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SAR study of bicyclo[4.1.0]heptanes as melanin-concentrating hormone receptor R1 antagonists: Taming hERG

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Abstract—To improve the ex vivo potency of MCH inhibitor **1a** and to address its hERG liability, a structure–activity study was carried out, focusing on three regions of the lead structure. Introduction of new side chains with basic nitrogen improved in vitro and ex vivo bindings. Many potent compounds with $K_i < 10$ nM were discovered (compounds **6a–j**) and several compounds (**14–17**) had excellent ex vivo binding at 6 h and 24 h. Attenuating the basicity of nitrogen on the side chain, and in particular, introduction of a polar group such as aminomethyl on the distal phenyl ring significantly lowered the hERG activity. Further replacement of the distal phenyl group with heteroaryl groups in the cyclohexene series provided compounds such as **28l** with excellent ex vivo activity with much reduced hERG liability.

1. Introduction

The last decade witnessed a steady rise of the obese population worldwide. This has happened in developed countries as well as developing countries and the potential economic impact can be significant. As maintaining weight loss solely by lifestyle changes remains difficult and the use of currently available drugs is limited by their side effects, the search for new drugs for the treatment of obesity continues to be an area of intense interest around the globe. In recent years, the melanin-concentrating hormone (MCH) receptor has emerged as an important target for obesity.[1] MCH, a cyclic 19-amino acid neuropeptide responsible for color changes in fish skin,[2] is present in the brains of all vertebrate species examined so far and it appears to be involved in the regulation of food intake and energy balance based on the following observations: direct icv administration of MCH in rats results in increases in food intake in a dose dependent manner;[3] MCH mRNA is overexpressed in ob/ob mice and in fasted mice;[4a] MCH overexpressing mice are hyperphagic, mildly obese, hyperglycemic, and insulin resistant;[4b] MCH knockout mice are leaner than wild-type mice.[5] It is generally believed that the MCH receptor R1 mediates the orexigenic effects of MCH.[6,7] Many reports on MCH receptor R1 antagonists for the potential treatment of obesity have appeared in recent years,[8,9] including at least two compounds in clinical trials.[10,11] In a recent publication from Schering-Plough, compound **1a** was identified as a potent orally active MCH R1 antagonist that did not have the Ames liability of the biphenylaniline series from which it was derived.[12] This compound had good ex vivo binding but was also a potent blocker of the hERG channel, as shown by the Rb efflux assay.[13] In this paper, we describe our SAR exploration in this

Keywords: Melanin-concentrating hormone receptor R1 antagonist; Ex vivo activity; hERG; Parallel synthesis.
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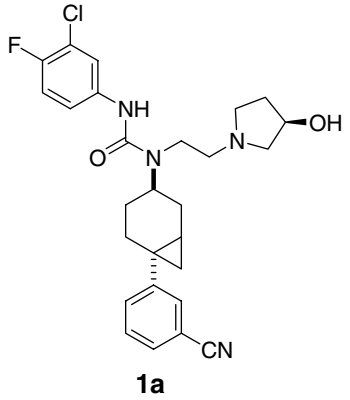
series and our discovery of several compounds with improved ex vivo binding and significantly diminished hERG liability.

2. Chemistry and results

Our SAR investigation on **1a** (Fig. 1) covered three regions of the molecule: the urea moiety, the side chain with basic nitrogen, and the distal phenyl ring. As shown in Scheme 1, a parallel synthesis approach was used to first modify the urea moiety. Compound **3** was synthesized from **2b**[12] via reductive amination. Subsequent treatment with an aryl isocyanate followed by resin cleanup afforded compounds **1a**–**p**.[14] A urea library of 1×70 dimensions was synthesized using this protocol and the SAR results are represented in Tables 1 and 3.[15] These data clearly suggested the following trends: (a) *N*-aryl ureas were more active than *N*-alkyl ones (compound **1b** vs **1l**);[15] (b) for mono-substitution on *N*-phenyl ring, 3- substitution was more active than 2- and 4-substitution (compound **1d** vs **1c**, **1f**), and electron withdrawing groups were more active than electron donating ones (compound **1d** vs **1e**); (c) disubstitution, particularly 3,4- and 3,5-disubstitution with electron withdrawing groups, was as active as the 3-substituted ones (compounds **1g** and **1h**). Other modifications in this region included replacing the urea moiety by amide, tertiary amine, and sulfonamide groups. All these modifications led to the loss of MCH R1 activity.[16]



1a

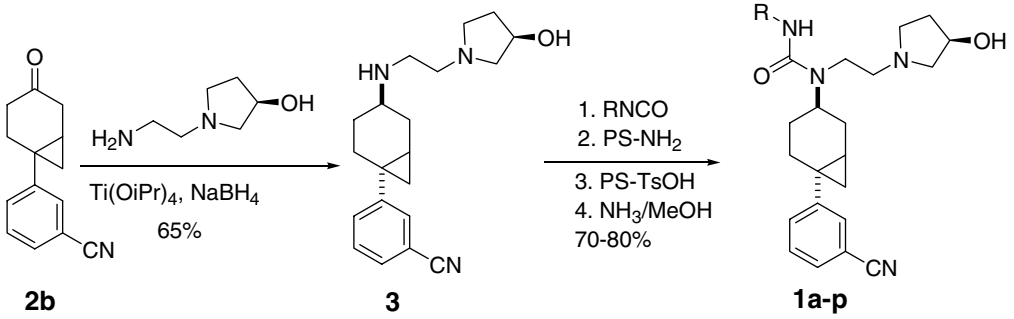
Figure 1.

Table 1. MCH R1 binding data for compounds **1a**–**p**

Compound	R	MCH R1 K_i (nM)
1b	Ph	132 ± 17
1c	2-FPh	1884 ± 232
1d	3-FPh	20 ± 2
1e	3-OMePh	373 ± 55
1f	4-FPh	54 ± 14
1g	3,5-F_2Ph	15 ± 2
1h	3,4-F_2Ph	20 ± 5
1i	3-F, 4-MePh	48 ± 8
1j	3,4-OCH_2OPh	134 ± 20
1k	3,5-Me_2Ph	539 ± 6
1l	Cyclohexyl	2213 ± 6

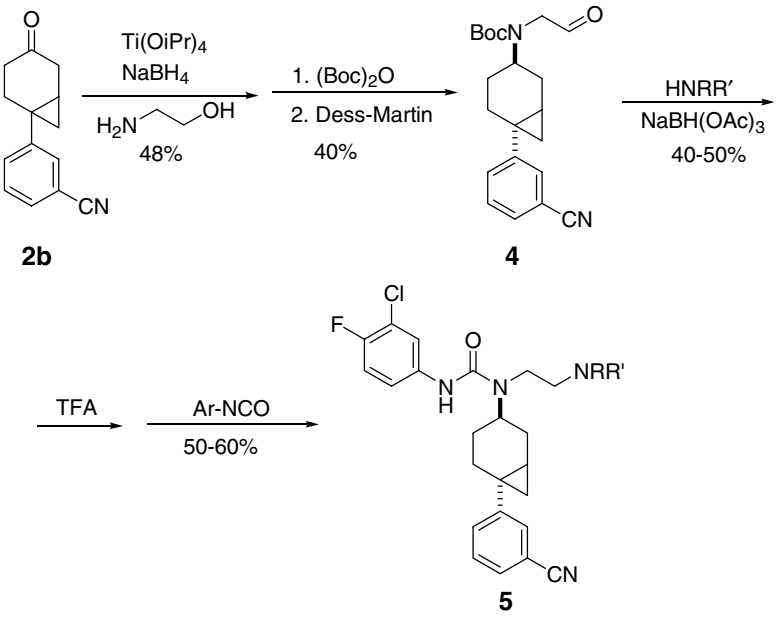
Scheme 2 outlines the synthesis of compounds for SAR exploration of the basic nitrogen side chain. Ketone **2b** was reacted with 1-hydroxyethylamine followed by Boc protection of the nitrogen atom and subsequent Dess–Martin oxidation to afford aldehyde **4**. N-Boc deprotection and urea formation provided the desired compounds represented in Table 2 (1×24 dimensions). These data indicate that a variety of amines were well tolerated for MCH R1 binding, including cyclic amines and non-cyclic amines. Among the cyclic amines, pyrrolidine, piperidine, and homopiperidine with substituents at various positions were essentially equally potent. The acyclic amine **6a** showed K_i 5 nM in the human receptor binding assay. In an effort to quickly determine the ability of a compound to reach the mouse brain and bind to the MCH R1 receptor at levels high enough to cause an effect, a mouse ex vivo assay was developed in house to directly measure MCH R1 receptor occupancy in brain sections of treated mice.[17] This assay obviates the need to radiolabel each individual compound and allows one to evaluate the correlation between the extent and duration of receptor occupancy with in vivo efficacy. Compound **6a** was found to be more potent in the mouse ex vivo assay (83% inhibition at 6 h, 30 mg/kg, po, Table 5) than compound **1a** (49% inhibition at 6 h). Compound **5d** also had strong binding in the ex vivo study (78% inhibition at 6 h).

The encouraging results of **6a** and **5d** prompted us to further explore the development of SAR around these leads. Based on their structural similarity, for simplicity of synthesis, we fixed the side chain as the one in **6a** and reinvestigated SAR in the urea region. A 1×65 urea library was assembled according to Scheme 3 and Table 3



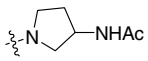
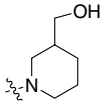
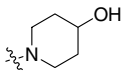
2b **3** **1a-p**

Scheme 1. Parallel synthesis of **1** with various ureas.



Scheme 2. Synthesis of compound **5**.

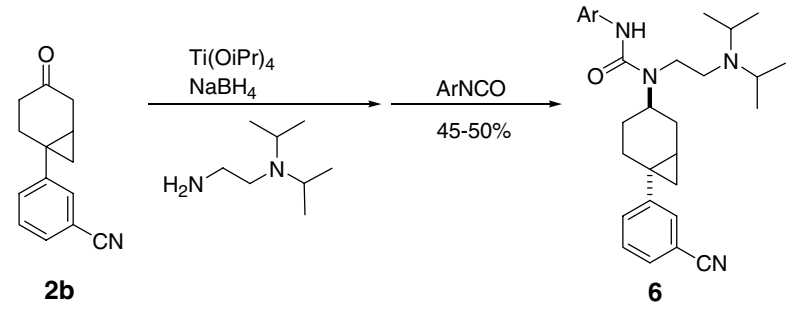
Table 2. MCH R1 binding data for compounds **5a–j** and **6a**

Compound	NRR′	MCH R1 K_i (nM)
5a		16 ± 2
5b		23 ± 6
5c		15 ± 3
5d		7 ± 0.9
5e		15 ± 3
5f		15 ± 2
5g		22 ± 2
5h		53 ± 10
5i		15 ± 1
5j		11 ± 2
6a		5 ± 1.6

shows some results with comparison to analog **1** which had (*R*)-3-hydroxyprrolidine on the side chain. These data confirmed our previous SAR observation that electron withdrawing groups at 3- and 4-positions were favored for MCH R1 activity. Many potent compounds with $K_i < 10$ nM were discovered in this library. In addition, it was found that the series of compounds **6a–j** were uniformly more active than their corresponding analogs from series **1**. These observations demonstrated the significance of *N*,*N*-diisopropyl group on the side chain and it was therefore decided to keep this basic nitrogen moiety unchanged while exploring SAR in the distal phenyl region.

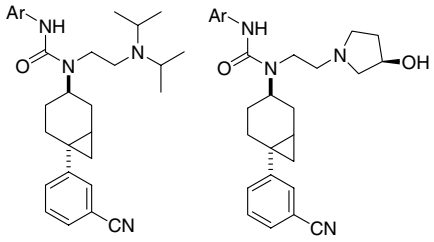
The synthetic route to compounds with different substituents on the distal phenyl ring is shown in Scheme 4. Based on the previous observation that a 3-CN group was critical for MCH R1 binding,[12] our investigation was concentrated on substitution at the 3-position. Indeed, Table 4 shows that a simple hydrogen at 3-position (compound **8a**) led to a 30-fold drop in MCH R1 binding. Analogs with methyl ester **8e** or alcohol **8f** were also much less potent. However, replacement of 3-CN with 3-Br (**8c**) or oxime (**8g**) provided compounds with good affinity for the MCH R1 receptor ($K_i < 10$ nM). In the mouse ex vivo study, the oxime **8g** showed 62% inhibition at 6 h, demonstrating for the first time in this series that a 3-CN group could be replaced while maintaining MCH R1 ex vivo activity.

Some ex vivo data of compounds with further modification on the side chain are shown in Table 5. As discussed before, compound **6a** showed 83% binding at 6 h. Replacing one of the *N*-isopropyl groups with various hydroxyalkyl groups did not affect their K_i's (compounds **9–11**). The use of *N*-fluoroethyl on the side chain resulted in similar binding (compound **12**). It was observed, however, that the use of 2,6-dichloropyridyl as an aryl group in the urea region consistently



Scheme 3. Parallel synthesis of compound **6**.

Table 3. Comparison of MCH binding between **1a**–**p** and **6a**–**j**



Ar	Compound	MCH R1 K_i (nM)	Compound	MCH R1 K_i (nM)
4-F, 3-ClPh	**6a**	5 ± 1.6	**1a**	9 ± 2
3-NO_2Ph	**6b**	2.7 ± 0.3	**1m**	60 ± 2
3-BrPh	**6c**	5.7 ± 1.9	**1n**	34 ± 0.5
3-FPh	**6d**	2.1 ± 0.7	**1d**	20 ± 2
3-ClPh	**6e**	6 ± 2.2	**1o**	27 ± 3
3-CNPh	**6f**	7.6 ± 1.6	**1p**	92 ± 10
3,5-F_2Ph	**6g**	4.5 ± 1.1	**1g**	15 ± 2
3,4-F_2Ph	**6h**	2.8 ± 1.2	**1h**	20 ± 5
4-FPh	**6i**	10.4 ± 3.8	**1f**	54 ± 14
2,6-Cl_2pyridyl	**6j**	2 ± 0.3		

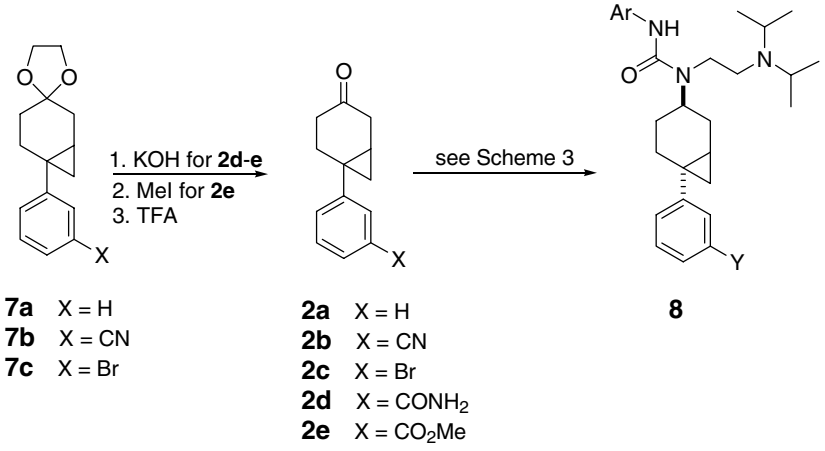
improved the ex vivo binding significantly. In one case (compound **15** vs **11**), the binding at 6 h was improved from 75% to 95%. Similar results were observed for compound **13** versus **6a**, **14** versus **9**, and **16** versus **12**. Among all the compounds tested, **16** showed almost full receptor occupancy at 24 h (99% at 6 h, 97% at 24 h).[18]

Table 4. MCH R1 binding data for compounds **8a**–**h**

Compound	R	Ar	MCH K_i (nM)
8a	H	3,4-F_2Ph	92 ± 5
6h	CN	3,4-F_2Ph	2.8 ± 1.2
8c	Br	3,4-F_2Ph	7.8 ± 3.1
8d	$CONH_2$	4-F, 3-ClPh	142 ± 12
8e	CO_2Me	3,4-F_2Ph	34 ± 2
8f	CH_2OH	4-F, 3-ClPh	48 ± 7
8g	CH=NOMe	4-F, 3-ClPh	4.1 ± 0.6
8h	CH=NOEt	4-F, 3-ClPh	29 ± 5

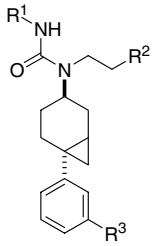
Compounds **17** and **18**, two of the possible metabolites of **16**, were also synthesized and both showed strong binding at 6 h. Additionally, the use of 2,5-disubstituted pyrrolidine such as compound **19** led to a drop in the ex vivo binding compared with prolinol **5d**. Once again, the preferred 2,6-dichloropyridyl urea moiety restored the ex vivo binding back to 82% at 6 h (compound **20**).

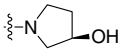
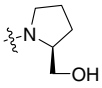
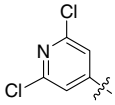
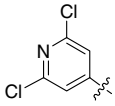
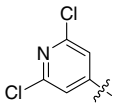
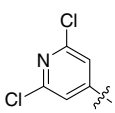
Although we were able to improve the ex vivo activities of these compounds, further studies and progression of them were not pursued due to their strong inhibition of hERG K^+ channel since blocking of the hERG K^+ channel could lead to prolonged QTc and potentially sudden cardiac death.[19] In the above SAR study it showed that in bicyclo[4.1.0]heptane series, the urea, the side chain, and the bicyclo[4.1.0]heptane moieties were essential for the MCH R1 antagonist activity. While deleting any one of these three moieties of this series could get rid of the hERG liability, it also depleted



Scheme 4. Synthesis of **8** with various substituents on the phenyl ring.

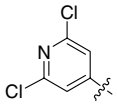
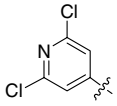
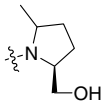
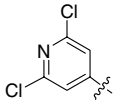
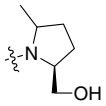
Table 5. MCH in vitro, ex vivo and hERG data for **6a** analogs

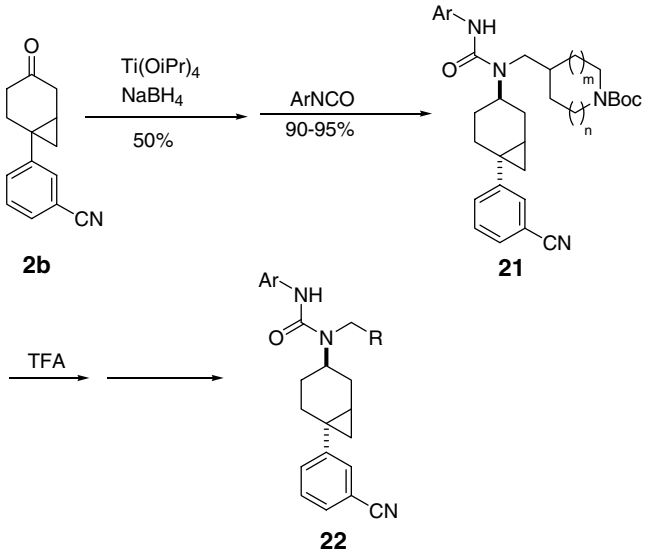


Compound	R^1	R^2	R^3	MCH K_i (nM)	Ex vivo % inh. at 6 h (30 mpk, po)	Ex vivo % inh. at 24 h	Rb % inh. at 5 μg/mL
1a	4-F, 3-ClPh		CN	9.2 ± 2.8	49 ± 2	NA	80
6a	4-F, 3-ClPh		CN	5.0 ± 1.6	83 ± 4	NA	78
5d	4-F, 3-ClPh		CN	7.0 ± 0.9	78 ± 7	NA	75
8g	4-F, 3-ClPh		CHNOMe	4.1 ± 0.6	62 ± 4	NA	76
9	4-F, 3-ClPh		CN	8.7 ± 0.6	73 ± 2	38 ± 2	88
10	4-F, 3-ClPh		CN	9.4 ± 1.3	73 ± 3	25 ± 2	NA
11	4-F, 3-ClPh		CN	5.2 ± 1.4	75 ± 2	35 ± 2	82
12	4-F, 3-ClPh		CN	12 ± 1	81 ± 5	66 ± 5	50
13			CN	2.4 ± 0.5	99 ± 4	58 ± 4	59
14			CN	1.6 ± 0.4	99 ± 3	NA	NA
15			CN	1.6 ± 0.2	99 ± 3	81 ± 3	60
16			CN	10 ± 3	99 ± 1	97 ± 1	50

(*continued on next page*)

Table 5 (*continued*)

Compound	R^1	R^2	R^3	MCH K_i (nM)	Ex vivo % inh. at 6 h (30 mpk, po)	Ex vivo % inh. at 24 h	Rb % inh. at 5 μg/mL
17			CN	1.9 ± 0.2	93 ± 2	70 ± 2	NA
18			CN	4.4 ± 0.7	89 ± 2	32 ± 2	84
19	4-F, 3-ClPh		CN	11 ± 2	31 ± 2	2 ± 2	78
20			CN	1.2 ± 0.1	82 ± 11	41 ± 11	60



Scheme 5. Synthesis of compound **22**.

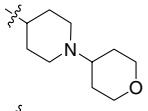
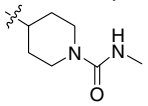
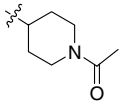
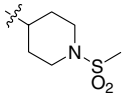
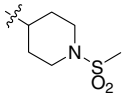
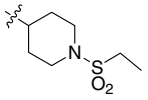
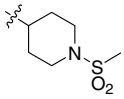
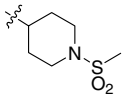
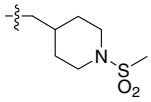
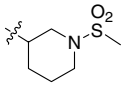
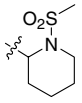
their MCH R1 activity (data not shown). Therefore, we decided to keep the skeleton of the series unchanged while exploring other peripheral changes to reduce the inhibition of hERG channel. One of our strategies was to decrease the basicity of the side-chain nitrogen. As shown in Scheme 5, a piperidine unit was installed in the side chain and several analogs were synthesized. The data (Table 6) suggested that introduction of urea and amide moieties at the piperidine nitrogen site could lead to decreased inhibition in the Rb efflux assay as well as decreased MCH R1 activity (compounds **22b** and **22c**). An exception was observed for compounds **22d** and **22e**, which had a methanesulfonamide moiety and maintained high MCH R1 affinity. Elongation to ethanesulfonamide **22f** led to a drop in MCH R1 activity (K_i 21 nM) and an increase in hERG activity. Other methanesulfonamides (compounds **22g** and **22h**) were also synthesized and demonstrated the similar trend. The position of the nitrogen on the piperidine was critical for MCH R1 binding as demonstrated by compounds **22j** and **22k**. Elongation of the side chain (compound **22i**) or replacing the piperidine ring with pyrrolidine (compound **22l**) resulted in 10-fold loss of MCH R1 binding.

Another strategy we pursued was to increase the polarity of our lead.[20] We had shown in Table 4 that replacing the 3-CN group on the distal phenyl maintained MCH R1 activity. However, all compounds in that table showed strong inhibition in the Rb efflux assay. The use of polar groups such as 3-hydroxymethyl (compound **8f**, Table 7) did slightly lower the hERG activity but its MCH R1 binding was also weaker. When primary amine **8i** or dimethylamine **8o** were introduced, they retained their MCH R1 activity. Importantly, they consistently showed much weaker hERG activity.

The combination of the above two strategies created compounds shown in Table 8. Indeed the hERG activity was further reduced to an acceptable level. To boost the ex vivo binding, 2,6-dichloropyridyl was introduced as the urea moiety. However, even though their MCH R1 bindings were excellent, their ex vivo bindings were disappointing. Selected compounds were tested in the CaCO-2 bidirectional assay and the results indicated that they were pgp substrates.[21]

Based on the observation that introduction of a polar group on the distal phenyl ring could significantly reduce hERG inhibition (compound **8i** versus **6a**), we decided to explore this region of the lead by replacing the distal phenyl group with more polar heterocycles, hoping that such modification could optimize the overall profile of the lead structure. To quickly get some SAR information, we decided to explore cyclohexene analogs **28** since Xu et al. demonstrated that aryl cyclohexenes closely mimicked bicyclo[4.1.0]heptanes in terms of MCH R1 activity.[12] Scheme 6 outlines the synthesis of these analogs. After reductive amination of **24** and Boc protection, the ketal group was cleaved using cerium chloride and a mixture of **25a/25b** was obtained.[22] After conversion of this mixture to the enol triflate **26a/26b**, compound **26b** was isolated and further

Table 6. MCH R1 in vitro, hERG data for compound **22**

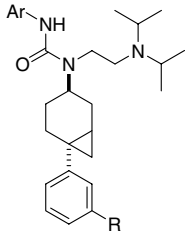
Compound	Ar	R	MCH K_i (nM)	Rb % inh. at 5 μg/mL	Rb % inh. at 1.5 μg/mL
22a	4-F, 3-ClPh		8.7 ± 0.8	91	75
22b	4-F, 3-CF_3Ph		181 ± 2	18	14
22c	4-F, 3-ClPh		312 ± 29	37	32
22d	4-F, 3-ClPh		7.2 ± 1	24	6
22e	3,4-F_2Ph		5.4 ± 1.1	34	15
22f	3,4-F_2Ph		21 ± 2	59	25
22g	4-F, 3-CF_3Ph		26 ± 4	−1	−1
22h	3-FPh		9.7 ± 1.5	47	25
22i	4-F, 3-CF_3Ph		80 ± 7	20	18
22j	4-F, 3-ClPh		211 ± 4	9	3
22k	4-F, 3-ClPh		295 ± 49	3	31
22l	4-F, 3-ClPh		559 ± 20	13	32

converted to urea **27**. The Suzuki coupling reaction provided the desired products **28** in good to excellent yields. Among 48 analogs that were synthesized, the furans **28d** and **28e** and thiophenes **28g–i** were very promising, especially **28i**, which showed excellent K_i and ex vivo binding, yet strong hERG activity. The reduction of the cyano group led to the primary amine **28j** with excellent K_i, a bit lower yet still significant ex vivo binding but much lower hERG activity. Based on these encouraging results, we further synthesized the thiazole derivatives **28k–n** to increase the polarity of this region. We were gratified to find that while **28n** had poor ex vivo binding at 6 h, its regioisomer **28l** did exhibit excellent ex vivo binding and much lower hERG activity. The strong ex vivo binding (75% at 24 h) came as a surprise since these compounds possess two basic nitrogen atoms.[23] This result indicated that it is possible for a molecule with two basic nitrogen atoms to cross the blood–brain barrier (BBB) at physiological pH. Overall, these results in Table 9 confirmed that replacing the distal phenyl ring with heterocycles did maintain MCH R1 activity and that increasing the polarity of the molecule in specific regions could decrease hERG activity significantly.

3. Summary

In summary, a systematic SAR study on three regions of lead **1** was carried out. Once the *N*,*N*-diisopropylethyelendiamine was discovered as an important side chain for MCH R1 activity, a re-examination of SAR in the urea

Table 7. MCH R1 in vitro, hERG data for compound **8**



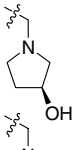
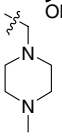
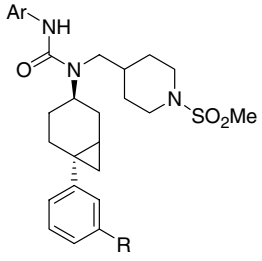
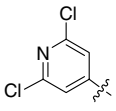
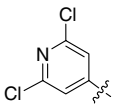
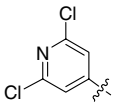
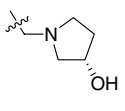
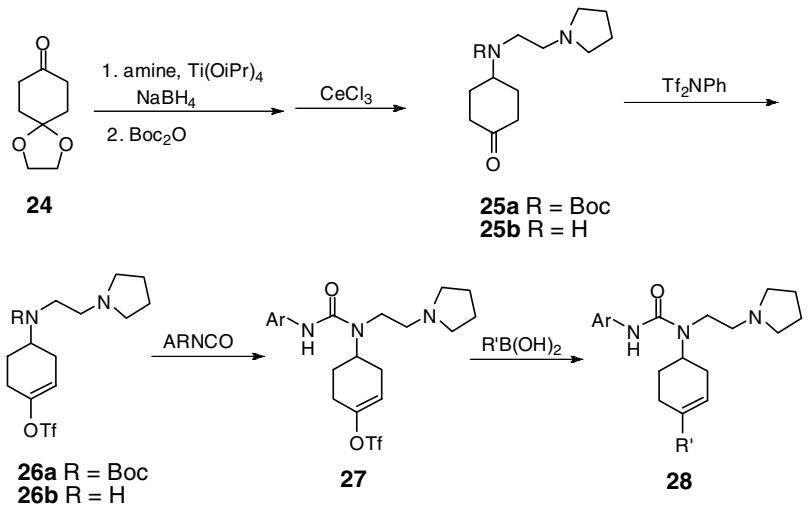
Compound	Ar	R	MCH K_i (nM)	Rb % inh. at 5 μg/mL	Rb % inh. at 1.5 μg/mL
6a	4-F, 3-ClPh	CN	5.0 ± 1.6	78	44
8e	3,4-F_2Ph	CO_2Me	34 ± 2	85	57
8f	4-F, 3-ClPh	CH_2OH	48 ± 7	67	43
8d	4-F, 3-ClPh	$CONH_2$	142 ± 12	44	21
8i	4-F, 3-ClPh	CH_2NH_2	2.3 ± 0.5	32	22
8j	4-F, 3-ClPh	CH_2NHSO_2Me	18 ± 3	46	17
8k	4-F, 3-ClPh	$CH_2NHCOMe$	31 ± 0.3	78	62
8l	4-F, 3-ClPh		21 ± 2	−1	−4
8m	4-F, 3-ClPh		54 ± 1	13	10
8n	4-F, 3-ClPh	CH_2NEt_2	46 ± 2	30	15
8o	4-F, 3-ClPh	CH_2NMe_2	13 ± 3	5	−1

Table 8. MCH R1 in vitro, ex vivo and hERG data for compounds **23**



Compound	Ar	R	MCH K_i (nM)	Rb % inh. at 5 μg/mL	Rb % inh. at 1.5 μg/mL	Ex vivo % at 6 h
23a	4-F, 3-ClPh	CH_2NH_2	9.9 ± 1.1	14	8	0 ± 5
23b	4-F, 3-ClPh	CH_2NMe_2	15 ± 1	8	7	26 ± 5
23c		CH_2NH_2	2.4 ± 0.2	3	−1	0 ± 4
23d		CH_2NMe_2	3.3 ± 0.6	7	8	0 ± 5
23e			8.9 ± 0.4	0	−7	1 ± 3
22d	4-F, 3-ClPh	CN	7.2 ± 1	24	6	0 ± 8



Scheme 6. Synthesis of compound **28**.

region was done and the results not only confirmed previous SAR but also led to many new compounds with $K_i < 10$ nM. A SAR study on the distal phenyl ring revealed that the 3-CN group could be replaced by other groups such as bromo or oxime. Further modification on the side chain resulted in compounds such as **16** with excellent ex vivo binding. Several different strategies were utilized to tackle the hERG issue of **1a** and other analogs. Our efforts to adjust the basicity of nitrogen on the side chain and to increase molecular polarity on the distal phenyl ring led to decreased hERG activity in many cases, with both compounds **8i** and **8o** showing excellent K_i's with a much improved hERG profile. Finally, these results prompted us to explore replacement of the distal phenyl ring with heterocycles and ultimately led to the discovery of new derivatives in the cyclohexene series such as **28j** and **28l** with reduced hERG liability.

4. Experimental

4.1. General methods

All reagents were used as received. ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-400 (400 MHz) instrument and are reported as ppm downfield from Me_4Si. LCMS analysis was performed on an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33 mm × 7 mm ID; gradient flow: 0 min—10% CH_3CN, 5 min—95% CH_3CN, 7 min—95% CH_3CN, 7.5 min—10% CH_3CN, 9 min—stop. Chromatography was performed with Selecto Scientific flash silica gel, 32–63 μM.

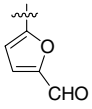
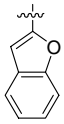
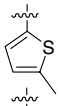
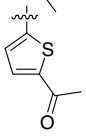
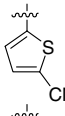
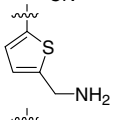
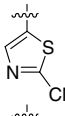
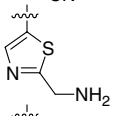
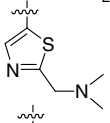
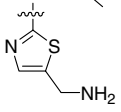
4.2. Biological assays

4.2.1. MCH R1 receptor binding assay. The K_i values of MCH receptor R1 antagonists were determined using a SPA-based radioligand binding assay. Membranes from CHO cells expressing MCH R1 (0.1 mg/mL) were incubated with SPA beads (1 mg/mL) in binding buffer (25 mM HEPES, 10 mM $MgCl_2$, 5 mM $MnCl_2$, and 0.1% BSA, pH 7.4) for 5 min on ice forming a bead/membrane mixture. The bead/membrane mixture was centrifuged (4 min at 300*g*) and resuspended in binding buffer. The bead/membrane mixture was then pelleted again (4 min at 300*g*), resuspended in binding buffer, and set aside. Binding buffer (50 μL/well) containing vehicle alone (2% DMSO), various compound concentrations, or 4 μM MCH (for non-specific binding) was added to a 96-well plate. Subsequently, 50 μL of binding buffer containing 0.5 nM ^{125}I-MCH was added to each well of the 96-well plate. Finally, 100 μL of the bead/membrane mixture was added to each well of the 96-well plate. The binding reaction mixture were incubated for 2–4 h at room temperature. Binding of ^{125}I-MCH to the bead/membrane mixture was detected using a TOPCOUNT (Packard). K_i values were determined using non-linear regression analysis. They are as mean values ± the range from two determinations, each performed in quadruplicate.

4.2.2. MCH R1 ex vivo assay. Animals were administered compounds via oral gavage and the brains were harvested and frozen at the indicated time point after dosing. Frontal sections from the caudate were placed on slides and incubated with radiolabeled [^{125}I]-S36057 (NEN) for 30 min. The sections were rinsed with binding buffer and dried, and radioactivity bound to the section was quantified using a Storm 860 phosphorimager. [^{125}I]-S36057 binding to the brain sections was specific to MCH binding sites, as addition of non-labeled MCH to the reaction completely abolished radiolabel binding.[24] Three mice were used for each time point for each compound.

4.2.3. Rubidium efflux assay. hERG-CHO cells were plated into 96-well flat-bottomed dishes and returned to the incubator for 24 h. On the day of study, culture medium was removed and replaced by 150 μL of a HEPES-buffered saline solution containing 5.4 mM RbCl (rubidium loading buffer), and the cells were then returned to the tissue culture incubator for 3 h to permit

Table 9. MCH R1 in vitro, ex vivo and hERG data for compound **28**

Compound	Ar	R′	MCH K_i (nM)	Rb % inh. at 5 μg/mL	Rb % inh. at 1.5 μg/mL	Ex vivo % inh. at 6 h	Ex vivo % inh. at 24 h
28a	4-F, 3-ClPh		147 ± 16	85			
28b	4-F, 3-ClPh		30 ± 1			16 ± 3	
28c	4-F, 3-ClPh		1969 ± 128				
28d	4-F, 3-ClPh		117 ± 10				
28e	4-F, 3-ClPh		51 ± 15	47			
28f	4-F, 3-ClPh		316 ± 0.6				
28g	4-F, 3-ClPh		85 ± 0.2	12			
28h	4-F, 3-ClPh		31 ± 7	43		59 ± 1	3 ± 1
28i	4-F, 3-ClPh		4.2 ± 0.1	74		84 ± 4	97 ± 4
28j	4-F, 3-ClPh		8.2 ± 0.4	26		77 ± 2	57 ± 2
28k	4-F, 3-ClPh		57 ± 0.5				
28l	4-F, 3-ClPh		13 ± 2	10		88 ± 1	75 ± 1
28m	4-F, 3-ClPh		648 ± 5				
28n	4-F, 3-ClPh		17 ± 0.5	14		37 ± 3	

rubidium-potassium exchange. Test compounds were prepared at a 4-fold final concentration in rubidium loading buffer containing 10% DMSO. Individual compounds were dispensed (50 μL) into wells on the cell plate, returned to the incubator, and allowed to equilibrate for 30 min at 37 °C. Cell plates were then washed three times with HEPES-buffered saline containing 5.4 mM KCl but no rubidium. After the final wash, cells were depolarized by the addition of 200 μL of HEPES-buffered saline containing 45.4 mM KCl. A 5-min depolarization was found to be adequate for efficient efflux of rubidium. Supernatants were collected and analyzed for

rubidium content using automated flame atomic absorbance spectroscopy (ICR-8000 spectrometer, Aurora Biosciences, Vancouver, BC, Canada). Percent inhibition was quantified based on a single window defined by vehicle (no block) and dofetilide (10 μM, full block) reference wells. Liquid handling for the rubidium efflux screen was implemented using a pipetting robot capable of making simultaneous additions and removals from 96 wells (Quadra 96, Tomtec, Hamden, CT).

4.3. General procedures for chemical synthesis

4.3.1. Synthesis of 3. 5.76 g of (*R*)-3-hydroxypyrrolidine (66.2 mmol, 1 equiv) was treated with iodoacetonitrile (11.50 g, 1.04 equiv), K_2CO_3 (27.60 g, 3 equiv) in 160 mL DCM and the mixture was stirred at rt for overnight. The crude was filtered through Celite and after removal of solvent, 9.7 g of brown oil was obtained. Part of this oil (8.5 g) was treated with $LiAlH_4$ (71 mL, 1 N in ethyl ether) in 100 mL THF at −30 °C under nitrogen. After gradually warming up to rt, the reaction was refluxed at 75 °C for 2.5 h. After cooling to rt, 2.7 mL of water, 8.1 mL of 15% NaOH, and 2.7 mL of water were added in sequence and the mixture was stirred for 30 min. The crude was filtered through Celite and washed with DCM, ether, and THF. After removal of solvent, 6.9 g of 2-(3*R*-hydroxypyrrolidin-1-yl)-ethylamine as yellow oil was obtained in 91% yield in two steps and used in the next reaction without further purification.

The ketone **2b**[12] (1.48 g, 7.01 mmol, 1 equiv), the above amine (1.37 g, 1.5 equiv), and $Ti(OiPr)_4$ (1.99 g, 1.0 equiv) in 20 mL DCM were stirred at rt for 3 h. The mixture was cooled to 0 °C and $NaBH_4$ (0.53 g, 2 equiv) was added. The reaction mixture was kept at this temperature for 4 h and MeOH was added to quench the reaction. The solvent was removed and 200 mL EtOAc was added. After washing with 10 mL of 1 N NaOH and removal of solvent, flash chromatography (5% MeOH in DCM + 1% NH_3 (2 N in MeOH)) provided the desired product **3** (1.38 g, 61% yield) along with 0.35 g of a mixture of ketone **2b** and the corresponding *cis*-alcohol. The use of other reducing agent such as $Na(OAc)_3BH$ gave a mixture of *cis*- and *trans*-isomers.

Compound **3**: ^1H NMR ($CDCl_3$): δ 0.79 (m, 1H) 0.98 (m, 1H) 1.00 (m, 1H) 1.20–1.35 (m, 2H) 1.60 (m, 2H) 1.90 (m, 1H) 2.10–2.35 (m, 4H) 2.40–2.50 (m, 2H) 2.50–2.78 (m, 5H) 2.82 (m, 1H) 4.30 (m, 1H) 7.30–7.58 (m, 4H).

MS for (MH^+) $C_{20}H_{28}N_3O$: 326.

4.3.2. Synthesis of 1. Compound **3** (10 mg) in 1 mL DCM was treated with 1.1 equiv of isocyanate and stirred at rt. Once the starting material was consumed (15–30 min), 2 equiv of resin-bound trisamine was added and stirred for 2 h. After filtration, the solution was treated with 10–20 equiv of resin-bound *p*-toluenesulfonic acid in MeOH for overnight. The final product was released from this resin by stirring with 2 N NH_3 in MeOH for 1 h twice and dried. For characterization of **1a**, see Ref. 12.

Compound **1b**: MS for (MH^+) $C_{27}H_{33}N_4O_2$: 445.

Compound **1c**: MS for (MH^+) $C_{27}H_{32}FN_4O_2$: 463.

Compound **1d**: MS for (MH^+) $C_{27}H_{32}FN_4O_2$: 463.

Compound **1e**: MS for (MH^+) $C_{28}H_{35}N_4O_3$: 475.

Compound **1f**: MS for (MH^+) $C_{27}H_{32}FN_4O_2$: 463.

Compound **1g**: MS for (MH^+) $C_{27}H_{31}F_2N_4O_2$: 481.

Compound **1h**: MS for (MH^+) $C_{27}H_{31}F_2N_4O_2$: 481.

Compound **1i**: MS for (MH^+) $C_{28}H_{34}FN_4O_2$: 477.

Compound **1j**: MS for (MH^+) $C_{28}H_{33}N_4O_4$: 489.

Compound **1k**: MS for (MH^+) $C_{29}H_{37}N_4O_2$: 473.

Compound **1l**: MS for (MH^+) $C_{27}H_{39}N_4O_2$: 451.

Compound **1m**: MS for (MH^+) $C_{27}H_{32}N_5O_4$: 490.

Compound **1n**: MS for (MH^+) $C_{27}H_{32}BrN_4O_2$: 523, 525.

Compound **1o**: MS for (MH^+) $C_{27}H_{32}ClN_4O_2$: 479.

Compound **1p**: MS for (MH^+) $C_{29}H_{32}N_5O_2$: 470.

4.3.3. Synthesis of 4. The ketone **2b** (0.97 g, 4.60 mmol, 1 equiv), hydroxyethylamine (0.308 g, 1.1 equiv), and $Ti(OiPr)_4$ (1.44 g, 1.1 equiv) in 20 mL DCM were stirred under nitrogen at rt for overnight. The mixture was cooled to 0 °C and $NaBH_4$ (0.16 g, 1 equiv) was added. The reaction mixture was kept at this temperature for 30 min and then warmed up to rt for 4 h. Five millimeters of MeOH was added to quench the reaction. The solvent was removed and 200 mL EtOAc was added. After washing with 10 mL 1 N of NaOH and removal of solvent, flash chromatography (5% MeOH in DCM + 1% NH_3 (2 N in MeOH)) provided the desired product (0.56 g, 48% yield). The amine was treated with Boc_2O (0.63 g, 1.3 equiv), Na_2CO_3 (0.35 g, 1.5 equiv) in a mixture of 17 mL THF and 17 mL of water. After stirring at rt for 1.5 h, the solvent was removed and the crude was extracted with EtOAc. Purification by flash chromatography (5% MeOH in DCM + 1% NH_3) provided the desired product (0.79 g, 100% yield). ^1H NMR ($CDCl_3$): δ 0.88 (m, 1H) 0.99 (m, 1H) 1.30 (m, 2H) 1.40 (s, 9H) 1.60–1.70 (m, 3H) 2.00 (m, 1H) 2.30 (m, 2H) 3.30 (br, 2H) 3.70 (m, 2H) 7.30–7.50 (m, 4H). MS for (MH^+) $C_{21}H_{29}N_2O_3$: 357.

Dess–Martin oxidation of this Boc-protected amino alcohol was done by treating the above alcohol (2.0 g, 5.62 mmol) with 2.86 g of Dess–Martin reagent (1.2 equiv) in 30 mL DCM at rt for 3 h. The solvent was removed and EtOAc was added. After washing with saturated Na_2CO_3 solution and filtration through Celite,

the solvent was removed followed by purification by flash chromatography (25% EtOAc/hexane). The desired product **4** was isolated in 70% yield (1.40 g). ^{1}H NMR ($CDCl_3$): δ 0.90 (m, 1H) 0.99 (m, 1H) 1.30 (m, 1H) 1.40 (s, 9H) 1.40–1.60 (m, 3H) 2.10 (m, 1H) 2.30 (m, 2H) 3.80 (m, 2H) 4.20 (m, 1H) 7.30–7.60 (m, 4H) 9.70 (s, 1H). MS for (MH^+) $C_{21}H_{27}N_2O_3$: 355.

4.3.4. Synthesis of 5. A general procedure as follows: the aldehyde **4** was treated with 2 equiv of amine and 2 equiv of $Na(OAc)_3BH$ in DCE at rt for overnight. After quenching the reaction with MeOH, the product was purified by flash chromatography. The desired product was treated with TFA (50% in DCM) for 12 h. After removal of solvent, EtOAc was added and the solution was washed with 1 N NaOH. The free base was then treated with 1.1 equiv of 3-chloro-4-fluorobenzonitrile in DCM at rt for 2 h. The workup procedure follows that for the synthesis of **1**.

Compound **5a**: MS for (MH^+) $C_{28}H_{33}ClFN_4O$: 496.

Compound **5b**: MS for (MH^+) $C_{29}H_{34}ClFN_5O_2$: 539.

Compound **5c**: MS for (MH^+) $C_{28}H_{33}ClFN_4O_2$: 512.

Compound **5d**: MS for (MH^+) $C_{28}H_{33}ClFN_4O_2$: 512.

Compound **5e**: MS for (MH^+) $C_{29}H_{35}ClFN_4O$: 510.

Compound **5f**: MS for (MH^+) $C_{29}H_{35}ClFN_4O_2$: 526.

Compound **5g**: MS for (MH^+) $C_{28}H_{33}ClFN_4O_2$: 512.

Compound **5h**: MS for (MH^+) $C_{27}H_{31}ClFN_4O_2$: 498.

Compound **5i**: MS for (MH^+) $C_{29}H_{35}ClFN_4O$: 510.

Compound **5j**: MS for (MH^+) $C_{27}H_{33}ClFN_4O_2$: 500.

Compound **6a**: ^{1}H NMR ($CDCl_3$): δ 0.79 (m, 1H) 1.00 (m, 1H) 1.10 (d, 12H, J = 7.5 Hz) 1.30 (m, 1H) 1.40 (m, 1H) 2.10 (m, 1H) 2.25 (m, 1H) 2.40 (m, 1H) 2.70 (br, 2H) 3.10 (m, 2H) 3.30 (m, 2H) 6.99 (t, 1H, J = 8.8 Hz) 7.10 (m, 1H) 7.30–7.80 (m, 5H) 10.80 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 18.11, 18.59, 20.35, 24.78, 25.52, 27.78, 31.54, 45.80, 48.62, 50.66, 52.32, 112.20, 116.21, 118.79, 119.06, 120.66, 121.48, 129.03, 129.43, 131.26, 132.23, 137.01, 149.07, 154.44, 157.58.

LCMS: rt = 5.29 min. Purity: 98.0%. MS for (MH^+) $C_{29}H_{37}ClFN_4O$: 511.3. HRMS: Calcd 511.2640. Found: 511.2656.

Compound **6b**: MS for (MH^+) $C_{29}H_{38}N_5O_3$: 505.

Compound **6c**: MS for (MH^+) $C_{29}H_{38}BrN_4O$: 539, 537.

Compound **6d**: MS for (MH^+) $C_{29}H_{38}FN_4O$: 477.

Compound **6e**: MS for (MH^+) $C_{29}H_{38}ClN_4O$: 493.

Compound **6f**: MS for (MH^+) $C_{30}H_{38}N_5O$: 485.

Compound **6g**: MS for (MH^+) $C_{29}H_{37}F_2N_4O$: 495.

Compound **6h**: MS for (MH^+) $C_{29}H_{37}F_2N_4O$: 495.

Compound **6i**: MS for (MH^+) $C_{29}H_{38}FN_4O$: 477.

Compound **6j**: MS for (MH^+) $C_{28}H_{36}Cl_2N_5O$: 529.

4.3.5. Synthesis of 7a. Compound **7a** was synthesized according to Ref. 12.

^{1}H NMR ($CDCl_3$): δ 0.78 (m, 1H) 1.00 (m, 1H) 1.20 (m, 1H) 1.42 (m, 1H) 1.63 (m, 1H) 1.80 (db, 1H, J = 13.5 Hz) 2.10–2.28 (m, 3H) 3.90–4.00 (m, 4H) 7.10 (m, 1H) 7.20 (m, 4H).

MS for (MH^+) $C_{15}H_{19}O_2$: 231.

Compound **7b** was synthesized according to Ref. 12.

Compound **7c** was synthesized according to Ref. 12.

^{1}H NMR ($CDCl_3$): δ 0.78 (m, 1H) 1.00 (m, 1H) 1.20 (m, 1H) 1.42 (m, 1H) 1.60 (m, 1H) 1.80 (db, 1H, J = 13.5 Hz) 2.10–2.30 (m, 3H) 3.90–4.00 (m, 4H) 7.10 (m, 1H) 7.20 (m, 2H) 7.41 (s, 1H).

MS for (MH^+) $C_{15}H_{18}BrO_2$: 309, 311.

4.3.6. Synthesis of 2e. Compound **7b** (19 g, 74.5 mmol) was treated with KOH (60 g), EtOH (180 mL), and water (120 mL), and the mixture was heated to 100 °C for 36 h. The crude was cooled to rt and most of the solvent removed. EtOAc was added and 2 N HCl was added to adjust the pH to 1. After extraction with EtOAc 3× 200 mL and removal of the solvent, the crude was treated with 60 g of K_2CO_3, 50 mL MeI, and 200 mL acetone at 66 °C for 6 h. The solution was filtered and solvent was removed. This crude was treated with 15 mL of concentrated HCl, 150 mL of acetone, and 30 mL of water at rt for overnight. Removal of solvent, extraction with EtOAc followed by flash chromatography (25% EtOAc/hexane) gave 12 g of the desired product **2e** in 66% yield.

^{1}H NMR ($CDCl_3$): δ 1.05 (m, 1H) 1.13 (m, 1H) 1.50 (m, 1H) 2.20 (m, 2H) 2.40 (m, 2H) 2.70 (m, 1H) 2.85 (m, 1H) 3.90 (s, 3H) 7.39 (m, 1H) 7.54 (d, 1H, J = 7.8 Hz) 7.88 (d, 1H, J = 7.9 Hz) 7.98 (s, 1H).

MS for (MH^+) $C_{15}H_{17}O_3$: 245.

Compound **2a**: ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 1H) 1.10 (m, 1H) 1.50 (m, 1H) 2.25 (m, 2H) 2.44 (m, 2H) 2.70 (m, 1H) 2.88 (m, 1H) 7.20 (m, 1H) 7.22 (m, 4H).

MS for (MH^+) $C_{13}H_{15}O$: 187.2.

Compound **2c**: ^{1}H NMR ($CDCl_3$): δ 1.00 (m, 2H) 1.10 (m, 1H) 1.42 (m, 1H) 2.20 (m, 2H) 2.40 (m, 2H) 2.61 (m, 1H) 2.80 (m, 1H) 7.20 (m, 3H) 7.30 (m, 1H).

MS for (MH^+) $C_{13}H_{14}BrO$: 265, 267.

Compound **2d**: Compound **2b** (8.09 g, 38.34 mmol) was treated with KOH (4.3 g, 2 equiv) in 150 mL EtOH and the mixture was heated to 80 °C for 14 h. The crude was cooled to rt and most of the solvent removed. Water (30 mL), EtOAc were added and HCl (5 N) was added to adjust pH to 2. After extraction with EtOAc 3× 200 mL, removal of the solvent, the organic layer was dried with Na_2SO_4. Removal of solvent gave 6.4 g of the desired product **2d** in 66% yield as brownish syrup (73% yield).

^1H NMR ($CDCl_3$): δ 1.00–1.10 (m, 2H) 1.50 (m, 1H) 2.20 (m, 2H) 2.40 (m, 2H) 2.64 (m, 1H) 2.80 (m, 1H) 6.20 (br s, 2H) 7.38 (t, 1H, $J = 8.1$ Hz) 7.42 (m, 1H) 7.60 (m, 1H) 7.80 (s, 1H).

MS for (MH^+) $C_{14}H_{16}NO_2$: 230.

Compound **8a**: MS for (MH^+) $C_{28}H_{38}F_2N_3O$: 470.

Compound **8c**: ^1H NMR ($CDCl_3$): δ 0.70 (m, 1H) 1.00 (m, 1H) 1.05 (d, 12H, $J = 6.7$ Hz) 1.22 (m, 1H) 1.38 (m, 1H) 1.60 (m, 2H) 2.10 (m, 1H) 2.20 (m, 1H) 2.38 (m, 1H) 2.65 (m, 2H) 3.10–3.25 (m, 4H) 4.20 (m, 1H) 6.90 (m, 1H) 6.95 (m, 1H) 7.10–7.20 (m, 2H) 7.40 (m, 2H) 10.80 (s, 1H).

MS for (MH^+) $C_{28}H_{37}BrF_2N_3O$: 548, 550.

Compound **8d**: ^1H NMR ($CDCl_3$): δ 0.72 (m, 1H) 1.00 (m, 1H) 1.05 (d, 12H, $J = 6.7$ Hz) 1.22 (m, 1H) 1.38 (m, 1H) 1.60 (m, 2H) 2.16 (m, 1H) 2.28 (m, 1H) 2.40 (m, 1H) 2.65 (m, 2H) 3.15 (m, 2H) 3.25 (m, 2H) 4.19 (m, 1H) 5.80 (br s, 1H) 6.30 (br s, 1H) 7.00 (m, 1H) 7.10 (m, 1H) 7.35 (m, 1H) 7.42 (m, 1H) 7.55 (m, 1H) 7.60 (m, 1H) 7.77 (s, 1H) 10.80 (s, 1H).

MS for (MH^+) $C_{29}H_{39}ClFN_4O_2$: 529.

Compound **8e**: ^1H NMR ($CDCl_3$): δ 0.70 (m, 1H) 1.05 (m, 1H) 1.10 (d, 12H, $J = 6.7$ Hz) 1.30 (m, 1H) 1.40 (m, 1H) 1.60 (m, 2H) 2.18 (m, 1H) 2.28 (m, 1H) 2.40 (m, 1H) 2.69 (br s, 2H) 3.18 (m, 2H) 3.30 (m, 2H) 3.95 (s, 3H) 4.19 (m, 1H) 6.95 (m, 1H) 7.00 (m, 1H) 7.30–7.50 (m, 3H) 7.82 (m, 1H) 7.95 (s, 1H) 10.80 (s, 1H).

MS for (MH^+) $C_{30}H_{40}F_2N_3O_3$: 528.

Compound **8f**: The methyl ester analog of **8f** (0.31 g, 0.57 mmol) in 2 mL THF under nitrogen at −78 °C was treated with 0.6 mL of 1 M $LiAlH_4$ in THF for 0.5 h. After quenching the reaction with 2 mL MeOH, the solvent was removed and after extraction with EtOAc and removal of solvent, the crude NMR indicated a mixture of starting material and the product. The product **8f** was purified by flash chromatography (16 mg, 5%).

^1H NMR ($CDCl_3$): δ 0.66 (m, 1H) 1.06 (m, 1H) 1.05 (d, 12H, $J = 6.7$ Hz) 1.22–1.40 (m, 2H) 1.60 (m, 2H) 2.16 (m, 1H) 2.28 (m, 1H) 2.40 (m, 1H) 2.65 (m, 2H) 3.18 (m, 2H) 3.25 (m, 2H) 4.20 (m, 1H) 4.64 (s, 2H) 7.00 (m, 1H) 7.10–7.30 (m, 5H) 7.55 (m, 1H) 10.80 (s, 1H).

MS for (MH^+) $C_{29}H_{40}ClFN_3O_2$: 516.

Compound **8g**: following the Dess–Martin oxidation condition for **2b**, **8f** (40 mg) was converted to the aldehyde intermediate which, after washing with saturated Na_2CO_3 and without purification, was treated with *N*-methylhydroxyamine hydrochloride (10 mg) in 0.2 mL pyridine at rt over weekend. Preparative TLC purification provided the desired product (16 mg, 38% yield).

^1H NMR ($CDCl_3$): δ 0.66 (m, 1H) 1.06 (m, 1H) 1.05 (d, 12H, $J = 6.7$ Hz) 1.20–1.40 (m, 2H) 1.60 (m, 2H) 2.18 (m, 1H) 2.22–2.40 (m, 2H) 2.65 (m, 2H) 3.18 (m, 2H) 3.25 (m, 2H) 4.00 (s, 3H) 4.20 (m, 1H) 7.00 (m, 1H) 7.10 (m, 1H) 7.22–7.30 (m, 2H) 7.70 (m, 2H) 8.00 (s, 1H) 10.80 (s, 1H).

LCMS: rt = 5.78 min. Purity: 89.7%. MS for (MH^+) $C_{30}H_{41}ClFN_4O_2$: 543.1.

Compound **8h**: MS for (MH^+) $C_{29}H_{40}ClFN_4O$: 515.

Compound **8i**: compound **8d** (0.50 g, 0.945 mmol) in 9 mL THF under nitrogen at −78 °C was treated with 1.4 mL of 1 M $LiAlH_4$ in THF. After slowly warming up to rt in 2.5 h, the mixture was heated to 35 °C for 6 h and then rt for overnight. After quenching the reaction with 0.07 mL water, 0.22 mL of 15% NaOH, and 0.07 mL water, the crude was filtered through Celite and the solvent was removed. The product **8i** was purified by flash chromatography (33 mg, 7% yield).

^1H NMR ($CDCl_3$): δ 0.60 (m, 1H) 0.99 (m, 1H) 1.03 (d, 12H, $J = 6.7$ Hz) 1.20–1.40 (m, 2H) 1.60 (m, 2H) 2.10–2.40 (m, 3H) 2.62 (m, 2H) 3.10 (m, 2H) 3.20 (m, 2H) 3.80 (s, 2H) 4.16 (m, 1H) 6.95 (m, 1H) 7.00–7.20 (m, 5H) 7.55 (m, 1H) 10.77 (s, 1H).

MS for (MH^+) $C_{29}H_{40}ClFN_4O$: 515.

Compound **8j**: ^1H NMR ($CDCl_3$): δ 0.60 (m, 1H) 0.99 (m, 1H) 1.00 (d, 12H, $J = 6.7$ Hz) 1.20–1.40 (m, 2H) 1.60 (m, 2H) 2.00–2.40 (m, 3H) 2.62 (m, 2H) 2.80 (s, 3H) 3.10 (m, 2H) 3.20 (m, 2H) 3.95 (m, 1H) 4.20 (s, 2H) 4.80 (br s, 1H) 6.99–7.20 (m, 6H) 7.50 (m, 1H) 10.77 (s, 1H).

MS for (MH^+) $C_{30}H_{43}ClFN_4O_3S$: 593.

Compound **8k**: MS for (MH^+) $C_{31}H_{43}ClFN_4O_2$: 557.

Compound **8l**: MS for (MH^+) $C_{33}H_{47}ClFN_4O_2$: 585.

Compound **8m**: MS for (MH^+) $C_{34}H_{50}ClFN_5O$: 598.

Compound **8n**: MS for (MH^+) $C_{33}H_{49}ClFN_4O$: 571.

Compound **8o**: MS for (MH^+) $C_{31}H_{45}ClFN_4O$: 543.

4.3.7. Synthesis of 9. The synthesis followed the procedure for **5** with key procedure as: (a) reductive amination of **4** with isopropylamine; (b) alkylation with 2-bromoethanol (1.5 equiv), $NaHCO_3$ (2 equiv), EtOH, 78 °C, 14 h; (c) 50% TFA/DCM, 2 h; (d) ArNCO (0.9 equiv).

(MH^+) $C_{28}H_{35}ClFN_4O_2$: 513.

4.3.8. Synthesis of 10. The synthesis followed the procedure for **5** with key procedure as: (a) (*R*)-alaninol (1 equiv), 2-iodopropane (1 equiv), CH_3CN, 40 °C, 14 h; (b) reductive amination with **4**; (c) 50% TFA/DCM, 2 h; (d) ArNCO (0.9 equiv).

MS for (MH^+) $C_{29}H_{37}ClFN_4O_2$: 527.

Compound **11**: synthesis followed the procedure for **10**. MS for (MH^+) $C_{29}H_{37}ClFN_4O_2$: 527.

Compound **12**: synthesis followed the procedure for **5** with key procedure as: (a) reductive amination of **4** with 2-fluoroethylamine; (b) reductive alkylation with acetone; (c) 50% TFA/DCM, 2 h; (d) ArNCO (1 equiv).

MS for (MH^+) $C_{28}H_{34}ClF_2N_4O$: 515.

Compound **13**: MS for (MH^+) $C_{28}H_{36}Cl_2N_5O$: 528.

Compound **14**: ^1H NMR ($CDCl_3$): δ 0.77 (m, 1H) 0.99 (m, 1H) 1.03 (d, 6H, $J = 6.7$ Hz) 1.20–1.40 (m, 2H) 1.60 (m, 2H) 2.10 (m, 1H) 2.30–2.40 (m, 2H) 2.60–2.80 (m, 4H) 3.10 (m, 1H) 3.30 (m, 2H) 3.80 (m, 2H) 4.16 (m, 1H) 7.35–7.60 (m, 6H) 10.77 (s, 1H).

MS for (MH^+) $C_{27}H_{34}Cl_2N_5O_2$: 530.

Compound **15**: MS for (MH^+) $C_{28}H_{36}Cl_2N_5O_2$: 544.

Compound **16**: ^1H NMR ($CDCl_3$): δ 0.77 (m, 1H) 1.01 (m, 1H) 1.04 (d, 6H, $J = 6.7$ Hz) 1.30–1.40 (m, 2H) 1.60 (m, 2H) 2.10 (m, 1H) 2.30–2.40 (m, 2H) 2.60 (m, 2H) 2.80–2.98 (m, 2H) 3.10 (m, 1H) 3.30 (m, 2H) 3.80 (m, 2H) 4.16 (m, 1H) 4.56 (m, 1H) 4.63 (m, 1H) 7.35–7.60 (m, 6H) 10.89 (s, 1H).

LCMS: rt = 4.88 min. Purity: 98.5%. MS for (MH^+) $C_{27}H_{33}Cl_2FN_5O$: 532.1.

Compound **17**: synthesis followed the procedure for **5** with key procedure as: (a) **4**, acetone, $NaBH(OAc)_3$, DCM; (b) TFAA (2 equiv), Et_3N (3 equiv), DCM, rt, 12 h; (c) 50% TFA in DCM, 24 h; (d) ArNCO; (e) NaOH (1 N in MeOH, 2 equiv), rt, 14 h.

MS for (MH^+) $C_{25}H_{30}Cl_2N_5O$: 486.

Compound **18**: MS for (MH^+) $C_{24}H_{27}Cl_2FN_5O$: 490.

Compound **19**: synthesis followed the procedure for **5** with key procedure as: (a) $LiAlH_4$ (1 equiv) reduction of 5-methyl-2-(*S*)-proline methyl ester to the alcohol, THF, 70 °C, 12 h, 68% yield; (b) iodoacetonitrile (1 equiv), K_2CO_3 (1 equiv), 45 °C, 14 h, 90% yield; (c) $LiAlH_4$ (1.1 equiv) reduction, THF, 70 °C, 12 h, 60% yield; (d) reductive alkylation with **2b**; (e) ArNCO (0.9 equiv).

MS for (MH^+) $C_{29}H_{35}ClFN_4O_2$: 525.

Compound **20**: MS for (MH^+) $C_{28}H_{34}Cl_2N_5O_2$: 542.

4.3.9. Synthesis of 22a. The synthesis was accomplished following the procedure for **1** with key procedure as: (a) reductive alkylation of **2b** with N-Boc 4-(aminomethyl)piperidine; (b) ArNCO; (c) 50% TFA/DCM; (d) reductive alkylation with tetrahydro-4*H*-pyran-4-one.

MS for (MH^+) $C_{32}H_{39}ClFN_4O_2$: 565.

Compound **22b**: MS for (MH^+) $C_{30}H_{34}F_4N_5O_2$: 572.

Compound **22c**: MS for (MH^+) $C_{29}H_{33}ClFN_4O_2$: 523.

Compound **22d**: ^1H NMR ($CDCl_3$): δ 0.82 (m, 1H) 1.00 (m, 1H) 1.40 (m, 3H) 1.50–1.70 (m, 2H) 1.80 (m, 3H) 2.10 (m, 1H) 2.36 (m, 2H) 2.60 (m, 2H) 2.77 (s, 3H) 3.10 (m, 2H) 3.70 (m, 1H) 3.80 (m, 2H) 6.56 (br s, 1H) 7.02 (m, 1H) 7.19 (m, 1H) 7.20–7.60 (m, 5H).

MS for (MH^+) $C_{28}H_{33}ClFN_4O_3S$: 559.

Compound **22e**: MS for (MH^+) $C_{28}H_{33}F_2N_4O_3S$: 543.

Compound **22f**: MS for (MH^+) $C_{29}H_{35}F_2N_4O_3S$: 557.

Compound **22g**: MS for (MH^+) $C_{29}H_{33}F_4N_4O_3S$: 593.

Compound **22h**: MS for (MH^+) $C_{28}H_{34}FN_4O_3S$: 525.

Compound **22i**: MS for (MH^+) $C_{30}H_{35}F_4N_4O_3S$: 607.

Compound **22j**: ^1H NMR ($CDCl_3$): δ 0.82 (m, 1H) 0.99 (m, 1H) 1.44 (m, 3H) 1.60–1.80 (m, 5H) 1.80–2.00 (m, 2H) 2.30 (m, 2H) 2.74 (s, 3H) 2.90 (m, 1H) 2.82–3.10 (m, 2H) 3.30–3.70 (m, 4H) 6.42 (d, 1H, $J = 9.3$ Hz) 7.00 (t, 1H, $J = 8.6$ Hz) 7.10 (m, 1H) 7.30–7.50 (m, 5H).

MS for (MH^+) $C_{28}H_{33}ClFN_4O_3S$: 559.

Compound **22k**: MS for (MH^+) $C_{28}H_{33}ClFN_4O_3S$: 559.

Compound **22l**: MS for (MH^+) $C_{27}H_{31}ClFN_4O_3S$: 545.

Compound **23a**: ^1H NMR ($CDCl_3$): δ 0.70 (m, 1H) 1.00 (m, 1H) 1.30 (m, 3H) 1.45 (m, 1H) 1.60–1.80 (m, 7H) 2.10 (m, 1H) 2.30 (m, 2H) 2.58 (m, 2H) 2.76 (s, 3H) 3.04 (m, 2H) 3.60–3.80 (m, 5H) 6.50 (br s, 1H) 7.00–7.20 (m, 5H) 7.44 (m, 1H).

MS for (MH^+) $C_{28}H_{37}ClFN_4O_3S$: 563.

Compound **23b**: MS for (MH^+) $C_{30}H_{41}ClFN_4O_3S$: 591.

Compound **23c**: MS for (MH^+) $C_{27}H_{36}Cl_2N_5O_3S$: 580.

Compound **23d**: MS for (MH^+) $C_{29}H_{40}Cl_2N_5O_3S$: 608.

Compound **23e**: MS for (MH^+) $C_{31}H_{42}Cl_2N_5O_4S$: 650.

4.3.10. Synthesis of 27. Ketone **24** (9.9 g, 63.5 mmol, 1 equiv)/200 mL DCM/N-(2-aminoethyl)pyrrolidine (8.7 g, 1.2 equiv)/$Ti(OiPr)_4$ (21.6 g, 1.2 equiv) was stirred at room temperature for overnight. The mixture was cooled to 0 °C followed by addition of $NaBH_4$ (3.4 g, 1.4 equiv). After another overnight stirring, 5 mL of MeOH was added. After 2 h, saturated Na_2CO_3 was added followed by extraction with EtOAc. Flash chromatography (10:1:90 MeOH/NH_3/DCM) provided 9.8 g of the desired product (60% yield).

^{1}H NMR ($CDCl_3$): δ 1.30–1.40 (m, 2H) 1.41–1.55 (m, 2H) 1.65 (br s, 6H) 1.80 (m, 2H) 2.40 (m, 5H) 2.52 (t, 3H, J = 7.1 Hz) 2.62 (t, 3H, J = 7.1 Hz) 3.80 (s, 4H).

MS: $C_{14}H_{27}N_2O_2$: 255 $(MH)^+$.

This material (3.1 g, 12.2 mmol, 1 equiv) was treated with Boc_2O (3.2 g, 1.2 equiv), $NaHCO_3$ (2 g, 1.5 equiv) in 40 mL THF and 40 mL water. The mixture was heated to 55 °C for 48 h. After cooling, extraction with EtOAc, and drying the organic layer with Na_2CO_3, evaporation of the solvent afforded colorless syrup (4.4 g). This syrup was treated with $CeCl_3 \cdot 7H_2O$ (9 g, 2 equiv), NaI (0.54 g, 0.3 equiv) in 80 mL of CH_3CN at 80 °C under nitrogen for 2 h. Another 4.5 g of $CeCl_3 \cdot 7H_2O$ (1 equiv), NaI (0.54 g, 0.3 equiv), and 60 mL of CH_3CN were added and the mixture was heated for 16 h. After cooling to room temperature, extraction with EtOAc, and drying with Na_2SO_4, evaporation of solvent provided light yellow syrup **25a** and **25b** (3.1 g total, **25a**/**25b** = 1.4:1).

The above material (3.1 g, 10 mmol) was dissolved in 1:1 toluene/THF 50 mL, cooled to −78 °C followed by addition of 5.36 g of Tf_2NPh (15 mmol, 1.5 equiv) and slow addition of KHMDS solution 30 mL (0.5 N in toluene, 1.5 equiv). After 4 h of stirring, 40 mL of water was added into reaction mixture. This reaction mixture was slowly warmed up to room temperature followed by extraction of EtOAc. Flash chromatography (3:1:100 MeOH/NH_3/DCM) gave the first fraction as colorless syrup **26a** (1.5 g).

^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H) 1.69 (m, 4H) 1.80 (m, 1H) 1.88 (m, 1H) 2.20 (m, 1H) 2.26–2.30 (m, 2H) 2.47 (m, 7H) 3.13 (br s, 2H) 4.03 (br s, 1H) 5.62 (m, 1H).

Chromatography also gave the second fraction as colorless syrup **26b** (1.1 g).

1H NMR ($CDCl_3$): δ 1.53 (m, 1H) 1.67 (m, 4H) 1.89–1.92 (m, 3H) 2.31 (m, 2H) 2.42 (m, 5H) 2.52 (t, 2H, J = 6 Hz) 2.67 (m, 3H) 5.59 (m, 1H).

This material **26b** (1 g, 2.9 mmol, 1 equiv)/ 15 mL DCM/ 4-fluoro-3-chlorophenyl isocyanate (0.6 g, 3.5 mmol, 1.2 equiv) was stirred at room temperature under N_2 for 3 h. Saturated NaCl solution was added followed by extraction with EtOAc. Flash chromatography (40:100 EtOAc/hexane) gave **27** as white solid (1.48 g, 96% yield).

^{1}H NMR ($CDCl_3$): δ 1.86 (m, 6 H) 2.19 (m, 1H) 2.32–2.36 (m, 2H) 2.56 (m, 1H) 2.67–2.72 (m, 6H) 3.23 (m, 2H) 4.36 (m, 1H) 5.69 (m, 1H) 6.96 (t, 1H, J = 8.8 Hz) 7.08 (m, 1H) 7.40 (m, 2H) 11.07 (m, 1H).

Suzuki coupling reaction: Starting material **27** (25 mg, 0.049 mmol), boronic acid (2 equiv), LiCl (1.5 equiv), Na_2CO_3 (3 equiv), $PdCl_2$ (dppf) (0.15 equiv), toluene/EtOH/H_2O (3:1:1) under nitrogen, at 50 °C for 10 min, then at 80 °C for 1 h. Prep TLC (5% MeOH in DCM with 1% NH_3) gave the desired product **28** in 50–80% yield.

Compound **28a**: MS for (MH^+) $C_{23}H_{28}ClFN_5O$: 444.

Compound **28b**: MS for (MH^+) $C_{24}H_{29}ClFN_4O$: 443.

Compound **28c**: MS for (MH^+) $C_{23}H_{29}ClFN_4O$: 431.

Compound **28d**: MS for (MH^+) $C_{23}H_{28}ClFN_3O_2$: 432.

Compound **28e**: MS for (MH^+) $C_{24}H_{28}ClFN_3O_3$: 460.

Compound **28f**: MS for (MH^+) $C_{27}H_{30}ClFN_3O_2$: 482.

Compound **28g**: MS for (MH^+) $C_{24}H_{30}ClFN_3OS$: 462.

Compound **28h**: MS for (MH^+) $C_{25}H_{30}ClFN_3O_2S$: 490.

Compound **28i**: ^{1}H NMR ($CDCl_3$): δ 1.50 (m, 2H) 1.70 (m, 1H) 1.80 (m, 4H) 2.19 (m, 1H) 2.40 (m, 1H) 2.55 (m, 2H) 2.70 (m, 5H) 4.20 (m, 1H) 6.20 (br s, 1H) 6.83 (m, 1H) 6.94 (m, 1H) 7.10 (m, 1H) 7.40 (m, 2H) 11.00 (s, 1H).

MS for (MH^+) $C_{24}H_{27}ClFN_4OS$: 473.

Compound **28j**: ^{1}H NMR ($CDCl_3$): δ 1.60–1.80 (m, 4H) 1.82 (m, 4H) 2.19 (m, 1H) 2.36 (m, 1H) 2.55 (m, 2H) 2.60–2.80 (m, 4H) 3.22 (m, 2H) 3.90 (s, 2H) 4.22 (m, 1H) 6.00 (br s, 1H) 6.70 (s, 2H) 6.94 (m, 1H) 7.10 (m, 1H) 7.40 (m, 2H) 11.00 (s, 1H).

MS for (MH^+) $C_{24}H_{31}ClFN_4OS$: 477.

Compound **28k**: MS for (MH^+) $C_{23}H_{26}ClFN_5OS$: 474.

Compound **28l**: ^{1}H NMR ($CDCl_3$): δ 1.60–1.90 (m, 8H) 2.10 (m, 1H) 2.30 (m, 1H) 2.56 (m, 2H) 2.70 (m, 4H) 3.22 (br s, 2H) 4.04 (br s, 2H) 4.20 (m, 1H) 5.98 (br s, 1H) 6.95 (m, 1H) 7.10 (m, 1H) 7.40 (m, 2H).

LCMS: rt = 3.77 min. Purity: 97.5%. MS for (MH^+) $C_{23}H_{30}ClFN_5OS$: 478.1.

Compound **28m**: MS for (MH^+) $C_{25}H_{34}ClFN_5OS$: 506.

Compound **28n**: the procedure is similar to the above: 2-tributylstannylthiazole (1.35 g, 3.62 mmol) was mixed

with **26a** (0.8 g, 1.81 mmol), $Pd(PPh_3)_4$ (63 mg, 0.03 equiv), and LiCl (0.23 g, 3 equiv) in 10 mL THF. The mixture was heated to 75 °C under nitrogen for 2 h. EtOAc was added and after washing with water, the solvent was removed and chromatography (5% MeOH in DCM with 1% NH_3) provided 0.51 g coupling product in 75% yield. This compound was dissolved in 5 mL THF and treated with LDA (1.25 equiv) at −78 °C MS for 20 min. DMF (3 equiv) was added to quench the reaction. After 1 h, water was added and after extraction with EtOAc, organic layer was dried and the crude syrup was directly dissolved in 50% DCM in MeOH and $NaBH_4$ (1.2 equiv) was added at −30 °C. Warming up to 0 °C in 30 min and extraction with EtOAc, drying the solvent, and chromatography provided the alcohol (0.135 g). This alcohol was treated with 4 equiv of dppa, 1.5 equiv of DBU in 3 mL of THF and the mixture was stirred at 70 °C for 2 h. After work-up, chromatography (5% MeOH in DCM with 1% NH_3) provided the desired azide which was immediately treated with 10% TFA in DCM at rt for 1.5 h. After removal of TFA, EtOAc was added and the organic layer was washed with Na_2CO_3. Drying the solvent provided 76 mg of the amine. This amine was then treated with aryl isocyanate followed by reduction of azide with resin-bound triphenylphosphine (2 equiv) in 2 mL THF/0.1 mL water at rt for 24 h. Chromatography provided the final desired product **28n** (68 mg). ^1H NMR ($CDCl_3$): δ 1.10 (m, 1H) 1.60–1.80 (m, 3H) 1.90 (m, 5H) 2.20 (m, 1H) 2.40 (m, 1H) 2.60–2.80 (m, 8H) 3.30 (m, 2H) 4.00 (s, 2H) 4.50 (m, 1H) 6.50 (m, 1H) 6.99 (m, 1H) 7.15 (m, 1H) 7.40 (m, 2H).

MS for (MH^+) $C_{23}H_{30}ClFN_5OS$: 478.

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15. (a) Among 70 isocyanates, 51 were aryl ones and 19 were alkyl ones. All alkyl products were inactive; (b) All K_i values were determined in the human MCH R1 receptor binding assay. See details in experimental part. All the compounds reported in this article had been tested in the MCH mediated Ca^{2+} influx functional FLIPR assay and all of them were full MCH R1 antagonists. For example, **6a**: K_b 7.0 nM; **8g**: K_b 4.6 nM; **16**: K_b 11.4 nM; **28l**: K_b 14.5 nM.
16. For example, the amide analog of **1h** (with 3,4-difluorophenylacetyl) has MCH R1 K_i of 7115 nM.
17. All compounds were dosed at 30 mg/kg. See also Ref. 9c.
18. The stability of this 2,6-dichloropyridine moiety was examined. For example, an analog of **23a** with R as hydroxymethyl (in place of aminomethyl) was mixed with 10 equiv of *N*-acyl cysteine in 50% water/DMSO at 37 °C for 21 h. LC/MS spectrum showed only the starting material.
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