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N-(1,2-Diphenylethyl)piperazines: A new class of dual serotonin/noradrenaline reuptake inhibitor

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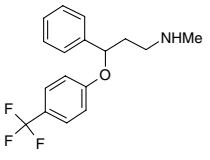
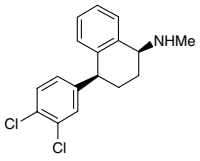
Abstract—The synthesis and structure–activity relationships of a novel series of piperazine derivatives as dual inhibitors of serotonin and noradrenaline reuptake is described. Two compounds possessed comparable in vitro profiles to the dual reuptake inhibitor duloxetine.

Release of the neurotransmitters serotonin (5-hydroxytryptamine, 5-HT), noradrenaline (norepinephrine, NA) and dopamine (DA) into the synaptic cleft results in receptor activation, and is followed by reuptake of the neurotransmitters by their respective cognate transporter proteins. Inhibition of these transporters constitutes an attractive approach to the treatment of a number of diseases.[1] For example, the selective serotonin reuptake inhibitors fluoxetine (**1**), sertraline (**2**) and paroxetine (**3**) are all established anti-depressants.[2] Reboxetine (**4**), a selective NA reuptake inhibitor, is also used to treat depression,[3] and clinical studies have been conducted in patients with seasonal affective disorder, Parkinson's disease, panic disorder and attention deficit hyperactivity disorder. Dual 5-HT/NA reuptake inhibitors, for example, venlafaxine (**5**)[4] and duloxetine (**6**),[5] have shown efficacy as anti-depressants. Duloxetine has also shown efficacy in stress urinary incontinence.[6] Inhibitors of dopamine reuptake are of interest as agents to treat Parkinson's disease and cocaine dependency,[7] and more recently the role of neurotransmitter uptake inhibitors has been examined in clinical trials and animal models of chronic and inflammatory pain.[8]



1 fluoxetine



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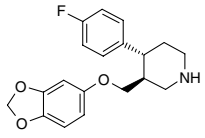
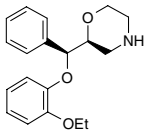
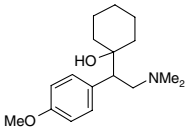


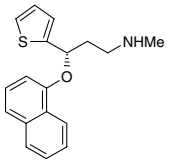
3 paroxetine



4 (±)-reboxetine

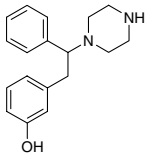


5 venlafaxine



6 duloxetine

It is notable that the compounds shown above are able to span a range of activities from selective 5-HT to selective NA and dual 5-HT/NA transporter inhibition, according to the particular structural features.[9] To identify novel leads as dual 5HT/NA reuptake inhibitors, the Pfizer compound files were searched for compounds sharing some of the structural features of compounds **1**–**6**. One particularly interesting compound was **7**, which had been prepared some years previously as an intermediate for a δ-opioid ligand programme.[10]



7
5-HT IC_{50} = 9.5 nM
NA IC_{50} = 14 nM
DA IC_{50} = 1400 nM

Keywords: Serotonin; Noradrenaline; Reuptake inhibition; Neurotransmitters; Depression; Incontinence.
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Compound **7** potently inhibited both [^{3}H]-5-HT and [^{3}H]-NA reuptake in HEK293 cells transfected with the human amine transporters with 100-fold selectivity over the dopamine transporter.[11] We therefore undertook to explore the structure–activity relationships of analogues of compound **7**.

Compounds **8**–**26** were conveniently prepared using modifications of Katritzky's amine synthesis (Scheme 1).[12,13]

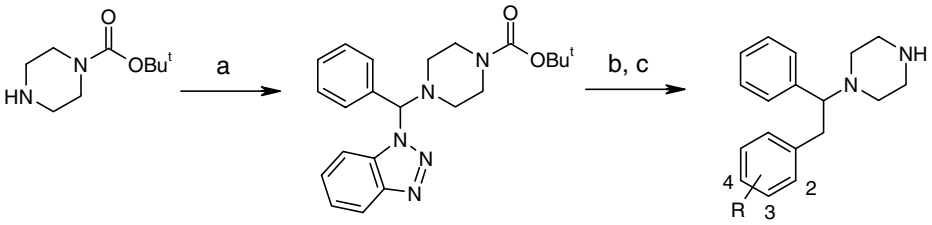
Thus, condensation of equimolar quantities of benzaldehyde, *N*-Boc-piperazine and benzotriazole in refluxing toluene with azeotropic removal of water afforded **27**, which was not isolated, but added directly as a solution in toluene to a solution of the relevant benzylic Grignard reagent (2 equiv) or zinc reagent.[14] The resulting *N*-Boc piperazines were then deprotected under standard conditions to give **8**–**10** and **12**–**24**.[15] Compounds **11** and **25** were prepared by hydrolysis of the corresponding nitriles **10** and **23** (3 equiv KOH, *t*-BuOH, reflux).[16] Compound **26** was prepared by the reaction of **27** with (2-methanesulfonyl)benzyl zinc bromide (from (2-methanesulfonyl)benzyl bromide[17] and activated zinc dust), followed by Boc-deprotection.

Compounds **8**–**27** were assayed for their ability to inhibit the uptake of [^{3}H]-5-HT and [^{3}H]-NA in HEK293 cells expressing a single human amine transporter.[11] Reference data were also measured for fluoxetine, reboxetine and duloxetine. In addition, selected compounds were also assayed against the dopamine transporter in HEK293 cells. Results are shown in Table 1.

Compound **7** has comparable potency to duloxetine versus both the 5-HT and NA transporters, with at least 100-fold selectivity over the DA transporter. The unsubstituted derivative **8** was marginally less potent against all three transporters. Of the other analogues bearing a single substituent in the 3-position (**9**–**13**), most retained good potency versus 5-HT reuptake, but were less potent than **7** versus NA reuptake, with the 3-carboxamide **11** derivative being particularly weak. This may indicate a severe steric restriction at this position.

A series of close 2-position analogues was then examined (compounds **14**–**26**). The chloro-substituted analogue **14** was comparable in potency and selectivity to duloxetine, whereas the bromo analogue **15** and the CF_3O (**16**), which is often considered a good isostere of chlorine, were about 2-fold less potent. The trifluoromethyl analogue **17** was similar, with a 3-fold difference between 5-HT and NA activities, but had >100-fold selectivity versus the DA transporter. In contrast, the methyl and ethyl analogues, **18** and **19**, possessed good potency versus 5-HT reuptake but were 3.5- to 4.5-fold less potent than duloxetine versus NA reuptake. The alkoxy analogues **20**–**23** showed a slight trend to decreasing potency with increasing size. Thus, in this series, the methoxy (**20**) and ethoxy (**21**) analogues were the best, and exhibited 2-fold lower potency than duloxetine versus 5-HT reuptake, but comparable potency to duloxetine versus NA reuptake and superior selectivity versus DA reuptake. The structure–activity relationships for substituents at the 2-position are relatively flat with both electron-withdrawing and electron-donating substituents giving good potency as long as they were not too large. Introduction of more polar substituents, as in **24**–**26**, led to a significant loss of potency.

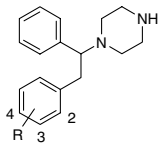
We have found that in this series of N-substituted piperazines it is possible to obtain dual 5-HT/NA reuptake inhibition similar to duloxetine (e.g., compounds **7** and **14**) or at slightly lower potency (e.g., compounds **8**, **15**–**17**) or with slightly modified 5-HT:NA reuptake inhibition ratios (duloxetine = 3:1, compounds **20** and **21** = approx 1:1). In the context of treating urinary incontinence, duloxetine, with a 5-HT:NA reuptake inhibition ratio of 3:1, has been shown to be efficacious, however, it is as yet unclear whether this ratio is optimal. It was, however, not possible to achieve very high potency (<10 nM) versus NA reuptake. It is of interest that an *ortho* substituent in one of the phenyl rings (optimally ethoxy, as in compound **22**) was necessary to obtain potent activity versus the noradrenaline transporter, cf. reboxetine, a highly selective NA reuptake inhibitor, yet potent blockade of the 5-HT transporter was also achieved. Of the compounds screened versus DA reuptake, most possessed very low potency. A recent paper[18] describes diaryl tropane derivatives as selective DA reuptake inhibitors, which would at first glance appear to have some similarity with the compounds described here, although the distance between the phenyl rings and the basic centre seems shorter. Such observations show just how subtle the dependence of activity is on structure.



27 **8-10, 12-24, 26**

Scheme 1. Reagents and conditions: (a) benzaldehyde, benzotriazole, toluene, Dean–Stark apparatus, reflux, 18 h; (b) $ArCH_2MgHal$, THF, −78 °C to 0 °C, 30 min or $ArCH_2ZnHal$, THF, 20 °C, 3 h, 35–75%; (c) 50% TFA, CH_2Cl_2, 20 °C, 80–95%.

Table 1. Inhibition of Human amine reuptake by N-substituted piperazines



Compound	R	IC_{50} (nM)		
		5-HT	NA	DA
7	3-OH	9.5	14	1400
8	H	14	39	>4000
9	3-Cl	9.4	54	NT
10	3-CN	4	300	NT
11	3-$CONH_2$	210	>400	NT
12	3-OMe	25	130	>4000
13	3-CF_3	13	>400	NT
14	2-Cl	5.4	22	1300
15	2-Br	15	35	NT
16	2-CF_3O	13	38	NT
17	2-CF_3	10	31	>4000
18	2-Me	12	90	NT
19	2-Et	16	72	>4000
20	2-MeO	18	22	11,000
21	2-EtO	13	16	>4000
22	2-*n*-PrO	22	31	NT
23	2-CF_3CH_2O	38	61	>4000
24	2-CN	87	73	NT
25	2-$CONH_2$	>400	>400	NT
26	2-SO_2CH_3	>400	270	NT
Fluoxetine		16	5200	4400
Reboxetine		590	11	>25,000
Duloxetine		6.0	19	870

Notes: IC_{50} values are a geometric mean of at least $n = 4$. A difference of <2-fold should not be considered significant.
NT, not tested.

These results were very encouraging and we therefore prepared further analogues, which are the subject of the following communication.

Acknowledgments

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11. The assays were a modification of those described by Blakely, R. D.; Clark, J. A.; Rudnick, G.; Amara, S. G.; *Anal. Biochem.* **1991**, *194*, 302. HEK293 cells expressing a single human amine transporter protein (7500 cells/well in Millipore 96-well filter bottom plates) were pre-incubated at 25 °C for 5 min with assay buffer containing vehicle (DMSO in water) or test compound. Uptake of neurotransmitter into the cells was initiated by the addition of tritiated 5-HT (50 nM), NA (200 nM) or DA (200 nM) substrates, the samples were shaken in an incubator at 25 °C for 5 min (5-HT, DA) or 15 min (NA). The assays were stopped by an ice-cold buffer wash followed by filtration. The filters were then dried before measuring the amount of radioactivity taken up into the cells by scintillation counting. Potency of test compounds was quantified as IC_{50} values, that is, concentration required to inhibit the specific uptake of radiolabelled substrate into the cells by 50% relative to maximum (vehicle only) over a 10-point dose response range. A minimum of four measurements of the IC_{50} were made. Typically, the IC_{50}s did not fit a normal distribution. Thus, geometric means were used to minimise the distorting effect of outliers. From validation data sets on all three transporter assays, we established that the 95% confidence intervals were 1.3-fold (5-HT, DAT) to 1.5-fold (NA) of the IC_{50}, that is, $IC_{50} = 4$ nM would have 95% confidence intervals of 1.4–6.6 nM.

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