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A general approach to homochiral α-amino substituted bromo-heteroaromatics suitable for two-dimensional rapid analogue synthesis

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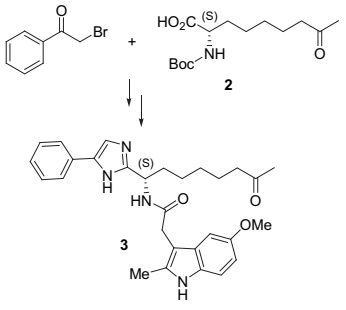
ABSTRACT

An efficient and general synthesis of homochiral α-amino substituted bromo-heteroaromatics **B** using a diastereoselective 1,2-addition has been developed. The obtained heteroaromatic intermediates allow for a rapid two-dimensional exploration of a new series of histone deacetylase inhibitors, through Suzuki–Miyaura cross-coupling reactions for the introduction of a second aromatic element, followed by global deprotection and derivatization of the amino group.

1. Introduction

In the context of our histone deacetylase inhibitor (HDACi) program we were interested in the rapid exploration of lead structure **3** (Scheme 1).[1] The previously used synthesis for **3** consisted of the formation of the imidazole by reacting aminoacid **2** with bromo-acetophenone (Scheme 1). Bromo- or chloro-methyl aryl ketones are not readily available, need to be prepared in a multistep protocol and many of them are unstable under the basic conditions used in the alkylation step (self-alkylation/polymerization). Therefore, in order to rapidly explore the SAR around lead structure **3** a new synthetic route was needed, which ideally should also be applicable to diverse heterocyclic imidazole replacements. A flexible late stage diversification of the substituents on the heterocycle (R^2, Fig. 1), as well as a functionalization of the amino group (R^1, Fig. 1) was also desirable. At an early stage of our program we found that inhibitors with a (*S*)-configuration at the chiral centre were significantly more active then the corresponding (*R*)-enantiomers. Therefore a stereoselective synthesis was required.[1]

In this communication we report a general approach for the synthesis of homochiral α-amino substituted imidazoles and related heterocycles **C** (Fig. 1).



Scheme 1. Previous synthesis of imidazole HDAC inhibitor **3**.[1]

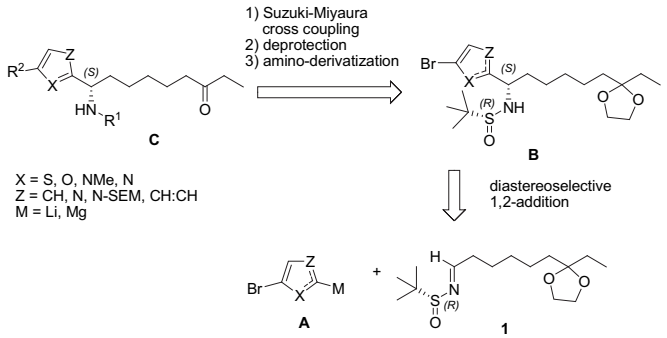


Figure 1. New approach for the synthesis of HDAC inhibitors with heteroaromatic core—retrosynthetic analysis.

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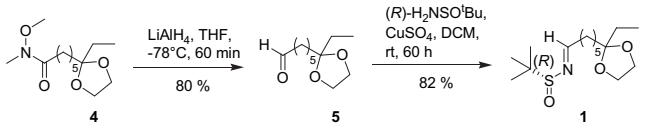
2. Results and discussion

We envisioned that the desired heterocyclic intermediate **B** could be accessible from metalated bromoheterocycles **A** through a diastereoselective 1,2-addition to the chiral *tert*-butanesulfinyl-imine **1**, similar to the chemistry developed by Ellman,[2] and recently applied by Chen et al.[3] Bromo intermediate **B** was thought to serve as a substrate for Suzuki–Miyaura cross-coupling reactions with different boronic acids to introduce the R^2-substituents. The R^1-substituents were envisaged to be introduced after amino-deprotection. Furthermore, the order of introduction of R^1 and R^2 should be invertable.

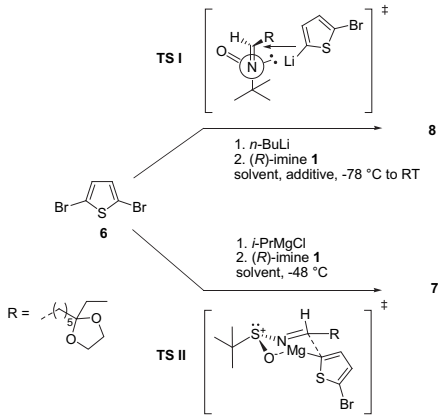
The chiral (*R*)-*tert*-butanesulfinyl-imine **1** was prepared in two steps from Weinreb amide **4** (Scheme 2).[4] A standard reduction of **4** to aldehyde **5** was followed by condensation with the commercially available (*R*)-2-methylpropane-2-sulfinamide to furnish imine **1** in good yield.[5,6]



Scheme 2. Synthesis of the chiral (*R*)-*N*-*tert*-butanesulfinyl-imine **1**.

Next, the diastereoselective 1,2-addition of metalated heterocycles to **1** was investigated, starting with 2,5-dibromothiophene **6** (Table 1, Scheme 3). The reaction was performed in two phases: a halogen–metal exchange at low temperature was followed by the addition of **1** to the reaction mixture. Given our interest in obtaining selectively the (R_S,*S*)-diastereomer we first performed the reaction with *n*-BuLi in THF. According to the literature, the use of lithium salts is expected to induce an open transition state, yielding the desired products **8** (Scheme 3, TS I).[7] Under these initial conditions only modest selectivity in favour of the desired (R_S,*S*) diasteromer was obtained (Table 1, entry 1), although with good yields.[8]

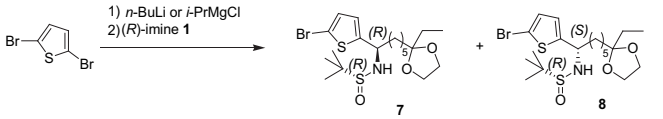
In order to increase the diastereoselectivity, different additives like TMEDA, or Lewis acids like TIPT, $AlMe_3$ and $BF_3{\cdot}OEt_2$ were added to the sulfinyl-imine **1** prior to addition to the lithiated thiophene (Table 1, entry 2–5). Pleasingly, in the case of $BF_3{\cdot}OEt_2$ a drastic increase in selectivity in favour of the desired (R_S,*S*) diastereomer was observed (Table 1, entry 5). Since the presence of $BF_3{\cdot}OEt_2$ caused a partial cleavage of the ketal group, the reaction mixture was stirred with an excess of the Lewis acid for a longer time yielding the deprotected ketone. In contrast, switching to a magnesium counterion, and conducting a Knochel Br–Mg exchange followed by addition of **1**, resulted in an inverted diastereoselectivity with a ratio of 4:1 in favour of the (R_S,*R*)-diastereomer **7** (Table 1, entry 7). Further improvements both in yield and diastereoselectivity could be made by replacing the solvent THF with toluene or DCM (Table 1, entries 8 and 9). These results can be rationalized by assuming a cyclic transition state induced by the presence of magnesium as counterion in less polar solvents (Scheme 3, TS II).[2c]



Scheme 3. Possible transition states of addition of metalated bromothiophene to sulfinyl-imine **1**.

The determination of the absolute configuration of **8** was performed by the Mosher method,[9] requiring the preparation of the corresponding MTPA amide derivatives **9** and **10** (Fig. 2). A mild deprotection of **8** was achieved with hydrochloric acid in methanol after 15 min. The resulting amine was then converted with (*R*)- or (*S*)-Mosher acids to diastereomers **9** and **10**; their ^{1}H NMR spectra were recorded and the differences in the chemical shifts ($\Delta\delta^{RS}=\delta^R-\delta^S$) calculated. As reported in Figure 2, negative $\Delta\delta^{RS}$ values were measured for the thiophene moiety, while positive $\Delta\delta^{RS}$ values were observed for the oxononyl moiety; according to the correlation models described in literature, the signs of $\Delta\delta^{RS}$ indicate (*S*)-configuration of **8**.

Table 1
Diasteroselective addition of metalated bromothiophene to sulfinyl-imine **1**



#	Base	Solvent	Additives	Yield[a] **7**+**8**	dr (R_S,*R*/R_S,*S*) **7**/**8**
1	*n*-BuLi[b]	THF	—	86	1:2
2			TMEDA	55	1:2
3			TIPT	51	1:1
4			$AlMe_3$	65	1:2
5			$BF_3{\cdot}OEt_2$	58[c]	1:7
6		Toluene	—	73	2:1
7	*i*-PrMgCl[d]	THF	—	42	4:1
8		Toluene	—	59	9:1
9		DCM	—	62	9:1

[a] Sum of yields of isolated separated diastereomers (in %).
[b] Lithium–bromine exchange at −78 °C.
[c] $BF_3{\cdots}OEt_2$ caused ketal deprotection. After prolonged reaction time the corresponding ketones were formed. Yield refers to isolated major isomer ketone (**8a**, see Supporting data).
[d] Magnesium–bromine exchange at −48 °C.

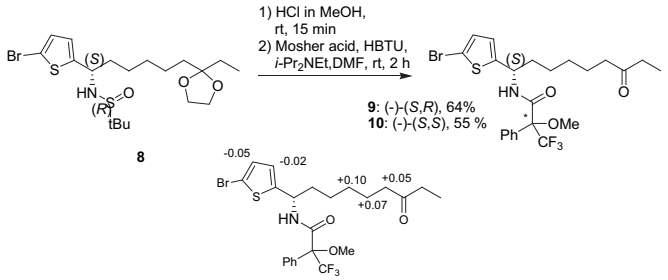
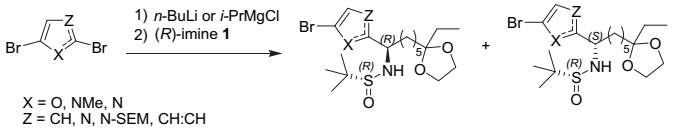


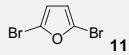
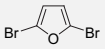
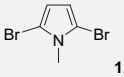
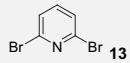
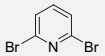
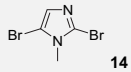
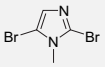
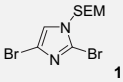
Figure 2. Determination of absolute configuration of **8** by the Mosher method; selected key values for $\Delta\delta^{RS}=\delta^R-\delta^S$ (in ppm) are reported for MTPA amide derivatives of **8**.

Next, the scope of the stereoselective addition of various metalated bromoheterocycles to sulfinyl-imine **1** was explored with a series of different dibromo-heterocycles (Table 2). With 2,5-dibromofuran **11**, 2,5-dibromo-*N*-methyl-pyrrole **12** and 2,6-dibromo-pyridine **13** the obtained diastereoselectivities were medium to low with the (R_S,*R*)-diastereomer being favoured (Table 2, entries 1–5). Surprisingly, the choice of the counterion and the

nature of the solvent had little influence on the selectivity. Only in the case of **13** a good diastereoselectivity was observed (entry 5, 5:1 in favour of (R_S,*R*)-isomer), although in poor yield (31%). In contrast, changing the heterocycle to 2,5-dibromo-*N*-methyl-imidazole **14** a reversed selectivity for the desired (R_S,*S*)-diastereomer was observed under both employed reaction conditions (*n*-BuLi/THF and *i*-PrMgCl/DCM, Table 2, entries 6, 7). These observations clearly demonstrate the critical role of the heterocycle for the stereochemical outcome of the addition reactions. In the case of the imidazole, improved diastereoselectivity for the desired (R_S,*S*)-diastereomer was achieved through the replacement of the *N*-methyl- for a *N*-SEM-group (**15**). Presumably a chelation of the lithium counterion by the oxygen atom of the SEM-group leads to high (R_S,*S*)-diastereoselectivity via a stabilization of the open transition state (TS I, Scheme 3) as the metal ion is not available for participation in a six-membered transition state. This is consistent with the reported diastereoselectivity of a similar addition reaction using *N*-phenylsulfonyl-protected indole-derivatives.[3]

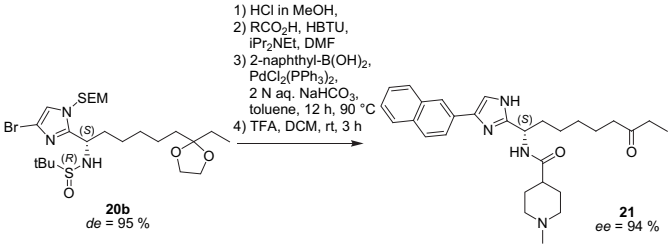
Table 2
Diastereoselective addition of metalated heterocycles to sulfinyl-imine **1**



#	Heterocycle	Base	Solvent	Yield[a]	dr (R_SR/R_SS)
1	 **11**	*n*-BuLi	THF	59	4:1 (**16a**/**16b**)
2		*i*-PrMgCl	DCM	39	3:1
3	 **12**	*n*-BuLi	THF	69	2:1 (**17a**/**17b**)
4	 **13**	*n*-BuLi	THF	17[b]	2:1[b]
5		*i*-PrMgCl	DCM	31[b]	5:1[b] (**18**)
6	 **14**	*n*-BuLi	THF	61	1:3 (**19a**/**19b**)
7		*i*-PrMgCl	DCM	76	1:3
8	 **15**	*n*-BuLi	THF	74	1:7 (**20a**/**20b**)

[a] Sum of yields of isolated separated diastereomers (in %).
[b] Mixture of diastereomers not seperable by silica gel chromatography.

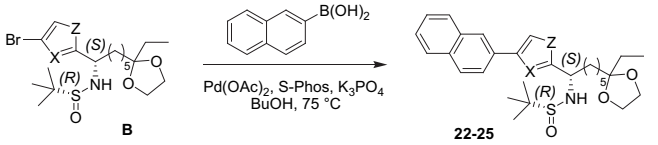
The absolute configurations of the obtained diastereomeric products were determined in all cases using the Mosher amide methodology as for the thiophene derivatives after separation of the diastereomers. In the case of the *N*-SEM-imidazole (**20b**) a chemical correlation was used to confirm the assignment obtained with the Mosher method (Scheme 4). Intermediate **20b** was transformed into final product **21** by deprotection, acylation, Suzuki–Miyaura cross-coupling and imidazole-deprotection. Compound **21** was compared by chiral HPLC with the same compound obtained with the previous synthesis using a (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-8-oxodeca-noic acid as starting material (Scheme 1). Both syntheses furnished identical material with the (*S*)-configuration at the chiral centre. Importantly, minimal racemization of the chiral centre was found during the synthesis of **21** starting from **20b**, allowing to obtain **21** with 94% ee.



Scheme 4. Schemical correlation to confirm absolute configuration of HDACi.

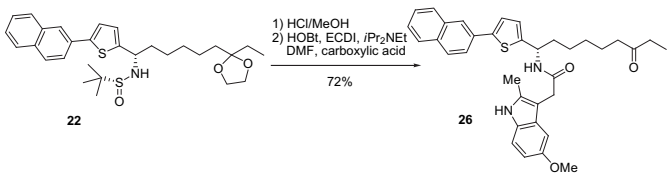
With bromoheterocycles **B** in hand we then proceeded to explore their utility for the planned rapid exploration of the HDAC pharmacophore around structure **3**. First, the Suzuki–Miyaura coupling reaction was investigated, with 2-naphthyl as prototypic aryl-substituent to be introduced. Optimized conditions were identified employing the Buchwald ligand *S*-Phos, K_3PO_4 as base and *n*-butanol as solvent, giving consistently high yields on all the employed bromoheterocycles (Table 3).[10] Finally, an acid promoted deprotections under mild conditions (1.2 N HCl in methanol) furnished the deptotected amino-ketones, which were then derivatized by standard chemistry into final HDACi as is exemplified in Scheme 5.

Table 3
Suzuki–Miyaura coupling reactions with intermediates **B** as substrates



#	Starting material	Heterocycle	Yield	Product
1	**8**		91	**22**
2	**16b**		82	**23**
3	**18**		68	**24**[a]
4	**20b**		70	**25**

[a] Mixture of diastereomers (R_SR/R_SS ca. 5:1).



Scheme 5. Acid promoted deprotection of **22** and formation of final compound as HDACi.

3. Conclusion

In summary, we have developed a general and efficient synthesis of homochiral α-amino substituted bromo-heteroaromatics. In a first step a regioselective mono metal–bromine exchange was

used to generate metalated bromo-heterocyclic species **A**. These intermediates were shown to undergo a diastereoselective 1,2-addition to chiral (*R*)-*tert*-butanesulfinyl-imine **1**. In the case of the thiophene the diastereselectivity could be controlled by the choice of different reaction conditions. However, a further exploration of the scope of the reaction demonstrated that the diastereoselectivity depended critically on the nature of the heterocycle. For the introduction of the imidazole the use of a *N*-SEM-protecting group increased the selectivity in favour of the desired (R_S,*S*)-isomer. The obtained bromoheterocycles **B** proved to be suitable for the rapid exploration of novel analogues of HDACi. Biological results on analogues prepared with the presented chemistry will be reported elsewhere.

4. Experimental

4.1. General

All reagents, starting materials and solvents were obtained from commercial sources and used without further purification. Flash chromatography was conducted on silica gel 60 (0.0040–0.063 mm, Merck). NMR spectra were recorded on Bruker Avance spectrometers at T=300 K. Chemical shifts are reported in parts per million (δ) and coupling constants (J) in Hz; proton chemical shift are referenced to the residual proton signal of the deuterated solvent ($CDCl_3$ at 7.26 ppm; DMSO-d_6 at 2.50 ppm); carbon chemical shift are referenced to the solvent signal of $CDCL_3$ at 77.0 ppm; signal multiplicity is reported as CHn. UPLC–MS analysis was performed with Waters Aquity™ Ultra Performance LC, using an Aquity UPLC™ BEH C18, 1.7 μm (2.1×50 mm) column, connected to a 2996 PDA detector and a Waters micromass ZQ. Gradient used: MeCN/water (0.1% formic acid), 10–100% MeCN in 2.0 min, than 0.3 min at 100% MeCN, flow rate 0.5 mL/min. High resolving power accurate mass measurement electrospray (ES) and atmospheric pressure chemical ionization (APCI) mass spectral data were acquired by use of a Bruker Daltonics 7T Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR MS). External calibration was accomplished with oligomers of polypropylene glycol.

4.2. Intermediates

*4.2.1. 6-(2-Ethyl-1,3-dioxolan-2-yl)hexanal (**5**).* To a solution of 6-(2-ethyl-1,3-dioxolan-2-yl)-*N*-methoxy-*N*-methylhexanamide (39 mmol; 1.0 equiv) in dry THF (120 ml) under Ar atmosphere at −78 °C was added dropwise $LiAlH_4$ (62 mmol; 1.6 equiv) in a period of 20 min. The mixture was stirred at −78 °C for 1 h. Then the reaction was quenched with 1 N aq NaOH (50 ml) at −78 °C. After warming up to room temperature the reaction mixture was extracted with EtOAc (3×50 ml). Combined organic phases were washed with brine (100 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by gradient column chromatography (silica; hexane/EtOAc; 0–55% of EtOAc) to obtain product **5** (75%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.89 (t, J=7.3 Hz, 3H), 1.33–1.37 (m, 4H), 1.57–1.65 (m, 6H), 2.39–2.43 (m, 2H), 3.92 (s, 4H), 9.75 (t, J=1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.0 (CH_3), 21.9 (CH_2), 23.4 (CH_2), 29.3 (CH_2), 29.8 (CH_2), 36.4 (CH_2), 43.7 (CH_2), 64.9 (CH_2), 111.9 (C), 202.7 (CH).

*4.2.2. (E)-N-(6-(2-Ethyl-1,3-dioxolan-2-yl)hexylidene)-2-methylpropane-2-sulfinamide (**1**/**1b**).* A solution of 6-(2-ethyl-1,3-dioxolan-2-yl)hexanal (13 mmol; 1.1 equiv), (*R*)- or (*S*)-2-methylpropane-2-sulfinamide (12 mmol; 1.0 equiv) and anhydrous $CuSO_4$ (26 mmol; 2.2 equiv) in dry DCM (100 ml) was stirred for 60 h at room temperature. The suspension changes colour from white to blue. The reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The residue was purified by gradient column chromatography (silica; petroleum ether/EtOAc; 0–60% of EtOAc) to obtain product (**1**) (78%) as colourless oil or product (**1b**) (66%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.90 (t, J=7.6 Hz, 3H), 1.19 (s, 9H), 1.37–1.39 (m, 4H), 1.58–1.65 (m, 6H), 2.49–2.54 (m, 2H), 3.93 (s, 4H), 8.06 (t, J=4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.3 (CH_3), 23.5 (CH_2), 25.4 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 36.0 (CH_2), 36.4 (CH_2), 56.5 (C), 64.9 (CH_2), 111.9 (C), 169.6 (CH). MS (ES) $C_{15}H_{29}NO_3S$ requires: 303, found: 304 $(M+H)^+$. HRMS (ESI) calcd for $[C_{15}H_{29}NO_3S+H]$: calcd 304.1946, meas. 304.1941.

*4.2.3. 2,5-Dibromo-1-methyl-1H-pyrrole (**12**).* To a solution of 1-methyl-1*H*-pyrrole (7.85 mmol; 1.0 equiv) in dry THF (20 ml) at −78 °C was added NBS (11.8 mmol; 1.5 equiv) in one portion. The mixture was removed from the cooling bath to solubilize the NBS. Then the reaction was left standing overnight at −10 °C. $Na_2S_2O_7$ (2 g) was added and the solvent was removed under reduced pressure at room temperature. The remaining solid was immediately suspended in hexane (10 ml) and the suspension was filtered through a pad of neutralized silica. (petroleumether; petroleum ether/DCM=4/1). The solvent was removed under reduced pressure at room temperature. Product (**12**) was obtained as white crystals (78%), which were immediately dissolved in THF. The product was kept in THF solution. Solid product **12** decomposed within 5 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ=3.53 (s, 3H), 6.25 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=34.0 (CH_3), 101.1 (C), 111.4 (CH).

*4.2.4. 2,4-Dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-imidazole (**15**).* To a solution of 2,4-dibromoimidazole (5.00 g, 0.022 mol) in dry THF (50 mL) at 0 °C under a nitrogen atmosphere was slowly added NaH (60% suspension in oil, 1.06 g, 0.027 mol). After 1 h 2-(trimethylsilyl)ethoxymethyl chloride (4.8 mL, 0.027 mol) was added and the mixture was stirred at room temperature. The reaction was quenched with water (75 mL) and the aq phase was extracted with EtOAc (3×75 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness under reduced pressure. Purification by flash chromatography on silica gel (ethyl acetate/pentane from 1:20 to 1:2) yielded the title compound (**15**) (6.9 g, 88%) as an oil (90% purity, impurity of 2,5-dibromo-1-{[2-(trimethylsilyl)ethoxy]-methyl}-imidazole). ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.00 (s, 9H), 0.92 (t, J=8.1 Hz, 2H), 3.54 (t, J=8.1 Hz, 2H), 5.22 (s, 2H), 7.09 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=−1.5 (CH_3), 17.6 (CH_2), 66.9 (CH_2), 76.3 (CH_2), 115.5 (C), 118.4 (CH), 121.4 (C). MS (ES) $C_9H_{16}Br_2N_2OSi$ requires: 355.9, found: 357.0 $(M+H^+)$.

4.3. Addition of heterocycles (A) to sulfinyl-imine (1)

*4.3.1. General procedure for addition of organolithium to (**1**).* To a solution of dibromo-heterocyclic compound (0.46 mmol; 1.4 equiv) in dry THF (1.5 ml) at −78 °C under Ar atmosphere was added dropwise *n*-BuLi (1.6 M in hexanes, 0.36 mmol; 1.1 equiv) and the mixture was stirred at −78 °C for 1 h. Then (**1**) or (**1b**) (0.33 mmol; 1.0 equiv) in THF (0.5 ml) was added dropwise and the mixture was stirred for 16 h.[‡] The temperature was allowed to reach room temperature during this time. The reaction was quenched with H_2O (10 ml), extracted with EtOAc (2×20 ml), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified on gradient column chromatography (silica; petroleum ether/EtOAc; 0–100% of EtOAc in petroleum ether, linear gradient) to afford the isolated

[‡] Additives were mixed with (**1**) at −78 °C in THF (0.5 ml) for 0.5 h and then this mixture was added dropwise to the reaction.

products (**7**,**8**,**16a**,**b**–**20a**,**b**). All products were isolated as colourless oils.

*4.3.2. General procedure for addition of organomagnesium to (**1**).* To a solution of dibromo-heterocyclic compound (0.46 mmol; 1.4 equiv) in dry solvent (0.1 ml) at −48 °C under Ar atmosphere was added dropwise *i*-PrMgCl (2.0 M in THF) (0.36 mmol; 1.1 equiv) and the mixture was stirred at −48 °C for 1 h. Mixture was diluted with dry DCM (2 ml). Then (**1**) or (**1b**) (0.33 mmol; 1.0 equiv) in DCM (0.8 ml) was added dropwise and the mixture was stirred for 16 h. The temperature was allowed reach room temperature during this time. The reaction was quenched with H_2O (10 ml), extracted with EtOAc (2×20 ml), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified on gradient column chromatography (silica; petroleum ether/EtOAc; 0–100% of EtOAc in petroleum ether, linear gradient) to afford the isolated products (**7**,**8**,**16a**,**b**–**19a**,**b**). All products were isolated as colourless oils.

4.3.3. Products.

*4.3.3.1. (R)-N-((R)-1-(5-Bromothiophen-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**7**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (t, *J*=7.3 Hz, 3H), 1.21 (s, 9H), 1.29–1.30 (m, 5H), 1.53–1.66 (m, 6H), 1.96–1.99 (m, 1H), 3.42 (d, *J*=4.3 Hz, 1H), 3.91 (s, 4H), 4.49–4.54 (m, 1H), 6.78 (d, *J*=3.8 Hz, 1H), 6.88 (d, *J*=3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.5 (CH_2), 23.5 (CH_2), 25.6 (CH_3), 29.5 (CH_2), 29.8 (CH_2), 36.5 (CH_2), 37.1 (CH_2), 55.5 (CH), 55.9 (C), 64.9 (CH_2), 111.7 (C), 111.9 (C), 125.8 (CH), 129.4 (CH), 148.1 (C). MS (ES) $C_{19}H_{32}BrNO_3S_2$ requires: 465/467, found: 488/490 (M+Na)+. HRMS (ESI) calcd for $C_{19}H_{32}BrNO_3S_2$+H: 466.1080, meas.: 466.1095.

*4.3.3.2. (R)-N-((S)-1-(5-Bromothiophen-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**8**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (t, *J*=7.3 Hz, 3H), 1.21 (s, 9H), 1.29–1.30 (m, 6H), 1.53–1.60 (m, 4H), 1.75–1.85 (m, 2H), 3.44 (br s, 1H), 3.91 (s, 4H), 4.56–4.60 (m, 1H), 6.72 (d, *J*=3.8 Hz, 1H), 6.87 (d, *J*=3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.5 (CH_2), 23.5 (CH_2), 25.7 (CH_3), 29.4 (CH_2), 29.8 (CH_2), 36.5 (CH_2), 39.0 (CH_2), 55.5 (CH), 55.8 (C), 64.9 (CH_2), 111.8 (C), 111.9 (C), 125.9 (CH), 129.2 (CH), 148.0 (C). MS (ES) $C_{19}H_{32}BrNO_3S_2$ requires: 465/467, found: 488/490 $(M+Na)^+$. HRMS (ESI) calcd for $C_{19}H_{32}BrNO_3S_2$+H: 466.1080, meas.: 466.1095.

*4.3.3.3. (R)-N-((S)-1-(5-Bromothiophen-2-yl)-7-oxononyl)-2-methylpropane-2-sulfinamide (**8a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.03 (t, *J*=7.3 Hz, 3H), 1.20 (s, 9H), 1.28–1.30 (m, 4H), 1.52–1.55 (m, 2H), 1.78–1.79 (m, 2H), 2.34–2.41 (m, 4H), 3.41 (d, *J*=6.4 Hz, 1H), 4.55–4.59 (m, 1H), 6.72 (d, *J*=3.8 Hz, 1H), 6.87 (d, *J*=3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.8 (CH_3), 22.5 (CH_2), 23.4 (CH_2), 25.4 (CH_3), 28.7 (CH_2), 35.9 (CH_2), 38.8 (CH_2), 42.0 (CH_2), 55.5 (CH), 55.8 (C), 111.8 (C), 125.8 (CH), 129.2 (CH), 148.0 (C), 211.5 (C).

*4.3.3.4. (R)-N-((R)-1-(5-Bromofuran-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**16a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (t, *J*=7.6 Hz, 3H), 1.18 (s, 9H), 1.31–1.32 (m, 6H), 1.56–1.62 (m, 4H), 1.79–1.83 (m, 1H), 1.89–1.93 (m, 1H), 3.28 (d, *J*=4.8 Hz, 1H), 3.92 (s, 4H), 4.33–4.38 (m, 1H), 6.18 (d, *J*=3.3 Hz, 1H), 6.21 (d, *J*=3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.0 (CH_3), 22.3 (CH_2), 23.4 (CH_2), 25.7 (CH_3), 29.4 (CH_2), 29.7 (CH_2), 35.2 (CH_2), 36.4 (CH_2), 53.8 (CH), 55.8 (C), 64.9 (CH_2), 110.0 (CH), 111.6 (CH), 111.9 (C), 121.0 (C), 156.5 (C). MS (ES) $C_{19}H_{32}BrNO_4S$ requires: 449/451, found: 472/474 $(M+H)^+$. HRMS (ESI) calcd for $C_{19}H_{32}BrNO_4S$+H: 450.1308, meas. 450.1326.

*4.3.3.5. (R)-N-((S)-1-(5-Bromofuran-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**16b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.89 (t, *J*=7.3 Hz, 3H), 1.21 (s, 9H), 1.31–1.32 (m, 6H), 1.56–1.64 (m, 4H), 1.85–1.87 (m, 2H), 3.37 (d, *J*=6.4 Hz, 1H), 3.92 (s, 4H), 4.25–4.31 (m, 1H), 6.22 (d, *J*=3.3 Hz, 1H), 6.27 (d, *J*=3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.5 (CH_2), 23.6 (CH_2), 25.7 (CH_3), 29.4 (CH_2), 29.8 (CH_2), 34.6 (CH_2), 36.5 (CH_2), 54.1 (CH), 56.0 (C), 64.9 (CH_2), 109.8 (CH), 111.8 (CH), 111.9 (C), 121.1 (C), 157.3 (C). MS (ES) $C_{19}H_{32}BrNO_4S$ requires: 449/451, found: 472/474 $(M+H)^+$. HRMS (ESI) calcd for $C_{19}H_{32}BrNO_4S$+H: 450.1308, meas. 450.1326.

*4.3.3.6. (R)-N-(1-(6-Bromopyridin-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**18**).* Compound (**18a**) (R_S,*S*): ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, *J*=7.3 Hz, 3H), 1.17(s, 9H), 1.25–1.40 (m, 6H), 1.54–1.60 (m, 4H), 1.86–1.91 (m, 2H), 3.81 (d, *J*=5.2 Hz, 1H), 3.90 (s, 3H), 4.37–4.42 (m, 1H), 7.19 (d, *J*=7.6 Hz, 1H), 7.35 (d, *J*=7.6 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H). Compound (**18b**) (R_S,*R*): ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, *J*=7.3 Hz, 3H), 1.17(s, 9H), 1.25–1.40 (m, 6H), 1.54–1.60 (m, 4H), 1.79–1.77 (m, 2H), 3.91 (s, 3H), 4.28–4.30 (m, 1H), 4.47 (d, *J*=7.8 Hz, 1H), 7.19 (d, *J*=7.6 Hz, 1H), 7.35 (d, *J*=7.6 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H). Compound (**18a**+**b**): ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 23.5 (CH_2), 25.7 (CH_3), 25.8 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 36.5 (CH_2), 37.3 (CH_2), 56.0 (C), 60.4 (CH), 60.5 (CH_2), 64.9 (CH_2), 111.9 (C), 126.7 (CH), 138.7 (CH), 138.9 (CH), 141.8 (C), 163.1 (C). MS (ES) $C_{20}H_{33}BrN_2O_3S$ requires: 460/462, found: 483/485 $(M+Na)^+$. HRMS (ESI) calcd for $C_{20}H_{33}BrN_2O_3S$+H: 461.1468, meas. 461.1485.

*4.3.3.7. (R)-N-((R)-1-(5-Bromo-1-methyl-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**19a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, *J*=7.3 Hz, 3H), 1.21 (s, 9H), 1.30–1.31 (m, 6H), 1.56–1.60 (m, 4H), 1.85–1.95 (m, 2H), 3.63 (s, 3H), 3.90 (s, 4H), 4.06 (d, *J*=6.8 Hz, 1H), 4.31–4.36 (m, 1H), 6.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.0 (CH_3), 22.7 (CH_2), 23.5 (CH_2), 25.7 (CH_3), 29.4 (CH_2), 29.7 (CH_2), 31.5 (CH_3), 36.0 (CH_2), 36.5 (CH_2), 52.6 (CH), 56.2 (C), 64.9 (CH_2), 104.1 (C), 111.9 (C), 127.6 (CH), 149.2 (C). MS (ES) $C_{19}H_{34}BrN_3O_3S$ requires: 463/465, found: 464/466 $(M+H)^+$. HRMS (ESI) calcd for $C_{19}H_{34}BrN_3O_3S$+H: 464.1577, meas. 464.1590.

*4.3.3.8. (R)-N-((S)-1-(5-Bromo-1-methyl-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**19b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, *J*=7.3 Hz, 3H), 1.17 (s, 9H), 1.25–1.40 (m, 6H), 1.56–1.60 (m, 4H), 2.01 (m, 1H), 2.15 (m, 1H), 3.60 (s, 3H), 3.63 (br s, 1H), 3.90 (s, 4H), 4.40–4.45 (m, 1H), 6.99 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.5 (CH_2), 23.6 (CH_2), 26.1 (CH_3), 29.6 (CH_2), 29.8 (CH_2), 31.4 (CH_3), 35.8 (CH_2), 36.5 (CH_2), 52.9 (CH), 56.3 (C), 64.9 (CH_2), 103.8 (C), 111.9 (C), 128.1 (CH), 148.3 (C). MS (ES) $C_{19}H_{34}BrN_3O_3S$ requires: 463/465, found: 464/466 $(M+H)^+$. HRMS (ESI) calcd for $C_{19}H_{34}BrN_3O_3S$+H: 464.1577, meas. 464.1588.

*4.3.3.9. (R)-N-((R)-1-(4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**20a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=−0.02 (s, 9H), 0.83–0.94 (m, 5H), 1.18 (s, 9H), 1.21–1.37 (m, 6H), 1.51–1.62 (m, 4H), 1.85–1.95 (m, 2H), 3.45 (t, *J*=7.8 Hz, 2H), 3.88 (s, 4H), 3.90 (br s, 1H), 4.36–4.42 (m, 1H), 5.09 (d, *J*=10.8 Hz, 1H), 5.51 (d, *J*=10.8 Hz, 1H), 6.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=−1.5 (CH_3), 8.0 (CH_3), 17.7 (CH_2), 22.6 (CH_2), 23.6 (CH_2), 25.9 (CH_3), 29.4 (CH_2), 29.7 (CH_2), 36.2 (CH_2), 36.5 (CH_2), 52.2 (CH), 56.2 (C), 64.9 (CH_2), 66.6 (CH_2), 75.1 (CH_2), 111.9 (C), 114.2 (C), 118.9 (CH), 149.5 (C). MS (ES) $C_{24}H_{46}BrN_3O_4SSi$ requires: 579/581, found: 580/582 $(M+H)^+$. HRMS (ESI) calcd for $C_{24}H_{46}BrN_3O_4SSi$+H: 580.2234, meas. 580.2250.

*4.3.3.10. (R)-N-((S)-1-(4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**20b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.00 (s,

9H), 0.83–0.95 (m, 5H), 1.15 (s, 9H), 1.19–1.36 (m, 6H), 1.51–1.65 (m, 4H), 1.99–2.02 (m, 1H), 2.10–2.13 (m, 1H), 3.49 (t, J=7.8 Hz, 2H), 3.83 (m, 1H), 3.90 (s, 4H), 4.46–4.52 (m, 1H), 5.12 (d, J=10.8 Hz, 1H), 5.40 (d, J=10.8 Hz, 1H), 6.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=−1.5 (CH_3), 8.0 (CH_3), 17.7 (CH_2), 22.4 (CH_2), 23.5 (CH_2), 26.1 (CH_3), 29.5 (CH_2), 29.8 (CH_2), 36.3 (CH_2), 36.5 (CH_2), 51.6 (CH), 56.3 (C), 64.9 (CH_2), 66.6 (CH_2), 74.9 (CH_2), 111.9 (C), 114.4 (C), 118.8 (CH), 148.7 (C). MS (ES) $C_{24}H_{46}BrN_3O_4SSi$ requires: 579/581, found: 580/582 $(M+H)^+$. HRMS (ESI) calcd for $C_{24}H_{46}BrN_3O_4SSi$+H: 580.2234, meas. 580.2251.

*4.3.3.11. (R)-N-((R)-1-(5-Bromo-1-methyl-1H-pyrrol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**17a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (t, J=7.3 Hz, 3H), 1.19 (s, 9H), 1.31–1.50 (m, 6H), 1.57–1.61 (m, 4H), 1.89–1.91 (m, 2H), 3.22 (d, J=3.3 Hz, 1H), 3.61 (s, 3H), 3.92 (s, 4H), 4.32–4.36 (m, 1H), 6.09 (d, J=3.8 Hz, 1H), 6.11 (d, J=3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.6 (CH_2), 23.6 (CH_2), 26.2 (CH_3), 29.7 (CH_2), 29.8 (CH_2), 32.4 (CH_3), 35.6 (CH_2), 36.6 (CH_2), 52.1 (CH), 55.7 (C), 64.9 (CH_2), 107.8 (CH), 109.5 (C), 110.7 (CH), 111.9 (C), 133.6 (C). MS (ES) $C_{20}H_{35}BrN_2O_3S$ requires: 462/464, found: 485/487 $(M+Na)^+$.

*4.3.3.12. (R)-N-((S)-1-(5-Bromo-1-methyl-1H-pyrrol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**17b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (t, J=7.6 Hz, 3H), 1.18 (s, 9H), 1.30–1.52 (m, 6H), 1.57–1.61 (m, 4H), 1.90–1.94 (m, 2H), 3.22 (d, J=6.0 Hz, 1H), 3.56 (s, 3H), 3.91 (s, 4H), 4.34–4.36 (m, 1H), 6.05 (d, J=3.8 Hz, 1H), 6.13 (d, J=3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.6 (CH_2), 23.5 (CH_2), 26.5 (CH_3), 29.6 (CH_2), 29.8 (CH_2), 32.6 (CH_3), 35.2 (CH_2), 36.7 (CH_2), 53.5 (CH), 55.8 (C), 64.9(CH_2), 108.1 (CH), 109.5 (C), 110.6 (CH), 111.9 (C), 132.9 (C). MS (ES) $C_{20}H_{35}BrN_2O_3S$ requires: 462/464, found: 485/487 $(M+Na)^+$.

4.4. Suzuki–Miyaura cross-coupling

4.4.1. General procedure. A solution of naphthyl boronic acid (1.15 mmol; 1.5 equiv) in 1-BuOH (8 ml) was degassed with Ar for 15 min, then $Pd(OAc)_2$ (0.076 mmol; 0.1 equiv) and *S*-Phos (0.19 mmol; 0.25 equiv) were added and the mixture was degassed for additional 10 min. A second solution of bromo-heterocyclic intermediates (**8**, **16b**, **18**, **20b**, 0.76 mmol; 1.0 equiv) in 1-BuOH (8 ml) was degassed with Ar for 15 min and added to the solution of naphthyl boronic acid and Pd catalyst, followed by the addition K_3PO_4 (1.9 mmol; 2.5 equiv). The mixture was stirred and heated to 75 °C for 4 h. The reaction was quenched with H_2O (20 ml), extracted with EtOAc (2×20 ml), dried over Na_2SO_4, filtered, concentrated to dryness under reduced pressure. The residue was purified by gradient column chromatography (silica; petroleum ether/EtOAc; 0–80% of EtOAc in petroleum ether, linear gradient) to obtain products (**22**–**25**) as colourless oils.

4.4.2. Products of Suzuki couplings.

*4.4.2.1. (R)-N-((S)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-(5-(naphthalen-2-yl)thiophen-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**22**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (t, J=7.3 Hz, 3H), 1.23 (s, 9H), 1.34–1.40 (m, 6H), 1.57–1.63 (m, 4H), 1.89–1.90 (m, 2H), 3.47 (br s, 1H), 3.90 (s, 4H), 4.65–4.69 (m, 1H), 6.99 (d, J=3.5 Hz, 1H), 6.27 (d, J=3.5 Hz, 1H), 7.43–7.50 (m, 2H), 7.70–7.72 (m, 1H), 7.80–7.84 (m, 3H), 8.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 22.6 (CH_2), 23.6 (CH_2), 25.8 (CH_3), 29.5 (CH_2), 29.8 (CH_2), 36.5 (CH_2), 39.2 (CH_2), 55.5 (CH), 55.7 (C), 64.9 (CH_2), 111.9 (C), 122.7 (CH), 123.9 (CH), 124.0 (CH), 125.9 (CH), 126.5 (CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 131.8 (C), 132.7 (C), 133.6 (C), 143.9 (C), 146.0 (C). MS (ES) $C_{29}H_{39}NO_3S_2$ requires: 513, found: 514 $(M+H)^+$. HRMS (ESI) calcd for $C_{29}H_{39}NO_3S_2$+H: 514.2444, meas. 514.2458.

*4.4.2.2. (R)-N-((S)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-(5-(naphthalen-2-yl)furan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**23**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, J=7.3 Hz, 3H), 1.24 (s, 9H), 1.30–1.40 (m, 6H), 1.56–1.61 (m, 4H), 1.97–1.99 (m, 2H), 3.48 (d, J=6.3 Hz, 1H), 3.90 (s, 4H), 4.43–4.48 (m, 1H), 6.41 (d, J=3.3 Hz, 1H), 6.69 (d, J=3.3 Hz, 1H), 7.41–7.49 (m, 2H), 7.72–7.74 (m, 1H), 7.79–7.87 (m, 3H), 8.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3) 22.6 (CH_2), 23.6 (CH_2), 25.8 (CH_3), 29.6 (CH_2), 29.8 (CH_2), 34.7 (CH_2), 36.6 (CH_2), 54.0 (CH), 56.1 (C), 64.9 (CH_2), 106.3 (CH), 109.3 (CH), 111.9 (C), 121.9 (CH), 122.2 (CH), 125.8 (CH), 126.4 (CH), 127.7 (CH), 128.0 (CH), 128.1 (C), 128.3 (CH), 132.6 (C), 133.5 (C), 153.4 (C), 155.1(C). MS (ES) $C_{29}H_{39}NO_4S$ requires: 497, found: 498 $(M+H)^+$. HRMS (ESI) calcd for $C_{29}H_{39}NO_4S$+H: 498.2673, meas. 498.2696.

*4.4.2.3. (R)-N-(6-(2-Ethyl-1,3-dioxolan-2-yl)-1-(6-(naphthalen-2-yl)pyridin-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**24**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.90 (t, J=7.3 Hz, 3H), 1.19 (s, 9H), 1.20–1.40 (m, 6H), 1.55–1.58 (m, 4H), 2.01–2.03 (m, 2H), 3.87 (s, 4H), 4.26 (d, J=6.5 Hz, 1H), 4.50–4.55 (m, 1H), 7.18 (d, J=7.1 Hz, 1H), 7.50–7.51 (m, 2H), 7.72–7.79 (m, 2H), 7.86–7.88 (m, 1H), 7.92–7.95 (m, 1H), 8.16–8.19 (m, 1H), 8.49 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=8.0 (CH_3), 22.5 (CH_2), 23.6 (CH_2), 25.8 (CH_3), 29.4 (CH_2), 29.8 (CH_2), 36.6 (CH_2), 38.1 (CH_2), 56.0 (C), 61.1 (CH), 64.9 (CH_2), 112.0 (C), 119.1 (CH), 120.2 (CH), 124.5 (CH), 126.3 (CH), 126.5 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 128.7 (CH), 132.5 (C), 133.7 (C), 136.5 (C), 137.1 (CH), 156.5 (C), 161.1 (C). MS (ES) $C_{30}H_{40}N_2O_3S$ requires: 508, found: 509 $(M+H)^+$. HRMS (ESI) calcd for $C_{30}H_{40}N_2O_3S$+H: 509.2832, meas. 509.2836.

*4.4.2.4. (R)-N-[(1S)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-(4-(2-naphthyl)-1-{[2-(trimethylsilyl)-ethoxy]methyl}-1H-imidazol-2-yl)hexyl]-2-methylpropane-2-sulfinamide (**25**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.00 (s, 9H), 0.85–0.94 (m, 5H), 1.17 (s, 9H), 1.22–1.46 (m, 6H), 1.57–1.70 (m, 4H), 2.09 (m, 1H), 2.25 (m, 1H), 3.55 (t, J=8.1 Hz, 2H), 3.87 (s, 4H), 4.05–4.15 (m, 1H), 4.60–4.70 (m, 1H), 5.24 (d, J=10.8 Hz, 1H), 5.44 (d, J=10.8 Hz, 1H), 7.29 (s, 1H), 7.37–7.47 (m, 2H), 7.76–7.88 (m, 4H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=0.0 (CH_3), 9.5 (CH_3), 19.2 (CH_2), 23.9 (CH_2), 25.0 (CH_3), 27.7 (CH_2), 31.1 (CH_2), 31.2 (CH_2), 37.9 (CH_2), 38.0 (CH_2), 55.8 (C), 57.7 (CH), 66.3 (CH_2), 67.9 (CH_2), 76.5 (CH_2), 112.0 (C), 113.4 (CH), 117.5 (CH), 124.6 (CH), 125.1 (C), 126.8 (CH), 127.5 (CH), 129.0 (CH), 129.4 (CH), 129.5 (CH), 132.7 (C), 134.0 (C), 135.2 (C), 150.1 (C). MS (ES) $C_{34}H_{53}N_3O_4SSi$ requires: 627, found: 628 $(M+H)^+$. HRMS (ESI) calcd for $C_{34}H_{53}N_3O_4SSi$+H: 628.3599, meas. 628.3615.

4.5. HDAC inhibitor

*4.5.1. (S)-2-(5-Methoxy-2-methyl-1H-indol-3-yl)-N-(1-(5-(naphthalen-2-yl)thiophen-2-yl)-7-oxononyl)acetamide (**26**).* Compound **22** (0.165 mmol) was stirred for 45 min in HCl/MeOH (1.25 M, 1 ml). The reaction was quenched with 1 N NaOH (2 ml) and the mixture was extracted with EtOAc (2×10 ml). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude amino-ketone was dissolved in dry DMF (2 ml) and a solution of (5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (0.197 mmol; 1.2 equiv), ECDI (0.213 mmol; 1.3 equiv) and HOBt (0.213 mmol; 1.3 equiv) in DMF (2 mL, preactivation for 45 min) was added, together with *i*-Pr_2NEt (0.394 mmol; 2.4 equiv). The mixture was stirred for 18 h and diluted with EtOAc (20 ml), washed with satd aq $NaHCO_3$ (2×20 ml), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude product was isolated by preparative RP-HPLC, using water/acetonitrile (0.1% TFA) as eluents. The pooled product fractions were lyophilized to obtain the searched product (**26**) as an amorphous material.

^{1}H NMR (400 MHz, $CDCl_3$) δ=0.90 (t, J=7.3 Hz, 3H), 1.22–1.39 (m, 6H), 1.79–1.83 (m, 2H), 2.30–2.40 (m, 7H), 3.47 (s, 2H), 3.70 (s, 3H),

5.01–5.03 (m, 1H), 6.60 (dd, J_1=8.5 Hz, J_2=2.3 Hz, 1H), 6.96 (d, J=3.5 Hz, 1H), 7.07–7.10 (m, 2H), 7.44–7.53 (m, 3H), 7.75 (dd, J_1=8.5 Hz, J_2=1.5 Hz, 1H), 7.88–7.95 (m, 3H), 8.03 (s, 1H), 8.43 (d, J=8.3 Hz, 1H), 10.58 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1 (CH_3), 12.0 (CH_3), 23.5 (CH_2), 26.0 (CH_2), 28.7 (CH_2), 31.2 (CH_2), 35.3 (CH_2), 36.2 (CH_2), 41.7 (CH_2), 48.5 (CH), 55.7 (CH_3), 100.9 (CH), 105.4 (C), 110.0 (CH), 111.1 (CH), 123.3 (CH), 124.1 (CH), 125.3 (CH), 126.4 (CH), 127.1 (CH), 127.2 (CH), 128.0 (CH), 128.3 (CH), 129.0 (C), 129.2 (CH), 130.5 (C), 131.8 (C), 132.6 (C), 134.2 (C), 148.5 (C), 152.7 (C), 153.4 (C), 170.8 (C), 211.3 (C). MS (ES) $C_{35}H_{38}N_2O_3S$ requires: 566, found: 567 $(M+H)^+$.

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Supplementary data

Full NMR data and analysis of the Mosher amide derivatives of intermediates **8** can be found as Supplementary data. Supplementary data associated with this article can be found at doi:10.1016/j.tet.2009.08.013.

References and notes

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