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1-(2-Phenoxyphenyl)methanamines: SAR for dual serotonin/noradrenaline reuptake inhibition, metabolic stability and hERG affinity

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Abstract—A novel series of 1-(2-phenoxyphenyl)methanamines is disclosed, which possess selective dual 5-HT and NA reuptake pharmacology. Analogues with good human in vitro metabolic stability, hERG selectivity and passive membrane permeability were identified.

We recently disclosed a number of novel series with dual serotonin (5-HT) and noradrenaline (NA) reuptake inhibition (SNRI), exemplified by piperazine **1**[1] and aminopyrrolidine **2**.[2] This dual pharmacology mechanism has been shown to be an attractive approach for the treatment of a number of diseases, such as depression,[3,4] neuropathic pain[5,6] and urinary incontinence.[7,8]

As part of a multi-template approach towards dual 5-HT/NA reuptake inhibitors, we investigated other scaffolds which were structurally diverse from **1** and **2** (Fig. 1). Recent disclosures have shown that diphenylether structures such as ODAM **3** and ADAM **4** have potent monoamine reuptake activity.[9] We now wish to report our results on this series **5**, focussing on SAR for dual SNRI pharmacology along with an assessment of drug-like properties based on in vitro human metabolic stability and hERG affinity.

The target compounds were prepared in a 2-step sequence (Scheme 1). 2-Fluorobenzaldehydes **6** were displaced with phenols **7**, and then reductive amination conditions were employed to introduce the benzylic amine. This parallel synthesis approach allowed rapid evaluation of SAR for dual activity in the A and B rings.

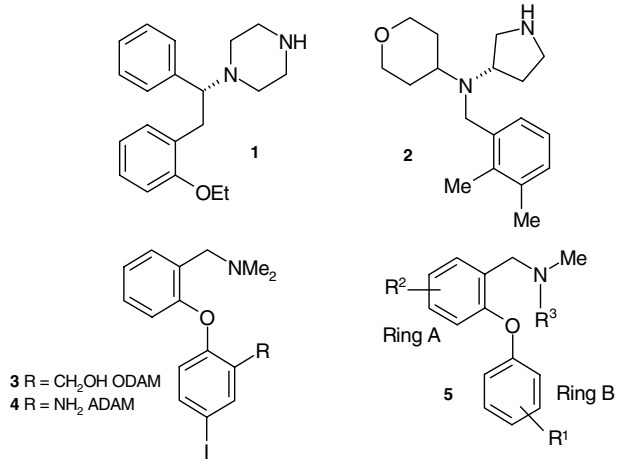

Figure 1. Recently disclosed SNRI's and structure of diphenylether template.

The tertiary amine lead **9** showed weak 5-HT activity but encouraging levels of NA potency. We then assessed the effect of substitution on the B ring. 2-Cl analogue **10** gave selective NA activity, the 3-Cl isomer **11** gave weak broad-spectrum activity and the 4-Cl isomer **12** was selective for 5-HT reuptake inhibition. Combination of 2 and 4-substitution (analogue **13)** delivered excellent dual 5-HT and NA activity with encouraging selectivity over dopamine (DA) reuptake. Having identified a substitution pattern for potent SNRI activity, we then expanded the SAR further. 2-OMe and 2-F groups were

Keywords: Serotonin; Noradrenaline; Monoamine reuptake inhibitor; Metabolic stability; hERG affinity.
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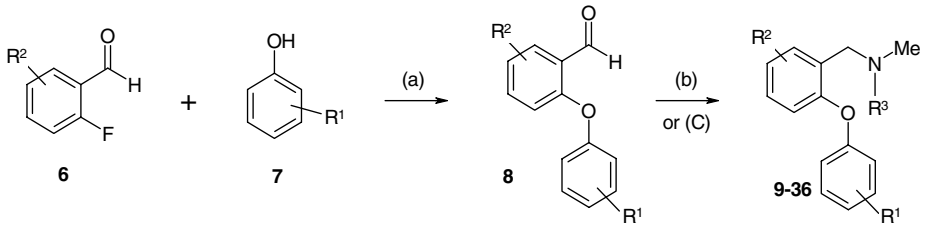


Scheme 1. Synthesis of 1-(2-phenoxyphenyl)methanamine target compounds. Reagents and conditions: (a) K_2CO_3, DMF, 100 °C; (b) R^3 = H; i—methylamine in ethanol; ii—$NaBH_4$, EtOH, rt; R^3 = Me, dimethylamine in ethanol, $NaBH(OAc)_3$, THF, rt.

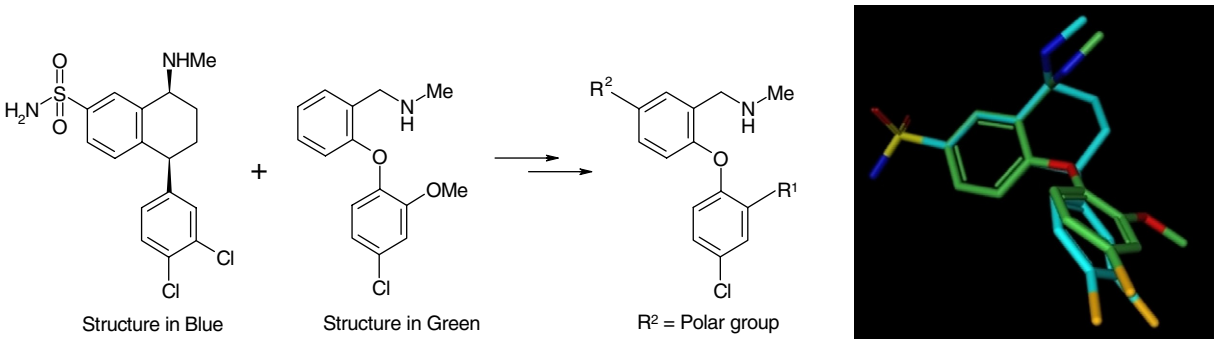
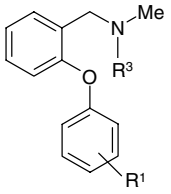


Figure 2. In silico overlap of tetrahydronaphthalene SSRIs with compound **17**.

Table 1. In vitro inhibition of monoamine reuptake,[a,b] in vitro metabolic stability,[c] hERG channel affinity[d] and *c*log *P* calculations[e] for compounds **9**–**22**



Compound	R^1	R^3	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	HLM Clint μl/min/mg	hERG K_i (nM)	*c*log *P*
1	—	—	13	16	>4000	—	—	4.2
2	—	—	9	7	727	<7	>7500	2.4
9	H	Me	660	70	NT	NT	NT	4.1
10	2-Cl	Me	282	15	2730	186	NT	4.6
11	3-Cl	Me	238	82	194	NT	NT	4.8
12	4-Cl	Me	18	256	124	NT	NT	4.6
13	2,4 di-Cl	Me	4	11	195	223	>7500	5.3
14	2-F 4-Cl	Me	6	21	421	NT	NT	4.7
15	2-Cl 4-F	Me	32	46	2130	219	NT	4.7
16	2-OMe 4-Cl	Me	6	14	3780	45	>7500	4.5
17	2-OMe 4-Cl	H	13	78	19,600	9	4380	4.0
18	2,4 di-Cl	H	56	42	506	NT	NT	4.8
19	2-Me 4-Cl	H	18	22	421	20	NT	4.8
20	2-Cl 4-F	H	NT	300	6510	NT	NT	4.2
21	2-F 4-Cl	H	73	429	NT	22	5932	4.3
22	2-Cl 4-OMe	H	22	157	5950	NT	NT	4.2

NT denotes not tested.

[a] See Ref. 10 for description of assay conditions.

[b] Monoamine reuptake IC_{50} values are geometric means of at least three experiments.

[c] Minimun measurable clearance was 7 μl/min/mg protein.

[d] K_i values are geometric means of two experiments.

[e] *c*log *P* values calculated using BioByte clogP software.

well tolerated, in particular the 2-OMe 4-Cl compound **16** retained SNRI potency and increased selectivity over DA reuptake.

All of the *N*,*N*-dimethyl amines suffered from poor metabolic stability,[11] so we then investigated the potency of the more polar secondary amines. In all cases there was

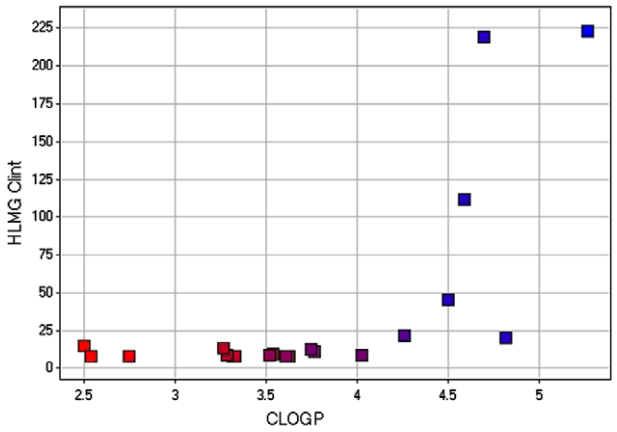


Figure 3. Plot of *c*log*P* against HLM Clint. Squares coloured by clogP.

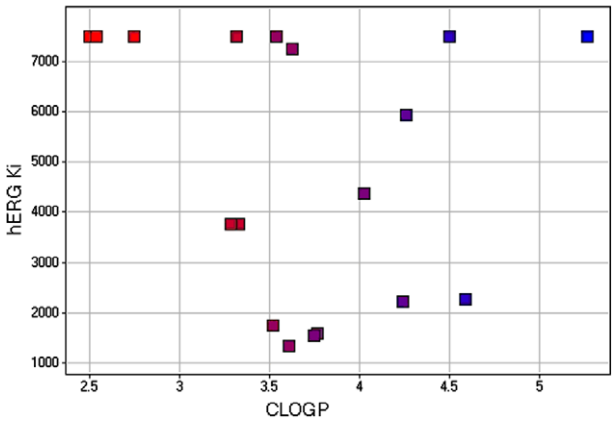
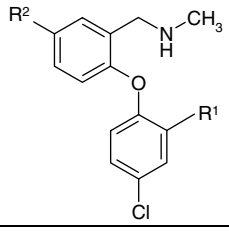


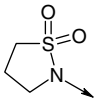
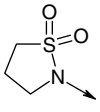
Figure 4. Plot of *c*log*P* against hERG activity. Squares coloured by clogP.

a drop in 5-HT/NA potency, but analogues **17**, **18** and **19** retained interesting levels of SNRI activity with moderate to good DA selectivity and improved metabolic stability. A number of these compounds were also assessed for their affinity for the hERG channel, and we were pleased to see weak hERG inhibition across both the secondary and tertiary amines.

We then decided to introduce a polar group onto ring A as a strategy for reducing lipophilicity further. In silico generated overlaps with a series of tetrahydro-naphthalene SSRIs,[12] indicated that polar groups may be tolerated in this area of the molecule (Fig. 2). Based on this overlap we thought that 5-HT reuptake inhibition

Table 2. In vitro inhibition of monoamine reuptake,[a,b] human microsomal stability,[c] hERG channel activity,[d] *c*log*P*[e] and Papp values for compounds **23**–**36**



Compound	R^1	R^2	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	HLM Clint uL/min/mg	hERG K_i (nM)	*c*log*P*	PAMPA Papp (10^{-6}cm/sec)
23	OMe	CN	5	>400	>40000	NT	NT	3.5	NT
24	OMe	$CONH_2$	12	62	21000	8	>7500	2.5	11
25	OMe	CONHMe	13	78	15700	8	>7500	2.8	14
26	OMe	$CONMe_2$	8	32	>40000	15	>7500	2.5	15
27	Cl	CN	28	>400	3010	NT	2213	4.2	NT
28	Cl	$CONH_2$	37	84	1210	8	>7500	3.3	10
29	Cl	CONHMe	13	38	800	9	1757	3.5	NT
30	Cl	$CONMe_2$	11	33	275	13	NT	3.3	14
31	Cl		12	17	138	12	1556	3.8	NT
32	Me	$CONH_2$	7	46	2820	8	3866	3.3	NT
33	Me	CONHMe	14	26	387	9	>7500	3.5	NT
34	Me	$CONMe_2$	17	17	172	9	3751	3.3	19
35	Me		10	11	47	11	1590	3.8	2.7
36	Me	$NHSO_2Me$	16	25	320	8	7250	3.6	2.2

NT denotes not tested.

[a] See Ref. 10 for description of assay conditions.

[b] Monoamine reuptake IC_{50} values are geometric means of at least three experiments.

[c] Minimun measurable clearance was 7 μl/min/mg protein.

[d] K_i values are geometric means of two experiments.

[e] *c*log*P* values calculated using BioByte clogP software.

would be retained, although it was unclear whether dual SNRI activity could be achieved.

A number of polar R^2 groups, such as nitriles, amides, acyclic and cyclic sulfonamides, were investigated with the B-ring substitution as 2-OMe 4-Cl, 2,4 di-Cl or 2-Me 4-Cl (Table 2). Nitriles **23** and **27** gave poor NA reuptake activity, whereas amides and sulfonamides retained good dual activity. The 2-OMe 4-Cl amides **24**–**26** had good SNRI potency and much better DA selectivity than the 2,4 di-Cl analogues **28**–**30** or 2-Me 4-Cl targets **32**–**34**. The cyclic sultam compounds **31** and **35** were potent 5-HT/NA reuptake inhibitors but selectivity was eroded in comparison to the amide R^2 substituents.

In all cases with a polar R^2 substituent, the in vitro human metabolic stability was good, with no Clint values higher than 15 μl/ml/mg. This was in contrast to the metabolic instability observed for the more lipophilic examples in Table 1, suggesting a relationship between metabolic stability and lipophilicity. This trend became clear upon analysis of all the HLM and $c\log P$ data from this series (Fig. 3), with a $c\log P$ of less than 4.0 giving good stability, and a $c\log P$ of greater than 4.5 leading to high metabolic turnover.

We also observed that lipophilicity had some influence on hERG activity, for example compounds with $c\log P < 3.0$ all had weak hERG activity. However, at $c\log P > 3.0$ it appeared that activity was more related to structure (Fig. 4), with hERG inactives spanning a wide $c\log P$ range.

We also determined whether addition of polar substituents would adversely affect membrane permeability. In vitro PAMPA screening[13] (Table 2) showed examples **24**–**26** had good passive permeability, in contrast to the sulfonamides **35** and **36**, which were poorly fluxed.

In summary, we have described a novel series of dual 5-HT/NA reuptake inhibitors with excellent selectivity over DA reuptake activity. B-ring SAR showed that a 2,4-disubstitution pattern was optimal for achieving dual pharmacology. 2-OMe 4-Cl compounds **17**, **24**, **25** and **26** combine excellent pharmacological properties along with good in vitro human metabolic stability, hERG selectivity and passive membrane permeability. By using correlations between $c\log P$ and either HLM stability or hERG affinity we were able to determine that metabolic turnover was primarily lipophilicity driven, whereas hERG affinity appeared to be more influenced by structure. Further advances in the SAR of this series will be reported in the near future.

Acknowledgments

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10. The assays were a modification of those described by Blakely et al. *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 three experiments were made.
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