Bioorganic & Medicinal Chemistry Letters 19 (2009) 428–432

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Studies on a series of potent, orally bioavailable, 5-HT$_1$ receptor ligands—Part II

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ARTICLE INFO

Article history:
Received 21 October 2008
Revised 13 November 2008
Accepted 14 November 2008
Available online 19 November 2008

Keywords:
5-HT$_1$
SSRI
Serotonin
5-HT$_{1A}$ antagonist
Depression

ABSTRACT

A series of 5-(piperidinylethyloxy)quinoline 5-HT$_1$ receptor ligands have been studied by elaboration of the series of dual 5-HT$_1$-SSRIs reported previously. These new compounds display a different in vitro pharmacological profile with potent affinity across the 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors and selectivity against the serotonin transporter. Furthermore, they have improved pharmacokinetic profiles and CNS penetration.

Antidepressants are thought to mediate their effects by improving 5-HT transmission, regardless of their modes of action. Selective serotonin reuptake inhibitors (SSRIs) block 5-HT reuptake mediated by the 5-HT transporter (SerT) located in 5-HT neuron terminals and cell bodies. SSRIs have been shown to be effective in the treatment of both depression and anxiety disorders. Compared to other antidepressants, such as tricyclics, they offer similar efficacy but with an improved side effect profile. However, there is still a medical need for the development of molecules with a superior profile to SSRIs by providing a faster onset of action and better tolerability with respect to the sleep disturbance and sexual dysfunction side effects associated with current SSRIs.[1]

The rationale for the delay to onset of antidepressant action has been the subject of considerable debate. A widely accepted view is that a neuro-adaptive process occurs as a result of constant inhibition of the monoamine reuptake process, presumably through desensitisation of presynaptic 5-HT$_{1A}$ receptors located on the cell bodies which control cell firing and the consequent release of 5-HT from presynaptic neurons of the dorsal raphe.[2] Two other receptors play an important role in the control of 5-HT release from presynaptic neurons, the 5-HT$_{1B}$ and 5-HT$_{1D}$ autoreceptors located on the 5-HT cell bodies and on the nerve terminals, and pre-clinical evidence suggests that chronic administration of antidepressants leads to desensitisation of the 5-HT$_{1B}$ autoreceptors. Thus, the simultaneous blockade of the 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ autoreceptors should restore post-synaptic 5-HT neuronal transmission and so provide a complementary approach to the SSRI or mixed SSRI/5-HT$_{1A}$ receptor antagonist strategies.[3]

Previous publications from our laboratories in this chemical series have described a range of pharmacological profiles across the 5-HT$_1$ receptors and 5-HT transporter. Modification of the benzoxazinone group has allowed identification of selective 5-HT$_{1D}$ antagonists,[4] mixed 5-HT$_{1A}$ antagonist/SSRIs[5] and 5-HT$_{1ABD}$ antagonists.[6] In particular, later studies have focussed on the identification of molecules which are potent, selective 5-HT$_1$ receptor ligands, that is molecules with pK_i > 8 against the 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors with low intrinsic activity and good selectivity over other receptors and transporters, including the 5-HT transporter.

The preceding report from these studies identified the first compounds to meet this target profile (Fig. 1).[5] However, during the course of this SAR investigation, we routinely struggled to meet the required pK_i for all three of the 5-HT$_1$ receptor subtypes. In particular, few compounds achieved a pK_i > 8 for the 5-HT$_{1B}$ receptor, which encouraged us to focus our efforts specifically on identification of new, potent antagonists for this receptor.

In earlier published work we described the identification of selective 5-HT$_{1B}$ receptor antagonists exemplified by SB-616234 (Fig. 2).[7] Here, the piperazine and its substituents were key to high 5-HT$_{1B}$ receptor affinity. In our previous series of 5-HT$_1$ receptor antagonists, basic centres were also tolerated as a substituent at the 3-position of the phenyl group (**1**).[6] This paper now describes a further investigation around substituents at the 3-position, including a range of substituted piperazines.

Previous SAR activity indicated that an H-bond acceptor in the *meta* position of the phenyl group was key for affinity, as exemplified

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doi:10.1016/j.bmcl.2008.11.052

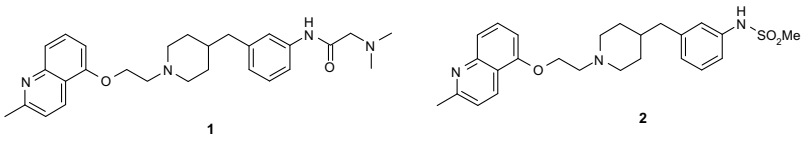


Figure 1. Examples of potent analogues from previous studies with basic and non-basic phenyl substituents.

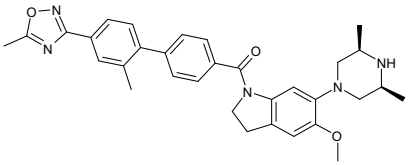


Figure 2. Structure of SB-616234, a selective 5-HT_{1B} receptor antagonist.

by **2** above; aniline derivatives lacking the carbonyl or sulfonyl group showed considerably reduced 5-HT_{1B} and 5-HT_{1D} receptor affinities.

Nonetheless, our first target was to incorporate the piperazine substituent present in SB-616234 into our series. This compound and its analogues were prepared (Scheme 1a) from 3-bromobenzylbromide **23** via Horner–Wadsworth–Emmons coupling to give intermediate **24**, which following deprotection to amine **25** was coupled to the quinoline fragment **26**[4] via alkylation. The key unsaturated bromophenyl derivative **27** was reacted under palladium (0) catalysis using Buchwald conditions to give intermediates **28** (Cy = cyclic amine). These compounds were then reduced to give the final molecules screened **29** (**3–8**, **10–14**).

Data displayed in Table 1 are for the molecules screened against h5-HT_{1A} receptors expressed in CHO cells using displacement of [^{3}H]-WAY100635 and against h5-HT_{1B} and h5-HT_{1D} receptors expressed in CHO cells using displacement of [^{3}H]-5-HT. The intrinsic activity of the compounds was determined using a [^{35}S]GTPγS binding assay in cells expressing the h5-HT_{1A}, h5-HT_{1B} or h5-HT_{1D} receptors, with data reported relative to the maximum response elicited by the endogenous agonist 5-HT. A ten point half serial dilution was used to generate a concentration response for each compound.

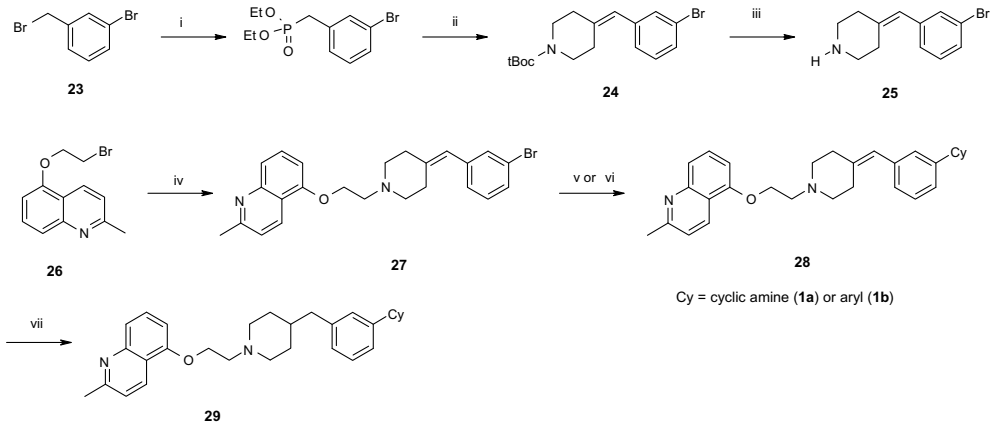
Gratifyingly, the direct analogue **3**, not only gave us the desired high affinity for the 5-HT_{1B} receptor, but also high affinity for the 5-HT_{1A} and 5-HT_{1D} receptors. Investigation of the effect of the methyl group substitution pattern and stereochemistry led to the preparation of **4–6**. One of the methyl substituents could be removed from **3** to give **4** with no change in receptor profile. However, removal of the alternative methyl from **3** to give the piperazine with the opposite stereochemistry **5** led to a drop in affinity for the 5-HT_{1B} receptor. A similar drop in affinity was observed by introducing another methyl substituent to **4** to give dimethyl piperazine **6**. This work was then carried further to look at simplification of the structure to afford achiral piperazine **7**. Pleasingly, this change again gave us a compound which met all target criteria for the 5-HT_1 receptors without the need for additional chiral centres.

On this simpler template, we then investigated the electronic nature of the piperazine nitrogens. Piperazinone derivatives **8** and **9** were prepared to investigate the difference in binding affinity between amide and amine environments. Both molecules showed a loss in receptor binding affinity—the terminal nitrogen as an amide was less potent than as a basic amine, and piperazinone **9** (Scheme 2), was less potent both than parent piperazine and than its unconstrained beta amino amide analogue **1**.

Data for compound **8** was corroborated by replacement of the basic nitrogen with oxygen, that is, another non-basic, polar group, giving **11**. This modification led to a drop in 5-HT_{1B} receptor affinity which could not be restored by introducing flanking methyl groups to afford **12**.

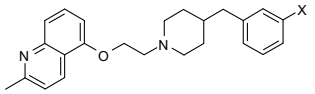
However, we were surprised to discover that replacement of the piperazine with a piperidine to give analogue **10** was not detrimental to binding affinities and gave a slightly improved 5-HT_{1B} affinity compared to initial piperazine **7**. This was the first molecule to maintain high receptor affinities which lacked either an aniline amide or sulfonamide unit or the terminal basic nitrogen, although microsomal clearance increased from 2.9 ml/min/kg (**7**) to 6.2 ml/min/kg (**10**). Varying the size of this piperidine ring to pyrrolidine analogue **14** led to a drop in affinities whilst the homo piperazine **13** maintained the receptor profile, but led to greater microsomal instability (rat CLi 26 ml/min/kg).

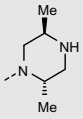
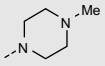
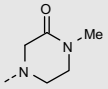
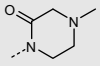
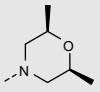
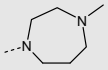
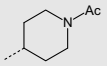
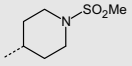
To further test the requirement of the *meta* nitrogen substituent on the phenyl ring, we decided to synthesise compound **15**. This piperidine derivative was prepared (Scheme 3) from the pyridyl



Scheme 1a (Buchwald) and 1b (Suzuki). Reagents and conditions: (i) $P(OEt)_3$, toluene, reflux, 24 h, (85%); (ii) *N*-Boc-piperid-4-one, NaH, THF, rt, 4 h (89%); (iii) 1 M HCl in Et_2O, rt, 72 h (57%); (iv) **25**, K_2CO_3, DMF, 100 °C, 16 h, 87%; (v) amine, $Pd(OAc)_2$, BINAP, Cs_2CO_3, 1,4-dioxane, reflux (39–100%); (vi) $CyB(OH)_2$, PPh_3, 2 M aq K_2CO_3, $Pd(OAc)_2$, reflux, 1,2-DME; (vii) 10% Pd on C, H_2, EtOH, rt, 24 h, (9–100%).

Table 1
Receptor binding affinity (pK_i[a]) for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} and SerT for novel compounds[b]



Compound	X	pK_i	I.A.[c]	pK_i	I.A.[c]	pK_i	I.A.[c]	SerT[d]	Synthesis
1	$NHCOCH_2NMe_2$	7.8	inv	8.2	0.2	9.0	0.4	6.4	
2	NHSO2Me	8.6	0	8.7	0.3	9.3	0	6.0	
3		8.7	0	8.4	0.3	9.1	0.5	ND	Scheme 1a
4		8.6	0	8.7	0.3	9.2	0.5	6.2	Scheme 1a
5		8.4	0	7.8	0.3	9.0	0.5	6.1	Scheme 1a
6		8.3	ND	7.5	ND	9.0	ND	6.1	Scheme 1a
7		9.0	0	8.2	0.3	9.3	0.4	ND	Scheme 1a
8		8.1	ND	6.9	ND	8.0	ND	ND	Scheme 1a
9		7.7	ND	7.2	ND	8.4	ND	ND	Scheme 2
10		8.4	0	8.7	0.6	9.0	0.7	6.8	Scheme 1a
11		8.3	0	6.9	0.4	8.6	0.6	6.6	Scheme 1a
12		8.6	ND	6.8	ND	8.8	ND	6.6	Scheme 1a
13		8.6	0	8.1	0.3	9.2	0.5	6.4	Scheme 1a
14		8.0	ND	7.4	ND	8.6	ND	ND	Scheme 1a
15		8.5	inv	8.3	0.3	9.7	0.4	6.3	Scheme 3
16		8.2	ND	8.2	ND	8.9	ND	ND	Scheme 3
17		7.9	ND	6.8	ND	8.4	ND	ND	Scheme 3
18		8.1	ND	7.1	ND	8.5	ND	ND	Scheme 3
19		8.1	ND	8.1	ND	9.0	ND	ND	Scheme 1b
20		8.3	ND	7.9	ND	8.7	ND	ND	Scheme 1b

(*continued on next page*)

Table 1 (*continued*)

Compound	X	pK_i	I.A.[c]	pK_i	I.A.[c]	pK_i	I.A.[c]	SerT[d]	Synthesis
21		7.2	ND	7.2	ND	8.1	ND	ND	Scheme 1b
22		7.5	ND	7.4	ND	8.2	ND	ND	Scheme 1b

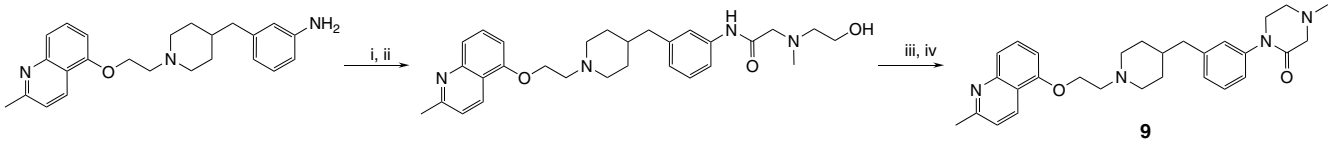
ND, not determined.

[a] Radioligand binding assay to determine affinity at human recombinant 5-HT receptors. Each determination lies within 0.3 log units of the mean with a minimum of three replicates.

[b] All compounds were characterized and purity was assessed using ^{1}H NMR and LCMS.

[c] I.A., intrinsic activity (inv, inverse agonist).

[d] Functional ^{3}[H]5-HT uptake assay in at cortical synaptosomes.



Scheme 2. Reagents and conditions: (i) chloroacetylchloride, Et_3N, rt, DCM; (ii) $MeNCH_2CH_2OH$, $^iPr_2NEt$, NaI, rt, ^{i}PrOH; (iii) $ClSO_2Me$, Pyr, rt; (iv) NaH, DMF, rt to 50 °C, 22% over entire sequence.

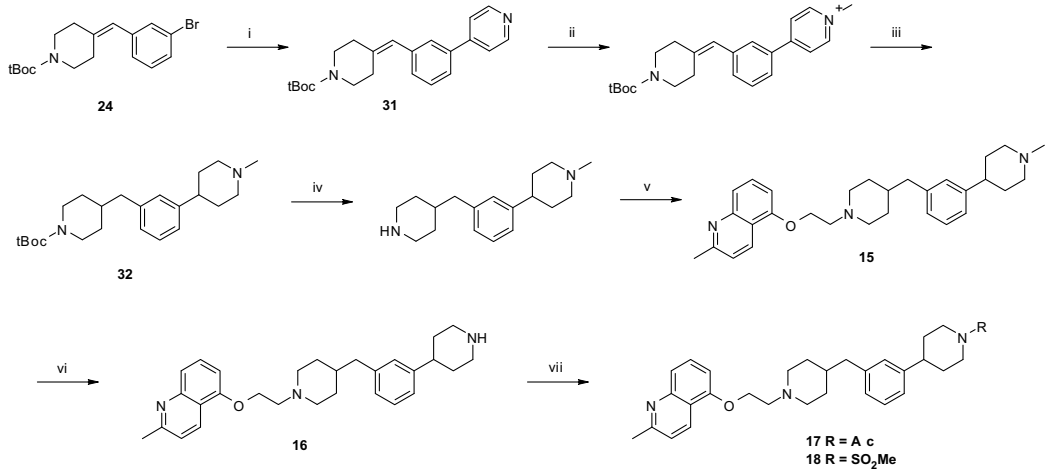
intermediate **31** via quaternisation and global reduction to *N*-methyl piperidyl **32**. Standard elaboration of this intermediate gave **15**.

In stark contrast to all previous findings,[5,6] we saw high receptor binding affinity for compound **15** with low intrinsic activity. This clearly demonstrated that although we had discovered that the piperazine substituent could be used as an alternative to the 3-amido/sulfonamido derivatives such as **2** to give us high 5-HT_1 receptor binding affinity, either nitrogen could be replaced by a methylene unit with no adverse impact on the receptor binding profile, despite the difference in nitrogen basicity and polarity.

This piperidine **15** then allowed us to envisage a set of analogues exploring different receptor and physicochemical space to those previously prepared, with the hope of being able to modulate the overall properties of the molecule to a greater degree than hitherto possible. Examination of the nature of the basic nitrogen in the piperidine showed that moving from the tertiary to secondary amine in **16** had a minimal impact on the affinities, but attempts to then derivatise the amine further into amide **17** or sulfonamide **18** led to a decrease in receptor binding affinity.

Given the data described, we reasoned that we should be able to replace the 3-phenyl substituent with an aromatic group. These analogues were prepared using similar methodology to the piperazines above using Suzuki coupling conditions to install the aryl groups (Scheme 1b, Cy = aryl). The activity of piperidine **15** led us to initially examine pyridine **19**, which gratifyingly maintained good receptor affinity across the compound set. In keeping with previous observations that the terminal nitrogen was not key to high affinity, the pyridine regioisomer **20** also showed a good profile. Further extension of this principle to removal of all heteroatoms to afford phenyl derivative **21** led to an unacceptable drop in binding affinities which could not be restored by reintroduction of a heteroatom in the 5-membered system to give furan **22**.

In line with earlier observations,[6] and that reported for **1** and **2**, low activity against the serotonin transporter was observed for all



Scheme 3. Reagents and conditions: (i) 4-pyridyl boronic acid, $Pd(Ph_3)_4$, Na_2CO_3, H_2O/DME, reflux, 54%; (ii) MeI, DCM, rt, 95%; (iii) Pt_2O, H_2, EtOH, 50 °C, 88%; (iv) HCl, Et_2O, rt, 100%; (v) **26**, K_2CO_3, DMF, 100 °C, 16 h, 40%; (vi) $ClO_2CCHClCH_3$, $^iPr_2NEt$, 1,2-dichloroethane, reflux, 62%; (vii) for R = Ac; Ac_2O, Pyr, DCM, rt, 61%; for R = SO_2Me, $MeSO_2Cl$, $^iPr_2NEt$, NEt_3, DCM, rt, 70%.

Table 2
Pharmacokinetic profiles of piperazine and piperidine analogues in rat

Compound	CLi (ml/min/g) human/rat[a]	CLb (ml/min/kg)[b]	$t½$[b] (h)	CNS br:bl[b]	V_{ss} (L/kg)	Brain C_{max}[c] (ng/g)
7	h 1.6; r 2.9	46	1.3	18	4.4	85
15	h < 0.5; r 2.0	14	12	1.3	12.4	34

[a] Intrinsic clearance determined in microsomes.
[b] In vivo data determined by 1 mg/kg iv study in rat.
[c] Brain C_{max} and brain:blood ratio determined by additional 3 mg/kg oral rat PK study (br:bl from whole brain AUC concentration measurements).

compounds profiled, often leading to greater than 100-fold selectivity for the 5-HT_1 receptors. A number of these compounds were profiled further, and pharmacokinetic data are presented for piperazine **7** and piperidine **15** (Table 2). Both are dibasic compounds; though compound **15** which contains two basic piperidine units showed an appreciably higher volume of distribution than the less basic compound **7**. This, coupled with its lower clearance resulted in compound **15** having a significantly longer half-life in blood than compound **7** and also than the compounds previously described.[5] Both compounds showed evidence of CNS penetration.

More detailed characterisation of these analogues including the use of **15** as a potential in vivo tool is on-going.

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