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Pyridyl-phenyl ether monoamine reuptake inhibitors: Impact of lipophilicity on dual SNRI pharmacology and off-target promiscuity

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Abstract—A novel series of pyridyl-phenyl ethers are disclosed, which possess dual 5-HT and NA reuptake pharmacology with good selectivity over dopamine reuptake inhibition. An analysis of the relationship between lipophilicity and pharmacology highlighted that potent dual SNRI activity was only achievable at clog $P > 3.5$. The series was found to possess significant polypharmacology issues, and we concluded that this off-target promiscuity was related to lipophilicity.

We recently disclosed a number of novel series with dual serotonin (5-HT) and noradrenaline (NA) reuptake inhibition (SNRI), exemplified by piperazine **1**,[1] amino-pyrrolidine **2**[2] and diphenylether **3**[3] (Fig. 1). This CNS mediated dual pharmacology mechanism has been shown to be an attractive approach for the treatment of a number of diseases, such as depression,[4,5] neuropathic pain [6,7] and urinary incontinence.[8,9]

The diphenylether series, exemplified by carboxamide **3**, delivered potent and selective SNRI activity. However, further testing demonstrated that this series had metabolic stability issues. Non-P450 mediated enzymatic hydrolysis of the amide to the corresponding carboxylic acid was observed as the major route of metabolism in human hepatocyte assays. Further modification of the amide substituents did not improve metabolic stability. To circumvent this metabolic pathway, we decided to replace the amide with a pyridyl nitrogen atom, leading to the compounds of structure **4**.[10]

We now wish to report our results on this novel series, focussing on SAR for dual SNRI pharmacology. In addition the relationship between clog P, SNRI activity and off-target polypharmacology will be discussed.

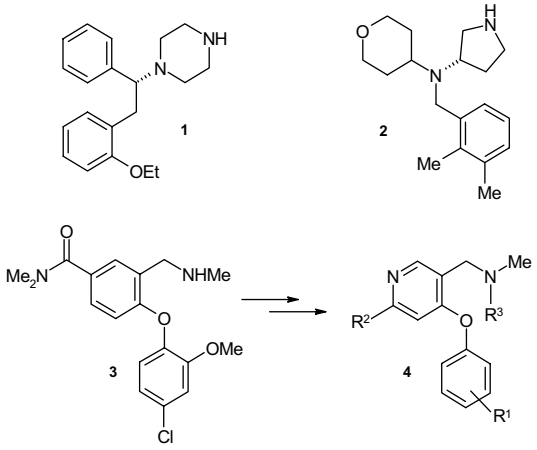

Figure 1. Structures of recently disclosed SNRIs 1–3, and new template 4.

The target compounds were prepared in a short synthetic sequence (Scheme 1). For those targets with $R^2 = H$, pyridyl chloro-aldehyde **5** was displaced with phenols **6**, and then reductive amination conditions were employed to introduce the benzylic amine. For targets with $R^2 = Me$, a different intermediate was employed. Chloro-amide **8**[10] was displaced with the required phenols **6**, then borane-THF reduction of amides **9** gave the secondary amines. Reductive alkylation with

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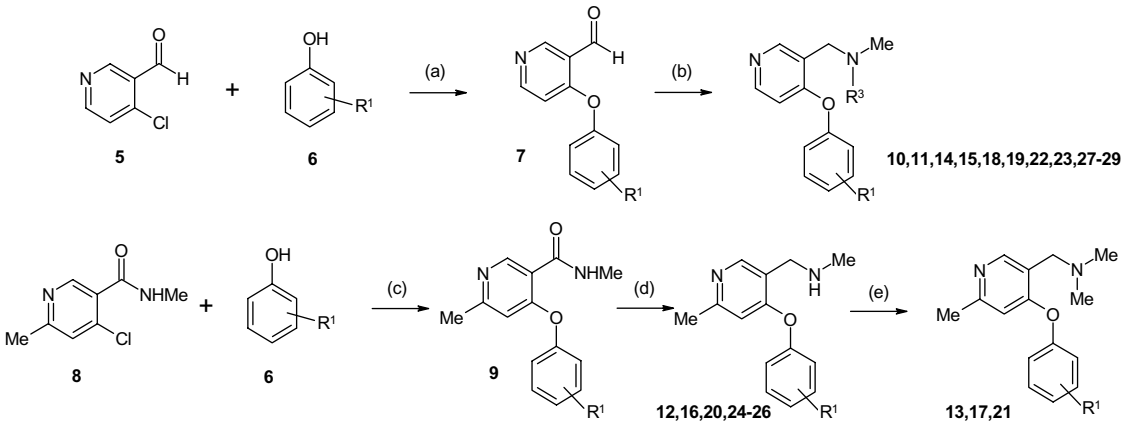
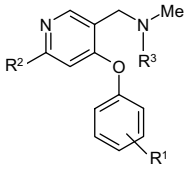


Scheme 1. Synthesis of target compounds. Reagents and conditions: (a) K_2CO_3, DMF, 60 °C; (b) R^3 = H; i—8 M methylamine in ethanol, rt; ii—$NaBH_4$, EtOH, rt; R^3 = Me AcOH, $Me_2NH{\cdot}HCl$, Et_3N, $NaBH(OAc)_3$, CH_2Cl_2, rt; (c) K_2CO_3, DMF, 100 °C; (d) 1 M BH_3–THF solution, THF, reflux; (e) HCHO, $NaBH(OAc)_3$, CH_2Cl_2, rt.

Table 1. In vitro inhibition of monoamine reuptake[a,b] and clog*P* calculations for compounds **10**–**29**



Compound	R^1	R^2	R^3	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	clog*P*
1	—	—	—	14	18	>4000	4.2
2	—	—	—	9	7	727	2.4
3	—	—	—	7	32	>4000	2.5
10	2-OMe 4-Cl	H	H	14	282	NT	2.5
11	2-OMe 4-Cl	H	Me	6	47	10,200	3.0
12	2-OMe 4-Cl	Me	H	4	83	NT	3.0
13	2-OMe 4-Cl	Me	Me	13	26	5040	3.5
14	2-Et 4-Cl	H	H	46	86	NT	3.8
15	2-Et 4-Cl	H	Me	11	18	>38,000	4.4
16	2-Et 4-Cl	Me	H	20	22	34,100	4.4
17	2-Et 4-Cl	Me	Me	19	30	>34,000	4.8
18	2-Me 4-Cl	H	H	14	246	NT	3.3
19	2-Me 4-Cl	H	Me	3	36	3230	3.8
20	2-Me 4-Cl	Me	H	6	51	NT	3.8
21	2-Me 4-Cl	Me	Me	6	26	1680	4.3
22	2-Br 4-Cl	H	H	23	85	NT	3.5
23	2-Br 4-Cl	H	Me	4	26	1970	3.9
24	2-Br 4-Cl	Me	H	10	38	NT	4.0
25	2-OMe 4-Me	Me	H	18	257	NT	2.7
26	2-Me 4-F	Me	H	231	>400	NT	3.3
27	2,4 di-Cl	H	H	39	159	NT	3.3
28	2,4 di-Cl	H	Me	8	25	2430	3.8
29	2-OEt 4-Cl	H	H	24	394	NT	3.1

NT denotes not tested.

[a] See Refs. 1–3 for description of assay conditions.

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

paraformaldehyde then yielded the corresponding tertiary amines (Table 1).

Based on the SAR for dual SNRI activity from the diphenylether series,[3] we chose to focus on 2,4-disubstitution on the phenyl ring of the pyridyl-phenyl ether series. The incorporation of a small group ortho to the pyridyl nitrogen was also investigated, due to the potential for unflanked pyridines to inhibit CYP450 enzymes.[11] The secondary amine **10** possessed potent

Table 2. ADME properties of compounds **3**, **13** and **21**

	3	13	21
clog *P*	2.5	3.5	4.3
HLM, Cl_i (μL/min/mg)	15	<7	<7
Hheps, Cl_i (μL/min/million cells)	21	<5	<5
CaCO-2 flux, AB/BA	NT	34/34	34/30
CYP2D6 IC_{50}	NT	>10 μM	>10 μM
CYP3A4 IC_{50}	NT	>10 μM	>10 μM

5-HT reuptake inhibition, with weak NA reuptake activity. Dual potency could be improved by the incorporation of the tertiary amine (examples **11** and **13**) or a methyl group on the pyridyl ring, example **12**. The best balance of SNRI pharmacology with good DA selectivity was achieved with example **13**. A similar SAR trend was then observed for other 2,4-disubstituted phenyl rings, such as 2-Et 4-Cl examples **14**–**17**, 2-Me 4-Cl analogues **18**–**21** and 2-Br 4-Cl compounds **22**–**24**. Other variations to the 4-substituent did not successfully achieve balanced SNRI activity, with both 4-Me and 4-F reducing NA reuptake activity (examples **25** and **26**). Other variations to the 2-position offered no potency advantage, for example, 2,4-di Cl analogues **27** and **28** and 2-OEt analogue **29**.

In addition to potent SNRI activity, with good selectivity over DA reuptake inhibition, examples from this series also possessed excellent in vitro metabolic stability, both in human liver microsomes and in hepatocytes (Table 2). This demonstrated that the strategy for the removal of the labile amide had successfully delivered improved metabolic stability, despite an increase in lipophilicity. Good membrane permeability with no P-gp mediated efflux (which may be predictive of good oral absorption and BBB penetration) was also achieved, along with weak P450 inhibition.

However, during this SAR investigation it became apparent that dual SNRI reuptake activity was highly dependent on lipophilicity (Fig. 2), with a clog *P* above 3.5 being required for NA activity less than 30 nM. Interestingly the relationship between clog *P* and 5-HT IC_{50} was totally different, with excellent SRI potency being achieved across a wide clog *P* range (Fig. 3).

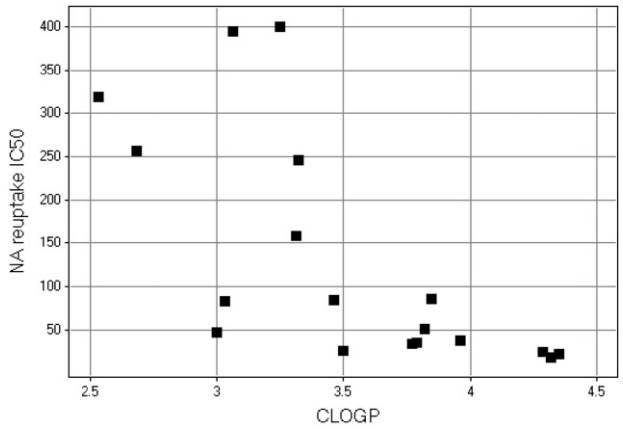


Figure 2. Plot of clog *P* against NA reuptake IC_{50}.

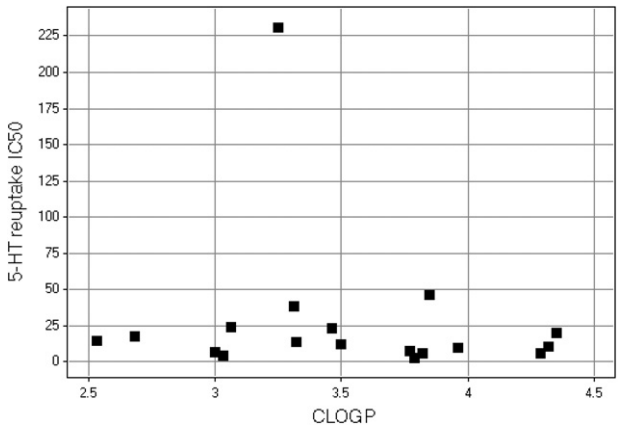


Figure 3. Plot of clog *P* against 5-HT reuptake IC_{50}.

Having to increase lipophilicity to achieve balanced dual SNRI potency was a concern, because of the potential of high lipophilicity to adversely impact pharmacokinetics,[12] polypharmacology[13] and toxicity.[14]

To determine if this series had polypharmacology issues, examples **13**, **16** and **21** were submitted to a wide range of receptor and ion channel screens (CEREP/Bioprint™ panel, 150 assays across receptor, ion channel and enzyme targets). All three examples were found to possess significant polypharmacology issues, hitting 19 targets above 50% at a screening concentration of 10 μM (Fig. 4). Importantly, many of the single point activities were potent (>80% inhibition), and these translated into multiple K_i's < 1000 nM and therefore a narrow TI between desired activity and off-target pharmacology (Fig. 5). As a comparison, the more polar amino-pyrrolidine **2** (clog *P* 2.4)[15] was submitted to the same panel, and showed a very different profile. Although the number of hits >50% at 10 μM was still quite high (Fig. 4), there were no potent hits and none of the single point data translated to K_i's of <1000 nM (Fig. 5). As a result of the off-target activity, this series of pyridyl-phenyl

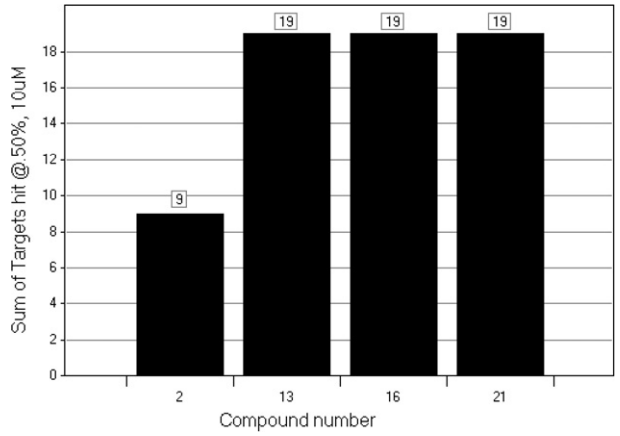


Figure 4. Plot of number of actives >50% at 10 μM in CEREP/Bioprint™ panel for compounds **2**, **13**, **16**, **21**.

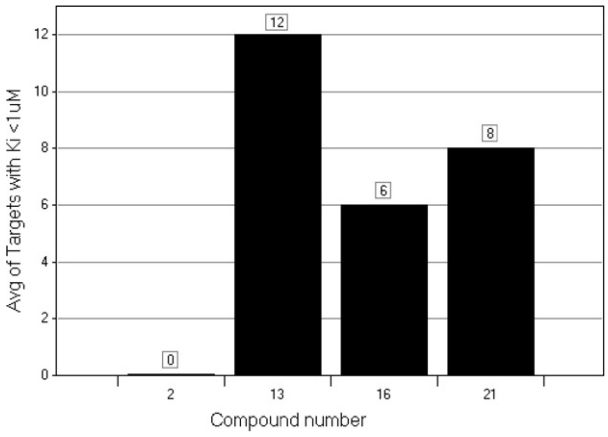


Figure 5. Plot of K_i's < 1000 nM in CEREP/Bioprint™ panel for compounds **2**, **13**, **16**, **21**.

ethers as dual SNRIs was halted. However, given that potent and selective SRI activity can be achieved at much lower lipophilicity, this template may deliver SSRIs with good drug-like properties, and this will be the subject of further publications.[16]

In summary, we have described a novel series of dual 5-HT/NA reuptake inhibitors with excellent selectivity over DA reuptake activity. The replacement of a metabolically labile amide with a pyridyl nitrogen was well tolerated pharmacologically and did deliver improved in vitro metabolic stability. Analogues from this series also possessed excellent membrane permeability and did not inhibit P450 enzymes. Potent SRI activity was achieved across a wide lipophilicity range, whereas balanced SNRI potency was only achieved at clog $P > 3.5$. This high lipophilicity contributed to a poor polypharmacology profile for the series, with examples **13**, **16** and **21** all hitting multiple targets when screened in the CEREP/Bioprint™ panel. In contrast, the more polar amino-pyrrolidine SNRI **2** demonstrated fewer off-target hits at 10 μM, no measured K_i's of <1000 nM but retained good membrane permeability. This study highlights the issues associated with chemical series, where primary potency is highly dominated by lipophilicity. Maximizing potency whilst retaining good drug-like properties is still a challenge within the monoamine reuptake inhibitor field, and additional publications will describe further advances in balancing these properties.

Acknowledgments

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15. Despite having a much lower clog P, compound **2** retained good membrane permeability with no evidence of P-pg mediated efflux. CaCO-2 flux A–B 31, B–A 30. This compound therefore retained the potential for good oral absorption and BBB penetration.
16. One example from this series with potent and selective SRI activity (clog P 2.7)[10] was also screened in the CEREP/Bioprint™ panel and showed 8 hits with >50% inhibition at 10 μM and one measured $K_i < 1000$ nM. This result reinforced the hypothesis that lipophilicity was the main contributor to the promiscuous nature of examples **13**, **16** and **21**.