Bioorganic & Medicinal Chemistry Letters 19 (2009) 5893–5897

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design and optimisation of selective serotonin re-uptake inhibitors with high synthetic accessibility: Part 2

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ARTICLE INFO

Article history:
Received 27 July 2009
Revised 10 August 2009
Accepted 19 August 2009
Available online 21 August 2009

Keywords:
Seretonin re-uptake
SRI
NRI
DRI
SSRI

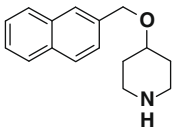
ABSTRACT

A second wave of potential SSRIs with high ease of synthetic accessibility were designed based on the reported selective serotonin re-uptake inhibitor litoxetine and our own previous work in this area. Preparation and subsequent optimisation 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 utilised 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 T_{max}'s would potentially offer significant benefit over currently available SSRIs, which have relatively long T_{max}'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], **4**—a potent, selective inhibitor with a very low level of synthetic complexity.



Litoxetine, **4**

SRI 5.9nM; DRI 6.7μM, NRI 1.4μM

We have previously reported how, using litoxetine as a starting point we identified a range of selective SSRIs, illustrated by compounds **5–8** (Fig. 2).[4] These systems 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. Encouraged by this success we utilised the same principles to design and prepare a second wave of targets, **9**–**12** (Fig. 3).[5]

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) [6] and binding to the IKr channel[7,8] are detailed in Table 1.

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

For the naphthoic acid amides **13–20** good SRI potency could be attained provided the amide was tertiary. Molecular modelling suggested that such systems were significantly twisted out of the plane around the amide bond/aromatic ring. By way of contrast secondary amide **13** modelled as essentially flat around the amide bond/aromatic ring and was found to have no significant SRI activity. In these naphthoic acid amides it was possible to attain excellent levels of SRI potency as well as NRI, DRI and IKr selectivity in both 4-piperidine and 3-(*R*)-pyrrolidine based analogues (see, e.g., compounds **15** and **19,** respectively). In the 3-(*R*)-pyrrolidine series, it was possible to replace the naphthyl substituent with a suitably substituted phenyl substituent whilst retaining good levels of potency and selectivity (see, e.g., **23**). However, it was found that in

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doi:10.1016/j.bmcl.2009.08.066

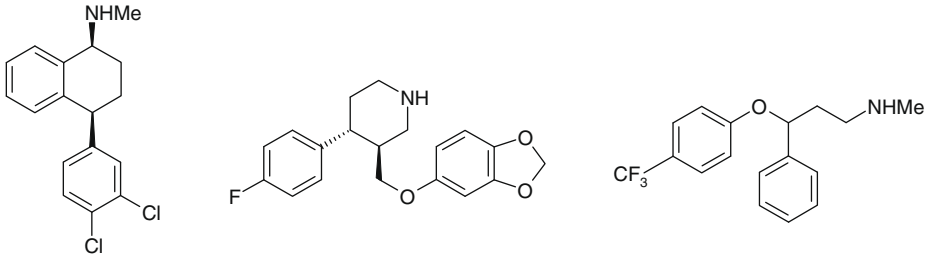


Figure 1. Representative approved SSRIs.

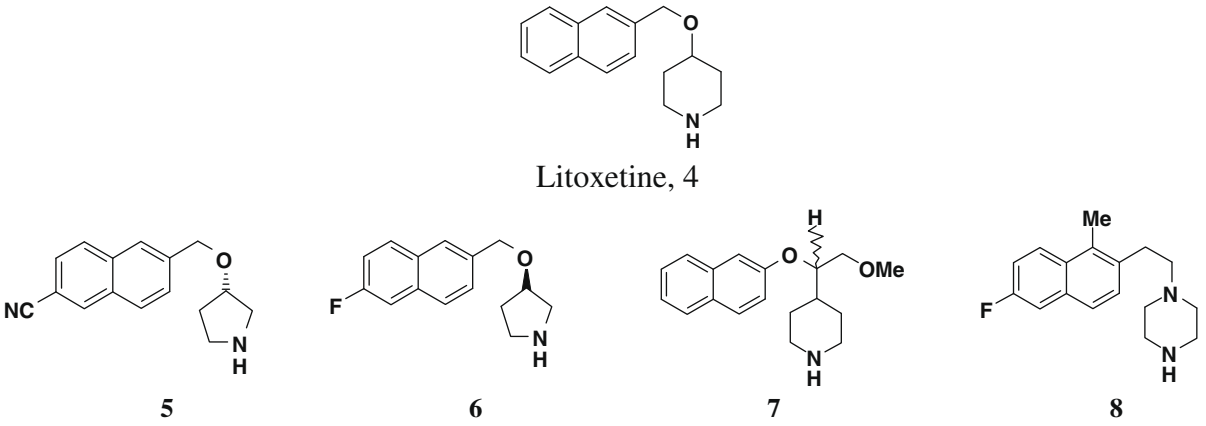


Figure 2. Litoxetine and analogues with high synthetic accessibility previously reported by our group.

the 3-(*S*)-pyrrolidine naphthoic acid amides larger right hand side substituents often resulted in somewhat reduce NRI selectivity (as illustrated by compound **25**).

The corresponding 3-(*S*)-pyrrolidine naphthoic acid amides (e.g., **20**) typically carried significant NRI activity as compared to the corresponding 3-(*R*) enantiomers (compare **20** with **19**). As a result these compounds were not pursued further for our SRI programme.

N-Naphthylmethylsulphonamides **26**–**29** showed excellent SRI activity. Once more the 4-piperidine and 3-(*R*)-pyrrolidine analogues typically carried good to excellent selectivity (see, e.g., compounds **27** and **28**, respectively). In contrast the corresponding 3-(*S*)-pyrrolidine systems (as in compound **29**) typically carried increased NRI activity.

N-Naphthylmethylamides also demonstrated excellent levels of SRI potency and selectivity, both in 4-piperidine based systems (**30**, **31**) and in the corresponding 3-(*R*)-pyrrolidine analogues (**33** and **34**). Interestingly, increasing the right hand side substituent from acetyl to propionyl (**30** to **31** and **33** to **34**) gave significantly increased DRI activity. Indeed **31** and **34** displayed amongst the highest degrees of DRI activity observed throughout our work on this litoxetine based programme.

Finally, replacement of the right hand side acetyl substituent with a pyrimidine gave **32** which also demonstrated good levels of SRI activity, albeit with a somewhat reduce NRI selectivity window.

The preparation of a representative analogue, compound **25** is described in Scheme 1.[9] Commercially available 2,3-dichlorophenol was regioselectively carboxylated using the Kolbe–Schmitt reaction[10] to give **36**. Conversion to the corresponding ester/triflate gave **37** which smoothly underwent Suzuki coupling with trimethylboroxine. Hydrolysis then gave key 1,2,3,4-substituted

Table 1
Potency and selectivity of new SRIs

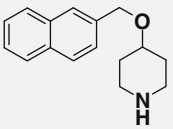
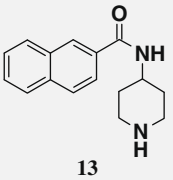
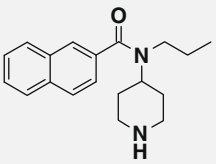
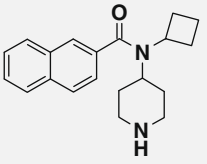
Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr K*i*
 **Litoxetine, 4**	5.9 nM	1.4 μM	6.7 μM	n.t.[a]
 **13**	>400 nM	n.t.[a]	n.t.[a]	n.t.[a]
 **14**	28.3 nM	>40 μM	>40 μM	12.7 μM
 **15**	10 nM	>40 μM	>40 μM	>10 μM

Table 1 (*continued*)

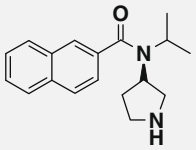
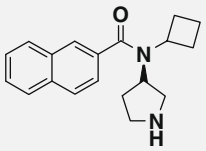
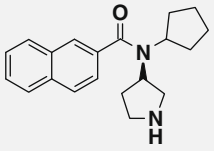
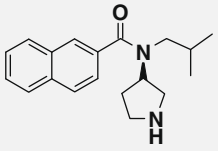
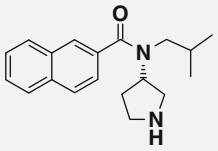
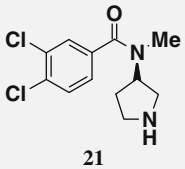
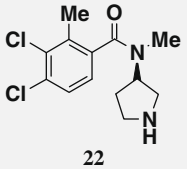
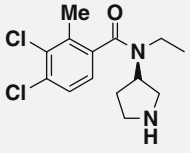
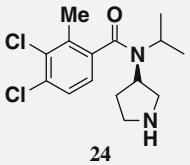
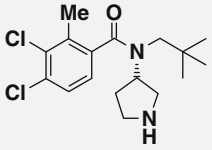
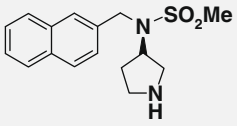
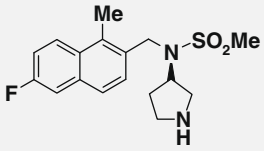
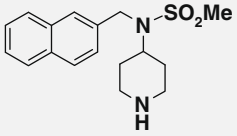
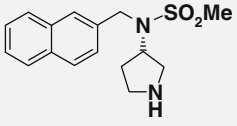
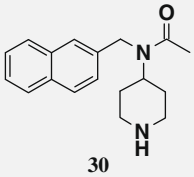
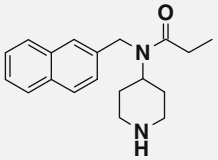
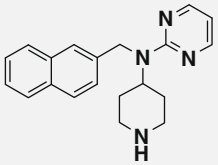
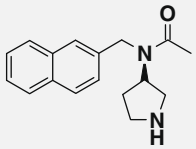
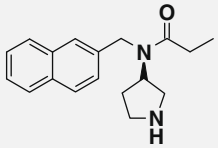
Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr *Ki*
 **16**	15 nM	7.5 μM	>14 μM	n.t.[a]
 **17**	9 nM	6 μM	5.8 μM	n.t.[a]
 **18**	12 nM	677 nM	7.4 μM	n.t.[a]
 **19**	5 nM	1.2 μM	9.5 μM	7 μM
 **20**	3 nM	24 nM	744 nM	n.t.[a]
 **21**	>400 nM	n.t.[a]	n.t.[a]	n.t.[a]
 **22**	58 nM	n.t.[a]	n.t.[a]	n.t.[a]
 **23**	10 nM	17.4 μM	>40 μM	n.t.[a]

Table 1 (*continued*)

Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr *Ki*
 **24**	7 nM	5.7 μM	>40 μM	n.t.[a]
 **25**	15 nM	357 nM	>28 μM	n.t.[a]
 **26**	17 nM	7 μM	>68 μM	4.2 μM
 **27**	4.6 nM	735 nM	>28 μM	1.6 μM
 **28**	3.5 nM	2.5 μM	4.9 μM	3.2 μM
 **29**	3.5 nM	370 nM	2.8 μM	11 μM
 **30**	4.5 nM	8.9 μM	1.5 μM	>20 μM
 **31**	1.0 nM	1.3 μM	339 nM	12 μM
 **32**	10 nM	1.2 μM	1.3 μM	n.t.[a]

(*continued on next page*)

Table 1 (*continued*)

Structure	SRI IC_{50}	NRI IC_{50}	DRI IC_{50}	IKr *Ki*
 **33**	5.2 nM	726 nM	>12 μM	8 μM
 **34**	2.4 nM	224 nM	266 nM	n.t.[a]

[a] Not tested.

benzoic acid **38** which was coupled (via the acid chloride) to BOC diamine **39**. Acid deprotection then furnished benzamide **25**.

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 **15**, **19**, **28**, **31** and **33** in particular, represent attractive potential leads in the search for a short T_{max} SSRI.[11]

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. *Handbook of Experimental Pharmacology*; Springer, 2004. 157 (Antidepressants), 241.
2. For more background on this short T_{max} based approach see: Middleton, D. S.; Andrews, M. D.; Glossop, P.; Gymer, G.; Hepworth, D.; Jessiman, A.; Johnson, P.

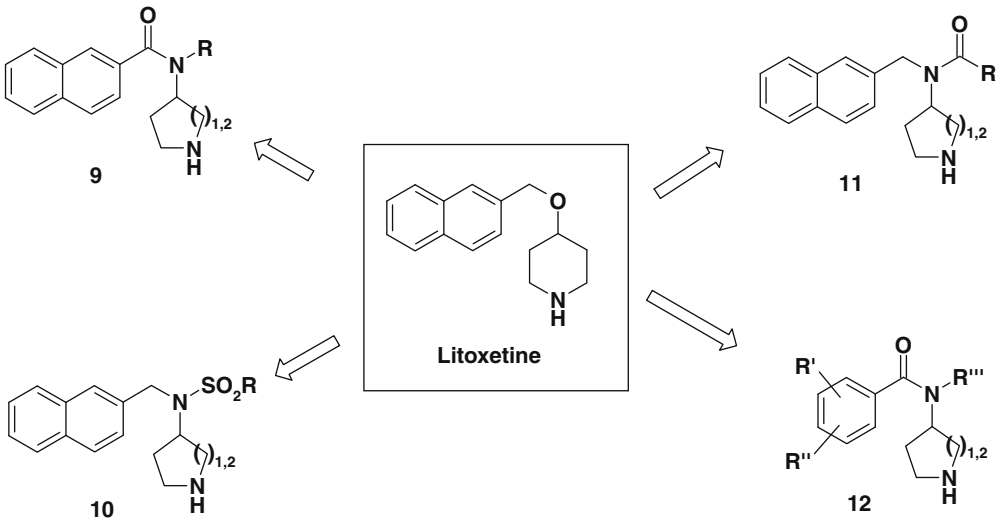
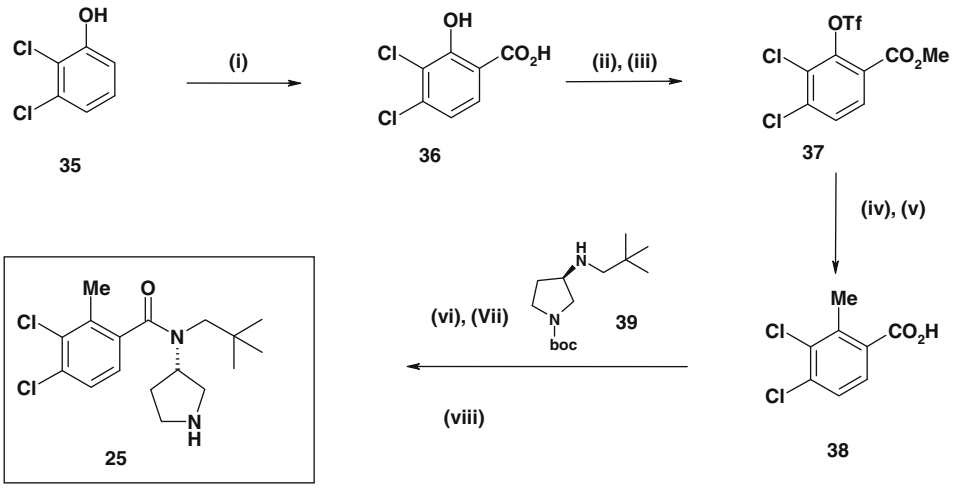


Figure 3. A second wave of targets with high synthetic accessibility based on the SSRI litoxetine.



Scheme 1. Synthesis of compound **25**. Reagents and conditions: (i) K_2CO_3/CO_2, 100 atm (71%); (ii) $TMSCHN_2$, toluene/MeOH (quant); (iii) Tf_2O, Et_3N, DCM; (iv) trimethylboroxine, $Pd(Ph_3)_4$, K_2CO_3, aq Dioxan, (quant, two steps); (v) 1 N NaOH (quant); (vi) ClCOCOCl, Et_3N, DCM, DMF; (vii) **39**, Et_3N, DCM (85%, two steps); (viii) HCl/DCM (quant).

J.; MacKenny, M.; Stobie, A.; Tang, K.; Morgan, P.; Jones, B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5303. and the references cited therein.
3. Angel, I.; Schoemaker, H.; Prouteau, M.; Garreau, M.; Langer, S. Z. *Eur. J. Pharmacol.* **1993**, *232*, 139.
4. (a) Andrews, M.; Brown, A.; Chiva, J-Y.; Fradet, D.; Gordon, D.; Lansdell, M.; MacKenny, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2329; For a recent review of new chemical entities see: (b) Walter, M. W. *Drug Dev. Res.* **2005**, *65*, 97.
5. 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. For example, (*S*) and (*R*)-3-(BOC-amino)pyrrolidine (the homochiral starting materials utilised in the synthesis of all of the chiral compounds described in this Letter) are both available from Sigma–Aldrich in ⩾98% purity (⩾96% ee).
6. (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. Specifically, these assays were a modification of those described by Blakey et al. *Anal. Biochem.* **1991**, *194*, 302. HEK293 cells expressing a single human amine transporter protein (7500 cells/well in Milliporte 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), Noradrenaline (200 nM) or Dopamine (200 nM) substrates. The samples were shaken in an incubator at 25 °C for 5 min (5-HT, Dopamine) or 15 min (Noradrenaline). 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. Monoamine reuptake IC_{50} values are geometric means of at least three experiments. Values within twofold of each other should be considered equivalent. (b) IKr data reflects the inhibition of binding of ^{3}H-radiolabelled dofetilide to human hERG Potassium channels expressed in HEK-293 cells. K_i values are geometric means of at least two experiments. Values within twofold of each other should be considered equivalent.
7. 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.
8. 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.
9. In fact, the synthesis of **25**, 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. Lindsey, A. S.; Jesley, H. *Chem. Rev.* **1957**, *57*, 583.
11. Our subsequent efforts in this area will be disclosed in due course.