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[4-(Phenoxy)pyridin-3-yl]methylamines: A new class of selective noradrenaline reuptake inhibitors

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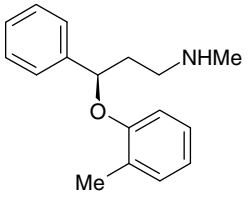
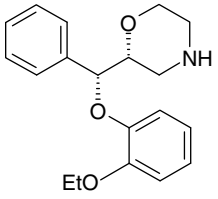
Abstract—[4-(Phenoxy)pyridine-3-yl]methylamines are disclosed as a new series of selective noradrenaline reuptake inhibitors (NRI). Structure–activity relationships established that potent NRI activity could be achieved by appropriate substitution at the 2-position of the phenoxy ring. Compound **31** demonstrated potent NRI activity combined with good selectivity over serotonin and dopamine reuptake and no significant off-target pharmacology.

Release of the neurotransmitter noradrenaline (NA) into the synaptic cleft results in adrenoceptor activation, and is followed by reuptake of noradrenaline via the noradrenaline transporter protein. Selective inhibition of noradrenaline reuptake (NRI) has been shown to be an attractive approach for the treatment of a number of diseases.[1,2] For example, atomoxetine (**1**) is a new therapy for the treatment of attention deficit hyperactivity disorder (ADHD)[3] and reboxetine (**2**) is used clinically for the treatment of depression.[4]



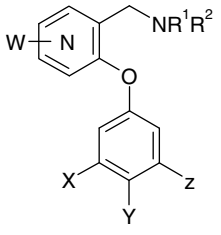
1: atomoxetine



2: (±)-reboxetine

As part of our research efforts to identify potential drug candidates, we have reported several new templates that inhibit monoamine reuptake.[5–8] In this letter, we disclose pyridinyl phenyl ethers as potent NRIs with good selectivity over serotonin (5-HT) and dopamine (DA) reuptake inhibition (SRI and DRI, respectively).

Pyridinyl phenyl ethers **3** were first disclosed as selective SRIs[9] and further modification of this template afforded dual SNRIs (e.g., **4** and **5**) (Table 1).[10] An emerging understanding of the SAR showed that the aryloxy ring played an important role in modulating SRI and NRI activity; that is, appropriate substitution at the 2-position conferred NRI activity whereas substitution at the 4-position gave SRI activity.[7,8,10] Hence, as an initial venture, we elected to delete the 4-Cl substituent from the aryloxy ring of **4** and **5** with the aim of reducing the SRI activity to furnish selective NRIs (i.e., **13** and **14**; R^3 = Et).



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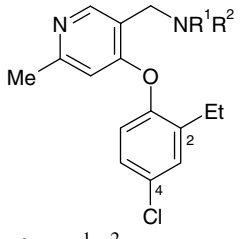

4: NR^1R^2 = NHMe
5: NR^1R^2 = NMe_2

Target compounds **15**–**32** (Table 1) were prepared using an efficient synthesis employing 4-chloro-6-methylnicotinamide **10** as an advanced intermediate (Scheme 1). This route allowed for the late stage installation of the aryloxy ring and would furnish both *sec*- and *tert*-amines **13**, **14**, respectively. Mannich reaction of 4-hydroxypyran-2-one **6** with $(MeO)_2CHNMe_2$ gave enamide **7** and aminolysis followed by rearrangement with

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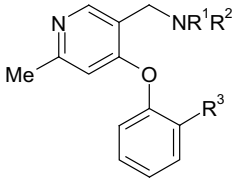
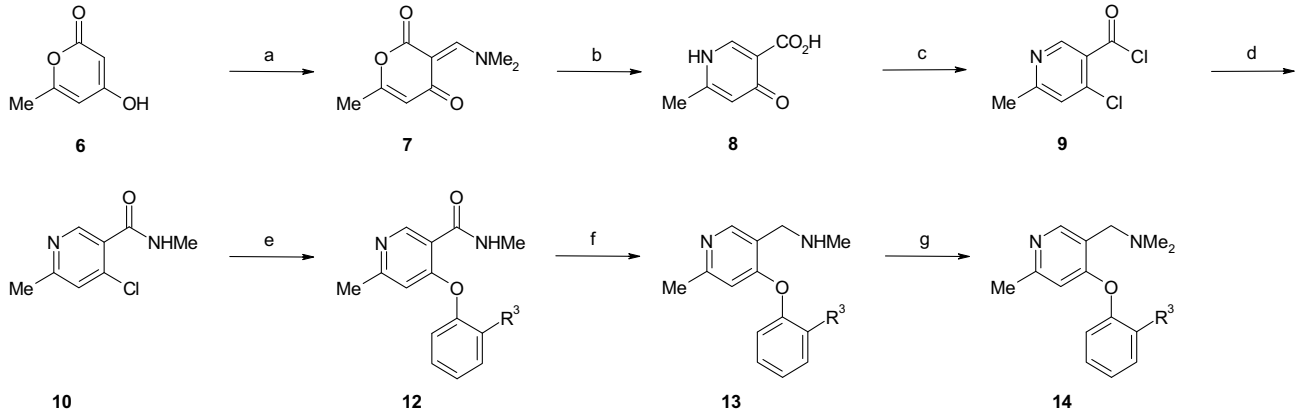
Table 1. In vitro inhibition of monoamine reuptake[a] and clog *P* for compounds **2**–**5**, **15**–**32**



15-32

Compound	NR^1R^2	R^3	NA K_i (nM)	5-HT K_i (nM)	DA K_i (nM)	clog *P*
2	—	—	5	1400	>10,000	3.3
4	NHMe	2-Et, 4-Cl	74	18	4350	4.4
5	NMe_2	2-Et, 4-Cl	22	13	NT	4.8
15	NHMe	Et	366	440	2280	3.6
16	NMe_2	Et	27	279	2660	4.1
17	NHMe	OMe	921	265	4800	2.2
18	NMe_2	OMe	296	1420	4060	2.6
19	NHMe	OEt	461	218	2390	2.7
20	NMe_2	OEt	179	4750	2150	3.2
21	NHMe	Me	951	136	1520	3.1
22	NMe_2	Me	194	235	1410	3.6
23	NHMe	SMe	232	133	1750	2.8
24	NMe_2	SMe	58	384	1930	3.2
25	NHMe	Cl	255	88	834	3.1
26	NMe_2	Cl	131	242	1160	3.6
27	NHMe	*i*-Pr	82	1980	2130	3.6
28	NMe_2	*i*-Pr	13	1470	2880	4.1
29	NHMe	*n*-Pr	438	821	1980	4.2
30	NMe_2	*n*-Pr	159	2820	2250	4.6
31	NHMe	OPh	10	823	1910	4.4
32	NMe_2	OPh	10	4060	2640	4.8

[a] See Ref. 8 for complete details of assay conditions. Monoamine reuptake K_i values are geometric means of at least three experiments. Differences of <2-fold should not be considered significant. NT denotes not tested.



Scheme 1. Synthesis of target compounds **13** and **14**. Reagents and conditions: (a) $(MeO)_2CHNMe_2$, dioxane, rt, 73%; (b) i—NH_3, H_2O, rt; ii—Me_2NH, H_2O, rt → 50 °C; iii—HCl, H_2O, rt, 70%; (c) $(COCl)_2$, cat. DMF, CH_2Cl_2, rt; (d) $MeNH_2$·HCl, NEt_3, CH_2Cl_2, rt, 78% over 2-steps; (e) ArOH (**11**), K_2CO_3, DMF, 100 °C; (f) BH_3·THF (1 M), THF, reflux; (g) HCHO, $NaBH(OAc)_3$, CH_2Cl_2, rt.

NH_3–Me_2NH–HCl afforded 4-pyridone **8**.[11] Treatment of **8** with oxalyl chloride gave pyridine **9** and reaction with $MeNH_2$ furnished amide **10**.[9] Displacement of the Cl group of **10** with phenols[12] **11** gave the aryloxy ethers **12** in good yield, reduction with borane–THF gave *sec*-amines **13**, and finally reductive alkylation with formaldehyde afforded the *tert*-amines **14**.

Deletion of the 4-Cl of *tert*-amine **5** proved to be successful strategy in the identification of selective NRIs as *tert*-amine **16** retained NRI activity whilst reducing SRI activity by 20-fold. Compound **16** was a potent NRI (K_i 27 nM) with selectivity over both SRI (10-fold) and DRI (100-fold) (Table 1). In contrast, the corresponding *sec*-amine **15** had a significant loss in both SRI and NRI activity compared to **4**. Compound **16** had drug-like physicochemical properties consistent with CNS target space[13] (m.wt. 270; clog *P* 4.1; log $D_{7.4}$ 2.1; TPSA 25 Å^2), combined with good metabolic stability in human liver microsomes (HLM, Cl_i < 7 μL/min/

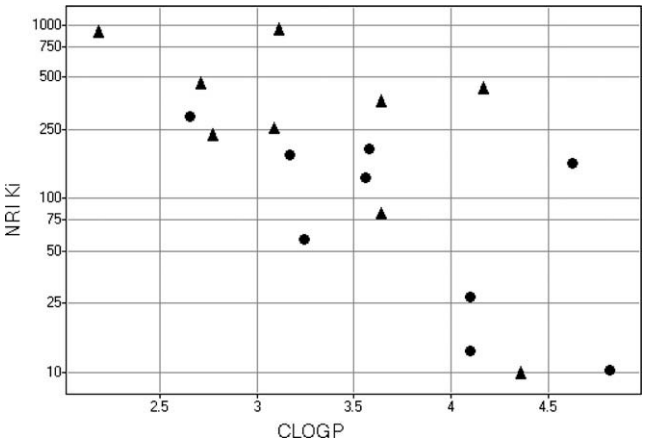


Figure 1. Plot of NRI activity versus clog *P* for *sec*-amines **13** (▲) and *tert*-amines **14** (•).

mg), and low ion channel activity as measured by binding to potassium hERG channels ([^{3}H]-dofetilide, $IC_{50} > 20$ μM). Hence **16** was selected as a lead for our drug discovery programme.

Further, SAR was directed at improving NRI activity by exploring a broader set of 2-substituents on the aryloxy ring in both the *sec*- and *tert*-amine series **17**–**32** (Table 1).[14] NRI activity was clearly dependant on the lipophilicity of the 2-substituent[15] with potent NRI activity tracking with increased lipophilicity (Fig. 1). In addition, clear trends in SAR of the *sec*- and *tert*-amines also emerged: *tert*-amines invariably showed a significant advantage in NRI activity compared to the corresponding *sec*-amines (e.g., **16** vs **15**; **28** vs **27**) (Fig. 1, • vs ▲) and *tert*-amines were generally weaker SRIs compared to *sec*-amines (e.g., **18** vs **17**; **20** vs **19**). No compound demonstrated any significant DRI activity. The combination of these SARs resulted in *tert*-amines yielding the most potent NRIs with better selectivity for SRI and DRI. Two exceptions to these trends were the 2-*n*-Pr group (**29**, **30**) which under performed relative to clog *P*, and the 2-OPh substituent which gave *sec*- and *tert*-amines (**31**, **32**) with equivalent NRI potencies.

From these experiments, **28**, **31** and **32** emerged as having a superior combination of NRI activity ($K_i < 15$ nM) combined with selectivity over SRI and DRI (>80-fold). Compound **31** offered the benefit of lower lipophilicity as measured by octanol-buffer distribution coefficients (log *D*) (Table 2). Minimising lipophilicity was an important selection criteria as lipophilic compounds have an increased risk of hepatic metabolic clearance,[16] off-target promiscuous pharmacology[17] and in vivo toxicological outcomes.[18]

Table 2. Physicochemical and ADME properties of **28**, **31** and **32**[a,b]

	28	**31**	**32**
log $D_{7.4}$	2.5	1.6	2.4
pK_a	ND	9.0 and 4.4	8.7 and 4.4
HLM, Cl_i μL/min/mg	17	<7	29
CYP2D6 inhib., IC_{50} μM	ND	3.4	0.61
MDCK-mdr1, AB/BA	38/39	25/41	41/36

[a] See Ref. 19.
[b] ND denotes not determined.

Evaluation of **28**, **31** and **32** in high throughput in vitro ADME screens showed **31** to have the advantage of better metabolic stability and weaker CYP2D6 inhibition (Table 2).

Previously, pyridinyl phenyl ethers such as **4** and **5** had shown an unacceptable level of promiscuous off-target pharmacology which had been attributed to the high lipophilicity of these structures.[10] Compound **31** was screened for off-target pharmacology against a panel of 110 receptors, enzymes and ion channels (CEREP, Bioprint) and was found to have binding affinity for only the 5-HT_{2C}, κ-opioid and μ-opioid receptors (>80% inhibition at 10 μM). Further evaluation showed **31** to have no confirmed functional activity at these targets at ⩽2.5 μM. Compounds **4** and **31** are isolipophilic (by clog *P*) which suggested an important structural component to the cleaner pharmacology profile of **31**.

Additional screening in vitro[19] showed **31** to have good membrane permeability (CaCO-2 11/19) with low affinity for P-gp efflux transporters (MDCK-mdr1 25/41) suggesting the potential for good oral absorption and CNS penetration. Compound **31** had good metabolic stability in human liver microsomes ($Cl_i < 7$ μL/min/mg) and human hepatocytes (Cl_i 8 μL/min/mg) consistent with low predicted clearance. Compound **31** had no significant inhibition of CYP450 enzymes (1A2, 2D6, 3A4; IC_{50}s > 3 μM) and modest ion channel activity as measured by binding to potassium hERG ([^{3}H]-dofetilide, K_i 5.8 μM), sodium (site 2, K_i 3.4 μM) and calcium (L-type diltiazem site, K_i 1.2 μM) channels.

Further pharmacological evaluation in vivo, in microdialysis experiments,[20] showed **31** increased NA levels in interstitial fluid of the prefrontal cortex of conscious rats by 400% above pre-drug baseline levels (0.3 mg/kg administered sc, $n = 4$).[21]

In summary, pyridinyl phenyl ethers are disclosed as a new series of selective NRIs. Structure–activity relationships established that potent NRI activity could be achieved by appropriate substitution at the 2-position of the phenoxy ring. Compound **31** demonstrated potent NRI activity combined with good selectivity over serotonin and dopamine reuptake and no significant off-target pharmacology. Based on this profile, **31** (PF-3665343)[22,23] was selected as a candidate for further evaluation in pre-clinical disease models. The results of these studies will be reported in future publications.

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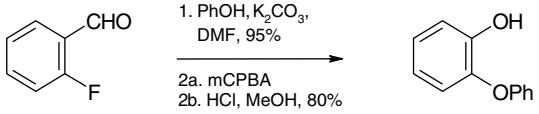
12. Phenols (**11**) are commercially available except for **11**: R^3 = OPh which was prepared as shown.



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19. CaCO-2: human colon adenocarcinoma cell line. MDCK-mdr1: Madin-Darby canine kidney cell line expressing the P-glycoprotein transporter (P-gp). Flux across cells were measured at 10 μM substrate concentrations. Figures quoted correspond to the flux rates ($P_{app} \times 10^{-6}$ cm s^{-1}) for apical to basolateral (AB) and basolateral to apical (BA) directions. The minimum measurable intrinsic clearance (Cl_i) in human liver microsomes and human hepatocytes was 7 μL/min/mg protein. The in vitro metabolic stability as expressed by Cl_i is derived from the measured half-life ($T_{1/2}$). For **31**, $T_{1/2} > 120$ min.
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21. Rat NA functional transporter activity was measured in HEK293 cells expressing the rat NA transporter with [^{3}H]-NA as substrate. For **31**, rNRI, IC_{50} = 2.5 nM (n = 7).
22. Data for **31**: ^{1}H NMR (CD_3OD, 400 MHz) δ 2.19 (s, 3H), 2.39 (s, 3H), 3.58 (s, 2H), 6.44 (s, 1H), 6.78 (d, 2H), 7.05 (m, 1H), 7.20 (m, 1H), 7.22–7.41 (m, 5H), 8.20 (s, 1H); LRMS APCI *m*/*z* 321 (MH^+). For **31** $PhSO_3H$ salt: mp 155 °C.
23. There is a significant discrepancy between calculated clog *P* (4.4) and measured log *P* (3.2) values for **31**. It is our hypothesis that **31** undergoes hydrophobic collapse to adopt a folded structure and so reduce the exposure of lipophilic faces.