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Novel, achiral aminoheterocycles as selective monoamine reuptake inhibitors

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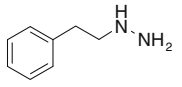
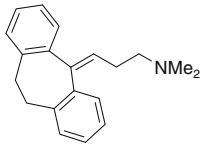
ABSTRACT

A variety of novel aminoheterocycle scaffolds as selective monoamine reuptake inhibitors have been prepared and one of these scaffolds is achiral. The main elements responsible for hERG channel, CYP2D6 and CYP3A4 inhibition were identified.

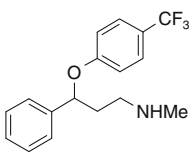
Depression is an often disabling condition that will affect greater than 15% of the general population in their lifetime.[1,3] The etiology of the disease was widely considered to be due to sub-optimal concentrations of the monoamine neurotransmitters serotonin (5-HT) and norepinephrine (NE) in the central nervous system (CNS).[2] It is now apparent that depression is a consequence of dysfunctional endocrine, immune and neurotransmitter systems.[3] However, most antidepressants have been developed based on the assumption that an imbalance in monoamine concentration is the primary cause. Early therapeutics, which included the monoamine oxidase inhibitors (MAOIs, e.g., Phenelzine, **1**) and the tricyclic antidepressants (TCAs, e.g., Amitryptyline, **2**), treated a broad array of symptoms commonly associated with depression (Fig. 1). This broad activity was largely due to their ability to increase the synaptic concentration of either all three (5-HT, NE and dopamine, DA), or two (5-HT and NE) monoamine neurotransmitters respectively. These therapeutics are far from ideal, however, due to side effects caused by 'off-target' pharmacology and a potential to cause drug–drug interactions.[4] One breakthrough in modern antidepressant therapy came in the 1980s with the introduction of the serotonin selective reuptake inhibitor (SSRI) class of drugs (e.g., Fluoxetine, **3**). The serotonin reuptake transporter (SERT) is located on the pre-synaptic membrane and is responsible for signal termination and recycling of 5-HT that is released into the synaptic cleft during synapse firing. Inhibition of the serotonin transporter increases the concentration and duration of action of 5-HT, thus alleviating the symptoms of major depressive disorder (MDD) associated with low levels of 5-HT (mood deregulation, anxiety and sleep disorders). Although these therapeutics treated a smaller range of symptoms, the high level of selectivity led to improved safety and tolerability through a remarkably reduced side effect profile. Unfortunately, full remission was only observed in approximately one third of treated patients. To address the remaining clinical need, serotonin norepinephrine selective reuptake inhibi-



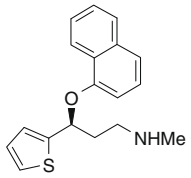
1, Phenelzine (Nardil), a MAOI



2, Amitriptyline (Elavil), a TCA



3, Fluoxetine (Prozac), an SSRI



4, Duloxetine (Cymbalta), an SNRI

Figure 1. Some marketed antidepressants.

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tors (SNRIs, e.g., Duloxetine, **4**) emerged that were able to treat as broad an array of symptoms as the earlier TCAs while showing limited affinity for the receptors that caused side-effects (muscarinic, α-adrenergic, histaminergic). This resulted in a tolerability and safety profile comparable to SSRIs while also addressing symptoms such as lack of energy, lack of concentration and co-morbid pain. The SNRI class of anti-depressants are more likely to result in remission, and some (e.g., Duloxetine, **4**) are also approved to treat other diseases such as anxiety, fibromyalgia and neuropathic pain.

Elevating DA levels in addition to 5-HT and NE would generate a class of therapeutics referred to as broad spectrum antidepressants or triple reuptake inhibitors (TRIs). TRIs would be expected to show superior efficacy to the SSRIs and SNRIs.[5] Inhibiting DA reuptake may address the anhedonia, lack of motivation, and lack of attention components of MDD that the SSRIs and SNRIs do not.[6] Duloxetine (**4**) has been approved by the Food and Drug Administration (FDA) for the treatment of diabetic neuropathic pain, and drugs which are TRIs may provide a broader spectrum of pain relief in animal models of experimental pain than single mechanism of action of reuptake inhibitors.[7] Thus, TRIs may provide the next major advance in antidepressant and pain therapy.

During our efforts to uncover novel series of monoamine reuptake inhibitors, we discovered that **7** (Table 1), a member of one of our SNRI series of indolyl aryl propylamines **5** (Fig. 2),[8] exhibited weak inhibition of DAT. We considered this compound an excellent starting point for our search for new TRI scaffolds. Herein we describe the synthesis and SAR of several novel achiral and chiral series of monoamine reuptake inhibitors derived from the C(5)-indoles **5** (**6a–c**, Fig. 2). Lead optimization of the achiral substructure **6a** provided molecules that were potent TRIs. Also described are our attempts to minimize undesirable hERG channel inhibition and CYP450 inhibition, and efforts to reduce the risk of forming active metabolites.

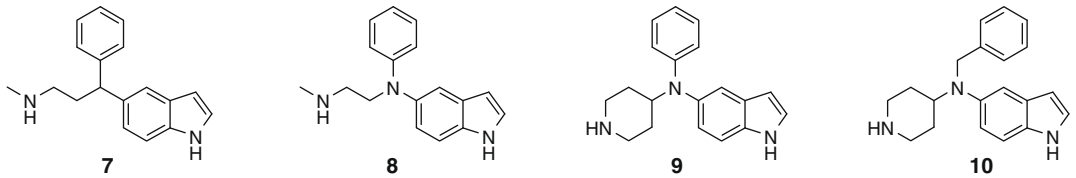
Interestingly, the majority of monoamine reuptake inhibitors that have been approved by the FDA possess a stereogenic centre. We were particularly excited about the prospect of finding and developing a novel achiral series. We had been frustrated by difficult enantioselective syntheses and inefficient enantioselective separations for advanced compounds with structures related to **5**. Thus, we sought to replace the C(5)-carbon of **7** with a nitrogen atom to form tertiary amine **8** (Table 1). We were disappointed to find that **8** was only weakly active. Nevertheless, we felt we would be able to develop this series of TRIs further. Our past experience with *N*-methyl amino-containing monoamine reuptake inhibitors[9] suggested that a significant metabolic pathway for this series would be N-demethylation. Our concern was that the resulting metabolites might be active and complicate future in vivo studies, carry additional clinical safety concerns, or both. To address this, we synthesized 4-aminopiperidine **9** (Table 1). Although a 3-aminopiperidine or 3-aminopyrrolidine would have offered a more appropriate structural mimic, these possessed a stereogenic centre and were less desirable. Unfortunately, **9** showed a decrease in potency at all three transporters. Undeterred, we reasoned that perhaps the restricted conformation might be preventing the molecule from adopting the optimal geometry to bind to the monoamine transporters. We were later delighted to discover that increasing the number of rotatable bonds by inserting a methylene linker between the phenyl hydrophobe and the C(5)-nitrogen resulted in an enormous increase in potency at SERT, NET and DAT (**10**, Table 1).

With this encouraging result we quickly assessed the physicochemical and pharmacological properties of compound **10**. We were concerned about the potential to form reactive metabolites through the formation of a diiminoquinone-like intermediate (Fig. 3).[10] In our hands, however, low or no risk of clinically relevant CYP3A4 time dependant inactivation in human liver microsomes was predicted for **10**.[11] Time dependent inactivation would have been one indicator of reactive metabolite formation. Reassured, we developed additional SAR.

Two potential liabilities that emerged were strong hERG channel inhibition and a potential for drug–drug interactions due to potent CYP2D6 inhibition (Tables 2 and 4). Although we had been keen to avoid generating a chiral molecule, we recognized that the relatively high pK_a of the 4-aminopiperidine **10** might be contributing to the potent hERG interaction.[12] Therefore, 3-aminopiperidine **11** and 3-aminopyrrolidine **12** were synthesized (Table 2). We expected these to show a reduced pK_a due to the 1,4-arrangement of polar heteroatoms. Piperidine **11** was a 10-fold less potent inhibitor of the serotonin and norepinephrine transporters and showed no reduction in hERG interaction. Although the pyrrolidine **12** was a fairly potent and balanced TRI, it also showed no reduction in hERG binding. It appeared that any reduced binding to the hERG channel due to a lowered pK_a was being counterbalanced by the increased lipophilicity. The measured log *D* values for **10**, **11** and **12** were 0.6, 1.20 and 1.25, respectively. The lack of a clear advantage of these chiral scaffolds led us to return our focus to the 4-aminopiperidine scaffold (**6a**).

We rapidly established that although several alternatives to the indole heteroaryl group were possible, a compelling replacement did not present itself (Table 2). Indazole (e.g., **13**) was tolerated for potency, but despite an increase in polar surface area its affinity for the hERG channel was even stronger. The *N*(1)-indole/indazole hydrogen bond donor seemed to be one element contributing to both hERG and CYP inhibition. Unfortunately, benzothiophene **14**

Table 1
In vitro inhibition of monoamine reuptake[a]



Compound	pK_i SERT	pK_i NET	pK_i DAT	hERG IC_{20} (μM)
4	9.3	8.1	6.6	<0.3
7	7.5	8.0	6.7	<1
8	6.4	6.7	6.3	—
9	6.0	5.9	<5.8	—
10	9.1	8.1	7.3	1

[a] pK_i values are the geometric mean of at least three experiments.

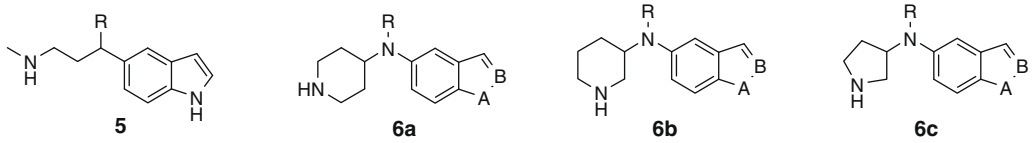


Figure 2. Examples of our novel monoamine reuptake inhibitors.

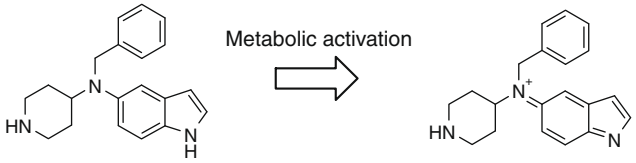
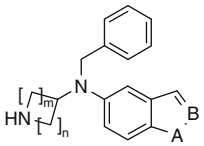


Figure 3. Postulated pathway to form a reactive diiminoquinone-like intermediate.

Table 2
In vitro inhibition of monoamine reuptake[a]



Compd	*n*	*m*	A	B	pK_i SERT	pK_i NET	pK_i DAT	hERG IC_{20} (μM)
10	2	2	NH	CH	9.1	8.1	7.3	1
11	3	1	NH	CH	8.2	7.2	7.4	<1[b]
12	2	1	NH	CH	7.7	8.0	7.5	<1
13	2	2	NH	N	8.9	7.8	7.3	<1
14	2	2	S	CH	7.9	6.7	6.7	1
15	2	2	NCH_3	CH	8.4	7.6	7.1	5.1

[a] pK_i values are the geometric mean of at least three experiments.
[b] Data for (+)-**11**.

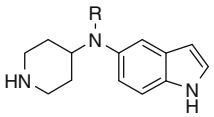
favoured the serotonin transporter and also carried a high risk of forming reactive intermediates,[13] and although the *N*(1)-methyl indole **15** showed a good in vitro profile and significantly reduced hERG affinity, we were concerned that it might generate pharmacologically active metabolites via N-demethylation.

Turning our attention to the benzyl side chain (Table 3), we found that an unsubstituted methylene linker was optimal for TRI potency. Substitution (e.g., **16**) or formation of the amide (e.g., **17**) was not tolerated for potency, and generated weakly active SSRIs. Extension of the linker, in contrast, generated a relatively good SNRI (e.g., **18**). Although replacement of the phenyl ring with an aliphatic group (e.g., tetrahydro-4-pyran **19**) was poorly tolerated for potency, it also led to reduced CYP2D6 and CYP3A4 binding (Table 4). Thus, it became clear that the aromatic hydrophobe was a strong contributor to the drug–drug interaction potential of this scaffold, likely due to its increased lipophilicity.

Having established that a methylene linked aromatic was optimal for potency, we next sought to optimize drug-like properties through appropriate substitution on the phenyl ring (Table 3, only selected examples shown for clarity). We discovered that *ortho*-substitution tended to generate balanced SNRIs (e.g., **20**, **23**), *meta*-substitution tended towards our desired TRI profile (e.g., **21**, **24**, **27**), and *para*-substitution tended to generate potent SSRIs (e.g., **22**, **25**).

We therefore concentrated our efforts on finding the optimal *meta*-substituent. We expected introduction of polarizing heteroatoms to reduce inhibition of CYP450 enzymes and the hERG ion channel simultaneously, while also improving stability towards human liver microsomes. This approach was met with some success. For example, while nitrile **24** maintained excellent potency, there was minimal effect on hERG binding, little improvement to the stability in human liver microsomes, and CYP3A4 inhibition grew stronger (Table 3). Sulfonamide **26** did show excellent stability towards human liver microsomes and no detectable hERG channel binding (Table 3), but unfortunately a combination of reduced membrane permeability and increased number of hydrogen bond donors resulted in moderate P-gp efflux. We had determined through in vitro and in vivo studies that even low levels of P-gp efflux (>2) led to significantly reduced CNS penetration in this series (data not shown). In addition, during our regular screening for the potential to form reactive intermediates, we were dismayed when **24** and **26** displayed moderate potential for clinically relevant CYP3A4 time dependent inactivation (data not shown). This data led us to conclude that for this scaffold it would be challenging

Table 3
In vitro inhibition of monoamine reuptake[a] and hERG[12]



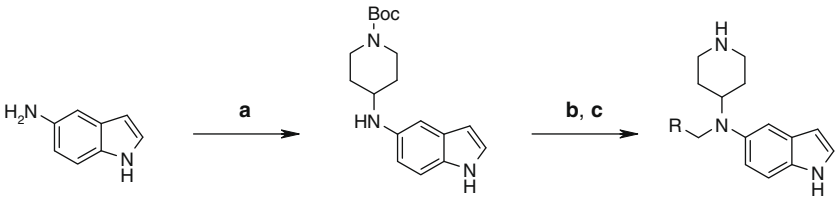
Compd	R	pK_i SERT	pK_i NET	pK_i DAT	hERG IC_{20} (μM)
10	CH_2Ph	9.1	8.1	7.3	1
16	$CH(CH_3)Ph$	7.4	5.8	5.8	—
17	C(O)Ph	7.6	6.1	5.4	—
18	CH_2CH_2Ph	8.2	7.3	6.8	—
19	CH_2(4-THP)	7.4	7.4	6.3	—
20	CH_2(2-F-Ph)	8.4	7.9	6.9	—
21	CH_2(3-F-Ph)	8.9	7.9	7.1	—
22	CH_2(4-F-Ph)	8.7	6.6	6.6	—
23	CH_2(2-CN-Ph)	8.4	8.2	6.3	—
24	CH_2(3-CN-Ph)	9.6	8.0	7.5	<1
25	CH_2(4-CN-Ph)	8.6	6.0	6.1	—
26	CH_2(3-SO_2NH_2-Ph)	8.2	7.1	7.6	>10
27	CH_2(3-MeO-Ph)	8.8	8.4	7.1	1.0

[a] pK_i values are the geometric mean of at least three experiments.

Table 4
In vitro human liver microsomal stability,[14] CYP2D6 and CYP3A4 inhibition[15] and CACO-2 efflux ratio[16] data for selected compounds

Compd	HLM (μL/min/mg)	CYP2D6 IC_{50} (μM)	CYP3A4 IC_{50} (μM)	ER (BA/AB) (cm/s × 10^{-6})
4	38	0.6	17	0.6 (9/15)
7	11	3	5	—
8	—	2	40	—
9	—	26	14	—
10	17	0.1	3	1 (6/6)
11	23[a]	0.3	5	—
12	36	2	2	—
13	—	0.5	0.4	—
14	18	19	35	0.3 (0.4/1.4)
15	26	5	>50	0.4 (4/7)
19	—	>50	27	—
24	13	2	0.5	3.6 (14/4)
26	2	2	3	4.2 (3/0.7)

[a] Data for (+)-**11**.



Scheme 1. Reagents and conditions: (a) 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 18 h; (b) RCH_2Br, Et_3N, DMAP, sealed tube, 100 °C, 18 h; (c) TFA, CH_2Cl_2, rt, 1 h.

to combine CNS drug-like properties, potent TRI activity, and low potential to form reactive metabolites in a single molecule.

In general, compounds of substructure **6a–c** were synthesized in an expedient three step sequence represented by Scheme 1. Thus, heterocyclic amine **27** underwent reductive amination with the appropriate *N*-Boc protected aminoketone to form **28**, and this was followed by N-alkylation and a final deprotection to furnish **29**. Compounds **6b** and **6c** were synthesized in a similar fashion, starting from the *N*-Boc-protected piperidin-3-one or pyrrolidin-3-one, respectively.

In conclusion, several novel scaffolds **6a–c** were discovered that were excellent inhibitors of monoamine reuptake. Scaffold **6a** was achiral, an uncommon characteristic amongst anti-depressant drugs developed since the early tricyclic antidepressants. We found that subtle modifications to the phenyl ring, quite remote from the suspected C(5)-aminoindole toxicophores, could still effect the propensity to form reactive metabolites. Key elements responsible for CYP2D6, CYP3A4 inhibition and hERG channel interaction were also found. Although scaffold **6a** did not deliver in a single molecule our desired target product profile, the key learnings described herein have been used to develop improved scaffolds that will be reported in due course.[17]

Acknowledgements

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10. Neither the postulated electrophilic diiminoquinone-like intermediate or its derivatives were identified in metabolite ID studies.
11. TDI was measured as the percentage of CYP3A4 inactivation after pre-incubation of the test compound for 25 min with human liver microsomes. The potential risk was ranked low if the measured value was less than that observed for ethynylestradiol (no clinical effects observed due to TDI), high if it was greater than that observed for verapamil (drug–drug interactions observed in the clinic), and moderate if it lay between ethynylestradiol and verapamil.
12. hERG IC_{20} values calculated using the PatchXpress 7000A (MDS, Inc. Toronto, Canada) to carry out electrical recording of K^+ currents in CHO cells expressing the human ERG channel. Recordings were made at 30 °C with test compounds at two concentrations (0.3 μM, 1 μM, or 1 μM, 10 μM).
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14. CL_{int} measured in HT format: total incubation volume 250 μL, 0.5 mg/mL microsomal protein, reaction started by adding NADPH and performed at 37 °C with no shaking. 40 μL aliquots at four time-points (0.1, 10, 20 and 30 min) were taken then the samples transferred to 384 well plates for LC/MS analysis.
15. CYP2D6 and CYP3A4 inhibition was measured in a fluorescence based assay where CYP marker substrates become fluorescent upon CYP metabolism.
16. Permeability was measured using Caco-2 cells at 21 days of culture. Efflux ratios are measured using the bi-directional (P_{app} A to B and B to A) values. Substrate concentration 10 μM.
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