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Bioorganic & Medicinal Chemistry Letters 17 (2007) 3130–3135
Bioorganic & Medicinal Chemistry Letters

Synthesis and biological evaluation of diamine-based histamine H_3 antagonists with serotonin reuptake inhibitor activity

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Received 9 February 2007; accepted 12 March 2007
Available online 15 March 2007

Abstract—The synthesis and structure–activity relationships of a series of novel phenoxyphenyl diamine derivatives with affinity for both the histamine H_3 receptor and the serotonin transporter is described.

Depression is a common and potentially debilitating disease with global prevalence. A widely held neurochemistry-based theory for depression is that it is caused by a deficiency or an imbalance of the biogenic amines noradrenaline (NE) and serotonin (5-HT) in the brain.[1–3] Thus, current forms of treatment for depression focus on increasing the levels of these neurotransmitters in the synaptic cleft. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (**1**), citalopram (**2**), paroxetine, and sertraline, work by inhibiting serotonin reuptake by the serotonin transporter (SERT) thereby increasing concentrations of serotonin in the synaptic cleft.[3] The SSRIs have become a standard treatment for depression because of their safety profile and relatively low incidence of side effects. However, one remaining drawback is a slow onset of anti-depressant activity (Fig. 1).

One strategy for improving the onset of action of SSRIs is to expand their pharmacological profile. For example, the dual SERT/NE reuptake inhibitor (SNRI) venlaflaxine (**3**) is reported to have an early onset of action, albeit at high dosages.[2] The combination of a 5-HT_{1A} antagonist with an SSRI has also been explored.[4–7] Finally, the

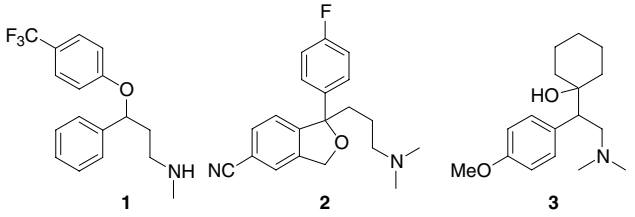

Figure 1. Structures of marketed anti-depressants: fluoxetine (**1**), citalopram (**2**), and venlaflaxine (**3**).

wake-promoting medication modafinil has been used to augment traditional anti-depressant therapy with data indicating that the combination therapy begins working earlier than an SSRI alone.[8,9] Despite these observations, there still remains a need for anti-depressants with a fast onset of action.[2]

Noting the potential limitations of existing anti-depressants we have explored the possibility of combining the pharmacology of a serotonin reuptake inhibitor with an H_3 antagonist.[10] Our rationale for this is based on the neurochemical and pharmacological effects observed for histamine H_3 antagonists. Antagonism at the H_3 receptor increases neurotransmitter (histamine, 5-HT, NE) release into the synaptic cleft.[11] In addition, H_3 antagonists are known to decrease REM sleep in animals and to have a mild stimulatory effect. It is believed that suppression of REM sleep is involved in anti-depressant activity.[12] Thus, the combination of an H_3 antagonist and a serotonin reuptake inhibitor may provide more immediate benefits to patients suffering from depression.

Keywords: Histamine; H3; Serotonin; Transporter; SERT; SSRI; Depression; Anti-depressant.
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doi:10.1016/j.bmcl.2007.03.034

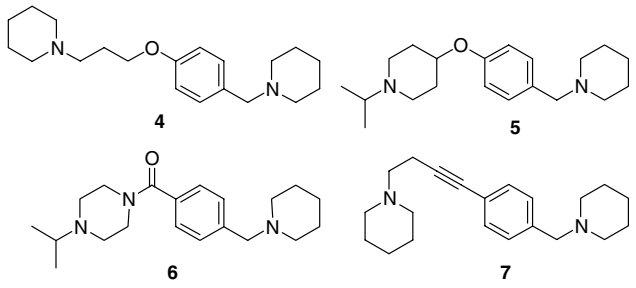


Figure 2. Structures of reported diamine-based H_3 antagonists (**4**–**7**).[13–17]

Our group has previously disclosed the diamine-based H_3 antagonists exemplified by structures **4**–**7** in Figure 2.[13–17] The pharmacophore model for the diamine-based H_3 derivatives consists of two basic functional groups flanking a lipophilic core that contains an aromatic ring.[13,14] We thought we might be able to use this model to construct a dual histamine H_3 receptor antagonist/serotonin reuptake inhibitor utilizing the known SSRI, fluoxetine (**1**).

Fluoxetine already contains a basic amine flanked by a lipophilic moiety (Fig. 3).[13] Therefore, placing known H_3 components containing the second basic amine (**I**–**IV**) on either the **A** or **B** ring of fluoxetine as shown in Figure 3 should provide a compound with affinity for both the H_3 receptor and serotonin transporter. As part of our efforts to design small molecules with both activities, we examined the SAR around the templates **8** and **9** in order to determine the best placement of the 3-piperidinyl-propyloxy H_3-component (**I**), the incorporation of the most preferred H_3-component (**I**–**IV**), and the optimal substitution of the phenoxy ring (**B**). For simplicity, we chose to synthesize H_3/SERT derivatives where R_1 and R_2 (Fig. 3) are methyl since the *N*,*N*-dimethyl derivative of fluoxetine **10** (Table 1) has comparable in vitro activity to fluoxetine itself (**1**).[18]

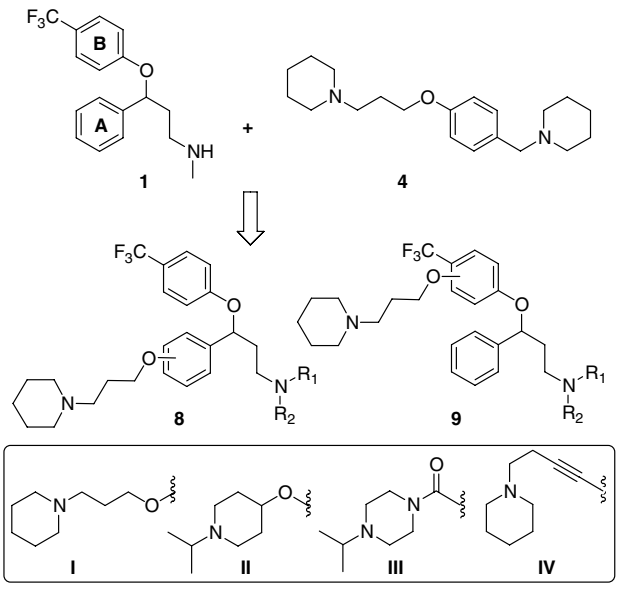


Figure 3. Proposed construction of dual H_3 antagonist/SERT inhibitors from fluoxetine (**1**) and known H_3 antagonist components (**I**–**IV**).

The synthesis of H_3/SERT analogs with the 3-piperidinyl-propyloxy H_3-component (**I**) on the phenyl ring (**A**) of fluoxetine is shown in Scheme 1. Alkylation of 4-hydroxyacetophenone with 1-bromo-3-chloropropane was followed by displacement of the chloride with piperidine to give **11**. Mannich reaction of **11** with paraformaldehyde and dimethylamine followed by reduction with sodium borohydride gave the alcohol **12**. Mitsunobu reaction with 4-trifluoromethyl phenol or phenol gave **13** and **14**, respectively. The *meta*-substituted analog **15** was synthesized in the same fashion as **14** starting from 3-hydroxyacetophenone. Additional phenyl (**A**) ring 3-piperidinyl-propyloxy derivatives with substitution on the phenoxy (**B**) ring shown in Table 3 were also prepared via the synthesis outlined in Scheme 1 using various substituted phenols.

The synthesis of analogs with the 3-piperidinyl-propyloxy H_3-component (**I**) on the phenoxy (**B**) ring of fluoxetine is shown in Scheme 2. The Mitsunobu reaction between 4-benzyloxyphenol and 3-piperidinyl-propan-1-ol gave **16**. Hydrogenation of **16** afforded **17**, which was treated with **18** under Mitsunobu conditions to give **19**. The *meta*-substituted compound **21** was synthesized from **18** via a Mitsunobu reaction with 3-methoxyphenol followed by BBr_3 mediated deprotection of **20** and Mitsunobu reaction with 3-piperidinyl-propan-1-ol.

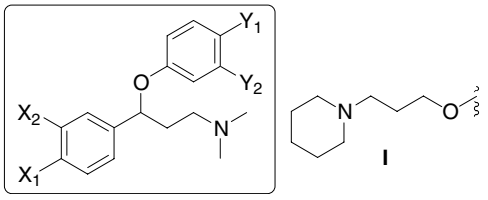
Analogs with the conformationally restricted H_3 components (**II**) and (**III**) were synthesized as shown in Schemes 3 and 4. In both cases, the H_3 component was introduced early in the synthesis. Either 4-fluoroacetophenone was treated with 1-isopropyl-piperidin-4-ol[14] in a S_NAr reaction to give **22** (Scheme 3), or 4-acetyl-benzoic acid was converted to the amide (**24**) with 1-isopropyl piperazine (Scheme 4). The substituted acetophenones were then converted to the final products **23**, **25**, and **26** in three steps as previously described.

The alkyne-linked H_3-component (**IV**) analogs were synthesized in four steps (Scheme 5). Compounds **27** and **28** were prepared under the aforementioned conditions. The resultant bromides were then coupled to 1-but-3-ynl-piperidine under Sonogashira conditions using the microwave or conventional heating to provide **29** and **30**.[19]

The regioisomers (**14**, **15**, **19**, and **21**) of the 3-piperidinyl-propyloxy (**I**) series of compounds were tested in vitro for rat SERT binding affinity (rSERT), human SERT binding affinity (hSERT), and human H_3 receptor binding affinity (hH_3) as shown in Table 1. Although all of the regioisomers had high affinity for the hH_3 receptor, the *para*-3-piperidinyl-propyloxy phenyl (**A**) ring analog **14** had the greatest affinity for rSERT. Therefore, we chose to further explore the substitution at this position with different H_3-components (**II**–**IV**).

As seen in Table 2, all of the side chains provided excellent affinity for the hH_3 receptor. However, varying the

Table 1. Structures and in vitro H_3/SERTdata for 3-piperidinyl-propyloxy (I) regioisomers

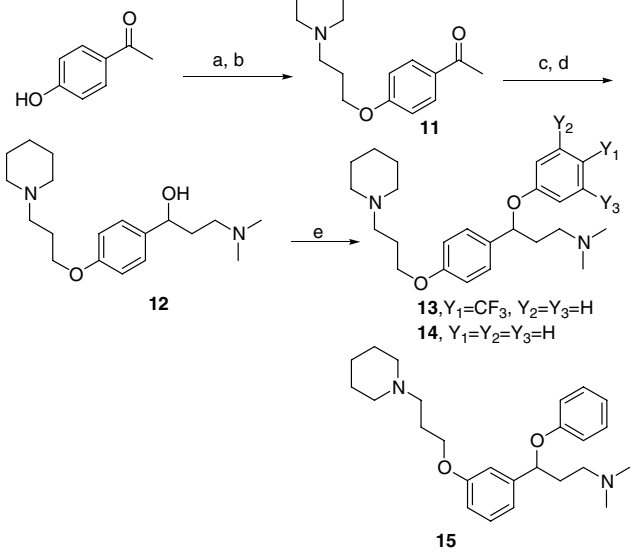


Compound	X_1[a]	X_2[a]	Y_1[a]	Y_2[a]	rSERT K_i[b] (nM)	hSERT K_i[b] (nM)	hH_3 K_i[b] (nM)
10	—	—	CF_3	—	7.7 ± 1.5	8.3 ± 0.4	6633 ± 108
13	**I**	—	CF_3	—	10 ± 2	14 ± 3	2.7 ± 0.8
14	**I**	—	—	—	1.0 ± 0.0	26 ± 1	0.6 ± 0.2
15	—	**I**	—	—	16 ± 3	199 ± 47	3.3 ± 0.4
19	—	—	**I**	—	18 ± 2	281 ± 20	1.0 ± 0.0
21	—	—	—	**I**	65 ± 7	1480 ± 342	0.7 ± 0.2

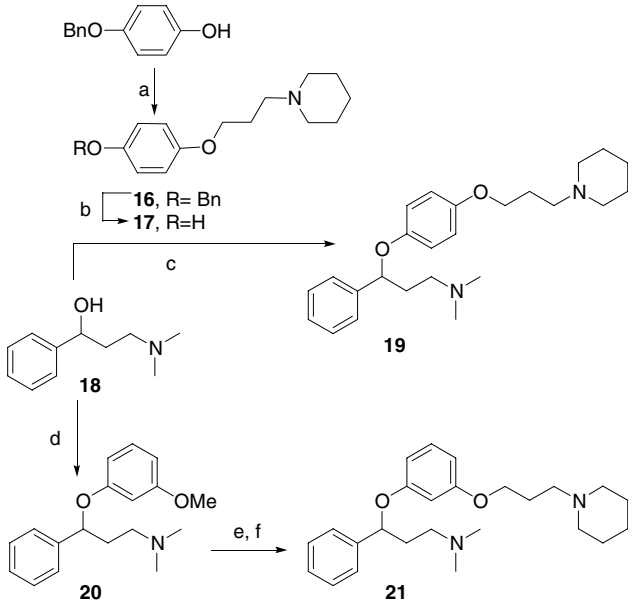
[a] —, indicates hydrogen.
[b] K_i values are reported as means ± SEM of three independent determinations.

H_3 side chain did have an effect on the SERT activity. The 3-piperidinyl-propyloxy side chain (**I**) provided the highest affinity at both rSERT and hSERT. Interestingly, the unsubstituted phenoxy (**B**) ring derivative **14** displayed less affinity in the hSERT assay than the rSERT assay. This trend was observed for all the derivatives in Table 2 when the phenoxy (**B**) ring bore no substitution. When the phenoxy (**B**) ring was substituted with 4-trifluoromethyl (i.e., **13**), there was less discrepancy between rSERT and hSERT affinity. In addition, a loss of rSERT affinity was observed when 4-trifluoromethyl substitution on the phenoxy (**B**) ring was paired with either the **I** or **IV** side chains on the phenyl (**A**) ring (**13**, **29**). The marked effect of the 4-trifluoromethyl substituents on hSERT and rSERT activity warranted further exploration of the phenoxy (**B**) ring substitution.

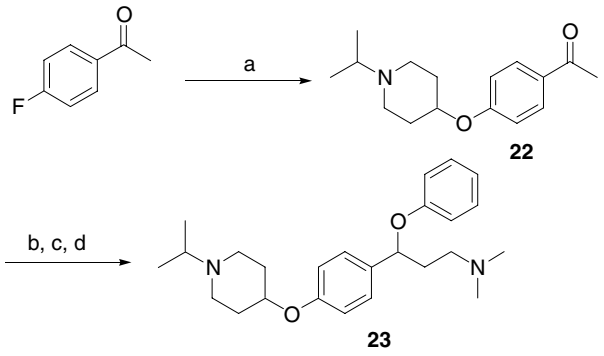
All of the phenoxy (**B**) ring derivatives synthesized (Table 3) displayed excellent binding affinity for the hH_3 receptor. Affinity was also maintained in the rSERT assay. However, in the hSERT assay, some SAR emerged. Among the compounds tested with electron donating substituents, the 4-methoxy derivative (**33**) gave the poorest affinity. Interestingly, the affinity of the 3-methoxy derivative (**34**) at hSERT was better, indicating position may have an effect on the affinity. The



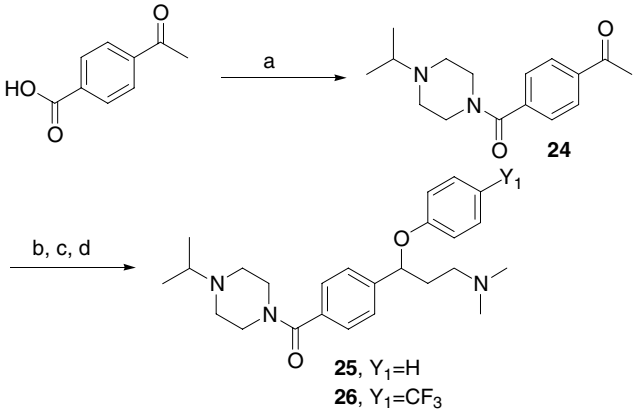
Scheme 1. Synthesis of phenyl-ring 3-piperidinyl-propyloxy analogs. Reagents and conditions: (a) 1-bromo-3-chloro-propane, K_2CO_3, acetone, reflux, 16 h (97%); (b) piperidine, Na_2CO_3, KI, *n*-BuOH, 105 °C, 36 h (100%); (c) paraformaldehyde, dimethylamine hydrochloride, HCl (concd), EtOH, 90 °C, 24 h (32%); (d) $NaBH_4$, EtOH, rt, 16 h (73%); (e) phenol, PS–PPh_3, DBAD, DCM, rt, 20 h (32–56%).



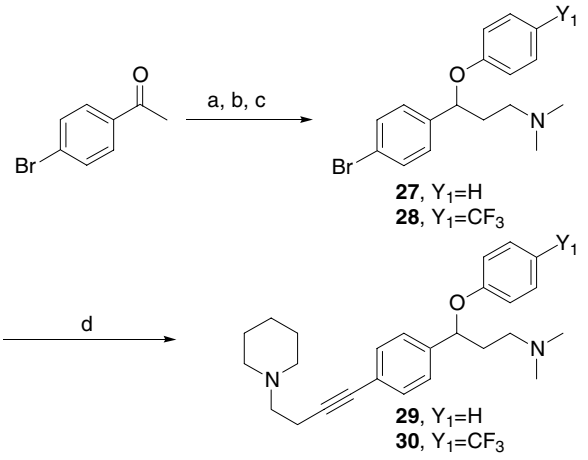
Scheme 2. Synthesis of phenoxy-ring 3-piperidinyl-propyloxy analogs. Reagents and conditions: (a) 3-piperidinyl-propan-1-ol, PS–PPh_3, DBAD, DCM, rt, 20 h (57%); (b) 10% Pd/C, EtOH, 1 atm. H_2, 72 h (85%); (c) PS–PPh_3, DBAD, DCM, rt, 20 h (10%); (d) 3-methoxy phenol, PS–PPh_3, DBAD, DCM, rt, 20 h (47%); (e) BBr_3, DCM, rt, 3 h (14%); (f) 3-piperidinyl-propan-1-ol, PS–PPh_3, DBAD, DCM, rt, 20 h (17%).



Scheme 3. Synthesis of H_3/SERT analogs with a conformationally restricted H_3 component (**II**). Reagents and conditions: (a) NaH (60%), DMF, 1-isopropylpiperidin-4-ol, 120 °C, 20 h (67%); (b) paraformaldehyde, dimethylamine hydrochloride, concd HCl, EtOH, 90 °C, 24 h (31%); (c) $NaBH_4$, EtOH, 3 h (73%); (d) phenol, PS–PPh_3, DBAD, DCM, rt, 20 h (24%).



Scheme 4. Synthesis of H_3/SERT analogs with a conformationally restricted piperazine amide H_3 component (**III**). Reagents and conditions: (a) 1-isopropyl-piperazine dihydrochloride, NMM, HOBT, EDCI, DMF, 0 °C to rt, 16 h (79%); (b) paraformaldehyde, dimethylamine hydrochloride, concd HCl, EtOH, 90 °C, 24 h (21%); (c) $NaBH_4$, EtOH, rt, 16 h (64%); (d) phenol, PS–PPh_3, DBAD, DCM, rt, 20 h (51%).

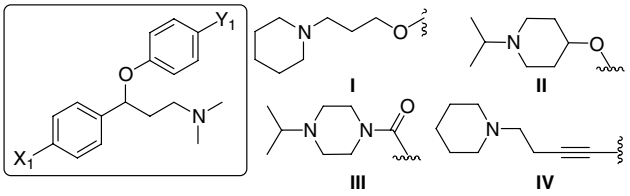


Scheme 5. Synthesis of H_3/SERT analogs with an alkyne-linked H_3 component (**IV**). Reagents and conditions: (a) paraformaldehyde, dimethylamine hydrochloride, concd HCl, 0.6 M EtOH, 90 °C, 24 h (71%); (b) $NaBH_4$, EtOH, rt, 16 h (79%); (c) phenol, PS–PPh_3, DBAD, 0.1 M DCM, rt, 20 h (55%); (d) 1-but-3-ynyl-piperidine, $Pd(PPh_3)_2Cl_2$, CuI, $HNEt_2$, DMF, 120 °C, 25 min (39%).

position of the substituents also seemed to be a factor for the electron withdrawing chlorinated derivatives. The 3-chloro-derivative, **37**, was more potent at hSERT than **36** (4-chloro) or **38** (2-chloro). Among the electron withdrawing substituents, **35** (4-fluoro) and **44** (4-cyano) provided the poorest affinity for hSERT. The enantiomers of **39** were separated via chiral HPLC to determine the eudismic ratio.[20] No significant differences in affinity were observed for hH_3, rSERT or hSERT for the enantiomers.

To ascertain the selectivity of these compounds, a prototypical compound **14** was screened against a panel of over 50 receptor targets, representing the major classes of biogenic amines and neuropeptide receptors, ion channels, and neurotransmitter transporters.[21] With the exception of histamine H_2 (66% binding at 1 μM) and noradrenaline transporter (73% binding at 1 μM),

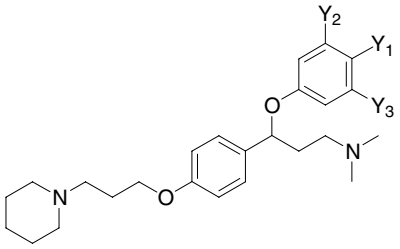
Table 2. Structures and in vitro H_3/SERT data for compounds containing side chains **I**–**IV** on the phenyl (**A**) ring



Compound	X_1[a]	Y_1[a]	rSERT K_i[b] (nM)	hSERT K_i[b] (nM)	hH_3 K_i[b] (nM)
10	—	CF_3	7.7 ± 1.5	8.3 ± 0.4	6633 ± 108
13	**I**	CF_3	10.0 ± 1.9	13.7 ± 3.2	2.7 ± 0.8
14	**I**	—	1.0 ± 0.0	26 ± 1	0.6 ± 0.2
23	**II**	—	36 ± 9	169 ± 30	0.8 ± 0.2
25	**III**	CF_3	44 ± 3	42 ± 8	2.3 ± 0.4
26	**III**	—	63 ± 6.2	245 ± 22	0.8 ± 0.2
29	**IV**	CF_3	33 ± 14	61 ± 4	5.0 ± 2.1
30	**IV**	—	6.0 ± 1.9	29 ± 2	1.3 ± 0.4

[a] —, indicates hydrogen.
[b] K_i values are reported as means ± SEM of at least three independent determinations.

Table 3. Structures and in vitro H_3/SERT data for 3-piperidinyl-propyloxy derivatives with varying substitution on the phenoxy (B) ring



Compound	Y_1[a]	Y_2[a]	Y_3[a]	rSERT K_i[b] (nM)	hSERT K_i[b] (nM)	hH_3 K_i[b] (nM)
13	CF_3	—	—	10.0 ± 1.9	14 ± 3	2.7 ± 0.8
14	—	—	—	1.0 ± 0.0	26 ± 1.1	0.6 ± 0.2
31	SCH_3	—	—	1.3 ± 0.4	10 ± 4	0.9 ± 0.1
32	CH_3	—	—	1.5 ± 0.6	16 ± 4	0.7 ± 0.2
33	OCH_3	—	—	2.0 ± 0.0	60 ± 26	1.0 ± 0.0
34	—	OCH_3	—	2.0 ± 0.0	11 ± 0	0.7 ± 0.2
35	F	—	—	1.3 ± 0.4	46 ± 13	1.0 ± 0.0
36	Cl	—	—	2.3 ± 0.42	16 ± 4	1.7 ± 0.4
37	—	Cl	—	1.7 ± 0.4	2.7 ± 0.4	0.9 ± 0.0
38	—	—	Cl	9.3 ± 1.5	21 ± 3	0.9 ± 0.1
39	Cl	Cl	—	7.0 ± 2.1	5.3 ± 0.8	6.7 ± 3.6
(−)-**39**	Cl	Cl	—	11 ± 3	3.0 ± 1.2	4.0 ± 1.2
(+)-**39**	Cl	Cl	—	9.7 ± 1.8	7.3 ± 0.7	4.3 ± 1.2
40	Cl	—	Cl	7.7 ± 2.7	9.7 ± 1.6	0.9 ± 0.1
41	Br	—	—	5.0 ± 0.7	9.0 ± 2.8	1.7 ± 0.4
42	—	Br	—	2.3 ± 0.8	4.0 ± 0.7	1.0 ± 0.0
43	NO_2	—	—	3.7 ± 0.4	8.7 ± 1.1	0.9 ± 0.1
44	CN	—	—	7.7 ± 0.4	159 ± 59	0.2 ± 0.0

[a] —, indicates hydrogen.

[b] K_i values are reported as means ± SEM of at least three independent determinations.

the affinities in the screen were all less than 40% binding at 1 μM. Compound **14** was tested against human noradrenaline transporter in-house and was shown to have a K_i of 201 nM. Compound **14** was also tested in a functional assay and was found to be an antagonist with a pA_2 of 9.3 at the human histamine H_3 receptor. The H_3 binding affinity of **14** ($pK_i = 9.2$) correlated well with the functional activity.

In summary, we have synthesized potent selective phenoxyphenyl diamine histamine H_3 receptor antagonists with affinity for the serotonin transporter. In the course of exploring the SAR of these compounds, we determined that the type (**I**–**V**) and position of H_3 side chain, as well as substitution on the phenoxy (**B**) ring, significantly affected the affinity at rSERT and/or hSERT, but had little effect on the hH_3 affinity. Overall, the 3-piperidinyl-propyloxy (**I**) side chain in the *para*-position of the phenyl (**A**) ring provided the highest affinity for SERT. In addition, we found that varying the substitution on the phenoxy (**B**) ring provided significant species differences in the hSERT and rSERT binding affinities with a few exceptions, including 3-chloro (**37**) and 3-bromo (**42**), which were nearly equipotent at both the human and rat serotonin transporters. Finally, these dual affinity aryloxyamine compounds represent a potential new class of anti-depressants with prospects for an improved clinical profile over currently prescribed SSRIs.

References and notes

1. Wong, M.-L.; Licinio, J. *Nat. Rev. Neurosci.* **2001**, *2*, 343.
2. Blier, P. *Eur. Neuropsychopharm.* **2003**, *13*, 57.
3. Bymaster, F. P.; McNamara, R. K.; Tran, P. V. *Expert Opin. Investig. Drug* **2003**, *12*, 531.
4. Takeuchi, K.; Kohn, T. J.; Honigschmidt, N. A.; Rocco, V. P.; Spinazze, P. G.; Koch, D. J.; Nelson, D. L.; Wainscott, D. B.; Ahmad, L. J.; Shaw, J.; Threlkeld, P. G.; Wong, D. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1903.
5. Meagher, K. L.; Meshaw, R. E.; Evrard, D. A.; Zhou, P.; Smith, D. L.; Scerni, R.; Spangler, T.; Abulhawa, S.; Shi, X.; Schechter, L. E.; Adree, T. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1885.
6. Martinez, J.; Pérez, S.; Oficialdegui, A. M.; Heras, B.; Orús, L.; Villanueva, H.; Palop, J. A.; Roca, J.; Mourelle, M.; Bosch, A.; Del Castillo, J. C.; Lasheras, B.; Tordera, R.; del Rio, J.; Monge, A. *Eur. J. Med. Chem.* **2001**, *36*, 55.
7. (a) Hjorth, S. J. *Neurochemistry* **1993**, *60*, 776; (b) Artigas, F.; Perez, V.; Alvarez, E. *Arch. Gen. Psychiatry* **1994**, *51*, 248; (c) Gartside, S. E.; Umbers, V.; Hajos, M.; Sharp, T. *Br. J. Pharmacol.* **1995**, *115*, 1064; (d) Dreshfield, L. J.; Wong, D. T.; Perry, K. W.; Engelman, E. A. *Neurochem. Res.* **1996**, *21*, 557.
8. Menza, M. A.; Kaufman, K. R.; Castellanos, A. *J. Clin. Psychiatry* **2000**, *61*, 378.
9. Maurizio, F.; Thase, M. E.; DeBattista, C. *J. Clin. Psychiatry* **2005**, *66*, 85.

10. (a) Letavic, M. A.; Keith, J. M.; Jablonowski, J. A.; Stocking, E. M.; Gomez, L. A.; Ly, K. S.; Miller, J. M.; Barbier, A. J.; Bonaventure, P.; Boggs, J. D.; Wilson, S. J.; Miller, K. L.; Lord, B.; McAllister, H. M.; Tognarelli, D. J.; Wu, J.; Abad, M. C.; Schubert, C.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1047; (b) Keith, J. M.; Gomez, L. A.; Letavic, M. A.; Ly, K. S.; Jablonowski, J. A.; Seierstad, M.; Barbier, A. J.; Wilson, S. J.; Boggs, J. D.; Fraser, I. C.; Mazur, C.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 702.
11. Hill, S. J.; Ganellin, C. R.; Timmerman, H.; Schwartz, J. C.; Shankley, N. P.; Young, J. M.; Schunack, W.; Levi, R.; Haas, H. L. *Pharmacol. Rev.* **1997**, *49*, 253.
12. Riemann, D.; Voderholzer, U.; Berger, M. *Neuropsychobiology* **2002**, *45*, 7.
13. Apodaca, R.; Dvorak, C.; Xiao, W.; Barbier, A.; Boggs, J. D.; Wilson, S. J.; Lovenberg, T. W.; Carruthers, N. I. *J. Med. Chem.* **2003**, *46*, 3938.
14. Dvorak, C. A.; Apodaca, R.; Barbier, A. J.; Berridge, C. W.; Wilson, S. J.; Boggs, J. D.; Xiao, W.; Lovenberg, T. W.; Carruthers, N. I. *J. Med. Chem.* **2005**, *48*, 2229.
15. Apodaca, R. L.; Jablonowski, J. A.; Ly, K. S.; Shah, C. R.; Swanson, D. M.; Xiao, W. *PCT Int. Appl.* **2004**, WO 2004037801 A1.
16. Apodaca, R.; Deng, X.; Jablonowski, J. A.; Mani, N.; Pandit, C. R.; Xiao, W. *US Pat. Appl. Publ.* **2004**, US 2004002604 A1.
17. Letavic, M. A.; Barbier, A. J.; Dvorak, C. A.; Carruthers, N. I. *Prog. Med. Chem.* **2006**, *44*, 181.
18. Fluoxetine affinity determined in-house: rSERT $K_i = 3.0$ nM (±) 0.7; hSERT $K_i = 1.8$ nM (±) 0.2 and hH_3 $K_i = 7333$ nM (±) 1080.
19. Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165.
20. Separation was achieved using a 20×250 mm Chiracel AD column, 65% EtOH in hexanes with 0.2% diethylamine at 5 mL/min.
21. Cerep ExpresSprofile® (www.cerep.fr).