless otherwise stated) using standard pulse methods on any of the following spectrometers and signal frequencies: Bruker AV-400 (^{1}H = 400 MHz, ^{13}C = 101 MHz), Bruker AV-600 (^{1}H = 600 MHz, ^{13}C = 150 MHz), Bruker DPX-250 (^{1}H = 250 MHz) and Varian INOVA (^{1}H = 300 MHz). Chemical shifts are reported in ppm and are referenced to tetramethylsilane (TMS) or the following solvent peaks: $CDCl_3$ (^{1}H = 7.27 ppm, ^{13}C = 77.00 ppm), DMSO-d_6 (^{1}H = 2.50 ppm, ^{13}C = 39.51 ppm) and MeOH-d_4 (^{1}H = 3.31 ppm, ^{13}C = 49.15 ppm). Coupling constants are quoted to the nearest 0.1 Hz and multiplicities are given by the following abbreviations and combinations thereof: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), m (multiplet), br (broad). IR spectra were obtained on a Perkin Elmer Spectrum 1 machine. Optical rotation of chiral products was measured using a Jasco P1030 polarimeter. Melting point analysis was carried out using a Stuart SMP40 melting

point apparatus. High resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof Ultima hybrid quadrupole time-of-flight mass spectrometer, with analytes separated on an Agilent 1100 Liquid Chromatograph equipped with a Phenomenex Luna C18(2) reversed phase column (100 mm x 2.1 mm, 3 µm packing diameter). LC conditions were 0.5 mL/min flow rate, 35 ºC, injection volume 2 - 5 µL. Gradient elution with (A) H_2O containing 0.1% (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. Gradient conditions were initially 5% B, increasing linearly to 100% B over 6 min, remaining at 100% B for 2.5 min then decreasing linearly to 5% B over 1 min followed by an equilibration period of 2.5 min prior to the next injection. LCMS analysis was carried out on a H_2Os Acquity UPLC instrument equipped with a BEH column (50 mm x 2.1 mm, 1.7 µm packing diameter) and H_2Os micromass ZQ MS using alternate-scan positive and negative electrospray. Analytes were detected as a summed UV wavelength of 210 – 350 nm. Two liquid phase methods were used: *Formic* – 40 °C, 1 mL/min flow rate. Gradient elution with the mobile phases as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min. *High pH* – 40 °C, 1 mL/min flow rate. Gradient elution with the mobile phases as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min. Mass-directed automatic purification (MDAP) was carried out using a H_2Os ZQ MS using alternate-scan positive and negative electrospray and a summed UV wavelength of 210 – 350 nm. Two liquid phase methods were used: *Formic* – Sunfire C18 column (100 mm x 19 mm, 5 µm packing diameter, 20 mL/min flow rate) or Sunfire C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution at ambient temperature with the mobile

phases as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. *High pH* – Xbridge C18 column (100 mm x 19 mm, 5 µm packing diameter, 20 mL/min flow rate) or Xbridge C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution at ambient temperature with the mobile phases as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile.

General procedure A: Amide Coupling

HATU (1.2 equiv.) was added to *carboxylic acid* (1.0 equiv.) and DIPEA (3.0 equiv.) in DMF or CH_2Cl_2 at rt under nitrogen. The resulting solution was stirred at rt for 5 min, before Amine (1.1 equiv.) was added. The resulting solution was stirred at rt for 2 h. The reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with LiCl solution (20 mL), passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product.

General procedure B: Suzuki Coupling

Boronic acid/ester (1.2 equiv.), *aromatic bromide* (1.0 equiv.), *base* (3.0 equiv.) and *Pd catalyst* (10 mol%) were dissolved in water (0.5 mL) and 1,4-dioxane (2.0 mL). The solution had nitrogen bubbled through it for 5 min and was then stirred at *temperature* until complete. The reaction was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product.

General procedure C: Hydrogenation

Benzofuran (1 equiv.) in EtOH (10 mL) was added to a hydrogenation flask containing palladium on activated carbon paste, type 424 (5 mol%) The vessel was evacuated and back-filled with hydrogen (x3) and allowed to stir under a hydrogen atmosphere at rt for 24 h. Once

complete, the reaction was filtered through a Celite plug, washing with EtOH (60 mL) and concentrated *in vacuo* to afford the crude product.

*Dimethyl 4-hydroxyisophthalate (**73**):* Thionyl chloride (15 mL, 206 mmol) was added drop-wise to a solution of 4-hydroxyisophthalic acid **13** (5 g, 27.5 mmol) in MeOH (50 mL) at 0 °C under nitrogen. The resulting solution was stirred at rt for 30 min before heating gently to reflux for 6 h. The reaction was allowed to cool. Upon cooling, a precipitate formed which was collected by filtration to afford dimethyl 4-hydroxyisophthalate **73** (5.32 g, 25.3 mmol, 92% yield) as a white solid. LCMS (Formic, ES^+): t_R = 1.02; no *m/z*; HRMS ($C_{10}H_{11}O_5$): $[M+H]^+$ calculated 211.0601, found 211.0602; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.01 (s, 1H), 8.36 (d, *J*=2.4 Hz, 1H), 8.04 (dd, *J*=8.6, 2.4 Hz, 1H), 7.10 (d, *J*=8.6 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 168.3, 165.6, 163.6, 136.1, 132.5, 121.2, 118.5, 114.4, 53.1, 52.5. *Methyl 4-hydroxy-3-(methylcarbamoyl)benzoate (**74**):* Methylamine (40% *w/w* in water, 20.59 mL, 238 mmol) was added to dimethyl 4-hydroxyisophthalate **73** (10 g, 47.6 mmol) in THF (100 mL) at rt. A precipitate formed and the resulting suspension was stirred at rt overnight. After this time the precipitate had dissolved. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 x 100 mL) and CH_2Cl_2 (2 x 100 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford methyl 4-hydroxy-3-(methylcarbamoyl)benzoate **74** (9.8 g, 46.8 mmol, 98% yield) as a pink solid. LCMS (Formic, ES^+): t_R = 0.80 min; *m/z* = 210.1; HRMS ($C_{10}H_{12}NO_4$): $[M+H]^+$ calculated 210.0761, found 210.0756; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.55 (d, *J*=4.6 Hz, 1H), 8.35 (d, *J*=2.8 Hz, 1H), 7.44 (dd, *J*=8.9, 2.8 Hz, 1H), 6.21 (d, *J*=8.9 Hz, 1H), 3.67 (s, 3H), 2.75 (d, *J*=4.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 176.8, 168.9, 167.5, 133.5, 132.4, 122.5, 118.8, 108.3, 51.0, 25.4; IR ν_{max} (cm^{-1}) 2964, 1728, 1679, 1586, 1435, 1350, 1307, 1206, 1239, 1110, 763, 698. *Methyl 4-hydroxy-3-iodo-5-*

*(methylcarbamoyl)benzoate (**10**):* NIS (3.36 g, 14.91 mmol) was added to methyl 4-hydroxy-3-(methylcarbamoyl)benzoate **74** (2.6 g, 12.43 mmol) in CH_2Cl_2 (15 mL) at rt. The resulting solution was stirred at rt overnight. The reaction was diluted with water before sodium hydrosulfite was added until the reaction was almost colourless. The solution was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford methyl 4-hydroxy-3-iodo-5-(methylcarbamoyl)benzoate **10** (3.62 g, 10.80 mmol, 87% yield) as a cream solid. LCMS (Formic, ES^+): t_R = 1.11 min; *m/z* = 335.9; HRMS ($C_{10}H_{11}INO_4$): $[M+H]^+$ calculated 335.9727, found 335.9725; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.50 (d, *J*=2.0 Hz, 1H), 8.18 (d, *J*=2.0 Hz, 1H), 7.09 (br. s., 1H), 3.89 (s, 3H), 3.04 (d, *J*=4.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 179.8, 169.5, 164.9, 164.6, 143.6, 129.3, 122.0, 87.4, 52.7, 26.7. *Methyl 4-hydroxy-3-(methylcarbamoyl)-5-(1-phenylvinyl)benzoate (**9**):* (1-Phenylvinyl)boronic acid (1.060 g, 7.16 mmol), methyl 4-hydroxy-3-iodo-5-(methylcarbamoyl)benzoate **10** (2.00 g, 5.97 mmol), K_3PO_4 (3.80 g, 17.91 mmol) and PEPPSI-*i*Pr (0.406 g, 0.597 mmol) were dissolved in 1,4-dioxane (21 mL) and water (9 mL) at rt and degassed under nitrogen. The resulting solution was stirred at 70 °C for 2 h. The reaction was allowed to cool to rt and diluted with water (50 mL), extracting with CH_2Cl_2 (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography, eluting with 0-30% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford methyl 4-hydroxy-3-(methylcarbamoyl)-5-(1-phenylvinyl)benzoate **9** (1.21 g, 3.89 mmol, 65% yield) as a cream gum. LCMS (Formic, ES^+): t_R = 1.23 min; *m/z* = 312.3; HRMS ($C_{18}H_{18}NO_4$): $[M+H]^+$ calculated 312.1230, found 312.1232; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.45 (d, *J*=2.2 Hz, 1H), 7.96 (d, *J*=2.2 Hz, 1H), 7.22–7.34 (m, 5H), 5.78 (d, *J*=1.2 Hz, 1H), 5.38 (d, *J*=1.2 Hz, 1H), 3.90 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 170.3, 166.4, 163.0, 145.9, 140.4, 135.3, 131.3,

128.2, 127.8, 127.2, 126.1, 119.8, 115.5, 114.4, 51.1, 25.1; IR ν_{max} (cm^{-1}) 3389, 2514, 1715, 1624, 1589, 1549, 1493, 1433, 1589, 1256, 1160, 995, 910, 862, 769, 685. *Methyl 4-hydroxy-3-(2-hydroxy-1-phenylethyl)-5-(methylcarbamoyl)benzoate (**8**):* A 25 mL round-bottomed flask equipped with a stirrer bar was dried under vacuum and then cooled using a stream of nitrogen. After cooling to 0 °C the reaction flask was charged with Borane-THF complex (1 M in THF, 8 mL, 8.00 mmol). 2,3-Dimethylbut-2-ene (2 M in THF, 4 mL, 8.00 mmol) was added drop-wise and the resulting solution was stirred at rt for 3 h to after which a solution of thexylborane in THF (0.66 M in THF) had formed. Thexylborane (0.66 M in THF, 9.74 mL, 6.43 mmol) was added to methyl 4-hydroxy-3-(methylcarbamoyl)-5-(1-phenylvinyl)benzoate **9** (1.3 g, 2.92 mmol) at rt under nitrogen. The resulting solution was stirred at rt overnight. Water (10 mL) was added, followed by 2 M NaOH (10 mL, 20.00 mmol) and hydrogen peroxide (35% *w/w* in water, 10 mL, 114 mmol). The resulting solution was stirred at rt for 2h. The reaction was quenched by addition of sat. aq. sodium thiosulfate (20 mL) and then acidified using 1 M HCl (20 mL) and extracted with EtOAc (2 x 50 mL) and CH_2Cl_2 (50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford methyl 4-hydroxy-3-(2-hydroxy-1-phenylethyl)-5-(methylcarbamoyl)benzoate **8** (600 mg, 1.822 mmol, 62% yield) as a cream solid. LCMS (Formic, ES^+): t_R = 0.96, *m/z* = 330.3; HRMS ($C_{18}H_{20}NO_5$): $[M+H]^+$ calculated 330.1336, found 330.1339; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.33 (d, *J*=2.2 Hz, 1H), 8.03 (d, *J*=2.2 Hz, 1H), 7.26–7.33 (m, 4H), 7.15–7.23 (m, 1H), 4.66 (t, *J*=7.3 Hz, 1H), 4.05–4.19 (m, 2H), 3.89 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 170.5, 166.6, 163.3, 141.2, 132.8, 131.2, 128.1, 128.0, 126.8, 126.1, 119.5, 114.0, 63.7, 51.1, 45.9, 25.1; IR ν_{max} (cm^{-1}) 2949, 2161, 1714, 1637, 1591, 1546, 1431, 1284, 1019, 767, 699. *Methyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**75**):* DIAD (0.149 mL, 0.765 mmol) was added drop-wise to triphenylphosphine (0.201 g, 0.765 mmol) and methyl 4-hydroxy-3-(2-hydroxy-1-phenylethyl)-5-

(methylcarbamoyl)benzoate **8** (0.210 g, 0.638 mmol) in THF (10 mL) at rt. The resulting solution was stirred at rt overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography, eluting with 0-80% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford methyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **75** (160 mg, 0.514 mmol, 81% yield) as a white solid. LCMS (Formic, ES^+): t_R = 1.04 min; *m/z* = 312.1; HRMS ($C_{18}H_{18}NO_4$): $[M+H]^+$ calculated 312.1230, found 312.1233; ^1H NMR ($CDCl_3$-*d*, 400 MHz):δ (ppm) 8.74 (d, *J*=1.2 Hz, 1H), 7.77–7.85 (m, 1H), 7.44–7.53 (m, 1H), 7.29–7.40 (m, 3H), 7.15–7.22 (m, 2H), 5.16 (t, *J*=8.8 Hz, 1H), 4.64–4.78 (m, 2H), 3.86 (s, 3H), 3.06 (d, *J*=4.6 Hz, 3H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 166.2, 165.0, 161.3, 141.8, 133.6, 131.4, 129.2, 128.7, 127.4, 127.2, 123.6, 115.6, 81.3, 51.2, 46.8, 25.4; IR ν_{max} (cm^{-1}) 3418, 2985, 275, 1711, 1654, 1608, 1556, 1475, 1430, 1269, 1157, 1031, 993, 927, 767, 699. *7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **(14):*** LiOH (15.38 mg, 0.642 mmol) was added to methyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **75** (100 mg, 0.321 mmol) in THF (2 mL) and water (2 mL) at rt. The resulting solution was stirred at 50 °C for 2 h. The reaction was allowed to cool, acidified with 1 M HCl and extracted with EtOAc (3 x 20 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **14** (95 mg, 0.320 mmol, 99% yield) as a colourless gum. LCMS (Formic, ES^+): tR = 0.89 min; *m/z* = 298.2;HRMS ($C_{17}H_{16}NO_4$): $[M+H]^+$ calculated 298.1074, found 298.1077; ^1H NMR (DMSO-d_6, 400 MHz): δ (ppm) 12.78 (br. s., 1H), 8.29 (d, *J*=1.5 Hz, 1H), 7.93 (d, *J*=4.6 Hz, 1H), 7.61 (dd, *J*=1.8, 1.1 Hz, 1H), 7.34-7.41 (m, 2H), 7.24-7.33 (m, 3H), 5.19 (t, *J*=9.3 Hz, 1H), 4.82-4.91 (m, 1H), 4.71 (dd, *J*=9.0, 6.8 Hz, 1H), 2.85 (d, *J*=4.9 Hz, 3H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 167.4, 165.2,

161.3, 141.8, 133.5, 131.7, 129.5, 128.7, 127.4, 127.1, 126.0, 124.2, 81.2, 46.8, 25.4; IR ν_{max} (cm^{-1}) 2941, 2521, 1712, 1631, 1545, 1474, 1252, 1152, 994, 924, 768, 697, 656. *Methyl 7-(methylcarbamoyl)benzofuran-5-carboxylate (**15**):* Methyl 4-hydroxy-3-iodo-5-(methylcarbamoyl)benzoate **10** (2.96 g, 8.83 mmol), ethynyltrimethylsilane (2.77 mL, 19.43 mmol), copper(I) iodide (0.17 g, 0.883 mmol), TEA (3.69 mL, 26.5 mmol), and $Pd(PPh_3)_2Cl_2$ (0.31 g, 0.442 mmol) were dissolved in DMF (20 mL) and degassed under nitrogen. The resulting solution was stirred at 80 °C for 18 h. The reaction was cooled, diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated in *vacuo* to afford the *crude intermediate*. TBAF (1M in THF, 17 mL, 17.67 mmol) was added to the crude and the resulting solution stirred for 2 hrs. The reaction was quenched with sodium carbonate (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with sat. aq. LiCl (50 mL), passed through a hydrophobic frit and concentrated in *vacuo* to afford the *crude product*. The crude product was taken up in CH_2Cl_2, at this point a precipitate formed and this was dried *in vacuo* to afford methyl 7-(methylcarbamoyl)benzofuran-5-carboxylate **15** (1.50 g, 6.43 mmol, 73% yield) as a pink solid. LCMS (Formic, ES^+): tR = 0.75 min; *m/z* = 234.2; HRMS ($C_{12}H_{12}NO_4$): $[M+H]^+$ calculated 234.0761, found 234.0758; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.44 (d, *J*=1.7 Hz, 1H), 8.35 (d, *J*=4.6 Hz, 1H), 8.29 (d, *J*=1.7 Hz, 1H), 8.22 (d, *J*=2.2 Hz, 1H), 7.20 (d, *J*=2.2 Hz, 1H), 3.91 (s, 3H), 2.89 (d, *J*=4.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 166.3, 163.9, 153.9, 148.5, 129.3, 126.1, 126.0, 125.2, 120.0, 108.0, 52.8, 26.9; IR ν_{max} (cm^{-1}) 3327, 1719, 1636, 1552, 1413, 1280, 1174, 1026, 765, 692. *3-Bromo-7-(methylcarbamoyl)benzofuran-5-carboxylic acid (**16**):* Bromine (1.648 mL, 32.2 mmol) was added to methyl 7-(methylcarbamoyl)benzofuran-5-carboxylate **15** (5.0 g, 21.44 mmol) in CH_2Cl_2 (50 mL). The resulting solution was stirred at rt for 2 h. The reaction was followed by TLC which appeared to show loss of SM. The reaction was concentrated *in vacuo* to afford an

orange gum. KOH (2.65 g, 47.2 mmol) was dissolved in EtOH (50 mL) then added to the crude product, and the resulting solution was stirred at rt overnight. Water (10.0 mL) was added, then the reaction was warmed to 40 °C and stirred for a further 4 h. The reaction was stirred for a further 2 h. The reaction was quenched with 10% aq. sodium metabisulfate (20 mL) and acidified with 2 M HCl. A white precipitate formed with was filtered off and dried under vacuum to afford 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylic acid **16** (6.0 g, 20.13 mmol, 94% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.77 min; *m/z* = 298.0, 300.0; HRMS ($C_{11}H_9BrNO_4$): $[M+H]^+$ calculated 297.9710, found 297.9711; ^1H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.35 (m, 2H), 8.28 (d, *J*=4.4 Hz, 1H), 8.13 (d, *J*=1.2 Hz, 1H), 2.85 (d, *J*=4.6 Hz, 3H), acid CO_2H peak missing; ^{13}C NMR (DMSO-*d_6*, 101 MHz): δ (ppm) 168.0, 164.7, 151.5, 144.6, 137.9, 127.8, 126.9, 122.7, 119.0, 98.4, 26.8; IR ν_{max} (cm^{-1}) 3315, 1663, 1625, 1589, 1552, 1456, 1383, 1267, 1086, 866, 849, 799, 767. *Ethyl 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylate (**17**):* Bromine (0.330 mL, 6.43 mmol) was added to methyl 7-(methylcarbamoyl)benzofuran-5-carboxylate **15** (1.0 g, 4.29 mmol) in CH_2Cl_2 (10 mL) at rt. The resulting solution was stirred at 40 °C for 1h, after which it was concentrated in *vacuo* to afford an orange gum. KOH (0.481 g, 8.58 mmol) was dissolved in Ethanol (10.00 mL) and poured onto the orange gum, the resulting solution was stirred for 5 mins until a cream precipitate formed. The precipitate was filtered off to afford ethyl 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylate **17** (821 mg, 2.52 mmol, 59% yield) as a cream solid. LCMS (Formic, ES^+): t_R = 1.03 min; *m/z* = 326.0, 328.0; ^1H NMR (DMSO-d_6, 400MHz): δ (ppm) 8.56 (s, 1H), 8.44 (d, *J*=4.5 Hz, 1H), 8.34 (d, *J*=1.7 Hz, 1H), 8.19 (d, *J*=1.7 Hz, 1H), 4.39 (q, *J*=7.1 Hz, 2H), 2.88 (d, *J*=4.5 Hz, 1H), 1.37 (t, *J*=7.1 Hz, 3H). *3-Bromo-N^5-cyclopropyl-N^7-methylbenzofuran-5,7-dicarboxamide (**18**):* 3-Bromo-7-(methylcarbamoyl)benzofuran-5-carboxylic acid **16** (2 g, 6.71 mmol), HATU (3.06 g, 8.05 mmol) and DIPEA (3.52 mL, 20.13 mmol) were stirred in DMF (40 mL) at rt for 5 mins.

Cyclopropanamine (0.558 mL, 8.05 mmol) was added and the reaction stirred at rt for 1h. The reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL), the organic phase was washed with 10% citric acid (50 mL) and 10% LiCl (50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford 3-bromo-N^5-cyclopropyl-N^7-methylbenzofuran-5,7-dicarboxamide **18** (894 mg, 2.65 mmol, 40% yield) as a cream solid. LCMS (Formic, ES^+): t_R = 0.78 min; *m/z* = 377.0, 399.0; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.70 (d, *J*=4.4 Hz, 1H), 8.49 (s, 1H), 8.37 (d, *J*=4.6 Hz, 1H), 8.25 (d, *J*=1.7 Hz, 1H), 8.17 (d, *J*=2.0 Hz, 1H), 2.90-2.94 (m, 1H), 2.87 (d, *J*=4.6 Hz, 3H), 0.69-0.78 (m, 2H), 0.59-0.66 (m, 2H). *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide (**19**):* HATU (918 mg, 2.415 mmol) was added to 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylic acid **16** (600 mg, 2.013 mmol) and DIPEA (1.055 mL, 6.04 mmol) in DMF (5 mL) at rt under nitrogen. The resulting solution was stirred at rt for 5 min before (1*R*,5*S*,6r)-3-oxabicyclo[3.1.0]hexan-6-amine (239 mg, 2.415 mmol) was added. The resulting solution was stirred at rt overnight. The reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were washed with sat. aq. LiCl solution (20 mL), passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-60% (3:1 EtOAc/EtOH)/EtOAc. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (460 mg, 1.213 mmol, 60% yield) as a cream solid. LCMS (Formic, ES^+): t_R = 0.75 min; *m/z* = 379.1, 381.1; HRMS ($C_{16}H_{16}BrN_2O_4$): $[M+H]^+$ calculated 379.0288, found 379.0286; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.74–8.81 (m, 1H), 8.51 (s, 1H), 8.37–8.45 (m, 1H), 8.22–8.27 (m, 1H), 8.16–8.19 (m, 1H), 3.89 (m, 2H), 3.62–3.68 (m, 3H), 2.63–

2.68 (m, 1H), 1.25 (m, 4H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 165.9, 163.7, 151.5, 145.9, 130.3, 128.0, 125.7, 121.5, 120.5, 97.6, 69.1, 38.7, 26.9, 24.5; IR ν_{max} (cm^{-1}) 3673, 3416, 2877, 1666, 1637, 1600, 1549, 1529, 1415, 1393, 1267, 1150, 1065, 1013, 827, 742, 665. *Ethyl 7-(methylcarbamoyl)-3-phenylbenzofuran-5-carboxylate (**76**):* Ethyl 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylate **17** (4.00 g, 12.26 mmol), phenylboronic acid (1.94 g, 15.94 mmol), potassium carbonate (5.09 g, 36.8 mmol) and PEPPSI (0.17 g, 0.245 mmol) were dissolved in 1,4-Dioxane (100 mL) and Water (20 mL) and degassed under nitrogen for 20 minutes. The reaction was left to stir at 50 °C overnight. The reaction was concentrated *in vacuo* and the residue was taken up in CH_2Cl_2 and washed with water. The organic phase was dried over sodium sulphate, filtered through a hydrophobic frit and concentrated *in vacuo* to afford ethyl 7-(methylcarbamoyl)-3-phenylbenzofuran-5-carboxylate **76** (3.68 g, 11.38 mmol, 93% yield). LCMS (HPH, ES^+): t_R = 1.17 min; *m/z* = 324.3; ^{1}H NMR (CHLOROFORM-*d*, 400 MHz): δ (ppm) 8.87 (d, *J*=1.7 Hz, 1H), 8.67 (d, *J*=1.7 Hz, 1H), 7.91 (s, 1H), 7.62-7.69 (m, 2H), 7.54 (t, *J*=7.5 Hz, 2H), 7.43-7.47 (m, 1H), 4.44 (q, *J*=7.1 Hz, 2H), 3.17 (d, *J*=4.6 Hz, 3H), 1.43 (t, *J*=7.1 Hz, 3H). *(±)-Ethyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(rac)-77**):* Ethyl 7-(methylcarbamoyl)-3-phenylbenzofuran-5-carboxylate **76** (3.68g, 11.38 mmol) was hydrogenated according to **general procedure C**. The crude product was purified by silica chromatography, eluting with 5-50% EtOAc/cyclohexane to afford (±)-ethyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-77** (3.5 g, 10.76 mmol, 95% yield). LCMS (HPH, ES^+): t_R = 1.11 min; *m/z* = 326.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.31 (d, *J*=1.7 Hz, 1H), 7.91-7.96 (m, 1H), 7.62 (s, 1H), 7.36 (d, *J*=7.6 Hz, 2H), 7.23-7.32 (m, 3H), 5.19 (s, 1H), 4.83-4.92 (m, 1H), 4.67-4.75 (m, 1H), 4.25 (dd, *J*=7.0, 5.5 Hz, 2H), 2.85 (d, *J*=4.6 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H). *(S)-Ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(S)-77**):* (+/-)-Ethyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-

carboxylate **(*rac*)-77** (2.40 g, 6.76 mmol) was dissolved in EtOH (60 mL) and injected onto the column (Column: 250 x 30 mm Chiralcel OD-H (5 μm)) which was eluted with 15% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm, 4. Ref 550, 100. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-Ethyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*S*)-77** (1.00 g, 2.84 mmol, 42%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak OD-H column, 20% EtOH/heptane, t_R = 8.571 min, *er* >99:1. *(S)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid (**20**):* (*S*)-Ethyl 7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **77** (1.00 g, 3.07 mmol) was taken up in Tetrahydrofuran (THF) (10 mL) and Water (10 mL). LiOH (0.44 g, 18.44 mmol) was added and the reaction left to stir at 50 °C overnight. The reaction was concentrated *in vacuo* and the residue was taken up in water and acidified to pH = 2 using 2 M HCl. The precipitate was filtered off to afford (*S*)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **20** (0.90 g, 3.03 mmol, 98% yield). LCMS (Formic, ES^+): t_R = 0.88 min; *m/z* = 298.2; ^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm) 8.28 (d, *J*=1.7 Hz, 1H), 7.92 (d, *J*=4.6 Hz, 1H), 7.58-7.64 (m, 1H), 7.33-7.41 (m, 2H), 7.23-7.32 (m, 3H), 5.17 (t, *J*=9.4 Hz, 1H), 4.80-4.91 (m, 1H), 4.70 (dd, *J*=9.0, 6.8 Hz, 1H), 2.85 (d, *J*=4.6 Hz, 3H). *7-(Methylcarbamoyl)-3-(o-tolyl)benzofuran-5-carboxylate (**78**):* Ethyl 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylate **17** (220 mg, 0.675 mmol), *o*-tolylboronic acid (138 mg, 1.012 mmol), K_2CO_3 (280 mg, 2.024 mmol) were reacted at 70 °C for 16 h according to **general procedure B**. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford ethyl 7-(methylcarbamoyl)-3-(*o*-tolyl)benzofuran-5-carboxylate **78** (140 mg, 415 mmol, 62%). LCMS (Formic, ES^+): t_R = 1.22

min; *m/z* = 338.3; ^{1}H NMR (DMSO-d_6, 40 0MHz): δ (ppm) 8.46-8.52 (m, 1H), 8.40 (d, *J*=2.0 Hz, 1H), 8.33 (d, *J*=2.0 Hz, 1H), 8.07 (d, *J*=2.0 Hz, 1H), 7.30-7.51 (m, 4H), 4.35 (d, *J*=7.0 Hz, 2H), 2.91 (d, *J*=4.6 Hz, 3H), 2.28 (s, 3H), 1.33 (t, *J*=7.0 Hz, 3H). *(±)-Ethyl 7-(methylcarbamoyl)-3-(o-tolyl)-2,3-dihydrobenzofuran-5-carboxylate (**79**):* Ethyl 7-(methylcarbamoyl)-3-(o-tolyl)benzofuran-5-carboxylate **78** (140 mg, 0.415 mmol) was hydrogenated according to **general procedure C**. Hydrogenation incomplete so the crude product was dissolved in EtOH (25 mL) hydrogenation using H-cube apparatus at 70 ºC and 70 bar pressure for 3 h. The reaction mixture was partitioned between EtOAc (25 mL) and water (30 mL). The organic layer was washed water (20 mL) and sat. aq. $NaHCO_3$ (2 x 20 mL), passed through hydrophobic frit and concentrated *in vacuo* to afford the second crude product. The second crude product purified by silica chromatography eluting with 20-80% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-ethyl 7-(methylcarbamoyl)-3-(o-tolyl)-2,3-dihydrobenzofuran-5-carboxylate **79** (58 mg, 0.171 mmol, 41% yield) as a colourless oil. LCMS (Formic, ES^+): t_R = 1.17 min; *m/z* = 340.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.30-8.37 (m, 1H), 7.88-7.99 (m, 1H), 7.60-7.69 (m, 1H), 7.10-7.29 (m, 3H), 6.85-6.93 (m, 1H), 5.19-5.30 (m, 1H), 5.05-5.15 (m, 1H), 4.47-4.60 (m, 1H), 4.21-4.31 (m, 2H), 2.85 (d, *J*=4.6 Hz, 3H), 2.39 (s, 3H), 1.24-1.31 (m, 3H). *(±)-7-(Methylcarbamoyl)-3-(o-tolyl)-2,3-dihydrobenzofuran-5-carboxylic (**21**):* (±)-Ethyl 7-(methylcarbamoyl)-3-(o-tolyl)-2,3-dihydrobenzofuran-5-carboxylate **79** (58 mg, 0.171 mmol) and LiOH (12 mg, 0.513 mmol) were dissolved in water (3.0 mL) and THF (3.0 mL). The resulting solution was stirred at rt for 3 h. The reaction was concentrated *in vacuo* before quenching with 2 M HCl until a precipitate formed. The precipitate was filtered off to afford (±)-7-(methylcarbamoyl)-3-(*o*-tolyl)-2,3-dihydrobenzofuran-5-carboxylic acid **21** (34 mg, 0.109 mmol, 64% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.92 min; *m/z* = 312.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.32 (d, *J*=2.0 Hz, 1H), 7.87-7.97 (m, 1H), 7.58-7.67

(m, 1H), 7.10-7.45 (m, 3H), 6.91 (d, *J*=7.3 Hz, 1H), 5.21 (d, *J*=9.0 Hz, 1H), 5.05-5.15 (m, 1H), 4.56 (d, *J*=2.0 Hz, 1H), 2.85 (d, *J*=4.6 Hz, 3H), 2.39 (s, 3H). *Ethyl 3-(1-(tert-butyldimethylsilyl)-1H-indol-4-yl)-7-(methylcarbamoyl)benzofuran-5-carboxylate (**80**):* (1-(*tert*-Butyldimethylsilyl)-*1H*-indol-4-yl)boronic acid (1.031 g, 3.75 mmol), ethyl 3-bromo-7-(methylcarbamoyl)benzofuran-5-carboxylate (0.940 g, 2.88 mmol), K_2CO_3 (1.195 g, 8.65 mmol) and PEPPSI-*i*Pr (0.059 g, 0.086 mmol) reacted at 70 °C **according to general procedure B** to give ethyl 3-(1-(*tert*-butyldimethylsilyl)-*1H*-indol-4-yl)-7-(methylcarbamoyl)benzofuran-5-carboxylate (1.94 g, 2.85 mmol, 99% yield) as an off-white solid. LCMS (Formic, ES^+): t_R = 1.56 min; *m/z* = 477.5; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.57-8.62 (m, 1H), 8.47-8.54 (m, 1H), 8.32-8.40 (m, 2H), 7.63-7.73 (m, 1H), 7.45-7.51 (m, 1H), 7.29-7.37 (m, 2H), 6.64-6.70 (m, 1H), 4.28-4.42 (m, 2H), 2.89-2.96 (m, 3H), 1.33 (s, 3H), 0.92 (s, 9H), 0.66 (s, 6H). *(±)-Ethyl 3-(1-(tert-butyldimethylsilyl)-1H-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylate (**81**):* Ethyl 3-(1-(*tert*-butyldimethylsilyl)-*1H*-indol-4-yl)-7-(methylcarbamoyl)benzofuran-5-carboxylate (1.94 g, 4.07 mmol) was hydrogenated according to **general procedure C** to give (±)-ethyl 3-(1-(*tert*-butyldimethylsilyl)-*1H*-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylate (1.24 g, 2.176 mmol, 84% yield) as a white solid. LCMS (Formic, ES^+): t_R = 1.51 min; *m/z* = 479.5; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.97-8.05 (m, 1H), 7.60-7.66 (m, 1H), 7.45-7.53 (m, 1H), 7.35-7.40 (m, 1H), 7.06-7.13 (m, 1H), 6.84-6.90 (m, 1H), 6.53-6.58 (m, 1H), 5.17-5.37 (m, 2H), 4.77-4.86 (m, 1H), 4.16-4.30 (m, 2H), 2.84-2.91 (m, 3H), 1.25 (s, 3H), 0.87 (s, 9H), 0.60 (d, *J*=8.6 Hz, 6H). *(±)-3-(1H-Indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylate (**82**):* TBAF (3.89 mL, 3.89 mmol) was added dropwise to (±)-ethyl 3-(1-(*tert*-butyldimethylsilyl)-*1H*-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylate (1.24 g, 2.59 mmol) in THF (15 mL). The resulting solution was stirred at rt for 30 min. The reaction was concentrated *in vacuo* and partitioned between

EtOAc (25 mL) and water (30 mL). The organic layer was washed with water (20 mL) and sat. aq. $NaHCO_3$ (2 x 20 mL), passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-100% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-ethyl 3-(*1H*-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylate (682 mg, 1.872 mmol, 72% yield) as a white solid. LCMS (Formic, ES^+): t_R = 1.01 min; *m/z* = 365.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.33 (d, *J*=2.0 Hz, 1H), 7.94-8.05 (m, 1H), 7.56-7.63 (m, 1H), 7.31-7.37 (m, 2H), 7.06 (s, 1H), 6.85 (d, *J*=6.8 Hz, 1H), 6.30 (br. s., 1H), 5.28 (s, 1H), 5.17-5.24 (m, 1H), 4.78-4.87 (m, 1H), 4.13-4.29 (m, 2H), 2.88 (d, *J*=4.9 Hz, 3H), 1.24 (t, *J*=7.1 Hz, 3H); *Indole NH not visible. (±)-3-(1H-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylic acid (**22**):* (±)-Ethyl 3-(*1H*-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylate (650 mg, 1.784 mmol) and LiOH (128 mg, 5.35 mmol) were dissolved in THF (15 mL) and water (15 mL). The reaction mixture was stirred at for 16 h. The reaction was concentrated *in vacuo* before quenching with 2 M HCl until a precipitate formed. The precipitate was filtered off to afford (±)-3-(*1H*-indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylic acid **22** (582mg, 1.644 mmol, 92% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.60 min; *m/z* = 337.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.31 (s, 1H), 7.99 (d, *J*=5.1 Hz, 1H), 7.57 (s, 1H), 7.23-7.43 (m, 2H), 7.06 (t, *J*=7.7 Hz, 1H), 6.85 (d, *J*=7.1 Hz, 1H), 6.32 (br. s., 1H), 5.12-5.34 (m, 2H), 4.84 (t, *J*=7.7 Hz, 1H), 2.88 (d, *J*=4.6 Hz, 3H); *Acid OH not visible, Indole NH not visible. N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**(rac)-23**):* 7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **14** (120 mg, 0.404 mmol) was reacted with ammonium chloride (43 mg, 0.807 mmol) in CH_2Cl_2 (5 mL) according to **general procedure A**. The crude product was triturated with EtOAc and dried *in vacuo* to afford (±)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-23** (52 mg, 0.168 mmol, 42% yield) as a white

powder. LCMS (formic, ES^+) t_R = 0.79 min, *m/z* = 297.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.26 (d, *J*=2.2 Hz, 1H), 7.90 (br. s, 2H), 7.62-7.69 (m, 1H), 7.34-7.41 (m, 2H), 7.23-7.32 (m, 3H), 7.15 (br. s., 1H), 5.15 (t, *J*=9.3 Hz, 1H), 4.78-4.93 (m, 1H), 4.65 (dd, *J*=9.0, 6.8 Hz, 1H), 2.86 (d, *J*=4.9 Hz, 3H). *(S)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-23)****:* (±)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-23** (45 mg, 0.152 mmol) was dissolved in EtOH (3 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak IC (5 μm) which was eluted with 50% (EtOH + 0.2% isopropylamine)/(heptane + 0.2% isopropylamine), flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-23** (22 mg, 0.071 mmol, 46%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak IC column, 40% EtOH/heptane, t_R = 13.820 min, *er* >99:1. *(±)-N^5,N^7-Dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((rac)-24)****:* (±)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **14** (80 mg, 0.269 mmol) was reacted with methanamine (0.135 mL, 0.269 mmol) in CH_2Cl_2 (5 mL) according to **general procedure A**. The crude product was purified by formic MDAP. Pure fractions were concentrated in *vacuo* to afford (±)-N^5,N^7-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **24** (32 mg, 0.103 mmol, 38% yield) as a cream solid. LCMS (formic, ES^+) t_R = 0.81 min, *m/z* = 311.3; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.34 (d, *J*=2.2 Hz, 1H), 7.62-7.65 (m, 1H), 7.34-7.40 (m, 2H), 7.23-7.32 (m, 3H), 5.21 (t, *J*=9.0 Hz, 1H), 4.82-4.88 (m, 1H), 4.72 (dd, *J*=9.0, 7.2 Hz, 1H), 3.01 (s, 3H), 2.87 (s, 3H). *(S)-N^5,N^7-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-24)****:* (±)-N^5,N^7-Dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (32 mg, 0.103 mmol) was dissolved in EtOH (2 mL) and injected onto the

column (Column: 30 mm x 25 cm Chiralpak IC (5 µm) which was eluted with 60% (EtOH + 0.2% isopropylamine)/(heptane + 0.2% isopropylamine), flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)- N^5,N^7-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-24** (16 mg, 0.071 mmol, 50%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak IC column, 60% (EtOH + 0.2% isopropylamine)/heptane, t_R = 11.256 min, *er* >99:1. *(±)-N^5-Cyclopropyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**(rac)-25**):* (±)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid (90 mg, 0.303 mmol) was reacted with cyclopropanamine (0.021 mL, 0.303 mmol) in DMF (3 mL) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 0-60% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford **25** (±)-N^5-cyclopropyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (60 mg, 0.179 mmol, 59%) as a cream solid. LCMS (Formic, ES^+): t_R = 0.91 min; *m/z* = 337.1; HRMS ($C_{20}H_{20}N_2O_3$): $[M+H]^+$ calculated 337.1547, found 337.1555; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.32 (d, *J*=1.5 Hz, 1H), 7.62 (d, *J*=1.5 Hz, 1H), 7.32–7.40 (m, 2H), 7.20–7.31 (m, 3H), 5.20 (dd, *J*=9.0, 9.0 Hz, 1H), 4.85 (dd, *J*=9.0, 7.2 Hz, 1H), 4.70 (dd, *J*=9.0, 7.2 Hz, 1H), 3.00 (s, 3H), 2.80 (dt, *J*=7.2, 3.5 Hz, 1H), 0.73–0.81 (m, 2H), 0.55–0.64 (m, 2H); *Amide NH not visible*; ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 169.0, 165.3, 160.2, 141.9, 133.3, 128.8, 128.7, 127.7, 127.4, 127.3, 127.1, 115.3, 81.1, 47.0, 25.4, 22.6, 5.1; m.p. 169.3 – 172.2 °C; IR ν_{max} (cm^{-1}) 3408, 3281, 2955, 1637, 1529, 1452, 1276, 839, 762, 699. *(S)-N^5-Cyclopropyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**(S)-25**):* (±)-N^5-Cyclopropyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-25** (55 mg, 0.164 mmol) was dissolved in EtOH (2.5 mL). and injected onto the column (Column: 30 mm x 25 cm

Chiralcel OD-H (5 µm)) which was eluted with 20% (EtOH + 0.2% isopropylamine)/(heptane + 0.2% isopropylamine), flow rate = 30 mL/min, detection wavelength, 215 nm, 4. Ref 550, 100. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The bulked pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^5-Cyclopropyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-25** (12 mg, 0.036 mmol, 22%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralcel OD-H column, 20% (EtOH + 0.2% isopropylamine)/(heptane + 0.2% isopropylamine), t_R = 10.899 min, *er* >99:1. *N^7-Methyl-N^5-((1S,2S)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**26**):* (±)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **14** (100 mg, 0.336 mmol) was reacted with (1*S*,2*S*)-2-methylcyclopropanamine (47 mg, 0.437 mmol) in DMF (5 ml) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 20-80% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^7-methyl-N^5-((1S,2S)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **26** (74 mg, 0.211 mmol, 60% yield) as a white solid and a mixture of diastereomers. LCMS (formic, ES^+) t_R = 0.98; *m/z* = 351.2; HRMS ($C_{21}H_{23}N_2O_3$): $[M+H]^+$ calculated 351.1703, found 351.1706; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.31 (d, *J*=2.0 Hz, 1H), 7.6.0 (d, *J*=2.0 Hz, 1H), 7.33–7.39 (m, 2H), 7.21–7.31 (m, 3H), 5.20 (t, *J*=9.0 Hz, 1H), 4.84 (s, 1H), 4.70 (dd, *J*=9.0, 7.2 Hz, 1H), 3.00 (s, 3H), 2.44-2.50 (m, 1H), 1.11 (d, *J*=6.1 Hz, 3H), 0.91–1.00 (m, 1H), 0.77 (dd, *J*=5.4, 3.7 Hz, 1H), 0.54 (d, *J*=7.3 Hz, 1H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 168.9, 165.3, 160.2, 141.9, 133.3, 128.8, 128.7, 127.8, 127.4, 127.3, 127.1, 115.3, 81.1, 47.0, 30.2, 25.4, 16.1, 13.6, 13.4. *(S,S,S)-N^5-Cyclopropyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide ((**S,S,S)-26**):* N^7-Methyl-N^5-((1*S*,2*S*)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **26** (74 mg, 0.211 mmol) was dissolved in EtOH (7 mL) and injected onto the

column (Column: 50 mm x 25 cm Regis Whelk-O1[R,R] (5 μm)) which was eluted with 40% EtOH/heptane, flow rate = 20 mL/min, detection wavelength, 280 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The bulked pure fractions from peak 2 were concentrated *in vacuo* to afford (*S,S,S*)-N^7-methyl-N^5-((1S,2S)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **26** (33 mg, 0.097 mmol, 22%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 50 cm Regis Whelk-O1[R,R], 25% EtOH/heptane, t_R = 6.086 min, *er* >99:1. *(±)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((rac)-27)****:* (±)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **14** (60 mg, 0.202 mmol) was reacted with (1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-amine (28 mg, 0.283 mmol) in DMF (3 mL) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 0-100% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **27** (76 mg, 0.196 mmol, 97% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.87 min; *m/z* = 379.3; HRMS ($C_{22}H_{22}N_2O_4$): $[M+H]^+$ calculated 379.1652, found 379.1659; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.46 (q, *J*=4.6 Hz, 1H), 8.21 (d, *J*=1.5 Hz, 1H), 7.91 (d, *J*=4.5 Hz, 1H), 7.61 (dd, *J*=1.5, 1.0 Hz, 1H), 7.33–7.40 (m, 2H), 7.21–7.32 (m, 3H), 5.14 (dd, *J*=9.3, 9.0 Hz, 1H), 4.84 (dd, *J*=9.3, 6.8 Hz, 1H), 4.63 (dd, *J*=9.0, 6.8 Hz, 1H), 3.82 (d, *J*=8.4 Hz, 2H), 3.60 (dd, *J*=8.4, 2.7 Hz, 2H), 2.85 (d, *J*=4.6 Hz, 3H), 2.52-2.58 (m, 1H), 1.84 (q, *J*=2.7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 166.3, 164.2, 162.7, 159.7, 142.7, 133.3, 129.4, 129.2, 128.1, 127.6, 127.3, 116.6, 81.0, 69.1, 46.7, 31.4, 26.8, 24.4; m.p. 222.7 – 224.3 °C; IR ν_{max} (cm^{-1}) 3288, 2857, 1639, 1529, 1455, 1263, 1073, 943, 698. *(S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-27)****:* (±)-N^5-((1*R*,5*S*,6*r*)-3-

Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **27** (68 mg, 0.180 mmol) was dissolved in EtOH (1.5 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak AD-H (5 µm, Lot No ADH13231)) which was eluted with 40% (EtOH + 0.2% isopropylamine)/(heptane + 0.2% isopropylamine), flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 2 were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **27** (19 mg, 0.050 mmol, 28%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak AD-H column, 40% (EtOH + 0.2% isopropylamine)/heptane, t_R = 35.857 min, *er* 98:2. *N^5-((1R,3R,5S,6r)-3-Hydroxybicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**28**):* (*S*)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **20** (90 mg, 0.303 mmol), and (1*R*,5*S*,6*r*)-6-aminobicyclo[3.1.0]hexan-3-ol (41.1 mg, 0.363 mmol) were reacted in DMF according to **general procedure A**. The crude product was purified by formic MDAP. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,3*R*,5*S*,6*r*)-3-hydroxybicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydro benzofuran-5,7-dicarboxamide **28** (25 mg, 0.064 mmol, 21% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.83 min; *m/z* = 393.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.16-8.27 (m, 2H), 7.86-7.93 (m, 1H), 7.58-7.64 (m, 1H), 7.34-7.41 (m, 2H), 7.22-7.33 (m, 3H), 5.08-5.19 (m, 1H), 4.79-4.89 (m, 1H), 4.60-4.69 (m, 1H), 4.39-4.51 (m, 1H), 4.08-4.21 (m, 1H), 2.96-3.04 (m, 1H), 2.82-2.91 (m, 3H), 1.91-2.02 (m, 2H), 1.63-1.73 (m, 2H), 1.34-1.45 (m, 2H). *tert-Butyl (1R,5S,6s)-6-((S)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate (**83**):* (*S*)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **20** (80 mg, 0.269 mmol) and *tert*-butyl

(1*R*,5*S*,6*s*)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (64.0 mg, 0.323 mmol) were reacted in DMF (2 ml) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 0-50% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford *tert*-butyl (1*R*,5*S*,6*s*)-6-((*S*)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate **83** (114 mg, 0.239 mmol, 89% yield) as a white solid. LCMS (Formic, ES^+): t_R = 1.10 min; *m/z* = 478.4. *(S)-N^5-((1R,5S,6s)-3-azabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzo furan-5,7-dicarboxamide (**84**):* *tert*-Butyl (1*R*,5*S*,6*s*)-6-((*S*)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate **83** (114 mg, 0.239 mmol) was dissolved in CH_2Cl_2 (2 mL). TFA (100 µL, 1.298 mmol) was added and the resulting solution was stirred at rt for 16 h. After this time the reaction was concentrated *in vacuo* and eluted through an NH_2 SPE (1 g) with MeOH, the eluent was concentrated and dried to give (S)-N^5-((1*R*,5*S*,6*s*)-3-azabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzo furan-5,7-dicarboxamide **84** (80 mg, 0.212 mmol, 89% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.57 min; *m/z* = 378.4. *(S)-N^7-Methyl-3-phenyl-N^5-((1R,5S,6s)-3-propionyl-3-azabicyclo[3.1.0]hexan-6-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide (**29**):* (S)-N^5-((1*R*,5*S*,6*s*)-3-Azabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **84** (80 mg, 0.212 mmol) and propionic anhydride (0.5 mL, 0.212 mmol) were stirred at rt for 1 h. The reaction was diluted with water (2 mL) and extracted with EtOAc (3 x 2 mL). The combined organics were washed with brine (2 mL), passed through a hydrophobic frit and concentrated *in vacuo* to give the crude product. The crude product was purified using silica chromatography eluting with 0-50% (25% EtOH:EtOAc)/EtOAc. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^7-methyl-3-phenyl-N^5-((1*R*,5*S*,6*s*)-3-propionyl-3-azabicyclo[3.1.0]hexan-6-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **29** (75 mg, 0.173

mmol, 82% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.87 min; *m/z* = 434.4; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.34 (t, *J*=2.0 Hz, 1H), 7.60-7.72 (m, 1H), 7.33-7.40 (m, 2H), 7.22-7.32 (m, 3H), 5.21 (t, *J*=9.3 Hz, 1H), 4.82-4.88 (m, 1H), 4.71 (dd, *J*=8.8, 7.1 Hz, 1H), 3.78-3.88 (m, 2H), 3.66 (dt, *J*=10.8, 2.2 Hz, 1H), 3.46 (dt, *J*=12.0, 1.9 Hz, 1H), 2.99-3.03 (m, 3H), 2.46 (t, *J*=2.4 Hz, 1H), 2.22-2.39 (m, 2H), 1.85-1.95 (m, 2H), 1.07-1.13 (m, 3H). *(S)-N^5-(4,4-diethoxybutyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**85**):* (*S*)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **20** (115 mg, 0.387 mmol) and 4,4-diethoxybutan-1-amine (0.10 mL, 0.580 mmol) were reacted in DMF (1 mL) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 60-100% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-(4,4-diethoxybutyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **85** (118 mg, 0.268 mmol, 69% yield) as a colourless solid. LCMS (formic, ES^+) t_R = 1.05; *does not ionise*; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.43 (s, 1H), 8.24 (d, *J*=2.0 Hz, 1H), 7.86-7.94 (m, 1H), 7.60-7.66 (m, 1H), 7.33-7.42 (m, 2H), 7.24-7.32 (m, 3H), 5.11-5.19 (m, 1H), 4.81-4.91 (m, 1H), 4.60-4.69 (m, 1H), 4.45 (s, 1H), 3.34-3.58 (m, 4H), 3.14-3.25 (m, 2H), 2.84-2.90 (m, 3H), 1.45-1.55 (m, 3H), 1.03-1.13 (m, 6H). *(S)-N^5-(3-((2S,5R)-5-amino-1,3-dioxan-2-yl)propyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**30**):* A suspension of *p*-toluenesulfonic acid monohydrate (38.6 mg, 0.203 mmol), (*S*)-N^5-(4,4-diethoxybutyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **85** (116 mg, 0.184 mmol) and 2-(1,3-dihydroxypropan-2-yl)isoindoline-1,3-dione (44.9 mg, 0.203 mmol) was dissolved in toluene (2 mL) under nitrogen. The resulting solution was stirred at 70 °C overnight. The reaction mixture was allowed to cool to rt, diluted with EtOAc (10 ml) and then washed with sat. aq. Na_2CO_3 (10 mL) and the layers separated. The aqueous phase was extracted with further EtOAc (2 x 10 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude intermediate as a brown solid.

The solid was redissolved in EtOH (2 mL). Hydrazine Hydrate (0.090 mL, 1.843 mmol) was added and the reaction mixture left to stir at 50 °C overnight. The reaction was allowed to cool to rt and concentrated *in vacuo* to afford the crude product. The crude product was purified by HPH MDAP. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-(3-((2*S*,5*R*)-5-amino-1,3-dioxan-2-yl)propyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **30** (15 mg, 0.034 mmol, 19% yield) as a pale yellow solid. LCMS (Formic, ES^+): t_R = 0.81 min; *m/z* = 440.4; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.41 (s, 1H), 8.23 (d, *J*=2.2 Hz, 1H), 7.89 (d, *J*=4.6 Hz, 1H), 7.59-7.66 (m, 1H), 7.34-7.41 (m, 2H), 7.22-7.33 (m, 3H), 5.15 (t, *J*=9.3 Hz, 1H), 4.81-4.89 (m, 1H), 4.64 (dd, *J*=8.9, 6.7 Hz, 1H), 4.37 (t, *J*=4.8 Hz, 1H), 3.85-3.94 (m, 2H), 3.07-3.24 (m, 4H), 2.86 (d, *J*=4.6 Hz, 3H), 2.73 (s, 1H), 1.45-1.57 (m, 4H), 1.37 (br. s., 2H). *N^7-Methyl-N^5-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***(31)****:* (*S*)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **20** (47.1 mg, 0.158 mmol) and 1-methyl-1H-pyrazol-4-amine, hydrochloride (30.2 mg, 0.226 mmol) were reacted in DMF (1 mL) according to **general procedure A**. The crude product was purified by HPH MDAP. The pure fractions were concentrated *in vacuo* to afford N^7-methyl-N^5-(1-methyl-*1H*-pyrazol-4-yl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **31** (49.5 mg, 0.132 mmol, 83% yield). LCMS (Formic, ES^+): t_R = 0.88 min; *m/z* = 377.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.34 (s, 1H), 8.37 (d, *J*=2.2 Hz, 1H), 7.88-7.98 (m, 2H), 7.74 (d, *J*=1.7 Hz, 1H), 7.52 (s, 1H), 7.34-7.43 (m, 2H), 7.24-7.33 (m, 3H), 5.17 (s, 1H), 4.84-4.94 (m, 1H), 4.62-4.71 (m, 1H), 3.80 (s, 3H), 2.88 (d, *J*=4.6 Hz, 3H). *(S)-N^7-methyl-N^5-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***(32)****:* (*S*)-7-(Methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **20** (40 mg, 0.135 mmol) and 2-(1-methyl-1H-pyrazol-4-yl)ethan-1-amine (0.018 mL, 0.161 mmol) were reacted in DMF (2 ml) according to **general procedure A**. The crude product was purified by silica chromatography, eluting with 0-100%

(25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^7-methyl-N^5-(2-(1-methyl-*1H*-pyrazol-4-yl)ethyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **32** (42.3 mg, 0.105 mmol, 78% yield) as a colourless gum. LCMS (Formic, ES^+): t_R = 0.87 min; *m/z* = 405.4; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.33 (d, *J*=2.2 Hz, 1H), 7.57-7.66 (m, 1H), 7.21-7.43 (m, 7H), 5.21 (t, *J*=9.3 Hz, 1H), 4.82-4.88 (m, 2H), 4.71 (dd, *J*=8.8, 7.1 Hz, 1H), 3.81 (s, 3H), 3.48 (t, *J*=7.2 Hz, 2H), 2.97-3.05 (m, 3H), 2.73 (t, *J*=7.3 Hz, 2H). *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(3,6-dihydro-2H-pyran-4-yl)-N^7-methylbenzofuran-5,7-dicarboxamide (**86**):* 2-(3,6-Dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.5 mg, 0.316 mmol), N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (100 mg, 0.264 mmol), K_2CO_3 (109 mg, 0.791 mmol) and XPhos Pd G2 (20.75 mg, 0.026 mmol) were reacted at 40 °C for 16 h according to **general procedure B**. The crude product was purified by formic MDAP. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(3,6-dihydro-2H-pyran-4-yl)-N^7-methylbenzofuran-5,7-dicarboxamide **86** (28 mg, 0.073 mmol, 28% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.73 min; *m/z* = 383.3; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.40 (d, *J*=1.5 Hz, 1H), 8.30 (d, *J*=1.5 Hz, 1H), 7.97 (s, 1H), 6.44 (br. s., 1H), 4.38 (d, *J*=2.5 Hz, 2H), 4.05 (d, *J*=8.5 Hz, 2H), 3.96 (t, *J*=5.5 Hz, 2H), 3.77 (d, *J*=8.5 Hz, 2H), 3.00–3.07 (m, 3H), 2.69 (t, *J*=2.5 Hz, 1H), 2.52 (d, *J*=1.5 Hz, 2H), 2.00 (t, *J*=2.5 Hz, 2H). *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide (**33**):* N^5-((1*R*,5*S*,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(3,6-dihydro-2H-pyran-4-yl)-N^7-methylbenzofuran-5,7-dicarboxamide **86** (8 mg, 0.021 mmol) was hydrogenated according to **general procedure C**. The crude product purified by formic MDAP. The solvent was evaporated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **33** (2 mg, 5.18 µmol,

25% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.68 min; *m/z* = 387.3; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.29 (d, *J*=1.8 Hz, 1H), 7.88 (dd, *J*=1.8, 0.9 Hz, 1H), 4.79 (d, *J*=7.3 Hz, 2H), 4.04 (d, *J*=8.6 Hz, 2H), 3.92–4.01 (m, 2H), 3.76 (d, *J*=8.6 Hz, 2H), 3.48–3.55 (m, 1H), 3.37 (s, 3H), 2.97 (s, 3H), 2.64 (s, 1H), 1.96 (t, *J*=2.6 Hz, 2H), 1.66–1.74 (m, 1H), 1.45–1.57 (m, 1H), 1.31-1.44 (m, 2H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 170.5, 162.1, 132.5, 130.3, 129.0, 128.5, 116.3, 101.5, 77.4, 70.4, 47.2, 40.4, 32.4, 31.2, 29.8, 26.9, 26.1. *N^5-((1R,5S,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-2-yl)benzofuran-5,7-dicarboxamide* (***87***): N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (150 mg, 0.396 mmol), potassium fluoride (138 mg, 2.373 mmol) and $Pd(PPh_3)_4$ (45.7 mg, 0.040 mmol) were dissolved in 1,4-dioxane (1 mL). 2-(tributylstannyl)pyridine (0.298 mL, 0.791 mmol) was added and the resulting solution was stirred at 100 °C for 1 h under mw irradiation. The reaction was diluted with CH_2Cl_2 (50mL) and water (50mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated in vacuo the afford the crude product. The crude product was purified by silica chromatography eluting with 0-100% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-2-yl)benzofuran-5,7-dicarboxamide **87** (62 mg, 0.164 mmol, 42% yield). LCMS (Formic, ES^+): t_R = 0.69 min; *m/z* = 378.3; ^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm) 8.98 (d, *J*=2.0 Hz, 1H), 8.90 (s, 1H), 8.75-8.80 (m, 1H), 8.71 (d, *J*=4.5 Hz, 1H), 8.38 (d, *J*=4.6 Hz, 1H), 8.20 (d, *J*=2.0 Hz, 1H), 7.99-8.04 (m, 1H), 7.90-7.98 (m, 1H), 7.40 (ddd, *J*=7.3, 4.9, 1.2 Hz, 1H), 3.89 (d, *J*=8.5 Hz, 2H), 3.67 (dt, *J*=8.5, 1.4 Hz, 2H), 2.91 (d, *J*=4.5 Hz, 3H), 2.67 (dt, *J*=4.5, 2.4 Hz, 1H), 1.92-1.97 (m, 1H). *(S)-N^5-((1R,5S,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-2-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide* (***34***): N^5-((1R,5S,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-2-yl)benzofuran-5,7-dicarboxamide **87**

(60 mg, 0.159 mmol) was hydrogenated according to **general procedure C**. The prude product was purified by HPH MDAP. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-2-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **34** (5.1 mg, 0.031 mmol, 8%) as a white solid. LCMS (Formic, ES^+): tR = 0.70 min; *m/z* = 380.3; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.54-8.63 (m, 1H), 8.24 (d, *J*=2.2 Hz, 1H), 7.83-7.90 (m, 1H), 7.69 (td, *J*=7.7, 2.0 Hz, 1H), 7.55-7.62 (m, 1H), 7.18-7.27 (m, 2H), 6.40-6.50 (m, 1H), 5.14-5.20 (m, 2H), 4.87-4.96 (m, 1H), 4.05 (dd, *J*=8.6, 2.0 Hz, 2H), 3.76 (dt, *J*=8.6, 2.6 Hz, 2H), 3.05 (d, *J*=4.9 Hz, 3H), 2.73 (q, *J*=2.6 Hz, 1H), 1.80-1.92 (m, 2H). *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-3-yl)benzofuran-5,7-dicarboxamide (**88**):* Pyridin-3-ylboronic acid (58.3 mg, 0.475 mmol), N^5-((1*R*,5*S*,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (150 mg, 0.396 mmol), PEPPSI-*i*Pr (26.9 mg, 0.040 mmol) and potassium phosphate (252 mg, 1.187 mmol) were reacted at 60 °C for 4h according to **general procedure B**. The crude product was purified by silica chromatography, eluting with 0-80% (3:1 EtOAc:EtOH)/EtOAc. The pure fractions were concentrated *in vacuo* to afford *N*5-((1*R*,5*S*,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-*N*7-methyl-3-(pyridin-3-yl)benzofuran-5,7-dicarboxamide **88** (55 mg, 0.146 mmol, 37% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.53 min; *m/z* = 378.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.04 (d, *J*=1.7 Hz, 1H), 8.77 (d, *J*=4.6 Hz, 1H), 8.68 (s, 1H), 8.66 (dd, *J*=4.9, 1.5 Hz, 1H), 8.46 (d, *J*=1.7 Hz, 1H), 8.40–8.44 (m, 1H), 8.26 (d, *J*=1.7 Hz, 1H), 8.19–8.23 (m, 1H), 7.57–7.62 (m, 1H), 3.88 (d, *J*=8.3 Hz, 2H), 3.65 (d, *J*=8.3 Hz, 2H), 2.89 (d, *J*=4.6 Hz, 3H), 2.61–2.66 (m, 1H), 1.93 (s, 2H). *N^5-((1R,5S,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-3-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide (**35**):* N^5-((1*R*,5*S*,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-3-yl) benzofuran-5,7-dicarboxamide **88** (50 mg, 0.132 mmol) was hydrogenated according to **general procedure C**. The crude product was purified by formic MDAP. The pure fractions

were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-3-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **35** (18 mg, 0.047 mmol, 36% yield). LCMS (Formic, ES^+): t_R = 0.43 min; *m/z* = 380.1; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.55 (d, *J*=2.0 Hz, 1H), 8.51 (dd, *J*=4.6, 1.5 Hz, 1H), 8.46 (d, *J*=4.0 Hz, 1H), 8.22 (d, *J*=1.5 Hz, 1H), 7.92 (d, *J*=4.6 Hz, 1H), 7.59–7.66 (m, 2H), 7.39 (dd, *J*=7.8, 4.6 Hz, 1H), 5.15 (t, *J*=9.2 Hz, 1H), 4.87–4.95 (m, 1H), 4.68 (dd, *J*=9.2, 6.8 Hz, 1H), 3.82 (d, *J*=8.6 Hz, 2H), 3.60 (dd, *J*=8.3, 2.7 Hz, 2H), 2.85 (d, *J*=4.0 Hz, 3H), 2.52–2.59 (m, 1H), 1.78–1.88 (m, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 164.2, 163.6, 159.6, 149.6, 149.0, 138.2, 135.6, 132.4, 129.3, 127.9, 126.9, 124.7, 116.7, 80.5, 69.1, 43.9, 31.4, 26.8, 24.4. *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-4-yl)benzofuran-5,7-dicarboxamide (**89**):* N^5-((1R,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (180 mg, 0.475 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (195 mg, 0.949 mmol), $PdCl_2$(dppf) (35 mg, 0.047 mmol) and K_2CO_3 (197 mg, 1.424 mmol) were reacted at 120 °C for 30 min under mw irradiation according to **general procedure B**. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc). The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-4-yl)benzofuran-5,7-dicarboxamide **89** (87 mg, 0.231 mmol, 49% yield), an orange solid. LCMS (Formic, ES^+): t_R = 0.45 min; *m/z* = 378.3; ^{1}H NMR (MeOD-d_4, 400MHz): δ (ppm) 8.63-8.72 (m, 2H), 8.45-8.55 (m, 2H), 8.37 (d, *J*=2.0 Hz, 1H), 7.76-7.90 (m, 2H), 4.05 (d, *J*=8.3 Hz, 2H), 3.78 (dt, *J*=8.4, 1.3 Hz, 2H), 3.06 (s, 3H), 2.69 (t, *J*=2.6 Hz, 1H), 2.00 (t, *J*=2.7 Hz, 2H); *NH not observed*. *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-4-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide (**36**):* N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-4-yl)benzofuran-5,7-dicarboxamide **89** (87 mg, 0.231 mmol) was hydrogenated according to **general procedure C**. The crude product was purified by silica chromatography eluting with

0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(pyridin-4-yl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **36** (25 mg, 0.066 mmol, 29% yield), a white solid. LCMS (Formic, ES^+): t_R = 0.65 min; *m/z* = 380.3; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.54-8.60 (m, 2H), 8.34 (d, *J*=2.2 Hz, 1H), 7.81 (dd, *J*=1.8, 0.9 Hz, 1H), 7.50 (q, *J*=4.8 Hz, 1H), 7.01-7.16 (m, 2H), 6.74-6.91 (m, 1H), 5.05-5.22 (m, 1H), 4.58-4.77 (m, 2H), 4.02 (d, *J*=8.6 Hz, 2H), 3.73 (dt, *J*=8.4, 0.8 Hz, 2H), 2.94-3.08 (m, 3H), 2.70 (q, *J*=2.5 Hz, 1H), 1.77-1.93 (m, 2H). *N^5-cyclopropyl-3-(3-methoxyphenyl)-N^7-methylbenzofuran-5,7-dicarboxamide (**90**):* 3-bromo-N^5-cyclopropyl-N^7-methylbenzofuran-5,7-dicarboxamide **18** (15 mg, 0.044 mmol), 2-(3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.015 mL, 0.067 mmol), K_2CO_3 (18.45 mg, 0.133 mmol) and PEPPSI-*i*Pr (3.10 mg, 4.45 µmol) were reacted at 40 °C for 2 h according to **general procedure B**. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-cyclopropyl-3-(3-methoxyphenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **90** (10 mg, 0.027 mmol, 62% yield) as an off white gum. LCMS (Formic, ES^+): t_R = 0.96 min; *m/z* = 365.3; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.59 (d, *J*=2.0 Hz, 1H), 8.38 (d, *J*=2.0 Hz, 1H), 7.89 (s, 1H), 7.45-7.50 (m, 1H), 7.42 (t, *J*=7.9 Hz, 1H), 7.22 (dt, *J*=7.7, 1.3 Hz, 1H), 7.15 (t, *J*=2.2 Hz, 1H), 6.95-7.01 (m, 1H), 6.62-6.71 (m, 1H), 3.89 (s, 3H), 3.15 (d, *J*=4.6 Hz, 3H), 2.92-3.01 (m, 1H), 0.85-0.93 (m, 2H), 0.64-0.72 (m, 2H). *N^5-Cyclopropyl-3-(3-methoxyphenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**37**):* N^5-Cyclopropyl-3-(3-methoxyphenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **90** (10 mg, 0.027 mmol) was hydrogenated according to **general procedure C**. The crude product was purified by HPH MDAP. The pure fractions were concentrated *in vacuo* to afford N^5-cyclopropyl-3-(3-methoxyphenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (3 mg, 8.19 µmol, 30 % yield), a white solid. LCMS (Formic, ES^+): t_R = 0.93 min; *m/z* = 367.3;

^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.23 (d, *J*=2.2 Hz, 1H), 7.82 (dd, *J*=2.1, 0.9 Hz, 1H), 7.50-7.60 (m, 1H), 7.24-7.27 (m, 1H), 6.84 (dt, *J*=8.1, 1.3 Hz, 1H), 6.78 (dt, *J*=7.6, 1.2 Hz, 1H), 6.71 (t, *J*=2.2 Hz, 1H), 6.37 (d, *J*=0.7 Hz, 1H), 5.07-5.19 (m, 1H), 4.65-4.76 (m, 2H), 3.80 (s, 3H), 3.06 (d, *J*=4.6 Hz, 3H), 2.83-2.94 (m, 1H), 0.80-0.89 (m, 2H), 0.58-0.66 (m, 2H). *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(3-methoxyphenyl)-N^7-methyl benzofuran-5,7-dicarboxamide (**91**):* 2-(3-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.144 mL, 0.633 mmol), N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (200 mg, 0.527 mmol), K_2CO_3 (219 mg, 1.582 mmol) and PEPPSI-*i*Pr (36.8 mg, 0.053 mmol) was reacted at 40 °C for 16 hours according to **general procedure B**. The crude product was purified by silica chromatography eluting with 0-75% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(3-methoxyphenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **91** (95 mg, 0.234 mmol, 44%) as a white solid. LCMS (Formic, ES^+): t_R = 0.93 min; *m/z* = 407.4; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.48-8.66 (m, 1H), 8.39 (d, *J*=1.2 Hz, 1H), 7.80-7.93 (m, 1H), 7.35-7.52 (m, 2H), 7.09-7.24 (m, 2H), 6.88-7.06 (m, 2H), 4.03-4.12 (m, 2H), 3.84-3.92 (m, 3H), 3.75-3.81 (m, 2H), 3.07-3.20 (m, 3H), 2.73-2.82 (m, 1H), 1.94 (br. s., 2H). *N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(3-methoxyphenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**38**):* N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(3-methoxyphenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **91** was hydrogenated according to **general procedure C**. The crude product was purified by silica chromatography eluting with 0-70% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(3-methoxyphenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **38** (80 mg, 0.196 mmol, 84% yield) as a white solid. . LCMS (Formic, ES^+): t_R = 0.89 min; *m/z* = 409.4; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.30 (d, *J*=2.2 Hz, 1H), 7.76-

7.81 (m, 1H), 7.53-7.61 (m, 1H), 7.24 (t, *J*=7.9 Hz, 1H), 6.86-6.90 (m, 1H), 6.79-6.85 (m, 1H), 6.75 (dt, *J*=7.7, 1.2 Hz, 1H), 6.69 (t, *J*=2.2 Hz, 1H), 5.05-5.18 (m, 1H), 4.62-4.74 (m, 2H), 4.02 (d, *J*=8.6 Hz, 2H), 3.77 (s, 3H), 3.02 (d, *J*=4.9 Hz, 3H), 2.68 (q, *J*=2.7 Hz, 1H), 1.85 (t, *J*=2.6 Hz, 2H). *N^5-Cyclopropyl-3-(3-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide (**92**):* 3-Bromo-N^5-cyclopropyl-N^7-methylbenzofuran-5,7-dicarboxamide **19** (300 mg, 0.890 mmol), (3-fluorophenyl)boronic acid (187 mg, 1.335 mmol), K_2CO_3 (369 mg, 2.67 mmol) and $PdCl_2$(dppf) (65 mg, 0.089 mmol) were reacted at 120 °C for 30 mins under mw irradiation. The crude product was purified by silica chromatography eluting with 0-75% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-cyclopropyl-3-(3-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **92** (118 mg, 0.335 mmol, 38% yield) as an orange solid. LCMS (Formic, ES^+): t_R = 0.96 min; *m/z* = 353.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.67-8.75 (m, 1H), 8.63 (s, 1H), 8.44 (d, *J*=2.0 Hz, 2H), 8.24 (d, *J*=1.7 Hz, 1H), 7.65 (d, *J*=3.4 Hz, 3H), 7.23-7.36 (m, 1H), 2.9-2.85 (m, 4H), 0.69-0.76 (m, 2H), 0.55-0.64 (m, 2H). *(±)-N^5-Cyclopropyl-3-(3-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**(rac)-39**):* N^5-Cyclopropyl-3-(3-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **92** (118 mg, 0.335 mmol, 38% yield) was hydrogenated according to **general procedure C**. The crude product was purified by silica chromatography eluting with 0-60% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* afford (±)-N^5-cyclopropyl-3-(3-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-39** (32 mg, 0.090 mmol, 27% yield) as a colourless solid. LCMS (Formic, ES^+): t_R = 0.92 min; *m/z* = 355.3; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.33 (d, *J*=2.0 Hz, 1H), 7.64-7.67 (m, 1H), 7.33-7.42 (m, 1H), 6.98-7.10 (m, 3H), 5.20 (t, *J*=9.3 Hz, 1H), 4.84-4.90 (m, 1H), 4.72 (dd, *J*=9.0, 6.8 Hz, 1H), 3.00 (s, 3H), 2.73-2.87 (m, 1H), 0.73-0.85 (m, 2H), 0.56-0.66 (m, 2H). *(S)-N^5-Cyclopropyl-3-(3-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**(S)-39**):* (±)-N^5-Cyclopropyl-3-(3-fluorophenyl)-N^7-methyl-2,3-

dihydrobenzo furan-5,7-dicarboxamide **(*rac*)-39** (32 mg, 0.090 mmol) was dissolved in EtOH (2 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralcel OD-H (5 μm) which was eluted with 10% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^5-cyclopropyl-3-(3-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-39** (13 mg, 0.037 mmol, 41%) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralcel OD-H column, 15% EtOH/heptane, t_R = 16.470 min, *er* >99:1. *N^5-Cyclopropyl-3-(4-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide (**93**):* 3-Bromo-N^5-cyclopropyl-N^7-methylbenzofuran-5,7-dicarboxamide **18** (150 mg, 0.445 mmol), (4-fluorophenyl)boronic acid (93 mg, 0.667 mmol), $PdCl_2$(dppf) (32.6 mg, 0.044 mmol) and K_2CO_3 (184 mg, 1.335 mmol) were reacted at 120 °C for 30 mins under microwave irradiation according to **general procedure B**. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-cyclopropyl-3-(4-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **93** (112 mg, 0.318 mmol, 71% yield) as an orange solid. LCMS (Formic, ES^+): t_R = 0.97 min; *m/z* = 353.1; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.56 (d, *J*=2.0 Hz, 1H), 8.39 (d, *J*=2.0 Hz, 1H), 7.88 (s, 1H), 7.58-7.65 (m, 3H), 7.17-7.25 (m, 2H), 6.63 (d, *J*=1.2 Hz, 1H), 3.17 (d, *J*=4.6 Hz, 3H), 2.92-3.02 (m, 1H), 0.87-0.95 (m, 2H), 0.64-0.73 (m, 2H). *(±)-N^5-Cyclopropyl-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide ((**rac**)-**40**):* N^5-Cyclopropyl-3-(4-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **93** was hydrogenated according to **general procedure C**. The crude product was purified by silica chromatography eluting with 0-60% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-N^5-cyclopropyl-3-(4-fluorophenyl)-N^7-methyl-2,3-

dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-40** (52 mg, 0.147 mmol, 46% yield) as an off white gum. LCMS (Formic, ES^+): t_R = 0.97 min; *m/z* = 353.1; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.23-8.29 (m, 1H), 7.77-7.81 (m, 1H), 7.56 (d, *J*=4.9 Hz, 1H), 7.12-7.17 (m, 2H), 6.98-7.07 (m, 2H), 6.59 (br. s., 1H), 5.07-5.18 (m, 1H), 4.69-4.77 (m, 1H), 4.62 (dd, *J*=8.9, 7.2 Hz, 1H), 3.05 (d, *J*=4.9 Hz, 3H), 2.81-2.92 (m, 1H), 0.79-0.88 (m, 2H), 0.57-0.64 (m, 2H). *(S)-N^5-Cyclopropyl-3-(3-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-40)****:* (±)-N^5-Cyclopropyl-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzo furan-5,7-dicarboxamide **(*rac*)-40** (45 mg, 0.127 mmol) was dissolved in EtOH (1 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralcel OD-H (5 µm) which was eluted with 25% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^5-cyclopropyl-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-40** (16 mg, 0.147 mmol, 36% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralcel OD-H column, 25% EtOH/heptane, t_R = 8.021 min, *er* >99:1. *N^5-((1R,5S,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide (**94**):* N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-bromo-N^7-methylbenzofuran-5,7-dicarboxamide **19** (100 mg, 0.264 mmol), (4-fluorophenyl)boronic acid (55.3 mg, 0.396 mmol), $PdCl_2$(dppf) (19.30 mg, 0.026 mmol) and K_2CO_3 (109 mg, 0.791 mmol) reacted at 120 ºC for 30 mins under mw irradiation according to **general procedure C**. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **94** (58 mg, 0.147 mmol, 56% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.92 min; *m/z* = 395.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm)

8.69-8.74 (m, 1H), 8.53 (s, 1H), 8.41 (d, *J*=1.7 Hz, 1H), 8.37 (d, *J*=4.6 Hz, 1H), 8.24 (d, *J*=2.0 Hz, 1H), 7.83 (dd, *J*=8.8, 5.4 Hz, 2H), 7.41 (t, *J*=8.9 Hz, 2H), 3.89 (d, *J*=8.3 Hz, 2H), 3.63-3.69 (m, 2H), 2.90 (d, *J*=4.6 Hz, 3H), 2.62-2.66 (m, 1H), 1.93 (t, *J*=2.8 Hz, 2H). *(±)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((rac)-41****): N^5*-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methylbenzofuran-5,7-dicarboxamide **94** (58 mg, 0.147 mmol) was hydrogenated according to **general procedure C**. The crude product was redissolved in EtOH (5 mL) and filtered through a thiol column, the eluent was concentrated *in vacuo* to afford (±)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-41** (50 mg, 0.126 mmol, 86% yield) as an off white solid. LCMS (Formic, ES^+): t_R = 0.88 min; *m/z* = 397.3; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.33 (d, *J*=2.2 Hz, 14H), 7.63 (t, *J*=1.7 Hz, 14H), 7.22-7.30 (m, 31H), 7.03-7.14 (m, 29H), 5.19 (t, *J*=9.3 Hz, 16H), 4.83-4.89 (m, 17H), 4.68 (dd, *J*=9.0, 6.8 Hz, 16H), 3.99 (d, *J*=8.6 Hz, 30H), 3.73 (dt, *J*=8.4, 1.3 Hz, 31H), 3.00 (s, 3H), 2.59 (t, *J*=2.7 Hz, 1H), 1.90 (t, *J*=2.8 Hz, 2H); *amide NH not visible. (S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-41)****:* (±)-N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluoro phenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-41** (43 mg, 0.108 mmol) was dissolved in EtOH (1 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak ID (5 µm) which was eluted with 50% (EtOH + 0.2% isopropylamine)/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(4-fluorophenyl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-41** (21 mg, 0.053 mmol, 49% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;*

Chiral LC: 4.6 mm x 25 cm Chiralpak ID column, 50% (EtOH + 0.2% isopropylamine)/heptane, t_R = 11.477 min, *er* >99:1. *(±)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(o-tolyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((rac)-42)****:* (±)-7-(Methylcarbamoyl)-3-(*o*-tolyl)-2,3-dihydrobenzofuran-5-carboxylic acid (35 mg, 0.112 mmol) and (1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-amine **21** (17 mg, 0.169 mmol) were reacted in DMF (4 mL) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 0-100% (25% EtOH:EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(o-tolyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-42** (20 mg, 0.051 mmol, 45% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.93 min; *m/z* = 393.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.44-8.49 (m, 1H), 8.24 (d, *J*=2.0 Hz, 1H), 7.86-7.93 (m, 1H), 7.63 (s, 1H), 7.23-7.28 (m, 1H), 7.11-7.21 (m, 2H), 6.86-6.94 (m, 1H), 5.15-5.23 (m, 1H), 5.03-5.11 (m, 1H), 4.47-4.56 (m, 1H), 3.83 (d, *J*=8.3 Hz, 2H), 3.62 (d, *J*=2.7 Hz, 2H), 2.85 (d, *J*=4.9 Hz, 3H), 2.53-2.58 (m, 2H), 2.39 (s, 3H), 1.86 (d, *J*=2.7 Hz, 2H). *(S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(o-tolyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-42)****:* (±)-N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(o-tolyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-42** (20 mg, 0.051 mmol) was dissolved in EtOH (1 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak AD-H (5 μm) which was eluted with 40% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7-methyl-3-(o-tolyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-42** (5 mg, 0.013 mmol, 25% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak AD-H column, 40%

EtOH/heptane, t_R = 13.515 min, *er* >99:1. *(±)-N^5-Cyclopropyl-3-(1H-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((rac)-43)****:* (±)-3-(*1H*-Indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylic acid **22** (86 mg, 0.256 mmol) was dissolved in CH_2Cl_2 (3 mL). DIPEA (0.134 mL, 0.767 mmol), cyclopropanamine (0.021 mL, 0.307 mmol) and T3P (50% w/w in EtOAc, 0.091 mL, 0.307 mmol) were added and the stirred at rt for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was triturated with Et_2O and concentrated *in vacuo* to afford (±)-N^5-cyclopropyl-3-(*1H*-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-43** (54 mg, 0.037 mmol, 56% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.87 min; *m/z* = 376.3; ^{1}H NMR (MeOD-d_4, 400MHz): δ (ppm) 7.58-7.65 (m, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.22 (d, *J*=3.4 Hz, 1H), 7.05-7.11 (m, 1H), 6.86 (d, *J*=7.1 Hz, 1H), 6.27 (dd, *J*=3.3, 0.9 Hz, 1H), 5.24-5.32 (m, 1H), 5.13-5.21 (m, 1H), 4.85-4.88 (m, 1H), 3.02 (s, 3H), 2.72-2.80 (m, 1H), 0.70-0.77 (m, 2H), 0.53-0.60 (m, 2H). *(S)-N^5-cyclopropyl-3-(1H-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-43)****:* (±)-N^5-cyclopropyl-3-(*1H*-indol-4-yl)-N^7-methyl-2,3-dihydrobenzo furan-5,7-dicarboxamide **(*rac*)-43** (54 mg, 0.037 mmol) was dissolved in EtOH (2 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak AD-H (5 μm) which was eluted with 20% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 2 were concentrated *in vacuo* to afford (*S*)-N^5-cyclopropyl-3-(*1H*-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-43** (14 mg, 0.037 mmol, 26% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak AD-H column, 20% EtOH/heptane, t_R = 14.888 min, *er* >99:1. *(±)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(1H-indol-4-yl)-*

N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide ***((rac)-44)****:* (±)-3-(*1H*-Indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzofuran-5-carboxylic acid **22** (120 mg, 0.357 mmol) and (1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-amine (42.4 mg, 0.428 mmol) were reacted in DMF (3 mL) in accordance with **general procedure A**. The crude product was purified by silica chromatography, eluting with 0-50% (25% EtOH in EtOAc):EtOAc to give (±)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(*1H*-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-44** (135 mg, 0.323 mmol, 91% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.83 min; *m/z* = 418.3; HRMS ($C_{24}H_{24}N_3O_4$): $[M+H]^+$ calculated 418.1761, found 418.1764; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.35 (d, *J*=1.7 Hz, 1H), 7.59–7.64 (m, 1H), 7.36 (d, *J*=8.1 Hz, 1H), 7.22 (d, *J*=3.2 Hz, 1H), 7.09 (s, 1H), 6.87 (d, *J*=7.1 Hz, 1H), 6.27 (d, *J*=2.7 Hz, 1H), 5.30 (s, 1H), 5.15–5.23 (m, 1H), 4.92 (s, 1H), 3.97 (dd, *J*=8.3, 1.1 Hz, 2H), 3.70 (d, *J*=8.3 Hz, 2H), 3.03 (s, 3H), 2.55 (s, 1H), 1.87 (s, 2H); ^{13}C NMR (MeOD-d_4, 101 MHz): δ (ppm) 168.8, 165.3, 160.4, 136.8, 133.2, 132.3, 128.8, 127.5, 127.3, 126.1, 124.5, 121.0, 117.9, 115.1, 110.5, 98.8, 80.0, 68.8, 45.6, 30.8, 25.4, 24.4. *(S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(1H-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***(44)****:* (±)-N^5-((1*R*,5*S*,6*r*)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(*1H*-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-44** (130 mg, 0.311 mmol) was dissolved in EtOH (12 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak AD-H (5 μm) which was eluted with 40% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(*1H*-indol-4-yl)-N^7-methyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-44** (68 mg, 0.163 mmol, 53% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak AD-H column, 40% EtOH/heptane, t_R = 12.004 min, *er*

>99:1. *(±)-3-(1H-Indol-4-yl)-N^7-methyl-N^5-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((rac)-45)****:* (±)-3-(*1H*-Indol-4-yl)-7-(methylcarbamoyl)-2,3-dihydrobenzo furan-5-carboxylic acid **22** (85 mg, 0.397 mmol) was dissolved in CH_2Cl_2 (3 mL). DIPEA (0.132 mL, 0.758 mmol), 2-(1-methyl-*1H*-pyrazol-4-yl)ethan-1-amine (0.048 mL, 0.379 mmol) and T3P (50% w/w in EtOAc, 0.090 mL, 0.303 mmol) were added and the stirred at rt for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford (±)-3-(*1H*-indol-4-yl)-N^7-methyl-N^5-(2-(1-methyl-*1H*-pyrazol-4-yl)ethyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-45** (55 mg, 0.124 mmol, 49% yield) as a white solid. LCMS (Formic, ES^+): t_R = 0.83 min; *m/z* = 444.4; ^{1}H NMR (MeOD-d_4, 400 MHz): δ (ppm) 8.35 (d, *J*=2.2 Hz, 1H), 7.58-7.62 (m, 1H), 7.33-7.38 (m, 2H), 7.30 (s, 1H), 7.22 (d, *J*=3.2 Hz, 1H), 7.09 (t, *J*=7.7 Hz, 1H), 6.87 (d, *J*=6.8 Hz, 1H), 6.28 (dd, *J*=3.2, 0.7 Hz, 1H), 5.25-5.33 (m, 1H), 5.19 (d, *J*=7.1 Hz, 1H), 4.89-4.92 (m, 1H), 3.76 (s, 3H), 3.44 (t, *J*=7.2 Hz, 2H), 3.02 (s, 3H), 2.69 (t, *J*=7.3 Hz, 2H). *(S)-3-(1H-Indol-4-yl)-N^7-methyl-N^5-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***((S)-45)****:* (±)-3-(*1H*-Indol-4-yl)-N^7-methyl-N^5-(2-(1-methyl-*1H*-pyrazol-4-yl)ethyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*rac*)-45** (55 mg, 0.124 mmol) was dissolved in EtOH (1 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak AD-H (5 μm) which was eluted with 60% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-3-(*1H*-indol-4-yl)-N^7-methyl-N^5-(2-(1-methyl-*1H*-pyrazol-4-yl)ethyl)-2,3-dihydrobenzofuran-5,7-dicarboxamide **(*S*)-45** (25 mg, 0.056 mmol, 46% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak AD-H column, 60% EtOH/heptane, t_R =

10.251 min, *er* >99:1. *(3-Bromoprop-1-en-2-yl)benzene (**95**):* Prop-1-en-2-ylbenzene (5.50 mL, 42.3 mmol) was dissolved in THF (100 mL) at rt under N_2. To the resulting solution was added NBS (7.91 g, 44.4 mmol) and tosic acid (0.805 g, 4.23 mmol) and the solution was refluxed at 100 °C for 4 h. The reaction was cooled to rt, taken up in Et_2O (20 mL) and washed with water (2 x 20 mL). The organic layer was passed through a hydrophobic frit and concentrated *in vacuo* to afford (3-bromoprop-1-en-2-yl)benzene **95** (7.15 g, 36.3 mmol, 86 % yield) as a yellow oil. LCMS (Formic, ES^+): t_R = 1.21 min; *does not ionise*; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 7.53-7.59 (m, 2H), 7.32-7.41 (m, 3H), 5.62 (d, *J*=0.7 Hz, 1H), 5.58 (d, *J*=0.7 Hz, 1H), 4.64 (s, 2H). *Methyl 3-iodo-4-((2-phenylallyl)oxy)benzoate (**52**):* Methyl 4-hydroxy-3-iodobenzoate **51** (1.00 g, 3.60 mmol), (3-bromoprop-1-en-2-yl)benzene **95** (1.42 g, 7.19 mmol) and K_2CO_3 (1.49 g, 10.79 mmol) were dissolved in acetone (50 mL) and heated to 80 °C for 1 h under N_2. The reaction was allowed to cool before quenching with sat. $NaHCO_3$ (aq) and extracting with CH_2Cl_2. The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica column chromatography eluting with 0-30% EtOAc/cyclohexane. The appropriate fractions were collected and concentrated *in vacuo* to afford methyl 3-iodo-4-((2-phenylallyl)oxy)benzoate **52** (1.36 g, 3.45 mmol, 96% yield) as a yellow solid. LCMS (Formic, ES^+): t_R = 1.21 min; *m/z* = 395.2; ; HRMS ($C_{17}H_{15}O_3I$): $[M+H]^+$ calculated 395.0144, found 395.0144; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 8.30 (d, *J*=2.2 Hz, 1H), 7.97 (dd, *J*=8.6, 2.2 Hz, 1H), 7.54–7.60 (m, 2H), 7.33–7.43 (m, 3H), 7.26 (d, *J*=8.6 Hz, 1H), 5.71 (d, *J*=1.0 Hz, 1H), 5.63 (d, *J*=1.0 Hz, 1H), 5.15 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (DMSO-*d*$_6$, 101 MHz): δ (ppm) 165.1, 160.9, 142.4, 140.3, 137.8, 131.7, 128.9, 128.6, 126.4, 124.3, 115.0, 113.1, 86.9, 70.6, 52.6; m.p. 43.1 – 48.3 °C; IR ν_{max} (cm^{-1}) 2948, 1715, 1593, 1308, 1268, 911, 703. *(±)-Methyl 3-methyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**53**):* Methyl 3-iodo-4-((2-phenylallyl)oxy)benzoate **52** (500 mg, 1.268 mmol) and $PdCl_2(MeCN)_2$ (33 mg, 0.127 mmol)

were dissolved in DMF (5 mL) at rt under nitrogen. PMP (1.38 mL, 7.61 mmol) was added followed by formic acid (0.19 mL, 5.07 mmol) and the reaction was heated to 50 °C for 2 h. The reaction was allowed to cool and diluted with Et_2O (50 mL). The organic phase was washed with brine (2 x 50 mL) and the aqueous phase was then extracted with EtOAc (50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-50% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-methyl 3-methyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **53** (281 mg, 1.047 mmol, 83% yield) as a colourless gum. LCMS (Formic, ES^+): t_R = 1.29 min; *m/z* = 269.2; HRMS ($C_{17}H_{16}O_3$): $[M+H]^+$ calculated 269.1183, found 269.1178; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 7.86 (dd, *J*=8.3, 2.0 Hz, 1H), 7.66 (d, *J*=2.0 Hz, 1H), 7.21–7.38 (m, 5H), 7.00 (d, *J*=8.3 Hz, 1H), 4.73 (d, *J*=9.0 Hz, 1H), 4.61 (d, *J*=9.3 Hz, 1H), 3.78 (s, 3H), 1.74 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, 101 MHz): δ (ppm) 166.8, 163.7, 145.7, 136.2, 131.4, 128.6, 126.8, 126.3, 126.2, 123.3, 109.7, 87.1, 51.8, 49.5, 26.3; IR ν_{max} (cm^{-1}) 2951, 1715, 1288, 1251, 772, 700. *(±)-Methyl 3-(hydroxymethyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**54**):* Methyl 3-iodo-4-((2-phenylallyl)oxy)benzoate **52** (3.0 g, 7.61 mmol), bispinacolatodiboron (3.87 g, 15.22 mmol), KOAc (2.241 g, 22.83 mmol) and XPhos Pd G2 (0.599 g, 0.761 mmol) were dissolved in EtOH (50 mL) at rt under nitrogen. The resulting solution was heated to 100 °C and stirred for 4 h. The reaction was allowed to cool to 0 ºC before NaOH (1.903 mL, 3.81 mmol) and aq. hydrogen peroxide (6.66 mL, 76 mmol) were added sequentially and the resulting solution stirred at 0 ºC for 10 mins. The reaction was quenched by addition of sat. aq. sodium thiosulfate (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-50% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-methyl 3-

(hydroxymethyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **54** (1.84 g, 6.47 mmol, 85% yield) as a cream solid. LCMS (formic, ES^+) t_R = 1.04 min, *m/z* = 285.2; HRMS ($C_{17}H_{16}O_4$): $[M+H]^+$ calculated 285.1127, found 285.1135; ^1H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.00 (dd, *J*=8.3, 1.8 Hz, 1H), 7.92 (d, *J*=1.8 Hz, 1H), 7.34–7.41 (m, 2H), 7.28–7.33 (m, 3H), 6.92 (d, *J*=8.3 Hz, 1H), 4.92 (d, *J*=9.1 Hz, 1H), 4.72 (d, *J*=9.1 Hz, 1H), 4.14–4.20 (m, 1H), 4.07–4.12 (m, 1H), 3.88 (s, 3H); *Alcohol OH not visible*; ^{13}C NMR ($CDCl_3$-*d*, 101 MHz): δ (ppm) 166.8, 164.6, 141.8, 132.2, 130.6, 128.9, 127.4, 127.2, 126.8, 123.2, 110.0, 82.2, 67.2, 55.4, 51.6; m.p. 95.6 – 97.2 °C; IR ν_{max} (cm^{-1}) 3496, 2976, 1708, 1254, 959, 774. *Methyl 3-iodo-4-(2-oxo-2-phenylethoxy)benzoate (**96**):* Methyl 4-hydroxy-3-iodobenzoate **52** (10.0 g, 36.0 mmol), 2-bromo-1-phenylethan-1-one (6.8 g, 34.3 mmol) and K_2CO_3 (14.2 g, 103 mmol) were suspended in acetone (100 mL) and left to stir at 80 °C under nitrogen for 2.5 h. The reaction was filtered to remove excess K_2CO_3, and the filtrate was concentrated *in vacuo.* The residue was taken up in EtOAc (350 mL), washed with 1 M NaOH (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. Et_2O (100 mL) was added to the crude product, sonicated, and stirred for 1.5 h. This was then filtered to isolate methyl 3-iodo-4-(2-oxo-2-phenylethoxy)benzoate **96** (10.6 g, 25.5 mmol, 74%) as a cream solid. LCMS (formic, ES^+) t_R = 1.27 min, *m/z* = 397.1; ^1H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.33 (d, *J*=2.2 Hz, 1H), 8.03 (dd, *J*=8.3, 1.5 Hz, 2H), 7.90 (dd, *J*=8.6, 2.2 Hz, 1H), 7.69-7.75 (m, 1H), 7.56-7.64 (m, 2H), 7.05 (d, *J*=8.8 Hz, 1H), 5.84 (s, 2H), 3.83 (s, 3H). *Methyl 3-iodo-4-((2-phenylbut-2-en-1-yl)oxy)benzoate (**55**):* Ethyltriphenylphosphonium bromide (9.42 g, 25.4 mmol) was suspended in THF (100 mL), at rt under nitrogen and cooled to 0 °C. KO*t*Bu (1 M in THF, 22 mL, 22.00 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 1 h. Methyl 3-iodo-4-(2-oxo-2-phenylethoxy)benzoate **96** (6.64 g, 16.75 mmol) in THF (50 mL) was added dropwise, and the reaction left to stir at rt overnight. The reaction was quenched with sat. aq. NH_4Cl (40 mL), water (80 mL) was added, and the layers were

separated. The aqueous was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude product was purified using silica gel column chromatography eluting with of 0-5% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to yield methyl 3-iodo-4-((2-phenylbut-2-en-1-yl)oxy)benzoate **55** (4.64 g, 10.80 mmol, 65% yield) as a yellow oil. LCMS (formic, ES^+) t_R = 1.51 min, *m/z* = 409.1; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.42-8.51 (m, 1H), 8.00 (dd, *J*=8.6, 2.2 Hz, 1H), 7.37-7.44 (m, 2H), 7.29-7.36 (m, 3H), 6.83 (d, *J*=8.6 Hz, 1H), 6.09 (dt, *J*=6.8, 1.5 Hz, 1H), 4.80 (t, *J*=1.5 Hz, 2H), 3.88-3.93 (m, 3H), 1.71 (dt, *J*=6.8, 1.5 Hz, 3H). *(±)-Methyl 3-phenyl-3-vinyl-2,3-dihydrobenzofuran-5-carboxylate (**97**):* Methyl 3-iodo-4-((2-phenylbut-2-en-1-yl)oxy)benzoate **55** (4.64 g, 11.37 mmol) was taken up in DMF (100 mL). Ag_2CO_3 (6.27 g, 22.75 mmol) was added, and N_2 was bubbled through the reaction mixture. $Pd(OAc)_2$ (0.26 g, 1.137 mmol) and triphenylphosphine (1.19 g, 4.55 mmol) were added, and the reaction left to stir at 80 °C for 27 h. Additional $Pd(OAc)_2$ (0.13 g, 0.568 mmol) and triphenylphosphine (0.60 g, 2.28 mmol) were added, and the reaction left to stir at 80 °C for 19 h. The reaction was filtered through Celite washing with EtOAc. Water (100 mL) was added to the filtrate, the layers were separated, and the aqueous was extracted with EtOAc (2 x 100 mL). The combined organics were filtered through Celite, then dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude was purified by reverse phase chromatography eluting with 45-90% acetonitrile/(10 mM aqueous ammonium bicarbonate solution). The pure fractions were concentrated *in vacuo* to yield (±)-methyl 3-phenyl-3-vinyl-2,3-dihydrobenzofuran-5-carboxylate **97** (1.008 g, 3.42 mmol, 30%) as an orange gum. LCMS (formic, ES^+) t_R = 1.31 min, *m/z* = 281.1; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.90 (dd, *J*=8.4, 1.8 Hz, 1H), 7.65 (d, *J*=2.0 Hz, 1H), 7.35-7.42 (m, 2H), 7.23-7.34 (m, 3H), 7.04 (d, *J*=8.6 Hz, 1H), 6.41 (dd, *J*=17.4, 10.5 Hz, 1H), 5.34 (d, *J*=10.5 Hz, 1H), 5.00 (d, *J*=16.6 Hz,

1H), 4.94 (d, *J*=9.5 Hz, 1H), 4.80 (d, *J*=9.5 Hz, 1H), 3.81 (s, 3H). *(±)-Methyl 3-ethyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**56**):* (±)-Methyl 3-phenyl-3-vinyl-2,3-dihydrobenzofuran-5-carboxylate **97** (1.01 g, 3.60 mmol) was hydrogenation according to **general procedure C** using 5% Pd/C (200 mg, 0.094 mmol). The reaction mixture was filtered through Celite and concentrated *in vacuo* to yield (±)-methyl 3-ethyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **56** (1.01 g, 3.40 mmol, 95%) as a pale brown gum. LCMS (formic, ES^+) t_R = 1.33 min, *m/z* = 283.1; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 7.97 (dd, *J*=8.4, 1.8 Hz, 1H), 7.82 (d, *J*=2.0 Hz, 1H), 7.31-7.38 (m, 4H), 7.23-7.27 (m, 1H), 6.90 (d, *J*=8.3 Hz, 1H), 4.67 (s, 2H), 3.87-3.91 (m, 3H), 2.20 (qd, *J*=7.3, 4.2 Hz, 2H), 0.88 (t, *J*=7.3 Hz, 3H). *(±)-Methyl-7-bromo-3-methyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**57**):* Bromine (0.134 mL, 2.61 mmol) was added to (±)-methyl 3-methyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **53** (140 mg, 0.522 mmol) in CH_2Cl_2 (5 mL) at rt under nitrogen. The resulting solution was stirred at rt for 1 h. The reaction was quenched with sat. aq. sodium thiosulfate (5 mL) and sodium hydrosulfite was added until the reaction turned colourless. The reaction was then extracted with CH_2Cl_2 (2 x 20 mL). The organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford (±)-methyl 7-bromo-3-methyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **57** (172 mg, 0.495 mmol, 95% yield) as a colourless gum. LCMS (Formic, ES^+): t_R = 1.40 min; *m/z* = 347.0, 349.0; HRMS ($C_{17}H_{15}O_3Br$): $[M+H]^+$ calculated 347.0283, found 347.0288; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.98 (d, *J*=1.5 Hz, 1H), 7.64 (d, *J*=1.5 Hz, 1H), 7.24–7.39 (m, 5H), 4.85 (d, *J*=9.3 Hz, 1H), 4.73 (d, *J*=9.3 Hz, 1H), 3.80 (s, 3H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$-*d*, 101 MHz): δ (ppm) 179.2, 165.5, 160.6, 144.6, 137.2, 134.1, 128.6, 127.1, 126.1, 124.8, 102.7, 87.4, 52.2, 50.4, 26.3; m.p. 60.8 – 63.3 °C; IR ν_{max} (cm^{-1}) 2956, 1707, 1432, 1276, 701. *(±)-Methyl 7-bromo-3-(hydroxymethyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**58**):* Bromine (0.163 mL, 3.17 mmol) was added to (±)-methyl 3-(hydroxymethyl)-3-phenyl-2,3-dihydrobenzofuran-5-

carboxylate **54** (180 mg, 0.633 mmol) in CH_2Cl_2 (5 mL) at rt under nitrogen. The resulting solution was stirred at rt for 1 h. The reaction was quenched with sat. aq. sodium thiosulfate (5 mL) and sodium hydrosulfite was added until the reaction turned colourless. The reaction was then extracted with CH_2Cl_2 (2 x 20 mL). The organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford (±)-methyl 7-bromo-3-(hydroxymethyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **58** (220 mg, 0.606 mmol, 96% yield) as a colourless gum. LCMS (formic, ES^+) t_R = 1.18 min, *m/z* = 363.1, 365.1; HRMS ($C_{17}H_{15}O_4Br$): $[M+H]^+$ calculated 363.0232, found 363.0237; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 7.99 (d, *J*=1.8 Hz, 1H), 7.75 (d, *J*=1.8 Hz, 1H), 7.24–7.39 (m, 5H), 4.97 (d, *J*=9.3 Hz, 1H), 4.79 (d, *J*=9.3 Hz, 1H), 3.93–4.04 (m, 2H), 3.82 (s, 3H); *Alcohol OH not visible*; ^{13}C NMR (DMSO-*d*$_6$, 101 MHz): δ (ppm) 179.3, 161.6, 143.2, 134.5, 133.6, 129.1, 127.4, 127.3, 126.6, 124.4, 119.6, 102.3, 82.7, 57.0, 52.6; m.p. 136.1 – 137.8 °C; IR ν_{max} (cm^{-1}) 3462, 1694, 1430, 1287, 764. *(±)-Methyl 7-bromo-3-ethyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**59**):* (±)-Methyl 3-ethyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **56** (1.95 g, 6.91 mmol) was taken up in CH_2Cl_2 (60 mL), cooled to 0 °C and put under nitrogen. Bromine (2 mL, 38.8 mmol) was added, and the reaction was allowed to warm to rt and stir for 5.5 h. The reaction was quenched with 10% sodium thiosulfate (50 mL) and sodium bisulfite was added until the reaction turned a pale yellow. The layers were separated and the aqueous was extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude was purified using silica chromatography, eluting with 1-10% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-methyl 7-bromo-3-ethyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **59** (2.104 g, 5.53 mmol, 80%) as a yellow oil. LCMS (formic, ES^+) t_R = 1.33 min, *m/z* = 361.1, 363.1; ^{1}H NMR (CHLOROFORM-d, 400MHz): δ (ppm) 8.14 (d, *J*=1.7 Hz, 1H), 7.74 (d, *J*=1.7 Hz, 1H), 7.23-7.40 (m, 5H), 4.70-4.84 (m, 2H), 3.90 (s, 3H), 2.21 (qd, *J*=7.3, 5.4 Hz, 2H), 0.83-0.93 (m, 3H).

*(±)-Methyl 3-methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(rac)-98**):* Methanamine hydrochloride (54 mg, 0.806 mmol), (±)-methyl 7-bromo-3-methyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **57** (140 mg, 0.403 mmol), $Pd(OAc)_2$ (45 mg, 0.202 mmol), Xantphos (117 mg, 0.202 mmol), DMAP (222 mg, 1.814 mmol), and cobalt carbonyl (138 mg, 0.403 mmol) were dissolved in 1,4-Dioxane (10 mL) at rt under nitrogen. The resulting solution was stirred at 100 ºC under mw irradiation for 4 h. The reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL) and Et_2O (50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-70% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford methyl (±)-3-methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-98** (79 g, 0.243 mmol, 60% yield) as a white solid. LCMS (Formic, ES^+): t_R = 1.09 min; *m/z* = 326.3; HRMS ($C_{19}H_{19}NO_4$): $[M+H]^+$ calculated 326.1392, found 326.1400; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.34 (d, *J*=1.7 Hz, 1H), 7.92 (q, *J*=4.5 Hz, 1H), 7.75 (d, *J*=1.7 Hz, 1H), 7.23–7.39 (m, 5H), 4.90 (d, *J*=9.0 Hz, 1H), 4.78 (d, *J*=9.0 Hz, 1H), 3.82 (s, 3H), 2.85 (d, *J*=4.5 Hz, 3H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 165.9, 163.7, 160.8, 145.8, 138.6, 131.5, 129.1, 127.9, 127.3, 126.6, 123.4, 117.3, 87.7, 52.5, 49.0, 26.8, 26.0; m.p. 138.3 – 141.3 °C; IR ν_{max} (cm^{-1}) 3357. 2946, 1707, 1650, 1270, 763. *(S)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(S)-98**):* (±)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-98** (2.19 g, 6.73 mmol) was dissolved in MeOH (110 mL) and injected onto the column (Column: 30 mm x 25 cm Chiralpak AS-H (5 μm) which was eluted with 50% MeOH/*i*PrOH, flow rate = 20 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-3-methyl-7-(methylcarbamoyl)-3-phenyl-2,3-

dihydrobenzofuran-5-carboxylate **(*S*)-98** (0.99 g, 3.04 mmol, 45% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak AS-H column, 50% MeOH/*i*PrOH, t_R = 6.033 min, *er* >99:1. *(S)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid (**60**):* Methyl (*S*)-3-methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzo furan-5-carboxylate (993 mg, 3.05 mmol) was taken up in THF (15 mL) and MeOH (15.00 mL). LiOH (1 M in water, 6.10 mL, 6.10 mmol) was added, and the reaction left to stir at 50 °C for 3 h. The reaction was concentrated *in vacuo* and the residue was taken up in water (20 mL), acidified with 2 M HCl and extracted with EtOAc (100 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford (*S*)-3-methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **60** (885 mg, 2.70 mmol, 88% yield) as a grey solid. LCMS (formic, ES^+) t_R = 0.94 min, *m/z* = 312.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.33 (d, *J*=1.7 Hz, 1H), 7.90 (d, *J*=4.6 Hz, 1H), 7.74 (d, *J*=2.0 Hz, 1H), 7.31-7.40 (m, 4H), 7.23-7.30 (m, 1H), 4.90 (d, *J*=9.0 Hz, 1H), 4.77 (d, *J*=9.0 Hz, 1H), 2.85 (d, *J*=4.6 Hz, 3H), 1.78 (s, 3H); *Acid OH not visible. (±)-Methyl 3-(hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(rac)-99**):* (±)-Methyl 7-bromo-3-(hydroxymethyl)-3-phenyl-2,3-dihydrobenzo furan-5-carboxylate **58** (450 mg, 1.239 mmol), methanamine hydrochloride (167 mg, 2.478 mmol), $Pd(OAc)_2$ (139 mg, 0.619 mmol), Xantphos (358 mg, 0.619 mmol), DMAP (681 mg, 5.58 mmol), and cobalt carbonyl (424 mg, 1.239 mmol) were dissolved in 1,4-dioxane (10 ml) at rt under nitrogen. The resulting solution was stirred at 100 ºC under mw irradiation for 4 h. The reaction was passed through a Celite plug, eluting with EtOAc (50 mL). The filtrate was washed with water (50 mL) and the aqueous layer was then extracted with CH_2Cl_2 (50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica chromatography eluting with 0-100% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-

methyl 3-(hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-99** (210 mg, 0.615 mmol, 50% yield) as a white solid. LCMS (formic, ES^+) t_R = 0.89 min, *m/z* = 342.3; HRMS ($C_{19}H_{19}NO_5$): $[M+H]^+$ calculated 342.1341, found 3342.1350; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.36 (d, *J*=1.8 Hz, 1H), 7.89 (q, *J*=4.5 Hz, 1H), 7.85 (d, *J*=1.8 Hz, 1H), 7.30–7.40 (m, 4H), 7.23–7.30 (m, 1H), 5.28 (t, *J*=5.0 Hz, 1H), 5.03 (d, *J*=9.1 Hz, 1H), 4.84 (d, *J*=9.1 Hz, 1H), 3.95–4.07 (m, 2H), 3.83 (s, 3H), 2.84 (d, *J*=4.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 166.0, 163.7, 161.7, 143.4, 134.8, 131.7, 129.5, 129.0, 127.3, 122.9, 119.6, 117.0, 83.4, 65.8, 55.3, 52.5, 26.8; m.p. 218.4 – 219.6 °C; IR ν_{max} (cm^{-1}) 3296, 1707, 1651, 1273, 769. (*S*)-Methyl 3-(hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(*S*)-99**): (±)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-99** (1.90 g, 6.73 mmol) was dissolved in EtOH (10 mL) and CH_2Cl_2 (10 mL), then injected onto the column (Column: 30 mm x 25 cm Chiralpak IC (5 μm) which was eluted with 40% EtOH/heptane, flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-Methyl 3-(hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*S*)-99** (0.83 g, 2.44 mmol, 44% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak IC column, 30% EtOH/heptane, t_R = 17.071 min, *er* >99:1. *(S)-3-(Hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid (**61**):* (*S*)-Methyl 3-(hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (832 mg, 2.437 mmol) was taken up in a 1:1 mixture of water (7 mL) and THF (7 mL). The resulting solution was treated with LiOH (117 mg, 4.87 mmol) and the reaction stirred at 50 °C for 4 h. The reaction was concentrated *in vacuo* to remove the THF and then acidified with 2M HCl. A precipitate formed which was removed by

filtration and dried to give (*S*)-3-(hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **61** (753 mg, 2.30 mmol, 94 % yield) as a white solid. LCMS (formic, ES^+) t_R = 0.75 min, *m/z* = 328.1; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.35 (d, *J*=2.0 Hz, 1H), 7.86-7.91 (m, 1H), 7.84 (d, *J*=2.0 Hz, 1H), 7.32-7.40 (m, 4H), 7.24-7.31 (m, 1H), 5.04 (d, *J*=9.0 Hz, 1H), 4.85 (d, *J*=9.0 Hz, 1H), 3.97-4.06 (m, 2H), 2.85 (d, *J*=4.5 Hz, 3H); *Acid OH and alcohol OH not visible. (±)-Methyl 3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (**(rac)-100**):* Methanamine hydrochloride (226 mg, 3.35 mmol), $Pd(OAc)_2$ (60 mg, 0.268 mmol), Xantphos (155 mg, 0.268 mmol), DMAP (737 mg, 6.04 mmol), imidazole (183 mg, 2.68 mmol) and cobalt carbonyl (229 mg, 0.671 mmol) were sealed in a microwave vial. The vessel was purged with nitrogen and methyl (±)-7-bromo-3-ethyl-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **58** (510 mg, 1.341 mmol) in 1,4-dioxane (12 mL) was added. The reaction vessel was sealed and heated to 90 °C for 4 hr under mw irradiation. The reaction was carried out three times to process 1.530 g of material. The reaction mixtures were combined and diluted with ethyl acetate (100 mL). Water (100 mL) was added and the mixture was filtered through Celite. The filtrate was separated and the organic layer was washed with brine (100 mL), at which point a grey precipitate formed. The mixture was filtered through Celite again, and the filtrate was separated. The organic was dried with Na_2SO_4, filtered and concentrated *in vacuo* to yield a brown solid. The crude product was purified by silica chromatography, eluting with 5-50% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (±)-methyl 3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-100** (1.007 g, 2.82 mmol, 70% yield) as a yellow gum. LCMS (formic, ES^+) t_R = 1.33 min, *m/z* = 340.1; ^{1}H NMR ($CDCl_3$-*d*, 400 MHz): δ (ppm) 8.78 (d, *J*=2.0 Hz, 1H), 7.91 (d, *J*=2.0 Hz, 1H), 7.48 (br. s., 1H), 7.33-7.41 (m, 2H), 7.25-7.32 (m, 5H), 4.82 (s, 2H), 3.91 (s, 3H), 3.06 (d, *J*=4.9 Hz, 3H), 2.23 (qd, *J*=7.3, 3.8 Hz, 2H), 0.87 (t, *J*=7.5 Hz, 3H). *(S)-Methyl 3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-*

*carboxylate **((S)-100)**:* (±)-Methyl 3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*rac*)-100** (1.46 g, 4.09 mmol) was dissolved in EtOH (5 mL) then injected onto the column (Column: 30 mm x 25 cm Chiralpak IC (5 μm) which was eluted with 20% (EtOH + 0.2% isopropylamine)/(heptane + 0.2% isopropylamine), flow rate = 30 mL/min, detection wavelength, 215 nm. Appropriate fractions for isomer 1 were bulked and labelled peak 1. Appropriate fractions for isomer 2 were bulked and labelled peak 2. The pure fractions from peak 1 were concentrated *in vacuo* to afford (*S*)-Methyl 3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate **(*S*)-100** (0.71 g, 1.99 mmol, 49% yield) as a white solid. *^{1}H NMR and LCMS data consistent with racemate;* Chiral LC: 4.6 mm x 25 cm Chiralpak IC column, 30% (EtOH + 0.2% isopropylamine)/heptane, t_R = 17.252 min, *er* >99:1. *(S)-3-Ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **(62)**:* (*S*)-Methyl 3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylate (709 mg, 2.089 mmol) was taken up in 1,4-dioxane (10 mL) and water (5 mL). LiOH in (1 M water, 4.18 mL, 4.18 mmol) was added, and the reaction left to stir at 50 °C for 1.5 h. The reaction was concentrated *in vacuo* and the residue was taken up in water (15 mL) and acidified with 2 M HCl (aq). The white precipitate formed was isolated by filtration and dried *in vacuo* to afford (*S*)-3-ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **62** (514 mg, 1.501 mmol, 72%) as a white solid. LCMS (formic, ES^+) t_R = 0.98 min, *m/z* = 326.4; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.32 (d, *J*=1.7 Hz, 1H), 7.88 (d, *J*=4.6 Hz, 1H), 7.80 (d, *J*=2.0 Hz, 1H), 7.36-7.40 (m, 4H), 7.24-7.30 (m, 1H), 4.82-4.94 (m, 2H), 2.84 (d, *J*=4.6 Hz, 3H), 2.09-2.33 (m, 2H), 0.77 (t, *J*=7.3 Hz, 3H). *(S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(63)**:* (*S*)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **60** (100 mg, 0.321 mmol) and (1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-amine hydrochloride (52 mg, 0.385 mmol) were reacted in DMF (2

mL) according to **general procedure A**. The crude product was purified with silica chromatography eluting with 5-50% (25% EtOH/EtOAc)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **63** (131 mg, 0.317 mmol, 99% yield) as a white solid. LCMS (formic, ES^+) t_R = 0.90 min, *m/z* = 393.4; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.25 (d, *J*=2.0 Hz, 1H), 7.74 (d, *J*=2.2 Hz, 1H), 7.24-7.40 (m, 5H), 4.84 (d, *J*=9.0 Hz, 1H), 4.73 (d, *J*=9.0 Hz, 1H), 3.85 (d, *J*=8.3 Hz, 2H), 3.63 (dd, *J*=8.3, 2.7 Hz, 2H), 2.85 (s, 3H), 2.57 (t, *J*=2.7 Hz, 1H), 1.89 (q, *J*=2.4 Hz, 2H), 1.77 (s, 3H); *Amide NH not visible.*

(S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-(hydroxymethyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide ***(64)****:* (*S*)-3-(Hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **61** (50 mg, 0.153 mmol), and (1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-amine (21 mg, 0.214 mmol) were dissolved in DMF (2 mL) and reacted according to **general procedure A**. The crude product was purified by formic MDAP. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-(hydroxymethyl)-N^7-methyl-3-phenyl-2,3-dihydrobenzo furan-5,7-dicarboxamide **64** (9 mg, 0.022 mmol, 29% yield) as a white solid. LCMS (formic, ES^+) t_R = 0.76 min, *m/z* = 409.2; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.49 (d, *J*=4.3 Hz, 1H), 8.26 (d, *J*=2.0 Hz, 1H), 7.86 (d, *J*=4.8 Hz, 1H), 7.82 (d, *J*=2.0 Hz, 1H), 7.31-7.40 (m, 4H), 7.28 (d, *J*=6.5 Hz, 1H), 5.28 (s, 1H), 5.02 (d, *J*=9.0 Hz, 1H), 4.82 (d, *J*=9.3 Hz, 1H), 3.99 (dd, *J*=10.4, 4.9 Hz, 2H), 3.86 (d, *J*=8.5 Hz, 2H), 3.64 (dd, *J*=8.4, 2.6 Hz, 2H), 2.85 (d, *J*=4.5 Hz, 3H), 2.57-2.62 (m, 1H), 1.90 (q, *J*=2.7 Hz, 2H). *(S)-N^5-((1R,5S,6r)-3-Oxabicyclo[3.1.0]hexan-6-yl)-3-ethyl-N^7-methyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide* ***(65)****:* (*S*)-3-Ethyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **62** (76 mg, 0.234 mmol) and (1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-amine, hydrochloride (38 mg, 0.280 mmol) were reacted in DMF (2 mL) according to **general**

procedure A. The crude product was purified by silica chromatography, eluting with 5-50% (25% EtOAc:EtOH)/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hexan-6-yl)-3-ethyl-N^7-methyl-3-phenyl-2,3-dihydrobenzo furan-5,7-dicarboxamide **65** (96 mg, 0.225 mmol, 96% yield) as a white solid. LCMS (formic, ES^+) t_R = 0.93 min, *m/z* = 407.6; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.49 (d, *J*=4.2 Hz, 1H), 8.24 (d, *J*=2.0 Hz, 1H), 7.85 (d, *J*=4.6 Hz, 1H), 7.80 (d, *J*=2.0 Hz, 1H), 7.33-7.40 (m, 4H), 7.23-7.30 (m, 1H), 4.83 (d, *J*=2.4 Hz, 2H), 3.85 (d, *J*=8.3 Hz, 2H), 3.60-3.66 (m, 2H), 2.84 (d, *J*=4.6 Hz, 3H), 2.58 (d, *J*=4.2 Hz, 1H), 2.07-2.31 (m, 2H), 1.86-1.92 (m, 2H), 0.78 (t, *J*=7.3 Hz, 3H). *(S)-N^5,N^7,3-trimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**66**):* (*S*)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **60** (31 mg, 0.100 mmol) was reacted with methanamine (4 mg, 0.120 mmol) in DMF (0.5 mL) according to **general procedure A**. The crude product was purified by formic MDAP. Pure fractions were concentrated in *vacuo* to afford (*S*)-N^5,N^7,3-trimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **66** (24 mg, 0.075 mmol, 67% yield) as a cream solid. LCMS (formic, ES^+) t_R = 0.86 min, *m/z* = 325.4; ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 8.39 (q, *J*=4.8 Hz, 1H), 8.25 (d, *J*=1.8 Hz, 1H), 7.87 (q, *J*=4.8 Hz, 1H), 7.74 (d, *J*=1.8 Hz, 1H), 7.30-7.39 (m, 4H), 7.23-7.28 (m, 1H), 4.85 (d, *J*=8.8 Hz, 1H), 4.73 (d, *J*=9.2 Hz, 1H), 2.85 (d, *J*=4.8 Hz, 3H), 2.75 (d, *J*=4.4 Hz, 3H), 1.77 (s, 3H). *(S)-N^5-Cyclopropyl-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**67**):* (*S*)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **60** (31 mg, 0.100 mmol) was reacted with cyclopropanamine (7 mg, 0.120 mmol) in DMF (0.5 mL) according to **general procedure A**. The crude product was purified by formic MDAP. The pure fractions were concentrated in *vacuo* to afford (*S*)-N^5-cyclopropyl-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **67** (32 mg, 0.092 mmol, 82% yield) as a cream solid. LCMS (formic, ES^+) t_R = 0.94 min, *m/z* = 350.3; ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm)

8.37-8.44 (m, 1H), 8.24 (d, *J*=2.2 Hz, 1H), 7.87 (q, *J*=4.8 Hz, 1H), 7.73 (d, *J*=1.8 Hz, 1H), 7.34-7.38 (m, 2H), 7.28-7.32 (m, 2H), 7.24-7.28 (m, 1H), 4.83 (d, *J*=8.8 Hz, 1H), 4.72 (d, *J*=9.2 Hz, 1H), 2.84 (d, *J*=4.8 Hz, 3H), 2.82 (td, *J*=7.3, 3.7 Hz, 1H), 1.77 (s, 3H). *(S)-N^7,3-dimethyl-N^5-((1S,2S)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**68**):* (*S*)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzofuran-5-carboxylic acid **60** (31 mg, 0.100 mmol) was reacted with (1*S*,2*S*)-2-methylcyclopropanamine (9 mg, 0.120 mmol) in DMF (0.5 mL) according to **general procedure A**. The crude product was purified by formic MDAP. The pure fractions were concentrated in *vacuo* to afford (*S*)-N^7,3-dimethyl-N^5-((1*S*,2*S*)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **68** (24 mg, 0.067 mmol, 60% yield) as a cream solid. LCMS (formic, ES^+) t_R = 1.02 min, *m/z* = 365.3; ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 8.35-8.41 (m, 1H), 8.23 (d, *J*=2.2 Hz, 1H), 7.87 (q, *J*=4.6 Hz, 1H), 7.73 (d, *J*=1.8 Hz, 1H), 7.33-7.38 (m, 2H), 7.28-7.31 (m, 2H), 7.23-7.28 (m, 1H), 4.83 (d, *J*=9.2 Hz, 1H), 4.72 (d, *J*=9.2 Hz, 1H), 2.84 (d, *J*=4.8 Hz, 3H), 2.51-2.53 (m, 1H), 1.73-1.79 (m, 3H), 1.02-1.08 (m, 3H), 0.92 (dtd, *J*=9.1, 6.1, 3.3 Hz, 1H), 0.72 (dt, *J*=8.9, 4.5 Hz, 1H), 0.45 (dt, *J*=7.7, 5.3 Hz, 1H). *(S)-3-(Hydroxymethyl)-N^7-methyl-N^5-((1S,2S)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**69**):* (*S*)-3-(Hydroxymethyl)-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzo furan-5-carboxylic acid **61** (420 mg, 1.283 mmol), and (1*S*,2*S*)-2-methylcyclopropan-1-amine hydrochloride (166 mg, 1.540 mmol) were reacted in DMF (10 mL) according to **general procedure A**. The crude product was purified using silica chromatography eluting with 0-10% MeOH/CH_2Cl_2. The pure fractions were concentrated *in vacuo* to afford (*S*)-3-(hydroxymethyl)-N^7-methyl-N^5-((1*S*,2*S*)-2-methylcyclopropyl)-3-phenyl-2,3-dihydrobenzo furan-5,7-dicarboxamide **69** (380 mg, 0.999 mmol, 78% yield) as a white solid. LCMS (formic, ES^+) t_R = 0.86 min, *m/z* = 381.3; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.40 (d, *J*=4.2 Hz, 1H), 8.23 (d, *J*=2.0 Hz, 1H), 7.77-7.87 (m, 2H), 7.30-7.40 (m, 4H), 7.22-7.29 (m, 1H), 5.24 (br. s., 1H), 5.00 (d, *J*=9.3 Hz, 1H), 4.81 (d,

J=9.0 Hz, 1H), 3.92-4.04 (m, 2H), 2.84 (d, *J*=4.6 Hz, 3H), 2.52-2.56 (m, 1H), 1.06 (d, *J*=6.1 Hz, 3H), 0.93 (ddt, *J*=9.1, 6.1, 2.9 Hz, 1H), 0.69-0.76 (m, 1H), 0.46 (dt, *J*=7.5, 5.3 Hz, 1H). *(S)-N^5-((1r,4S)-4-Hydroxycyclohexyl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**70**):* (*S*)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzo furan-5-carboxylic acid **60** (31 mg, 0.100 mmol) was reacted with (1*r*,4*r*)-4-aminocyclohexanol (14 mg, 0.120 mmol) in DMF (0.5 mL) according to **general procedure A**. The crude product was purified by formic MDAP. The pure fractions were concentrated in *vacuo* to afford (*S*)-N^5-((1*r*,4*S*)-4-hydroxycyclohexyl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **71** (41 mg, 0.100 mmol, 90% yield) as a cream solid. LCMS (formic, ES^+) t_R = 0.87 min, *m/z* = 409.2; ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 8.25 (d, *J*=2.2 Hz, 1H), 8.15 (d, *J*=8.1 Hz, 1H), 7.87 (q, *J*=4.6 Hz, 1H), 7.74 (d, *J*=2.2 Hz, 1H), 7.33-7.38 (m, 2H), 7.29-7.32 (m, 2H), 7.24-7.28 (m, 1H), 4.82 (d, *J*=9.2 Hz, 1H), 4.71 (d, *J*=8.8 Hz, 1H), 3.70 (td, *J*=7.8, 3.9 Hz, 1H), 3.35-3.41 (m, 1H), 2.84 (d, *J*=4.8 Hz, 3H), 1.84 (dt, *J*=13.3, 2.2 Hz, 2H), 1.74-1.81 (m, 5H), 1.31-1.40 (m, 2H), 1.17-1.27 (m, 2H). *(3S)-N^5-((1R,5S,6r)-3-((tert-Butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide, (**101**) (1:3) mixture of diastereomers:* (*S*)-3-Methyl-7-(methylcarbamoyl)-3-phenyl-2,3-dihydrobenzo furan-5-carboxylic acid **60** (150 mg, 0.482 mmol) and (1R,5S,6r)-3-((tert-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-6-amine (131 mg, 0.578 mmol) were dissolved in CH_2Cl_2 (4 mL) according to **general procedure A**. The crude product was purified by silica chromatography eluting with 0-50% EtOAc/cyclohexane. The pure fractions were concentrated *in vacuo* to afford (3*S*)-N^5-((1*R*,5*S*,6*r*)-3-((tert-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phen yl-2,3-dihydrobenzofuran-5,7-dicarboxamide **100** (249 mg, 0.478 mmol, 99% yield) as a (1:3) mixture of *cis* and *trans* diastereomers. LCMS (formic, ES^+) t_R = 0.75 min; *m/z* = 409.2; ^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm) 8.30 [A] (d, *J*=3.4 Hz, 0.25H), 8.24 [B] (d, *J*=4.2 Hz,

0.75H), 8.19–8.22 (m, 1H), 7.82-7.89 (m, 1H), 7.73 [B] (d, *J*=2.0 Hz, 0.75H), 7.71 [A] (d, *J*=2.0, 0.25H), 7.22-7.39 (m, 5H), 4.83 (d, *J*=9.0 Hz, 1H), 4.71 (d, *J*=9.0 Hz, 1H), 4.26-4.31 [B] (m, 0.75H), 3.97-4.02 [A] (m, 0.25H), 2.99-3.03 (m, 1H), 2.84 (d, *J*=4.6 Hz, 3H), 1.99-2.12 (m, 2H), 1.76 (s, 3H), 1.68 (d, *J*=13.7 Hz, 2H), 1.42-1.48 (m, 2H), 0.86 [B] (s, 6.75H), 0.85 [A] (s, 2.25H), 0.03 (s, 6H). *(S)-N^5-((1R,3R,5S,6r)-3-Hydroxybicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**71**) and (S)-N^5-((1R,3S,5S,6r)-3-hydroxybicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**72**):* (3*S*)-N^5-((1*R*,5*S*,6*r*)-3-((*tert*-Butyldimethylsilyl)oxy)bicyclo [3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **100** (230 mg, 0.442 mmol) was taken up in HCl (4 M in 1,4-dioxane, 1.10 mL, 4.42 mmol) and stirred at rt for 1 h. The reaction was concentrated *in vacuo* the afford the crude product. The crude product was purified by formic MDAP. The pure fractions were concentrated *in vacuo* to afford (*S*)-N^5-((1*R*,3*R*,5*S*,6*r*)-3-hydroxybicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **71** (29 mg, 0.071 mmol, 16% yield) and (*S*)-N^5-((1*R*,3*S*,5*S*,6*r*)-3-hydroxybicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **72** (93 mg, 0.229 mmol, 52% yield) as white solids. (*S*)-N^5-((1*R*,3*R*,5*S*,6*r*)-3-hydroxybicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide (**71**): LCMS (formic, ES^+) t_R = 0.92 min, *m/z* = 407.3; HRMS ($C_{24}H_{26}N_2O_4$): $[M+H]^+$ calculated 407.1971, found 407.1972; ^{1}H NMR (DMSO-d_6, 400M Hz): δ (ppm) 8.29 (d, *J*=3.9 Hz, 1H), 8.21 (d, *J*=2.0 Hz, 1H), 7.86 (q, *J*=4.6 Hz, 1H), 7.71 (d, *J*=2.0 Hz, 1H), 7.22-7.39 (m, 5H), 4.83 (d, *J*=9.0 Hz, 1H), 4.71 (d, *J*=9.0 Hz, 1H), 4.56 (d, *J*=5.4 Hz, 1H), 3.78-3.87 (m, 1H), 2.84 (d, *J*=4.6 Hz, 3H), 2.43-2.47 (m, 1H), 2.03 (dd, *J*=12.5, 7.1 Hz, 2H), 1.76 (s, 3H), 1.60 (ddd, *J*=12.4, 7.9, 4.4 Hz, 2H), 1.36-1.46 (m, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 166.4, 164.2, 159.2, 146.1, 137.5, 129.2, 129.0, 128.1, 127.2, 126.6, 126.3, 116.9, 87.3, 69.9, 36.6, 32.9, 26.7, 26.2, 23.6, 23.4; m.p. 137.9 – 141.3 °C; IR ν_{max} (cm^{-1}) 3300, 1637, 1534, 840, 699. (*S*)-N^5-((1*R*,3*S*,5*S*,6*r*)-3-

Hydroxybicyclo[3.1.0]hexan-6-yl)-N^7,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-5,7-dicarboxamide **(72)**: LCMS (formic, ES^+) t_R = 0.90 min, *m/z* = 407.6; ^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm) 8.22 (d, *J*=2.2 Hz, 2H), 7.86 (q, *J*=4.6 Hz, 1H), 7.72 (d, *J*=2.0 Hz, 1H), 7.21-7.39 (m, 5H), 4.83 (d, *J*=9.0 Hz, 1H), 4.71 (d, *J*=9.0 Hz, 1H), 4.17 (t, *J*=6.2 Hz, 1H), 3.02 (dt, *J*=4.5, 2.3 Hz, 1H), 2.84 (d, *J*=4.6 Hz, 3H), 1.90-2.04 (m, 2H), 1.70 (d, *J*=13.7 Hz, 2H), 1.36-1.49 (m, 2H); *Alcohol OH not visible*.

BRD4 Mutant TR-FRET Assay[38]

Tandem bromodomains of 6His-Thr-BRD4(1−477) were expressed, with an appropriate mutation in BD2 (Y390A) to monitor compound binding to BD1, or in BD1 (97A) to monitor compound binding to BD2. Analogous Y→A mutants were used to measure binding to the other BET bromodomains: 6His-Thr-BRD2 (1−473 Y386A or Y113A), 6His-Thr-BRD3 (1−435 Y348A or Y73A), 6His-FLAG-Tev-BRDT (1−397 Y309A or Y66A). The AlexaFluor 647 labeled BET bromodomain ligand was prepared as follows: To a solution of AlexaFluor 647 hydroxysuccinimide ester in DMF was added a 1.8-fold excess of N-(5-aminopentyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]-diazepin-4-yl)acetamide, also in DMF, and when thoroughly mixed, the solution was basified by the addition of a 3-fold excess of diisopropylethylamine. Reaction progress was followed by electrospray LC/MS, and when judged complete, the product was isolated and purified by reversed-phase C18 HPLC. The final compound was characterized by mass spectroscopy and analytical reversed-phase HPLC.

Compounds were titrated from 10 mM in 100% DMSO and 50 nL transferred to a low volume black 384 well micro titre plate using a Labcyte Echo 555. A Thermo Scientific Multidrop Combi was used to dispense 5 μL of 20 nM protein in an assay buffer of 50 mM HEPES, 150 mM NaCl, 5% glycerol, 1 mM DTT and 1 mM CHAPS, pH 7.4, and in the presence of 100 nM fluorescent ligand (~K_d concentration for the interaction between BRD4

BD1 and ligand). After equilibrating for 30 min in the dark at rt, the bromodomain protein:fluorescent ligand interaction was detected using TR-FRET following a 5 µL addition of 3 nM europium chelate labelled anti-6His antibody (Perkin Elmer, W1024, AD0111) in assay buffer. Time resolved fluorescence (TRF) was then detected on a TRF laser equipped Perkin Elmer Envision multimode plate reader (excitation = 337 nm; emission 1 = 615 nm; emission 2 = 665 nm; dual wavelength bias dichroic = 400 nm, 630 nm). TR-FRET ratio was calculated using the following equation: Ratio = ((Acceptor fluorescence at 665 nm) / (Donor fluorescence at 615 nm)) * 1000. TR-FRET ratio data were normalised to high (DMSO) and low (compound control derivative of I-BET762) controls and IC_{50} values determined for each of the compounds tested by fitting the fluorescence ratio data to a four parameter model:

$$\mathbf{y = A + (B - A)/(1 + (10\text{^}c/x)\text{^}D\ )}$$

where 'a' is the minimum, 'b' is the Hill slope, 'c' is the IC_{50} and 'd' is the maximum.

Physicochemical Properties

Permeability across a lipid membrane, chromatographic logD at pH 7.4, and CLND solubility by precipitation into saline were measured using published protocols.[42, 66-68]

FaSSIF solubility

Compounds were dissolved in DMSO at 2.5 mg/mL and then diluted in Fast State Simulated Intestinal Fluid (FaSSIF pH 6.5) at 125 µg/mL (final DMSO concentration is 5%). After 16 h of incubation at 25 °C, the suspension was filtered. The concentration of the compound was determined by a fast HPLC gradient. The ratio of the peak areas obtained from the standards and the sample filtrate was used to calculate the solubility of the compound.

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol.

Intrinsic Clearance (CL_{int}) Measurements

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol.

Hepatocyte Intrinsic Clearance data were determined by Cyprotex UK. Test compound (0.5 µM) was incubated with cryopreserved hepatocytes in suspension. Samples were removed at 6 time points over the course of a 60 min (rat) or 120 min (human & dog) experiment and test compound analyzed by LC-MS/MS. Cryopreserved pooled hepatocytes were purchased from a reputable commercial supplier and stored in liquid nitrogen prior to use. Williams E media supplemented with 2 mM L-glutamine and 25 mM HEPES and test compound (final substrate concentration 0.5 µM; final DMSO concentration 0.25%) was pre-incubated at 37 °C prior to the addition of a suspension of cryopreserved hepatocytes (final cell density 0.5 x 10^6 viable cells/mL in Williams E media supplemented with 2 mM L-glutamine and 25 mM HEPES) to initiate the reaction. The final incubation volume was 500 µL. The reactions were stopped by transferring 50 µL of incubate to 100 µL acetonitrile at the appropriate time points. The termination plates were centrifuged at 2500 rpm at 4 °C for 30 min to precipitate the protein. The remaining incubate (200 µL) was crashed with 400 µL acetonitrile at the end of the incubation. Following protein precipitation, the sample supernatants were combined in cassettes of up to 4 compounds and analyzed using Cyprotex generic LC-MS/MS conditions.

Intrinsic Clearance (CL_{int}) Data Analysis

From a plot of ln peak area ratio (compound peak area/internal standard peak area) against time, the gradient of the line was determined. Subsequently, half-life ($t_{½}$) and intrinsic clearance (CL_{int}) were calculated using the equations below:

Elimination rate constant (k) = (- gradient)

Half-life ($t_{½}$)(min) = $\frac{0.693}{k}$

Intrinsic clearance (CL_{int})(µL/min/million cells) = $\frac{V \times 0.693}{t_{½}}$

where V = Incubation volume (µL)/Number of cells

Fraction Unbound in Blood

Control blood from Wistar Han Rat and Beagle Dog were obtained on the day of experimentation from in house GSK stock animals. The fraction unbound in blood of each species was determined using rapid equilibrium dialysis technology (RED plate (Linden Bioscience, Woburn, MA) at a concentration of 200 & 1000 ng/mL. Blood was dialyzed against phosphate buffered saline solution by incubating the dialysis units at 37 °C for 4 h. Following incubation aliquots of blood and buffer were matrix matched prior to analysis by LC−MS/MS. The unbound fraction was determined using the peak area ratios in buffer and in blood as a mean value of the two concentrations investigated.

***in vivo* DMPK Studies**

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.

For all *in vivo* studies, the temperature and humidity were nominally maintained at 21 °C ± 2 °C and 55% ± 10%, respectively. The diet for rodents was 5LF2 Eurodent Diet 14% (PMI Labdiet, Richmond, IN) and for dogs was Harlan Teklad 2021C (HarlanTeklad, Madison, WI). There were no known contaminants in the diet or water at concentrations that could interfere with the outcome of the studies.

Rat surgical preparation for IV n=1 PK study

Male Wistar Han rats (supplied by Charles River UK Ltd.) were surgically prepared at GSK with implanted cannulae in the femoral vein (for drug administration) and jugular vein (for blood sampling). The rats received Cefuroxime (116 mg/kg sc) and carprofen (7.5 mg/kg sc) as a preoperative antibiotic and analgesic, respectively. The rats were allowed to recover for at least 2 days prior to dosing and had free access to food and water throughout.

Rat IV n=1 PK study

Surgically prepared male Wistar Han Rats received a 1 h intravenous (iv) infusion of Compound 25 as a discrete dose, formulated in DMSO and 10% (w/v) Kleptose HPB in saline aq (2%:98% (v/v)) at a concentration of 0.2 mg/mL to achieve a target dose of 1 mg/kg. Serial blood samples (25 μL) were collected predose and up to 7 h after the start of the iv infusion. Diluted blood samples were analyzed for parent compound using a specific LC−MS/MS assay (LLQ = 1 ng/mL). At the end of the study the rats were euthanized by a Schedule 1 technique.

Rat PO n=3 PK study

3 naïve Male Wistar Han Rats with no surgical preparation received an oral gavage administration of Compound 25 as a discrete dose, suspended in 1% (w/v) methylcellulose aq

at a concentration of 0.6 mg/mL to achieve a target dose of 3 mg/kg. Serial blood samples (25 μL) were collected via temporary tail vein cannulation up to 7 h after oral dosing and additional blood sampling via tail vein venepuncture up to 24 h after oral dosing. Diluted blood samples were analyzed for parent compound using a specific LC−MS/MS assay (LLQ = 1 ng/mL). At the end of the study the rats were euthanized by a Schedule 1 technique.

Rat IV PO n=1 crossover PK study

These studies were conducted at Charles River USA as a crossover design over two dosing occasions, with 3 days between dose administrations in 1 surgically prepared male Wistar Han Rat per compound. On the first dosing occasion, a rat received a discrete 1 h intravenous (iv) infusion of Compound of interest formulated in DMSO and 10% (w/v) Kleptose HPB in saline aq (2%:98% (v/v)) at a concentration of 0.2 mg/mL to achieve a target dose of 1 mg/kg. On the second dosing occasion, the same rat was administered with the same Compound of interest suspended in 1% (w/v) methylcellulose 400 aq at a concentration of 0.6 mg/mL orally, at a target dose of 3 mg/kg. Serial blood samples (75 μL) were collected predose and up to 24 h after the start of the iv infusion and after oral dosing. Diluted blood samples were analyzed using a specific LC−MS/MS assay (LLQ = 2 ng/mL). At the end of the study the rats were euthanized by a Schedule 1 technique.

Dog PK Study

One healthy, laboratory-bred, male Beagle dog (supplied by Harlan Laboratories, U.K.) was used. The dog was fasted overnight prior to each dose administration and fed approximately 4 h after the start of dosing and had free access to water throughout the study. This study was conducted as a crossover design, with 7 days between dose administrations. On the first dosing occasion, the dog received a 1 h intravenous (iv) infusion of **71** formulated in DMSO and 10%

(w/v) Kleptose HPB in saline aq (2%:98% (v/v)), at a concentration of 0.1 mg/mL to achieve a target dose of 0.5 mg/kg. On a subsequent dosing occasion, the same dog was administered with **71**, suspended in 1% (w/v) methylcellulose aq at a concentration of 0.1 mg/mL to achieve a target dose of 1 mg/kg. A temporary cannula was inserted into the cephalic vein from which serial blood samples (50 μL) were collected predose and up to 24 h after the start of dosing. After collection of the 2 h time point the cannula was removed and later time points were taken via direct venepuncture of the jugular vein. Diluted blood samples were analyzed for parent drug concentration using a specific LC−MS/MS assay (LLQ = 1 ng/mL). At the end of each study the dog was returned to the colony.

Blood Sample Analysis

Diluted blood samples (1:1 with water) were extracted using protein precipitation with acetonitrile containing an analytical internal standard. An aliquot of the supernatant was analyzed by reverse phase LC−MS/MS using a heat assisted electrospray interface in positive ion mode. Samples were assayed against calibration standards prepared in control blood.

PK Data Analysis from PK Studies

PK parameters were obtained from the blood concentration−time profiles using noncompartmental analysis with WinNonlin Professional 6.3 (Pharsight, Mountain View, CA).

hWB MCP-1 Assay

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol.

Compounds to be tested were diluted in 100% DMSO to give a range of appropriate concentrations at 140x the required final assay concentration, of which 1 μL was added to a 96

well tissue culture plate. 130 µL of human whole blood, collected into sodium heparin anticoagulant, (1 unit/mL final) was added to each well and plates were incubated at 37°C (5% C02) for 30 min before the addition of 10 µL of 2.8 µg/mL LPS (Salmonella Typhosa), diluted in complete RPMI 1640 (final concentration 200 ng/mL), to give a total volume of 140 µL per well. After further incubation for 24 h at 37 °C, 140 µL of PBS was added to each well. The plates were sealed, shaken for 10 min and then centrifuged (2500 rpm x 10 min). 100 µL of the supernatant was removed and MCP-1 levels assayed immediately by immunoassay (MesoScale Discovery technology).

PBMC MCP-1 Assay:

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol. Human PBMCs (cryopreserved in 90% serum, 10% DMSO) were thawed and 5 mL warm media per 1 mL cells was added dropwise, and centrifuged at 1600 rpm for 5 min. The supernatant was decanted and the pellet was resuspended in 10 mL pre-warmed assay medium (RPMI-1640, Foetal Calf Serum (50 mL in 500 mL), Penicillin/Streptomycin (5 mL to 500 mL), L-Glutamine 200 mM (5 mL to 500 mL)). The cells were counted on a CEDEX cell counter and diluted to a final conc. of 0.32 x 10^6 (40000 cells)/mL. Compounds to be tested were diluted in 100% DMSO to give a range of appropriate concentrations. 130 µL of the cell suspension was added to each well of the compound plates containing 0.5 µL of compound in each well and incubated at 37°C, 5% CO2 for 30 min. After 30 min 10 µL of 14 ng/mL LPS (Salmonella Typhosa), diluted in complete RPMI 1640, was added to each well (final = 1ng/mL) (total volume per well of 140.5 µL). The plates were incubated at 37 degrees, 5% CO2 for 24 hours. 20 µL of supernatant was transferred to an MCP-1 coated 96 well MSD plate and incubated for 1-2 hr on a plate shaker. 20 µL 1X sulfo-TAG antibody (final conc 1 µg) was added to each well and the plates

were incubated for 1-2 hr at room temperature whilst shaking. The plates were washed 3 times using a plate washer and 150 μL MSD read buffer P/T (2X) was added to the plate. The plates were read on the MSD reader to determine MCP-1 levels by immunoassay (MesoScale Discovery technology).

ASSOCIATED CONTENT

DiscoverX BROMOscan® Bromodomain Profiling of **71**, comparison of CAD and CLND solubility measurements, sequence alignment and differences of BET proteins, X-ray crystallographic data, synthesis of (1*R*,5*S*,6*r*)-3-((tert-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-6-amine and LCMS and NMR Spectra for **71** (PDF)

Molecular formula strings (CSV)

PDB IDs

PDB ID of New Crystal (X-ray) Structures: 7OE8 (**(*S*)-44**) and 7OE9 (**71**). Authors will release the unpublished PDB ID, atomic coordinates and experimental data upon article publication.

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ABBREVIATIONS

AMP, artificial membrane permeability; BD1, first (N-terminal) bromodomain; BD2, second (C-terminal) bromodomain; BET, bromodomain and extra terminal domain; BRD, bromodomain; BRD2/3/4, bromodomain-containing protein 2/3/4; BRDT, bromodomain,

testes specific; CAD, charged aerosol detection; ChromLogD, Chromatographic LogD; DBF, 2,3-dihydrobenzofuran; DMSO, dimethyl sulfoxide; FRET, fluorescence resonance energy transfer, HRMS, high-resolution mass spectra; IVC, *in vitro* clearance; KAc, acetylated lysine; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; MDAP, mass directed automatic purification; PK, pharmacokinetics; PMP, 1,2,2,6,6-pentamethylpiperidine; THP, tetrahydropyran; WB, whole blood; WPF, tryptophan-proline-phenylalanine.

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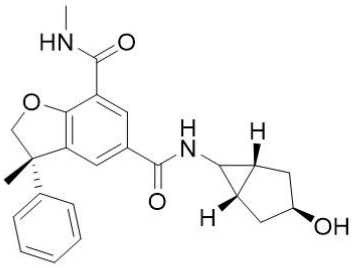
Table of Contents Graphic



GSK852

BRD4 BD2 pIC_{50} = 7.9

Fold selectivity = 1260x

FaSSIF >1000 µg mL ⇧

%F rat/dog = 32/64 ⇧