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Potent BRAF kinase inhibitors based on 2,4,5-trisubstituted imidazole with naphthyl and benzothiophene 4-substituents

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ABSTRACT

The RAS–RAF–MEK–ERK pathway is hyperactivated in 30% of human cancers. BRAF is a serine–threonine kinase, belonging to this pathway that is mutated with high frequency in human melanoma and other cancers thus BRAF is an important therapeutic target in melanoma. We have designed inhibitors of BRAF based on 2,4,5-trisubstituted imidazoles with naphthyl and benzothiophene-4-substituents. Two compounds were discovered to be potent BRAF inhibitors: 1-(6-{2-[4-(2-dimethylamino-ethoxy) phenyl]-5-(pyridin-4-yl)-1*H*-imidazol-4-yl} benzo[*b*]thiophen-3-yl)-2,2,2-trifluoroethanol (**1i**) with BRAF IC_{50} = 190 nM and with cellular GI_{50} = 2100 nM, and 6-{2-[4-(2-dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-naphthalen-1-ol (**1q**) with IC_{50} = 9 nM and GI_{50} = 220 nM.

1. Introduction

There are 200,000 newly diagnosed cases of malignant melanoma worldwide each year, of which ~20% are incurable. Approximately 40% of melanomas exhibit a mutation in the BRAF protein,[1] a serine/threonine kinase responsible for MAPK/ERK kinase (MEK) phosphorylation in the mitogen-activated protein kinase (MAPK) pathway, a conserved signalling cascade responsible for cell proliferation and survival. The majority of BRAF mutations (90%) consist of a glutamic acid substitution of the valine at position 600 (V600E).[2] This mutation causes a destabilisation of the inactive form of the enzyme, which in turn leads to its constitutive activation resulting in uncontrolled proliferation of cells.[3]

Many mutant BRAF inhibitors have been developed, some having been assessed clinically. GSK2118436,[4] RAF265,[5] and XL281[6] are currently being evaluated in phase I-III clinical trials. PLX4032 (vemurafenib, Zelboraf) has shown promising results in mutant BRAF driven melanoma[7–10] and was approved for the treatment of ^{V600E}BRAF metastatic melanoma.

We initiated a drug discovery programme to identify alternative BRAF inhibitors.[11–18] One example is shown in Figure 1.

Triaryl substituted imidazole-based compound **1**[18] is the most potent mutant BRAF inhibitor within its series. Although **1** is reasonably potent on isolated mutant BRAF, it is less potent in a mutant BRAF driven cell line, and greater cell line potency is desirable. We therefore investigated the triaryl imidazole scaffold further to generate improved kinase and cellular activity compared to compound **1.** We have named the imidazole core ring C and the putative hinge binder ring A; ring B interacts in the hydrophobic pocket of the enzyme (BPII)[19] and ring D extends outside the BRAF ATP-binding pocket pointing towards, and interacting with, the solvent.

Compounds containing 2,4,5-trisubstituted, five-membered, aromatic heterocycles have been reported previously as potent inhibitors of BRAF, targeting the active conformation of the kinase.[20–26] It is clear that the nature of group B, targeting the hydrophobic pocket next to the gatekeeper residue is crucial for activity. Three types of B-rings have been described in active triarylimidazole BRAF inhibitors: indanone-oximes, chlorophenols and tricyclic pyrazoles.[18,21,24,26] Recently, diarylthiazoles with phenyl-arylsulfonamides as B-rings have also been reported.[25] Our aim was to discover new related compounds as BRAF inhibitors by focusing on exploring the ring B substituents. These substituents were designed to probe the inner environment of the BPII pocket of the protein by exposing it to different combinations of

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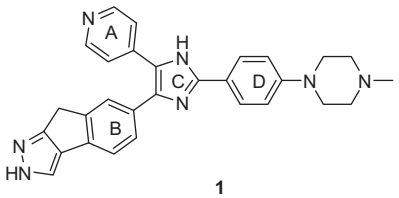


Figure 1. Structure of 2,4,5 trisubstituted imidazole-based BRAF inhibitor with tricyclic pyrazole ring B.

polar and nonpolar groups, as well as hydrogen bond donor and/or acceptor groups.

We have described[18] a series of pyrazole triaryl imidazoles and diarylfuran carboxamide mutant BRAF inhibitors bearing tricyclic ring B. We showed that the triarylimidazole scaffold yielded more potent BRAF inhibitors than the diarylfuran-carboxamides. Herein we have kept the central imidazole and the 2- and 5-substituents constant: the 2-substituent is 2-(4-diaminoethoxyphenyl), which is used as a solubilising group, and the 5-position is occupied by a 4-pyridyl group, which is the putative hinge-binder.[23] Here we focus on the SAR of two new types of B rings: (a) substituted benzofurans and benzothiophenes (compounds **2**, Fig. 2); (b) substituted naphthyls (compounds **3**, Fig. 2).

The benzofurans and benzothiophenes were proposed on the basis of their similarity with the indane scaffold of the indanone-oximes, the key group responsible for the activity of SB590885[23] (Fig. 2) and GDC-0879.[22] A range of H-bond donor, H-bond acceptor, polar and non-polar substituents were probed on the benzofuran and benzothiophene fragment, including isosteres of oxime, such as the hydroxymethyl group.

Naphthyls substituted with H-bond donors were proposed based on the rationale that H-bond donors such as oximes, phenols or pyrazoles[21,24,26] are required as B-rings for enhanced activity against BRAF. The increased lipophilicity of the naphthyl group lying in the hydrophobic pocket of BRAF is hypothesised to be desirable for improved potency against BRAF, favoring also the cellular activity of the ligand presumably due to increased cell permeability. This hypothesis is supported by the reported SAR of triaryl imidazole BRAF inhibitors. For example a triarylimidazole with 4-chloro-3-hydroxyphenyl ring B is 3.5 fold more potent in the BRAF assay than the equivalent compound with 3-hydroxyphenyl ring B;[21] 2,4-dihydroindeno[1,2-*c*]pyrazole ring B on the same scaffold is >50 fold more active than the equivalent 2,8-dihydroindeno [1,2-*d*][1,2,3]triazole.[18] Examples of naphthol groups as B-rings, albeit linked to different core scaffolds, were reported to provide good BRAF inhibition.[26,27] Interestingly, the screening of triarylimidazole BRAF inhibitors in our group identified the lipophilic 3,4-dichlorophenyl ring B motif associated with activity against BRAF of 0.58 μM (compound **1a**, Table 1). This effect can be attributed to the increased lipophilicity and Van der Waals radius (size of ring B) of the inhibitor rather than to improved electrostatic interactions, since the close analogue with 3-chloro-4-fluorophenyl ring B (**1b**) is inactive. The naphthyl group was considered a suitable extrapolation of the 3,4-dichlorophenyl fragment, which can be further substituted with H-bond donors or acceptors.

2. Results and discussion

2.1. Chemistry

The 2,4,5-trisubstitution of the imidazole scaffold was achieved using 2,4,5-tribromoimidazole (**4**) as starting material (Scheme 1). *N*1 was protected with a methoxymethyl (MOM) group to give **5**, which was subsequently functionalised selectively at the 2-position with a *p*-hydroxyphenyl group using a Suzuki coupling reaction to give **6**. A 2-*N*,*N*-dimethylaminoethyl solubilizing group was then attached through the phenolic oxygen atom to give intermediate **7**. The remaining two bromine atoms on the imidazole ring were displaced consecutively, first at the 5-position by a 4-pyridyl ring and, secondly, with a number of functionalised aromatic systems at the 4-position, in both cases employing Suzuki coupling reactions. Depending on the stability of the 4-substituent, two distinct routes were followed: route 1 relies on the deprotection of 4-bromo intermediate **8** followed by coupling of a boronic acid with the resulting free imidazole **9**; in route 2, on the other hand, the 4-substituent is put in place first and the imidazole *N*1 of the resulting compound **10** is then deprotected in the last step. Compounds **1a–z** were synthesised in moderate to good yields using one of the two approaches.

Some of the boronic acids or esters used for the arylation of the imidazole 4-position were commercially available (e.g., **11** and **12**, Scheme 2), however most of them required synthesis. The routes towards these building blocks are depicted in Schemes 3–11.

For the synthesis of boronic esters **17** and **20**, 3-bromophenol (**13**) was used as the starting material (Scheme 3). First, **13** was formylated and the resulting *ortho*-hydroxybenzaldehyde **14** was treated with ethyl diazoacetate to give derivatised benzofuran **15** in quantitative yield. Reduction of **15** with DIBAL-H followed by boronylation gave hydroxymethyl synthon **17**. Saponification, amidation and boronylation of intermediate **15** gave amide synthon **20**. The coupling of compounds **17** and **20** with intermediate **9** under standard Suzuki coupling conditions (see Section 4) gave inhibitors **1c** and **1d**.

Derivatised benzothiophenes were synthesised from the key intermediate 3,6-dibromobenzothiophene (**25**), which was obtained from 4-bromo-2-fluorobenzaldehyde (**21**) in four steps. Compound **21** was treated with ethyl thioglycolate to give **22** in excellent yield. Hydrolysis of the ester functionality and subsequent copper-mediated decarboxylation gave **24**; selective 3-bromination with NBS gave **25**. Compound **25** could be lithiated at the 3-position and quenched with appropriate electrophiles to give

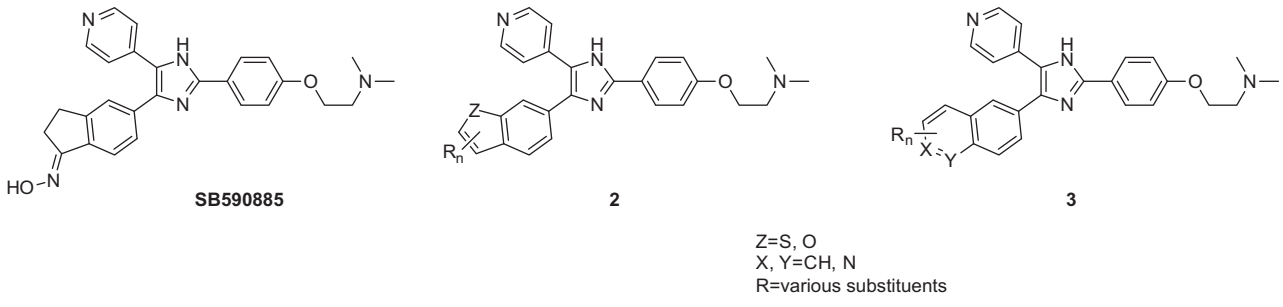
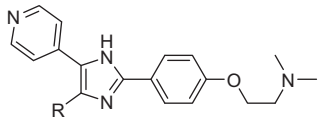


Figure 2. General structure of inhibitors with benzofuran/benzothiophene or naphthyl isosteres of indanoneoximes.

Table 1
Biological activities of compounds **1a–z**



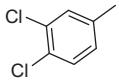
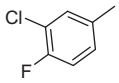
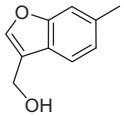
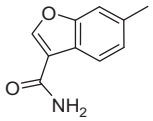
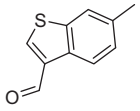
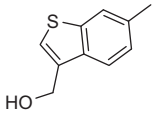
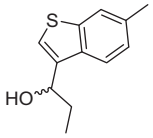
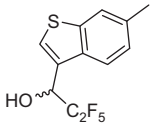
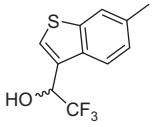
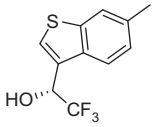
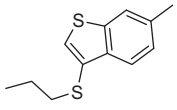
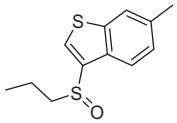
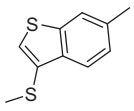
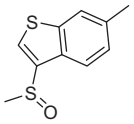
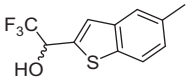
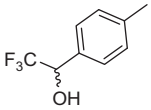
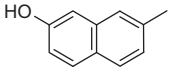
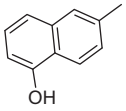
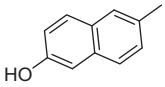
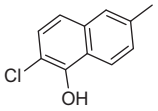
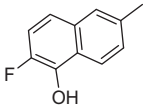
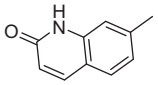
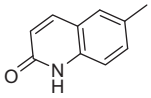
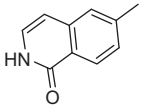
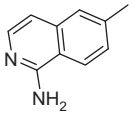
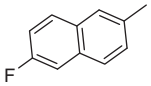
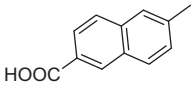
#	R	BRAF IC_{50} (μM) ±SEM (number of replicates)	pERK IC_{50} (μM) ±SEM (number of replicates)	SRB GI_{50} (μM) ±SEM[a]
1a		0.58 ± 0.07(3)	5.9 ± 2.0(2)	1.6 ± 0.06
1b		>10	n.d.	n.d.
1c		>10	n.d.	n.d.
1d		>10	n.d.	n.d.
1e		>10	n.d.	n.d.
1f		>10	n.d.	n.d.
±1g		>10	n.d.	n.d.
±1h		>10	n.d.	n.d.
±1i		0.33 ± 0.10(3)	2.7 ± 0.02(3)	3.1 ± 0.1
***R*-1i**		0.19 ± 0.03(2)	2.3 ± 0.3(2)	2.1 ± 0.3
1j		9.4 ± 0.3(2)	31(1)	2.3 ± 0.07
1k		>10	n.d.	n.d.
1l		14	n.d.	n.d.

Table 1 (*continued*)

#	R	BRAF IC_{50} (μM) ±SEM (number of replicates)	pERK IC_{50} (μM) ±SEM (number of replicates)	SRB GI_{50} (μM) ±SEM[a]
1m		>10	n.d.	n.d.
±1n		>10	n.d.	n.d.
±1o		>10	n.d.	n.d.
1p		1.4 ± 0.08(3)	3.6 ± 0.3(2)	3.2 ± 0.03
1q		0.009 ± 0.003(3)	0.39 ± 0.04(3)	0.22 ± 0.02
1r		8.8 ± 1.4(2)	14 ± 2.0(2)	4.3 ± 0.02
1s		0.042 ± 0.007(3)	1.25 ± 0.09(3)	1.1 ± 0.04
1t		0.029 ± 0.028(2)	0.25 ± 0.03(3)	11 ± 1.2
1u		>100	n.d.	n.d.
1v		>100	n.d.	n.d.
1w		>10	n.d.	n.d.
1x		1.1 ± 0.14(3)	5.1 ± 1.4(3)	5.7 ± 0.05
1y		>10	n.d.	n.d.
1z		>10	n.d.	n.d.

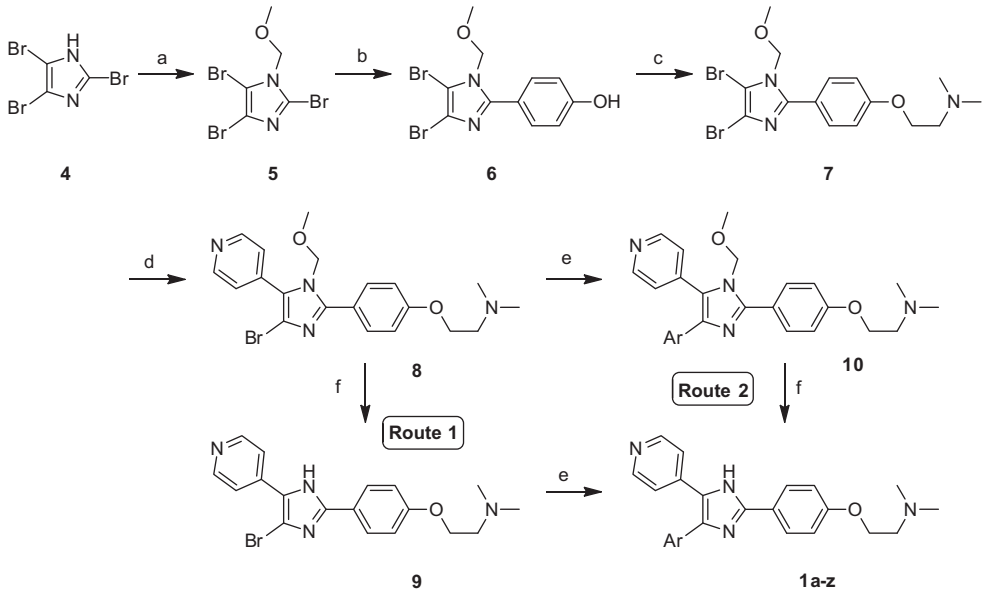
[a] Cell proliferation assays (SRB GI_{50}) were performed in quadruplicate.

the desired 3-substituted benzothiophenes in moderate yields (see Schemes 4 and 5).

In one series, **25** was converted to aldehyde **26** *via* lithiation followed by quenching with DMF. Standard boronylation gave intermediate **27**, which afforded inhibitor **1e** by Suzuki coupling. Reduction of aldehyde **1e** with sodium borohydride produces alcohol **1f**. The same intermediate **27** was converted first to the racemic ±**28** by treatment with ethyl magnesium bromide and then coupled with **9** to give racemic inhibitor ±**1g**. Alternatively, **25** could be converted to **29** with 2,2,3,3,3-pentafluoro-*N*,*N*-dimethyl propionamide. Reduction to racemic alcohol ±**30** with $NaBH_4$, followed by boronylation to ±**31** and coupling with **9** gave racemic ±**1h** (Scheme 4).

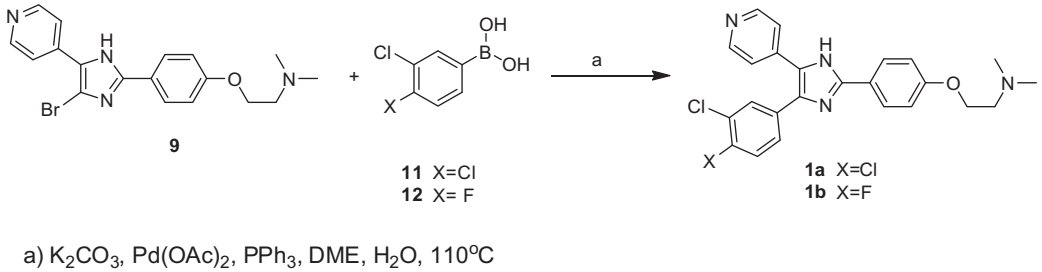
An analogous route using 2,2,2-trifluoro-*N*,*N*-dimethyl acetamide gave racemic ±**1i**. Enantiomerically enriched (91%) ***R*-1i** was synthesised by performing the reduction of ketone **32** with (*S*)-2-methyl-CBS-oxazaborolidine (Scheme 5).

Quenching of 3-lithiated **25** with either *n*-propyl or methyl disulfide led to thioethers **35** and **37**, respectively. Boronylation gave compounds **36** and **38**, which were subsequently coupled



a) MOMBr, NaH, THF; b) *p*-$HOC_6H_4B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, toluene, MeOH, reflux; c) $Cl(CH_2)_2N(CH_3)_2$, Cs_2CO_3, DMF, 40°C; d) pyridyl boronic ester, K_2CO_3, $Pd(OAc)_2$, PPh_3, DME, H_2O, 90°C; e) Suzuki coupling: arylboronic acids or esters, K_2CO_3, $Pd(OAc)_2$, PPh_3, DME, H_2O, 110°C; f) deprotection: 5M HCl, 60°C

Scheme 1. General synthetic route towards triarylimidazole-based inhibitors.



a) K_2CO_3, $Pd(OAc)_2$, PPh_3, DME, H_2O, 110°C

Scheme 2. Synthesis of compounds **1a**, **1b**.

with **9** to give inhibitors **1j** and **1l**. These, in turn, were converted into the corresponding sulfoxides **1k** and **1m**, respectively, by treatment with Oxone® (Scheme 5).

In order to obtain 2-substituted benzothiophenes, 6-bromobenzothiophene **24** was lithiated and quenched with *N,N*-dimethyltrifluoroacetamide to give intermediate **39** which after reduction, boronylation and coupling with intermediate **9** was converted to the racemic inhibitor ±**1n** (Scheme 6).

The racemic 4-(2-trifluoro-1-hydroxy)-phenyl boronic ester (**43**) was synthesised by reduction of 1,1,1-trifluoroacetophenyl bromide (**41**) followed by the usual boronylation procedure and was coupled to intermediate **9** to give the racemic inhibitor ±**1o** (see Scheme 7).

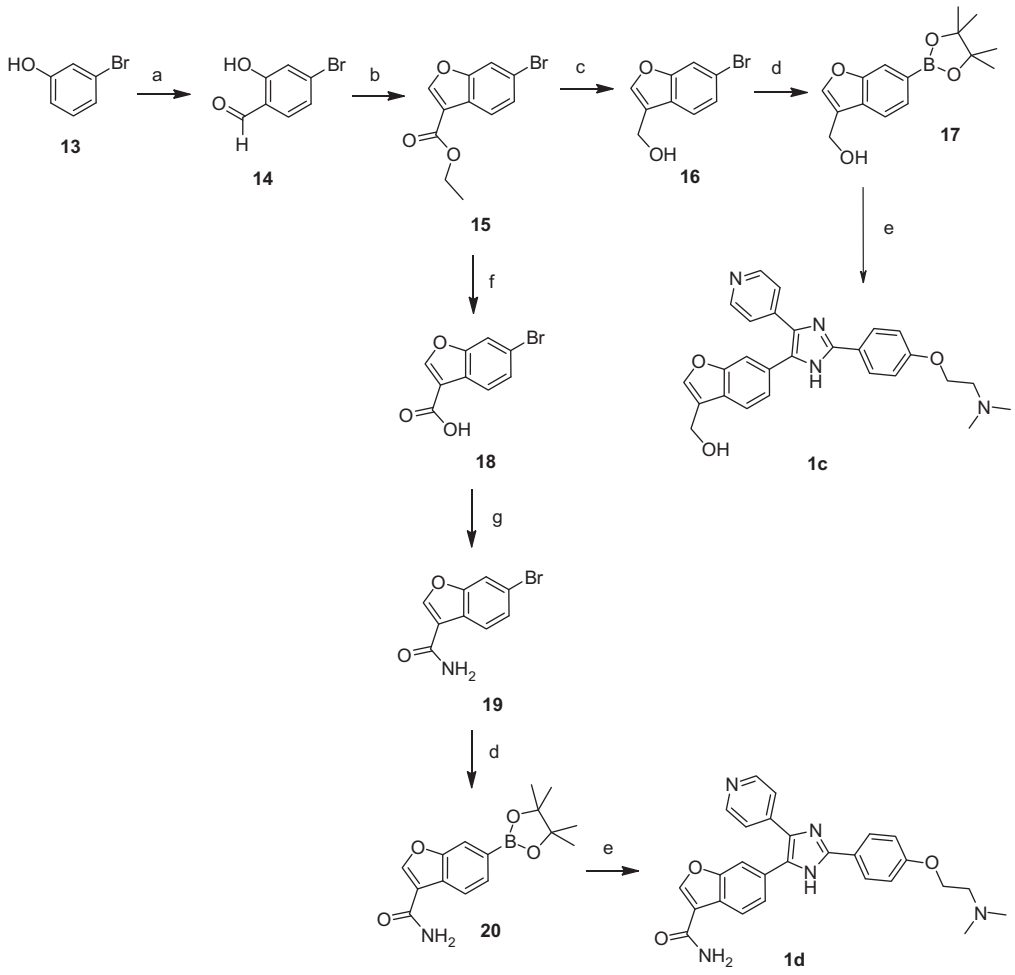
7-Methoxy-naphthalen-2-ol (**44**) was converted into **45** by electrophilic bromination with Br_2/PPh_3. Boronylation to **46** and coupling with **9** gave inhibitor **1p**. The isomer **1q** was synthesised from 6-aminotetralone (**47**) in several steps (Scheme 8). Intermediate **47** was converted into **48** via a diazotization reaction. Generation of vinyl silylether **49** followed by oxidation to **50** and desilylation gave 6-bromonaphthalen-1-ol (**51**). Boronylation and coupling with **9** gave **1q**.

6-Hydroxynaphthyl substituted inhibitor **1r** was synthesised by deprotection of **54**, which was obtained by Suzuki coupling of **8** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol.

The 2-chloro and 2-fluoro-1-naphthol derivatives **1s** and **1t**, were synthesised as shown in Scheme 9. 6-Bromo-1-naphthol **55** was chlorinated using NaOCl/*t*-BuOH to give **56**, followed by boronylation and coupling with **9** to give **1s**. The fluoro analogue **1t** had to be synthesised via a more elaborate route. Treatment of 5-bromo-indan-1-one (**58**) with trimethylsilyl fluorosulfonyldifluoroacetate (TFDA)[28] led to rearranged compound **59** in low yield, which was boronylated to **60** and coupled with **8** to give **61**. Deprotection of both the imidazole and the naphthol functionalities was performed with HBr/HOAc at 120 °C in a sealed vessel to yield 14% of inhibitor **1t** (Scheme 9).

A few other bicyclic systems were also considered as possible pharmacophores (Scheme 10). Particularly quinolones and aminoisoquinolines were anticipated to be of interest. 7-Bromo-2-chloroquinoline (**62**) served as the starting material for inhibitor **1u**. Substitution of the chlorine atom with a hydroxyl group gave **63**, and a subsequent boronylation and coupling with intermediate **8** gave N-protected compound **65**, which was subsequently deprotected to give **1u**. Its isomer **1v** was synthesised from the corresponding boronic ester **67** and intermediate **8**. Isoquinolone **1w** was obtained by Suzuki coupling of boronic ester **70** with unprotected bromoimidazole **9.**

The amino-isoquinoline substituted inhibitor **1x** was synthesised from **71** in 4 steps through **73** via a coupling reaction with



a) CH_2O, $MgCl_2$, NEt_3, CH_3CN, reflux; b) fluoroboric acid.Et_2O, $EtOOCCHN_2$, H_2SO_4, DCM; c) DIBAL-H, DCM, -78°C; d) boronylation (general procedure); e) coupling (general procedure); f) NaOH 2N, EtOH, reflux; g) oxalyl chloride, NH_4OH, DMF, DCM.

Scheme 3. Synthesis of benzofuran inhibitors **1c**, **1d**.

the protected intermediate **8** (see Scheme 11). Fluoronaphthyl-functionalized inhibitor **1y** was synthesised by boronylation of **75**, coupling with **8**, and deprotection of intermediate **77** according to the general methods. 2-Naphthoic acid **1z** was obtained according to the same route.

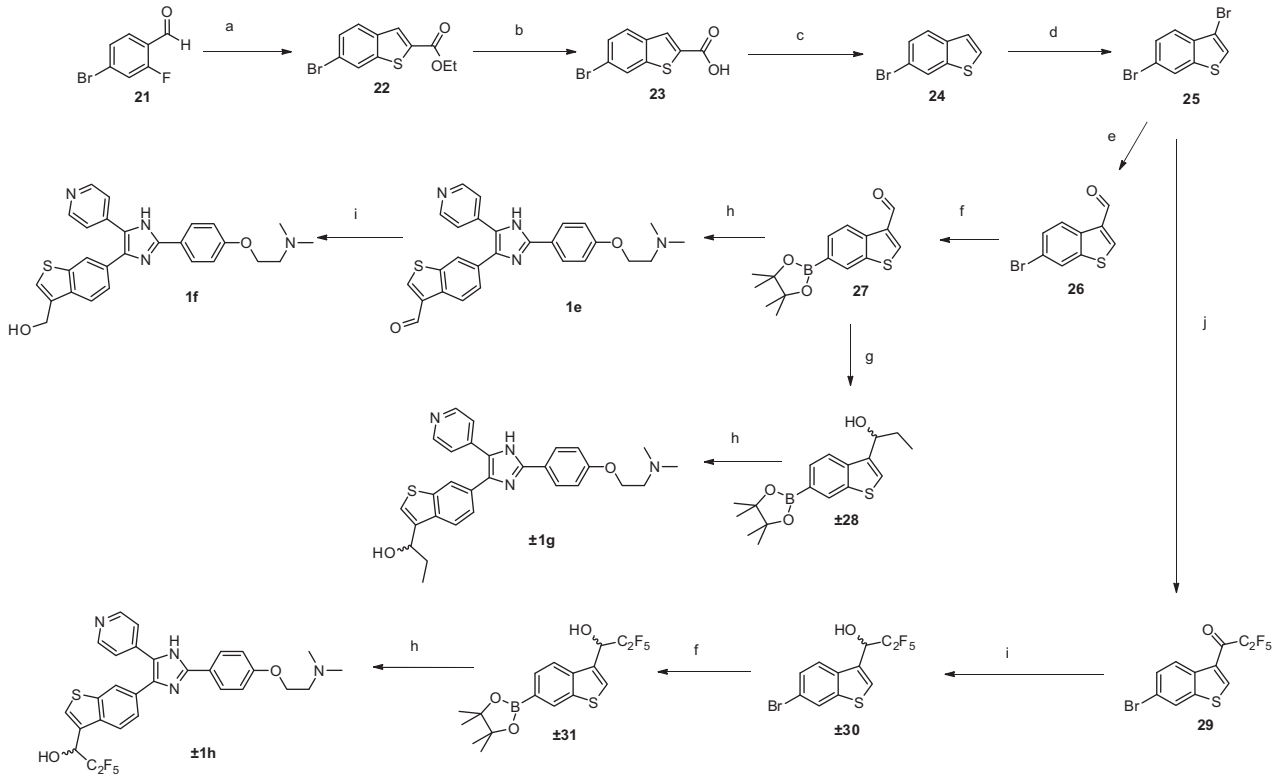
2.2. Biological results

Three assays were used to determine the biological activities of compounds **1a-z**. The IC_{50} of the ^{V600E}BRAF mutant enzyme inhibition in vitro (IC_{50}, BRAF) was measured for all compounds. Those compounds showing promising activity in the kinase assay were submitted to two cellular assays: inhibition of the phosphorylation of extracellular signal-regulated kinase (ERK) (IC_{50}, pERK) and growth inhibition of BRAF dependent WM266.4 cells (GI_{50}, SRB).[14] These data are summarised in Table 1.

2.3. SAR of compounds with benzofuran or benzothiophene ring B

The benzofuran and benzothiophene rings were designed as isosteres of the indane group of indanone-oximes.[21,23,24] Despite the shape similarity with indanone-oxime, the H-bond donors benzofuran and benzothiophene alcohols **1c** and **1f** are inactive. The H-bond acceptor aldehyde analogue **1e** is also inactive. We considered reasons for the greater activity of indanone oxime SB590885 compared to the isosteric **1c** and **1f**. One possible explanation is that the H-donor in benzofuran/benzothiophene is situated on a freely rotating bond, whereas in the oxime the position is fixed. This is also supported by the reported increased activity of 2,4-dihydroindeno[1,2-*c*]pyrazole as compared to phenylpyrazoles.[21,24] However other potential explanations for this decrease in BRAF inhibition are possible, such as: (a) a heteroatom pair (such as nitrogen and oxygen of oxime[21,24] or the two nitrogen groups of pyrazole) rather than H-bond donor ability is required in the active site; (b) a H-bond donor in the active site is required, and it has to be more acidic than an alcohol (pK_as of oximes are around 11 and pK_a of chlorophenol is 9);[21] (c) the indane ring of indanone is more lipophilic than the benzothiophene and especially the benzofuran group. The good activity of compound **1a** supports the idea that increased lipophilicity is favorable for BRAF inhibition.

We used these hypotheses to guide the design of our BRAF inhibitors. Based on hypothesis (a) we selected sulfoxide as a pair of vicinal heteroatoms lacking the H-bond donor function. Methyl and propyl sulfoxide compounds **1m** and **1k** are inactive; the reduced thiomethyl ether analogues **1l** and **1j** respectively show only



a) ethylthioglycolate, K_2CO_3, DMF; b) EtOH, KOH, reflux; c) Cu powder, quinoline, 185°C; d) NBS, AcOH, $CHCl_3$; e) *n*BuLi, DMF, Et_2O, -70°C; f) boronylation (general procedure); g) EtMgBr, THF; h) Suzuki coupling with **9** (general procedure); i) $NaBH_4$, EtOH or MeOH; j) nBuLi, 2,2,3,3,3-pentafluoro-*N*,*N*-dimethylpropionamide, -70°C

Scheme 4. Synthesis of 3-substituted benzothiophene inhibitors **1e**–**h**.

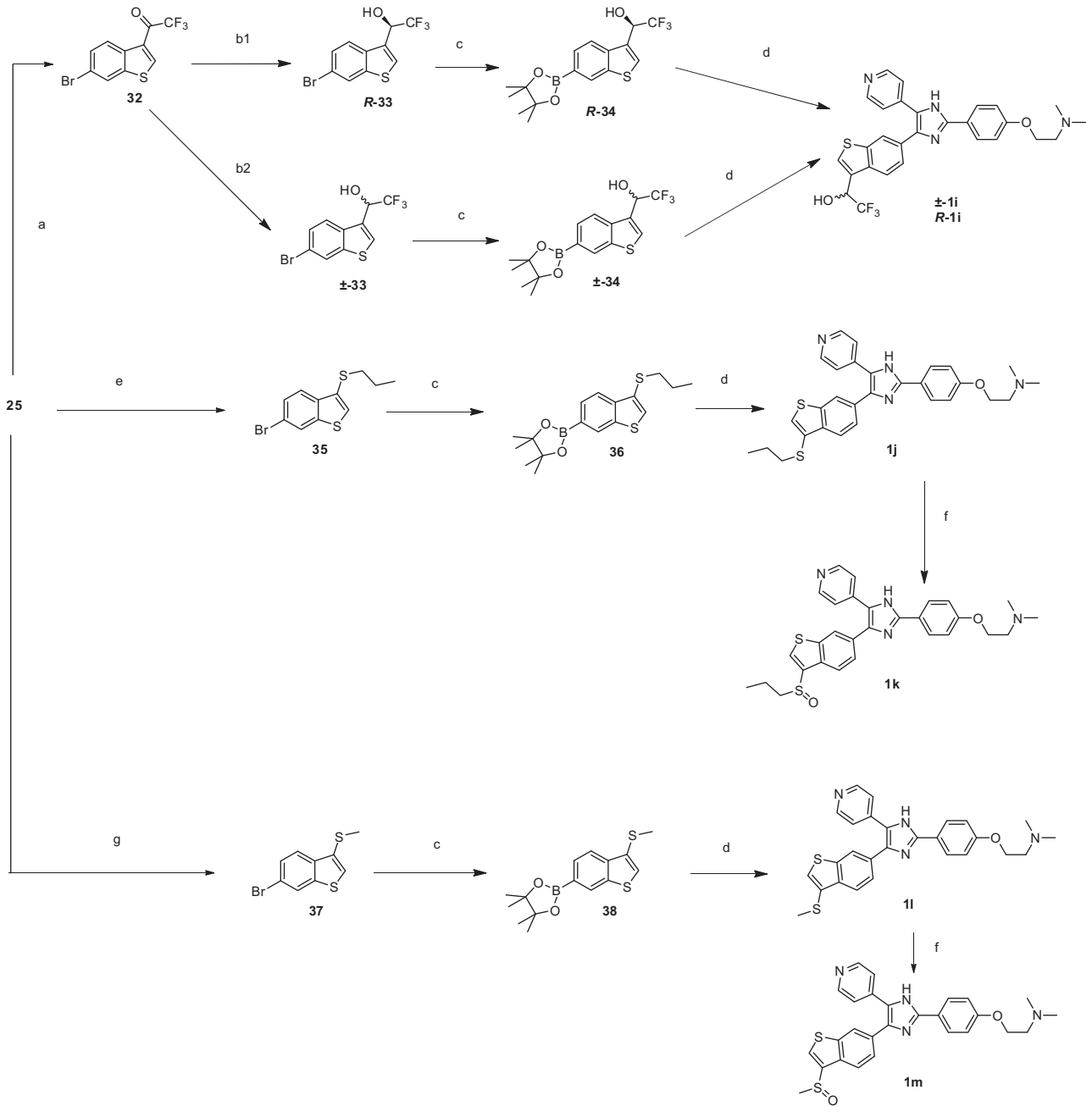
weak activity (BRAF IC_{50} = 14 μM and 9.4 μM). Since the sulfoxide might not have been the best choice of heteroatom pairs, possibly due to lack of H-bond donor capability, we tested the amide group containing the carbonyl acceptor and the NH_2 donor, albeit in a 1,3-position. However the corresponding compound **1d** is also inactive.

In order to test hypothesis (b), we sought benzothiophenes bearing more acidic H-bond donors. Trifluoroethanol is more acidic than ethanol (pK_a = 12.5 vs 15.9), therefore the racemic 1-(benzothiophen-3-yl)-2,2,2-trifluoroethanol derivative **1i** was synthesised. Pleasingly, this compound is more active (BRAF IC_{50} = 0.33 μM). The *R*-enantiomer ***R*-1i** is active at similar levels (BRAF IC_{50} = 0.19 μM) and low micromolar cell activity. The activity appears to be due to electronic effects, as compound **1g** with ethyl substituent with a similar van der Waals volume (39.8 $Å^3$ for CF_3 and 38.9 $Å^3$ for Et)[29] is inactive. The larger pentafluoroethyl-substituted analogue **1h** is not active, presumably for steric reasons. The 3-position of the 2,2,2-trifluoroethanol substituent on the benzothiophene ring B is crucial, since neither the 2-substituted benzothiophene **1n** nor the 4-phenyl substituted **1o** are active.

2.4. SAR of compounds with naphthyl ring B

The naphthyl group was selected as a more lipophilic ring B alternative, as per hypothesis (c), which is amenable to substitution with H-bond donors in a rigid framework. The potent BRAF inhibition shown by compound **1i** points towards the requirement for a relatively acidic hydroxyl group on ring B for BRAF inhibition, therefore naphthols **1p**, **1q** and **1r** were initially synthesised. The hydroxyl H-bond donor on the naphthyl ring has a beneficial effect on binding to BRAF, with activity observed for all three naphthols. This is in agreement with another recent report of a naphthol-containing BRAF inhibitor.[26] The position of the hydroxyl group has a profound effect on affinity, with the 6-substituted 1-naphthol **1q** being >100-fold more potent than the 7-substituted 2-naphthol **1p** and 1000 fold more potent than the 6-substituted 2-naphthol **1r**. This large increase in BRAF inhibition can be explained by an H-bond interaction of the correctly positioned hydroxyl group with an H-bond acceptor of the protein. Compound **1q** has potent inhibitory activity on BRAF (BRAF IC_{50} = 9 nM), good cellular activity on the MAPK pathway (pERK IC_{50}=390 nM) and growth inhibition of WM266.4 cells (GI_{50} SRB = 219 nM).

Two halogenated analogues of **1q** were synthesised, chloronaphthol **1s** and fluoronaphthol **1t**, in order to increase the acidity of the naphthol. The chloro substitution in **1s** decreases the kinase inhibition 4-fold, and the cellular activity correspondingly to micromolar inhibition. The smaller fluorine substituent in **1t** still causes a 3-fold decrease in kinase inhibition, although the cellular inhibition of the pathway is comparable to **1s**. The WM266.4 growth inhibition value is surprisingly high, since in most cases the pERK IC_{50} and GI_{50} SRB are correlate very well. This decrease in activity in the kinase assay can be potentially attributed to partial ionisation of **1t** and **1s** to inactive negatively charged phenolates at the pH of the assays. The pK_a of 2-chloro-1-naphthol is 7.8; the pK_a of 2-fluoro-1-naphthol can be estimated to be around 7.9 based on the pK_a of 2-fluorophenol (8.7) and the difference



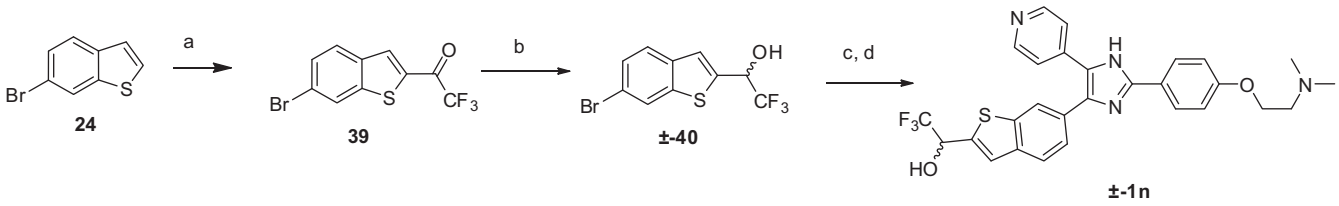
a) *n*BuLi, *N,N*-dimethyltrifluoroacetamide, hexane, -100°C; b1) $NaBH_4$, EtOH or MeOH; b2) (S)-oxazaborolidine, catecholborane, DCM; c) boronylation (general procedure); d) coupling with **9** (general procedure); e) *n*BuLi, propyldisulfide, Et_2O, -70°C; f) oxone, H_2O-Me_2CO; g) *n*BuLi, methyldisulfide, Et_2O, -70°C.

Scheme 5. Synthesis of 3-substituted benzothiophene inhibitors **1i**–**1m**.

between the pKa values of 2-chlorophenol (8.6) and 2-chloro-1-naphthol (7.8). By comparison, the pK_a of 1-naphthol is 9.3, and is mainly non-ionised at physiological pH.

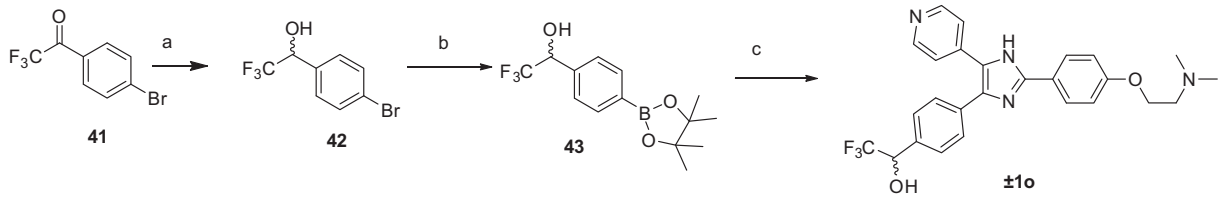
The importance of the hydroxyl H-bond donor group of naphthol is underlined by comparison of **1q** with **1w** and **1t** with **1y**. The predominant tautomer of 1-hydroxyisoquinoline **1w** is the isoquinolone, lacking the crucial H-donor group of the 1-naphthol **1q** and is completely devoid of activity. Compound **1y,** the fluoronaphthyl analogue of fluoronaphthol **1t**, is also inactive. A similar loss of activity is seen for the quinolones **1u** and **1v** when compared to the corresponding naphthols **1p** and **1r**. The activity can be partially restored (to BRAF IC_{50} = 1 μM) when the isoquinolone is replaced with 1-aminoisoquinoline **1x**, which possesses an H-bond donor group in the same position as naphthol **1q**. The naphthoic acid **1z** is also inactive, which is not surprising considering it is deprotonated to the corresponding carboxylate at neutral pH.

Based on these results we concluded that appropriate acidity (pK_a = 9–11) of a correctly positioned H-bond donor within a rigid framework is the main driving factor for potent BRAF inhibition in the triarylimidazole scaffold presented here.



a) *n*BuLi, *N,N*-dimethyltrifluoroacetamide, Et_2O, -70°C; b) $NaBH_4$, EtOH; c) boronylation (general procedure); d) Suzuki coupling with **9** (general procedure).

Scheme 6. Synthesis of 2-substituted benzothiophene inhibitor **1n**.



a) $NaBH_4$, NaOH, MeOH; b) boronylation (general procedure); c) K_2CO_3, $Pd(OAc)_2$, PPh_3, DME, H_2O, 110°C.

Scheme 7. Synthesis of 1,1,1-trifluoro-2-hydroxyethyl phenyl inhibitor **1o**.

3. Conclusions

A new series of BRAF inhibitors has been prepared, based on 2,4,5-trisubstituted imidazoles containing in the 4 position a substituted naphthyl, benzofuranyl or benzothiophenyl group. The presence of a correctly positioned H-bond donor of appropriate pK_a on these bicyclic ring systems is important for activity. Benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-ethanol is a novel moiety that interacts with the BPII pocket of BRAF resulting in potent BRAF kinase inhibition in vitro and in cells. Benzo[b]thiophen-3-yl)-2,2,2-trifluoro-ethanol **1i** and naphthols **1q, 1s** and **1t** are particularly active against BRAF with compound **1q** in particular showing BRAF IC_{50} of 9 nM, and cellular potency at submicromolar levels. These findings suggest new avenues for designing BRAF inhibitors.

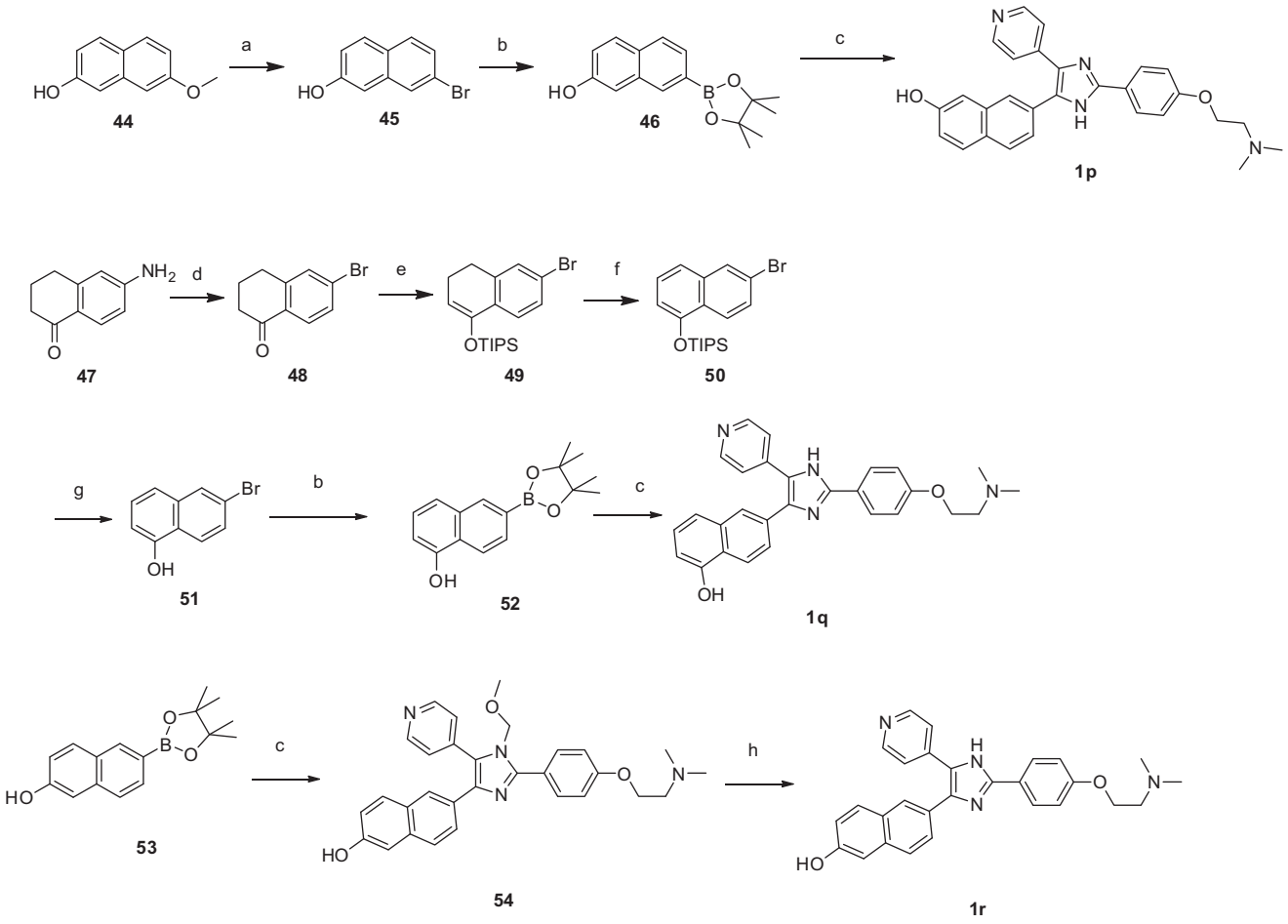
4. Experimental

4.1. General

All starting materials, reagents and solvents for reactions were reagent grade and used as purchased. Chromatography solvents were HPLC grade and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) analysis using Merck silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out on Merck silica gel 60 (0.015–0.040 mm) or in disposable Isolute Flash Si and Si II silica gel columns. LC–MS analyses were performed on a Micromass LCT/Water's Alliance 2795 HPLC system using 5 μm Atlantis C18, 50 mm × 2.1 mm columns at 22 °C with the following solvent system: Aqueous: water + 0.1% formic acid; Organic: 0.1% formic + acetonitrile, at a flow rate of 1 mL/min. Method A: gradient starting with 100% aqueous to 100% organic in 2.5 min at room temperature and a flow rate of 0.6 mL/min or method B gradient starting with 100% aqueous to 100% organic in 5 min at 40 °C (column temperature) at a flow rate of 0.6 mL/min. UV detection was at 215 nM and ionisation was positive or negative ion electrospray. The molecular weight scan range was 50–1000. Samples were injected at 3 μl on a partial loop fill. All automated HPLC purification were performed on Gilson Prep LC modules running on software version 1.71 or 3.0 on HyperprepHSC18 100 mm × 21.2 mm columns, 12 μm, at a flow rate of 30 mL/min at room temperature using as aqueous phase: water + 0.1% TFA and as organic phase: acetonitrile + 0.1% trifluoroacetic acid (TFA) (UV detector, at 215 and 254 nM). Chiral HPLC was run on Chiracel OD-H columns using as eluent: (a) heptane/methanol 9:1 + 0.1% triethylamine (TEA) or (b) heptane/ethanol 85:15 at a flow rate of 30 mL/min (UV detector, at 215 and 254 nm). NMR spectra were recorded in DMSO-d_6 on a Bruker DPX 250 MHz or a Bruker Advance 500 MHz spectrometer. Chemical shifts (δ) are given in ppm and are referenced to residual, not fully deuterated solvent signal (i.e. DMSO-d_5). Coupling constants (J) are given in Hz. Accurate Mass Measurement was performed with a Waters Micromass LCT Premier orthogonal acceleration Time-of-Flight Mass Spectrometer 4 GHz TDC with LockSpray™ enable mass measurements of 5 ppm or better for m/z of 400 or greater and 2 mDa or better for m/z of 400 or less. Calibration reference: Wpos_150208.cal or Wneg_150208a.cal. MassLynx v4.1 SCN 633 was the operating software using the inbuilt elemental composition to report data. Minimum 10 scans combined across a MS peak. Microwave reactions were run on a CM discovery unit operating at 200 watts with simultaneous stirring.

4.2. 2-Hydroxy-4-bromobenzaldehyde (14)

3-Bromophenol (**13**) (2 g, 11.6 mmol), magnesium chloride (1.66 g, 17.4 mmol) and triethylamine (6.2 mL, 44.4 mmol) were dissolved in acetonitrile (60 mL) and stirred at rt for 20 min before adding paraformaldehyde (2.34 g, 78 mmol) and heating at reflux for 8 h. After cooling to rt, the reaction was acidified with 2 N HCl and extracted with MTBE (2 × 60 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica gel eluting with 0–5% EtOAc in heptane and the product recrystallised from hot heptane. Yield: 595 mg (25%). ^{1}H NMR ($CDCl_3$), δ: 7.18 (dd, 1H, ArH), 7.21 (d, J = 1.8, 1H, ArH), 7.42 (d, J = 8.2, 1H, ArH), 9.87 (br, 1H, OH), 11.13 (s, 1H, CHO).



Scheme 8. Synthesis of naphthol inhibitors **1p–r**.

4.3. Ethyl 6-bromobenzofuran-3-carboxylate (15)

To a solution of 2-hydroxy-4-bromobenzaldehyde (**14**) (345 mg, 1.7 mmol) and ethereal fluoroboric acid (23 μl, 0.2 mmol) in DCM (1 mL) was added a solution of ethyl diazoacetate (0.28 mL, 2.7 mmol) in DCM (3 mL) over 12 min. After 2 h, the solvent was evaporated and concentrated sulfuric acid (0.15 mL) added. After 10 min, the reaction was diluted with DCM (5 mL) and the acid neutralized with solid sodium bicarbonate. The desired product was purified by chromatography on silica gel eluting with DCM. Yield: 490 mg (quantitative). ^{1}H NMR ($CDCl_3$), δ: 1.43 (t, J = 7.1, 3H, CH_3), 4.41 (q, J = 7.1, 2H, CH_2), 7.49 (dd, J = 8.4, 1.7, 1H, ArH), 7.72 (d, J = 1.7, 1H, ArH), 7.93 (d, J = 8.5, 1H, ArH), 8.22 (s, 1H, ArH).

4.4. (6-Bromo-benzofuran-3-yl)-methanol (16)

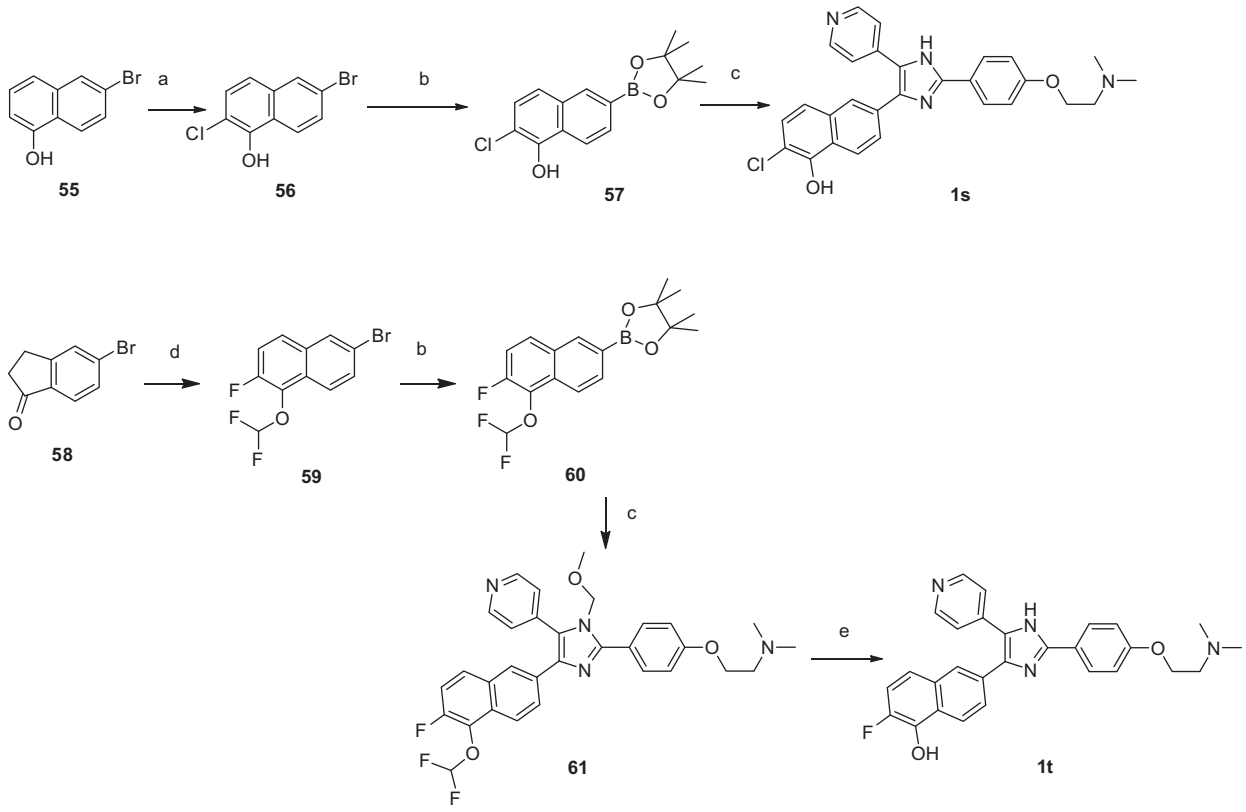
A solution of ethyl 6-bromobenzofuran-3-carboxylate (**15**) (135 mg, 0.5 mmol) in DCM (2.7 mL) was cooled to −78 °C. DIBAL-H (1.5 M in toluene) (0.83 mL, 1.2 mmol) was added over 2 min and the reaction stirred at rt for 4.5 h before adding water (0.45 mL) and EtOAc (10 mL). After separation, the organic phase was washed with 1 N HCl (10 mL), dried ($MgSO_4$), filtered and evaporated. The product was purified by chromatography on silica gel eluting with 0–40% EtOAc in heptane to afford 84 mg (74%) of desired material. ^{1}H NMR ($CDCl_3$), δ: 2.22 (s, 1H, OH), 4.80 (s, 2H, CH_2), 7.38 (dd, 1H, ArH), 7.51 (d, J = 8.6, 1H, ArH), 7.57 (s, 1H, ArH), 7.66 (d, J = 1.8, 1H, ArH).

4.5. 6-Bromobenzofuran-3-carboxylic acid (18)

A mixture of ethyl 6-bromobenzofuran-3-carboxylate (220 mg, 0.8 mmol) and 2 N NaOH (0.6 mL, 1.2 mmol) in ethanol (1.2 mL) was heated for 1 h. The bulk of the solvent was evaporated and the residue acidified with 2 N HCl (1.2 mL) to give a thick precipitate. This was diluted with water, cooled to rt and filtered to leave the product after washing with more water. Yield: 99 mg (50%). ^{1}H NMR (DMSO-d_6), δ: 7.56 (dd, J = 8.4, 1.8, 1H, ArH), 7.91 (d, J = 8.4, 1H, ArH), 8.04 (d, J = 1.7, 1H, ArH), 8.70 (s, 1H, ArH), 13.09 (s, 1H, COOH). LC–MS: R_f = 1.87 min; m/z 239/241 ([M+H]$^+$, 100). HRMS (EI): m/z calcd for $C_9H_5BrO_3$ ([M+H]$^+$): 238.9344; found: 238.9355.

4.6. 6-Bromobenzofuran-3-carboxylic acid amide (19)

Compound **18** (99 mg, 0.4 mmol) was suspended in DCM (1 mL) and oxalyl chloride (43 μl, 0.5 mmol) added, followed by a drop of DMF. After 1 h, the reaction was evaporated to dryness and 0.5 N ammonia in dioxane (3.3 mL, 1.7 mmol) added, followed after 2 h by concentrated ammonium hydroxide (1 mL). After stirring at rt for 16 h, the dioxane was evaporated, water (1 mL) added and extracted with DCM (3 × 2 mL). The precipitate which formed was



Scheme 9. Synthesis of halogenated naphthol inhibitors **1s**, **1t**.

filtered off and washed with DCM. The combined organic phases were washed with potassium carbonate solution and water then dried ($MgSO_4$), filtered and evaporated. This was combined with the initial precipitate to give the desired product (32 mg, 32%). LC–MS: R_f = 1.65 min; *m*/*z* 240/242 ([M+H]$^+$, 100).

4.7. Ethyl, 6-bromobenzothiophene-2-carboxylate (22)

4-Bromo-2-fluorobenzaldehyde, **21**, (3.12 g, 15.4 mmol) and potassium carbonate (2.76 g, 20.0 mmol) were suspended in dry DMF (15 mL) and cooled to 0 °C under nitrogen. Ethyl thioglycolate (1.7 mL, 15.5 mmol) was added portionwise over 1 h and the reaction warmed slowly to rt and stirred at rt for 16 h. The reaction was then heated at 60 °C for 5.5 h before cooling and adding water (30 mL). The mixture was stirred for 30 min at rt then filtered, washed with water and dried to leave the product **22** (4.31 g) as a solid. (Yield: 98%). ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, *J* = 7.0, 3H, CH_3), 4.42 (q, *J* = 7.0, 2H, CH_2), 7.52 (dd, *J* = 8.4, 1.6, 1H, ArH), 7.73 (d, *J* = 8.6, 1H, ArH), 8.01 (s, 1H, ArH), 8.02 (d, *J* = 1.4, 1H, ArH).

4.8. 6-Bromobenzothiophene-2-carboxylic acid (23)

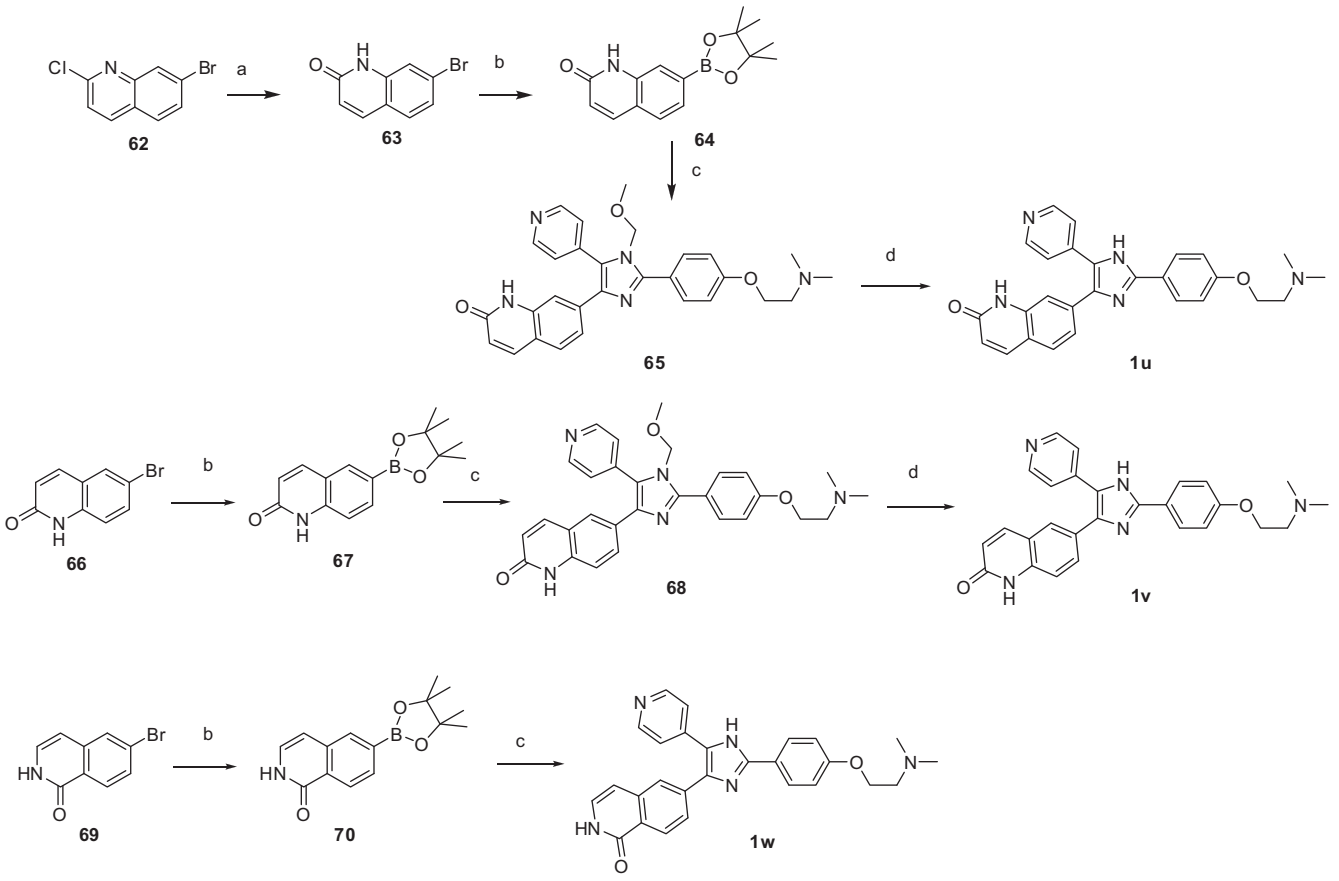
Compound **22** (4.31 g, 15.1 mmol) was dissolved in hot ethanol (43 mL) and potassium hydroxide (4.66 g, 83.2 mmol) in water (43 mL) added. The suspension was heated at reflux for 1.5 h during which time it mostly dissolved. After cooling slightly, 6 N HCl (17 mL) was added portionwise. Much of the ethanol was evaporated in vacuo and the residual solid filtered, washed with water and dried to give **23** (3.67 g) as an off-white solid. Yield: 95%. ^{1}H NMR ($CDCl_3$), δ: 7.62 (dd, *J* = 8.6, 1.8, 1H, ArH), 7.95 (d, *J* = 8.6, 1H, ArH), 8.11 (*s*, 1H, ArH), 8.37 (d, *J* = 1.8, 1H, ArH), 13.55 (br, 1H, COOH).

4.9. 6-Bromobenzothiophene (24)

Compound **23** (3.67 g, 14.3 mmol) and copper powder (0.45 g, 7.1 mmol) were suspended in quinoline (18 mL) and heated at 185 °C for 2 h. After cooling down to rt, EtOAc (25 mL) was added and the suspension filtered. The solid was washed with further EtOAc and the combined organic solutions washed with 2 N HCl (2 × 50 mL). After drying ($MgSO_4$), filtration and evaporation in vacuo, the residue was purified by chromatography on silica with pentane to afford the desired material (2.21 g) as a crystalline white solid. Yield: 73%. ^{1}H NMR ($CDCl_3$), δ: 7.31 (dd, *J* = 5.4, 0.9, 1H, ArH), 7.43 (d, *J* = 5.4, 1H, ArH), 7.48 (dd, *J* = 8.4, 1.6, 1H, ArH), 7.69 (d, *J* = 8.6, 1H, ArH), 8.03 (d, *J* = 1.8, 1H, ArH).

4.10. 3,6-Dibromobenzo[*b*]thiophene (25)

Compound **24** (1.5 g, 7.0 mmol) was dissolved in chloroform (11 mL). Acetic acid (11 mL) was added and the mixture cooled on ice before adding *N*-bromosuccinimide (1.57 g, 8.8 mmol) portionwise over 1 h. The reaction was allowed to warm to rt then stirred at rt for 16 h before washing with saturated sodium thiosulfate (22 mL), saturated sodium bicarbonate (2 × 22 mL) and water (22 mL). The solution was dried (Na_2SO_4) before filtration and evaporation in vacuo. The product was purified by chromatography on silica gel with pentane to afford the desired material



Scheme 10. Synthesis of quinolones **1u, 1v** and isoquinolone **1w**.

(1.49 g) as a crystalline solid. Yield: 73%. ^{1}H NMR ($CDCl_3$), δ: 7.42 (s, 1H, ArH), 7.58 (dd, J = 8.6, 1.4, 1H, ArH), 7.69 (d, J = 8.4, 1H, ArH), 8.01 (d, J = 1.4, 1H, ArH).

4.11. 6-Bromo-benzo[*b*]thiophene-3-carbaldehyde (26)

3,6-Dibromobenzo[*b*]thiophene, **25** (338 mg, 1.2 mmol) was dissolved in diethyl ether (10 mL) and cooled to −70 °C. 1.6 M *n*-BuLi in hexanes (0.8 mL, 1.3 mmol) was added over 35 minutes and the reaction stirred at −70 °C for a further 40 min before adding *N*,*N*-dimethylformamide (94 μl, 1.2 mmol). After stirring at −70 °C for 4 h, the reaction was quenched with 2 N HCl (6 mL), warmed to rt and the layers separated. The aqueous was extracted with diethyl ether (10 mL) and the combined organic phases were washed with saturated $NaHCO_3$ (10 mL) and brine (5 mL) before evaporation in vacuo. The desired compound was isolated by chromatography on silica gel with 0–20% EtOAc in heptane (112 mg, 40%). ^{1}H NMR ($CDCl_3$), δ: 7.63 (dd, J = 8.7, 1.8, 1H, ArH), 8.01 (d, J = 1.4, 1H, ArH), 8.31 (s, 1H, ArH), 8.56 (d, J = 8.7, 1H, ArH), 10.13 (s, 1H, CHO).

4.12. ±1-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzo[*b*]thiophen-3-yl]-propan-1-ol (±28)

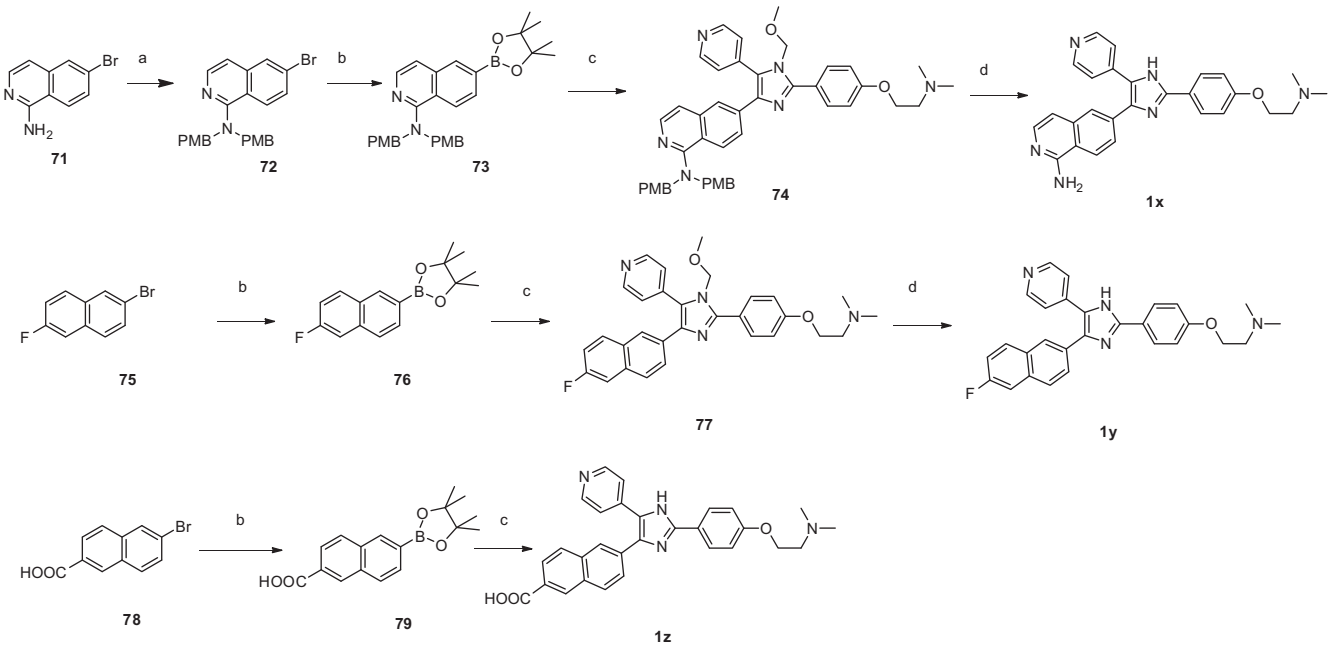
A solution of **27** (46 mg, 0.2 mmol) in dry THF (0.5 mL) was cooled on ice/water before adding ethyl magnesium bromide (1 M in THF) (0.18 mL, 0.2 mmol). The reaction was stirred at 0 °C for 30 min then at rt for 1.5 h before quenching with 2 N HCl (0.5 mL), extracting with EtOAc (2 mL), washing with brine (1 mL), drying ($MgSO_4$) and evaporating in vacuo. The product was purified by chromatography on silica gel with 50% EtOAc/heptane (24 mg, 47%). ^{1}H NMR ($CDCl_3$), δ: 1.00 (t, J = 7.3, 3H, CH_3), 1.38 (s, 12H, CH_3), 1.89–2.04 (m, 2H, CH_2), 5.04 (t, J = 6.4, 1H, CH), 7.45 (s, 1H, ArH), 7.78 (dd, J = 8.2, 0.9, 1H, ArH), 7.88 (d, J = 8.2, 1H, ArH), 8.36 (s, 1H, ArH).

4.13. 2,2,3,3,3-Pentafluoro-*N*,*N*-dimethyl-propionamide

Dimethylamine (2 M in MeOH) (3 mL, 6.0 mmol) was dissolved in DCM (4 mL) and cooled on ice/water. Pentafluoropropionic anhydride (0.4 mL, 2.0 mmol) was added over 10 min and the reaction stirred at 0 °C for 30 min and at rt for 1 h. The volatiles were evaporated and the residue re-dissolved in DCM (2 mL), washed with water (3 × 2 mL), dried ($MgSO_4$), filtered and evaporated to leave the desired compound (187 mg, 50%). ^{1}H NMR ($CDCl_3$), δ: 3.06 (t, J = 1.0, 3H, CH_3), 3.19 (t, J = 2.2, 3H, CH_3). ^{19}F NMR ($CDCl_3$), δ: −115.3 (s, 2F, CF_2), −82.2 (s, 3F, CF_3).

4.14. 1-(6-Bromo-benzo[*b*]thiophen-3-yl)-2,2,3,3,3-pentafluoro-propan-1-one (29)

Compound **25** (146 mg, 0.5 mmol) was dissolved in diethyl ether (4 mL) and cooled to −70 °C. 1.6 M *n*-BuLi in hexanes (0.34 mL, 0.55 mmol) was added over 15 min and the reaction stirred at −70 °C for a further 30 min before adding 2,2,3,3,3-pentafluoro-*N*,*N*-dimethylpropionamide (84 μl, 0.55 mmol). After stirring



Scheme 11. Synthesis of inhibitors **1x–z**.

at −70 °C for 4 h, the reaction was quenched with 2 N HCl (2 × 1 mL), warmed to rt and the layers separated. The organic phase was washed with water (2 mL) and brine (2 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The desired compound was isolated by chromatography on silica gel with 0–10% EtOAc in heptane (97 mg, 54%). ^{1}H NMR ($CDCl_3$), δ: 7.65 (dd, J = 8.7, 1.8, 1H, ArH), 8.04 (d, J = 1.7, 1H, ArH), 8.57 (d, J = 8.7, 1H, ArH), 8.67 (s, 1H, ArH). ^{19}F NMR ($CDCl_3$), δ: −115.6 (s, 2F, CF_2), −81.4 (s, 3F, CF_3).

4.15. ±1-(6-Bromo-benzo[*b*]thiophen-3-yl)-2,2,3,3,3-pentafluoro-propan-1-ol (±-30)

Sodium borohydride (44 mg, 1.2 mmol) was dissolved in 1 N NaOH (94 μl) and methanol (2 mL) and a solution of compound **29** (97 mg, 0.3 mmol) in methanol (1.5 mL) was added. After stirring at rt for 1.5 h, water (2 mL) was added and the methanol evaporated. The residue was extracted with diethyl ether (2 × 2 mL) and the combined organic phases washed with water (2 mL) and brine (2 mL). This was loaded directly onto a silica gel column and run using 0–20% EtOAc in heptane to give the desired compound (79 mg, 81%). ^{1}H NMR ($CDCl_3$), δ: 2.88 (d, J = 5.3, 1H, OH), 5.53 (dt, J = 17.1, 5.9, 1H, CH), 7.52 (dd, J = 8.7, 1.8, 1H, ArH), 7.65 (s, 1H, ArH), 7.76 (d, J = 8.7, 1H, ArH), 8.02 (d, J = 1.8, 1H, ArH). ^{19}F NMR ($CDCl_3$), δ: k −128.4 (d, J = 275, 1F, CF_2), −120.8 (d, J = 275, 1F, CF_2), −81.4 (s, 3F, CF_3).

4.16. 1-(6-Bromo-benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-ethanone (32)

Compound **25** (175 mg, 0.6 mmol) was dissolved in dry Et_2O (2 mL) and placed under a nitrogen flow. The reaction mixture was cooled to −100 °C and *n*BuLi in hexanes (0.47 mL, 0.7 mmol) was added dropwise, and the mixture was stirred at −70 °C for 30 min. The reaction was cooled to −100 °C, and *N*,*N*-dimethyl-trifluoroacetamide was added dropwise in dry Et_2O (1 mL). The mixture was stirred at −60 °C for 1 h, then allowed to warm up to rt, acidified with 1 M HCl (3 mL), extracted with methyl *tert*-butyl ether (MTBE, 3 × 1 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by chromatography using heptane to afford the desired material as white crystals. Yield: 80 mg (38%). ^{1}H NMR ($CDCl_3$), δ: 7.68 (dd, J = 9.1, 1.8, 1H, ArH), 8.08 (d, J = 1.4, 1H, ArH), 8.61 (m, J = 5.0, 3.6, 2H, ArH). LC–MS: R_f = 2.49 min; m/z not observed. HRMS (EI): m/z calcd for $C_{10}H_4BrF_3OS$ ([M+H]$^+$): 352.9095; found: 352.9078.

4.17. ±1-(6-Bromo-benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-ethanol (±33)

Compound **32** (40 mg, 0.1 mmol) was suspended in MeOH (0.4 mL) and added to $NaBH_4$ in a 4:5 MeOH/1 M NaOH (1.8 mL) solution. THF (0.5 mL) was added and the reaction stirred for 1 h at rt. Water (2 mL) was added and the aqueous layer was extracted with Et_2O (3 × 1 mL), washed with brine (1 × 1 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by chromatography using a stepped gradient of 0–5% EtOAc in heptane to afford the desired material as a colourless glue. Yield: 43 mg (100%). ^{1}H NMR ($CDCl_3$), δ: 2.79 (br, 1H, OH), 5.42 (m, 1H, CH), 7.54 (dd, J = 8.8, 1.6, 1H, ArH), 7.66 (s, 1H, ArH), 7.80 (d, J = 8.8, 1H, ArH), 8.04 (d, J = 1.7, 1H, ArH). LC–MS: R_f = 2.50 min; m/z not observed.

4.18. (*R*)-1-(6-Bromo-benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-ethanol (*R*-33)

Compound **32** (31 mg, 0.1 mmol) was dissolved in DCM (3 mL) and added to a solution of *S*-oxoazaborolidine (30 mg, 0.1 mmol) in DCM (1 mL) under a nitrogen flow. The solution was cooled to −90 °C. Cathecholborane (0.2 mL, 2 M in THF, 0.2 mmol) was diluted with dry toluene (4 mL), and added dropwise over 30 min, after which the mixture was allowed to warm up to room temperature. Water (2 mL) and $NaHCO_3$ (2 mL) were added and the aqueous layer was extracted with EtOAc (3 × 1 mL), washed with brine

(1 × 1 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by chromatography using a stepped gradient of 0–2% EtOAc in heptane to afford the desired material as white solid. Yield: 30 mg, quantitative. Chiral HPLC (method 2): 81% R-isomer, t_r 10.80, (10% S-isomer). ^{1}H NMR ($CDCl_3$), δ: 2.79 (br, 1H, OH), 5.42 (m, 1H, CH), 7.54 (dd, J = 8.8, 1.6, 1H, ArH), 7.66 (s, 1H, ArH), 7.80 (d, J = 8.8, 1H, ArH), 8.04 (d, J = 1.7, 1H, ArH). LC–MS: R_f = 2.16 min; m/z not observed.

4.19. 6-Bromo-3-propylsulfanyl-benzo[*b*]thiophene (35)

3,6-Dibromobenzo[*b*]thiophene **25** (292 mg, 1.0 mmol) was dissolved in diethyl ether (12 mL) and cooled to −70 °C. 1.6 M *n*-BuLi in hexanes (0.69 mL, 1.1 mmol) was added over 35 min and the reaction stirred at −70 °C for a further 40 min before adding *n*-propyl disulfide (0.17 mL, 1.1 mmol). After stirring at −70 °C for 5.5 h, the reaction was warmed to rt, diluted with EtOAc and water, the layers separated and the organic washed with dilute potassium carbonate (5 mL). After drying (Na_2SO_4), filtering and evaporating in vacuo, the desired compound was isolated by chromatography on silica gel with pentane (119 mg, 41%). ^{1}H NMR ($CDCl_3$), δ: 1.05 (t, J = 7.5, 3H, CH_3), 1.61–1.73 (m, 2H, CH_2), 2.88 (t, J = 7.5, 2H, CH_2), 7.37 (s, 1H, ArH), 7.56 (dd, J = 8.6, 1.8, 1H, ArH), 7.81 (d, J = 8.2, 1H, ArH), 8.02 (d, J = 1.8, 1H, ArH).

4.20. 6-Bromo-3-methylsulfanyl-benzo[*b*]thiophene (37)

Compound **25** (292 mg, 1.0 mmol) was dissolved in diethyl ether (12 mL) and cooled to −70 °C. 1.6 M *n*-BuLi in hexanes (0.69 mL, 1.1 mmol) was added over 45 min and the reaction stirred at −70 °C for a further 30 min before adding methyl disulfide (97 μl, 1.1 mmol). After stirring at −70 °C for 4 h, the reaction was warmed to rt, diluted with MTBE and washed with saturated potassium carbonate (2 × 5 mL). After drying (Na_2SO_4), filtering and evaporating in vacuo, the desired compound was isolated by chromatography on silica gel with pentane (111 mg, 43%). ^{1}H NMR ($CDCl_3$), δ: 2.53 (s, 3H, CH_3), 7.15 (s, 1H, ArH), 7.53 (dd, 1H, ArH), 7.72 (d, J = 8.6, 1H, ArH), 8.00 (d, J = 1.4, 1H, ArH).

4.21. 1-(5-Bromo-benzo[*b*]thiophen-2-yl)-2,2,2-trifluoro-ethanone (39)

5-Bromobenzo[*b*]thiophene (700 mg; 3.3 mmol) was dissolved in dry Et_2O (14 mL) and placed under nitrogen flow. 1.6 M nBuLi in hexanes (2.25 mL, 3.6 mmol) was added dropwise, and the mixture was stirred at rt for 5 min. The reaction was cooled to −70 °C and *N*,*N*-dimethyl-trifluoroacetamide (0.42 mL; 3.6 mmol) was added dropwise. The mixture was stirred at −70 °C for 2 h, then allowed to warm up to rt, acidified with 1 M HCl to pH = 1, extracted with MTBE (3 × 50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by chromatography using 5% EtOAc in heptane to afford the desired material as a yellow solid. Yield: 717 mg (73%). ^{1}H NMR ($CDCl_3$), δ: 7.68 (d, J = 1.83 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 8.15 (d, J = 1.83 Hz, 2H, ArH).

4.22. ±1-(5-Bromo-benzo[*b*]thiophen-2-yl)-2,2,2-trifluoro-ethanol (±40)

Compound **39** (717 mg, 2.3 mmol) was suspended in MeOH (10 mL) and added to a solution of $NaBH_4$ (380 mg; 10.0 mmol) in 9:1 MeOH/1 M NaOH (13.4 mL). The reaction was stirred for 2 h at rt then water (20 mL) was added and the aqueous layer was extracted with tert-butyl methyl ether (3 × 50 mL), washed with brine (1 × 30 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by chromatography using a stepped gradient of 5–10% EtOAc in heptane to afford the desired material as a colourless oil. Yield: 447 mg (62%). ^{1}H NMR ($CDCl_3$), δ: 2.94 (d, J = 0.9 Hz, 1H, OH), 5.38 (q, J = 6.1 Hz, 1H, CH), 7.38 (s, 1H, ArH), 7.48 (dd, J = 8.7, 1.83 Hz, 1H, ArH), 7.72 (d, J = 8.5 Hz, 1H. ArH), 7.94 (d, J = 1.7 Hz, 1H, ArH), LC–MS: R_f = 2.50 min; m/z not observed.

4.23. ±1-(4-Bromo-phenyl)-2,2,2-trifluoro-ethanol (±42)

Sodium borohydride (327 mg, 8.7 mmol) was dissolved in a mixture of 1 N NaOH (0.7 mL) and MeOH (6.7 mL). A solution of bromotrifluoroacetophenone, **41** (0.34 mL, 2.0 mmol) in MeOH (3.3 mL) was added and the reaction stirred at rt for 1.5 h before adding water (8 mL). The mixture was extracted with MTBE (2 × 10 mL) and the combined organic phases washed with water (10 mL) and brine (10 mL) before drying ($MgSO_4$), filtering and evaporating in vacuo to leave the product as a clear oil (817 mg, quantitative). ^{1}H NMR ($CDCl_3$), δ: 3.45 (br, 1H, OH), 4.98 (q, J = 6.8, 1H, CH), 7.35 (d, J = 8.6, 2H, ArH), 7.55 (d, J = 8.6, 2H, ArH).

4.24. 7-Bromo-naphthalen-2-ol (45)

Triphenylphosphine (500 mg, 2.9 mmol) was dissolved in MeCN (5 mL), and bromine (0.15 mL, 2.9 mmol) was added at 0 °C whilst stirring. The solution was allowed to warm up to rt, and 7-methoxy-naphthalen-2-ol, **44** (490 mg, 2.8 mmol) was added portionwise. The solution was refluxed for 2 h, and the solvent removed in vacuo. The residue was heated to 250 °C in a sealed tube overnight. After cooling to rt, the residue was purified by chromatography using a stepped gradient of 10–20% EtOAc in heptane to yield **45** as a beige solid. Yield: 120 mg (19%). ^{1}H NMR ($CDCl_3$), δ: 5.17 (br, 1H, OH), 7.06 (d, J = 2.5, 1H, ArH), 7.11 (dd, J = 8.7, 2.4, 1H, ArH), 7.40 (dd, J = 8.7, 2.0, 1H, ArH), 7.63 (d, J = 8.9, 1H, ArH), 7.72 (d, J = 8.9, 1H, ArH), 7.84 (s, 1H, ArH). LC–MS: R_f = 2.01 min; m/z 221/223 ($[M+H]^+$, 100).

4.25. 6-Bromo-3,4-dihydro-2*H*-naphthalen-1-one (48)

6-Aminotetralone (**47**, 500 mg, 3.1 mmol) was dissolved in 25% HBr (1 mL). The mixture was cooled to 0 °C and a solution of $NaNO_2$ (263 mg, 3.8 mmol) in water (1 mL) was slowly added. The reaction mixture was further added to a solution of CuBr (458 mg, 3.2 mmol) in 48% HBr (1 mL) and the reaction was stirred for 1.5 h while warming to rt. The solution was extracted with EtOAc (3 × 5 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. The crude material was purified by column chromatography (0–20% DCM in heptane) to afford the desired product (435 mg, 74%). ^{1}H NMR ($CDCl_3$), δ: 2.08–2.19 (m, 2H, CH_2), 2.65 (dd, J = 7.2, 5.9, 2H, CH_2), 2.96 (t, J = 5.9, 2H, CH_2), 7.42–7.47 (m, 2H, ArH), 7.89 (d, J = 8.8, 1H, ArH). LC–MS: R_f = 2.04 min; m/z 225/227 ($[M+H]^+$, 100).

4.26. (6-Bromo-3,4-dihydro-naphthalen-1-yloxy)-triisopropyl-silane (49)

Under N_2 atmosphere, **48** (418 mg, 1.9 mmol) was dissolved in dry DCM (4.2 mL). NEt_3 (0.47 mL, 3.3 mmol) was added, followed by triisopropylsilyl triflate (0.6 mL, 2.2 mmol). The reaction was stirred at rt for 2 h, washed with cold $NaHCO_3$ (3 × 2 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue (845 mg, 119%) was sufficiently pure to be used directly for the next step. ^{1}H NMR ($CDCl_3$), δ: 1.10–1.15 (m, 18H, $CH(CH_3)_2$), 1.16–1.33 (m, 3H, CH), 2.24–2.34 (m, 2H, CH_2), 2.73 (t, J = 7.9, 2H, CH_2), 5.19 (t, J = 4.6, 1H, CH), 7.25–7.27 (m, 1H, ArH), 7.29–7.36 (m, 1H, ArH), 7.37–7.42 (m, 1H, ArH).

4.27. (6-Bromo-naphthalen-1-yloxy)-triisopropyl-silane (50)

Crude **49** (800 mg, 2.1 mmol) was dissolved in dioxane (8 mL) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (968 mg, 4.2 mmol) was added. The mixture was heated at 80 °C for 30 min, cooled to rt and diluted with heptane (16 mL). The solid was filtered off and washed with more heptane. The solution was loaded onto a silica column and run with heptane to give the desired compound (754 mg, 95%). ^{1}H NMR ($CDCl_3$), δ: 1.16 (d, J = 7.3, 18H, $CH(CH_3)_2$), 1.32–1.48 (m, 3H, CH), 6.88 (dd, J = 4.9, 3.8, 1H, ArH), 7.32 (d, J = 1.2, 1H, ArH), 7.34 (s, 1H, ArH), 7.53 (dd, J = 8.9, 1.9, 1H, ArH), 7.96 (d, J = 1.8, 1H, ArH), 8.13 (d, J = 9.0, 1H, ArH). LC–MS: R_f = 5.21 min; m/z 378/380 ([M+H]$^+$, 100).

4.28. 6-Bromonaphthalen-1-ol (51)

Compound **50** (786 mg, 2.07 mmol) was dissolved in NMP (0.8 mL). To this solution was added a solution of NaOH (530 mg, 13.25 mmol) in water (0.53 mL) and MeOH (1.4 mL) and the reaction mixture heated at 60 °C for 1.5 h. The methanol was evaporated, the residue diluted with water (10 mL) and washed with heptane (10 mL). The aqueous layer was acidified with 6 N HCl (3 mL) and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with water (3 × 10 mL) and evaporated to dryness. The desired product was isolated by chromatography on silica gel using 0–20% EtOAc in heptane (342 mg, 74%). ^{1}H NMR ($CDCl_3$), δ: 5.31 (br, 1H, OH), 6.81 (dd, J = 5.7, 2.7, 1H, ArH), 7.33 (d, J = 3.0, 1H, ArH), 7.34 (s, 1H, ArH), 7.55 (dd, J = 9.0, 2.0, 1H, ArH), 7.97 (d, J = 2.0, 1H, ArH), 8.07 (d, J = 9.0, 1H, ArH).

4.29. 6-Bromo-2-chloro-naphthalen-1-ol (56)

Compound **55** (90 mg, 0.4 mmol) was dissolved in DCM (0.9 mL). To this solution, a mixture of bleach (0.25 mL, 0.4 mmol), *t*-BuOH (57 μl, 0.6 mmol) and DCM (0.9 mL), which had previously been stirred for 10 min, was added. After 30 min, the residual oxidant was destroyed with saturated sodium thiosulfate solution (0.5 mL) and the reaction acidified with 2 N HCl (0.5 mL). The layers were separated and the aqueous extracted with DCM (2 mL). The combined organic phases were washed with water and purified by chromatography on silica gel using heptane as solvent. Yield: 58 mg (56%). ^{1}H NMR ($CDCl_3$), δ: 6.03 (br, 1H, OH), 7.29 (d, J = 3.0, 1H, ArH), 7.40 (s, 1H, ArH), 7.59 (dd, J = 9.0, 2.0, 1H, ArH), 7.95 (d, J = 2.0, 1H, ArH), 8.10 (d, J = 9.0, 1H, ArH).

4.30. 6-Bromo-1-difluoromethoxy-2-fluoro-naphthalene (59)

NaF (30 mg, 0.72 mmol) was dissolved in *o*-xylene (18 mL) and 5-bromo-indan-1-one, **58** (2.53 g, 12.0 mmol) was added. The mixture was refluxed for 1 h under nitrogen. Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA, 6 g, 24.0 mmol) was cautiously added over 20 min and reflux continued for 2 h. Two further batches of TFDA (2 × 6 g, 2 × 24 mmol) were added and reflux continued for 3 h, upon which the reaction was allowed to cool to rt. The solvents were removed under vacuum and the residue purified by chromatography using heptane to yield **59** as a brown solid. Yield: 1.3 g, 37%. ^{1}H NMR ($CDCl_3$), δ: 6.40–7.08 (m, 1H, CH), 7.32–7.44 (m, 1H, ArH), 7.59–7.72 (m, 2H, ArH), 8.00–8.10 (m, 2H, ArH). LC–MS: R_f = 2.37 min; m/z not observed.

4.31. 7-Bromo-quinolin-2-ol (63)

7-Bromo-2-chloro-quinoline **62** (300 mg; 1.3 mmol) was suspended in 2 M NaOH (2 mL) and heated at 190 °C in the microwave reactor (150 Watt, 250 psi) for 30 min. The resulting precipitate was diluted with water (5 mL), filtered and washed with water (10 mL) to yield **63** as a pale yellow solid. Yield: 282 mg, 94%. ^{1}H NMR ($CDCl_3$), δ: 6.71 (d, J = 9.5, 1H, ArH), 7.33–7.37 (s, 1H, ArH), 7.41–7.46 (m, 1H, ArH), 7.52 (d, J = 1.8, 1H, ArH), 7.77 (d, J = 9.5, 1H, ArH), 11.15 (br, 1H, OH). LC–MS: R_f = 1.48 min; m/z 224/226 ([M+H]$^+$, 100).

4.32. (6-Bromo-isoquinolin-1-yl)-bis-(4-methoxy-benzyl)-amine (72)

Compound **71** (320 mg, 1.4 mmol) was dissolved in DMF (5 mL) and NaH (60% in mineral oil, 126 mg, 3.2 mmol) was added portionwise. The suspension was stirred for 10 min and *para*-methoxybenzyl chloride (PMBCl, 493 mg, 3.2 mmol) was added dropwise. The reaction was stirred at rt for 90 min. Water (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layer was washed with water (2 × 20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The residue was purified by chromatography using a stepped gradient of 0–5% EtOAc in heptane to yield **72** as a yellow glue. Yield: 295 mg, 44%.

^{1}H NMR ($CDCl_3$), δ: 3.80 (s, 6H, CH_3), 4.51 (s, 4H, CH_2), 6.84 (d, J = 8.6, 4H, ArH), 7.11–7.19 (m, 5H, ArH), 7.56 (dd, J = 8.9, 2.0, 1H, ArH), 7.93 (d, J = 1.8, 1H, ArH), 8.11–8.18 (m, 2H, ArH). LC–MS: R_f = 2.58 min; m/z 463, 465 ([M+H]$^+$, 100).

4.33. General procedures: Synthesis of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane esters from aryl halides

Aryl halide (1 equiv), bis-pinacolato-diboron (1.5–3 equiv), $Pd(dppf)Cl_2$ (0.05–0.1 equiv), and KOAc (3–6 eq.) were suspended in DMF (2–6 mL). The mixture was then heated at 90 °C for 2–6 h, cooled to rt, diluted with H_2O (10 mL) and extracted with EtOAc (3 × 5 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by chromatography using a stepped gradient of 0–10% EtOAc in heptane to yield the desired boronic ester.

4.33.1. [6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzofuran-3-yl]-methanol (17)

Compound **16** (84 mg, 0.37 mmol) was boronylated according to the general procedure to give the desired compound (93 mg, 92%). ^{1}H NMR ($CDCl_3$), δ: 1.37 (s, 12H, CH_3), 2.06 (s, 1H, OH), 4.82 (s, 2H, CH_2), 7.63 (dd, 1H, ArH), 7.65 (d, J = 8.6, 1H, ArH), 7.70 (s, 1H, ArH), 7.94 (s, 1H, ArH). HRMS (EI): m/z calcd for $C_{15}H_{17}BO_3$ ([M-H_2O+H]$^+$): 256.1385; found: 256.1377.

4.33.2. 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzofuran-3-carboxylic acid amide (20)

Compound **19** (32 mg, 0.13 mmol) was boronylated according to the general procedure to give the desired compound (32 mg, 83%). ^{1}H NMR (CD_3OD), δ: 1.37 (s, 12H, CH_3), 7.71 (d, J = 7.7, 1H, ArH), 7.89 (s, 1H, ArH), 8.07 (d, J = 7.7, 1H, ArH), 8.41 (s, 1H, ArH). LC–MS: R_f = 1.87 min; m/z 288 ([M+H]$^+$, 100).

4.33.3. 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzo[*b*]thiophene-3-carbaldehyde (27)

Compound **26** (107 mg, 0.44 mmol) was boronylated according to the general procedure to give the desired compound (103 mg, 81%). ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 12H, CH_3), 7.84 (dd, J = 8.2, 0.9, 1H, ArH), 8.28–8.31 (m, 2H, ArH), 8.58 (dd, J = 8.2, 0.9, 1H, ArH), 10.07 (s, 1H, CHO). LC–MS: R_f = 2.36 min; m/z 289 ([M+H]$^+$, 100).

4.33.4. ±2,2,3,3,3-Pentafluoro-1-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzo[*b*]thiophen-3-yl]-propan-1-ol (±31)

Compound **±-30** (71 mg, 0.2 mmol) was boronylated according to the general procedure to give the desired compound (51 mg,

62%). ^{1}H NMR ($CDCl_3$), δ: 1.38 (s, 12H, CH_3), 3.21 (d, J = 5.3, 1H, OH), 5.53 (dt, J = 17.1, 5.8, 1H, CH), 7.70–7.77 (m, 3H, ArH), 8.83 (s, 1H, ArH). ^{19}F NMR ($CDCl_3$), δ: −128.7 (d, J = 275, 1F, CF_2), −120.8 (d, J = 275, 1F, CF_2), −81.4 (s, 3F, CF_3).

4.33.5. ±2,2,2-Trifluoro-1-[6-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-benzo[*b*]thiophen-3-yl]-ethanol (±34)

Compound **±-33** (40 mg, 0.13 mmol) was boronylated according to the general procedure to give the desired compound (39 mg, 84%) as a white solid. ^{1}H NMR ($CDCl_3$), δ: 1.38 (s, 12H, CH_3), 2.90 (br, 1H, OH), 5.49 (m, 1H, CH), 7.77 (s, 1H, ArH), 7.80–7.91 (m, 2H, ArH), 8.37 (s, 1H, ArH). LC–MS: R_f = 2.36 min; m/z 359 ([M+H]$^+$, 100).

4.33.6. (*R*)-2,2,2-Trifluoro-1-[6-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-benzo[*b*] thiophen-3-yl]-ethanol (*R*-34)

Compound ***R*-33** was boronylated according to the general procedure to give a white solid that was used immediately in the next step. ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 12H, CH_3), 2.94 (d, J = 5.0, 1H, OH), 5.37–5.46 (m, 1H, CH), 7.70 (s, 1H, ArH), 7.71–7.76 (m, 1H, ArH), 7.78–7.84 (m, 1H, ArH), 8.29 (s, 1H, ArH). LC–MS: R_f = 2.33 min; m/z not observed.

4.33.7. 4,4,5,5-Tetramethyl-2-(3-propylsulfanyl-benzo[*b*]thiophen-6-yl)-[1,3,2]-dioxa borolane (36)

Compound **35** (68 mg, 0.24 mmol) was boronylated according to the general procedure to give the title compound (45 mg, 56%) as a white solid. ^{1}H NMR ($CDCl_3$), δ: 1.00 (t, J = 7.3, 3H, CH_3), 1.38 (s, 12H, CH_3), 1.54–1.71 (m, 2H, CH_2), 2.85 (t, J = 7.3, 2H, CH_2), 7.46 (s, 1H, ArH), 7.84 (dd, J = 8.6, 1.8, 1H, ArH), 7.94 (d, J = 8.2, 1H, ArH), 8.35 (d, J = 1.8, 1H, ArH).

4.33.8. 4,4,5,5-Tetramethyl-2-(3-methylsulfanyl-benzo[*b*]thiophen-6-yl)-[1,3,2]-dioxaborolane (38)

Compound **37** (111 mg, 0.43 mmol) was boronylated according to the general procedure to give the title compound (105 mg, 80%) as a white solid. ^{1}H NMR ($CDCl_3$), δ: 1.38 (s, 12H, CH_3), 2.53 (s, 3H, CH_3), 7.27 (s, 1H, ArH), 7.84–7.87 (m, 2H, ArH), 8.35 (s, 1H, ArH).

4.33.9. ±2,2,2-Trifluoro-1-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzo[b]thiophen-2-yl]-ethanol (±40a)

Compound ±**40** (384 mg, 1.2 mmol) was boronylated according to the general procedure to give the desired compound (320 mg, 72%) as a white solid. ^{1}H NMR ($CDCl_3$), δ: 1.38 (s, 12H, CH_3), 2.90–3.16 (m, 1H, OH), 5.20–5.56 (m, 1H, CH), 7.40 (s, 1H, ArH), 7.67–7.98 (m, 2H, ArH), 8.26 (s, 1H, ArH); LC–MS: R_f = 2.36 min; m/z 359 ([M+H]$^+$, 100).

4.33.10. ±2,2,2-Trifluoro-1-[4-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-phenyl]-ethanol (±43)

Compound ±**42** (255 mg, 1.0 mmol) was boronylated according to the general procedure to give the title compound (199 mg, 66%) as a white solid. ^{1}H NMR ($CDCl_3$), δ: 1.36 (s, 12H, CH_3), 2.96 (br, 1H, OH), 5.02 (q, J = 6.8, 1H, CH), 7.47 (d, J = 8.2, 2H, ArH), 7.85 (d, J = 8.2, 2H, ArH). LC–MS: R_f = 2.16 min; m/z not observed.

4.33.11. 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-ol (46)

Compound **45** (120 mg; 0.55 mmol) was boronylated according to the general procedure to give the title compound (35 mg, 24%). ^{1}H NMR ($CDCl_3$), δ: 1.35 (s, 12H, CH_3), 5.52 (br, 1H, OH), 7.14 (d, J = 2.5, 1H, ArH), 7.19 (dd, J = 8.7, 2.4, 1H, ArH), 7.70 (dd, J = 8.7, 2.0, 1H, ArH), 7.75 (m, 2H, ArH), 8.21 (s, 1H, ArH). LC–MS: R_f = 2.17 min; m/z not observed.

4.33.12. 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-1-ol (52)

Compound **51** (40 mg, 0.2 mmol) was boronylated according to the general procedure to give the title compound (37 mg, 68%). ^{1}H NMR ($CDCl_3$), δ: 1.33 (s, 12H, CH_3), 5.36 (br, 1H, OH), 6.79 (dd, J = 7.5, 0.9, 1H, ArH), 7.22 (t, J = 3.0, 1H, ArH), 7.40 (t, J = 8.4, 1H, ArH), 7.78 (dd, J = 8.5, 1.1, 1H, ArH), 8.07 (d, J = 8.5, 1H, ArH), 8.27 (s, 1H, ArH).

4.33.13. 2-Chloro-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-1-ol (57)

Compound **56** (34 mg, 0.13 mmol) was boronylated according to the general procedure to give the title compound (29 mg, 72%). ^{1}H NMR ($CDCl_3$), δ: 1.41 (s, 12H, CH_3), 6.02 (br, 1H, OH), 7.36 (d, J = 3.0, 1H, ArH), 7.43 (d, J = 9.0, 1H, ArH), 7.89 (d, J = 8.4, 1H, ArH), 8.20 (d, J = 8.4, 1H, ArH), 8.31 (s, 1H, ArH).

4.33.14. 2-(5-Difluoromethoxy-6-fluoro-naphthalen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]-dioxa borolane (60)

Compound **59** (240 mg, 0.8 mmol) was boronylated according to the general procedure to give the title compound (111 mg, 39%). ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 12H, CH_3), 6.39–7.04 (m, 1H, CH), 7.29–7.40 (m, 1H, ArH), 7.79 (dd, J = 9.0, 5.0, 1H, ArH), 7.96 (d, J = 8.4, 1H, ArH), 8.14 (d, J = 8.5, 1H, ArH), 8.36 (s, 1H, ArH). LC–MS: R_f = 1.69 min; m/z not observed.

4.33.15. 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-ol (64)

Compound **63** (282 mg; 1.3 mmol) was boronylated according to the general procedure to give the title compound. ^{1}H NMR ($CDCl_3$), δ: 1.38 (s, 12H, CH_3), 6.72 (d, J = 9.6, 1H, ArH), 7.50–7.66 (m, 3H, ArH), 7.78 (d, J = 9.6, 1H, ArH), 9.44 (br, 1H, OH). LC–MS: R_f = 1.79 min; m/z 272 ([M+H]$^+$, 100).

4.33.16. 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-ol (67)

6-Bromoquinolin-2-ol (244 mg; 1.1 mmol) was boronylated according to the general procedure to give the title compound (184 mg; 62%). ^{1}H NMR ($CDCl_3$), δ: 1.38 (s, 12H, CH_3), 6.71 (d, J = 9.59 Hz, 1H, ArH), 7.35 (d, J = 8.22 Hz, 1H, ArH), 7.83 (d, J = 9.59 Hz, 1H, ArH), 7.92 (dd, J = 8.22, 1.22 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 11.50–11.72 (m, 1H, NH). LC–MS: R_f = 1.77 min; m/z 272 ([M+H]$^+$, 100).

4.33.17. 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2*H*-isoquinolin-1-one (70)

Compound **69** (100 mg; 0.45 mmol) was boronylated according to the general procedure to give the title compound (56 mg; 46%). ^{1}H NMR (CD_3OD), δ: 1.38 (s, 12H, CH_3), 6.70 (d, J = 7.0, 1H, ArH), 7.18 (d, J = 7.2, 1H, ArH), 7.82 (d, J = 8.1, 1H, ArH), 8.04 (s, 1H, ArH), 8.27 (d, J = 8.1, 1H, ArH). LC–MS: R_f = 0.91 min; m/z 190 ([M+H]$^+$, 100).

4.33.18. Bis-(4-methoxy-benzyl)-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoquinolin-1-yl]-amine (73)

Compound **72** (295 mg; 0.64 mmol) was boronylated according to the general procedure to give the title compound (101 mg, 31%). ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 12H, CH_3), 3.79 (s, 6H, CH_3), 4.52 (s, 4H, CH_2), 6.82 (d, J = 8.6, 4H, ArH), 7.14 (d, J = 9.1, 4H, ArH), 7.28 (s, 1H, ArH), 7.87 (d, J = 9.1, 1H, ArH), 8.14 (d, J = 5.4, 1H, ArH), 8.23–8.30 (m, 2H, ArH). LC–MS: R_f = 1.62 min; m/z 511 ([M+H]$^+$, 100). HRMS (EI): m/z calcd for $C_{31}H_{35}BN_2O_4$ ([M+H]$^+$): 510.2804; found: 510.2807.

4.33.19. 2-(6-Fluoro-naphthalen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (76)

Compound **75** (300 mg; 1.3 mmol) was boronylated according to the general procedure to give the title compound (191 mg,

54%). ^{1}H NMR ($CDCl_3$), δ: 1.28 (s, 12H, CH_3), 7.14 (td, J = 8.9, 2.7, 1H, ArH), 7.32 (dd, J = 9.8, 2.5, 1H, ArH), 7.65 (d, J = 8.2, 1H, ArH), 7.72–7.79 (m, 2H, ArH), 8.26 (s, 1H, ArH). LC–MS: R_f = 2.67 min; m/z not observed.

4.33.20. 6-(4,4,5,5-Tetramethyl-[1,3,2]-dioxaborolan-2-yl)-naphthalen-2-carboxylic acid (79)

6-Bromonaphthalene-2-carboxylic acid (500 mg; 2.0 mmol) was boronylated using the general procedure to give the desired compound (478 mg; 80%). ^{1}H NMR (CD_3OD), δ: 1.40 (s, 12H, CH_3), 7.79–7.90 (m, 1H, ArH), 7.93–8.11 (m, 3H, ArH), 8.37 (s, 1H, ArH), 8.61 (s, 1H, ArH). LC–MS: R_f = 2.17 min; m/z 299 ([M+H]$^+$, 5), 340 (100). HRMS (EI): m/z calcd for $C_{17}H_{19}BO_4$ ([M+H]$^+$): 298.1491; found: 298.1483.

4.34. Suzuki coupling of 4-bromoimidazole compounds

{2-[4-(4-Bromo-5-pyridin-4-yl-1H-imidazol-2-yl)-phenoxy]-ethyl}-dimethyl-amine (**9**)[18] (1 equiv), the appropriate boronic ester (1.2–2 equiv), PPh_3 (0.1 equiv), and K_2CO_3 (8–10 equiv) were suspended in a 2:1 mixture of DME:H_2O (3–9 mL). The suspension was stirred vigorously whilst de-gassing with N_2 for 20 min before adding $Pd(OAc)_2$ (0.01 equiv). The mixture was then refluxed for 2 h to overnight, cooled to rt, acidified to pH = 1 with 1 M HCl and washed with EtOAc (3 × 5 mL). The aqueous layer was basified with 2 M NaOH to pH = 14 and extracted with EtOAc (3 × 5 mL). This organic layer was dried ($MgSO_4$) and the solvent removed under vacuum. The residue was purified by preparative HPLC to yield the desired product.

4.34.1. (2-{4-[4-(3,4-Dichloro-phenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-dimethyl-amine (1a)

Compound **9** (50 mg; 0.13 mmol) and 3,4-dichlorophenyl boronic acid **11** (50 mg; 0.26 mmol) were coupled according to the general procedure to give the desired compound (7 mg, 12%). ^{1}H NMR (CD_3OD), δ: 3.01 (s, 6H, $N(CH_3)_2$), 3.65 (t, J = 4.8, 2H, CH_2), 4.45 (t, J = 4.8, 2H, CH_2), 7.20 (d, J = 9.1, 2H, ArH), 7.54 (dd, J = 8.2, 2.3, 1H, ArH), 7.72 (d, J = 8.2, 1H, ArH), 7.85 (s, 1H, ArH), 8.06 (d, J = 9.1, 2H, ArH), 8.12 (d, J = 6.8, 2H, ArH), 8.62 (d, J = 6.8, 2H, ArH). LC–MS: R_f = 2.51 min; m/z 453, 455, 457 ([M+H]$^+$, 100). HRMS (EI): m/z calcd for $C_{24}H_{23}Cl_2N_4O$ ([M+H]$^+$): 453.1249; found: 453.1244.

4.34.2. (2-{4-[5-(3-Chloro-4-fluoro-phenyl)-4-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-dimethyl-amine (1b)

Compound **9** (40 mg; 0.09 mmol) and 3-chloro-4-fluorophenyl boronic acid **12** (32 mg; 0.19 mmol) were coupled using the general procedure to give the desired product (3 mg; 7%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.65 (t, J = 4.8, 2H, CH_2), 4.45 (t, J = 4.8, 2H, CH_2), 7.20 (d, J = 8.6, 2H, ArH), 7.45 (t, J = 8.9, 2H, ArH), 7.57 (br, 1H, ArH), 7.81 (d, J = 8.2, 1H, ArH), 8.06 (t, J = 8.4, 4H, ArH), 8.61 (d, J = 6.4, 2H, ArH). LC–MS: R_f = 2.44 min; m/z 437 ([M+H]$^+$, 10), 219 (100).

4.34.3. (6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-benzofuran-3-yl)-methanol (1c)

Compound **17** (60 mg, 0.22 mmol) and **9** (50 mg, .0.13 mmol) were coupled according to the general procedure to give the desired compound (20 mg, 50%). ^{1}H NMR (CD_3OD), δ: 2.42 (s, 6H, $N(CH_3)_2$), 2.87 (t, J = 5.3, 2H, CH_2), 4.22 (t, J = 5.3, 2H, CH_2), 4.83 (s, 2H, CH_2), 7.12 (d, J = 8.9, 2H, ArH), 7.42 (d, J = 7.9, 1H, ArH), 7.58 (d, J = 3.6, 2H, ArH), 7.68 (s, 1H, ArH), 7.80 (d, J = 7.9, 1H, ArH), 7.84 (s, 1H, ArH), 7.99 (d, J = 8.9, 2H, ArH), 8.43 (d, J = 5.0, 2H, ArH). LC–MS: R_f = 2.23 min; m/z 455 ([M+H]$^+$, 100), 228. HRMS (EI): m/z calcd for $C_{27}H_{26}N_4O_3$ ([M+H]$^+$): 455.2083; found: 455.2087.

4.34.4. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-benzofuran-3-carboxylic acid amide (1d)

Compounds **20** (20 mg, 0.07 mmol) and **9** (12 mg, 0.03 mmol) were coupled according to the general procedure to give the desired compound (0.7 mg, 5%) as a yellow glassy solid. ^{1}H NMR (CD_3OD), δ: 2.37 (s, 6H, $N(CH_3)_2$), 2.81 (t, J = 5.40 Hz, 2H, CH_2), 4.19 (t, J = 5.44 Hz, 2H, CH_2), 7.10 (d, J = 9.0 Hz, 2H, ArH), 7.49 (dd, J = 8.2, 1.4 Hz, 1H, ArH), 7.53–7.63 (m, 2H, ArH), 7.73 (d, J = 0.8 Hz, 1H, ArH), 7.92–8.00 (m, 2H, ArH), 8.08–8.17 (m, 1H, ArH), 8.36–8.46 (m, 2H, ArH), 8.50–8.59 (m, 1H, ArH). LC–MS: R_f = 2.23 min; m/z 468 ([M+H]$^+$, 100), 234. HRMS (EI): m/z calcd for $C_{27}H_{26}N_5O_3$ ([M+H]$^+$): 468.2036; found: 468.2031.

4.34.5. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-benzo[*b*]thiophene-3-carbaldehyde (1e)

Compounds **27** (96 mg, 0.33 mmol) and **9** (100 mg, 0.26 mmol) were coupled according to the general procedure to give the desired compound (63 mg, 51%). ^{1}H NMR (acetone-d_6), δ: 2.15 (s, 6H, $N(CH_3)_2$), 2.57 (t, 2H, J = 5.9 Hz, CH_2), 4.03 (t, 2H, J = 5.9 Hz, CH_2), 6.94 (d, 2H, J = 9.1 Hz, ArH), 7.35–7.50 (m, 2H, ArH), 7.57–7.69 (m, 1H, ArH), 7.96 (d, 2H, J = 8.6 Hz, ArH), 8.13–8.23 (m, 1H, ArH), 8.33 (d, 2H, J = 4.1 Hz, ArH), 8.39–8.58 (m, 1H, ArH), 8.68–8.79 (m, 1H, ArH), 10.10 (s, 1H, CH), 11.80 (br s, 1H, NH), LC–MS: R_f = 2.39 min; m/z 469 ([M+H]$^+$, 10), 235 (100). HRMS (EI): m/z calcd for $C_{27}H_{24}N_4O_2S$ ([M+H]$^+$): 469.1698; found: 469.1682.

4.34.6. (6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-benzo[*b*]thiophen-3-yl)-methanol (1f)

Compound **1e** (13 mg, 28 μmol) was partly dissolved in ethanol (0.5 mL) before adding sodium borohydride (2 mg, 53 μmol). After stirring for 2 h at rt, water (1 mL) and 2 N HCl (1 drop) were added and the reaction extracted with EtOAc (1 mL). The aqueous was basified with 2 N NaOH and extracted with EtOAc/MeOH (2 × 1 mL). The combined organic phases were washed with water (1 mL) and evaporated to dryness to leave the desired compound (10 mg, 75%). ^{1}H NMR (CD_3OD), δ: 2.41 (s, 6H, $N(CH_3)_2$), 2.85 (t, 2H, J = 5.2 Hz, CH_2), 4.23 (t, 2H, J = 5.4 Hz, CH_2), 4.85 (s, 2H, CH_2), 7.13 (d, 2H, J = 8.6 Hz, ArH), 7.53 (d, 1H, J = 8.2 Hz, ArH), 7.57–7.63 (m, 3H, ArH), 7.97–8.03 (m, 3H, ArH), 8.10 (s, 1H, ArH), 8.44 (d, 2H, J = 5.9 Hz, ArH). LC–MS: R_f = 2.29 min; m/z 471 ([M+H]$^+$, 10), 236 (100). HRMS (EI): m/z calcd for $C_{27}H_{26}N_4O_2S$ ([M+H]$^+$): 471.1854; found: 471.1844.

4.34.7. ±1-(6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-benzo[*b*]thiophen-3-yl)-propan-1-ol (±1g)

Compounds **28** (24 mg, 75 μmol) and **9** (25 mg, 60 μmol) were coupled according to the general procedure to give the desired compound (17 mg, 54%). ^{1}H NMR (CD_3OD), δ: 1.06 (t, 3H, J = 7.0 Hz, CH_3), 1.92–2.13 (m, 2H, CH_2), 3.06 (s, 6H, $N(CH_3)_2$), 3.70 (br. s, 2H, CH_2), 4.51 (br. s, 2H, CH_2), 5.06 (t, 1H, J = 6.4 Hz, CH), 7.27 (d, 2H, J = 8.6 Hz, ArH), 7.63 (d, 1H, J = 8.2 Hz, ArH), 7.69 (s, 1H, ArH), 8.11–8.19 (m, 5H, ArH), 8.24 (s, 1H, ArH), 8.63 (d, 2H, J = 5.9 Hz, ArH). LC–MS: R_f = 2.44 min; m/z 499 ([M+H]$^+$, 10), 250 (100). HRMS (EI): m/z calcd for $C_{29}H_{30}N_4O_2S$ ([M+H]$^+$): 499.2167; found: 499.2181.

4.34.8. ±1-(6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-benzo[*b*]thiophen-3-yl)-2,2,3,3,3-pentafluoro-propan-1-ol (±1h)

Compounds **±31** (51 mg, 0.14 mmol) and **9** (41 mg, 0.11 mmol) were coupled according to the general procedure to give the desired compound (42 mg, 68%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 5.2, 2H, CH_2), 4.46 (t, J = 5.2, 2H, CH_2), 5.67 (dd, J = 19.3, 6.1, 1H, CH), 7.22 (d, J = 9.1, 2H, ArH), 7.63 (d, J = 8.6, 1H, ArH), 7.97 (s, 1H, ArH), 8.08 (d, J = 8.6, 2H, ArH), 8.13 (d, J = 6.8, 2H, ArH), 8.20–8.25 (m, 2H, ArH), 8.58 (d, J = 6.8, 2H, ArH). LC–MS: R_f = 2.64 min; m/z 589 ([M+H]$^+$, 10), 295 (100). HRMS

(EI): *m/z* calcd for $C_{29}H_{25}F_5N_4O_2S$ ([M+H]$^+$): 589.1696; found: 589.1691.

4.34.9. ±1-(6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-ethanol (±1i)

Compounds ±**34** (45 mg, 0.12 mmol) and **9** (24 mg, 60 μmol) were coupled according to the general procedure to give the desired compound as its TFA salt (6.7 mg, 17%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.65 (t, J = 5.2, 2H, CH_2), 4.47 (t, J = 5.2, 2H, CH_2), 5.55 (t, J = 6.4, 1H, CH), 7.22 (d, J = 9.1, 2H, ArH), 7.63 (d, J = 8.6, 1H, ArH), 7.96 (s, 1H, ArH), 8.09 (d, J = 9.1, 2H, ArH), 8.13 (d, J = 6.8, 2H, ArH), 8.18–8.27 (m, 2H, ArH), 8.57 (d, J = 6.4, 2H, ArH). LC–MS: R_f = 2.61 min; *m/z* 539 ([M+H]$^+$, 10), 270 (100).

4.34.10. (*R*)-1-(6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-ethanol (*R*-1i)

Compounds ***R*-34** (30 mg, 80 μmol) and **9** (24 mg, 60 μmol) were coupled according to the general procedure to give the desired compound as its TFA salt (25 mg, 64%). Chiral HPLC (method 1): free base: 91% R-isomer, t_r 34.51 (9% S-isomer). ^{1}H NMR (CD_3OD), δ ppm 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, 2H, CH_2), 4.46 (t, 2H, J = 4.8 Hz, CH_2), 5.49–5.62 (m, 1H, CH), 7.21 (d, 2H, J = 6.8 Hz, ArH), 7.63 (dd, 1H, J = 8.6, 1.4 Hz, ArH), 7.95 (s, 1H, ArH), 8.08 (d, 2H, J = 8.6 Hz, ArH), 8.12 (d, 2H, J = 6.8 Hz, ArH), 8.21–8.26 (m, 2H, ArH), 8.56 (d, 2H, J = 6.8 Hz, ArH); LC–MS: R_f = 2.47 min; *m/z* 539 ([M+H]$^+$, 10), 270 (100). HRMS (EI): *m/z* calcd for $C_{28}H_{25}F_3N_4O_2S$ ([M+H]$^+$): 539.1728; found: 539.1729.

4.34.11. Dimethyl-(2-{4-[5-(3-propylsulfanyl-benzo[*b*]thiophen-6-yl)-4-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-amine (1j)

Compounds **36** (45 mg, 0.13 mmol) and **9** (43 mg, 0.11 mmol) were coupled according to the general procedure to give the desired compound (42 mg, 74%). ^{1}H NMR (CD_3OD), δ: 1.06 (t, J = 7.3, 3H, CH_3), 1.60–1.77 (m, 2H, CH_2), 2.97 (t, J = 7.3, 2H, CH_2), 3.02 (s, 6H, $N(CH_3)_2$), 3.65 (t, J = 4.8, 2H, CH_2), 4.46 (t, J = 4.6, 2H, CH_2), 7.22 (d, J = 9.0, 2H, ArH), 7.65 (d, J = 8.4, 1H, ArH), 7.72 (s, 1H, ArH), 8.03–8.24 (m, 6H, ArH), 8.58 (d, J = 5.6, 2H, ArH). LC–MS: R_f = 2.98 min; *m/z* 515 ([M+H]$^+$, 10), 258 (100). HRMS (EI): *m/z* calcd for $C_{29}H_{30}N_4OS_2$ ([M+H]$^+$): 515.1939; found: 515.1940.

4.34.12. ±Dimethyl-[2-(4-{5-[3-(propane-1-sulfinyl)-benzo[*b*]thiophen-6-yl]-4-pyridin-4-yl-1*H*-imidazol-2-yl}-phenoxy)-ethyl]-amine (1k)

Compound **1j** (60 mg, 70 μmol) was dissolved in water (1.5 mL) and acetone (1.5 mL). Oxone® (43 mg, 0.1 mmol) was subsequently added and after 10 min, the reaction was basified with saturated K_2CO_3, brine added and the reaction mixture extracted with EtOAc/MeOH (2 × 1 mL). The desired product was isolated by chromatography on silica gel using 10:1:1 EtOAc/MeOH/TEA. Yield = 8 mg (21%). ^{1}H NMR (CD_3OD), δ: 1.12 (t, J = 7.4, 3H, CH_3), 1.71–1.88 (m, 2H, CH_2), 3.03 (s, 6H, $N(CH_3)_2$), 3.21–3.28 (m, 2H, CH_2), 3.66 (t, J = 4.8, 2H, CH_2), 4.47 (t, J = 4.6, 2H, CH_2), 7.23 (d, J = 9.0, 1H, ArH), 7.73 (d, J = 8.4, 1H, ArH), 8.06–8.16 (m, 4H, ArH), 8.28 (d, 1H, J = 8.4, ArH), 8.37 (s, 1H, ArH), 8.41 (s, 1H, ArH), 8.60 (br, 2H, ArH), 2H concealed by solvent peak. LC–MS: R_f = 2.51 min; *m/z* 531 ([M+H]$^+$, 10), 266 (100). HRMS (EI): *m/z* calcd for $C_{29}H_{31}N_4O_2S_2$ ([M+H]$^+$): 531.1889; found: 531.1882.

4.34.13. Dimethyl-(2-{4-[5-(3-methylsulfanyl-benzo[*b*]thiophen-6-yl)-4-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-amine (1l)

Compounds **38** (69 mg, 0.23 mmol) and **9** (73 mg, 0.19 mmol) were coupled according to the general procedure to give the desired compound (43 mg, 47%). ^{1}H NMR (CD_3OD), δ: 2.61 (s, 3H, CH_3), 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 5.2, 2H, CH_2), 4.46 (t, J = 5.2, 2H, CH_2), 7.22 (d, J = 8.6, 2H, ArH), 7.54 (s, 1H, ArH), 7.64 (dd, J = 8.4, 1.6, 1H, ArH), 8.01 (d, J = 8.6, 1H, ArH), 8.06–8.12 (m, 4H, ArH), 8.21 (s, 1H, ArH), 8.57 (d, J = 6.8, 2H, ArH). LC–MS: R_f = 2.80 min; *m/z* 487 ([M+H]$^+$, 10), 244 (100). HRMS (EI): *m/z* calcd for $C_{27}H_{26}N_4OS_2$ ([M+H]$^+$): 487.1626; found: 487.1608.

4.34.14. ±(2-{4-[5-(3-Methanesulfinyl-benzo[*b*]thiophen-6-yl)-4-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-dimethyl-amine (1m)

Compound **1l** (69 mg, 80 μmol) was dissolved in water (1 mL) and oxone® (26 mg, 40 μmol) added. After 15 min, the reaction was basified with a little 2 N NaOH, evaporated to dryness and the residue extracted with EtOAc/MeOH (2 × 1 mL). The desired product was isolated by chromatography on silica gel using 7:2:1 EtOAc/MeOH/TEA. Yield: 20 mg (50%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.12 (s, 3H, CH_3), 3.66 (t, J = 5.2, 2H, CH_2), 4.46 (t, J = 5.2, 2H, CH_2), 7.22 (d, J = 8.6, 2H, ArH), 7.73 (dd, J = 8.5, 1.4, 1H, ArH), 8.05–8.15 (m, 4H, ArH), 8.30 (d, J = 8.4, 1H, ArH), 8.36 (d, J = 1.4, 1H, ArH), 8.42 (s, 1H, ArH), 8.57 (d, J = 6.8, 2H, ArH). LC–MS: R_f = 2.32 min; *m/z* 503 ([M+H]$^+$, 10), 252 (100). HRMS (EI): *m/z* calcd for $C_{27}H_{26}N_4O_2S_2$ ([M+H]$^+$): 503.1575; found: 503.1565.

4.34.15. ±1-(5-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-benzo[*b*]thiophen-2-yl)-2,2,2-trifluoro-ethanol (±1n)

Compound **9** (63 mg; 0.16 mmol) and boronate ester **±40a** (88 mg; 0.24 mmol) were coupled using the general procedure. The residue was purified by preparative LC to give the desired product (13 mg; 13%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 5.2, 2H, CH_2), 4.46 (t, J = 5.2, 2H, CH_2), 5.44–5.55 (m, 1H, CH), 7.22 (d, J = 9.0, 2H, ArH), 7.53–7.59 (m, 2H, ArH), 8.03–8.14 (m, 6H, ArH), 8.56 (d, J = 7.0, 2H, ArH). LC–MS: R_f = 2.51 min; *m/z* 539 ([M+H]$^+$, 10), 270 (100). HRMS (EI): *m/z* calcd for $C_{28}H_{26}F_3N_4O_2S$ ([M+H]$^+$): 539.1723; found: 539.1730.

4.34.16. ±-1-(4-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-phenyl)-2,2,2-trifluoro-ethanol (±1o)

Compounds **±43** (32 mg, 0.1 mmol) and **9** (34 mg, 90 μmol) were coupled according to the general procedure to give the desired compound (21 mg, 50%). ^{1}H NMR (CD_3OD), δ: 2.64 (s, 6H, $N(CH_3)_2$), 3.15 (t, J = 5.2, 2H, CH_2), 4.30 (t, J = 5.2, 2H, CH_2), 5.13 (q, J = 6.8, 1H), 7.14 (d, J = 9.1, 2H, ArH), 7.56–7.64 (m, 6H, ArH), 7.99 (d, J = 8.6, 2H, ArH), 8.46 (d, J = 4.5, 2H, ArH). LC–MS: R_f = 2.41 min; *m/z* 483 ([M+H]$^+$, 10), 242 (100). HRMS (EI): *m/z* calcd for $C_{26}H_{25}F_3N_4O_2$ ([M+H]$^+$): 483.2008; found: 483.2016.

4.34.17. 7-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-naphthalen-2-ol (1p)

Compound **9** (48 mg; 0.12 mmol) was coupled to compound **46** (40 mg, 0.15 mmol) using the general procedure to give the desired compound as a beige solid (13 mg; 24%). ^{1}H NMR (CD_3OD), δ: 2.45 (s, 6H, $N(CH_3)_2$), 2.92 (t, J = 5.1, 2H, CH_2), 4.22 (t, J = 5.2, 2H, CH_2), 7.06–7.18 (m, 4H, ArH), 7.34 (d, J = 8.6, 1H, ArH), 7.59 (br, 2H, ArH), 7.74–7.86 (m, 3H, ArH), 7.98 (d, J = 8.9, 2H, ArH), 8.41 (d, J = 4.3, 2H, ArH). LC–MS: R_f = 2.42 min; *m/z* 451 ([M+H]$^+$, 100), 226. HRMS (EI): *m/z* calcd for $C_{28}H_{26}N_4O_2$ ([M+H]$^+$): 451.2134; found: 451.2127.

4.34.18. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-naphthalen-1-ol (1q)

Compound **9** (49 mg, 0.11 mmol) was coupled with compound **52** (37 mg, 0.14 mmol) according to the general procedure to give

the desired compound. Yield: 34 mg (68%). Part of this (28 mg) was converted to the triple TFA salt by dissolving in MeOH (1 mL), adding trifluoroacetic acid (0.1 mL) and evaporating to dryness. Yield: 48 mg (86%). ^{1}H NMR (CD_3OD), δ: 2.92 (s, 6H, $N(CH_3)_2$), 3.56 (t, J = 4.8, 2H, CH_2), 4.39 (t, J = 4.8, 2H, CH_2), 6.86 (dd, J = 6.1, 2.0, 1H, ArH), 7.17 (d, J = 9.1, 1H, ArH), 7.27–7.35 (m, 2H, ArH), 7.46 (d, J = 8.6, 1H, ArH), 8.00–8.06 (m, 6H, ArH), 8.30 (d, J = 8.6, 1H, ArH), 8.56 (d, J = 6.4, 2H, ArH). LC–MS: R_f = 2.36 min; m/z 451 ([M+H]$^+$, 10), 226 (100). HRMS (EI): m/z calcd for $C_{28}H_{26}N_4O_2$ ([M+H]$^+$): 451.2134; found: 451.2116.

4.34.19. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-1-methoxymethyl-5-pyridin-4-yl-1*H*-imidazol-4-yl}-naphthalen-2-ol (54)

{2-[4-(4-Bromo-1-methoxymethyl-5-pyridin-4-yl-1H-imidazol-2-yl)- phenoxy]-ethyl}-dimethyl-amine (**8**)[18] (80 mg; 0.19 mmol) was coupled to 6-hydroxynaphthalene-2-boronic acid **53** (43 mg; 0.23 mmol) using the general procedure to give the desired compound (44 mg, 48%). ^{1}H NMR ($CDCl_3$), δ: 2.42 (s, 6H, $N(CH_3)_2$), 2.84 (t, J = 5.6, 2H, CH_2), 3.32 (s, 3H, CH_3), 4.18 (t, J = 5.6, 2H, CH_2), 4.98 (s, 2H, CH_2), 6.96–7.08 (br, 4H, ArH), 7.36–7.46 (m, 2H, ArH), 7.47–7.53 (m, 2H, ArH), 7.57 (d, J = 9.5, 1H, ArH), 7.81 (d, J = 8.9, 2H, ArH), 7.97 (s, 1H, ArH), 8.67 (d, J = 5.9, 2H, ArH). LC–MS: R_f = 2.57 min; m/z 495 ([M+H]$^+$, 100), 248. HRMS (EI): m/z calcd for $C_{30}H_{31}N_4O_3$ ([M+H]$^+$): 495.2396; found: 495.2392.

4.34.20. 2-Chloro-6-{2-[4-(2-dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-naphthalen-1-ol (1s)

Compounds **57** (29 mg, 95 μmol) and **9** (27 mg, 95 μmol) were coupled according to the general procedure to give the desired compound (1 mg, 3%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 4.8, 2H, CH_2), 4.46 (t, J = 4.8, 2H, CH_2), 7.22 (d, J = 9.1, 2H, ArH), 7.43–7.52 (m, 2H, ArH), 7.65 (d, J = 8.6, 1H, ArH), 8.07–8.13 (m, 5H, ArH), 8.43 (d, J = 8.6, 1H, ArH), 8.56 (d, J = 6.8, 2H, ArH). LC–MS: R_f = 2.54 min; m/z 485 ([M+H]$^+$, 10), 243 (100).

4.34.21. (2-{4-[4-(5-Difluoromethoxy-6-fluoro-naphthalen-2-yl)-1-methoxymethyl-5-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-dimethyl-amine (61)

Compounds **8** (54 mg; 0.13 mmol) and **60** (55 mg; 0.16 mmol) were coupled using the general procedure to give the desired product (23 mg; 26%). Compound **61** was used in the next step without further purification. LC–MS: R_f = 1.49 min; m/z 563 ([M+H]$^+$, 10), 282 (100).

4.34.22. 7-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-1-methoxymethyl-5-pyridin-4-yl-1*H*-imidazol-4-yl}-quinolin-2-ol (65)

Compounds **64** (120 mg; 0.44 mmol) and **8** (127 mg; 0.29 mmol) were coupled according to the general procedure to give the desired compound (100 mg; 68%). ^{1}H NMR ($CDCl_3$), δ: 2.38 (s, 6H, $N(CH_3)_2$), 2.79 (t, J = 5.7, 2H, CH_2), 3.29 (s, 3H, CH_3), 4.16 (t, J = 5.7, 2H, CH_2), 4.95 (s, 2H, CH_2), 6.63 (d, J = 9.5, 1H, ArH), 7.07 (d, J = 9.1, 2H, ArH), 7.19–7.29 (m, 1H, ArH), 7.40 (d, J = 8.2, 1H, ArH), 7.43–7.50 (m, 2H, ArH), 7.54 (br, 1H, ArH), 7.71 (d, J = 9.5, 1H, ArH), 7.80 (d, J = 9.1, 2H, ArH), 8.57 (d, J = 6.4, 2H, ArH). LC–MS: R_f = 1.09 min; m/z 496 ([M+H]$^+$, 10), 249 (100). HRMS (EI): m/z calcd for $C_{29}H_{29}N_5O_3$ ([M+H]$^+$): 496.2349; found: 496.2358.

4.34.23. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-1-methoxymethyl-5-pyridin-4-yl-1*H*-imidazol-4-yl}-quinolin-2-ol (68)

Compounds **67** (184 mg; 0.68 mmol) and **8** (50 mg; 0.17 mmol) were coupled according to the general procedure to give the desired compound as a yellow glass (12 mg; 16%). Compound **68** was used in next step without further purification. LC–MS: R_f = 0.99 min; m/z 496 ([M+H]$^+$, 10), 248 (100).

4.34.24. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-2*H*-isoquinolin-1-one (1w)

Compounds **70** (56 mg, 0.21 mmol) and **9** (44 mg; 0.14 mmol) were coupled according to the general procedure to give the desired compound (2 mg, 2%). ^{1}H NMR (CD_3OD), δ: 3.00 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 4.8, 2H, CH_2), 4.46 (t, J = 4.8, 2H, CH_2), 6.74 (d, J = 7.3, 1H, ArH), 7.22 (d, J = 8.2, 2H, ArH), 7.28 (d, J = 7.3, 1H, ArH), 7.71 (d, J = 8.6, 1H, ArH), 7.96 (s, 1H, ArH), 8.04–8.17 (m, 4H, ArH), 8.45 (d, J = 8.6, 1H, ArH), 8.59 (br, 2H, ArH). LC–MS: R_f = 2.14 min; m/z 452 ([M+H]$^+$, 10), 226 (100). HRMS (EI): m/z calcd for $C_{27}H_{25}N_5O_2$ ([M+H]$^+$): 452.2086; found: 452.2068.

4.34.25. (6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-1-methoxymethyl-5-pyridin-4-yl-1*H*-imidazol-4-yl}-isoquinolin-1-yl)-bis-(4-methoxy-benzyl)-amine (74)

Compound **8** (50 mg; 0.12 mmol) and compound **73** (89 mg; 0.17 mmol) were coupled using the general procedure to give the desired compound (7 mg; 8%). LC–MS: R_f = 1.46 min; m/z 735 ([M+H]$^+$, 10), 368 (100). HRMS (EI): m/z calcd for $C_{45}H_{46}N_6O_4$ ([M+H]$^+$): 735.3659; found: 735.3652.

4.34.26. (2-{4-[4-(6-Fluoro-naphthalen-2-yl)-1-methoxymethyl-5-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-dimethyl-amine (77)

Compounds **8** (50 mg; 0.12 mmol) and **76** (49 mg, 0.18 mmol) were coupled using the general procedure to give the desired product (50 mg; 71%). ^{1}H NMR ($CDCl_3$), δ: 2.05 (s, 6H, $N(CH_3)_2$), 2.78 (t, J = 5.7, 2H, CH_2), 4.07–4.19 (m, 5H, CH_3 + CH_2), 4.98 (s, 2H, CH_2), 7.07 (d, J = 9.1, 2H, ArH), 7.21 (td, J = 8.7, 2.5, 1H, ArH), 7.39 (dd, J = 9.8, 2.5, 1H, ArH), 7.48 (d, J = 5.9, 2H, ArH), 7.54 (d, J = 9.5, 1H, ArH), 7.62–7.67 (m, 1H, ArH), 7.73 (dd, J = 8.9, 5.7, 1H, ArH), 7.82 (d, J = 8.6, 2H, ArH), 8.10 (s, 1H, ArH), 8.69 (d, J = 6.4, 2H, ArH). LC–MS: R_f = 1.00 min; m/z 497 ([M+H]$^+$, 10), 249 (100).

4.34.27. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-naphthalene-2-carboxylic acid (1z)

Compound **9** (50 mg; 0.12 mmol) was coupled to 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid, **79** (69 mg; 0.23 mmol) according to the general procedure to give the desired compound (2 mg, 1%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.65 (t, J = 4.8, 2H, CH_2), 4.46 (t, J = 4.8, 2H, CH_2), 7.22 (d, J = 8.6, 2H, ArH), 7.75 (d, J = 8.6, 1H, ArH), 8.04 (d, J = 8.6, 1H, ArH), 8.07–8.18 (m, 5H, ArH), 8.21 (d, J = 8.2, 1H, ArH), 8.26 (s, 1H, ArH), 8.58 (d, J = 6.8, 2H, ArH), 8.72 (s, 1H, ArH). LC–MS: R_f = 2.36 min; m/z 479 ([M+H]$^+$, 100), 240. HRMS (EI): m/z calcd for $C_{29}H_{27}N_4O_3$ ([M+H]$^+$): 479.2083; found: 479.2076.

4.35. MOM-deprotection

The protected imidazole (ie: **10**) (0.16 mmol) was dissolved in 1 mL 5 M HCl and the reaction heated at 60 °C for 1 h. The solvents were removed in vacuo to yield the deprotected imidazole as its HCl salt in quantitative yield.

4.35.1. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-naphthalen-2-ol (1r)

Compound **54** (63 mg, 0.13 mmol) was deprotected according to the general procedure to give the title compound (15 mg, 26%) as its HCl salt. ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 5.1, 2H, CH_2), 4.46 (t, J = 5.2, 2H, CH_2), 7.13–7.28 (m, 4H, ArH), 7.50–7.58 (m, 1H, ArH), 7.84 (t, J = 9.1, 2H, ArH), 8.04–8.15 (m, 5H, ArH), 8.55 (d, J = 5.0, 2H, ArH). LC–MS: R_f = 2.37 min; m/z 451 ([M+H]$^+$, 100), 226. HRMS (EI): m/z calcd for $C_{28}H_{27}N_4O_2$ ([M+H]$^+$): 451.2134; found: 451.2132.

4.35.2. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-2-fluoro-naphthalen-1-ol (1t)

Compound **61** (23 mg, 0.04 μmol) was dissolved in 48% aq HBr (1 mL) and AcOH (1.6 mL) and the solution was heated to 120 °C in a sealed tube overnight. The solution was allowed to cool to rt, diluted with water (5 mL) and washed with EtOAc. The acidic layer was concentrated in vacuo and the the residue purified by preparative HPLC to yield the TFA salt as a yellow glue. Yield: 4.6 mg, 14%. ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.66 (t, J = 4.8, 2H, CH_2), 4.46 (t, J = 4.8, 2H, CH_2), 7.22 (d, J = 9.1, 2H, ArH), 7.36–7.51 (m, 2H, ArH), 7.63 (d, J = 9.1, 1H, ArH), 8.04–8.14 (m, 5H, ArH), 8.41 (d, J = 8.6, 1H, ArH), 8.56 (d, J = 6.4, 2H, ArH). LC–MS: R_f = 2.37 min; m/z 469 ([M+H]$^+$, 10), 235 (100). HRMS (EI): m/z calcd for $C_{28}H_{26}FN_4O_2$ ([M+H]$^+$): 469.2034; found: 469.2033.

4.35.3. 7-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-quinolin-2-ol (1u)

Compound **65** (25 mg; 0.024 μmol) was deprotected using the general procedure to give the desired product as its HCl salt (30 mg; quantitative). ^{1}H NMR (CD_3OD), δ: 3.03 (s, 6H, $N(CH_3)_2$), 3.70 (t, J = 5.7, 2H, CH_2), 4.54 (t, J = 5.7, 2H, CH_2), 6.76 (d, J = 9.5, 1H, ArH), 7.39 (d, J = 8.2, 2H, ArH), 7.54 (d, J = 7.3, 1H, ArH), 7.69 (br, 1H, ArH), 7.93 (d, J = 7.3, 1H, ArH), 8.10 (d, J = 9.5, 1H, ArH), 8.18–8.30 (m, 4H, ArH), 8.89 (d, J = 4.5, 2H, ArH). LC–MS: R_f = 2.09 min; m/z 452 ([M+H]$^+$, 10), 226 (100). HRMS (EI): m/z calcd for $C_{27}H_{25}N_5O_2$ ([M+H]$^+$): 452.2086; found: 452.2083.

4.35.4. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-3*H*-imidazol-4-yl}-quinolin-2-ol (1v)

Compound **68** (12 mg; 50 μmol) was deprotected using the general procedure to give the desired product as its HCl salt (5 mg; 46%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.67 (t, J = 5.0, 2H, CH_2), 4.49 (t, J = 5.0, 2H, CH_2), 6.71 (d, J = 9.5, 1H, ArH), 7.27 (d, J = 8.6, 2H, ArH), 7.55 (d, J = 8.6, 1H, ArH), 7.78 (d, J = 8.2, 1H, ArH), 7.99–8.06 (m, 2H, ArH), 8.10–8.18 (m, 4H, ArH), 8.62–8.71 (d, J = 5.6, 2H, ArH). LC–MS: R_f = 2.21 min; m/z 452 ([M+H]$^+$, 100), 276. HRMS (EI): m/z calcd for $C_{27}H_{26}N_5O_2$ ([M+H]$^+$): 452.2087; found: 452.2082.

4.35.5. 6-{2-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-pyridin-4-yl-1*H*-imidazol-4-yl}-isoquinolin-1-ylamine (1x)

Compound **74** (7 mg; 10 μmol) was heated in TFA (1.5 mL) at 120 °C for 18 h. The acid was removed in vacuo and the residue dissolved in water and washed with EtOAc. Evaporation of the water gave the desired compound as the TFA salt (3.5 mg; 81%). ^{1}H NMR (CD_3OD), δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.65 (t, J = 4.5, 2H, CH_2), 4.46 (t, J = 4.5, 2H, CH_2), 7.22 (d, J = 8.6, 2H, ArH), 7.26 (d, J = 7.3, 1H, ArH), 7.64 (d, J = 7.3, 1H, ArH), 7.97 (d, J = 7.7, 1H, ArH), 8.10 (d, J = 8.6, 4H, ArH), 8.20 (s, 1H, ArH), 8.56 (d, J = 8.2, 1H, ArH), 8.67 (br, 2H, ArH). LC–MS: R_f = 1.87 min; m/z 451 ([M+H]$^+$, 10), 226 (100). HRMS (EI): m/z calcd for $C_{27}H_{28}N_6O$ ([M+H]$^+$): 451.2240; found: 451.2242.

4.35.6. (2-{4-[5-(6-Fluoro-naphthalen-2-yl)-4-pyridin-4-yl-1*H*-imidazol-2-yl]-phenoxy}-ethyl)-dimethyl-amine (1y)

Compound **77** (50 mg; 0.1 mmol) was reacted as in the general procedure to give the desired product (31 mg; 70%). ^{1}H NMR (CD_3OD), δ: 3.04 (s, 6H, $N(CH_3)_2$), 3.70 (t, J = 4.8, 2H, CH_2), 4.55 (t, J = 4.8, 2H, CH_2), 7.41 (d, J = 8.6, 2H, ArH), 7.48 (t, J = 8.9, 1H, ArH), 7.73 (d, J = 7.9, 2H, ArH), 8.10 (d, J = 9.3, 2H, ArH), 8.24 (d, J = 7.3, 4H, ArH), 8.36 (s, 1H, ArH), 8.87 (d, J = 5.9, 2H, ArH). LC–MS: R_f = 2.57 min; m/z 453 ([M+H]$^+$, 10), 227 (100). HRMS (EI): m/z calcd for $C_{28}H_{25}FN_4O$ ([M+H]$^+$): 3.2090; found: 453.2079.

Disclosure statement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.12.035. These data include MOL files and InChiKeys of the most important compounds described in this article.

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