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Design and optimization of selective serotonin re-uptake inhibitors with high synthetic accessibility Part 1

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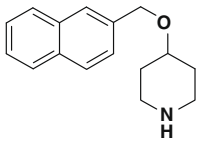
ABSTRACT

The reported selective serotonin Re-uptake Inhibitor Litoxetine was used as the starting point in the design of a range of potential SSRIs with high ease of synthetic accessibility. Preparation and subsequent optimization yielded a range of potent and highly selective SSRIs.

Over the last 25 years selective serotonin re-uptake inhibitors (SSRIs) have emerged as a key mechanistic class in the treatment of depression.[1] Sertraline (Zoloft®) **1**, paroxetine (Paxil®) **2** and fluoxetine (Prozac®) **3** have, amongst others, been utilized extensively in the clinical treatment of this debilitating condition (Fig. 1).

Our own interest in this area stemmed from the potential benefit of SSRIs in a range of other indications including pre-menstrual-syndrome and male sexual dysfunction. For these acute therapy compatible indications we felt that targeting SSRIs which demonstrated very short pharmacokinetic Tmax's would potentially offer significant benefit over currently available SSRIs, which have relatively long Tmax's (typically 4–8 h in the clinic).[2]

To facilitate this approach we set out to identify rapidly a range of structurally diverse, potent, selective SSRIs for subsequent pharmacokinetic profiling. A decision was therefore taken to target systems with a high degree of synthetic accessibility. With this in mind attention was focused on the previously reported SSRI Litoxetine[3]—a potent, selective inhibitor with a very low level of synthetic complexity.



Litoxetine
SRI 6nM; DRI 6.5μM, NRI 1.3μM

Using Litoxetine as a starting point we designed a set of simple analogues **4**–**8** (Fig. 2). These systems, which had, to the best of our knowledge, not previously been reported as SSRIs, were designed based on the simple principles of maintaining the relative orientation of the naphthyl (benzene) ring to a basic centre (vs litoxetine) and ensuring that targets had high synthetic accessibility.[4]

Key data for representative examples of each of these series, including Serotonin re-uptake inhibition (SRI) potency, selectivity over the related Dopamine and Noradrenalin transporters (Dopamine re-uptake inhibition and Noradrenaline re-uptake inhibition, DRI and NRI, respectively)[5] and binding to the IKr channel[6,7] are detailed in Table 1.

Key SAR points for each of these series are as follows.

For the pyrrolidine ethers **9** and **10** reasonable potency and selectivity was achieved in the parent structures for both enantiomers. Subsequent optimization work (for SRI) revealed that incorporation of an electron withdrawing 6-substituent, as in **11** and **12**, gave a significant improvement in serotonin re-uptake activity whilst allowing good levels of Dopamine re-uptake inhibition (DRI) selectivity and Noradrenalin re-uptake inhibition (NRI) selectivity to be maintained. Selectivity over the human IKr channel was found to be consistently high for all of the pyrrolidine ethers profiled in this series.

A larger (⩾ethyl) *N*-alkyl substituent was typically required for on-scale potency for piperidine and pyrrolidine sulphonamides **13**–**18** (compare, e.g., **14** vs **13**) Although larger substituents allowed reasonable levels of potency to be achieved, as in **14** and **18**, these compounds were found to have unacceptably high levels of affinity for the human IKr channel.

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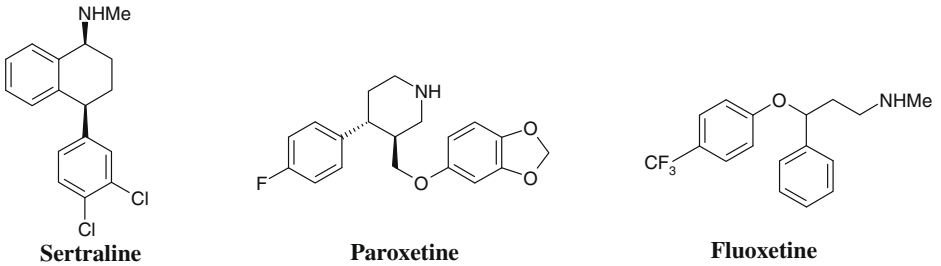


Figure 1. Representative approved SSRIs.

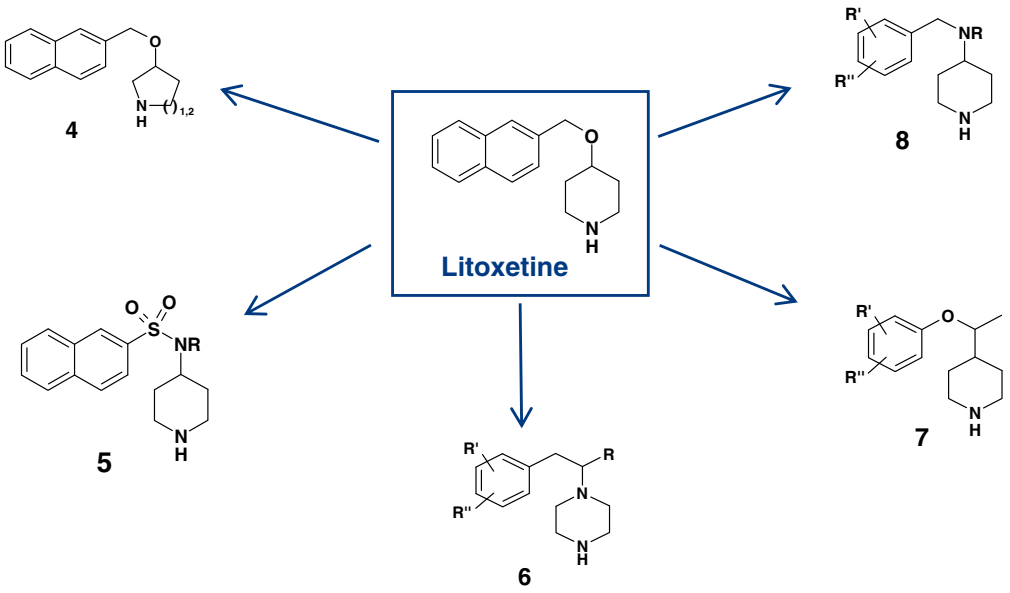
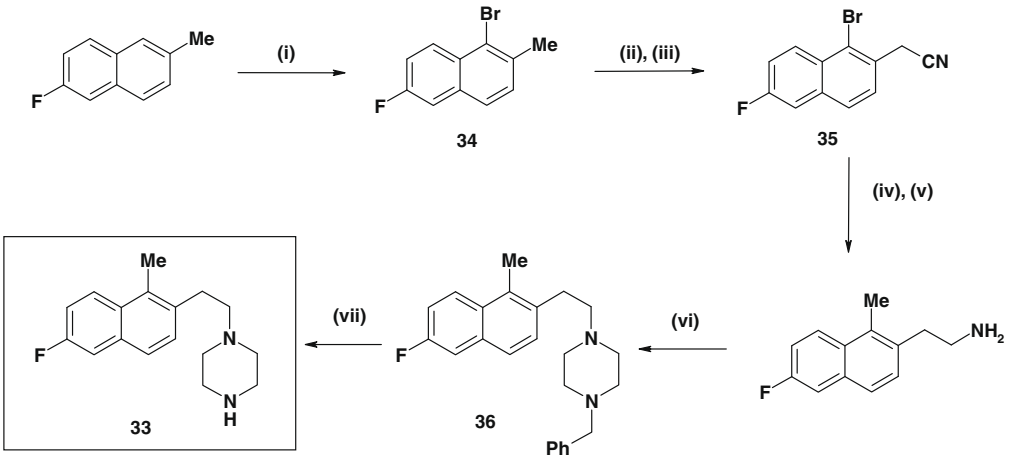


Figure 2. Targets with high synthetic accessibility based on the SSRI Litoxetine.

Attempts to improve the SRI potency of diamines such as **19**–**23** through incorporation of larger right hand side *N*-alkyl substituents also led to an improvement in SRI activity. However, this was typically accompanied by an increase in DRI and NRI activity, such that it proved challenging to consistently attain acceptable levels of selectivity over these targets.

'Reverse' pyrrolidine ether **24** (racemic) initially appeared to represent a promising lead. However, sub 10 nM potency proved elusive in this series. For example, incorporation of an electron withdrawing 6-substituent, which had proved highly beneficial in 'normal' pyrrolidine ethers **9** and **10**, gave, if anything, a slight drop-off in potency (compounds **25** and **26**). For the corresponding



Scheme 1. Synthesis of compound **33**. Reagents and conditions: (i) Br_2, AcOH, 58%[10]; (ii) NBS, Vazo 88[11], NBS; (iii) NaCN, aq CH_3CN, 93% (2 steps); (iv) trimethylboroxine, $Pd(Ph_3)_4$, K_2CO_3, aq dioxan, 77%; (v) $NaBH_4/CoCl_2$, 75%; (vi) $(ClCH_2CH_2)_2NCH_2Ph{\cdot}HCl$, $NaHCO_3$, NMP, 55%; (vii) NH_4HCO_2, 10% Pd/C, EtOH, 61%.

Table 1
Potency and selectivity of new SRIs

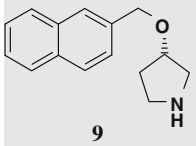
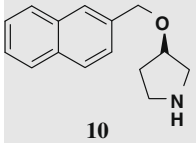
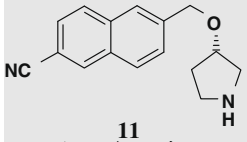
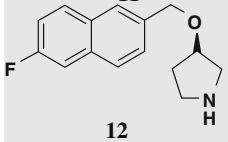
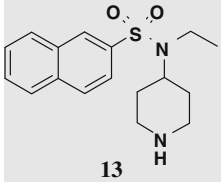
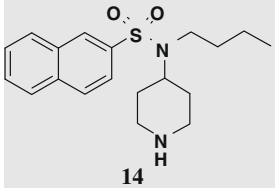
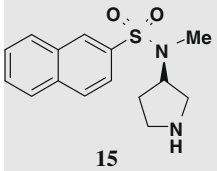
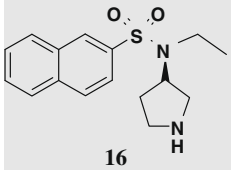
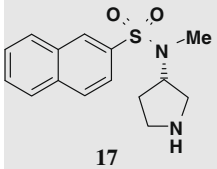
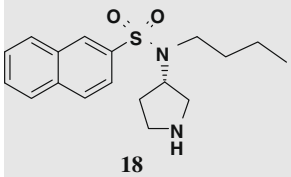
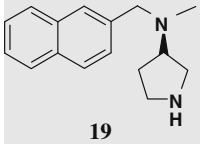
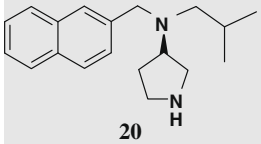
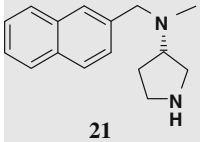
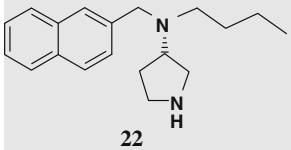
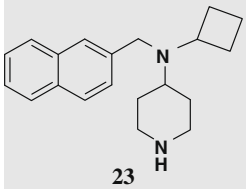
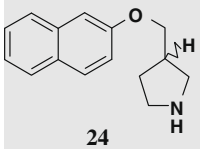
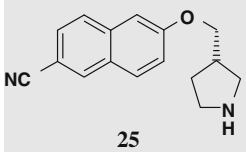
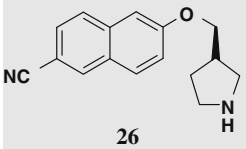
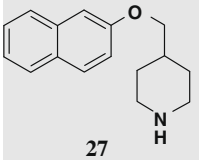
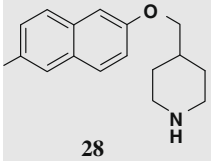
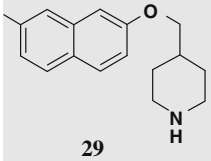
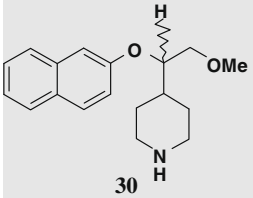
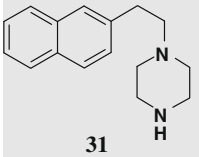
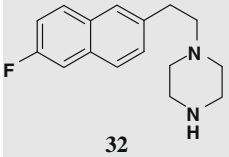
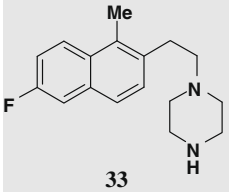
Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr Ki
 **9**	23 nM	2.9 μM	15 μM	15.7 μM
 **10**	20 nM	1.2 μM	3.8 μM	16.4 μM
 **11**	3 nM	6.8 μM	861 nM	4.5 μM
 **12**	4 nM	10.6 μM	2.1 μM	10.3 μM
 **13**	>400 nM	>10 μM	>10 μM	n.t.[a]
 **14**	14 nM	40 μM	19 μM	716 nM
 **15**	138 nM	3 μM	n.t.[a]	n.t.[a]
 **16**	30 nM	2.6 μM	>30 μM	n.t.[a]
 **17**	>400 nM	n.t.[a]	n.t.[a]	n.t.[a]

Table 1 (*continued*)

Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr Ki
 **18**	16 nM	5.6 μM	>30 μM	412 nM
 **19**	119 nM	3 μM	3 μM	n.t.[a]
 **20**	5 nM	80 nM	66 nM	n.t.[a]
 **21**	13 nM	5.4 μM	7.7 μM	>5 μM
 **22**	0.3 nM	80 nM	88 nM	n.t.[a]
 **23**	2 nM	1.5 μM	210 nM	n.t.[a]
 **24**	25 nM	1.4 μM	1 μM	>5.5 μM
 **25**	37 nM	200 nM	n.t.[a]	n.t.[a]

(*continued on next page*)

Table 1 (*continued*)

Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr Ki
 **26**	42 nM	772 nM	n.t.[a]	n.t.[a]
 **27**	8 nM	1.8 μM	>7 μM	3.8 μM
 **28**	15 nM	1.9 μM	6 μM	n.t.[a]
 **29**	3 nM	4.4 μM	8.8 μM	3.5 μM
 **30**	5 nM	827 nM	n.t.[a]	n.t.[a]
 **31**	88 nM	n.t.[a]	n.t.[a]	n.t.[a]
 **32**	11 nM	10.5 μM	24 μM	8.5 μM
 **33**	4 nM	8.4 μM	>31 μM	10.1 μM

[a] Not tested.

'reverse' piperidine ethers, the parent compound, **27**, carried an attractive potency and DRI/NRI selectivity profile. Interestingly, incorporation of a 6-cyano substituent was again slightly detrimental to SRI activity (compound **28**). However, incorporation of a 7-cyano substituent, as in **29**, did result in an improvement in potency and NRI selectivity. Further profiling of compounds **27** and **29** revealed that both also carried significant 5-HT_3 antagonism (Ki's 311 nM and 404 nM, respectively,[8]). Incorporation of a right hand side methoxy substituent, as in (racemic) compound **30** led to a rapid drop off in 5-HT_3 activity (compound **30** 5-HT_3 Ki > 10 μM), albeit that this improvement was achieved by incorporation of a chiral centre, thus reducing the ease of synthesis of compounds such as **30**.

Finally we prepared a range of piperazines **7**. The parent compound, **31**, had encouraging SRI activity which was further improved by subsequent incorporation of a 6-fluoro substituent to give compound **32**. Subsequent optimization yielded the 1-methyl-6-fluoro analogue, **33**, a potent, selective SSRI. Affinity for the human IKr channel was found to be consistently low for all of the piperazines profiled in this series.

The preparation of compound **33** is described in Scheme 1.[9] Commercially available 2-fluoro-6-methylnaphthylene was regioselectively brominated[10] to give **34**. Subsequent benzylic bromination[11], followed by cyanide displacement gave naphtylacetonitrile **35**. Pd(0) catalysed cross coupling with trimethylboroxine and nitrile reduction was followed by reaction with *N*-benzyl mustard to give benzylpiperazine **36**, which was deprotected by hydrogenation to yield target compound **33**.

In summary, using litoxetine as a starting point we have identified a range of potent, highly selective SSRIs all of which have a high degree of synthetic accessibility, compared to existing SSRIs such as Sertraline, Paroxetine and Fluoxetine. Compounds **11**, **12**, **30** and **33** in particular, represent attractive potential leads in the search for a short Tmax SSRI.[12]

Acknowledgements

We would like to acknowledge the contributions of the following co-workers: James Gosset, Hugh Verrier and Robin Ward.

References and notes

1. Preskorn, S. H.; Ross, R.; Stanga, C. Y.. In *Handbook of Experimental Pharmacology*; Springer, 2004; Vol. 157. Antidepressants.
2. For more background on this short Tmax based approach see: Middleton, D. S.; Andrews, M. D.; Glossop, P.; Gymer, G.; Hepworth, D.; Jessiman, A.; Johnson, P. J.; MacKenny, M.; Stobie, A.; Tang, K.; Morgan, P.; Jones, B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5303. and the references therein.
3. Angel, I.; Schoemaker, H.; Prouteau, M.; Garreau, M.; Langer, S. Z. *Eur. J. Pharmacol.* **1993**, *232*, 139.
4. The perceived high degree of synthetic accessibility of pyrrolidine containing targets was based upon the (wide) range of commercially available, suitably protected, homochiral 3-substituted pyrrolidines.
5. (a) SRI, NRI and DRI data reflects inhibition of the relevant (radiolabelled) monoamine uptake into HEK-293 cells transfected with the appropriate human monoamine transporter. (b) IKr data reflects the inhibition of binding of ^{3}H-radiolabelled dofetilide to human hERG Potassium channels expressed in HEK-293 cells.
6. For a review of IKr (hERG) affinity and the issues that it presents in small molecule drug discovery, see: Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. *J. Med. Chem.* **2006**, *49*, 5029.
7. In-house experience suggested that, for certain SRI series, IKr affinity can represent a significant issue. We were therefore keen to identify at an early stage whether or not this issue was likely to arise in any newly identified lead series.
8. 5-HT_3 Ki data reflects the inhibition of binding of ^{3}H-granisetron to human 5-HT3 receptors expressed in HEK-293 cells.
9. In fact, the synthesis of **33**, straightforward as it was, represents, by some way, the most complex synthesis (in terms of total steps) carried out during the course of the work described in this Letter, where our focus was very much on accessing new templates which had a high degree of synthetic accessibility.
10. Ellingboe, J. W.; Lombardo, L. J.; Alessi, T. R.; Nguyen, T. T.; Guzzo, F.; Guinosso, C. J.; Bullington, J.; Browne, E. N. C.; Bagli, J. F.; Wrenn, J.; Steiner, K.; McCaleb, M. L. *J. Med. Chem.* **1993**, *36*, 2485.
11. See, for example: Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2958.
12. Our subsequent efforts in this area will be disclosed in due course.