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Synthesis and structure–activity relationships of *N*-aryl-piperidine derivatives as potent (partial) agonists for human histamine H3 receptor

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ABSTRACT

4-((1*H*-Imidazol-4-yl)methyl)-1-aryl-piperazine and piperidine derivatives were designed and synthesized as candidate human histamine type 3 agonists. The piperazine derivatives were found to have low (or no) affinity for human histamine H3 receptor, whereas the piperidine derivatives showed moderate to high affinity, and their agonistic activity was greatly influenced by substituents on the aromatic ring. Among the piperidine-containing compounds, **17d** and **17h** were potent human histamine H3 receptor agonists with high selectivity over the closely related human H4 receptor. Our results indicate that appropriate conformational restriction, that is, by the piperidine spacer moiety, favors specific binding to the human histamine H3 receptor.

1. Introduction

The histamine H3 receptor was discovered in 1983 by Arrang et al.,[1] as a presynaptic autoreceptor belonging to the superfamily of G-protein coupled receptors, which are inhibitory modulators of the synthesis and release of histamine in the central nervous system.[2,3] Further studies have clarified that the H3 receptor also modulates various neurotransmitters, including acetylcholine,[4,5] dopamine,[6,7] serotonin,[8] and noradrenaline,[9] in both the central and peripheral nervous systems. These characteristics of H3 receptor suggest that H3 agonists could be therapeutic agents for a broad range of disorders, including myocardial ischemia,[10] inflammation,[11] migraine,[12] sleep disorders,[13] and anxiety disorders.[14]

It has been suggested that the pharmacophore for H3 agonistic activity consists of an imidazole ring substituted only at the 4-position, an alkyl spacer, and a basic moiety.[15,16] This basic moiety is expected to be physiologically protonated and to interact with an aspartate residue (Asp^{114}) of the receptor's transmembrane domain 3, which is highly conserved in the histamine receptor family.[17,18] The potency and selectivity of agonists of this type for H3 receptor could be increased by appropriate conformational restriction, for example, substitution on the alkyl spacer ((*R*)-α-methylhistamine **1**[1]), or incorporation of a (substituted) ring structure (immepip **2**,[19] methimepip **3**[20] and AEIC **4**[21])(Figure. 1). In addition, H3 agonists of another type, without the basic side chain, have been reported; they consist of an imidazole ring, an alkyl spacer, and a lipophilic tail.[15,16,20,22–26] Although the binding modes have not been established, De Esch and co-workers hypothesized that peripheral lipophilic groups of these ligands occupy a hydrophobic pocket of the H3 receptor, while the imidazole group is arranged near the aspartate residue (Asp^{114}) in transmembrane domain 3.[26] The lack of the basic moiety and incorporation of the lipophilic part would be expected to improve pharmacokinetic properties, such as absorption, and penetration of the blood–brain barrier. As an agonist of this type, we reported **5**,[25] which possesses a (4-*tert*-butylphenylthio)ethyl lipophilic moiety at the 4 position of the imidazole ring. Compound **5** has high affinity and agonist potency at the H3 receptor, and showed a good pharmacokinetic profile following oral administration in rodents. These features allowed us to establish that H3 agonists act as anti-stress agents, at least in the resident intruder aggression model in mice. Therefore, **5** should be a useful tool to investigate the roles of the H3 receptor. However, **5** also has high affinity for human histamine H4 receptor, and improvement of the selectivity for H3 receptor is required for development of the ligand as a potential therapeutic agent.

The human histamine H4 receptor was cloned in 2000, using sequence information from the human H3 receptor, and identified as a Gi/o protein coupled receptor like H3 receptor.[27–31] The H4 receptor is expressed predominantly in mast cells, eosinophils and bone marrow and may be involved in immune responses, so that it is a potential therapeutic target for inflammation.[32] The human H4 receptor shares 31% sequence identity at the protein level and 54% identity in the transmembrane domains, compared with human H3 receptor.[27,28] The high homology between human H3 receptor and human H4 receptor has complicated the development of selective H3 receptor ligands.

We hypothesized that the flexible thioether spacer of **5** might allow the ligand to interact strongly with both human H3 receptor and H4 receptor. In other words, we considered that

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conformational fixation of **5** might yield new types of ligands with improved selectivity. In the present work, we designed and synthesized conformationally constrained analogs of **5** based on piperidine or piperazine as a spacer. Binding affinities, and functional activities in the [^{35}S]GTPγS binding assay to human histamine H3 receptor in vitro were evaluated to assess the potency of the newly designed compounds. The binding affinity of selected compounds for other human histamine receptor congeners, H1, H2 and H4, was also measured.

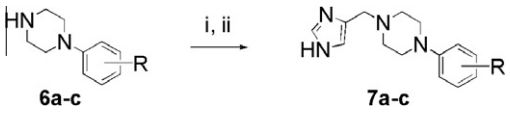
2. Chemistry

The synthesis of compounds **7** is outlined in Scheme 1. Commercially available piperazine derivatives were treated with 4-formylimidazole under basic conditions to form the imine, then reduced with $NaBH_4$ to give the target compounds **7a**–**c** in moderate to high yield (63–94%).

Compounds **17** were prepared as shown in Scheme 2. 1-Boc-4-piperidinemethanol **8** was converted to the aldehyde **9** by Swern oxidation,[33] and coupled with the Grignard reagent derived from protected 4-iodoimidazole **10**[34] to give alcohol **11** in good yield (93%). The alcohol **11** was chlorinated with thionyl chloride to obtain **12** (86%), which was subsequently hydrogenated in the presence of Pd/C to give **13** (50%). Selective deprotection of the Boc group with trifluoroacetic acid provided imidazole-protected immepip **14** (quant.). Compound **14** was coupled with corresponding aryl bromides using active palladium(0) catalyst precursor [Pd-μ-BrP(*t*-Bu)$_3$]$_2$,[35] to introduce various aryl groups in good yield (73%-quant.). These reaction conditions worked well even with an electron-rich aryl bromide that was expected to be inactive in Pd-catalyzed reactions. Subsequent acid or basic hydrolysis of the protecting group provided the desired target compounds **17a**–**n** (29–83%).

3. Pharmacology

The affinity values for human histamine H3 receptor were measured in terms of displacement of [^{3}H]-(R)–α-methylhistamine binding to membranes of CHO cells expressing the human H3 receptor in the presence of the compounds. Functional activities of these ligands were measured by means of [^{35}S]GTPγS binding assay to membranes of CHO-K1 cells expressing human H3 receptor. Intrinsic activity (ia) is the ratio of the maximum response to each ligand to the maximum response to (*R*)-α-methylhistamine. To avoid overlooking compounds that possess affinity for the receptor, but exhibit low intrinsic activity, the antagonist potency of each ligand at 10^{-5} M was measured as the ability to inhibit the binding of [^{35}S]GTPγS in the presence of 10 nM (*R*)-α-methylhistamine. The affinity values for human histamine H1,[36] H2,[37] and H4[38,39] receptors were measured in terms of displacement of [^{3}H]rilamine (for H1), [^{125}I]aminopotentidine (for H2), and [^{3}H]histamine (for H4) in the presence of the compounds. The receptors were expressed in membranes of CHO cells (H1) and CHO-K1 cells (H2, H4) for these assays.



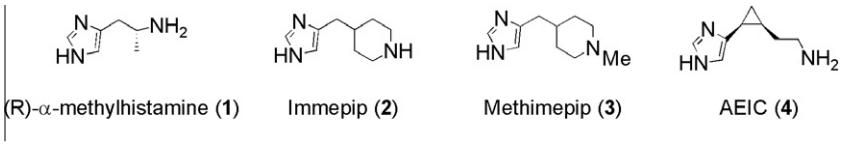
6a-c 7a-c

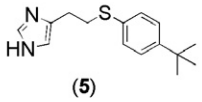
Scheme 1. Synthesis of compounds **7a**–**c**. Reagents and conditions: (i) 4-formylimidazole, Et_3N, MeOH-1,4-dioxane, rt, overnight; (ii) $NaBH_4$, MeOH, rt, 1 h—overnight, 63–94% in two steps.

4. Results and discussion

Binding affinity, functional activity and antagonist potency of the synthesized compounds are summarized in Table 1. Immepip and **5** exhibited high affinity and agonistic activity (K_i = 0.30 nM, EC_{50} = 0.67 nM, ia = 82% and K_i = 0.43 nM, EC_{50} = 0.75 nM, ia = 76%, respectively). Although the binding manner of **5** to the receptor must be different from that of immepip, the hydrophobic interaction might enable **5** to bind with the receptor as strongly as immepip. All compounds with a piperidine ring (**17a**–**n**, R_1 = CH) as a spacer showed moderate to high affinity for human histamine H3 receptor (K_i = 1.0–127 nM). It is plausible that these ligands interact with both the imidazole-binding site and with a hydrophobic pocket of human histamine H3 receptor like **5** does. On the other hand, the compounds with a piperazine ring (**7a**–**c**, R_1 = N) as a spacer showed a drastic loss of affinity, which is due to unfavorable interaction of the alkyl-amine part of piperazine ring with the hydrophobic pocket.

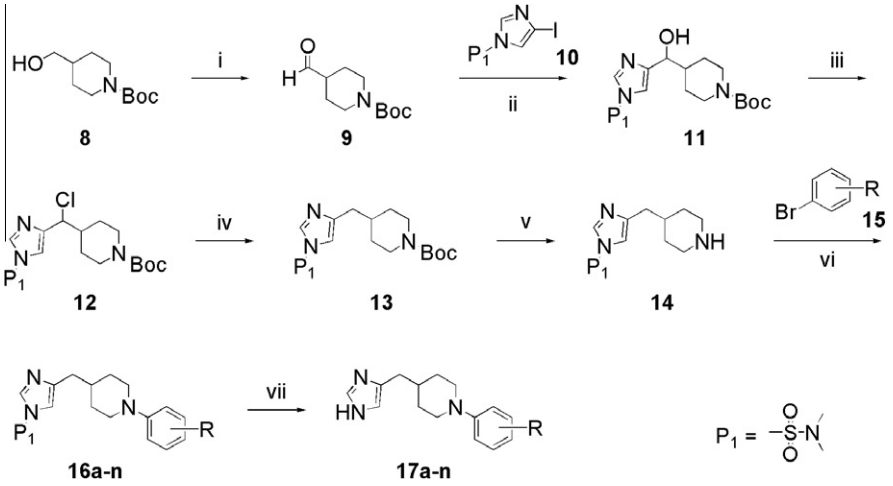
In the series of piperidine derivatives, binding affinity and agonistic activity were greatly influenced by the substituents on the aryl ring. Unsubstituted compound **17a** showed moderate affinity and EC_{50} value (30 nM and 41 nM, respectively), with low intrinsic activity (57%), showing a slightly antagonistic profile at high concentration (13% at 10^{-5} M) with the full agonist (*R*)-α-methylhistamine in the [^{35}S]GTPγS binding assay. Conversion of the phenyl ring to a pyridine ring **17n** decreased the affinity and EC_{50} value (127 nM and 177 nM, respectively), presumably because of unfavorable basic interaction with the hydrophobic pocket, but intrinsic activity was increased (74%). A *meta* or *para* substituent on the hydrophobic moiety generally served to increase the affinity, although the biphenyl derivative (**17m**), which had the greatest molecular length, showed decreased affinity (61 nM). This result indicated that there is a restriction on the molecular length of the ligand if it is to be accommodated in the hydrophobic pocket of human H3 receptor. *meta*-Substituted compounds **17e** and **17g** showed dramatically increased affinity, but the intrinsic activity was reduced. In particular, the bulky isopropyl *meta* substituent **17g** resulted in antagonistic activity (IC_{50} = 6.6 nM). Hydrophobic substitution at the *meta* position was favorable for interaction with the hydrophobic pocket of human histamine H3 receptor. But, such





(5)

Figure 1. H3 receptor agonists.



Scheme 2. Synthesis of compounds **17a**–**n**. Reagents and conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 2 °C, 30 min; (ii) **10**, EtMgBr, CH_2Cl_2–THF, −40 °C, then **9**, rt, 5 h, 93% in two steps based on **10**; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, rt, 30 min, 86%; (iv) Pd/C, H_2, toluene, rt, overnight, 50%; (v) TFA, H_2O, CH_2Cl_2, rt, 1 h, quant; (vi) **15**, [Pd-μ-BrP(*t*-Bu)$_3$]$_2$, *t*-BuONa, toluene, reflux, 3 h overnight, 73%-quant; (vii) 47% HBr aq, 100 °C, overnight; and/or KOH, $EtOCH_2CH_2OH$, H_2O, 120 °C, overnight, 29–83%.

substitution may inhibit the conformational change[40] of the receptor to the active form for coupling to G-protein to transmit the agonist signals. The naphthyl compound (**17l**), which can be classified as a *meta*-substituted derivative, also showed diminished agonistic activity. Comparatively small substituents at the *para* position increased the affinity and EC_{50} value. Compounds **17b**, **17c**, **17d**, **17h**, and **17j** (F–, NO_2–, CF_3–, OMe and NHMe, respectively) were partial agonists of H3 with moderate to high affinity. Among them, **17c** and **17d** exhibited antagonistic potency at high concentration (12% and 23% at 10^{-5} M, respectively), because of their moderate intrinsic activity (69% and 59%). But, the *para* substituent –OMe (**17h**) was found to increase the intrinsic activity (77%) and did not show antagonistic potency. The high intrinsic activity (74%) of the 3-pyridyl derivative **17n** and **17h** suggested that the combination of weak polarity and proton-accepting ability in the aryl moiety could influence the intrinsic activity. Bulkier lipophilic *para* substituents, such as isopropyl, *t*-Bu, and Ph (**17f**, **17i** and **17m**), diminished the agonistic activity. The bulkiness of these para substituents might also hamper the conformational change of human histamine H3 receptor to the active form, as in the case of *meta*-substituted compounds. The slight agonistic activity of **17k**, which had the bulky substituent –NMe_2, might again reflect the combination of weak polarity and proton-accepting ability.

We evaluated the affinity of two selected compounds, **17d** and **17h**, for other human histamine receptor congeners, H1, H2 and H4 (Table 2). Compounds **17d** and **17h** showed low (or no) affinity for human H1 and H2 receptor, like **5**. As for human H4 receptor, **5** had high affinity, resulting in no selectivity over H3 receptor (H3 K_i/H4 K_i = 2.6). However, **17d** and **17h** showed significantly reduced H4 receptor affinity (K_i = 216 nM, 3100 nM, respectively), with high selectivity (H3 K_i/H4 K_i = 120, 574, respectively). Conformational fixation by the piperidine ring spacer did not greatly influence the ligand interaction with the hydrophobic pocket of the H3 receptor, but this change appears to disfavor interaction with the hydrophobic pocket of H4 receptor. In addition, **17h** had approximately the same affinity for human histamine H3 receptor as **17d** did, even though **17h** showed over 10-fold lower affinity than **17d** at human H4 receptor. These results suggested that the configuration of the hydrophobic pocket is different between H3 and H4. In another point of view, the novel agonists could be generated by introducing the aryl moiety directly to the N-atom of immepip. And it showed improved selectivity over H3 receptor compared with immepip without inducing antagonistic activity (immepip: H3 K_i/H4 K_i = 46). Further SAR-studies on ligands of this type should provide not only highly selective human histamine H3 agonists, but also detailed information about the structural differences of the hydrophobic pocket between H3 and H4.

5. Conclusion

As a part of our search for selective human histamine H3 receptor agonists, we designed and synthesized 4-((1*H*-imidazol-4-yl)-methyl)-1-aryl-piperazine and piperidine derivatives. These compounds are conformationally constrained by their piperazine or piperidine spacer moiety. The piperazine derivatives showed low (or no) affinity for human histamine H3 receptor, whereas the piperidine derivatives showed moderate to high affinity. In the piperidine series, some aromatic *para* substituents increased the H3 agonist activity, but *meta* substituents and bulky *para* substituents diminished the agonist activity, or generated an antagonistic profile. Among this series of compounds, **17d** and **17h** are potent human histamine H3 receptor agonists with 120-fold and 574-fold selectivity, respectively, over the closely related human H4 receptor. These results indicate that appropriate conformational fixation by introduction of a suitable spacer permits specific recognition of the hydrophobic pocket of the receptor, affording highly selective human histamine H3 receptor ligands.

6. Experimental

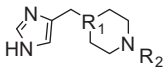
6.1. Chemistry

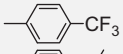
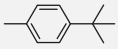
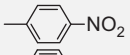
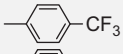
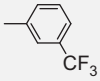
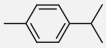
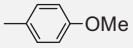
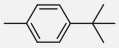
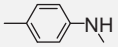
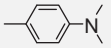
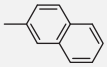
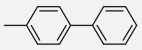
NMR spectra were obtained on JEOL GX-400 FT-NMR spectrometers. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. MS were measured with Hitachi M-80B, Agilent HP5989A and JEOL JMS-700 instruments. Column chromatography was carried out using silicagel 60 N 40–50 μm (Kanto Chemical) or NH-Chromatography silicagel 100–200 mesh (Fulisilysia Chemical). Thin layer chromatography was performed on Silica Gel 60 F_{254} plates (Merck).

6.1.1. 1-((1*H*-Imidazol-4-yl)methyl)-4-phenylpiperazine (7a)

To a mixture of 4-formylimidazole (61.1 mg, 0.64 mmol) and 1-phenylpiperazine (**6a**) (100.6 mg, 0.62 mmol) in MeOH (2.5 ml) and 1,4-dioxane (2.5 ml) was added Et_3N (0.17 ml, 1.24 mmol), and stirred at room temperature over night. Then the solvent

Table 1
Affinity, functional activity and antagonist potency of the synthesized compounds at human H3 receptor



Compd	R_1	R_2	Human histamine H3 receptor			
			K_i[a] (nM)	EC_{50} ± SEM[b] (nM)	ia[c] ± SEM[b] (%)	Antagonist inhibition[d] ± SEM[b] (%)
7a	N		>1000	n.c.[e]	n.d.[f]	n.d.[f]
7b	N		>1000	n.c.[e]	n.d.[f]	n.d.[f]
7c	N		>1000	n.c.[e]	n.d.[f]	n.d.[f]
17a	CH		30	41 ± 13	57 ± 1	13 ± 3
17b	CH		12	1.1 ± 0.2	67 ± 2	n.d.[f]
17c	CH		20	8.8 ± 5.9	69 ± 2	12 ± 1
17d	CH		1.8	1.1 ± 0.2	59 ± 2	23 ± 3
17e	CH		1.0	0.21 ± 0.05	36±2	46 ± 1
17f	CH		14	12 ± 3	31 ± 1	52 ± 2
17g	CH		1.0	n.c.[e]	n.d.[f]	80 ± 1 (IC_{50} = 6.6 nM)
17h	CH		5.4	7.6 ± 1.7	77 ± 2	n.d.[f]
17i	CH		14	18 ± 4	37 ± 1	41 ± 5
17j	CH		1.6	1.7 ± 0.7	66 ± 2	n.d.[f]
17k	CH		1.4	2.0 ± 0.7	54 ± 1	21 ± 5
17l	CH		16	1.6 ± 0.6	33 ± 1	38 ± 5
17m	CH		61	n.c.[e]	n.d.[f]	102 ± 1 (IC_{50} = 347 nM)
17n	CH		127	177 ± 29	74±3	n.d.[f]
Immepip			0.30	0.67 ± 0.10	82 ± 2	n.d.[f]
5			0.43	0.75 ± 0.10	76 ± 1	n.d.[f]

[a] Mean of two experiments.
[b] Results are presented as mean ± SEM of at least three independent experiments.
[c] Intrinsic activity, being the ratio of the maximum response of each ligand to the maximum response of RAMH.
[d] Inhibition of RAMH-induced binding of [^{35}S]GTPγS at the concentration of 10^{-5} M.
[e] Not calculable.
[f] Not detected.

Table 2
Binding affinity of selected compounds for human histamine H1, H2, H3, and H4 receptors

Compd	Human histamine receptors binding affinity K_i[a] (nM)				Selectivity K_i (H4)/K_i (H3)
	H1	H2	H3	H4	
5	>1000	>1000	0.43	1.1	2.6
17d	>1000	>1000	1.8	216	120
17h	>1000	>1000	5.4	3100	574
Immepip		>1000[19]	0.48[41]	22[41]	46

[a] Mean of two experiments.

was evaporated to give the crude imine. This imine was used at next step without further purification.

$NaBH_4$ (49.8 mg, 1.32 mmol) was added to a mixture of above imine in MeOH (2.5 ml), and stirred at room temperature over night. The reaction was quenched with H_2O (20 ml), and extracted with $CHCl_3$ (30 ml × 5). The combined organic layer was washed with brine (30 ml), dried (Na_2SO_4), and evaporated. The resulting residue was purified with column chromatography ($CHCl_3$:MeOH: 28% aqueous NH_3 = 80:1:0.1–20:1:0.1) to give **7a** as a white solid (94.8 mg, 63%, two steps), mp 182 °C. ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 7.29–7.25 (m, 2H), 6.97 (s, 1H), 6.95–6.90 (m, 2H), 6.85 (m, 1H), 3.60 (br s, 2H), 3.21–3.14 (m, 4H), 2.65 (br s, 4H); MS (FAB+) *m/z* 243 $(M+H)^+$; HRMS (FAB+) $C_{14}H_{19}N_4$ $(M+H)^+$ calcd 243.1610, found 243.1612.

6.1.2. 1-((1*H*-Imidazol-4-yl)methyl)-4-(4-trifluoromethylphenyl)-piperazine (7b)

Synthesized as a white solid, using the procedure for **7a** from 1-(4-(trifluoromethyl)phenyl)piperazine (**6b**) (94%, two steps), mp 179–180 °C. ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1H), 7.48–7.45 (m, 2H), 6.98 (s, 1H), 6.94–6.89 (m, 2H), 3.60 (br s, 2H), 3.29–3.26 (m, 4H), 2.66–2.63 (m, 4H); MS (FAB+) *m/z* 311 $(M+H)^+$; HRMS (FAB+) $C_{15}H_{18}F_3N_4$ $(M+H)^+$ calcd 311.1484, found 311.1491.

6.1.3. 1-((1*H*-Imidazol-4-yl)methyl)-4-(4-*tert*-butylphenyl)-piperazine (7c)

Synthesized as a white solid, using the procedure for **7a** from 1-(4-*tert*-butylphenyl)piperazine (**6c**) (83%, two steps), mp 169–170 °C. ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.30–7.26 (m, 2H), 6.96 (s, 1H), 6.88–6.84 (m, 2H), 3.60 (br s, 2H), 3.18–3.15 (m, 4H), 2.66–2.63 (m, 4H), 1.28 (s, 9H); MS (FAB+) *m/z* 299 $(M+H)^+$; HRMS (FAB+) $C_{18}H_{27}N_4$ $(M+H)^+$ calcd 299.2236, found 299.2237.

6.1.4. 1-Boc-4-((1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazol-4-yl)-(hydroxy)methyl)piperidine (11)

To a solution of $(COCl)_2$ (0.92 ml, 10.54 mmol) in CH_2Cl_2 (50 ml) was added DMSO (0.99 ml, 13.96 ml) at −78 °C, and stirred for 10 min at the same temperature. A solution of 1-(*tert*-butoxycarbonyl)-4-piperidinemethanol **8** (1.50 g, 6.99 mmol) in CH_2Cl_2 (9 ml) was added and stirred for 30 min at −78 °C. Et_3N (4.9 ml, 35.15 mmol) was added, then the mixture was warmed to 2 °C, and stirred for 20 min at that temperature. The reaction mixture was poured into H_2O (100 ml), and extracted with EtOAc (200 ml). The organic layer was washed with aqueous 1 N HCl (100 ml), H_2O (100 ml), saturated aqueous $NaHCO_3$ (100 ml) and brine (100 ml), sequentially. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give the crude 1-Boc-4-formylpiperazine (**9**).

To a solution of 4-iodo-imidazole-1-sulfonic acid dimethylamide (**10**) (1.75 g, 5.81 mmol) in CH_2Cl_2 (12 ml) was added EtMgBr (0.91 N in THF, 6.4 ml, 5.82 mmol) at −40 °C, and stirred for 5 min. The solution of above aldehyde **9** in THF (9 ml) was added to the mixture, and warmed to room temperature. The reaction mixture was stirred for 5 h at room temperature, and quenched with saturated aqueous NH_4Cl (10 ml). The mixture was poured into brine (50 ml) and extracted with EtOAc (100 ml × 2). The organic layer was dried ($MgSO_4$), evaporated, and the resulting residue was purified with column chromatography (EtOAc then MeOH:EtOAc = 1:19) to give **11** as a white solid (2.12 g, 93% based on **10**). ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.13 (s, 1H), 4.44 (d, 1H, *J* = 6.6 Hz), 4.15–4.10 (m, 2H), 2.87 (s, 6H), 2.79–2.51 (m, 3H), 1.93 (m, 1H), 1.85–1.70 (m, 2H), 1.44 (s, 9H), 1.30–1.21 (m, 2H); MS (ESI+) *m/z* 389 $(M+H)^+$.

6.1.5. 1-Boc-4-(chloro(1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazol-4-yl)methyl)piperidine (12)

To a solution of alcohol **11** (108.5 mg, 279 μmol) in CH_2Cl_2 was added Et_3N (0.16 ml, 1.15 mmol) and thionylchloride (25 μl, 327 μmol) at 0 °C, and stirred at room temperature for 30 min. The solvent was evaporated, and the residue was purified with short column chromatography (EtOAc:Hex = 1:2) to give chloride **12** as a clear oil (97.9 mg, 86%). ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, *J* = 1.0 Hz), 7.21 (d, 1H, *J* = 1.0 Hz), 4.73 (d, 1H, *J* = 6.8 Hz), 4.29–4.05 (m, 2H), 2.88 (s, 6H), 2.78–2.61 (m, 2H), 2.28 (m, 1H), 1.89 (m, 1H), 1.55 (m, 1H), 1.45 (s, 9H), 1.34–1.20 (m, 2H); MS (EI+) *m/z* 406 (M^+).

6.1.6. 1-Boc-4-((1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazol-4-yl)methyl)piperidine (13)

A suspension of chloride **12** (97.9 mg, 240 μmol) and 10% Pd/C (209.1 mg) was stirred at room temperature under H_2 atmosphere over night. The reaction mixture was filtered by a pad of Celite, and the filtrate was evaporated. The residue was purified with preparative thin layer chromatography (EtOAc) to give **13** as a clear oil (42.6 mg, 50%). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 6.96 (s, 1H), 4.15–4.11 (m, 2H), 2.88 (s, 6H), 2.68–2.65 (m, 2H), 2.49 (d, 2H, *J* = 7.1 Hz), 1.82 (m, 1H), 1.64 (br d, 2H, *J* = 12.7 Hz), 1.45 (s, 9H), 1.15 (dq, 2H, *J* = 4.2, 12.7 Hz); MS (FAB+) *m/z* 373 $(M+H)^+$.

6.1.7. 4-((1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)methyl)-piperidine (14)

TFA (7 ml) and H_2O (0.1 ml) was added to a solution of **13** (2.007 g, 5.39 mmol) and stirred at room temperature for 1 h. To the mixture was added saturated aqueous K_2CO_3 (50 ml) and diluted with brine (50 ml). After the extraction with $CHCl_3$ (50 ml × 4), the combined organic layer was dried (Na_2SO_4). The solvent was evaporated and the resulting residue was purified with NH–SiO_2 column chromatography (MeOH:$CHCl_3$ = 1:20) to give amine **14** as a white solid (2.177 g, quant.). ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 1H, *J* = 1.2 Hz), 6.96 (d, 1H, *J* = 1.2 Hz), 3.07–3.02 (m, 2H), 2.88 (s, 6H), 2.58 (dt, 2H, *J* = 2.7, 12.1 Hz), 2.49 (d, 2H, *J* = 7.1 Hz), 1.82 (m, 1H), 1.68–1.64 (m, 2H), 1.14 (dq, 2H, *J* = 3.9, 12.1 Hz); MS (FAB+) *m/z* 273 $(M+H)^+$.

6.1.8. *N*,*N*-Dimethyl-4-((1-phenylpiperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16a)

A mixture of **14** (91.0 mg, 0.33 mmol) and bromobenzene (69.9 μl, 0.67 mmol) and *t*-BuONa (66.3 mg, 0.69 mmol) and [Pd-μ-Br$P(t\text{-}Bu)_3]_2$ (16.6 mg, 21.4 μmol) in toluene (4 ml) was stirred under reflux condition for 2 h. The reaction mixture was poured into H_2O (15 ml), and extracted with EtOAc (30 ml). The organic layer was washed with brine (15 ml), dried (Na_2SO_4), evaporated, and purified with column chromatography (MeOH:$CHCl_3$:28% aqueous NH_3 = 1:150:0.1) to give **16a** as a pale brown oil (107.4 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, *J* = 1.0 Hz), 7.22 (dd, 2H, *J* = 7.3, 7.8 Hz), 6.99 (d, 1H, *J* = 1.0 Hz), 6.93 (d, 2H, *J* = 7.8 Hz), 6.82 (t, 1H, *J* = 7.3 Hz), 3.67 (br d, 2H, *J* = 12.4 Hz), 2.86 (s, 6H), 2.68 (dt, 2H, *J* = 2.7, 12.4 Hz), 2.54 (d, 2H, *J* = 6.8 Hz), 1.87–1.77 (m, 3H), 1.44 (dq, 2H, *J* = 3.1, 12.4 Hz); MS (EI+) *m/z* 348 (M^+).

6.1.9. *N*,*N*-Dimethyl-4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16b)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-4-fluorobenzene (82%). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 6.99 (s, 1H), 6.96–6.92 (m, 2H), 6.91–6.86 (m, 2H), 3.55–3.51 (m, 2H), 2.86 (s, 6H), 2.63 (dt, 2H, *J* = 2.2, 12.2 Hz), 2.54 (d, 2H, *J* = 6.6 Hz), 1.84–1.77 (m, 3H), 1.49–1.37 (m, 2H); MS (FAB+) *m/z* 367 $(M+H)^+$.

6.1.10. *N*,*N*-Dimethyl-4-((1-(4-nitrophenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16c)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-4-nitrobenzene (96%). ^{1}H NMR ($CDCl_3$) δ 8.13–8.08 (m, 2H), 7.85 (d, 1H, *J* = 1.0 Hz), 6.98 (d, 1H, *J* = 1.0 Hz), 6.82–6.77 (m, 2H), 3.95 (br d, 2H, *J* = 13.0 Hz), 2.95 (dt, 2H, *J* = 2.4, 13.0 Hz), 2.87 (s, 6H), 2.53 (d, 2H, *J* = 7.1 Hz), 2.02 (m, 1H), 1.82 (br d, 2H, *J* = 13.0 Hz), 1.32 (dq, 2H, *J* = 3.9, 13.0 Hz); MS (FAB+) *m/z* 394 $(M+H)^+$.

6.1.11. *N*,*N*-Dimethyl-4-((1-(4-(trifluoromethyl)phenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16d)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-4-(trifluoromethyl)benzene (87%). ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, *J* = 1.2 Hz), 7.45 (d, 2H, *J* = 8.8 Hz), 6.98 (s, 1H), 6.90 (d, 2H, *J* = 8.8 Hz), 3.79 (br d, 2H, *J* = 12.7 Hz), 2.88 (s, 6H), 2.79 (dt, 2H, *J* = 2.4, 12.7 Hz), 2.53 (d, 2H, *J* = 7.1 Hz), 1.87 (m, 1H),

1.79 (br d, 2H, J = 12.7 Hz), 1.33 (dq, 2H, J = 3.9, 12.7 Hz); MS (ESI+) m/z 417 $(M+H)^+$.

6.1.12. *N,N*-Dimethyl-4-((1-(3-(trifluoromethyl)phenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16e)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-3-(trifluoromethyl)benzene (81%). ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 1.2 Hz), 7.33 (m, 1H), 7.11–6.99 (m, 4H), 3.73–3.69 (m, 2H), 2.83 (s, 6H), 2.78 (dt, 2H, J = 2.4, 12.5 Hz), 2.54 (d, 2H, J = 6.8 Hz), 1.91–1.78 (m, 3H), 1.38 (dq, 2H, J = 4.1, 12.5 Hz); MS (ESI+) m/z 417 $(M+H)^+$.

6.1.13. *N,N*-Dimethyl-4-((1-(4-isopropylphenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16f)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-4-isopropylbenzene (96%). ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 1.2 Hz), 7.11 (d, 2H, J = 8.8 Hz), 6.98 (d, 1H, J = 1.2 Hz), 6.87 (d, 2H, J = 8.8 Hz), 3.61 (br d, 2H, J = 12.2 Hz), 2.86 (s, 6H), 2.82 (m, 1H), 2.65 (dt, 2H, J = 2.0, 12.2 Hz), 2.53 (d, 2H, J = 6.6 Hz), 1.85–1.76 (m, 3H), 1.49–1.37 (m, 2H), 1.21 (d, 6H, J = 6.8 Hz); MS (EI+) m/z 390 M^+.

6.1.14. *N,N*-Dimethyl-4-((1-(3-isopropylphenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16g)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-3-isopropylbenzene (quant.). ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 1.0 Hz), 7.18 (t, 1H, J = 7.8 Hz), 6.99 (d, 1H, J = 1.0 Hz), 6.82 (m, 1H), 6.76–6.71 (m, 2H), 3.65 (br d, 2H, J = 12.2 Hz), 2.84 (s, 6H), 2.81 (m, 1H), 268 (dt, 2H, J = 2.2, 12.2 Hz), 2.54 (d, 2H, J = 6.6 Hz), 1.87–1.80 (m, 3H), 1.49–1.38 (m, 2H), 1.22 (d, 6H, J = 6.8 Hz); MS (EI+) m/z 390 M^+.

6.1.15. *N,N*-Dimethyl-4-((1-(4-methoxyphenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16h)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-4-methoxybenzene (82%). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 6.99 (s, 1H), 6.93–6.90 (m, 2H), 6.85–6.80 (m, 2H), 3.76 (s, 3H), 3.49 (br d, 2H, J = 12.0 Hz), 2.86 (s, 6H), 2.64–2.55 (m, 2H), 2.52 (d, 2H, J = 6.6 Hz), 1.80–1.76 (m, 3H), 1.49–4.42 (m, 2H); MS (FAB+) m/z 378 M^+.

6.1.16. *N,N*-Dimethyl-4-((1-(4-*tert*-butylphenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16i)

Synthesized as a pale brown oil, using the procedure for **16a** from 1-bromo-4-*tert*-butylbenzene (73%). ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.29–7.25 (m, 2H), 6.90–6.86 (m, 3H), 3.73 (br d, 2H, J = 12.2 Hz), 2.89 (s, 6H), 2.72 (d, 2H, J = 6.3 Hz), 2.67 (dt, 2H, J = 2.2, 12.2 Hz), 1.82–1.74 (m, 3H), 1.40 (dq, 2H, J = 3.8, 12.2 Hz), 1.29 (s, 9H); MS (ESI+) m/z 404 M^+.

6.1.17. *N,N*-Dimethyl-4-((1-(4-(*N*-Boc,*N*-methylamino)phenyl)-piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16j)

Synthesized as a pale brown oil, using the procedure for **16a** from 4-bromo-(*N*-Boc, *N*-methyl)aniline (quant.). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.07 (d, 2H, J = 8.8 Hz), 6.99 (s, 1H), 6.87 (d, 2H, J = 8.8 Hz), 3.63 (br d, 2H, J = 12.0 Hz), 3.20 (s, 3H), 2.86 (s, 6H), 2.70–2.64 (m, 2H), 2.52 (d, 2H, J = 6.6 Hz), 1.86–1.80 (m, 3H), 1.49–1.37 (m, 2H), 1.44 (s, 9H); MS (ESI+) m/z 478 $(M+H)^+$.

6.1.18. *N,N*-Dimethyl-4-((1-(4-dimethylaminophenyl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16k)

Synthesized as a pale brown oil, using the procedure for **16a** from 4-bromo-(*N,N*-dimethyl)aniline (87%). ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 1.0 Hz), 6.99 (d, 1H, J = 1.0 Hz), 6.91 (d, 2H, J = 8.0 Hz), 6.74 (d, 2H, J = 8.0 Hz), 3.49–3.48 (m, 2H), 2.86 (s, 12H), 2.68–2.54 (m, 2H), 2.52 (d, 2H, J = 6.6 Hz), 1.80–1.76 (m, 3H), 1.52–1.37 (m, 2H); MS (ESI+) m/z 392 $(M+H)^+$.

6.1.19. *N,N*-Dimethyl-4-((1-(naphthalen-2-yl)piperidin-4-yl)-methyl)-1*H*-imidazole-1-sulfonamide (16l)

Synthesized as a pale brown oil, using the procedure for **16a** from 2-bromonaphtalene (quant.). ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, J = 1.2 Hz), 7.70 (d, 2H, J = 9 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.39 (dt, 1H, J = 1.2, 7.0 Hz), 7.36–7.24 (m, 2H),7.11 (d, 1H, J = 1.2 Hz), 7.00 (d, 1H, J = 0.8 Hz), 3.79 (br d, 2H, J = 12.4 Hz), 2.88 (s, 6H), 2.69 (dt, 2H, J = 1.2, 12.4 Hz), 2.56 (d, 2H, J = 6.8 Hz), 1.92–1.84 (m, 3H), 1.53 (dq, 2H, J = 4.0, 12.4 Hz); MS (EI+) m/z 398 M^+.

6.1.20. 4-((1-(Biphenyl-4-yl)piperidin-4-yl)methyl)-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide (16m)

Synthesized as a pale brown oil, using the procedure for **16a** from 4-bromobiphenyl (90%). ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H, J = 1.2 Hz), 7.57–7.52 (m, 2H), 7.50–7.47 (m, 2H), 7.42–7.37 (m, 2H), 7.29–7.25 (m, 1H), 7.00–6.98 (m, 3H), 3.74 (br d, 2H, J = 12.2 Hz), 2.86 (s, 6H), 2.75 (dt, 2H, J = 2.2, 12.2 Hz), 2.56 (d, 2H, J = 6.6 Hz), 1.89–1.78 (m, 3H), 1.44 (dq, 2H, J = 3.4, 12.2 Hz); MS (EI+) m/z 424 M^+.

6.1.21. *N,N*-Dimethyl-4-((1-(pyridin-3-yl)piperidin-4-yl)methyl)-1*H*-imidazole-1-sulfonamide (16n)

Synthesized as a pale brown oil, using the procedure for **16a** from 3-bromopyridine (92%). ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, J = 1.2 Hz), 8.06 (d, 1H, J = 3.6 Hz), 7.84 (d, 1H, J = 1.0 Hz), 7.20–7.11 (m, 2H), 6.99 (d, 1H, J = 1.0 Hz), 3.68 (br d, 2H, J = 12.2 Hz), 2.87 (s, 6H), 2.71 (dt, 2H, J = 2.4, 12.2 Hz), 2.54 (d, 2H, J = 6.8 Hz), 1.91–1.84 (m, 3H), 1.46 (dq, 2H, J = 4.1, 12.2 Hz); MS (ESI+) m/z 350 $(M+H)^+$.

6.1.22. 4-((1*H*-Imidazol-4-yl)methyl)-1-(4-*tert*-butylphenyl)piperidine (17i)

The solution of **16i** (80 mg, 0.20 mmol) in 48% aqueous HBr (1 ml) was stirred at 100 °C over night. The reaction mixture was basified with 5 N aqueous NaOH, and diluted with brine (10 ml). The mixture was extracted with $CHCl_3$ (30 ml × 3), and organic layer was dried (Na_2SO_4), evaporated, purified with preparative thin layer chromatography (MeOH:$CHCl_3$ = 1:9) to give **17i** as a pale brown solid (44 mg, 75%), mp 168 °C. ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.28–7.24 (m, 2H), 6.93–6.82 (m, 2H), 6.79 (s, 1H), 3.71 (br d, 2H, J = 12.2 Hz), 2.64 (dt, 2H, J = 2.2, 12.2 Hz), 2.57 (d, 2H, J = 6.9 Hz), 1.80–1.67 (m, 3H), 1.44–1.35 (m, 2H), 1.28 (s, 9H); MS (FAB+) m/z 298 $(M+H)^+$; HRMS (FAB+) $C_{19}H_{28}N_3$ $(M+H)^+$ calcd 298.2283, found 298.2282.

6.1.23. 4-((1*H*-Imidazol-4-yl)methyl)-1-phenylpiperidine (17a)

Synthesized as a white solid, using the procedure for **17i** from **16a** (70%), mp 176 °C. ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.26–7.22 (m, 2H), 6.95–6.94 (m, 2H), 6.92–6.80 (m, 2H), 3.69–3.65 (m, 2H), 2.68 (dt, 2H, J = 2.0, 12.2 Hz), 2.58 (d, 2H, J = 6.6 Hz), 1.82–1.73 (m, 3H), 1.42 (dq, 2H, J = 4.0, 12.2 Hz); MS (FAB+) m/z 242 $(M+H)^+$; HRMS (FAB+) $C_{15}H_{20}N_3$ $(M+H)^+$ calcd 242.1657, found 242.1657.

6.1.24. 4-((1*H*-Imidazol-4-yl)methyl)-1-(4-fluorophenyl)piperidine (17b)

Synthesized as a pale brown solid, using the procedure for **17i** from **16b** (29%), mp 156 °C. ^{1}H NMR (CD_3OD) δ 7.57 (s, 1H), 6.98–6.91 (m, 4H), 6.79 (s, 1H), 3.53–3.52 (m, 2H), 2.62 (dt, 2H, J = 2.2, 12.2 Hz), 2.56 (d, 2H, J = 7.1 Hz), 1.78–1.65 (m, 3H), 1.37 (dq, 2H, J = 3.8, 12.2 Hz); MS (FAB+) m/z 260 $(M+H)^+$; HRMS (FAB+) $C_{15}H_{19}FN_3$ $(M+H)^+$ calcd 260.1563, found 260.1562.

6.1.25. 4-((1*H*-Imidazol-4-yl)methyl)-1-(4-nitrophenyl)piperidine (17c)

Synthesized as a pale brown solid, using the procedure for **17i** from **16c** (69%), mp 198 °C. ^{1}H NMR (CD_3OD) δ 8.08–8.04 (m, 2H), 7.58 (s, 1H), 6.95–6.90 (m, 2H), 6.80 (s, 1H), 4.03 (br d, 2H, J = 13.2 Hz), 2.94 (dt, 2H, J = 2.4, 13.2 Hz), 2.54 (d, 2H, J = 7.1 Hz), 1.94 (m, 1H), 1.77 (br d, 2H, J = 12.8 Hz), 1.27 (dq, 2H, J = 3.9, 12.8 Hz); MS (FAB+) m/z 287 $(M+H)^+$; HRMS (FAB+) $C_{15}H_{19}N_4O_2$ $(M+H)^+$ calcd 287.1508, found 287.1508.

6.1.26. 4-((1*H*-Imidazol-4-yl)methyl)-1-(4-(trifluoromethyl)-phenyl)piperidine (17d)

Synthesized as a white solid, using the procedure for **17i** from **16d** (70%), mp 160 °C. ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.44 (d, 2H, J = 9.0 Hz), 6.90 (d, 2H, J = 9.0 Hz), 6.80 (s, 1H), 3.78 (br d, 2H, J = 12.4 Hz), 2.80 (dt, 2H, J = 2.2, 12.4 Hz), 2.57 (d, 2H, J = 6.6 Hz), 1.89–1.79 (m, 3H), 1.41–1.31 (m, 2H); MS (FAB+) m/z 310 $(M+H)^+$; HRMS (FAB+) $C_{16}H_{19}F_3N_3$ $(M+H)^+$ calcd 310.1531, found 310.1531.

6.1.27. 4-((1*H*-Imidazol-4-yl)methyl)-1-(3-(trifluoromethyl)-phenyl)piperidine (17e)

Synthesized as a white solid, using the procedure for **17i** from **16e** (83%), mp 97–98 °C. ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.32 (t, 1H, J = 12.0 Hz), 7.10 (br s, 1H), 7.07–7.01 (m, 2H), 6.81 (s, 1H), 3.70 (br d, 2H, J = 12.3 Hz), 2.74 (dt, 2H, J = 2.2, 12.3 Hz), 2.59 (d, 2H, J = 6.6 Hz), 1.83–1.76 (m, 3H), 1.38 (dq, 2H, J = 3.4, 12.3 Hz); MS (FAB+) m/z 310 $(M+H)^+$; HRMS (FAB+) $C_{16}H_{19}F_3N_3$ $(M+H)^+$ calcd 310.1531, found 310.1531.

6.1.28. 4-((1*H*-Imidazol-4-yl)methyl)-1-(4-isopropylphenyl)piperidine (17f)

Synthesized as a pale brown solid, using the procedure for **17i** from **16f** (69%), mp 139 °C. ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.12–7.09 (m, 2H), 6.89–6.85 (m, 2H), 6.80 (s, 1H), 3.58 (br d, 2H, J = 12.2 Hz), 2.84 (m, 1H), 2.66 (dt, 2H, J = 2.2, 12.2 Hz), 2.57 (d, 2H, J = 6.6 Hz), 1.80–1.68 (m, 3H), 1.39 (dq, 2H, J = 4.4, 12.2 Hz), 1.20 (d, 6H, J = 6.8 Hz); MS (FAB+) m/z 284 $(M+H)^+$; HRMS (FAB+) $C_{18}H_{26}N_3$ $(M+H)^+$ calcd 284.2127, found 284.2127.

6.1.29. 4-((1*H*-Imidazol-4-yl)methyl)-1-(3-isopropylphenyl)piperidine (17g)

Synthesized as a brown oil, using the procedure for **17i** from **16g** (65%). ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H, J = 2.0 Hz), 7.17 (t, 1H, J = 8.0 Hz), 6.82–6.80 (m, 2H), 6.76–6.70 (m, 2H), 3.64 (br d, 2H, J = 12.2 Hz), 2.86 (m, 1H), 2.68 (dt, 2H, J = 2.2, 12.2 Hz), 2.58 (d, 2H, J = 6.6 Hz), 1.83–1.72 (m, 3H), 1.42 (dq, 2H, J = 3.7, 12.2 Hz), 1.23 (d, 6H, J = 7.1 Hz); MS (FAB+) m/z 284 $(M+H)^+$; HRMS (FAB+) $C_{18}H_{26}N_3$ $(M+H)^+$ calcd 284.2127, found 284.2127.

6.1.30. 4-(4-((1*H*-Imidazol-4-yl)methyl)piperidin-1-yl)-*N*,*N*-dimethylaniline (17k)

Synthesized as a brown solid, using the procedure for **17i** from **16k** (80%), mp 137 °C. ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, s), 7.00–6.89 (m, 2H), 6.79 (s, 1H), 6.74–6.72 (m, 2H), 3.45–3.29 (m, 2H), 3.00–2.45 (m, 10H), 1.80–1.62 (m, 3H), 1.49–1.38 (m, 2H); MS (FAB+) m/z 284 (M^+); HRMS (FAB+) $C_{17}H_{25}N_4$ $(M+H)^+$ calcd 285.2079, found 285.2081.

6.1.31. 4-((1*H*-Imidazol-4-yl)methyl)-1-(naphthalen-2-yl)piperidine (17l)

Synthesized as a pale brown solid, using the procedure for **17i** from **16l** (54%), mp 179 °C. ^{1}H NMR ($CDCl_3$) δ 7.70–7.66 (m, 3H), 7.58 (d, 1H, J = 1.0 Hz), 7.39–7.37 (m, 1H), 7.28–7.24 (m, 2H), 7.10 (d, 1H, J = 2.2 Hz), 6.82 (s, 1H), 3.78 (br d, 2H, J = 12.2 Hz), 2.74 (dt, 2H, J = 2.2, 12.2 Hz), 2.60 (d, 2H, J = 6.6 Hz), 1.86–1.76 (m, 3H), 1.52–1.42 (m, 2H); MS (FAB+) m/z 292 $(M+H)^+$; HRMS (FAB+) $C_{19}H_{22}N_3$ $(M+H)^+$ calcd 292.1814, found 292.1818.

6.1.32. 4-((1*H*-Imidazol-4-yl)methyl)-1-(biphenyl-4-yl)piperidine (17m)

Synthesized as a white solid, using the procedure for **17i** from **16m** (75%), mp 233 °C. ^{1}H NMR ($CDCl_3$) δ 7.57–7.49 (m, 6H), 7.42–7.38 (m, 2H), 7.03–7.00 (m, 2H), 6.76 (s, 1H), 3.73–3.69 (m, 2H), 2.75–2.69 (m, 2H), 2.58–2.56 (m, 2H), 1.83–1.75 (m, 3H), 1.46–1.41 (m, 2H); MS (FAB+) m/z 318 $(M+H)^+$; HRMS (FAB+) $C_{21}H_{24}N_3$ $(M+H)^+$ calcd 318.1970, found 318.1970.

6.1.33. 3-(4-((1*H*-Imidazol-4-yl)methyl)piperidin-1-yl)pyridine (17n)

Synthesized as a white solid, using the procedure for **17i** from **16n** (65%), mp 144 °C. ^{1}H NMR ($CDCl_3$) δ 8.27 (d, 1H, J = 2.7 Hz), 8.04 (dd, 1H, J = 1.4, 4.4 Hz), 7.59 (s, 1H), 7.20–7.12 (m, 2H), 6.81 (s, 1H), 3.75 (br d, 2H, J = 12.4 Hz), 2.75–2.71 (m, 2H), 2.68 (d, 2H, J = 6.6 Hz), 1.83–1.74 (m, 3H), 1.44–1.33 (m, 2H); MS (FAB+) m/z 243 $(M+H)^+$; HRMS (FAB+) $C_{14}H_{19}N_4$ $(M+H)^+$ calcd 243.1610, found 243.1614.

6.1.34. 4-((1*H*-Imidazol-4-yl)methyl)-1-(4-methoxyphenyl)piperidine (17h)

To a mixture of **16h** (78.5 mg, 0.21 mmol) in 2-ethoxyethanol (2.4 ml) and H_2O (2.4 ml) was added KOH (322 mg, 4.87 mmol), and stirred at 120 °C over night. The reaction mixture was extracted with $CHCl_3$ (20 ml), and organic layer was washed with brine (10 ml), dried (Na_2SO_4), and evaporated. The resulting residue was purified with preparative thin layer chromatography (MeOH:$CHCl_3$:28% aqueous NH_3 = 1:5:0.1) to give **17h** as a pale brown solid (40 mg, 71%), mp 139–140 °C. ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 6.91–6.85 (m, 2H), 6.85–6.80 (m, 3H), 3.76 (s, 3H), 3.48 (br d, 2H, J = 12.0 Hz), 2.61–2.54 (m, 4H), 1.81–1.66 (m, 3H), 1.43 (dq, 2H, J = 3.9, 12.0 Hz); MS (FAB+) m/z 272 $(M+H)^+$; HRMS (FAB+) $C_{16}H_{22}N_3O$ $(M+H)^+$ calcd 272.1763, found 272.1766.

6.1.35. 4-(4-((1*H*-Imidazol-4-yl)methyl)piperidin-1-yl)-*N*-methylaniline (17j)

A mixture of **16j** (190 mg, 0.38 mmol) in 48% aqueous HBr (4 ml) was stirred at 100 °C for 7 h. The solvent was evaporated and diluted with saturated aqueous K_2CO_3 (20 ml). The mixture was extracted with EtOAc (50 ml), and organic layer was washed with brine (20 ml), dried (Na_2SO_4), evaporated. The resulting residue was dissolved in 2-ethoxyethanol (3.5 ml), and H_2O (3.5 ml), KOH (605 mg, 9.17 mmol) was added. The mixture was stirred for 120 °C over night, then extracted with $CHCl_3$ (20 ml). The organic layer was washed with brine (10 ml), dried (Na_2SO_4), and evaporated. The resulting residue was purified with preparative thin layer chromatography (MeOH:$CHCl_3$:28% aqueous NH_3 = 1:5:0.1) to give **17j** as a brown solid (32 mg, 30%), mp 126 °C. ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 6.93–6.86 (m, 2H), 6.78 (s, 1H), 6.60–6.56 (m, 2H), 3.56–3.53 (m, 2H), 2.79 (br s, 3H), 2.59–2.44 (m, 4H), 1.80–1.64 (m, 3H), 1.48–144 (m, 2H); MS (ESI+) m/z 271 $(M+H)^+$; HRMS (FAB+) $C_{16}H_{22}N_4$ $(M+H)^+$ calcd 271.1923, found 271.1917.

6.2. Pharmacology

Profiling of binding affinity for receptors other than H3 receptor was done by MDS Pharma Services.

6.2.1. H3 Receptor binding assay

Membranes prepared from CHO cells stably expressing human recombinant histamine H3 receptors were incubated with [^{3}H] (*R*)-α-methylhistamine (3 nM, PerkinElmer Life Sciences) and test

compounds in a buffer containing 50 mM Tris–HCl (pH 7.4), 10 mM $MgCl_2$ and 0.04% BSA at 25 °C for 1 h. Non-specific binding was assessed with (*R*)-α-methylhistamine (1 μM). Radioligand binding was terminated by filtering through GF/B filters (PerkinElmer Life Sciences) and the amount of bound radiolabel was determined by liquid scintillation counting.

6.2.2. [^{35}S]GTPγS Binding assay

Membranes prepared from CHO cells stably expressing human recombinant histamine H3 receptors were incubated with [^{35}S]GTPγS (200 pM, GE Healthcare Bio-Sciences) and test compounds alone or in the presence of (*R*)-α-methylhistamine (10 nM, Sigma–Aldrich) in a buffer containing 50 mM Tris–HCl (pH 7.4), 100 mM NaCl, 3 mM $MgCl_2$, 0.2 mM EDTA, 1 mM DTT and 10 μM GDP at 25 °C for 1 h. Radioligand binding was terminated by filtering through GF/B filters and the amount of bound radiolabel was determined by liquid scintillation counting.

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