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Article

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Identification of Selective Dual ROCK1 and ROCK2 Inhibitors Using Structure Based Drug Design

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KEYWORDS Rho kinase, ROCK1, ROCK2, PKA, Kinase Inhibitor, Structure-based drug design.

ABSTRACT: A HTS campaign identified compound **1**, an excellent hit-like molecule to initiate medicinal chemistry efforts to optimize a dual ROCK1 and ROCK2 inhibitor. Substitution (2-Cl, 2-NH_2, 2-F, 3-F) of the pyridine hinge binding motif or replacement with pyrimidine afforded compounds with a clean CYP inhibition profile. Co-crystal structures of an early lead compound were obtained in PKA, ROCK1 and ROCK2. This provided critical structural information for medicinal chemistry to drive compound design. The structural data indicated the preferred configuration at the central benzylic carbon would be (R) and application of this information to compound design resulted in compound **16**. This compound was shown to be a potent and selective dual ROCK inhibitor in both enzyme and cell assays and efficacious in the retinal nerve fiber layer model after oral dosing. This tool compound has been made available through the AbbVie Compound Toolbox. Finally, the co-crystal structures also identified that aspartic acid residues 176 and 218 in ROCK2, which are glutamic acids in PKA, could be targeted as residues to drive both potency and kinome selectivity. Introduction of a piperidin-3-ylmethanamine group to the compound series resulted in compound **58**, a potent and selective dual ROCK inhibitor with excellent predicted drug-like properties.

INTRODUCTION

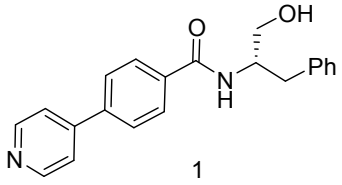
Rho-associated coiled-coil-containing protein kinase[1] is a serine/threonine protein kinase that is more commonly referred to simply as ROCK kinase. ROCK exists as two isoforms, ROCK1[2] (also known as ROKβ[3]) and ROCK2[2] (also known as ROKα[4]). In its activated form ROCK participates in numerous signaling mechanisms including the phosphorylation of myosin light chain,[5] the serine/threonine kinases Lim kinase 1 and 2,[6] adducin,[7] and ezrin/radixin/moesin protein complex.[8] This has resulted in ROCK inhibition being pursued as a possible therapeutic for multiple diseases,[9] most notably cerebral vasospasm,[10] glaucoma,[11] neurodegenerative diseases[12] and hypertension.[13,14] This interest has resulted in the discovery of multiple ATP-competitive ROCK inhibitors. For an excellent review of Rho

kinases and their therapeutic potential, see Feng,[15] which highlights the physiological and biological functions of rho kinases and the different chemical series that have been developed as ROCK inhibitors. These inhibitors deploy various groups for the critical interaction with the hinge region that joins the N- and C-terminal portions of the conserved protein kinase domain, including indazole,[16, 17, 18] aminofurazan,[19] pyridine,[20, 21] pyrazole,[22] and isoquinoline.[23, 24, 25]

Our interest was heightened by several publications demonstrating the effects of ROCK inhibitors in areas of immunology including, effects on histamine-induced airflow obstruction,[26] inhibition of pulmonary eosinophilia, bronchoconstriction and airway hyperresponsiveness[27] and anti-inflammatory activities.[28]

Encouraged by this we conducted a high-throughput screening (HTS) campaign to identify novel ROCK inhibitors. The HTS assay used ROCK2 enzyme (amino acids 11-552), with peptide substrate phosphorylation monitored via ^{33}P-labeled ATP. Approximately 700,000 compounds were screened, and >3,100 of these produced inhibition of ROCK2 in concentration response testing. Herein we report the discovery of an attractive hit series exemplified by compound 1 (Figure 1) and the subsequent structure-activity relationship studies guided by critical structural information. This ultimately resulted in the discovery of compound **58**, a highly potent inhibitor of both ROCK1 and ROCK2 with broad selectivity across the kinome.

RESULTS AND DISCUSSION



1

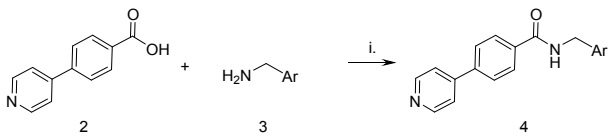
Mol wt	332
PSA	67
cLogP	2.7
ROCK2 BEI[29]	20.2

Figure 1. Structure of HTS hit compound 1

Over 3,000 active hits were identified from a HTS campaign and prioritized using hit-like criteria[29, 30, 31] and an affinity prediction plot.[32] After structure and purity confirmation by liquid chromatography mass spectrometry (LCMS) of the prioritized hits, compound **1** was selected for further investigation. In addition to the hit-like properties exhibited by compound **1**, it's synthetic tractability was also very appealing as it was afforded in just one step from 4-pyrid-4-ylbenzoic acid **2**, which was offered in gram quantity from Maybridge Chemical Co. Ltd[33] and available through Ryan Scientific.[34] This made it an ideal candidate for follow up with focused libraries in the centralized high-throughput chemistry group (HTC) at AbbVie. In addition there have been multiple reports on the successful development of ROCK inhibitors with pyridine as the hinge binding motif.[15, 21, 24, 35, 36, 37]

To expand the SAR for **1**, several libraries were produced by HTC. Using standard amide bond forming conditions, commercially available 4-pyrid-4-ylbenzoic acid **2** was reacted with various benzylamines **3** to afford the desired compounds with the general formula **4** (Specific compounds **5** - **15** shown in Table 1)

Scheme 1. Synthetic scheme for HTC library follow up on compound 1

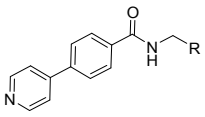


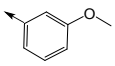
Reagents and conditions: i) PS-DCC, DIEA, DMA, microwave, 100 °C, 10 min.

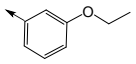
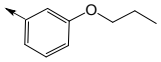
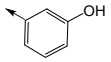
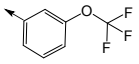
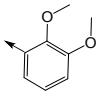
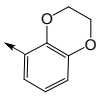
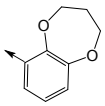
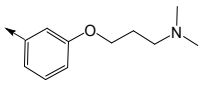
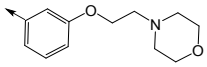
The compounds were evaluated in enzyme activity assays for both ROCK1 and ROCK2, with PKA used as a surrogate kinase to provide an early read on general kinome selectivity. Encouragingly, these libraries afforded immediate SAR and identified many potent ROCK1 and ROCK2 inhibitors. Compound **5** (Table 1) with the unsubstituted aryl ring resulted in a slight increase in the Binding Efficiency Index (BEI) relative to the HTS hit while having no selectivity versus PKA. Introduction of the 3-methoxy in compound **6** maintained the high BEI and increased the selectivity window over PKA

from 8 to almost 40-fold. Homologues **7** and **8** caused a slight drop in BEI while improving the selectivity against PKA to 65- and 85-fold respectively. The 3-hydroxy analogue **9** produced the highest BEI of nearly 28 while having a similar selectivity to the 3-methoxy compound. The larger 3-OCF_3 analogue **10** and the 2,3-dimethoxy compound **11** resulted in a loss of potency, with both compounds being >1 μM at all 3 kinases. Benzodioxolane compound **12**, the ring constrained version of **11**, had a similar potency and selectivity profile to compound **6**. Ring expansion to benzodioxepine **13** maintained the potency and BEI of the benzodioxolane at ROCK2 while affording a much larger window of selectivity over PKA of 130. The final two analogues were designed to investigate the tolerance for the introduction of solubilizing basic nitrogen groups to enable moderation of compound properties, should this be necessary later in the project. Unfortunately while dimethylamine **14** and morpholine **15** maintained the potency and selectivity profile of **6** this was with the penalty of a much reduced BEI of 18.1 and 15.8 respectively.

Table 1. SAR for compounds 5 - 15



Cpd	R	IC_{50} / μM at 100 μM ATP			ROCK2 BEI	PKA/ ROCK2 Selectivity
		ROCK1	ROCK2	PKA		
5		0.55±0.08	0.12±0.007	0.94±0.02	23.9	8
6		0.16±0.07	0.021±0.007	0.86±0.43	24.0	39

7		0.78	0.11	7.4	20.9	65
8		0.52	0.118	10	20.0	85
9		0.019	0.003	0.11	27.9	36
10		4.4	1.3	7.1	15.8	5
11		16.0±7.5	3.8±1.6	10	15.6	3
12		0.28	0.037	0.92	21.4	24
13		0.28	0.034	4.6	20.7	130
14		0.34	0.087	2.3	18.1	27
15		1.0	0.25	10	15.8	40

In addition, these compound libraries enabled profiling in our HT-ADME panel of assays (Table 2). This data showed that this series had good solubility, free fraction in plasma, and cellular permeability as assessed using PAMPA.[38] As predicted, compound **14** in which the dimethylamine was introduced, displayed the highest solubility and free fraction. However, it was evident that the major liability was their pan-inhibition of CYP enzymes, especially 3A4, predicting unwanted drug-drug interactions. It is

well known that 2,6-unsubstituted pyridines act as potent CYP inhibitors[39], and so modification of this motif would need to be addressed during the medicinal chemistry project.

Table 2. HT-ADME data for compounds 6, 7, 8, 12 and 14

Cpd	Solubility / μM	PPB / % free	PAMPA / 10^{-6} cms^{-1}	CYP inhibition IC_{50} / μM		
				2C9	2D6	3A4
6	-	98.0	20.2	0.12	0.97	0.85
7	9.9	99.6	18.1	0.48	0.24	0.08
8	9.3	99.7	16.2	0.26	0.09	0.08
12	33.9	97.2	14.9	2.04	0.20	0.08
14	63.3	76.8	2.47	16.0	0.08	2.00

While the pragmatic amide bond-forming libraries afforded useful SAR, this was a one-dimensional strategy, and a more rational design approach was desired as the project progressed. To this end several crystallography campaigns were initiated using compounds from the HTC libraries. At the time, there were no public crystal structures of ROCK2 and limited structures of ROCK1.[40] In previous studies we had successfully used PKA as a structure surrogate for ROCK kinases.[41] Initial structures in this study were therefore obtained in PKA. We and others (Akama[42] and Boland[43]) later succeeded in obtaining some structures in ROCK kinases. The structure of the early lead compound **12** was therefore obtained in PKA, ROCK1 and ROCK2, affording a great opportunity to compare and contrast the 3 active sites.

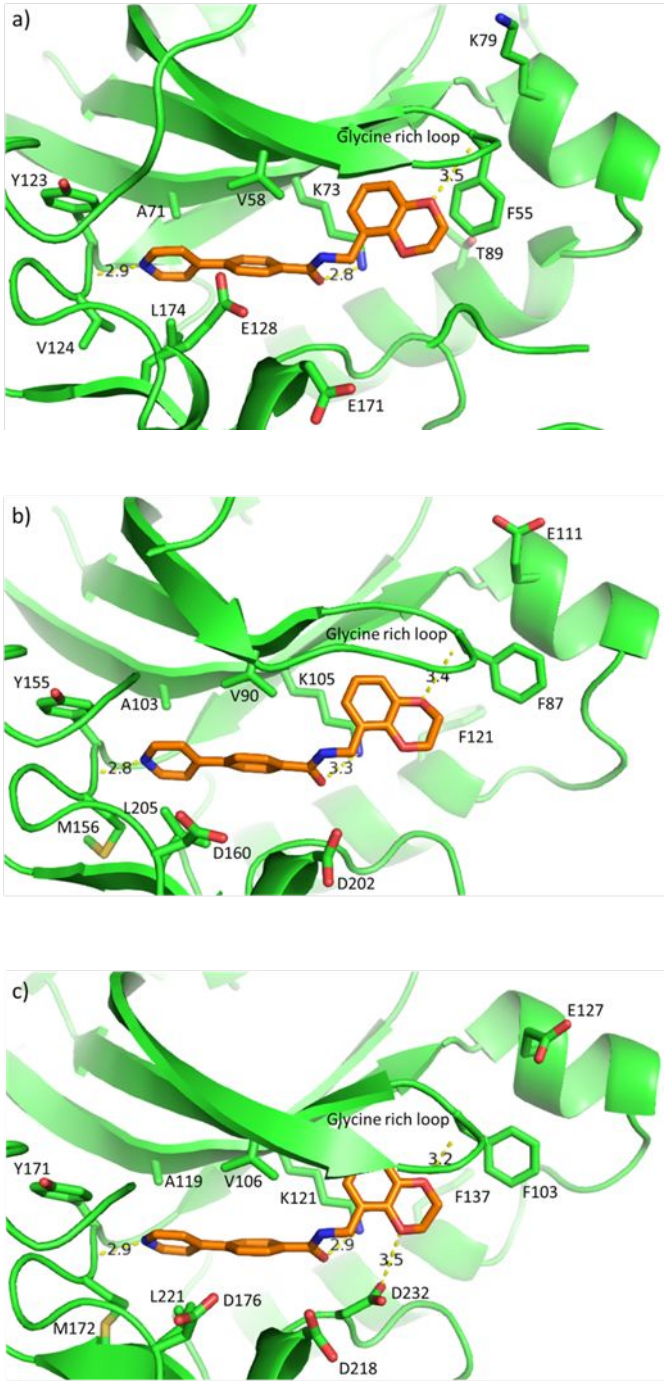


Figure 2. Crystal structures of compound 12 in a) PKA (PDB 6E9L), b) Rock 1 (PDB 6E9W) and c) Rock 2 (PDB 6ED6). All structures were obtained by co-crystallization.

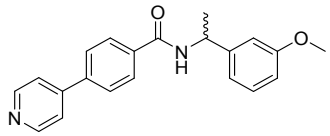
In PKA (Figure 2a) the hinge interaction is with the backbone nitrogen of valine 124. The hydrophobic core of the compound is sandwiched between alanine 71 and valine 58 above and leucine 174 below.

The carbonyl of the amide makes a hydrogen bond with lysine 73, while the benzodioxine group forms a large van der Waals surface interaction with the glycine rich loop which is situated above it. The backbone nitrogen for phenylalanine 55 is within 3.5 Å of an oxygen of the dioxine which is accommodated, but not likely to be a productive hydrogen bond. Phenylalanine 55 also stacks against the benzodioxine group. For ROCK1 (Figure 2b) the binding is very similar. Here binding to the hinge is with the backbone nitrogen of methionine 156. Again the residues of alanine 103 and valine 90 above and leucine 205 below sandwich the compound core. The amide carbonyl forms a hydrogen bond to lysine 105 and the benzodioxine ring system is forming an extensive van der Waals interaction with the glycine rich loop. Here, however, phenylalanine 87 is extended out from the glycine rich loop and does not stack against the benzodioxine group. Differences in the region of PKA Lys79 to Thr89 (ROCK 1 resi-dues Glu111 to Phe121, ROCK 2 Glu 127 to Phe 137) likely allows for differential dynamics of the gly-cine rich loop between PKA and ROCK1, in particular PKA Phe55 versus ROCK1 Phe87. The glycine rich loop and PKA Phe55 are more constrained than the glycine rich loop of either ROCK1 or ROCK2 and perhaps a driver of the observed selectivity of these compounds. For ROCK2 (Figure 2c) the bind-ing mode is very similar to ROCK1. The hinge interaction is with the nitrogen backbone of methionine 172. Again the amide carbonyl makes a hydrogen bond to lysine 121. Once again, the benzodioxine ring system is forming an extensive van der Waals interaction with the glycine rich loop. However, in the case of ROCK2, the glycine rich loop is even less constrained than that of ROCK1 with additional flex-ibility observed in the neighbouring region of E127 to F137 which can further contribute to potency dif-ferences observed between ROCK1 and ROCK2 allowing for more optimal van der Waals contacts be-tween the glycine rich loop substituents (benzodioxine in this case) in ROCK2 than ROCK1 or PKA.

Further in these structures there are acid residues nearby which could be reached by extension off the compound core. In ROCK1 and ROCK2 these are both aspartic acids (160 and 202 in ROCK1 and 176

and 218 in ROCK2). In PKA these residues are both glutamic acids (128 and 171) and so targeting these residues could provide some selectivity against PKA and AKT.

Table 3. SAR for compounds 16 and 17

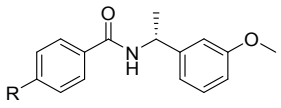


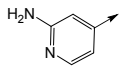
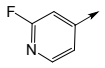
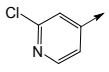
Cpd	Configuration	IC_{50} / μM at 100 μM ATP			Solubility / μM	PPB / % free	PAMPA / 10^{-6} cms^{-1}	CYP inhibition IC_{50} / μM		
		ROCK1	ROCK2	PKA				2C9	2D6	3A4
16	(R)	0.017±0.005	0.002±0.001	0.24±0.14	74.3	83.1	19.6	0.64	3.62	0.08
17	(S)	5.1±0.1	2.4±0.9	>10	-	-	-	-	-	-

The structural data also suggested that the preferred configuration at the benzylic carbon would be (R). To test this hypothesis compounds with both (R)-1-(3-methoxyphenyl)ethan-1-amine and (S)-1-(3-methoxyphenyl)ethan-1-amine were synthesized. Gratifyingly, the two methyl isomers **16** and **17** confirmed the structural hypothesis of the preferred configuration (Table 3). While compound **16** with the (R) configuration at the benzylic carbon was ten-fold more potent than the corresponding des-methyl analogue **6**, compound **17** with the (S)-configuration at the benzylic carbon was more than 3 logs less potent.

To address CYP inhibition, analogues incorporating substituted pyridine or heterocyclic replacements of pyridine were designed. To secure these, a straightforward 2-step synthetic route was followed. The desired pyridyl replacement was purchased as the 4-halogen analogue and reacted with 4-bromobenzoic acid under palladium catalyzed conditions. The resultant carboxylic acid was then coupled with the benzylamine component using standard conditions.

Table 4. SAR for compounds 18 - 25

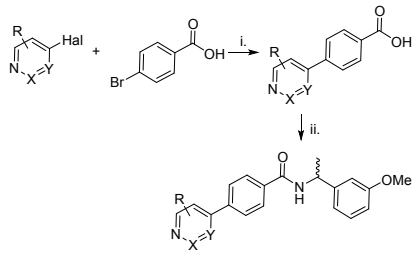


Cpd	R	IC_{50} / μM at 100 μM ATP			Solubility / μM	PPB / % free	PAMPA / 10^{-6} cms^{-1}	CYP inhibition IC_{50} / μM		
		ROCK1	ROCK2	PKA				2C9	2D6	3A4
18		0.11±0.01	0.012±0.001	0.34±0.02	21.7	88.3	-	>20	17.8	11.9
19		0.085±0.02	0.014±0.003	1.2±0.1	24.1	90.8	14.7	18.1	>20	>20
20		0.72±0.09	0.14±0.02	7.8	-	-	-	-	-	-
21		0.61±0.04	0.096±0.005	5.7±0.5	-	-	-	-	-	-

22		>10	>10	>10	-	-	-	-	-	-
23		0.011±0.001	0.001±0.001	0.058±0.005	68.4	93.0	21.4	7.7	-	6.4
24		0.21	0.027	2.0	73.5	72.0	19.7	6.0	11.6	19.6
25		9.4	0.70	-	50.5	66.9	12.5	>20	>20	16.7

Introduction of 2-amino and 2-fluoro in compounds **18** and **19** resulted in a slight loss in potency at ROCK2. However, these compounds now had a clean profile in the CYP inhibition assays. Introduction of 2-chloro and 2-methyl in compounds **20** and **21** caused a much larger reduction in potency, while the 2,6-dimethyl analogue **22** was inactive. As a result, none of these compounds were advanced to HT-ADME for screening. The most surprising result was 3-fluoro compound **23**. Despite the lack of groups ortho to the pyridine nitrogen to afford steric hindrance, this compound had much reduced inhibition of both CYP2C9 and CYP3A4 while being the most potent ROCK2 inhibitor yet identified. There was a concern over the lability and possible reactivity of the halo-pyridine analogues **19** and **20**. To address this both compounds were tested in our ALARM NMR assay[44] and shown to be non-reactive. The final two compounds were heterocyclic replacements of the pyridine. As expected pyrimidine **24** displayed an improved CYP inhibition profile which was accompanied by a moderate loss in potency at ROCK2. Disappointingly, introduction of the pyridazine in compound **25** was not tolerated and resulted in essentially complete loss of potency at ROCK2.

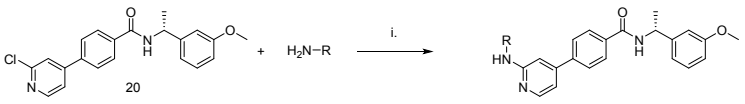
Scheme 2. Synthetic route towards (benzyloxy)benzene analogues 16 - 25



Reagents and Conditions: i) $Pd(PPh_3)_4$, Cs_2CO_3, DME, DIPEA, 80 °C, 72 h; ii) (R)- or (S)-1-(3-methoxyphenyl)ethan-1-amine, EDAC, HOBt, 0 °C to RT, O/N.

Compound **18** with the 2-aminopyridine hinge binding motif had shown good potency at ROCK2 and a clean CYP inhibition profile. Data from the crystal structures suggested that substitution off the amino group would be more tolerated in ROCK1 and ROCK2 than PKA. Such an approach could be used to access the extended hinge driving selectivity versus PKA and also enabling moderation of compound properties. To interrogate this hypothesis analogues were synthesized that introduced small alkyl and alkoxy groups off the 2-amino group. The desired compounds were obtained in one-step from the chloro-pyridine compound **20**. Treatment of compound **20** with the chosen amine under palladium catalyzed conditions afforded the desired compounds in 34 - 69% yield.

Scheme 3. Synthetic route towards (benzyloxy)benzene analogues 26 - 30

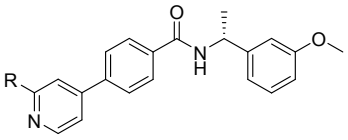


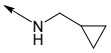
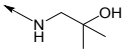
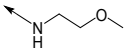
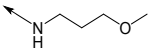
Reagents and Conditions: i) $Pd_2(dba)_3$, sodium 2-methylpropan-2-olate, ^{t}BuXPhos, dioxane, N_2, 80 °C, O/N.

The most striking SAR from this series was the oblation of activity at PKA with all the compounds having high micro molar IC_{50}s (Table 5). Both compound **26** with an ethyl substituent and compound **27** with the methylene cyclopropyl substituent maintained respectable potency at both ROCK1 and ROCK2 while displaying good selectivity versus PKA and only a small reduction in BEI. The

methylene propan-2-ol of compound **28** and the methoxy ethyl of compound **29** were less well tolerated at ROCK1 and ROCK2. Compound **30**, the homologue of **29**, with the methoxy propyl group had a similar overall profile to compounds **26** and **27**.

Table 5. SAR for compounds 26 - 30



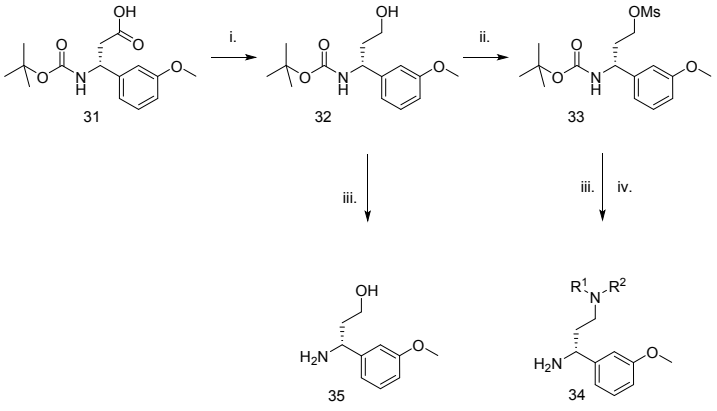
Cpd	R	IC_{50} / μM at 100 μM ATP			ROCK2 BEI
		ROCK1	ROCK2	PKA	
26		0.65±0.01	0.084±0.02	>10	18.8
27		0.40±0.04	0.068±0.002	8.0±0.3	17.8
28		2.4±0.4	0.39±0.05	>10	15.3
29		1.5±0.1	0.22±0.1	>10	16.4
30		0.58±0.05	0.075±0.02	>10	17.0

Having identified suitable motifs to ameliorate the CYP inhibition, the project now turned its focus to leveraging the structural data. This suggested that compounds with improved potency at ROCK1 and ROCK2 could be obtained through targeting an interaction with the aspartic acids on the side of the pocket (ROCK1 160, 202, ROCK2 176, 218).

While many enantiomerically pure α-substituted benzylamines are commercially available, the α-substituents are typically small alkyl or aryl in nature. As a result a flexible synthetic route that provided the opportunity to introduce hydrophilic groups in a late synthetic step was investigated. To reach the aspartic acids on the side of the pocket for ROCK1 and ROCK2, the structural data suggested that a two carbon linker from the benzylic carbon would be the optimal spacer length for incorporation of the amine. Fortunately many enantiomerically pure 3-amino-3-phenylpropanoic acids are available. (R)-3-Amino-3-(3-methoxyphenyl)propanoic acid was identified as the key starting material as this incorporated both the correct configuration at the benzylic carbon and the optimal 3-methoxyphenyl that had been identified in the previous SAR studies.

Treatment of boc-(R)-3-amino-3-(3-methoxy-phenyl)-propionic acid **31** with butyl chloroformate followed by subsequent reaction with sodium borohydride afforded alcohol **32**. Treatment with mesyl chloride efficiently afforded key intermediate **33** which was appropriately functionalized to enable the introduction of nitrogen containing motifs that were hydrophilic in character. Finally, treatment with HCl/dioxane afforded, after aqueous work-up or trituration, the desired enantiomerically pure benzylamines **34** with hydrophilic groups attached from the benzylic carbon in high chemical purity (Scheme 4). This synthetic route also provided a route to alcohol **35** which enabled additional analogues to be synthesized.

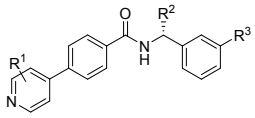
Scheme 4. Synthetic route towards key intermediates for compounds 36 - 44.

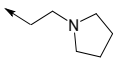
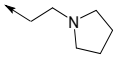


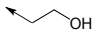
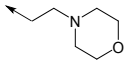
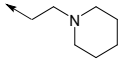
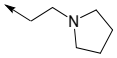
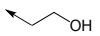
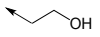
Reagents and Conditions: i) EDAC, HOBt, 0 °C - RT, O/N, 61%; ii) Na_2CO_3, DMSO, 110 °C, 34%; iii. $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, Dioxane/H_2O, 100 °C, 75%; iv. Chiral separation; v. TFA, DCM, 61%.

The first analogue compound **36** (Table 6) gave great encouragement being 15 times more potent than compound **5**, the corresponding compound without the ethyl pyrrolidine. Unfortunately this increase in potency was likely due to the preferred (R)-configuration rather than a beneficial interaction with ASP202 (ROCK1) and ASP218 (ROCK2). Compounds **37** and **38** maintained a very respectable BEI at ROCK2 and the pyrrolidine and hydroxyl may impart benefits to drug-like properties. However compounds **39** to **43** were all substantially less potent. The only compound of note was **43,** which both reinforced the positive view of the 3-fluoro pyridine motif identified in compound **23** and also showed good selectivity versus PKA. To confirm the importance of the benzylic carbon configuration as a potency driver, the (R)-methyl was incorporated with the propyloxy from compound **8** that drove selectivity versus PKA. This afforded compound **44** with an impressive BEI at ROCK2 of 21.7 in conjunction with over 600-fold selectivity versus PKA.

Table 6. SAR for compounds 36 - 44

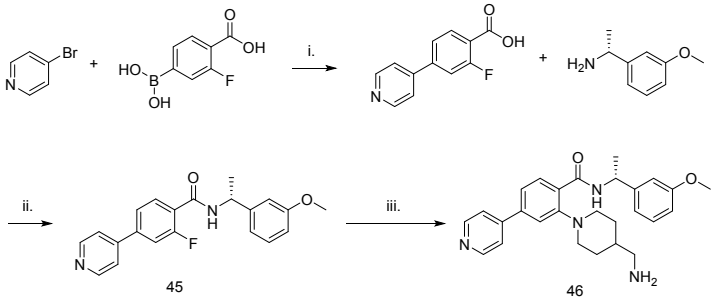


Cpd	R^1	R^2	R^3	IC_{50} / μM at 100 μM ATP			ROCK2 BEI	PKA/ ROCK2 Selectivity
				ROCK1	ROCK2	PKA		
36	H		H	0.046	0.008	0.065	21.1	9
37	H		OMe	0.014	0.003	0.095	20.7	37

38	H		OMe	0.039	0.006	0.36	22.7	60
39	2-F		OMe	0.139	0.032	1.0	16.7	32
40	2-F		O^{n}Pr	0.55	0.18	>10	14.2	56
41	2-F		F	0.24	0.082	0.33	16.8	4
42	2-F		O^{n}Pr	1.6	0.35	>10	15.8	28
43	3-F		O^{n}Pr	0.72	0.14	>10	16.8	290
44	H	Me	O^{n}Pr	0.16±0.07	0.015±0.012	>10	21.7	670

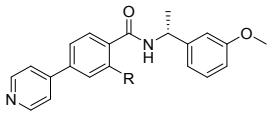
In an attempt to improve the selectivity profile, the next synthetic effort was directed at targeting an interaction with Asp160 (ROCK1) and Asp176 (ROCK2). Consideration of the structural data suggested that the central aryl ring afforded the preferred sites for attachment, optimally from the meta-position relative to the hinge binding pyridine. For compounds **46** – **49,** it was possible to effect the displacement of the 3-fluoro from the central aryl ring of **45** with the desired amine (Scheme 5).

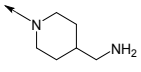
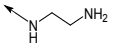
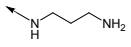
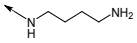
Scheme 5. Synthetic route towards compounds 46 - 49



Reagents and Conditions: i) $Pd(PPh_3)_4$, Cs_2CO_3, DME, DIPEA, 80 ºC, 72 h; ii) EDAC, HOBt, 0 ºC to RT, O/N. iii) N-ethyl-N-isopropylpropan-2-amine, diamine, DMSO, 110 ºC, O/N.

Table 7. SAR for compounds 46 - 49



Cpd	R	IC_{50} / μM at 100 μM ATP			PKA/ ROCK2 Selectivity
		ROCK1	ROCK2	PKA	
46		0.003±0.001	0.001±0.001	0.008±0.002	8
47		0.19	0.021	1.0	48
48		0.095	0.012	0.87	76
49		0.31±0.03	0.021±0.003	2.3±0.1	110

Inspection of the crystal structure suggested that introduction of a 3-5 atom linker from the meta-position (with respect to the hinge binding pyridine) of the central aryl ring should be suitable to position a nitrogen in the vicinity of the ASP160 in ROCK1 and ASP176 in ROCK2 and present the opportunity to make an interaction. The first analogue **46** introduced piperidin-4-ylmethanamine which unfortunately resulted in the most potent compound across ROCK1, ROCK2 and PKA (Table 7). To furnish compounds with more flexibility to secure an interaction with the aspartic acid 160 ROCK1 and

176 ROCK2 the next analogues investigated varying lengths of acyclic diamines. Increasing the linker length with compounds **47** (ethane-1,2-diamine) **48** (propane-1,3-diamine) and **49** (butane-1,4-diamine) gave the desired increased selectivity over PKA which can be explained by looking at the structure of compound **47** in PKA (Figure 3). Here the shorter linker of compound **47** allows a hydrogen bond to be made in PKA with glutamic acid 128. As the linker length increases to 4 atoms in **49,** binding here would seem to be reduced. For ROCK1 and ROCK2, the linker length of compound **48** would seem to interface the shorter aspartic acid residues in these proteins.

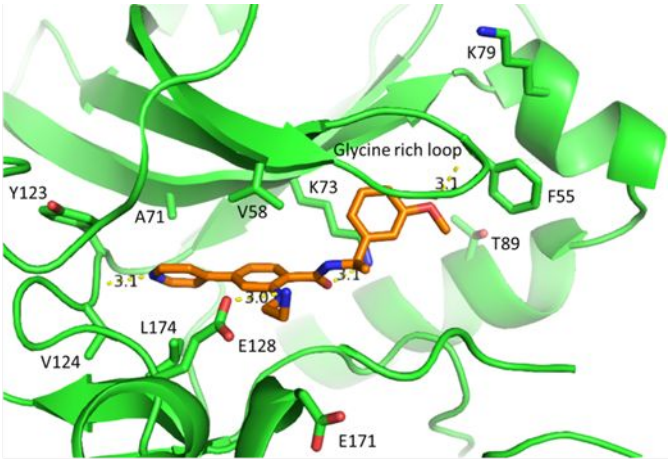
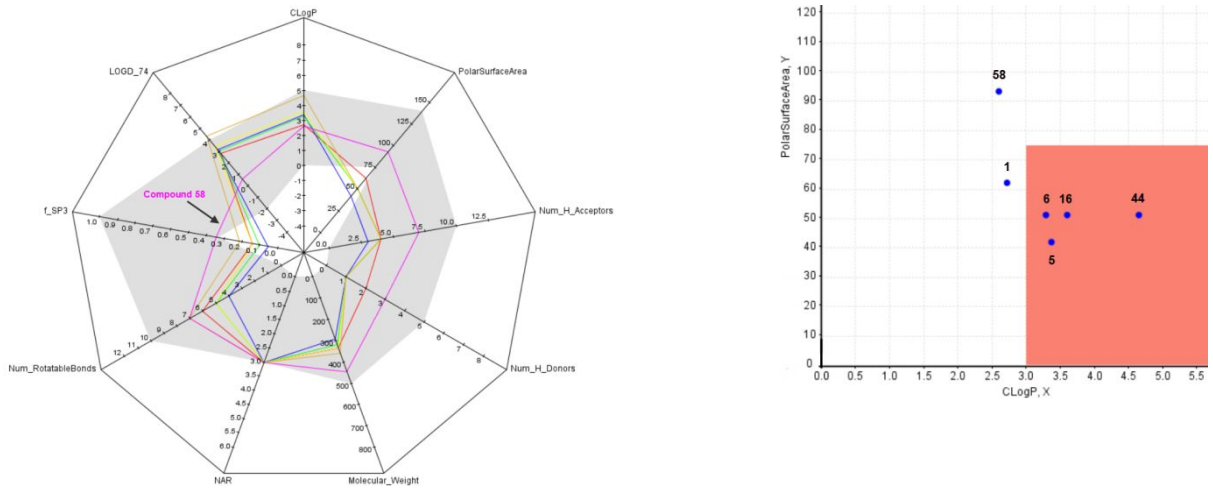


Figure 3. Crystal structure of compound 47 in the active site of PKA (PDB 6E99). Structure was obtained by co-crystallization.

Having established that a 5-atom linker afforded compounds with the best selectivity, ring constrained variants of butane-1,4-diamine were considered. For the design of these compounds emphasis was placed on the calculated physicochemical properties of the resulting compounds based on medicinal chemistry guidelines like drug-like properties,[45] fraction sp^3 carbon[46] and 3/75.[47] Cognizant of the CYP inhibition liability of compound **49** due to the unsubstituted pyridine, an alternative hinge binding motif was selected for these analogues. Piperidine was selected ahead of 2-aminopyridine, 2-fluoropyridine and 3-fluoropyrdine because it increases both the PSA and Fsp3 to values associated with a safer predicted toxicity profile.



(a) (b)

Figure 4. (a) Radar plot of calculated physicochemical properties and (b) predicted reduced risk of toxicity, for compounds 1, 5, 6, 16, 44 and 58.

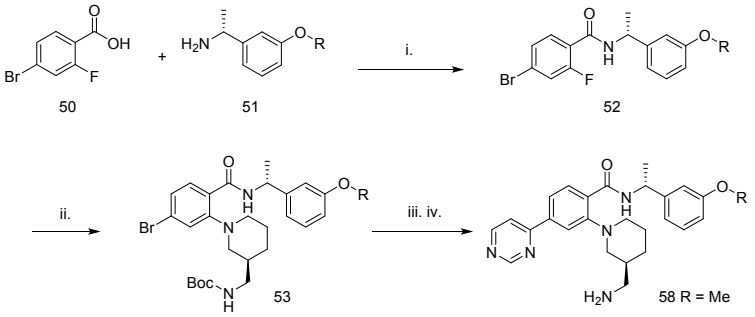
From the radar plot visualization (Figure 4) it is evident that only compound **58** has excellent predicted drug-like properties including Fsp^3. The radar plot data is also shown in tabular form below (Table 8). In addition compound **1**, the initial hit, and compound **58** have calculated PSA and cLogP that suggest a reduced risk of toxicity based on the 3/75 rule. These clearly show that compound **58** has excellent calculated drug-like properties.

Table 8. (a) Calculated physicochemical properties for compounds 1, 5, 6, 16, 44 and 58

Cpd	CLogP	PSA	HBA	LogD 7.4	HBD	Mol wt	NAR	NRB	Fsp^3
1	2.72	62.2	4	2.86	2	332.4	3	6	0.14
5	3.37	42.0	3	3.20	1	288.3	3	4	0.05
6	3.29	51.2	4	3.04	1	318.4	3	5	0.10
16	3.60	51.2	4	3.46	1	332.4	3	5	0.14
44	4.65	51.2	4	4.34	1	360.4	3	7	0.22
58	2.60	93.4	7	0.63	3	445.6	3	7	0.35

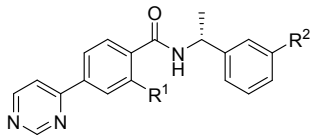
To facilitate these analogues an alternative synthetic route was required. The (R)-(+)-1-(3-substituted-phenyl)ethylamine **51** was reacted with 4-bromo-2-fluorobenzoic acid **50** to afford intermediate **52**. Nucleophilic displacement of the fluorine of **52** with mono boc-protected diamines was efficiently mediated using standard conditions and afforded the target compounds without the hinge binding motif **53**. These diastereomeric mixtures were subjected to chiral chromatography to afford stereochemically pure material. Palladium catalyzed coupling with 4-chloropyrimidine afforded the boc-protected analogues, which upon treatment with TFA furnished the desired compound **58** (Scheme 6).

Scheme 6. Synthetic route towards compounds 54 - 58

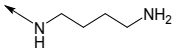
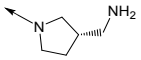
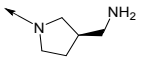
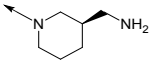
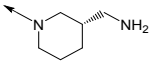


Reagents and Conditions: i) EDAC, HOBt, 0 °C to RT, O/N; ii) N-ethyl-N-isopropylpropan-2-amine, diamine, DMSO 110 °C. O/N; iii) CH_3CO_2K, 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane), 4-chloropyrimidine hydrochloride, $PdCl_2$(dppf)-DCM, Cs_2CO_3, K_2CO_3, dioxane, 65 °C, 3 h; iv) TFA.

Table 9. SAR for compounds 54 - 58



Cpd	R1	R2	IC50 / μM at 100 μM ATP	PKA/ROCK2 Selectivity	Solubility / μM	PPB / %	PAMPA / 10^{-6}

			ROCK1	ROCK2	PKA			free	cms^{-1}
54		3-OMe	0.99	0.072	>10	140	-	-	-
55		3-O^{n}Pr	1.9	0.32	>10	31	63.9	70.6	1.4
56		3-O^{n}Pr	1.7	0.27	>10	38	-	-	-
57		3-OMe	0.16	0.019	0.88	46	65.5	66.0	2.6
58		3-OMe	0.12	0.014	3.3	230	51.2	57.1	2.5

Compound **54** (Table 9) was prepared as the pyrimidine analogue of compound **49** to establish the concept of replacing the pyridine hinge binding motif. This was confirmed with both compounds having very similar profiles for both potency and selectivity. Replacement of the butane-1,4-diamine with pyrrolidin-3-ylmethanaminethat also incorporated the propyloxy group on the terminal aryl ring was not promising. Both compounds **55** and **56** were not only less potent at ROCK2 but were also far less selective versus PKA. Incorporation of piperidin-3-ylmethanamine in compounds **57** and **58** was far more beneficial. (R)-isomer **57** was found to be a potent inhibitor of ROCK2 with modest selectivity over PKA. However the (S)-isomer **58** retained this potency against ROCK1 and ROCK2 and introduced more than a 200-fold selectivity versus PKA. The absolute configuration of compounds **55**, **56**, **57** and **58** was not determined. The configuration was assigned arbitrarily using the crystal

structures to predict which the most selective compound was. Further studies are ongoing to assign the absolute stereochemistries of these 4 compounds. Additional profiling of compounds **57** and **58** showed they have good solubility and free fraction, with not surprisingly moderate permeability as assessed by PAMPA due to the primary amine.

To identify the optimal compound for *in vivo* studies 44 of the above described ROCK inhibitors were screened in the AbbVie kinome panel that includes 80 kinases (Supplementary Information). This highlighted compound **16** as the best candidate. It provides IC_{50} values >10 μM for 63 of the kinases and over 1 μM for a further 10 kinases. Consistent with the project screening data it was highly potent at both ROCK1 (IC_{50} 1 nM) and ROCK2 (IC_{50} 1 nM). It only inhibited two other kinases at the low nanomolar level PKG1A (IC_{50} 1 nM) and PKA (IC_{50} 47 nM) showing this to be a highly selective dual ROCK1 and ROCK2 inhibitor suitable for *in vivo* studies. The broad kinome profiling showed that compounds **55**, **56**, **57** and **58** were the most selective against PKG1A, while compound **22**, the hindered 2,6-dimethyl pyridine was shown to be inactive at all 80 kinases.

Table 10. Lead compounds in pMYPT1 ELISA cell assay

Cpd	pMYPT1 / IC_{50} μM*	PAMPA / 10^{-6} cms^{-1}	PSA / Å
6	0.075	20.2	51.2
8	0.961	16.2	51.2
12	0.45	14.9	60.5
14	2.23±1.3	2.5	54.5
16	0.012±0.01	19.6	51.2

17	49.8	-	51.2
18	0.173±0.03	-	77.2
19	0.116±0.09	14.7	51.2
24	0.415±0.24	19.7	64.1
25	7.83	12.5	64.1
27	0.963	5.1	63.3
30	0.802	9.2	72.5
44	0.056±0.01	18.8	51.2
58	0.094	2.5	93.4

* Errors shown for compounds tested multiple times.

A subset of these molecules were then progressed into a pMYPT1 ELISA, which is a ROCK dependent cell-based assay (Table 10). Compound **6**, the 3-methoxy analogue showed good potency while compounds **8**, **12** and **14**, with the larger aryl substituents, were less potent. Compound **16**, was the most potent compound (IC_{50} 0.012 μM) and confirmed this as an excellent dual ROCK1 and ROCK2 tool compound. This compound has been made available through the AbbVie Compound Toolbox.[48] Compound **17**, the isomer of **16**, was 3 logs less potent, consistent with the enzyme assay result. Compounds **18**, **19**, **24**, **27** and **30** in which the hinge binding motif was modified to reduce CYP inhibition demonstrated an 8 - 15 fold shift in the cell assay. Cell data for pyridazine **25** was almost 10 μM which agreed with the observed enzyme data and confirmed that this functional group was not tolerated. Compounds **44** and **58** were shown to be excellent dual ROCK1 and ROCK2 inhibitors with IC_{50}s of 0.056 and 0.094 μM respectively.

Table 11. Pharmacokinetics of compound 16 in C57BL6 mouse and Sprague Dawley rat

Species	Sample Analyzed	IV				IP					PO				
		$t_{1/2}$ hr	AUC ug*h/mL	CL L/h/kg	Vss L/kg	$t_{1/2}$ hr	Tmax hr	Cmax ug/mL	AUC ug*h/mL	F %	$t_{1/2}$ hr	Tmax hr	Cmax ug/mL	AUC ug*h/mL	F %
SD Rat	Plasma	1.5	2.19	1.5	2.0	1.0	0.25	1.03	1.80	82	1.1	0.67	0.42	0.85	39
SD Rat	Plasma	-	-	-	-	0.8	0.25	2.36	2.30	-	-	-	-	-	-
	Brain	-	-	-	-	1.2	0.25	1.92	2.63	-	-	-	-	-	-
C57BL6 Mouse	Plasma	-	-	-	-	1.5	0.42	1.66	2.08	-	2.0	0.33	0.84	1.42	-
	Brain	-	-	-	-	1.8	0.33	0.99	1.78	-	-	-	-	-	-

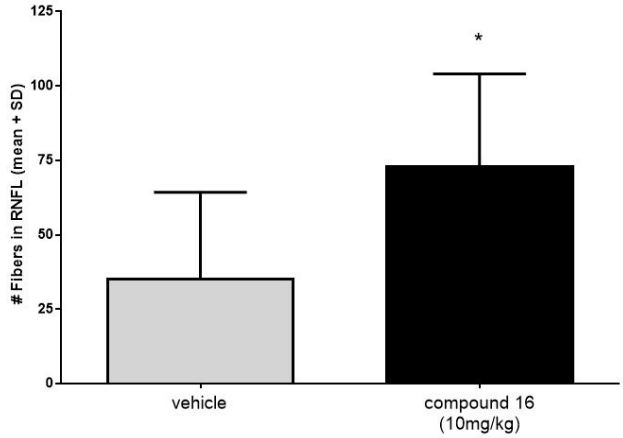
All groups n = 3, dose of 10 μmol/kg

Pharmacokinetic analyses (Table 11) of compound **16** in both C57BL6 mice and Sprague Dawley rats all 10 μmol/kg with group size n = 3, were performed using IV, IP and PO administration. The compound has a reasonable half-life and good exposure in both plasma and brain. While the oral bioavailability was moderately low it was sufficient to advance the compound for *in vivo* testing

Beneficial effects of ROCK inhibitors, like Fasudil and Y-27632, have been reported in a variety of animal models of different neurodegenerative diseases.[49] To confirm such potential in this hit series, compound **16** was investigated in an optic nerve crush model[50] in rats. In this model, compression of the optic nerve leads to axon dissection followed by degeneration of the retinal nerve fiber layer (RNFL) in the eye over time. Compound **16** was orally administered once daily at a dose of 10 mg/kg for 5

weeks and compared to a vehicle control. Subsequent immunohistochemical staining of the retina revealed a significant increase in the number of ßIII tubulin positive fibers in compound **16** treated animals indicative of a protection of the axons in the retinal nerve fiber layer by ROCK inhibition (Figure 5). Further studies are ongoing to identify clear positive controls for this assay.[51]

Figure 5. Protection of the retinal nerve fiber layer with compound 16



CONCLUSIONS

Following a high-throughput screen compound **1**, a 4-(pyridin-4-yl)benzamide, was identified as the starting point for a medicinal chemistry project to identify a potent and kinome-selective dual ROCK1 and ROCK2 inhibitor. This compound was selected due to its excellent physicochemical properties and synthetic accessibility. Parallel synthesis was employed to generate focused compound libraries that furnished immediate SAR and most notably compound **12**. Crystal structures were obtained for this compound in PKA, ROCK1 and ROCK2. This provided critical structural information to the medicinal chemistry team to drive compound design and enabled a unique comparison of the 3 binding sites with the same bound inhibitor. Interrogation of the co-crystal structures indicated the preferred configuration at the central benzylic carbon would be (R). This information was used to select monomers for focused library design resulting in compound **16** with the (R)-configuration and compound **17** with the (S)-

configuration. Comparison of the potency of these two compounds clearly supported the structural hypothesis that the (R)-configuration was preferred. Profiling of these early leads in a HT-ADME assay panel showed the compounds were pan-inhibitors of CYP enzymes, especially 3A4, predicting unwanted drug-drug interactions. Substitution (2-Cl, 2-NH_2, 2-F, 3-F) of the pyridine or replacement with pyrimidine afforded compounds with a clean CYP inhibition profile. Piperidine was selected ahead of 2-aminopyridine, 2-fluoropyridine and 3-fluoropyrdine because it increases both the PSA and Fsp3 to values associated with a safer predicted toxicity profile. Additional profiling of compound **16** showed it was a potent and selective dual ROCK1 and ROCK2 inhibitor in both enzyme and cell assays and efficacious in the retinal nerve fiber layer model after oral dosing. This tool compound has been made available through the AbbVie Compound Toolbox. Finally, the co-crystal structures also identified that aspartic acid residues 176 and 218 in ROCK2, which are glutamic acids in PKA, could be targeted as residues to drive both potency and kinome selectivity. Introduction of a piperidin-3-ylmethanamine group to the compound series resulted in compound **58**, a potent and selective dual ROCK1 and ROCK2 inhibitor with excellent predicted drug-like properties including a significantly reduced Cyp inhibition profile.

EXPERIMENTAL SECTION

Unless otherwise stated, reagents were purchased from Sigma Aldrich, Acros, Alfa Aesar or the Sigma Aldrich Custom Packaged Reagent service. Reagent/reactant names given are as named on the commercial bottle or as generated by IUPAC conventions or CambridgeSoft® ChemDraw Ultra 9.0.7. Compound names are generated by IUPAC conventions or CambridgeSoft® ChemDraw Ultra 9.0.7. For all final compounds purity was established by HPLC and purity confirmed to be ≥95%.

Analytical data is included within the procedures below, in the illustrations of the general procedures, or in the tables of examples. Unless otherwise stated, all ^{1}H, ^{13}C and ^{19}F NMR data were collected on a Varian Mercury Plus 400 MHz or a Bruker AVIII 300 MHz or a Bruker 500 MHz instrument; chemical

shifts are quoted in parts per million (ppm). HPLC analytical data are either detailed within the experimental or referenced to the table of LCMS and HPLC conditions, using the lower case letter in high resolution mass spectra (HRMS) were obtained using an Agilent 6550 Q-TOF spectrometer with an ESI source.

Chiral LC analysis was performed using Varian 218 LC pumps, a Varian CVM 500 with switching valves and heaters for automatic solvent, column and temperature control. Detection methods included a variable wavelength UV detector (Varian Prostar 320), an in-line polarimeter (PDR-chiral advanced laser polarimeter, model ALP2002) used to measure qualitative optical rotation (+/-) and an evaporative light scattering detector (ELSD) (a PS-ELS 2100 (Polymer Laboratories)). ELSD settings were as follows: evaporator: 46 ºC, nebulizer: 24 ºC and gas flow: 1.1 SLM.

Chiral SFC analyses were performed using a Shimadzu Nexera UC SFCMS instrument. Detection methods included a PDA detector (Model SPD-M20A), ESI (+/-) MS (model LCMS-2020), and an in-line polarimeter (PDR-Separations advanced laser polarimeter, model 4G-ALP) used to measure qualitative optical rotation (+/-).

Table 12. List of HPLC methods

Method	HPLC Conditions
a	HPLC: A gradient of 10-100 % MeCN (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 2.0mL/min (0-0.1 min 10% A, 0.1-2.6 min 10-100% A, 2.6-2.9 min 100% A, 2.9-3.0 min 100-10% A. 0.5min post-run delay).
b	HPLC: The gradient was 5-60% B in 0.75 min then 60-95% B to 1.15 min with a hold at 95% B for 0.75 min (1.3 mL/min flow rate). Mobile phase A was 10mM ammonium acetate, mobile phase B was HPLC grade MeCN. The column used for the chromatography

	is a 4.6x50 mm MAC-MOD Halo C8 column (2.7 μm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
c	HPLC: The gradient was 5-60% B in 1.5 min then 60-95% B to 2.5 min with a hold at 95% B for 1.2 min (1.3 mL/min flow rate). Mobile phase A was 10 mM ammonium acetate, mobile phase B was HPLC grade acetonitrile. The column used for the chromatography is a 4.6x50 mm MAC-MOD Halo C8 column (2.7 μm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
d	HPLC: The gradient was 5-60% B in 1.5 min then 60-95% B to 2.5 min with a hold at 95% B for 1.2 min (1.3 mL/min flow rate). Mobile phase A was 10 mM ammonium acetate, mobile phase B was HPLC grade acetonitrile. The column used for the chromatography is a 4.6x50 mm MAC-MOD Halo C8 column (2.7 μm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.)
e	HPLC: A gradient of 10-100% acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 2 mL/min (0-0.1 min 10% A, 0.1-2.6 min 10-100% A, 2.6-2.9 min 100% A, 2.9-3.0 min 100-10% A. 0.5min post-run delay).

Table 13. Chiral HPLC and SFC methods

Method	Conditions
A	HPLC: The gradient was 10-50% A in 19 min with a hold at 50% A for 1.5 min (1.0

	mL/min flow rate). Mobile phase A was HPLC grade isopropanol, mobile phase B was HPLC grade heptane with 0.1 % diethylamine added. The column used for the chromatography was a Daicel ADH, 4.6 x 250 mm column (5 μm particles). Detection methods were UV, evaporative light scattering (ELSD) detection as well as optical rotation.
B	HPLC: The gradient was 15-60% A in 19 min with a hold at 60% A for 1.5 min (1.0 mL/min flow rate). Mobile phase A was a 1:1 mixture of HPLC grade methanol and 200 proof ethanol, mobile phase B was HPLC grade heptane with 0.1 % diethylamine added. The column used for the chromatography was a Daicel IC, 4.6 x 250 mm column (5 μm particles). Detection methods were UV, evaporative light scattering (ELSD) detection as well as optical rotation.
C	HPLC: The gradient was 10-70% A in 19 min with a hold at 70% A for 1.5 min (1.0 mL/min flow rate). Mobile phase A was HPLC grade isopropanol, mobile phase B was HPLC grade heptane with 0.1 % diethylamine added. The column used for the chromatography was a Daicel IA, 4.6 x 250 mm column (5 μm particles). Detection methods were UV, evaporative light scattering (ELSD) detection as well as optical rotation.
D	HPLC: The gradient was 10-70% A in 19 min with a hold at 70% A for 1.5 min (1.0 mL/min flow rate). Mobile phase A was 200 proof ethanol, mobile phase B was HPLC grade heptane with 0.1 % diethylamine added. The column used for the chromatography was a Daicel ASH, 4.6 x 250 mm column (5 μm particles). Detection methods were UV, evaporative light scattering (ELSD) detection as well as optical rotation.
E	HPLC: Isocratic 30% A for 15min (1.0 mL/min flow rate). Mobile phase A was a 1:1

	mixture of HPLC grade methanol and 200 proof ethanol, mobile phase B was HPLC grade heptane with 0.2 % diethylamine added. The column used for the chromatography was a Daicel ODH, 4.6 x 250 mm column (5 μm particles). Detection methods were UV, evaporative light scattering (ELSD) detection.
F	HPLC: The gradient was 10-50% A in 19 min with a hold at 50% A for 1.5 min (20.0 mL/min flow rate). Mobile phase A was HPLC grade isopropanol, mobile phase B was HPLC grade heptane with 0.1 % diethylamine added. The column used for the chromatography was a Daicel ADH, 20 x 250 mm column (5 μm particles). Detection methods were UV, evaporative light scattering (ELSD) detection as well as optical rotation.
G	SFC: The gradient was 10-55% A in 3.2 min with a hold at 55% A for 0.5 min (3.5 mL/min flow rate). Mobile phase A was 200 proof ethanol with 0.2% diethylamine additive, mobile phase B was SFC grade CO_2. The column used for the chromatography was a Daicel IG, 4.6 x 100 mm column (3 μm particles). Detection methods were UV, ESI (+/-) MS and optical rotation.
H	SFC: The gradient was 10-55% A in 3.2 min with a hold at 55% A for 0.5 min (3.5 mL/min flow rate). Mobile phase A was an 80:20 mixture of HPLC grade isopropanol and acetonitrile with 0.2% diethylamine additive, mobile phase B was SFC grade CO_2. The column used for the chromatography was a YMC SA, 4.6 x 100 mm column (3 μm particles). Detection methods were UV, ESI (+/-) MS and optical rotation.

(S)-N-(1-Hydroxy-3-phenylpropan-2-yl)-4-(pyridin-4-yl)benzamide (1). Synthesis was performed using a Personal Chemistry Emry's optimizer microwave. A microwave tube was charged with PS-DCC resin (253 mg, 3 eq.) 4-(pyridin-4-yl)benzoic acid (20 mg, 0.1 mmol) and DMA (1 mL). (S)-2-

amino-3-phenylpropan-1-ol (17 mg, 0.11 mmol) in DMA (0.5 mL) was added followed by HOBt (14 mg, 0.11 mmol) in DMA (0.3 mL). DIEA (40 uL, 0.2 mmol) was added and the reaction heated in the microwave for 600 seconds at 100 °C. The reaction was filtered through Si-Carbonate (6mL-1g) and concentrated to dryness. The residue was dissolved in methanol and subjected to purification by SFC to afford the title compound (7 mg, 21 %).

LCMS (Table 9. Method c) R_t = 0.94 min.; MS m/z: 333.3 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.65 (2 H, d, J 6.1), 8.25 (1 H, d, J 8.4), 7.95 – 7.83 (4 H, m), 7.74 (2 H, d, J 6.2), 7.29 – 7.19 (4 H, m), 7.13 (1 H, ddd, J 8.4, 5.5, 2.4), 4.81 (1 H, s), 4.17 (1 H, tq, J 10.9, 5.5), 3.56 – 3.39 (2 H, m), 2.95 (1 H, dd, J 13.7, 5.2), 2.80 (1 H, dd, J 13.6, 9.0). δ C (101 MHz, DMSO) 165.82, 150.69, 146.57, 139.88, 139.85, 135.67, 129.51, 128.52, 128.51, 127.07, 126.31, 121.77, 63.33, 53.80, 36.94.

N-Benzyl-4-(pyridin-4-yl)benzamide (5). As per compound **9** except phenylmethanamine (12 mg, 0.11 mmol) to afford the title compound (9 mg, 31 %).

LCMS (Table 9. Method b) R_t = 1.11 min.; MS m/z: 289.13 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.13 (1 H, t, J 6.0), 8.65 (2 H, d, J 6.0), 8.03 (2 H, d, J 8.3), 7.90 (2 H, d, J 8.3), 7.75 (2 H, d, J 6.0), 7.32 (4 H, d, J 4.3), 7.22 (1 H, dd, J 8.5, 4.3), 4.50 (2 H, d, J 6.0). δ C (101 MHz, DMSO) 166.05, 150.77, 146.48, 140.16, 140.03, 135.23, 128.73, 128.55, 127.66, 127.25, 127.19, 121.78, 43.13. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O$ 289.12626; Found 289.12655.

N-(3-Methoxybenzyl)-4-(pyridin-4-yl)benzamide (6). As per compound **9** except (3-methoxyphenyl)methanamine (24 mg, 0.11 mmol) to afford the title compound (24 mg, 39 %).

LCMS (Table 9. Method b): R_t = 1.13 min.; MS m/z: 319.14 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.16 (1 H, t, J 6.0), 8.83 (2 H, d, J 6.4), 8.12 (2 H, d, J 6.5), 8.09 – 7.99 (4 H, m), 7.23 (1 H, t, J 8.1), 6.89 (2 H, d, J 7.5), 6.84 – 6.77 (1 H, m), 4.47 (2 H, d, J 6.0), 3.72 (3 H, s). δ C (101 MHz, DMSO) 165.87,

159.77, 146.74, 141.55, 138.61, 136.27, 129.82, 128.68, 127.95, 123.25, 119.84, 113.45, 112.56, 55.44, 43.11. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2$ 319.13683; Found 319.1372.

N-(3-Ethoxybenzyl)-4-(pyridin-4-yl)benzamide (7). As per compound **9** except (3-ethoxyphenyl)methanamine (17 mg, 0.11 mmol) to afford the title compound (27 mg, 55 %).

LCMS (Table 9. Method a): R_t = 0.62 min.; MS m/z: 333.3 $(M+H)^+$. δ H NMR (400 MHz, DMSO-d6) 9.14 (t, J = 5.90 Hz, 1H), 8.81 (d, J = 6.39 Hz, 2H), 8.11 – 7.98 (m, 6H), 7.22 (t, J = 7.88 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.79 (dd, J = 1.98, 7.46 Hz, 1H), 4.47 (d, J = 5.97 Hz, 2H), 3.99 (t, J = 6.92 Hz, 2H), 1.35 – 1.25 (m, 3H). δ C NMR (101 MHz, DMSO) 165.87, 159.02, 158.39, 150.40, 147.24, 141.53, 138.80, 136.13, 129.80, 128.66, 127.87, 123.07, 119.72, 113.94, 113.02, 109.99, 63.32, 43.10, 15.10. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}N_2O_2$ 332.15248; Found 332.15293.

N-(3-Propoxybenzyl)-4-(pyridin-4-yl)benzamide (8). As per compound **9** except (3-propoxyphenyl)methanamine (28 mg, 0.11 mmol) to afford the title compound (29 mg, 44 %).

LCMS (Table 9. Method b): R_t = 1.43 min.; MS m/z: 347.17 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.14 (1 H, t, J 6.0), 8.84 – 8.78 (2 H, m), 8.11 – 7.98 (6 H, m), 7.21 (1 H, t, J 8.1), 6.91 – 6.84 (2 H, m), 6.79 (1 H, dd, J 7.9, 2.1), 4.47 (2 H, d, J 6.0), 3.89 (2 H, t, J 6.5), 1.70 (2 H, p, J 7.0), 0.94 (3 H, t, J 7.4). δ C (101 MHz, DMSO) 165.87, 159.19, 150.41, 147.23, 141.52, 138.80, 136.14, 129.80, 128.66, 127.87, 123.07, 119.73, 114.00, 113.05, 69.27, 43.11, 22.48, 10.85. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}N_2O_2$ 347.16813; Found 347.16862.

N-(3-Hydroxybenzyl)-4-(pyridin-4-yl)benzamide (9). In a 4 ml vial a solution of 4-(pyridin-4-yl)benzoic acid (28 mg, 0.14 mmol) dissolved in DMA (1 mL) was added, followed by a solution of HATU (65 mg, 0.17 mmol) dissolved in DMA (0.6 mL), followed by triethylamine (60 uL). Then a solution of 3-(aminomethyl)phenol (21 mg, 0.17 mmol) was added dissolved in DMA (0.5 uL) and the

reaction shaken at 60 ℃ overnight. The reaction was dried down and dissolved in MeOH:DMSO and purified by reverse phase HPLC to afford the title compound (19 mg, 31 %).

LCMS (Table 9. Method b): R_t = 0.87 min.; MS m/z: 305.12 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.28 (1 H, s), 9.12 (1 H, t, J 5.9), 8.80 (2 H, d, J 6.4), 8.10 – 8.04 (4 H, m), 8.01 (2 H, d, J 8.4), 7.10 (1 H, t, J 8.0), 6.76 – 6.70 (2 H, m), 6.65 – 6.58 (1 H, m), 4.42 (2 H, d, J 6.0). δ C (101 MHz, DMSO) 165.80, 157.84, 150.31, 147.32, 141.36, 138.80, 136.16, 129.68, 128.65, 127.84, 123.04, 118.21, 114.44, 114.16, 43.04. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.12118; Found 305.12162.

4-(Pyridin-4-yl)-N-(3-(trifluoromethoxy)benzyl)benzamide (10). As per compound **9** except (3-(trifluoromethoxy)phenyl)methanamine (33 mg, 0.11 mmol) to afford the title compound (32 mg, 46 %).

LCMS (Table 9. Method b): R_t = 1.46 min.; MS m/z: 373.11 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.25 (1 H, t, J 5.9), 8.82 (2 H, d, J 6.3), 8.13 – 7.99 (6 H, m), 7.47 (1 H, t, J 7.9), 7.36 (1 H, d, J 7.7), 7.30 (1 H, s), 7.23 (1 H, d, J 8.0), 4.55 (2 H, d, J 5.9). δ C (101 MHz, DMSO) 166.06, 150.61, 148.91, 147.04, 142.92, 138.85, 135.97, 130.73, 128.67, 127.96, 126.72, 123.16, 121.80, 119.98, 119.69, 42.67. δ F (376 MHz, DMSO) -56.65. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}F_3N_2O_2$ 373.10856; Found 373.10911.

N-(2,3-Dimethoxybenzyl)-4-(pyridin-4-yl)benzamide (11). As per compound **9** except (2,3-dimethoxyphenyl)methanamine (19 mg, 0.11 mmol) to afford the title compound (23 mg, 53 %).

LCMS (Table 9. Method b): R_t = 1.12 min.; MS m/z: 349.15 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.03 (1 H, t, J 5.8), 8.83 (2 H, d, J 6.5), 8.15 – 7.98 (6 H, m), 7.01 (2 H, t, J 7.9), 6.94 (1 H, d, J 6.9), 6.86 (1 H, d, J 7.6), 4.51 (2 H, d, J 5.8), 3.79 (3 H, s), 3.77 (3 H, s). δ C (101 MHz, DMSO) 165.88, 152.74,

150.86, 146.83, 146.70, 138.60, 136.30, 133.04, 128.68, 127.91, 124.22, 123.21, 120.35, 112.13, 60.49, 56.16, 38.00. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_3$ 349.14739; Found 349.14792.

N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)-4-(pyridin-4-yl)benzamide (12). As per compound **9** except (2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methanamine hydrochloride (24 mg, 0.12 mmol) to afford the title compound (23 mg, 51 %).

LCMS (Table 9. Method b): R_t = 1.15 min.; MS m/z: 347.13 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.98 (1 H, t, J 5.8), 8.81 (2 H, d, J 6.5), 8.12 – 7.98 (6 H, m), 6.80 – 6.71 (3 H, m), 4.45 (2 H, d, J 5.8), 4.30 (2 H, dd, J 5.6, 2.4), 4.24 (2 H, dd, J 5.0, 2.6). δ C (101 MHz, DMSO) 166.00, 150.52, 147.14, 143.56, 141.39, 138.74, 136.19, 128.70, 127.86, 127.74, 123.11, 120.74, 119.96, 116.06, 64.68, 64.31, 37.67. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_2O_3$ 347.13174; Found 347.1322.

N-((3,4-Dihydro-2H-benzo[b][1,4]dioxepin-6-yl)methyl)-4-(pyridin-4-yl)benzamide (13). A 4mL vial was charged with a solution of 4-(pyridin-4-yl)benzoic acid in DMA (20 mg, 0.1 mmol), a solution of HATU in DMA (46 mg, 0.12 mmol), triethylamine (42 µL, 0.3 mmol), and 402µL of a 0.6mmol pre-weighed solution in DMA (1 mL) of (3,4-dihydro-2H-benzo[b][1,4]dioxepin-6-yl)methanamine (22 mg, 0.12 mmol). The vial was capped and stirred at 60 °C overnight. Upon completion the crude mixture was dried under vacuum and dissolved in DMSO/MeOH and purified by reverse phase HPLC purification to afford the title compound (22 mg, 47 %).

LCMS (Table 9. Method b): R_t = 1.15 min.; MS m/z: 361.15 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.99 (1 H, t, J 5.7), 8.82 (2 H, d, J 6.4), 8.11 – 7.98 (6 H, m), 6.96 – 6.83 (3 H, m), 4.49 (2 H, s), 4.12 (4 H, dt, J 20.4, 5.4), 2.10 (2 H, p, J 5.5). δ C (101 MHz, DMSO) 165.84, 151.88, 150.67, 149.63, 147.01, 138.66, 136.27, 132.23, 128.68, 127.87, 123.15, 122.82, 120.67, 70.96, 70.93, 38.54, 32.16. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_2O_3$ 361.14739; Found 361.14777.

N-(3-(3-(Dimethylamino)propoxy)benzyl)-4-(pyridin-4-yl)benzamide (14). As per compound **9** except 3-(3-(aminomethyl)phenoxy)-N,N-dimethylpropan-1-amine (36 mg, 0.11 mmol) to afford the title compound (23 mg, 27 %).

LCMS (Table 9. Method b): R_t = 0.74 min.; MS m/z: 390.21 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.17 (1 H, t, J 5.8), 8.78 (2 H, d, J 6.2), 8.09 – 7.95 (6 H, m), 7.25 (1 H, t, J 7.9), 6.95 – 6.86 (2 H, m), 6.82 (1 H, d, J 8.2), 4.47 (2 H, d, J 5.9), 4.01 (2 H, t, J 5.9), 3.28 – 3.13 (2 H, m), 2.79 (7 H, d, J 3.2), 2.07 (2 H, dq, J 12.0, 5.9). δ C (101 MHz, DMSO) 165.90, 158.74, 149.39, 148.11, 141.70, 139.19, 135.84, 129.87, 128.63, 127.73, 122.75, 120.18, 114.05, 113.00, 65.05, 54.77, 43.07, 42.78, 24.44. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}N_3O_2$ 390.21033; Found 390.21085.

N-(3-(2-Morpholinoethoxy)benzyl)-4-(pyridin-4-yl)benzamide (15). As per compound **13** except (3-(2-morpholinoethoxy)phenyl)methanamine (41 mg, 0.11 mmol) to afford the title compound (41 mg, 54 %).

LCMS (Table 9. Method b): R_t = 0.72 min.; MS m/z: 418.21 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.18 (1 H, t, J 5.9), 8.77 (2 H, d, J 6.4), 8.09 – 7.95 (6 H, m), 7.28 (1 H, t, J 7.9), 7.00 – 6.93 (2 H, m), 6.92 – 6.85 (1 H, m), 4.48 (2 H, d, J 5.9), 4.36 – 4.24 (2 H, m), 4.06 – 3.62 (4 H, m), 3.59 – 3.52 (2 H, m), 3.52 – 3.09 (4 H, m). δ C (101 MHz, DMSO) 165.92, 158.06, 148.30, 141.85, 139.29, 135.76, 129.95, 128.62, 127.71, 122.69, 120.72, 114.29, 113.20, 63.68, 62.27, 55.63, 52.16, 43.04. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}N_3O_3$ 418.20524; Found 418.20583.

(R)-N-(1-(3-Methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (16). A mixture of 4-(pyridin-4-yl)benzoic acid (0.969 g, 4.87 mmol),(R)-1-(3-methoxyphenyl)ethanamine (0.883 g, 5.84 mmol), N-ethyl-N-isopropylpropan-2-amine (1.7 mL, 9.8 mmol), and O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (1.87 g, 5.83 mmol) in DMF (10 mL)was stirred overnight at RT, diluted with EtOAc, washed with 1 M NaOH, sat NaHCO3, and brine, dried (Na_2SO_4), filtered and

purified on silica gel (50-85% EtOAc/DCM as eluent). The residue was triturated with ether to afford the title compound (1.32 g, 82 %) as a white solid.

LCMS (Table 9. Method c): R_t = 1.22 min.; MS m/z: 333.0 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.85 (1 H, d, J 8.1, 9), 8.69 – 8.62 (2 H, m), 8.01 (2 H, d, J 8.3), 7.90 (2 H, d, J 8.3), 7.78 – 7.72 (2 H, m), 7.23 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, dd, J 8.0, 2.2), 5.15 (1 H, p, J 7.1), 3.73 (3 H, s), 1.47 (3 H, d, J 7.1). δ C (101 MHz, DMSO) 165.38, 159.74, 150.77, 146.98, 146.51, 140.08, 135.46, 129.73, 128.67, 127.14, 121.78, 118.77, 112.46, 112.25, 55.44, 48.99, 22.73.. Elemental analysis: calculated, C = 75.88% H = 6.06% N = 8.43%; found, C = 75.67% H = 5.85% N = 8.38%. $[\alpha]^{20}_D$ = -20.7 (c 1.0, MeOH). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_2$ 333.15248; Found 333.15295.

(S)-N-(1-(3-Methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (17). A mixture of 4-(pyridin-4-yl)benzoic acid (0.970 g, 4.87 mmol),(S)-1-(3-methoxyphenyl)ethanamine (0.884 g, 5.84 mmol), N-ethyl-N-isopropylpropan-2-amine (1.7 mL, 9.80 mmol), and O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (1.87 g, 5.82 mmol) in DMF (10 mL)was stirred at RT overnight, diluted with EtOAc, washed with 1 M NaOH, sat $NaHCO_3$, and brine, dried (Na_2SO_4), and purified on silica gel (20-85% EtOAc/DCM as eluent). The residue was triturated ether to afford the title compound (1.07 g, 66%) as a white solid.

LCMS (Table 9. Method c): R_t = 1.99 min.; MS m/z: 333.2 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.85 (1 H, d, J 8.1), 8.69 – 8.62 (2 H, m), 8.01 (2 H, d, J 8.3), 7.90 (2 H, d, J 8.3), 7.78 – 7.72 (2 H, m), 7.23 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, dd, J 8.1, 2.2), 5.14 (1 H, q, J 7.3), 3.73 (3 H, s), 3.28 (2 H, s), 1.47 (3 H, d, J 7.1). δ C (101 MHz, DMSO) 165.38, 159.74, 150.77, 146.98, 146.51, 140.08, 135.46, 129.73, 128.67, 127.14, 121.78, 118.77, 112.46, 112.25, 55.44, 48.99, 22.73. Elemental analysis: calculated, C = 75.88% H = 6.06% N = 8.43%; found, C = 75.89% H = 5.97% N = 8.46.

$[\alpha]^{20}_D$ = +22.4 (c 1.0, MeOH). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_2$ 333.15248; Found 333.15288.

4-(2-Aminopyridin-4-yl)benzoic acid. 4-Bromopyridin-2-amine (1.0 g, 5.78 mmol), 4-boronobenzoic acid (0.959 g, 5.78 mmol), and cesium carbonate (4.71 g, 14.45 mmol) were loaded into a 200 mL round bottom flask. DME (40 mL) and water (10 mL) were added to the mixture and nitrogen was bubbled through the mixture for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.334 g, 0.29 mmol) was added and the reaction heated to 80 °C under nitrogen. The DME was removed in vacuo and the aqueous residue diluted with water (80 mL) and washed with DCM (25 mL). The aqueous solution was filtered and the aqueous filtrate acidified with acetic acid to a pH 4.5, to afford a precipitate. The resulting solid was collected and washed with water, then dried to constant weight to afford the title compound (720 mg, 57 %) as a grey solid.

LCMS (Table 9. Method b): R_t = 0.51 min.; MS m/z: 214.97 $(M+H)^+$. δ H (400 MHz, DMSO) ppm 8.24 (s, 1H), 8.11 (d, J = 8.25 Hz, 2H), 8.07 (d, J = 6.75 Hz, 1H), 7.89 (d, J = 8.25 Hz, 2H), 7.27 (s, 1H), 7.25 (d, J = 6.77 Hz, 1H).

(R)-4-(2-Aminopyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (18). Under an atmosphere of nitrogen, at RT, a grey suspension of 4-(2-aminopyridin-4-yl)benzoic acid (100 mg, 0.47 mmol) and 1-hydroxybenzotriazole hydrate (72 mg, 0.47 mmol) in anhydrous DMF (15 mL) was stirred for 15 minutes before the addition of N-methylmorpholine (0.114 mL, 1.03 mmol) and (R)-(+)-1-(3-methoxyphenyl)ethylamine (78 mg, 0.52 mmol) followed by N-(3-dimethylaminopropyl)-n'-ethylcarbodiimide hydrochloride (99 mg, 0.52 mmol). The reaction mixture was stirred at RT for 14 day. Over that period the grey suspension decreased and a yellow solution formed. The reaction mixture was poured into water (150 mL). The product was extracted with EtOAc (3 X 50 mL) and the combined extracts, washed with 1 M HCl (2 X 30 mL) -[do not discard see below], 0.5 M NaOH (2 X 60 mL) and water (3 X 60 mL), dried ($MgSO_4$), filtered and solvent removed to afford a pale yellow

gum 55 mg (A). The acid aqueous extracts were combined, washed with EtOAc (2 X 20 mL) before being basified with 5 M NaOH (20 mL). The product was partitioned between the basic aqueous phase and the EtOAc (3 X 20 mL). The combined extracts were washed with water (3 X 25 mL), dried ($MgSO_4$), filtered and solvent removed in vacuo to afford a pale yellow powdery solid 65 mg (B). The crude isolated material (A&B) was combined and purified by mass triggered purification to afford the title compound (49 mg, 30 %).)

LCMS (Table 9. Method c) Rt = 1.7 min.; MS m/z: 348.2 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.1, 14), 8.00 – 7.93 (3 H, m), 7.71 (2 H, d, J 8.2), 7.22 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.84 – 6.70 (3 H, m), 5.97 (2 H, s), 5.14 (1 H, p, J 7.1), 3.73 (3 H, s), 1.46 (3 H, d, J 7.1). δ C (101 MHz, DMSO) 165.50, 160.91, 159.74, 149.04, 147.69, 147.01, 141.41, 135.00, 129.72, 128.53, 126.70, 118.77, 112.47, 112.23, 110.48, 105.59, 55.44, 48.95, 22.73. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}N_3O_2$ 348.16338; Found 348.16311.

4-(2-Fluoropyridin-4-yl)benzoic acid. A mixture of 4-bromobenzoic acid (0.5 g, 2.49 mmol), 2-fluoropyridine-4-boronic acid (0.386 g, 2.74 mmol) and cesium carbonate (2.84 g, 8.71 mmol) in DME (20 mL) and water (10 mL) was purged under vacuum and charged with nitrogen (4X). To the mixture was added tetrakis(triphenylphosphine)palladium(0) (0.144 g, 0.12 mmol). The reaction mixture was heated at 80 °C for 24 hours under nitrogen. The DME was removed in vacuo, the aqueous residue diluted with water (80 mL) and the basic aqueous was washed with DCM (3 X 40mL). The basic aqueous layer was filtered through a Celite™ pad, washed with water (2 X 20mL) and DCM (2 X 30mL). The filtrate was acidified to pH 4 with 1 M HCl (20 mL) and the product suspension extracted with DCM (4 X 100 mL). The solid was collected and dried to afford the title compound (193 mg, 36%) as a grey powdery solid.

LCMS (Table 9. Method b) R_t = 1.26 min.; MS m/z: 218.1 $(M+H)^+$.

(R)-4-(2-Fluoropyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (19). In a 25 mL round-bottomed flask, 4-(2-fluoropyridin-4-yl)benzoic acid (100 mg, 0.46 mmol), 1-hydroxybenzotriazole hydrate (85 mg, 0.55 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (106 mg, 0.55 mmol) in DMF (2 mL) were added to give a green solution. The resulting solution was stirred at 20 °C for 30 minutes. N-methylmorpholine (0.15 mL, 1.38 mmol) and (R)-1-(3-methoxyphenyl)ethanamine (70 mg, 0.46 mmol) were each added sequentially in one portion to the solution. The resulting solution was stirred at 20 °C overnight. The DMF was removed and the sample purified by prep LC. The fractions containing product were dried and dissolved in DCM/MeOH and concentrated/chased with ether/heptane. The residue was dried at 65 °C in a vacuum oven overnight to afford the title compound (67 mg, 42%).

LCMS (Table 9. Method c) R_t = 2.28 min.; MS m/z: 351.12 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.88 (1 H, d, J 8.2), 8.32 (1 H, d, J 5.3), 8.02 (2 H, d, J 8.3), 7.95 (2 H, d, J 8.3), 7.75 (1 H, d, J 5.2), 7.59 (1 H, s), 7.22 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, d, J 7.8), 5.16 (1 H, q, J 7.3), 3.73 (3 H, s), 1.47 (3 H, d, J 7.0). δ C (101 MHz, DMSO) 165.70, 165.25, 163.36, 152.65 (d, J 8.4), 148.69 (d, J 15.8), 146.94, 138.79 (d, J 3.5), 136.01, 129.74, 128.66, 127.47, 120.22 (d, J 3.8), 118.76, 112.46, 112.26, 107.31 (d, J 38.8), 55.44, 49.01, 22.71. δ F NMR (376 MHz, DMSO) -68.57. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}FN_2O_2$ 351.14306; Found 351.14289.

Ethyl 4-(2-chloropyridin-4-yl)benzoate. A mixture of 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.26 g, 5.24 mmol), tetrakis(triphenylphosphine)palladium(0) (0.303 g, 0.26 mmol), ethyl 4-(2-chloropyridin-4-yl)benzoate (0.887 g, 3.39 mmol), cesium carbonate (4.27 g, 13.10 mmol), DME (12 mL) and water (6 mL) was heated at 80 °C overnight under nitrogen. The layers were separated and the organic layer concentrated. The residue was purified on silica gel (0-25% EtOAc/heptane as eluent) to afford the title compound (0.887 g, 78 %) as a white solid.

LCMS (Table 9. Method b) R_t = 1.54 min.; MS m/z: 262.1 $(M+H)^+$.

4-(2-Chloropyridin-4-yl)benzoic acid. A mixture of ethyl 4-(2-chloropyridin-4-yl)benzoate (0.887 g, 3.39 mmol) and lithium hydroxide hydrate (0.711 g, 16.95 mmol) in THF (24 mL) and water (8.0 mL) was stirred at RT overnight. After removal of the organic solvent the residue was diluted with water (30 mL) and adjusted to pH 5 with acetic acid. The precipitate was collected by filtration, washed with water and dried in a vacuum oven to afford the title compound (780 mg, 98 %) as a white solid.

LCMS (Table 9. Method b) R_t = 1.29 min.; MS m/z: 234.1 $(M+H)^+$.

4-(2-Chloropyridin-4-yl)benzoyl chloride. To a suspension of 4-(2-chloropyridin-4-yl)benzoic acid (730 mg, 3.12 mmol) in DCM (70 mL) was added oxalyl chloride (2.14 mL, 4.28 mmol) followed by a drop of DMF. The mixture was stirred at RT overnight. The solvent was removed to give a light yellow solid that was used immediately in the next step.

(R)-4-(2-Chloropyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (20). To a mixture of 4-(2-chloropyridin-4-yl)benzoyl chloride (788 mg, 3.13 mmol) in DCM (30 mL) was added (R)-1-(3-methoxyphenyl)ethanamine (520 mg, 3.44 mmol) followed by DIEA (1.64 mL, 9.38 mmol). The mixture was stirred at RT overnight. The reaction mixture was washed with 1 M HCl (50 mL), 0.5 M NaOH (30 mL) and saturated brine (30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to afford a residue that was purified on silica gel (25-50% EtOAc/heptane as eluent). Fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (1.1 g, 96 %) as a white solid.

LCMS (Table 9. Method c): R_t = 2.34 min.; MS m/z: 367.18 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.1), 8.03 (1 H, d, J 5.3), 7.97 (2 H, d, J 8.3), 7.72 (2 H, d, J 8.3), 7.22 (1 H, t, J 8.1), 6.99 – 6.92 (2 H, m), 6.82 – 6.74 (2 H, m), 6.70 (1 H, s), 6.51 (1 H, t, J 5.5), 5.14 (1 H, p, J 7.1), 3.73 (3 H, s), 3.28 (2 H, d, J 3.6), 1.46 (3 H, d, J 7.1), 1.13 (3 H, t, J 7.1). δ C (101 MHz, DMSO) 165.51, 159.97, 159.74, 148.89, 147.30, 147.01, 141.52, 134.97, 129.72, 128.51, 126.73, 118.77, 112.46, 112.23,

109.98, 105.56, 55.43, 48.95, 35.96, 22.74, 15.24. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}ClN_2O_2$ 367.11351; Found 367.11444.

(R)-N-(1-(3-Methoxyphenyl)ethyl)-4-(2-methylpyridin-4-yl)benzamide (21). To a degassed suspension of (R)-4-bromo-N-(1-(3-methoxyphenyl)ethyl)benzamide (210 mg, 0.63 mmol), 2-methylpyridin-4-ylboronic acid (110 mg, 0.80 mmol) and cesium carbonate (620 mg, 1.90 mmol) in a dioxane/water (10 mL, 1:1) was added bis(triphenylphosphine)palladium(II) dichloride (45 mg, 0.06 mmol) and the mixture heated at 100 °C overnight. The mixture was partitioned between EtOAc (20 mL) and water (20 mL) and the layers separated. The organic later was dried (Na_2SO_4), filtered, evaporated to dryness and then partitioned between 1 M HCl (20 mL) and EtOAc (20 mL). The aqueous phase was neutralized with saturated Na_2CO_3 (20 mL), extracted with EtOAc (2 X 20 mL). The combined organic layers were concentrated and purified on silica gel (0-100% EtOAc/heptane as eluent). The fractions containing the desired product were combined, concentrated and dried in a vacuum oven at 55-60 °C overnight. Water (10 mL) and MeCN (3 mL) were added and the mixture lyophilized to afford the title compound (40 mg, 18 %) as a white solid.

LCMS (Table 9. Method b) R_t = 1.2 min.; MS m/z: 347.17 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.84 (1 H, d, J 8.1), 8.51 (1 H, d, J 5.2), 8.00 (2 H, d, J 8.3), 7.87 (2 H, d, J 8.3), 7.62 (1 H, s), 7.53 (1 H, d, J 5.1), 7.22 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, dd, J 8.2, 2.4), 5.15 (1 H, p, J 7.1), 3.73 (3 H, s), 2.53 (3 H, s), 1.47 (3 H, d, J 7.0). δ C (101 MHz, DMSO) 165.40, 159.74, 159.15, 150.05, 146.99, 146.76, 140.36, 135.31, 129.73, 128.61, 127.09, 121.00, 118.96, 118.77, 112.47, 112.25, 55.44, 48.97, 24.58, 22.72. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}N_2O_2$ 347.16813; Found 347.16851.

(R)-4-(2,6-Dimethylpyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (22). As per compound **21** except 2,6-dimethylpyridin-4-ylboronic acid (172 mg, 1.14 mmol). The title compound (50 mg, 16 %) as a white solid.

LCMS (Table 9. Method b) R_t = 1.05 min.; MS m/z: 361.19 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.84 (1 H, d, J 8.1), 7.99 (2 H, d, J 8.3), 7.84 (2 H, d, J 8.4), 7.40 (2 H, s), 7.22 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, dd, J 8.2, 2.4), 5.15 (1 H, p, J 7.1), 3.73 (3 H, s), 2.48 (6 H, s), 1.47 (3 H, d, J 7.1). δ C (101 MHz, DMSO) 165.41, 159.74, 158.38, 147.16, 146.99, 140.64, 135.17, 131.87, 129.73, 129.12, 128.55, 127.04, 118.78, 118.14, 112.48, 112.24, 55.43, 48.96, 24.51, 22.71. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_2O_2$ 361.18378; Found 361.18431.

(R)-4-(3-Fluoropyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (23). As per compound **21**except 3-fluoropyridin-4-ylboronic acid hydrate (114 mg, 0.72 mmol). The title compound (77 mg 37 %).

LCMS (Table 9. Method c) R_t = 2.20 min.; MS m/z: 351.18 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.88 (1 H, d, J 8.1), 8.67 (1 H, d, J 2.5), 8.52 (1 H, d, J 4.9), 8.02 (2 H, d, J 8.3), 7.76 (2 H, d, J 7.1), 7.66 (1 H, dd, J 6.9, 5.0), 7.23 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, dd, J 8.0, 2.1), 5.15 (1 H, p, J 7.0), 3.73 (3 H, s), 1.47 (3 H, d, J 7.1). δ C (101 MHz, DMSO) 165.38, 159.75, 156.49 (d, J 256.2), 146.94, 146.86 (d, J 5.2), 139.21 (d, J 25.2), 135.67, 135.32, 134.76 (d, J 10.3), 129.74, 129.17 (d, J 3.3), 128.35, 124.90, 118.75, 112.44, 112.27, 55.44, 49.02, 22.74. δ F (376 MHz, DMSO-d6) -133.28 (d, J 6.7, 26). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}FN_2O_2$ 351.14306; Found 351.14329.

4-(Pyrimidin-4-yl)benzoic acid. A mixture of 4-carboxyphenylboronic acid (0.604 g, 3.64 mmol), 4-chloropyrimidine hydrochloride (0.500 g, 3.31 mmol), DME (20 mL) and water (10 mL) was treated with N,N-diisopropylethylamine (0.859 ml, 4.97 mmol) and stirred for 5 minutes before the addition of cesium carbonate (0.927 ml, 11.59 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes before the addition of tetrakis(triphenylphosphine)palladium(0) (0.191 g, 0.17 mmol). The reaction was heated at 80 °C under nitrogen for 72 hours. The DME was removed in vacuo and the aqueous residue diluted with water (80 mL). The basic aqueous layer was washed with DCM (3 X 40 mL) before being filtered through Celite™. The Celite™ was washed with water (2 X 20 mL) and

DCM (2 X 30 mL). The filtrate was acidified to pH 4 with 1 M HCl (20 mL). The resultant suspension was collected, washed with DCM (4 X 100 mL) and dried to afford the title compound (0.565 g, 85 %) as a grey powdery solid.

LCMS (Table 9. Method b): R_t = 1.09 min.; MS m/z: 201.1 $(M+H)^+$. δ H (400 MHz, DMSO) 13.29-13.04 (m, 1H), 9.34-9.29 (d, J = 1.18, 1H), 8.96-8.91 (m, J = 5.36, 1H), 8.37-8.30 (m, 2H), 8.20-8.17 (dd, J = 1.30, 5.37, 1H), 8.13-8.08 (m, 2H).

(R)-N-(1-(3-Methoxyphenyl)ethyl)-4-(pyrimidin-4-yl)benzamide (24). Under an atmosphere of nitrogen, at RT, a solution of 4-(pyrimidin-4-yl)benzoic acid (100 mg, 0.50 mmol)and 1-hydroxybenzotriazole hydrate (77 mg, 0.50 mmol), N-methylmorpholine (0.122 mL, 1.10 mmol) and (R)-(+)-1-(3-methoxyphenyl)ethylamine (84 mg, 0.55 mmol) in anhydrous DMF (15 mL) was stirred for 15 minutes before the addition of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (106 mg, 0.55 mmol). The solution was stirred at RT for 18 h and then poured into water (150 mL) and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with 0.5 M NaOH (2 X 60 mL), water (3 X 60 mL), dried ($MgSO_4$), filtered and solvent removed to afford a residue dried to constant weight in the vacuo at 60 °C for 24 hours. This afforded the title compound (142 mg, 81 %) as a pale yellow solid.

LCMS (Table 9. Method c): R_t = 1.96 min.; MS m/z: 334.2 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.27 (1 H, s), 8.93 – 8.86 (2 H, m), 8.29 (2 H, d, J 8.3), 8.15 (1 H, d, J 5.4), 8.04 (2 H, d, J 8.2), 7.23 (1 H, t, J 8.1), 7.00 – 6.94 (2 H, m), 6.78 (1 H, dd, J 8.2, 2.4), 5.15 (1 H, p, J 7.1), 3.75 – 3.70 (3 H, m), 1.47 (3 H, d, J 7.0). δ C (101 MHz, DMSO) 165.32, 162.18, 159.74, 159.27, 158.73, 146.91, 138.76, 137.18, 129.75, 128.52, 127.32, 118.78, 118.03, 115.13, 112.48, 112.28, 55.44, 49.03, 22.70. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}N_3O_2$ 334.14773; Found 334.14766.

(R)-N-(1-(3-Methoxyphenyl)ethyl)-4-(pyridazin-4-yl)benzamide (25). As per compound **24** except 4-(pyridazin-4-yl)benzoic acid (95 mg, 0.48 mmol).. The title compound (32 mg 25 %).

LCMS (Table 9. Method b): R_t = 1.25 min.; MS m/z: 334.20 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.68 (1 H, d, J 1.3), 9.30 (1 H, d, J 5.4), 8.89 (1 H, d, J 8.1), 8.09 – 7.99 (5 H, m), 7.23 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.78 (1 H, dd, J 8.2, 2.4), 5.15 (1 H, p, J 7.2), 3.73 (3 H, s), 1.47 (3 H, d, J 7.0). δ C (101 MHz, DMSO) 165.22, 159.75, 152.15, 149.83, 146.93, 136.92, 136.74, 136.17, 129.75, 128.78, 127.58, 123.88, 118.76, 112.45, 112.28, 55.44, 49.03, 22.72. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}N_3O_2$ 334.14773; Found 334.14817.

(R)-4-(2-(Ethylamino)pyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (26). A suspension of sodium 2-methylpropan-2-olate (17 mg, 0.18 mmol), (R)-4-(2-chloropyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (55 mg, 0.15 mmol) and ethanamine (2.0 M in THF, 0.112 ml, 0.22 mmol) in dioxane (1 mL) was degassed by bubbling nitrogen through it for 3 minutes. A suspension of $Pd_2(dba)_3$ (14 mg, 0.02 mmol) and ^{t}BuXPhos (28 mg, 0.07 mmol) in dioxane (0.6 mL) was degassed by bubbling nitrogen through for 3 min, heated to 80 °C for 1 min, cooled down to RT for 10 min then added to the reaction mixture. The resulting mixture was stirred at 80 °C overnight and then evaporated to dryness. The crude material was purified on silica gel (15-95% MeCN/Water as eluent) to afford the title compound (39 mg, 69 %) as a white fluffy solid.

LCMS (Table 9. Method c): R_t = 1.81 min.; MS m/z: 376.24 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.1), 8.03 (1 H, d, J 5.3), 7.97 (2 H, d, J 8.3), 7.72 (2 H, d, J 8.3), 7.22 (1 H, t, J 8.1), 6.99 – 6.92 (2 H, m), 6.82 – 6.74 (2 H, m), 6.70 (1 H, s), 6.51 (1 H, t, J 5.5), 5.14 (1 H, p, J 7.1), 3.73 (3 H, s), 3.28 (2 H, d, J 3.6), 1.46 (3 H, d, J 7.1), 1.13 (3 H, t, J 7.1). δ C (101 MHz, DMSO) 165.51, 159.97, 159.74, 148.89, 147.30, 147.01, 141.52, 134.97, 129.72, 128.51, 126.73, 118.77, 112.46, 112.23, 109.98, 105.56, 55.43, 48.95, 35.96, 22.74, 15.24. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}N_3O_2$ 376.19468; Found 376.1952.

(R)-4-(2-(Cyclopropylmethylamino)pyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (27). As per compound **26** except cyclopropylmethanamine (0.02 mL, 0.23 mmol). The title compound was afforded (32 mg, 54 %) as a white fluffy solid.

LCMS (Table 9. Method c): R_t = 2.03 min.; MS m/z: 402.23 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.1), 8.02 (1 H, d, J 5.2), 7.97 (2 H, d, J 8.3), 7.72 (2 H, d, J 8.3), 7.22 (1 H, t, J 8.1), 6.99 – 6.92 (2 H, m), 6.81 – 6.74 (3 H, m), 6.62 (1 H, t, J 5.6), 5.14 (1 H, p, J 7.1), 3.73 (3 H, s), 3.16 (2 H, t, J 6.1), 1.46 (3 H, d, J 7.1), 1.11 – 0.99 (1 H, m), 0.47 – 0.36 (2 H, m), 0.27 – 0.16 (2 H, m). δ C (101 MHz, DMSO) 165.51, 160.03, 159.74, 148.80, 147.27, 147.01, 141.50, 134.98, 129.72, 128.51, 126.72, 118.77, 112.46, 112.23, 109.98, 105.77, 55.43, 48.95, 45.75, 22.74, 11.41, 3.80. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}N_3O_2$ 402.21033; Found 402.21088.

(R)-4-(2-(2-Hydroxy-2-methylpropylamino)pyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (28). As per compound **26** except 1-amino-2-methylpropan-2-ol (20 mg, 0.23 mmol). The title compound was afforded (39 mg, 62 %) as a white fluffy solid.

LCMS (Table 9. Method c): R_t = 1.78 min.; MS m/z: 420.24 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.1), 8.03 – 7.93 (3 H, m), 7.73 (2 H, d, J 8.3), 7.22 (1 H, t, J 8.1), 6.99 – 6.93 (2 H, m), 6.89 (1 H, s), 6.82 – 6.74 (2 H, m), 6.41 (1 H, t, J 5.8), 5.14 (1 H, p, J 7.0), 4.69 (1 H, s), 3.73 (3 H, s), 3.27 (2 H, s), 1.46 (3 H, d, J 7.1), 1.12 (6 H, s). δ C (101 MHz, DMSO) 165.50, 160.48, 159.74, 148.44, 147.32, 147.01, 141.41, 134.99, 129.72, 128.50, 126.72, 118.77, 112.47, 112.24, 110.06, 106.12, 70.22, 55.44, 52.49, 48.95, 28.00, 22.73. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{30}N_3O_3$ 420.22089; Found 420.22137.

(R)-4-(2-(2-Methoxyethylamino)pyridin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)benzamide (29). As per compound **26** except 2-methoxyethanamine (0.02 mL, 0.23 mmol). The title compound was afforded (33 mg, 54 %) as a white fluffy solid.

LCMS (Table 9. Method c): R_t = 1.85 min.; MS m/z: 406.22 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.0), 8.06 – 8.00 (1 H, m), 7.97 (2 H, d, J 7.6), 7.72 (2 H, d, J 7.7), 7.22 (1 H, td, J 8.1, 1.0), 6.96 (2 H, d, J 5.0), 6.82 – 6.74 (3 H, m), 6.59 (1 H, s), 5.13 (1 H, q, J 7.2), 3.73 (3 H, d, J 1.0), 3.46 (4 H, s), 3.26 (3 H, s), 1.46 (3 H, d, J 7.0). δ C (101 MHz, DMSO) 165.51, 159.87, 159.74, 148.74, 147.33, 147.01, 141.42, 135.00, 129.72, 128.51, 126.73, 118.77, 112.46, 112.24, 110.19, 106.03, 71.39, 58.40, 55.43, 48.95, 40.83, 22.74. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}N_3O_3$ 406.20524; Found 406.20556.

(R)-N-(1-(3-Methoxyphenyl)ethyl)-4-(2-(3-methoxypropylamino)pyridin-4-yl)benzamide (30). As per compound **27** 3-methoxypropan-1-amine (0.02 mL, 0.23 mmol). The title compound was afforded (22 mg, 34 %) as a white fluffy solid.

LCMS (Table 9. Method c): R_t = 1.85 min.; MS m/z: 420.24 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.81 (1 H, d, J 8.1), 8.03 (1 H, d, J 5.3), 7.97 (2 H, d, J 8.2), 7.72 (2 H, d, J 8.3), 7.22 (1 H, t, J 8.0), 6.99 – 6.93 (2 H, m), 6.83 – 6.74 (2 H, m), 6.72 (1 H, s), 6.56 (1 H, t, J 5.6), 5.14 (1 H, p, J 6.9), 3.73 (3 H, s), 3.39 (2 H, t, J 6.3), 3.34 – 3.29 (2 H, m), 3.25 – 3.20 (3 H, m), 1.76 (2 H, p, J 6.6), 1.46 (3 H, d, J 7.1). δ C (101 MHz, DMSO) 165.51, 160.05, 159.74, 148.85, 147.31, 147.01, 141.48, 134.98, 129.72, 128.51, 126.73, 118.77, 112.46, 112.23, 110.03, 105.60, 70.33, 58.35, 55.43, 48.95, 38.49, 29.63, 22.73. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{30}N_3O_3$ 420.22089; Found 420.22138.

(R)-tert-butyl 3-hydroxy-1-phenylpropylcarbamate. Di-tert-butyl dicarbonate (413 mg, 1.89 mmol) was added to a stirred mixture of (R)-3-amino-3-phenylpropan-1-ol hydrochloride (237 mg, 1.26 mmol), DCM (3 mL) and Et_3N (0.37 mL, 2.65 mmol) and the mixture stirred at RT overnight. The mixture was concentrated and purified on silica gel (0-50% EtOAc/heptane as eluent). Fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (309 mg, 97 %) as an oil.

LCMS (Table 9. Method b): R_t = 1.35 min.; MS m/z: no ionization.

(R)-3-(tert-Butoxycarbonylamino)-3-phenylpropyl methanesulfonate. A solution of (R)-tert-butyl 3-hydroxy-1-phenylpropylcarbamate (295 mg, 1.174 mmol) in pyridine (2 mL) was cooled down to 0 °C. Methanesulfonyl chloride (0.10 mL, 1.29 mmol) was added dropwise. The mixture was slowly warmed up to RT and stirred overnight then diluted with DCM and washed with water. The organic layer was concentrated to afford the title compound (390 mg, 101 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.46 min.; MS m/z: no ionization

(R)-tert-Butyl 1-phenyl-3-(pyrrolidin-1-yl)propylcarbamate. To a mixture of (R)-3-(tert-butoxycarbonylamino)-3-phenylpropyl methanesulfonate (380 mg, 1.15 mmol) and K_2CO_3 (319 mg, 2.31 mmol) in MeCN (3 mL) was added pyrrolidine (0.19 mL, 2.31 mmol) dropwise. The mixture was heated at 50 °C for 4 h, filtered, washed with MeCN and concentrated. The residue was partitioned between DCM and 1 M HCl and the organic layer dried ($MgSO_4$) and concentrated to afford the title compound (301 mg, 86 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.24 min.; MS m/z: no ionization.

(R)-1-Phenyl-3-(pyrrolidin-1-yl)propan-1-amine dihydrochloride. A mixture of (R)-tert-butyl 1-phenyl-3-(pyrrolidin-1-yl)propylcarbamate (301 mg, 0.99 mmol) and 4 M HCl in dioxane (2 mL, 8.0 mmol) was stirred at RT for 1 hour then concentrated. Ether was added and the solution decanted. The residue was dissolved in MeOH and concentrated dry to give an oil (276 mg, 101%) that was used in the next step.

(R)-N-(1-Phenyl-3-(pyrrolidin-1-yl)propyl)-4-(pyridin-4-yl)benzamide (36). To a vial charged with 4-(pyridin-4-yl)benzoic acid (50 mg, 0.25 mmol), HOBt (42 mg, 0.28 mmol) and EDC (53 mg, 0.28 mmol) was added a solution of (R)-1-phenyl-3-(pyrrolidin-1-yl)propan-1-amine dihydrochloride (76 mg, 0.28 mmol) in DMF (1 mL), followed by DIEA (88 µl, 0.50 mmol). The mixture was stirred at RT for 1 hour then purified by HPLC (5-65% MeCN/10 mM ammonium acetate as eluent). Fractions

containing the desired compound were combined and evaporated to dryness to afford the title compound (35 mg, 36 %).

LCMS (Table 9. Method c): R_t = 1.50 min.; MS m/z: 386.19 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.11 (1 H, d, J 8.0), 8.69 – 8.62 (2 H, m), 7.98 (2 H, d, J 8.3), 7.90 (2 H, d, J 8.3), 7.75 (2 H, dd, J 4.7, 1.5), 7.38 (2 H, d, J 7.2), 7.31 (2 H, t, J 7.6), 7.21 (1 H, t, J 7.3), 5.11 (1 H, q, J 7.9), 2.48 – 2.41 (6 H, m), 1.99 (2 H, dq, J 14.5, 7.3), 1.74 – 1.62 (4 H, m). δ C (101 MHz, DMSO) 165.53, 150.77, 146.49, 144.22, 140.15, 135.45, 128.68, 128.52, 127.20, 127.10, 126.89, 121.79, 54.06, 53.16, 52.50, 35.07, 23.61. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}N_3O$ 386.21541; Found 386.21655.

(R)-tert-Butyl 3-hydroxy-1-(3-methoxyphenyl)propylcarbamate. To a cold solution (0 °C) of (R)-3-(tert-butoxycarbonylamino)-3-(3-methoxyphenyl)propanoic acid (0.5 g, 1.69 mmol) in DME (5 mL) was added N-methylmorpholine (0.20 mL, 1.86 mmol) followed by isobutyl carbonochloridate (0.24 mL, 1.86 mmol). The mixture was stirred at 0 °C for 30 min and then the precipitate was filtered off and washed with small amount of DME. The mixture was cooled to 0 °C and a suspension of $NaBH_4$ (0.1 g, 2.54 mmol) in water (1 mL) added. The mixture was stirred at RT for 10 min then water (20 mL) was added. The mixture was extracted with EtOAc (3 X 25 mL) and the combined organic layers dried (Na_2SO_4), filtered and evaporated to dryness to afford the title compound as a colourless oil that was used in the next step without further purification.

LCMS (Table 9. Method b): R_t =1.34 min.; MS m/z: 282.15 $(M+H)^+$.

(R)-3-(tert-Butoxycarbonylamino)-3-(3-methoxyphenyl)propyl methanesulfonate. A stirred solution of (R)-tert-butyl 3-hydroxy-1-(3-methoxyphenyl)propylcarbamate (0.48 g, 1.69 mmol), DCM (5 mL) and Et_3N (0.24 mL, 1.69 mmol) was cooled to 0 °C. Methanesulfonyl chloride (0.16 mL, 2.03 mmol) was added dropwise and the mixture warmed RT and stirred overnight. The mixture was diluted with DCM (20 mL), washed with water (20 mL), 1 M HCl (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated to dryness to give an colourless oil that was triturated with ether. The resulting

solid was collected by filtration, washed with ether and dried to afford the title compound (421 mg, 69 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.45 min.; MS m/z: weak ionization. δ H (400 MHz, DMSO) 7.48 (d, J = 8.6, 1H), 7.24 (t, J = 7.8, 1H), 6.84 (dd, J = 8.0, 24.2, 3H), 4.59 (dd, J = 8.1, 15.7, 1H), 4.23 - 4.05 (m, 2H), 3.74 (s, 3H), 3.15 (s, 3H), 2.08 - 1.93 (m, 2H), 1.36 (s, 9H).

(R)-tert-Butyl 1-(3-methoxyphenyl)-3-(pyrrolidin-1-yl)propylcarbamate. To a mixture of (R)-3-(tert-butoxycarbonylamino)-3-(3-methoxyphenyl)propyl methanesulfonate (250 mg, 0.70 mmol) and K_2CO_3 (192 mg, 1.39 mmol) in MeCN (3 mL) was added pyrrolidine (0.12 mL, 1.39 mmol) dropwise. The mixture was heated at 50 °C for 6 h then filtered, washed with MeCN and concentrated. The residue was partitioned between DCM and 1 M HCl and the organic layer dried ($MgSO_4$), filtered and concentrated to afford the title compound (243 mg, 104 %) as a semi-solid.

LCMS (Table 9. Method b): R_t = 1.25 min; MS m/z: 335.20 $(M+H)^+$.

(R)-1-(3-Methoxyphenyl)-3-(pyrrolidin-1-yl)propan-1-amine dihydrochloride. A mixture of (R)-tert-butyl 1-(3-methoxyphenyl)-3-(pyrrolidin-1-yl)propylcarbamate (233 mg, 0.70 mmol) and 4 M HCl in dioxane (1.5 mL, 6.00 mmol) was stirred at RT for 1 hour (turned from a solution to a milky solution). Ether was added and the solution decanted. The residue was dissolved in MeOH and concentrated dry to afford the title compound as a semi-solid that was used in the next step.

(R)-N-(1-(3-Methoxyphenyl)-3-(pyrrolidin-1-yl)propyl)-4-(pyridin-4-yl)benzamide (37). To a vial charged with 4-(pyridin-4-yl)benzoic acid (60 mg, 0.301 mmol), HOBt (55 mg, 0.36 mmol) and EDC (69 mg, 0.36 mmol) was added a solution of (R)-1-(3-methoxyphenyl)-3-(pyrrolidin-1-yl)propan-1-amine dihydrochloride (102 mg, 0.331 mmol) in DMF (1 mL), followed by DIEA (116 µL, 0.663 mmol) and the mixture stirred at RT for 1 hour. The mixture was concentrated and purified by HPLC (5-65% MeCN/10 mM ammonium acetate over 40 min; flow rate 21 ml/min). Fractions containing the

desired compound were combined and evaporated to dryness to afford the title compound (77 mg, 62 %) as a hydroscopic solid.

LCMS (Table 9. Method c): R_t = 1.52 min.; MS m/z: 416.18$(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.08 (1 H, d, J 8.0), 8.69 – 8.62 (2 H, m), 7.98 (2 H, d, J 8.3), 7.90 (2 H, d, J 8.4), 7.75 (2 H, d, J 6.1), 7.22 (1 H, t, J 8.1), 6.98 – 6.91 (2 H, m), 6.78 (1 H, dd, J 8.3, 2.3), 5.08 (1 H, q, J 8.0), 3.73 (3 H, s), 2.46 – 2.38 (6 H, m), 1.97 (2 H, ddt, J 20.1, 13.6, 6.9), 1.68 (4 H, s). δ C (101 MHz, DMSO) 165.52, 159.72, 150.77, 146.49, 145.92, 140.14, 135.47, 129.70, 128.50, 127.22, 121.79, 119.19, 112.80, 112.30, 55.43, 54.05, 53.17, 52.50, 35.17, 23.62. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{30}N_3O_2$ 416.22598; Found 416.22656. Chiral analysis (Table 10, a) 95% ee, negative (-) optical rotation.

(R)-3-Amino-3-(3-methoxyphenyl)propan-1-ol hydrochloride. A mixture of (R)-tert-butyl 3-hydroxy-1-(3-methoxyphenyl)propylcarbamate (476 mg, 1.69 mmol) and 4 M HCl in dioxane (4 mL, 16.00 mmol) was stirred at RT for 30 minutes. The reaction mixture was concentrated, ether added and a sticky semisolid formed, decanted and evaporated to dryness. This gave the title compound (368 mg, 100%) as a semi-solid.

LCMS (Table 9. Method b): R_t = 1.10 min.; MS m/z: 182.12 $(M+H)^+$.

(R)-N-(3-Hydroxy-1-(3-methoxyphenyl)propyl)-4-(pyridin-4-yl)benzamide (38). To a vial charged with 4-(pyridin-4-yl)benzoic acid (50 mg, 0.25 mmol), HOBt (46 mg, 0.30 mmol) and EDC (58 mg, 0.30 mmol) was added a solution of (R)-3-amino-3-(3-methoxyphenyl)propan-1-ol hydrochloride (66 mg, 0.30 mmol) in DMF (1 mL), followed by DIEA (53 µL, 0.30 mmol). The mixture was stirred at RT for 1 hour then purified by HPLC (10-70% MeCN/10 mM ammonium acetate over 40 min; flow rate 21 ml/min). Fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (55 mg, 60 %) as a white solid.

LCMS (Table 9. Method b): R_t = 0.98 min.; MS m/z: 363.16 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.82 (1 H, d, J 8.2), 8.65 (2 H, d, J 5.9), 7.99 (2 H, d, J 8.3), 7.90 (2 H, d, J 8.3), 7.78 – 7.71 (2 H, m), 7.22 (1 H, t, J 8.1), 6.95 (2 H, d, J 7.5), 6.81 – 6.74 (1 H, m), 5.19 – 5.09 (1 H, m), 4.54 (1 H, s), 3.73 (3 H, s), 3.28 (2 H, s), 2.02 (1 H, ddd, J 14.5, 8.7, 4.6), 1.89 (1 H, dq, J 13.2, 6.4). δ C (101 MHz, DMSO) 165.63, 159.71, 150.77, 146.51, 146.16, 140.09, 135.53, 129.68, 128.60, 127.17, 121.78, 119.25, 112.87, 112.26, 58.35, 55.42, 50.86, 39.45. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}N_2O_3$ 363.16304; Found 363.16352. Chiral analysis (Table 10, a), >99% ee, negative (-) optical rotation.

4-(2-Fluoropyridin-4-yl)benzoate. A stirred mixture of 2-fluoropyridin-4-ylboronic acid (2.36 g, 16.74 mmol) and methyl 4-bromobenzoate (2.95 g, 12.76 mmol), $Pd(PPh_3)_4$ (0.967 g, 0.84 mmol), cesium carbonate (13.64 g, 41.9 mmol), DME (50 mL) and water (6 mL) was heated at 80 °C overnight under nitrogen. The aqueous layer was removed and the organic layer concentrated and purified on silica gel (0-20% EtOAc/heptane as eluent) to afford the title compound (2.95 g, 91 %) as a white solid.

LCMS (Table 9. Method c): R_t =2.35 min.; (no ionization). ^{1}H (400 MHz, CDCl3) δ 8.31 (d, J = 5.3 Hz, 1H), 8.17 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 5.3 Hz, 1H), 7.16 (s, 1H), 3.96 (s, 3H).

4-(2-Fluoropyridin-4-yl)benzoic acid hydrochloride. To a 100 mL round-bottomed flask charged with methyl 4-(2-fluoropyridin-4-yl)benzoate (1.53 g, 6.62 mmol) and LiOH (0.317 g, 13.23 mmol) was added 1,4-dioxane (20 mL) and water (1 mL) to give a white suspension. The resulting suspension was stirred at 40 °C for 2 hours then cooled to RT. The reaction mixture was acidified to pH 1 by addition of 6 M HCl then cooled down to about 4 °C in an ice bath. The precipitate was collected by filtration, washed with cold water (10 mL), dried under to afford the title compound (1.3 g, 77 %) as a white solid.

LCMS (Table 9. Method c): R_t =1.72 min.; MS m/z: 216 $(M-H)^-$. δ H (400 MHz, methanol-D4) 8.29 (d, J = 5.3 Hz, 1H), 8.16 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 5.3 Hz, 1H), 7.43 (s, 1H).

(R)-tert-Butyl 3-hydroxy-1-(3-methoxyphenyl)propylcarbamate. To a cold solution (0 °C) of (R)-3-(tert-butoxycarbonylamino)-3-(3-methoxyphenyl)propanoic acid (4.03 g, 13.64 mmol) in DME (40 mL) was added N-methylmorpholine (1.65 mL, 15.01 mmol) followed by isobutyl carbonochloridate (1.96 mL, 15.01 mmol) and the mixture stirred at 0 °C for 30 minutes. The precipitate was filtered off and washed with a small amount of DME and cooled to 0 °C. A suspension of $NaBH_4$ (0.774 g, 20.46 mmol) in water (8 mL) was then added in one portion. The mixture was stirred at RT for 10 min then water (20 mL) was added. The mixture was extracted with EtOAc (3 X 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a colourless oil (3.82 g, 99 %) that was used in the next step without further purification.

LCMS (Table 9. Method c): R_t = 1.97 min.; MS m/z: 282 $(M+H)^+$. δ H (400 MHz, DMSO) 7.29 (d, J = 8.6, 1H), 7.21 (t, J = 8.1, 1H), 6.84 (d, J = 6.6, 2H), 6.80 - 6.73 (m, 1H), 4.57 (d, J = 6.7, 1H), 4.45 (t, J = 4.9, 1H), 3.73 (s, 3H), 3.35 (d, J = 5.4, 1H), 3.31 - 3.25 (m, 1H), 1.89 - 1.59 (m, 2H), 1.36 (s, 9H).

(R)-3-(tert-Butoxycarbonylamino)-3-(3-methoxyphenyl)propyl methanesulfonate. To a solution of (R)-tert-butyl 3-hydroxy-1-(3-methoxyphenyl)propylcarbamate (3 g, 10.66 mmol) and DCM (40 mL) under nitrogen at 0 °C was added Et_3N (1.49 mL, 10.66 mmol). Methanesulfonyl chloride (1.0 mL, 12.80 mmol) was then added dropwise. After stirring for 3 hours, the solution was diluted with DCM (50 mL) and washed with water (50 mL), 0.5 M aq HCl (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to afford the title compound (3.58 g, 93 %) as a white solid.

LCMS (Table 9. Method c): R_t = 2.34 min.; MS m/z: 377 $(M+H_2O)^+$. δ H (400 MHz, DMSO) 7.48 (d, J = 7.8 1H), 7.24 (t, J = 7.8, 1H), 6.90 - 6.78 (m, 3H), 4.63 - 4.54 (m, 1H), 4.24 - 4.05 (m, 2H), 3.74 (s, 3H), 3.15 (s, 3H), 2.09 - 1.94 (m, 2H), 1.36 (s, 9H).

(R)-tert-Butyl 1-(3-methoxyphenyl)-3-morpholinopropylcarbamate. To a solution of (R)-3-(tert-butoxycarbonylamino)-3-(3-methoxyphenyl)propyl methanesulfonate (3.58 g, 9.96 mmol) and

acetonitrile (50 mL) under nitrogen was added morpholine (3.47 mL, 39.8 mmol). Cesium carbonate (6.49 g, 19.92 mmol) was then added in one portion. The resulting mixture was warmed to 75 °C for 16 hours. The mixture was allowed to cool to RT and then filtered. The volatiles were removed under reduced pressure and the residue partitioned between 50% saturated aqueous $NaHCO_3$ (100 mL) and DCM (50 mL). The layers were separated and the aqueous layer extracted with DCM (50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude material was purified on silica gel to afford the title compound (3.13 g, 90 %) as a thick, clear, colourless oil.

LCMS (Table 9. Method d): R_t = 1.71 min.; MS m/z: 351 $(M+H)^+$. δ H (400 MHz, DMSO) 7.38 (d, J = 8.7, 1H), 7.21 (t, J = 7.9, 1H), 6.88 - 6.82 (m, 2H), 6.79 - 6.73 (m, 1H), 4.60 - 4.43 (m, 1H), 3.73 (s, 3H), 3.62 - 3.50 (m, 4H), 2.33 - 2.26 (m, 4H), 2.19 (t, J = 7.1, 2H), 1.86 - 1.60 (m, 2H), 1.35 (s, 9H).

(R)-1-(3-Methoxyphenyl)-3-morpholinopropan-1-amine, 2 hydrochloric acid. To (R)-tert-butyl 1-(3-methoxyphenyl)-3-morpholinopropylcarbamate (1.57 g, 4.48 mmol) was added 4 M HCl in dioxane (24.64 mL, 99 mmol). The solution was stirred at RT for 2.5 hours. The volatiles were removed under reduced pressure and the residue triturated with Et_2O (2 X 10 mL) to afford the title compound (1.66 g, 115%) as a yellow-white solid which was used without further purification.

LCMS (Table 9. Method d): R_t = 0.56 min.; MS m/z: 251 $(M+H)^+$. δ H (400 MHz, DMSO) 11.69 - 11.43 (m, 1H), 8.80 (s, 3H), 7.34 (t, J = 6.8, 1H), 7.25 (s, 1H), 7.12 (d, J = 7.2, 1H), 6.99 - 6.90 (d, J = 7.6, 1H), 4.50 - 4.35 (m, 1H), 3.95 - 3.80 (m, 4H), 3.77 (s, 3H), 3.73 - 3.60 (m, 1H), 3.50 - 3.40 (m, 1H), 3.17 - 2.77 (m, 5H), 2.38 - 2.22 (m, 1H).

(R)-4-(2-Fluoropyridin-4-yl)-N-(1-(3-methoxyphenyl)-3-morpholinopropyl)benzamide (39). To a flask containing 4-(2-fluoropyridin-4-yl)benzoic acid hydrochloride (85 mg, 0.33 mmol), EDC (96 mg, 0.50 mmol), (R)-1-(3-methoxyphenyl)-3-morpholinopropan-1-amine dihydrochloride (140 mg, 0.37 mmol) and HOBt (56 mg, 0.37 mmol) was added DIEA (0.29 mL, 1.67 mmol) followed by DMF (2

mL). The mixture was stirred at RT for 1 h, evaporated to dryness and purified on silica gel (0-3% MeOH/DCM as eluent) to afford the title compound (122 mg, 81 %) as a white solid.

LCMS (Table 9. Method b): R_t = 0.98 min.; MS m/z: 450.21 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.93 (1 H, d, J 8.2), 8.32 (1 H, d, J 5.3), 8.04 – 7.93 (4 H, m), 7.75 (1 H, d, J 5.3), 7.59 (1 H, s), 7.22 (1 H, t, J 7.9), 7.00 – 6.93 (2 H, m), 6.82 – 6.74 (1 H, m), 5.07 (1 H, q, J 8.3), 3.73 (3 H, s), 3.59 – 3.52 (4 H, m), 2.35 – 2.25 (6 H, m), 1.96 (2 H, dq, J 25.6, 7.3). δ C (101 MHz, DMSO) 165.49,164.53 (d, J 234.7, 1), 159.72,152.64 (d, J 8.6, 5),148.70 (d, J 15.7), 145.90, 138.82, 136.05, 129.71, 128.59, 127.52,120.23 (d, J 3.8), 119.25, 112.85, 112.37,107.32 (d, J 38.7), 66.70, 55.91, 55.43, 53.89, 52.30, 33.15. δ F (376 MHz, DMSO) -68.57. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{29}FN_3O_3$ 450.21147; Found 450.21169.

(R)-Propyl 3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoate. A mixture of (R)-3-(tert-butoxycarbonylamino)-3-(3-hydroxyphenyl)propanoic acid (2.5 g, 8.9 mmol), 1-iodopropane (3.47 mL, 35.5 mmol) and K_2CO_3 (6.14 g, 44.4 mmol) in DMF (15 mL) was heated at 60 °C overnight. Water (100 mL) was added and the mixture extracted with EtOAc (3 X 30 mL). The combined organic layers were concentrated and purified on silica gel (0-25% EtOAc/heptane as eluent) to afford the title compound (2.48 g, 76 %).

LCMS (Table 9. Method b): R_t = 1.68 min.; MS m/z: 366.22 $(M+H)^+$. δ H (400 MHz, DMSO) 7.41 (d, J = 8.9, 1H), 7.18 (t, J = 7.9, 1H), 6.86 (d, J = 1.8, 1H), 6.83 (d, J = 7.7, 1H), 6.76 (dd, J = 1.9, 8.2, 1H), 4.87 (dd, J = 8.2, 15.5, 1H), 3.97 - 3.90 (m, 2H), 3.88 (t, J = 6.5, 2H), 2.75 - 2.58 (m, 2H), 1.76 - 1.64 (m, 2H), 1.56 - 1.45 (m, 2H), 1.33 (s, 9H), 0.95 (t, J = 7.4, 3H), 0.82 (t, J = 7.4, 3H).

(R)-3-(tert-Butoxycarbonylamino)-3-(3-propoxyphenyl)propanoic acid. To a solution of (R)-propyl 3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoate (2.48 g, 6.79 mmol) in THF (45 mL) was added lithium hydroxide hydrate (1.42 g, 33.9 mmol) followed by water (15 mL). The mixture was then stirred at RT overnight. The organic solvent was removed under reduced pressure and the residue

diluted with water (50 mL) and adjusted to pH 7 with 6 M HCl. The reaction mixture was extracted with EtOAc (3 X 30 mL) and the combined organic layers washed with brine (30 mL), dried (Na_2SO_4), filtered and evaporated to dryness to afford the title compound (2.09 g, 95 %) as a gummy solid.

LCMS (Table 9. Method d): R_t = 2.23 min.; MS m/z: 322.2 $(M-H)^-$.

(R)-tert-Butyl 3-hydroxy-1-(3-propoxyphenyl)propylcarbamate. To a cold solution (0 °C) of (R)-3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoic acid (2.09 g, 6.47 mmol) in THF (10 mL) was added N-methylmorpholine (0.78 mL, 7.11 mmol) followed by isobutyl carbonochloridate (0.93 mL, 7.11 mmol). After stirring at 0 °C for 30 min, the precipitate was filtered off and washed with a small amount of THF. The mixture was cooled to 0 °C and treated with a suspension of $NaBH_4$ (0.37 g, 9.70 mmol) in water (2 mL) in one portion. The mixture was stirred at RT for 3 hours. Water (50 mL) was added and the mixture extracted with EtOAc (3 X 25 mL). The combined organic layers were evaporated to dryness to give a colourless oil that was purified on silica gel (25 - 50 % EtOAc/heptane as eluent). Removal of solvent afforded the title compound (1.74 g, 87 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.45 min.; MS m/z: 310.20 $(M+H)^+$. δ H (400 MHz, DMSO) 7.28 (d, J = 8.5, 1H), 7.19 (t, J = 7.8, 1H), 6.86 - 6.78 (m, 2H), 6.75 (dd, J = 2.3, 8.1, 1H), 4.56 (dd, J = 8.1, 14.9, 1H), 4.44 (t, J = 4.9, 1H), 3.89 (t, J = 6.5, 2H), 3.41 - 3.24 (m, 2H), 1.85 - 1.61 (m, 4H), 1.35 (s, 9H), 0.98 (t, J = 7.4, 3H).

(R)-3-(tert-Butoxycarbonylamino)-3-(3-propoxyphenyl)propyl methanesulfonate. A solution of (R)-tert-butyl 3-hydroxy-1-(3-propoxyphenyl)propylcarbamate (1.4 g, 4.52 mmol) in DCM (15 mL) was cooled to 0 °C. Et_3N (0.76 mL, 5.43 mmol) was added followed by dropwise addition of methanesulfonyl chloride (0.42 mL, 5.43 mmol). The mixture was stirred at 0 °C for 6 h and then diluted with DCM (20 mL), washed with water (20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to dryness to afford an oil. Ether (20 mL) was added and then concentrated to dryness to afford the title compound (1.89 g, 100 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.53 min.(no ionization). δ H (400 MHz, DMSO) 7.47 (d, J = 9.1, 1H), 7.22 (t, J = 7.8, 1H), 6.90 - 6.81 (m, 2H), 6.79 (dd, J = 2.3, 8.2, 1H), 4.58 (dd, J = 6.1, 14.0, 1H), 4.19 (dd, J = 7.0, 16.5, 1H), 4.14 - 4.04 (m, 1H), 3.91 (t, J = 6.5, 2H), 3.15 (s, 3H), 2.09 - 1.89 (m, 2H), 1.72 (dd, J = 7.3, 14.0, 2H), 1.36 (s, 9H), 0.98 (t, J = 7.4, 3H).

(R)-tert-Butyl 3-(piperidin-1-yl)-1-(3-propoxyphenyl)propylcarbamate. To a mixture of (R)-3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propyl methanesulfonate (1.89 g, 4.89 mmol) and K_2CO_3 (1.35 g, 9.78 mmol) in MeCN (20 mL) was added piperidine (0.97 mL, 9.78 mmol) dropwise. The mixture was then heated at 50 °C overnight, filtered, washed with MeCN and concentrated. The residue was partitioned between DCM (50 mL) and 0.1 M HCl (50 mL), the layers separated and the organic layer concentrated to give an oil that was purified on silica gel (0-5% 7M NH_3 in methanol/DCM as eluent) to afford the title compound (1.20 g, 66 %) as a semi-solid.

LCMS (Table 9. Method b): R_t = 1.37 min.; MS m/z: 377.24 $(M+H)^+$. δ H (400 MHz, DMSO) 7.41 (d, J = 8.7, 1H), 7.18 (t, J = 7.9, 1H), 6.84 (d, J = 1.3, 1H), 6.81 (d, J = 7.6, 1H), 6.75 (dd, J = 2.2, 7.9, 1H), 4.48 (dd, J = 7.7, 14.9, 1H), 3.89 (t, J = 6.5, 2H), 2.25 (s, 4H), 2.14 (t, J = 6.9, 2H), 1.78 - 1.65 (m, 5H), 1.48 (dt, J = 5.5, 10.7, 5H), 1.35 (s, 9H), 0.97 (t, J = 7.4, 3H).

(R)-3-(Piperidin-1-yl)-1-(3-propoxyphenyl)propan-1-amine dihydrochloride. To a vial charged with (R)-tert-butyl 3-(piperidin-1-yl)-1-(3-propoxyphenyl)propylcarbamate (1.21 g, 3.21 mmol) was added HCl (4.0 M in dioxane) (8.01 mL, 32.1 mmol). The solution was stirred at RT for 15 min and then the solvent was removed under reduced pressure to give a white solid. Trituration with ether gave a solid that was collected by filtration affording the title compound (1.13 g, 100 %) as an off-white solid.

LCMS (Table 9. Method b): R_t = 1.04 min.; MS m/z: 277.2 $(M+H)^+$.

(R)-4-(2-Fluoropyridin-4-yl)-N-(3-(piperidin-1-yl)-1-(3-propoxyphenyl)propyl)benzamide (40). To a flask containing 4-(2-fluoropyridin-4-yl)benzoic acid hydrochloride (85 mg, 0.33 mmol), EDC (96 mg, 0.50 mmol), (R)-3-(piperidin-1-yl)-1-(3-propoxyphenyl)propan-1-amine dihydrochloride (123 mg, 0.35 mmol) and HOBt (56.4 mg, 0.37 mmol) was added DIEA (0.234 mL, 1.34 mmol) followed by DMF (2mL). The mixture was stirred at RT overnight then diluted with water (30 mL). The reaction mixture was then extracted with DCM (3 X 20 mL) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated to give an orange oil that was purified on silica gel (0-5% MeOH/DCM as eluent). This gave an oil that was triturated several times with ether to afford the title compound (96 mg, 57 %) as a white solid.

LCMS (Table 9. Method c): R_t = 1.93 min.; MS m/z: 476.24 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.99 (1 H, d, J 8.1), 8.32 (1 H, d, J 5.2), 8.04 – 7.93 (4 H, m), 7.75 (1 H, d, J 5.3), 7.59 (1 H, s), 7.20 (1 H, t, J 7.8), 6.98 – 6.89 (2 H, m), 6.77 (1 H, dd, J 7.9, 2.1), 5.05 (1 H, q, J 7.9), 3.89 (2 H, t, J 6.5), 2.44 – 2.17 (6 H, m), 2.12 – 1.87 (2 H, m), 1.70 (2 H, h, J 7.1), 1.56 – 1.43 (4 H, m), 1.39 – 1.34 (2 H, m), 0.95 (3 H, t, J 7.4). δ C (101 MHz, DMSO) 165.45, 164.53 (d, J 234.7), 159.15, 152.62 (d, J 8.5), 148.71 (d, J 15.7), 145.77, 138.86 (d, J 3.4), 136.02, 129.68, 128.57, 127.53, 120.23 (d, J 3.8), 119.11, 113.30, 112.89, 107.32 (d, J 38.8), 69.26, 55.98, 54.47, 52.45, 33.19, 25.87, 24.30, 22.52, 10.87. δ F (376 MHz, DMSO) -68.57. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{35}FN_3O_2$ 476.26351; Found 476.2633. Chiral analysis (Table 10, b), 98% ee, negative (-) optical rotation.

tert-Butyl (R)-(1-(3-fluorophenyl)-3-hydroxypropyl)carbamate. A solution of (R)-3-(tert-butoxycarbonylamino)-3-(3-fluorophenyl)propanoic acid (10 g, 35.3 mmol) (Chem Impex) in DME (80 mL) was cooled to 5 °C and N-methylmorpholine (4.27 mL, 38.8 mmol) and isobutyl carbonochloridate (5.30 g, 38.8 mmol) added sequentially. The mixture was stirred at 5 °C for 30 minutes then filtered. The filtrate was cooled in ice bath and $NaBH_4$ (2.0 g, 52.9 mmol) in water (10 mL) added slowly as a slurry. The suspension was stirred at 5 °C for 1 hour then partitioned between water (30 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 X 30 mL).

The combined organic layers were dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified on silica gel (55-60% EtOAc/heptane as eluent). Fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (9.3 g, 98 %) as an oil.

LCMS (Table 9. Method c): R_t = 2.03 min.; MS m/z: 270.15 $(M+H)^+$.

(R)-3-((tert-Butoxycarbonyl)amino)-3-(3-fluorophenyl)propyl methanesulfonate. A mixture of (R)-tert-butyl 1-(3-fluorophenyl)-3-hydroxypropylcarbamate (6.2 g, 23.02 mmol) in DCM (60 mL) was cooled to 0 °C in an ice bath and then Et_3N (2.33 g, 23.02 mmol) added dropwise. Methanesulfonyl chloride (3.16 g, 27.6 mmol) was then added dropwise via a syringe. The resulting suspension was stirred at 5 °C for 3 hours then at RT overnight. The reaction was partitioned between DCM (50 mL) and water (50 mL) and the layers separated. The organic layer was washed with 0.5 M HCl (25 mL), saturated $NaHCO_3$ solution (20 mL), dried ($MgSO_4$), filtered and concentrated to dryness to afford the title compound (7.7 g, 96 %).

LCMS (Table 9. Method c): R_t = 2.27 min.; MS m/z: 346.15 $(M-H)^-$. δ H (400 MHz, $CDCl_3$) 7.33 (dd, J = 7.9, 14.1, 1H), 7.07 (d, J = 7.6, 1H), 6.98 (t, J = 7.9, 2H), 4.90 (s, 2H), 4.33 - 4.16 (m, 2H), 3.01 (d, J = 4.9, 3H), 2.20 (d, J = 6.1, 2H), 1.42 (s, 9H).

tert-Butyl (R)-(1-(3-fluorophenyl)-3-(pyrrolidin-1-yl)propyl)carbamate. Potassium carbonate (3.02 g, 21.88 mmol) was added in one portion to stirred mixture of (R)-3-(tert-butoxycarbonylamino)-3-(3-fluorophenyl)propyl methanesulfonate (3.8 g, 10.94 mmol) and MeCN (50 mL). Pyrrolidine (1.56 g, 21.88 mmol) was added dropwise via syringe and the mixture heated at 50 °C overnight. The mixture was filtered and the solids washed with MeCN. The filtrate was concentrated and partitioned between DCM (50 mL) and water (50 mL). The layers were separated and the organic layer dried ($MgSO_4$), filtered and evaporated to dryness to afford a residue that was purified on silica gel (0-20%

MeOH/DCM as eluent). The fractions containing the desired product were combined and evaporated to dryness to afford the title compound (3.5 g, 99 %).

LCMS (Table 9. Method c): R_t = 1.73 min.; MS m/z: 323.19 $(M+H)^+$.

(R)-1-(3-Fluorophenyl)-3-(pyrrolidin-1-yl)propan-1-amine hydrochloride. A mixture of (R)-tert-butyl 1-(3-fluorophenyl)-3-(pyrrolidin-1-yl)propylcarbamate (3.3 g, 10.24 mmol) and 4 M HCl in dioxane (20 mL, 82 mmol) were stirred at RT for 1 hour. The reaction mixture was concentrated, chased with ether and the suspension stirred overnight. The mixture was filtered and washed with ether and dried in vacuo to afford the title compound (1.8 g, 68 %) as a white solid.

LCMS (Table 9. Method c): R_t = 0.46 min.; MS m/z: 223.18 $(M+H)^+$. δ H (400 MHz, DMSO) 8.82 - 8.57 (m, 1H), 7.57 - 7.41 (m, 2H), 7.39 (s, 1H), 7.30 - 7.21 (m, 1H), 4.61 - 4.36 (m, 1H), 3.55 - 3.46 (m, 2H), 3.25 - 3.03 (m, 1H), 3.01 - 2.80 (m, 3H), 2.46 - 2.34 (m, 1H), 2.34 - 2.19 (m, 1H), 2.04 - 1.91 (m, 2H), 1.92 - 1.78 (m, 2H).

N-(1-(3-Fluorophenyl)-3-(pyrrolidin-1-yl)propyl)-4-(2-fluoropyridin-4-yl)benzamide (41). To a flask containing 4-(2-fluoropyridin-4-yl)benzoic acid hydrochloride (85 mg, 0.33 mmol), EDC (96 mg, 0.50 mmol), (R)-1-(3-fluorophenyl)-3-(pyrrolidin-1-yl)propan-1-amine dihydrochloride (109 mg, 0.37 mmol) and HOBt (56 mg, 0.37 mmol) was added DIEA (0.23 mL, 1.34 mmol) followed by DMF (2 mL). The mixture was stirred at RT overnight and then water added (10 mL). The mixture was extracted with DCM (3 X 15 mL) and the organic layers combined and concentrated to give an orange oil that was purified on silica gel (0-5% MeOH/DCM as eluent). The fractions containing the desired compound were combined to give an oil that was dried under vacuum to afford the title compound (115.1 mg, 81 %) as a white solid.

LCMS (Table 9. Method c): R_t = 1.79 min.; MS m/z: 422.21 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.15 (1 H, d, J 7.8), 8.32 (1 H, d, J 5.2), 8.02 – 7.93 (4 H, m), 7.75 (1 H, d, J 5.2), 7.59 (1 H, s), 7.41 – 7.31 (1

H, m), 7.28 – 7.17 (2 H, m), 7.08 – 6.99 (1 H, m), 5.13 (1 H, q, J 8.0), 2.43 (6 H, t, J 5.1), 2.07 – 1.89 (2 H, m), 1.71 – 1.66 (4 H, m). δ C (101 MHz, DMSO) 164.80 (d, J 180.4), 162.42 (d, J 188.8), 152.61 (d, J 8.4), 148.71 (d, J 15.8), 147.30 (d, J 6.7), 138.95 (d, J 3.4),135.82,130.61 (d, J 8.3), 128.52, 127.56,123.07 (d, J 2.6), 120.24 (d, J 3.8), 113.74 (d, J 11.0), 113.74 (d, J 53.5), 107.34 (d, J 38.7), 54.04, 53.05, 52.25, 34.97, 23.62. δ F (376 MHz, DMSO) -68.56. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{26}F_2N_3O$ 422.19657; Found 422.19722.

Propyl (R)-3-((tert-butoxycarbonyl)amino)-3-(3-propoxyphenyl)propanoate. A mixture of (R)-3-(tert-butoxycarbonylamino)-3-(3-hydroxyphenyl)propanoic acid (2.5 g, 8.9 mmol), 1-iodopropane (3.47 mL, 35.5 mmol) and K_2CO_3 (6.14 g, 44.4 mmol) in DMF (15 mL) was heated at 60 °C overnight. Water (100 mL) was added and the mixture extracted with EtOAc (3 X 30 mL). The combined organic layers were concentrated and purified on silica gel (0-25% EtOAc/heptane as eluent). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (2.48 g, 76 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.68 min.; MS m/z: 366.22 $(M+H)^+$. δ H (400 MHz, DMSO) 7.41 (d, J = 8.9, 1H), 7.18 (t, J = 7.9, 1H), 6.86 (d, J = 1.8, 1H), 6.83 (d, J = 7.7, 1H), 6.76 (dd, J = 1.9, 8.2, 1H), 4.87 (dd, J = 8.2, 15.5, 1H), 3.97 - 3.90 (m, 2H), 3.88 (t, J = 6.5, 2H), 2.75 - 2.58 (m, 2H), 1.76 - 1.64 (m, 2H), 1.56 - 1.45 (m, 2H), 1.33 (s, 9H), 0.95 (t, J = 7.4, 3H), 0.82 (t, J = 7.4, 3H).

(R)-3-((tert-Butoxycarbonyl)amino)-3-(3-propoxyphenyl)propanoic acid. To a solution of (R)-propyl 3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoate (2.48 g, 6.8 mmol) in THF (45 mL) was added lithium hydroxide hydrate (1.42 g, 33.9 mmol) followed by water (15 mL). The mixture was stirred at RT overnight. Removal of the organic solvent under reduced pressure gave a residue that was diluted with water (50 mL), adjusted to pH 7 with 6 M HCl and extracted with DCM (3 X 30 mL). The combined organic layers were washed with saturated brine, dried (Na_2SO_4), filtered and evaporated to dryness to afford the title compound (2.09 g, 95 %) as a gummy solid.

LCMS (Table 9. Method d): R_t = 2.23 min.; MS m/z: 322.2 $(M-H)^-$.

tert-Butyl (R)-(3-hydroxy-1-(3-propoxyphenyl)propyl)carbamate. To a cold solution (0 °C) of (R)-3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoic acid (2.09 g, 6.47 mmol) in THF (10 mL) was added N-methylmorpholine (0.78 mL, 7.11 mmol) followed by isobutyl carbonochloridate (0.93 mL, 7.11 mmol). The mixture was stirred at 0 °C for 30 minutes, the precipitate filtered off and washed with a small amount of THF. After cooling to 0 °C a suspension of $NaBH_4$ (0.367 g, 9.70 mmol) in water (2 mL) was added in one portion. The mixture was stirred at RT for 3 hours. Water (50 mL) was then added and the mixture extracted with EtOAc (3 x 25 mL). The combined organic layers were evaporated to dryness to give a colourless oil that was purified on silica gel (25 - 50 % EtOAc/heptane as eluent). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (1.74 g, 87 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.45 min.; MS m/z: 310.20 $(M+H)^+$. δ H (400 MHz, DMSO) 7.28 (d, J = 8.5, 1H), 7.19 (t, J = 7.8, 1H), 6.86 - 6.78 (m, 2H), 6.75 (dd, J = 2.3, 8.1, 1H), 4.56 (dd, J = 8.1, 14.9, 1H), 4.44 (t, J = 4.9, 1H), 3.89 (t, J = 6.5, 2H), 3.41 - 3.24 (m, 2H), 1.85 - 1.61 (m, 4H), 1.35 (s, 9H), 0.98 (t, J = 7.4, 3H).

(R)-3-Amino-3-(3-propoxyphenyl)propan-1-ol hydrochloride. A mixture of (R)-tert-butyl 3-hydroxy-1-(3-propoxyphenyl)propylcarbamate (0.30 g, 0.97 mmol) and 4 M HCL in dioxane (1.21 mL, 4.85 mmol) was stirred at RT for 1 hour. The volatiles were removed under reduced pressure to afford the title compound as a white solid that was used directly in the next step.

(R)-4-(2-Fluoropyridin-4-yl)-N-(3-hydroxy-1-(3-propoxyphenyl)propyl)benzamide (42). A mixture of 4-(2-fluoropyridin-4-yl)benzoic acid hydrochloride (100 mg, 0.39 mmol), EDC (113 mg, 0.59 mmol), (R)-3-amino-3-(3-propoxyphenyl)propan-1-ol hydrochloride (102 mg, 0.41 mmol), HOBt (66.4 mg, 0.43 mmol), DIEA (0.20 mL, 1.18 mmol) and DMF (2 mL) was stirred at RT over the weekend. Water was added (30 mL) and the mixture extracted with EtOAc (3 X 30 mL). The combined organic layers

were concentrated to give an orange oil that was purified on silica gel (0-75% EtOAc/Hexane as eluent). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (109 mg, 67 %) as a white fluffy solid.

LCMS (Table 9. Method c): R_t =2.22 min.; MS m/z: 409.19 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.83 (1 H, d, J 8.2), 8.32 (1 H, d, J 5.3), 8.04 – 7.92 (4 H, m), 7.74 (1 H, d, J 5.3), 7.59 (1 H, s), 7.20 (1 H, t, J 7.9), 6.98 – 6.89 (2 H, m), 6.76 (1 H, dd, J 8.1, 2.2), 5.13 (1 H, q, J 8.4), 4.53 (1 H, t, J 4.9), 3.89 (2 H, t, J 6.5), 3.41 (2 H, dq, J 10.8, 5.3), 3.28 (2 H, s), 2.03 (1 H, td, J 14.3, 5.7), 1.89 (1 H, dq, J 13.5, 6.6), 1.70 (2 H, q, J 6.9), 0.95 (3 H, t, J 7.4). δ C (101 MHz, DMSO) 164.53 (d, J 234.7), 165.45, 159.14,152.65 (d, J 8.4),148.70 (d, J 15.7), 146.06, 138.80 (d, J 3.4), 136.07, 129.66, 128.58, 127.50,120.23 (d, J 3.8), 119.17, 113.35, 112.77,107.31 (d, J 38.7) , 69.25, 58.34, 50.88, 22.52, 10.87. δ F (376 MHz, DMSO) -68.57. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}FN_2O_3$ 409.18492; Found 409.18542. Chiral analysis (Table 10, c), >99% ee, negative (-) optical rotation.

Propyl (R)-3-((tert-butoxycarbonyl)amino)-3-(3-propoxyphenyl)propanoate. A stirred mixture of (R)-3-(tert-butoxycarbonylamino)-3-(3-hydroxyphenyl)propanoic acid (2.36 g, 8.4 mmol), 1-iodopropane (2.45 mL, 25.2 mmol) and K_2CO_3 (5.79 g, 41.9 mmol) in MeCN (40 mL) was heated at 60 °C overnight. The solvent was removed under reduced pressure and the residue partitioned between DCM (50 mL) and water (50 mL). The layers were separated and the aqueous layer extracted with DCM (3 X 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated to dryness and purified on silica gel (0-25% EtOAc/hexane as eluent). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (2.36 g, 77 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.68 min.; MS m/z: 366.2 $(M+H)^+$.

(R)-3-((tert-Butoxycarbonyl)amino)-3-(3-propoxyphenyl)propanoic acid. To a solution of (R)-propyl 3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoate (2.87 g, 7.9 mmol) in THF (45

mL) was added lithium hydroxide hydrate (1.65 g, 39.3 mmol) followed by water (15 mL). The mixture was stirred at RT overnight and then heated at 50 °C for 1 hour. The organic solvent was removed under reduced pressure and the residue diluted with water (50 mL) water and adjusted to pH 7 with 6 M HCl. The mixture was extracted with DCM (3 X 30 mL) and the combined organic layers washed with brine (40 mL), dried (Na_2SO_4), filtered and evaporated to dryness to afford the title compound (2.54 g, 100 %) as a gummy solid.

LCMS (Table 9. Method b): R_t = 1.44 min.; MS m/z: 322.19 $(M-H)^-$. δ H (400 MHz, DMSO) 12.19 (s, 1H), 7.39 (d, J = 8.9, 1H), 7.19 (t, J = 7.8, 1H), 6.86 (d, J = 1.9, 1H), 6.84 (d, J = 7.7, 1H), 6.77 (dd, J = 2.4, 8.2, 1H), 4.84 (dd, J = 8.5, 15.6, 1H), 3.89 (t, J = 6.5, 2H), 2.59 (ddd, J = 7.5, 15.6, 22.1, 2H), 1.81 - 1.69 (m, 2H), 1.35 (s, 9H), 0.97 (t, J = 7.4, 3H).

tert-Butyl (R)-(3-hydroxy-1-(3-propoxyphenyl)propyl)carbamate. To a cold solution (0 °C) of (R)-3-(tert-butoxycarbonylamino)-3-(3-propoxyphenyl)propanoic acid (2.54 g, 7.87 mmol) in DME (20 mL) was added N-methylmorpholine (0.95 mL, 8.65 mmol) followed by isobutyl carbonochloridate (1.18 g, 8.65 mmol). The mixture was stirred at 0 °C for 1 hour, the precipitate filtered off and washed with a small amount of DME. After cooling to 0 °C, a suspension of $NaBH_4$ (0.446 g, 11.80 mmol) in water (3 mL) was added in one portion. The mixture was stirred at RT for 3.5 hours then water (50 mL) was added. The mixture was extracted with EtOAc (3 X 25 mL) and the combined organic layers evaporated to dryness to give a colourless oil that was purified on silica gel (25 - 50 % EtOAc/heptane as eluent). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (2.08 g, 86 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.44 min.; MS m/z: 310.2 $(M+H)^+$.

(R)-4-(3-Fluoropyridin-4-yl)-N-(3-hydroxy-1-(3-propoxyphenyl)propyl)benzamide (43). A mixture of (R)-tert-butyl 3-hydroxy-1-(3-propoxyphenyl)propylcarbamate (74 mg, 0.24 mmol) and 4 M HCL in dioxane (0.3 mL, 1.19 mmol) was stirred at RT for 30 minutes. The solvent was removed under

reduced pressure to afford a residue. A mixture of 4-(3-fluoropyridin-4-yl)benzoic acid hydrochloride (55 mg, 0.22 mmol), HATU (99 mg, 0.26 mmol) and DMF (2 mL) was stirred at RT for 2 minutes then added to the residue. Et_3N (0.15 mL, 1.08 mmol) was added and the mixture stirred at RT overnight. Water (15 mL) was added and the mixture extracted with EtOAc (4 X 15 mL). The combined organic layers were concentrated and purified on silica gel (50-100% EtOAc/heptane as eluent). A minor impurity was identified by NMR and the residue further purified by HPLC (30-80% MeCN/10 mM ammonium acetate over 30 min; flow rate 21 ml/min). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (32 mg, 36%).

LCMS (Table 9. Method b): R_t = 1.36 min.; MS m/z: 409.18 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.83 (1 H, d, J 8.2), 8.67 (1 H, d, J 2.4), 8.52 (1 H, d, J 4.9), 8.00 (2 H, d, J 8.3), 7.76 (2 H, d, J 7.4), 7.66 (1 H, dd, J 6.8, 5.1), 7.20 (1 H, t, J 7.8), 6.98 – 6.90 (2 H, m), 6.76 (1 H, dd, J 8.2, 2.1), 5.13 (1 H, q, J 8.4), 4.53 (1 H, t, J 4.6), 3.89 (2 H, t, J 6.5), 3.42 (2 H, tt, J 10.3, 5.4), 2.02 (1 H, td, J 14.4, 5.6), 1.89 (1 H, dq, J 13.0, 6.4), 1.70 (2 H, q, J 6.9), 0.95 (3 H, t, J 7.4). δ C (101 MHz, DMSO) 165.58, 159.14, 156.49 (d, J 256.3), 146.86 (d, J 5.2), 146.06, 139.20 (d, J 25.2), 135.72, 135.32, 134.76 (d, J 10.4), 129.66, 129.20 (d, J 3.2), 128.28, 124.91, 119.16, 113.33, 112.78, 69.25, 58.34, 50.88, 22.52, 10.87. δ F (376 MHz, DMSO-d6) -133.29. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}FN_2O_3$ 409.18492; Found 409.18468.

(R)-N-(1-(3-Propoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (44). A mixture of 4-(pyridin-4-yl)benzoic acid (250 mg, 1.25 mmol), EDC (361 mg, 1.88 mmol), (R)-1-(3-propoxyphenyl)ethanamine hydrochloride (298 mg, 1.38 mmol), HOBt (211 mg, 1.38 mmol), DIEA (0.44 mL, 2.51 mmol) and DMF (5 mL) was stirred at RT overnight. The volatiles were removed under reduced pressure and water (50 mL) added. The mixture was extracted with DCM (3 X 30 mL) and the combined organic layers concentrated and purified on silica gel (0 -5% MeOH/DCM as eluent) to give an oil that was dried on high vacuum pump overnight. This afforded the title compound (246 mg, 54 %) as a white solid.

LCMS (Table 9. Method b): R_t = 1.52 min.; MS m/z: 361.19 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 8.84 (1 H, d, J 8.1), 8.68 – 8.62 (2 H, m), 8.01 (2 H, d, J 8.4), 7.90 (2 H, d, J 8.4), 7.78 – 7.72 (2 H, m), 7.20 (1 H, t, J 7.8), 6.98 – 6.90 (2 H, m), 6.77 (1 H, ddd, J 8.2, 2.6, 1.0), 5.14 (1 H, p, J 7.2), 3.89 (2 H, t, J 6.5), 1.70 (2 H, h, J 7.1), 1.46 (3 H, d, J 7.0), 0.95 (3 H, t, J 7.4). δ C NMR (101 MHz, DMSO) 165.36, 159.19, 150.78, 146.96, 146.52, 140.10, 135.46, 129.72, 128.68, 127.16, 121.79, 118.69, 112.97, 112.73, 69.27, 48.98, 22.74, 22.52, 10.87. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_2O_2$ 361.1911; Found 361.1911.

(R)-2-(4-(Aminomethyl)piperidin-1-yl)-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (46). A mixture of (R)-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (97 mg, 0.28 mmol), K_2CO_3 (77 mg, 0.55 mmol), and tert-butyl piperidin-4-ylmethylcarbamate (71 mg, 0.33 mmol) and ethanol (3 mL) was heated in a CEM microwave at 160 °C for 3 hours (250 psi maximum pressure, 2 min ramp, 300 max watts). The reaction mixture was quenched with saturated Na_2CO_3 solution and extracted with DCM (2 X 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated and purified by prep-HPLC (21.2 x 250 mm Hypersil C_{18} HS column, 8 μm particles, 0-100% B over 35 min, 20 mL/min flow rate). Mobile phase A was 0.05 M aqueous ammonium acetate buffer (pH 4.5) and mobile phase B was MeCN). The fractions containing the desired compound were combined and pH adjusted to 8 with saturated Na_2CO_3 solution. The mixture was extracted with DCM (2 X 150mL) and the combined organic layers concentrated and purified on silica gel (0-10% MeOH/DCM as eluent). The fractions containing the desired compound were combined, concentrated and dried in a vacuum oven at RT for 2 hours to afford the title compound (17 mg, 14 %) as an oil.

LCMS (Table 9. Method c): R_t = 1.54 min.; MS m/z: 445.39 $(M+H)^+$. δ H (400 MHz, DMSO-d_6) 10.11 (d, J = 7.3 Hz, 1H), 8.67 – 8.60 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.64 (d, J = 1.8 Hz, 1H), 7.58 (dd, J = 8.0, 1.7 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.83 (dd, J = 8.2, 2.5 Hz, 1H), 5.09 (p, J = 6.9 Hz, 1H), 3.10 (dd, J = 28.5, 11.8 Hz, 4H), 2.88 – 2.69 (m, 3H), 2.32 (d,

J = 6.5 Hz, 2H), 1.77 (d, *J* = 12.8 Hz, 1H), 1.61 (d, *J* = 13.2 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 2H), 1.35 – 1.09 (m, 4H), 0.79 (qd, *J* = 12.1, 11.6, 3.7 Hz, 2H).

(R)-2-((2-Aminoethyl)amino)-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (47). A mixture of N-ethyl-N-isopropylpropan-2-amine (352 mg, 2.72 mmol), ethane-1,2-diamine (157 mg, 2.61 mmol), (R)-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (305 mg, 0.87 mmol) and DMSO (5 mL) was stirred at 110 °C overnight. The mixture was quenched with water (20 mL) and the aqueous layer extracted with DCM (3 X 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated and purified by HPLC (21.2 x 250 mm Hypersil C_{18} HS column, 8 μm particles. 0-80% B over 35 min (20 mL/min flow rate). Mobile phase A was 0.05 M aqueous ammonium acetate buffer (pH 4.5) and mobile phase B was MeCN. The fractions containing the desired compound were combined and the pH adjusted to 8 with saturated Na_2CO_3 solution. The mixture was extracted with DCM (2 X 150mL), concentrated, dissolved in MeCN (50 mL) and concentrated then dried under vacuum at RT overnight. This afforded the title compound (81 mg, 24 %) as a yellow solid.

LCMS (Table 9. Method c): R_t = 1.60 min.; MS m/z: 391.19 $(M+H)^+$. δ H (400 MHz, $CDCl_3$) 8.86 (s, 0H), 8.70 – 8.60 (m, 2H), 8.42 (s, 0H), 7.85 (s, 1H), 7.50 – 7.40 (m, 3H), 7.27 (d, J = 8.8 Hz, 1H), 7.02 – 6.86 (m, 3H), 6.81 (td, J = 8.0, 2.0 Hz, 2H), 6.38 (d, J = 7.4 Hz, 1H), 5.26 (p, J = 7.0 Hz, 1H), 3.99 (s, 0H), 3.81 (s, 3H), 3.63 (s, 0H), 3.30 (q, J = 5.8 Hz, 2H), 3.17 (s, 0H), 3.00 (t, J = 6.0 Hz, 2H), 2.83 (s, 0H), 1.59 (d, J = 6.9 Hz, 3H). δ C NMR (101 MHz, $CDCl_3$) 168.41, 159.91, 150.25, 150.20, 148.14, 144.88, 142.50, 129.80, 128.14, 121.65, 118.31, 115.45, 113.36, 112.42, 112.28, 110.03, 55.22, 48.97, 46.13, 41.15, 21.94. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}N_4O_2$ 391.2129; Found 391.2126.

(R)-2-((3-Aminopropyl)amino)-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (48). As for compound **47** except N-ethyl-N-isopropylpropan-2-amine (221 mg, 1.71 mmol), propane-1,3-

diamine (127 mg, 1.71 mmol) and (R)-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (200 mg, 0.57 mmol) This afforded the title compound (193 mg, 84 %) as a yellow solid.

LCMS (Table 9. Method c): R_t = 1.65 min.; MS m/z: 405.28 $(M+H)^+$. δ H (400 MHz, $CDCl_3$) 8.70 – 8.60 (m, 2H), 7.71 (s, 1H), 7.57 – 7.39 (m, 3H), 7.35 – 7.23 (m, 1H), 7.03 – 6.86 (m, 3H), 6.81 (ddd, J = 12.2, 8.1, 1.8 Hz, 2H), 6.36 (d, J = 7.4 Hz, 1H), 5.25 (p, J = 7.0 Hz, 1H), 3.99 (s, 0H), 3.81 (d, J = 1.5 Hz, 3H), 3.63 (s, 0H), 3.48 – 3.22 (m, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.85 (q, J = 6.8 Hz, 2H), 1.59 (d, J = 6.8 Hz, 4H). δ C (101 MHz, $CDCl_3$) 168.47, 159.92, 150.18, 148.21, 144.90, 142.50, 129.81, 128.06, 121.67, 118.32, 115.16, 113.10, 112.43, 112.28, 109.88, 55.23, 48.96, 40.72, 39.98, 32.86, 21.95. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{29}N_4O_2$ 405.2285; Found 405.2285.

(R)-2-((4-Aminobutyl)amino)-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (49). As for compound **47** except (R)-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)-4-(pyridin-4-yl)benzamide (100 mg, 0.285 mmol) and butane-1,4-diamine. This afforded the title compound (25 mg, 21 %) as a solid.

LCMS (Table 9. Method c): R_t = 1.69 min.; MS m/z: 419.39 $(M+H)^+$. δ H (400 MHz, $CDCl_3$) 8.65 (d, J = 5.8 Hz, 2H), 7.71 (s, 1H), 7.46 (dd, J = 15.2, 7.0 Hz, 3H), 7.03 (s, 0H), 7.02 – 6.90 (m, 2H), 6.90 – 6.73 (m, 3H), 6.34 (d, J = 7.4 Hz, 1H), 5.25 (p, J = 7.0 Hz, 1H), 3.99 (s, 0H), 3.81 (s, 3H), 3.71 (q, J = 7.0 Hz, 2H), 3.63 (s, 0H), 3.22 (t, J = 6.8 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 1.74 (dt, J = 14.8, 6.9 Hz, 2H), 1.59 (d, J = 6.8 Hz, 6H), 1.24 (t, J = 7.1 Hz, 3H). δ C (101 MHz, $CDCl_3$) 168.47, 159.91, 150.17, 148.25, 144.90, 142.49, 129.79, 128.05, 121.67, 118.32, 115.02, 113.01, 112.42, 112.28, 109.81, 58.29, 55.23, 48.95, 42.91, 41.94, 31.38, 26.50, 21.95, 18.41. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{31}N_4O_2$ 419.2442; Found 419.2439.

(R)-4-Bromo-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)benzamide. To a stirred mixture of 4-bromo-2-fluorobenzoic acid (8.0 g, 36.5 mmol) in DMF (50 mL) was added 1-hydroxybenzotriazole hydrate (6.15 g, 40.2 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (7.70 g, 40.2 mmol) and the resulting mixture stirred at 20 °C for 15 minutes. N,N-diisopropylethylamine (19 mL,

110 mmol) and (R)-1-(3-methoxyphenyl)ethanamine (5.52 g, 36.5 mmol) were then added and the mixture stirred at 20 °C overnight. The mixture was quenched with water (300 mL) and extracted with DCM (2 X 300 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated to dryness and purified on silica gel (0-10% MeOH/DCM as eluent). The fractions containing the desired compound were evaporated to dryness and dried in a vacuum oven at 55°C overnight to afford the title compound (8.0 g, 61 %) as a white solid.

LCMS (Table 9. Method c): R_t = 2.52 min.; MS m/z: 354.07 $(M+H)^+$. δ H (400 MHz, DMSO) 8.83 (d, J = 8.1, 1H), 7.67 (d, J = 9.9, 1H), 7.51 (t, J = 6.3, 2H), 7.25 (t, J = 8.1, 1H), 6.95 (d, J = 7.3, 2H), 6.87 - 6.74 (m, 1H), 5.07 (p, J = 7.1, 1H), 3.75 (d, J = 8.2, 3H), 1.41 (d, J = 7.0, 3H).

(R)-tert-Butyl 4-(5-bromo-2-(1-(3-methoxyphenyl)ethylcarbamoyl)phenylamino)butylcarbamate. A mixture of (R)-4-bromo-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)benzamide (1.44 g, 4.09 mmol), tert-butyl 4-aminobutylcarbamate (1.54 g, 8.18 mmol), DIPEA (2 mL, 11.45 mmol) and DMSO (10 mL) was stirred at 110 °C for overnight. The reaction was quenched with saturated Na_2CO_3 solution (20 mL) and the aqueous phase was extracted with ether (2 X 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated and purified on silica gel (0-50% EtOAc/heptane as eluent). The fractions containing the desired compound were combined and dried under vacuum at RT for 1 hour to afford the title compound (1.9 g, 89 %) as white solid.

LCMS (Table 9. Method c): R_t = 2.96 min.; MS m/z: 523.0 $(M+H)^+$.

(R)-tert-Butyl 4-(2-(1-(3-methoxyphenyl)ethylcarbamoyl)-5-(pyrimidin-4-yl)phenylamino)butylcarbamate. A mixture of potassium acetate (528 mg, 5.38 mmol), Pd(dppf) (110 mg, 0.13 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (342 mg, 1.34 mmol), (R)-tert-butyl 4-(5-bromo-2-(1-(3-methoxyphenyl)ethylcarbamoyl)phenylamino)butylcarbamate (700 mg, 1.34 mmol) and 1,4-dioxane (10 mL) was stirred at 65 °C for 3 hours. Cesium carbonate (1.75 g, 5.38 mmol), $PdCl_2$(dppf)-DCM adduct (110 mg, 0.13 mmol), 4-chloropyrimidine hydrochloride (203

mg, 1.34 mmol) (Medinorh) and water (4 mL) were each added sequentially in one portion. The mixture was stirred at 80 °C overnight then quenched with water (20 mL). The layers were separated and the aqueous layer extracted with DCM (2 X 250 mL). The combined organic were dried (Na_2SO_4), filtered, concentrated and purified on silica gel (0-5% MeOH/DCM as eluent). The fractions containing the desired compound were combined, concentrated and dried under vacuum at RT for 3 hours to afford the title compound (270 mg, 36 %) as sticky oil.

LCMS (Table 9. Method c): R_t = 2.54 min.; MS m/z: 518.3 $(M-H)^-$.

(R)-2-((4-Aminobutyl)amino)-N-(1-(3-methoxyphenyl)ethyl)-4-(pyrimidin-4-yl)benzamide (54). A mixture of (R)-tert-butyl 4-(2-(1-(3-methoxyphenyl)ethylcarbamoyl)-5-(pyrimidin-4-yl)phenylamino)butylcarbamate (270 mg, 0.48 mmol) and TFA (2 mL, 26.0 mmol) in DCM (10 mL) was stirred at RT for 6 hours. The reaction mixture was quenched with saturated Na_2CO_3 solution and the aqueous phase was extracted with DCM (2 X 50 mL). The organic layers were combined, dried, (Na_2SO_4), filtered, concentrated and purified on silica gel (DCM/MeOH/7 M NH_3 in MeOH 300/10/10 as eluent). The fractions containing the desired compound were combined evaporated to dryness and dried in a vacuum oven at 55 °C overnight to afford the title compound (181 mg, 90 mmol).

LCMS (Table 9. Method c): R_t = 1.68 min.; MS m/z: 420.49 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.25 (1 H, s), 8.85 (1 H, d, J 5.4), 8.73 (1 H, d, J 7.9), 8.10 (1 H, d, J 5.3), 7.82 (1 H, d, J 8.2), 7.76 (1 H, t, J 4.9), 7.45 (1 H, s), 7.37 (1 H, d, J 8.2), 7.22 (1 H, t, J 8.1), 6.98 – 6.92 (2 H, m), 6.83 – 6.74 (1 H, m), 5.11 (1 H, p, J 7.1), 3.73 (3 H, s), 3.17 (2 H, q, J 6.6), 2.56 (2 H, t, J 6.8), 1.60 (2 H, p, J 7.1), 1.48 – 1.37 (5 H, m). δ C (101 MHz, DMSO) 168.30, 162.83, 159.74, 159.14, 158.50, 150.09, 147.09, 139.71, 129.79, 129.73, 118.73, 118.07, 117.22, 112.90, 112.42, 112.23, 109.44, 55.43, 48.64, 42.71, 41.79, 31.25, 26.54, 22.72. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{30}N_5O_2$ 420.23213; Found 420.2327.

3-Propoxybenzaldehyde. A mixture of 1-iodopropane (23.9 mL, 246 mmol), 3-hydroxybenzaldehyde (25.0 g, 205 mmol) and K_2CO_3 (42.4 g, 307 mmol) in anhydrous DMF (82 mL) was stirred at RT for 18 hours. TLC indicated starting material still remained and additional iodopropane (10.6 g; 82 mmol) was added and the reaction mixture stirred at RT for an additional 18 hours. The reaction mixture was poured into water (500 mL) and extracted with EtOAc (3 X 90 mL). The combined organic layers were washed with 2.5 M NaOH (3 X 80 mL), water (4 X 90 mL), dried ($MgSO_4$), filtered, evaporated to dryness and dried in a vacuum oven at 60 °C to afford the title compound (31.3g, 88 %) as an orange oil.

LCMS (Table 9. Method b): R_t = 1.53 min.; MS m/z: 165 $(M+H)^+$. δ H (400 MHz, DMSO) 9.98 (s, 1H), 7.51 (dd, J = 3.0, 5.3, 2H), 7.43 - 7.41 (m, 1H), 7.27 (dt, J = 2.5, 7.1, 1H), 4.01 (t, J = 6.5, 2H), 1.76 (dd, J = 6.6, 14.0, 2H), 0.99 (t, J = 7.4, 3H).

(S,E)-2-Methyl-N-(3-propoxybenzylidene)propane-2-sulfinamide. To a solution of (S)-2-methylpropane-2-sulfinamide (10.08 g, 83 mmol) and 3-propoxybenzaldehyde (13.0 g, 79 mmol) in THF (128 mL) was added tetraethoxytitanium (32.8 mL, 158 mmol). The mixture was stirred at RT overnight then poured into water (200 mL) and stirred for 30 minutes. The mixture was filtered through a Celite™ pad, the filter cake washed with EtOAc (3 X 100mL). The layers were separated and the aqueous layer extracted with EtOAc (2 X 50 mL). The combined organic layers were washed with water (3 X 50mL), dried ($MgSO_4$), filtered and solvent removed in vacuo to afford the title compound (20.3 g, 94 %) as a yellow oil.

LCMS (Table 9. Method b): R_t = 1.63 min.; MS m/z: 268.1 $(M+H)^+$. δ H (600 MHz, $CDCl_3$) 8.55 (s, 1H), 7.39 (dd, J = 3.0, 6.3, 2H), 7.08 - 7.04 (m, 1H), 3.98 (q, J = 6.3, 2H), 1.83 (dd, J = 6.9, 14.1, 2H), 1.27 (s, 9H), 1.06 (t, J = 7.4, 3H).

(S)-2-Methyl-N-((R)-1-(3-propoxyphenyl)ethyl)propane-2-sulfinamide. A mixture of (S,E)-2-methyl-N-(3-propoxybenzylidene)propane-2-sulfinamide (5.3 g, 19.82 mmol) in DCM (100 mL) was

cooled to -45 °C in a dry ice/MeCN bath. Methylmagnesium bromide in diethyl ether (50 mL, 149 mmol) was added dropwise via syringe over 45 min to the solution and the resulting mixture stirred at -48 °C for 5 hours. The mixture was allowed to warm slowly to RT and stirred overnight. The reaction was quenched with saturated NH_4Cl slowly in an ice bath. The mixture was partitioned between EtOAc (50 mL) and water (50 mL), filtered and layers separated. The aqueous layer was extracted with EtOAc (3 X 50 mL) and the combined organic layers dried ($MgSO_4$), filtered and evaporated to dryness to afford a residue that was purified on silica gel (0-50% EtOAc/heptane as eluent). The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (4.8 g, 85 %) as an oil.

LCMS (Table 9. Method b): R_t = 2.37 min.; MS m/z: 284.16 $(M+H)^+$. δ H (400 MHz, DMSO) 7.18 (t, J = 7.9, 1H), 6.88 (dd, J = 5.0, 9.3, 2H), 6.75 (dd, J = 2.1, 7.8, 1H), 5.28 (d, J = 5.3, 1H), 4.44 - 4.24 (m, 1H), 3.99 - 3.76 (m, 2H), 1.78 - 1.61 (m, 2H), 1.41 (d, J = 6.7, 3H), 1.15 - 1.06 (m, 9H), 0.95 (t, J = 7.4, 3H). Chiral analysis (Table 10, d), >99% de, positive (+) optical rotation.

(R)-1-(3-Propoxyphenyl)ethan-1-amine hydrochloride. 4 M hydrochloric acid in dioxane (13 mL, 50.8 mmol) was added in one portion to a solution of (S)-2-methyl-N-((R)-1-(3-propoxyphenyl)ethyl)propane-2-sulfinamide (4.8 g, 16.94 mmol) and MeOH (12 mL). The mixture was stirred at 20 °C for 30 minutes. Removal of solvent gave a residue that was triturated with ether to afford a solid that was collected by filtration. The solid was dried at 60 °C overnight in a vacuum oven to afford the title compound (3.18 g, 87 %).

LCMS (Table 9. Method b): R_t = 1.48 min.; MS m/z: 180.12 $(M+H)^+$. δ H (400 MHz, DMSO) 8.46 (s, 3H), 7.31 (t, J = 7.9, 1H), 7.15 - 7.11 (m, 1H), 7.04 (d, J = 7.8, 1H), 6.92 (dd, J = 2.2, 8.0, 1H), 4.33 (q, J = 6.8, 1H), 3.94 (t, J = 6.5, 2H), 1.80 - 1.67 (m, 2H), 1.49 (d, J = 6.8, 3H), 0.98 (t, J = 7.4, 3H). Chiral analysis (Table 10, e), >99% ee.

(R)-4-Bromo-2-fluoro-N-(1-(3-propoxyphenyl)ethyl)benzamide. HOBT (388 mg, 2.54 mmol) and EDC (486 mg, 2.54 mmol) were each added sequentially in one portion to a solution of 4-bromo-2-fluorobenzoic acid (509 mg, 2.325 mmol) in DMF (10 mL) and stirred at RT for 1 hour after which (R)-1-(3-propoxyphenyl)ethanamine hydrochloride (456 mg, 2.11 mmol) and DIPEA (1.1 mL, 6.34 mmol) were added. The reaction mixture was stirred at RT overnight and then quenched with water (20 mL). The aqueous phase was extracted with EtOAc (3 X 30 mL) and the combined organic layers washed with brine (30 mL), concentrated and purified on silica gel (0-4 EtOAc/heptane as eluent The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (714 mg, 89 %) as a white solid.

LCMS (Table 9. Method c): R_t = 1.60 min.; MS m/z: 380.06 $(M+H)^+$.

tert-Butyl (((S)-1-(5-bromo-2-(((R)-1-(3-propoxyphenyl)ethyl)carbamoyl)phenyl)pyrrolidin-3-yl)methyl)carbamate. A mixture of (R)-4-bromo-2-fluoro-N-(1-(3-propoxyphenyl)ethyl)benzamide (1.0 g, 2.63 mmol), (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate (1.05 g, 5.26 mmol) (Astatech), N-ethyl-N-isopropylpropan-2-amine (1.02 g, 7.89 mmol) and DMSO (20 mL) was stirred at 100 °C overnight. The reaction was quenched with water (20 mL) and extracted with ether (3 X 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness to afford a residue that was purified on silica gel (0-50% EtOAc/heptane as eluent). The fractions containing the desired compound were combined and evaporated to dryness and dried in a vacuum oven at 60 °C for 1 hour to afford the title compound (1.4 g, 95 %) as a white solid.

LCMS (Table 9. Method c): R_t = 3.03 min.; MS m/z: 560.16 $(M+H)^+$. δ H (400 MHz, DMSO) 8.69 (d, J = 8.3, 1H), 7.22 (t, J = 7.8, 1H), 7.03 (d, J = 8.0, 1H), 6.93 (d, J = 7.6, 3H), 6.78 (ddd, J = 1.7, 9.1, 12.3, 3H), 5.10 - 4.97 (m, 1H), 3.91 (t, J = 6.5, 2H), 3.17 (dd, J = 8.3, 15.2, 3H), 2.86 (dd, J = 9.0, 16.3, 3H), 2.32 - 2.17 (m, 1H), 1.85 (dd, J = 5.9, 12.1, 1H), 1.80 - 1.66 (m, 2H), 1.52 (dd, J = 7.8, 12.2, 1H), 1.39 (d, J = 5.1, 12H), 0.98 (t, J = 7.4, 3H).

tert-Butyl (((S)-1-(2-(((R)-1-(3-propoxyphenyl)ethyl)carbamoyl)-5-(pyrimidin-4-yl)phenyl)pyrrolidin-3-yl)methyl)carbamate. A mixture of potassium acetate (273 mg, 2.78 mmol), tert-butyl ((S)-1-(5-bromo-2-((R)-1-(3-propoxyphenyl)ethylcarbamoyl)phenyl)pyrrolidin-3-yl)methylcarbamate (390mg, 0.70 mmol), Pd(dppf) (56.8 mg, 0.07 mmol), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (177 mg, 0.70 mmol), and 1,4-dioxane (10 ml) was stirred at 60 °C for 2 hours. Cesium carbonate (907 mg, 2.78 mmol), $PdCl_2$(dppf)-DCM adduct (57 mg, 0.07 mmol), 4-chloropyrimidine hydrochloride (105 mg, 0.70 mmol) and water (2 mL) were then each added sequentially and the mixture stirred at 80 °C overnight. The reaction mixture was quenched with water (20 mL) and the aqueous layer extracted with DCM (2 X 250mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford a residue that was purified on silica gel. The fractions containing the desired compound were combined and evaporated to dryness to afford the title compound (160 mg, 41 %) as an oil.

LCMS (Table 9. Method c): R_t = 2.66 min.; MS m/z: 560.8 $(M+H)^+$

2-((S)-3-(Aminomethyl)pyrrolidin-1-yl)-N-((R)-1-(3-propoxyphenyl)ethyl)-4-(pyrimidin-4-yl)benzamide (55). A mixture of tert-butyl ((S)-1-(2-((R)-1-(3-propoxyphenyl)ethylcarbamoyl)-5-(pyrimidin-4-yl)phenyl)pyrrolidin-3-yl)methylcarbamate (160 mg, 0.29 mmol) in DCM (10 mL) was cooled to 0 °C in an ice bath. TFA (0.4 mL, 5.19 mmol) was added dropwise and the mixture stirred at about RT overnight. The reaction mixture was quenched with saturated Na_2CO_3 (50 mL) and the aqueous layer extracted with DCM (2 X 50 mL). The combined organic were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that was purified on silica gel (DCM/MeOH/7 M NH_3 in MeOH 300/10/5 as eluent). The fractions containing the desired compound were combined and evaporated to dryness then dried in a vacuum oven at 60 °C overnight to afford the title compound (93 mg, 72 %) as a solid.

LCMS (Table 9. Method c): R_t = 1.76 min.; MS m/z: 458.3 $(M-H)^-$. δ H (400 MHz, DMSO-d6) 9.22 (1 H, s), 8.82 (1 H, d, J 5.4), 8.76 (1 H, d, J 8.3), 8.05 (1 H, d, J 4.5), 7.48 (1 H, s), 7.44 (1 H, d, J 7.9), 7.26 (1 H, d, J 7.9), 7.22 (1 H, t, J 7.9), 6.99 – 6.91 (2 H, m), 6.78 (1 H, dd, J 8.1, 2.0), 5.11 – 5.03 (1 H, m), 3.91 (2 H, t, J 6.5), 3.32 – 3.19 (3 H, m), 2.96 (1 H, dd, J 16.8, 9.5), 2.22 – 2.06 (1 H, m), 1.96 – 1.82 (1 H, m), 1.72 (2 H, h, J 7.1), 1.62 – 1.50 (1 H, m), 1.40 (3 H, d, J 7.0), 0.97 (3 H, t, J 7.4). δ C (101 MHz, DMSO) 168.97, 163.12, 159.16, 159.12, 158.38, 146.58, 146.56, 137.44, 130.30, 129.68, 126.36, 118.81, 117.82, 114.40, 112.94, 112.22, 69.27, 53.71, 49.30, 48.72, 45.02, 42.04, 29.22, 22.72, 22.54, 10.89. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{34}N_5O_2$ 460.26343; Found 460.26348. Chiral analysis (Table 10, g), 95% ee, positive (+) optical rotation.

tert-Butyl (((R)-1-(5-bromo-2-(((R)-1-(3-propoxyphenyl)ethyl)carbamoyl)phenyl)pyrrolidin-3-yl)methyl)carbamate. A mixture of N-ethyl-N-isopropylpropan-2-amine (1.06 g, 8.21 mmol), (S)-tert-butyl pyrrolidin-3-ylmethylcarbamate (1.0 g, 4.99 mmol), (R)-4-bromo-2-fluoro-N-(1-(3-propoxyphenyl)ethyl)benzamide (1.04 g, 2.74 mmol) and DMSO (20 mL) was stirred at 100 °C for 48 h then quenched with water (20 mL). The aqueous phase was extracted with ether (2 X 80 mL) and the combined organic layers dried (Na_2SO_4), filtered, evaporated to dryness and purified on silica gel (0-50% EtOAc/heptane as eluent). The fractions containing the desired compound were evaporated to dryness to afford the title compound (0.9 g, 59 %) as a solid.

LCMS (Table 9. Method c): R_t = 3.01 min.; MS m/z: 562.4 $(M+H)^+$

tert-Butyl (((R)-1-(2-(((R)-1-(3-propoxyphenyl)ethyl)carbamoyl)-5-(pyrimidin-4-yl)phenyl)pyrrolidin-3-yl)methyl)carbamate. A mixture of potassium acetate (273 mg, 2.78 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (177 mg, 0.70 mmol), tert-butyl ((R)-1-(5-bromo-2-((R)-1-(3-propoxyphenyl)ethylcarbamoyl)phenyl)pyrrolidin-3-yl)methylcarbamate (390 mg, 0.70 mmol), Pd(dppf) (56.8 mg, 0.070 mmol) and 1,4-dioxane (10 ml) was stirred at 65 °C for 2 h. Cesium carbonate (907 mg, 2.78 mmol), $PdCl_2$(dppf)-DCM adduct (56.8 mg, 0.07 mmol), 4-

chloropyrimidine hydrochloride (105 mg, 0.70 mmol) and water (94 mL) were then each added sequentially and the mixture stirred at 80 °C for overnight. The reaction mixture was quenched with water (20 mL) and the aqueous layer extracted with DCM (2 X 250 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that was purified on silica gel (0-100 EtOAc/DCM as eluent). The fractions containing the desired compound were evaporated to dryness and dried in vacuum oven at RT for 2 hours to afford the title compound (180 mg, 46 %) as yellow solid.

LCMS (Table 9. Method c): R_t = 2.67 min.; MS m/z: 560.8 $(M+H)^+$.

2-((R)-3-(Aminomethyl)pyrrolidin-1-yl)-N-((R)-1-(3-propoxyphenyl)ethyl)-4-(pyrimidin-4-yl)benzamide (56). A mixture of tert-butyl ((R)-1-(2-((R)-1-(3-propoxyphenyl)ethylcarbamoyl)-5-(pyrimidin-4-yl)phenyl)pyrrolidin-3-yl)methylcarbamate (180 mg, 0.32 mmol) and DCM (10 mL) was cooled to 0 °C in an ice bath. TFA (0.4 mL, 5.19 mmol) was added dropwise and the mixture stirred at RT overnight. The mixture was partitioned between DCM (20 mL) and 1 M HCl (20 mL). The aqueous layer was adjusted to pH 9 with saturated Na_2CO_3 and extracted with DCM (2 X 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that was purified on silica gel (DCM/MeOH/7 M NH_3 in MeOH 300/10/5 as eluent). The fractions containing the desired compound were evaporated to dryness and dried in vacuum oven at 60 °C overnight to afford the title compound (100 mg, 68 %) as a solid.

LCMS (Table 9. Method c): R_t = 1.76 min.; MS m/z: 460.3 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 9.22 (1 H, s), 8.82 (1 H, d, J 5.4), 8.77 (1 H, d, J 8.2), 8.05 (1 H, d, J 5.0), 7.47 (1 H, s), 7.44 (1 H, d, J 7.8), 7.28 (1 H, d, J 7.9), 7.20 (1 H, t, J 7.8), 6.97 – 6.89 (2 H, m), 6.77 (1 H, dd, J 7.9, 2.0), 5.04 (1 H, p, J 7.0), 3.89 (2 H, t, J 6.5), 3.27 – 3.14 (3 H, m), 3.00 – 2.92 (1 H, m), 2.49 – 2.44 (2 H, m), 2.15 – 2.04 (1 H, m), 1.88 (1 H, d, J 5.8), 1.71 (2 H, h, J 6.9), 1.49 (1 H, dd, J 11.9, 8.3), 1.41 (3 H, d, J 7.0), 0.96 (3 H, t, J 7.4). δ C (101 MHz, DMSO) 168.96, 163.13, 159.12, 158.38, 146.60, 146.58, 137.45, 130.37,

129.60, 126.28, 118.83, 117.82, 114.36, 112.92, 112.90, 112.18, 69.26, 53.61, 49.43, 48.85, 44.90, 42.05, 29.31, 22.70, 22.54, 10.89. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{34}N_5O_2$ 460.26343; Found 460.26301. Chiral analysis (Table 10, g), 90% ee, negative (-) optical rotation

tert-Butyl ((1-(5-bromo-2-(((R)-1-(3-methoxyphenyl)ethyl)carbamoyl)phenyl)piperidin-3-yl)methyl)carbamate. A mixture of N-ethyl-N-isopropylpropan-2-amine (550 mg, 4.26 mmol), tert-butyl piperidin-3-ylmethylcarbamate (608 mg, 2.84 mmol), (R)-4-bromo-2-fluoro-N-(1-(3-methoxyphenyl)ethyl)benzamide (500 mg, 1.42 mmol) and DMSO (10 mL) was stirred at 110 °C overnight. The reaction mixture was quenched with water (30 mL) and extracted with ether (2 X 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that purified on silica gel (0-50% EtOAc/heptane as eluent). The fractions containing the desired compound were evaporated to dryness and dried in a vacuum oven at RT for 1 hour to afford the title compound (0.76 g, 98 %) as a sticky oil.

LCMS (Table 9. Method c): R_t = 2.47 min.; MS m/z: 549.0 $(M+H)^+$.

tert-Butyl (((R)-1-(2-(((R)-1-(3-methoxyphenyl)ethyl)carbamoyl)-5-(pyrimidin-4-yl)phenyl)piperidin-3-yl)methyl)carbamate and tert-butyl (((S)-1-(2-(((R)-1-(3-methoxyphenyl)ethyl)carbamoyl)-5-(pyrimidin-4-yl)phenyl)piperidin-3-yl)methyl)carbamate. A mixture of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (353 mg, 1.39 mmol), potassium acetate (546 mg, 5.56 mmol), and Pd(dppf) (114 mg, 0.14 mmol), tert-butyl (1-(5-bromo-2-((R)-1-(3-methoxyphenyl)ethylcarbamoyl)phenyl)piperidin-3-yl)methylcarbamate (760 mg, 1.39 mmol) and 1,4-dioxane (60 mL) was stirred at 65 °C for 3 hours. Cesium carbonate (1.8 g, 5.56 mmol), $PdCl_2$(dppf)-DCM adduct (114 mg, 0.14 mmol), 4-chloropyrimidine hydrochloride (210 mg, 1.39 mmol) and water (4 mL) were then added and the mixture stirred at 80 °C overnight. The mixture was quenched with water (30 mL) and extracted with DCM (2 X 250 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that purified on silica gel (0-5%

MeOH/DCM as eluent). The fractions containing the desired compound were evaporated to dryness and dried in a vacuum oven at 60 °C for 48 hours to afford a residue that was purified by chiral HPLC.

Chiral separation details Chiral analysis (Table 10, f). LCMS (Table 9. Method c): Rt = 1.63 min.; MS m/z: 446.6 $(M+H)^+$. LCMS (Table 9. Method c): Rt = 1.63 min.; MS m/z: 446.6 $(M+H)^+$.

2-((R)-3-(Aminomethyl)piperidin-1-yl)-N-((R)-1-(3-methoxyphenyl)ethyl)-4-(pyrimidin-4-yl)benzamide (57). A mixture of tert-butyl ((R)-1-(2-((R)-1-(3-methoxyphenyl)ethylcarbamoyl)-5-(pyrimidin-4-yl)phenyl)piperidin-3-yl)methylcarbamate (115 mg, 0.211 mmol) (rotation (-), >99%ee), TFA (0.5 mL, 6.49 mmol) and DCM (5 mL) was stirred at RT overnight. The mixture was quenched with saturated Na_2CO_3 (20 mL) extracted with DCM (2 X 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that purified by HPLC (21.2 x 250 mm Hypersil C_{18} HS column (8 μM particles, gradient 0-80% B over 35 min, 20 mL/min flow rate, mobile phase A 0.05 M aqueous ammonium acetate buffer (pH 4.5) and mobile phase B MeCN). The fractions containing the desired compound were evaporated to dryness and partitioned between saturated Na_2CO_3 (20 mL) and DCM (20 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated to dryness and dried in a vacuum oven at 60 °C overnight to afford the title compound (54 mg, 57 %).

LCMS (Table 9. Method c): R_t = 1.63 min.; MS m/z: 446.65 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 10.09 (1 H, d, J 7.8), 9.26 (1 H, s), 8.88 (1 H, d, J 5.4), 8.15 (1 H, d, J 6.6), 8.11 (1 H, d, J 11.4), 8.01 – 7.89 (2 H, m), 7.26 (1 H, t, J 7.9), 7.02 – 6.92 (2 H, m), 6.86 – 6.79 (1 H, m), 5.16 – 5.07 (1 H, m), 3.73 (3 H, s), 3.16 (1 H, d, J 11.6), 3.09 (1 H, d, J 10.8), 2.74 (1 H, t, J 10.4), 2.47 – 2.25 (3 H, m), 1.75 – 1.64 (2 H, m), 1.49 (4 H, d, J 6.9), 1.32 – 1.15 (1 H, m), 1.15 – 0.87 (1 H, m). δ C (101 MHz, DMSO) 164.99, 162.13, 159.90, 159.22, 158.69, 153.12, 146.12, 139.20, 131.29, 131.21, 129.99, 122.65, 120.01, 118.92, 118.08, 112.69, 112.66, 58.07, 55.49, 54.19, 49.04, 46.08, 40.01, 28.06, 25.59, 22.62.

HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}N_5O_2$ 446.24778; Found 446.24798. Chiral analysis (Table 10, h), >99% ee, negative (-) optical rotation.

2-((S)-3-(Aminomethyl)piperidin-1-yl)-N-((R)-1-(3-methoxyphenyl)ethyl)-4-(pyrimidin-4-yl)benzamide (58). A mixture of tert-butyl ((S)-1-(2-((R)-1-(3-methoxyphenyl)ethylcarbamoyl)-5-(pyrimidin-4-yl)phenyl)piperidin-3-yl)methylcarbamate (114 mg, 0.209 mmol) (rotation (+), >99%ee), TFA (0.5 mL, 6.49 mmol) and DCM (5 mL) was stirred at RT overnight. The mixture was quenched with saturated Na_2CO_3 (20 mL) extracted with DCM (2 X 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness to afford a residue that purified by HPLC (21.2 x 250 mm Hypersil C_{18} HS column (8 μM particles), gradient 0-80% B over 35 min (20 mL/min flow rate), mobile phase A 0.05 M aqueous ammonium acetate buffer (pH 4.5) and mobile phase B MeCN). The fractions containing the desired compound were evaporated to dryness and partitioned between saturated Na_2CO_3 (20 mL) and DCM (20 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated to dryness and dried in a vacuum oven at 60 °C overnight to afford the title compound (52 mg, 56 %).

LCMS (Table 9. Method c): R_t = 1.65 min.; MS m/z: 446.65 $(M+H)^+$. δ H (400 MHz, DMSO-d6) 10.12 (1 H, d, J 7.5), 9.26 (1 H, s), 8.88 (1 H, d, J 5.4), 8.18 – 8.07 (2 H, m), 8.02 – 7.86 (2 H, m), 7.30 – 7.18 (1 H, m), 7.01 – 6.93 (2 H, m), 6.86 – 6.79 (1 H, m), 5.15 – 5.07 (1 H, m), 3.76 – 3.67 (4 H, m), 3.30 – 3.20 (1 H, m), 3.02 (1 H, d, J 12.3), 2.74 – 2.63 (1 H, m), 2.59 – 2.37 (7 H, m), 1.67 – 1.55 (3 H, m), 1.50 (3 H, d, J 6.9), 1.30 – 1.16 (1 H, m), 1.06 – 0.92 (1 H, m). δ C (101 MHz, DMSO) 164.96, 162.12, 159.90, 159.22, 158.69, 153.14, 146.10, 139.23, 131.30, 131.23, 129.99, 122.75, 120.15, 118.88, 118.08, 112.74, 112.50, 57.54, 55.47, 54.79, 49.06, 45.97, 40.12, 28.07, 25.19, 22.82. HRMS (ESI/Q-TOF) m/z: $[M + H]_+$ Calcd for $C_{26}H_{32}N_5O_2$ 446.24778; Found 446.24776. Chiral analysis (Table 10, h), >99% ee, positive (+) optical rotation.

ASSOCIATED CONTENT

Supporting Information

HTRF Assay Protocol, Optic Nerve Crush Model Protocol, Kinome Panel Protocol and Data, PK Protocol and Curves for Compound **16**, MYPT1 Cell Assay Protocol, Crystallization methods and X-Ray Crystallography Diffraction Statistics for Compound **12** in ROCK1, ROCK2 and PKA, X-Ray Crystallography Diffraction Statistics for Compound **47** in PKA, ^{1}H NMR for Compounds **12**, **16**, **43**, **44**, **54** and **56**, ^{13}C NMR for Compounds **12**, **16**, **43**, **44**, **54** and **56**, and ^{19}F NMR for Compounds **12** and **43**. Molecular formula strings are also available.

Animal Welfare

All animal experiments performed in the manuscript were conducted in compliance with institutional guidelines.

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Author Contributions

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ABBREVIATIONS

ALARM NMR: a La assay to detect reactive molecules by nuclear magnetic resonance, ATP: Adenosine triphosphate, BEI: Binding efficiency index, tBuXPhos: 2-Di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl, DCM: Dichloromethane, DIAD: Diisopropyl azodicarboxylate, DIEA: Diisopropylethylamine, DIPEA: N,N-Diisopropylethylamine, DMA: Dimethyl acetamide, DME: Dimethoxyethane, DMSO: Dimethyl sulfoxide, EDAC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, Fsp^3: Fraction sp_3 carbon, HBA: Hydrogen bond acceptor, HBD,: Hydrogen bond donor, HOBt: 1-Hydroxybenzotriazole hydrate, HT-ADME: High throughput absorption, distribution, metabolism, and excretion, HTC: High throughput chemistry, HTS: High throughput screen, LCMS: Liquid chromatography mass spectrometry, NAR: Number of aromatic rings, O/N: Overnight, PAMPA: Parallel artificial membrane permeability assay, $Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0), PKA: Protein kinase A, PPB: Plasma protein binding, PSA: Polar surface area, PS-DCC: Polymer supported dicyclohexylcarbodiimide, NRB: Number of rotatable bond, SAR: Structure activity relationship, TFA: Trifluoro acetic acid.

PDB CODES

Figure 2a Compound **12** in active site of PKA - PDB code 6E9L

Figure 2b Compound **12** in active site of ROCK1 - PDB code 6E9W

Figure 2c Compound **12** in active site of ROCK2 - PDB code 6ED6

Figure 3 Compound **47** in active site of PKA - PDB code 6E99

Structures for ROCK1, ROCK2 and PKA with compound **12** and PKA with compound **47** have been deposited in the PDB. Authors will release the atomic coordinates and experimental data upon article publication.

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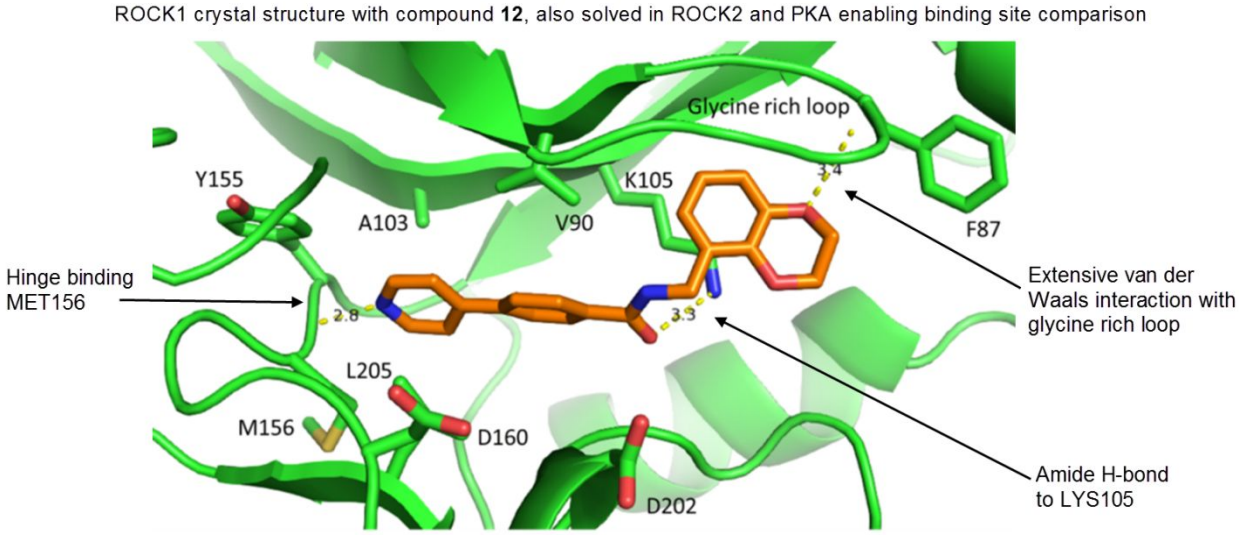

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