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8-[2-(4-Aryl-1-piperazinyl)ethyl]-2*H*-1,4-benzoxazin-3(4*H*)-ones: Dual-acting 5-HT$_1$ receptor antagonists and serotonin reuptake inhibitors—Part II

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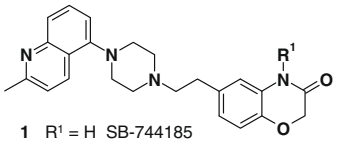
ABSTRACT

8-[2-(4-Aryl-1-piperazinyl)ethyl]-2*H*-1,4-benzoxazin-3(4*H*)-ones have been identified as highly potent 5-HT$_{1A/B/D}$ receptor antagonists with and without additional SerT activity and a high degree of selectivity over hERG potassium channels. Modulation of the different target activities gave compounds with a range of profiles suitable for further in vivo characterization.

Over the past decades, a wealth of pre-clinical and clinical evidence has confirmed a link between extracellular levels of serotonin (5-HT) and a plethora of psychiatric indications, in particular anxiety and depression.[1] In fact, enhanced serotonergic neurotransmission has become the unifying mechanism of action of modern day antidepressants and the selective serotonin reuptake inhibitors (SSRIs) have become established as the most effective antidepressant agents in current clinical use.[2] Despite the success of SSRIs, one undesirable characteristic is a long latency to therapeutic onset which is hypothesized to be due to the requirement for desensitisation of 5-HT$_1$ autoreceptors to maintain increased 5-HT levels.[3]

5-HT$_1$ autoreceptors are located on both cell bodies (5-HT$_{1A}$ and 5-HT$_{1D}$ receptor subtypes) and nerve terminals (5-HT$_{1B}$ and 5-HT$_{1D}$ receptor subtypes).[4] They are widely distributed in the brain and in addition to SerT are known to have a major role in the control of synaptic 5-HT levels.[4] Blockade of 5-HT$_{1A/B/D}$ autoreceptors, with or without concomitant SerT inhibition, rapidly increases brain 5-HT levels and consequently should provide a fast onset of antidepressant/anxiolytic action relative to current therapies.[5]

We recently disclosed a series of 6-[2-(4-aryl-1-piperazinyl)ethyl]-2*H*-1,4-benzoxazin-3(4*H*)-ones as potent 5-HT$_{1A/B/D}$ receptor antagonists some of which had additional hSerT reuptake inhibitory activity (Fig. 1).[6] Modulation of the balance between the different target affinities allowed us to identify compounds with interesting in vitro and in vivo profiles. Unfortunately, the further progression of these molecules into development was precluded by the finding that they had significant binding affinity for human ether-a-go-go-related gene (hERG) potassium channels.[7] For instance **1** had a pK_i of 7.2 in a hERG binding assay (Table 1) which translated to potent functional inhibition of hERG tail current in whole cell electrophysiology studies[8] (pEC$_{50}$ 8.1). Inhibition of hERG in vitro is associated to increases in the QT interval prolongation in vivo and the induction of potentially life-threatening ventricular arrhythmias in the clinic (Torsades de Pointes).[9] Therefore, the removal or reduction of hERG affinity became a key requirement in order to identify compounds which could be further progressed into development. This Letter reports a success-



1 R^1 = H SB-744185

2 R^1 = Me

Figure 1.

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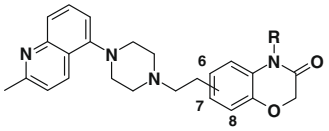
Table 1
Functional activity (f-pK_i or pEC$_{50}$)[a,b] for human 5-HT$_{1A/B/D}$ receptors with intrinsic activity (IA) and SerT and hERG binding affinities (pK_i)[b]: substitution of the benzoxazinone



Compd[c]	Sub	R	f-pK_i or *pEC$_{50}$[a,b]			pK_i[b]	
			5-HT$_{1A}$ (I.A.)	5-HT$_{1B}$ (I.A.)	5-HT$_{1D}$ (I.A.)	hSerT	hERG
1	6	H	10.2 (0.0)	6.6 (0.0)	*9.3 (0.6)	8.9	7.2
2	6	Me	10.1 (0.3)	8.7 (0.3)	10.0 (0.0)	7.7	6.1
3	8	H	9.6 (0.0)	9.0 (0.0)	10.3 (0.0)	6.5	5.6
4	8	Me	9.8 (0.0)	8.4 (0.0)	9.5 (0.0)	8.0	5.4
5	7	H	9.6 (0.0)	7.5 (0.3)	9.1 (0.0)	7.0	7.0
6	7	Me	<5.5 (0.0)	*8.2 (0.4)	8.3 (0.0)	6.8	5.5

[a] Data from the agonist mode (pEC$_{50}$)* are reported for those compounds with intrinsic activity (IA) ⩾ 0.4 in this mode (i.e., partial or full agonists), whereas, for those compounds with IA <0.4 in the agonist mode (i.e., antagonists) data from the antagonist mode is reported (f-pK_i).
[b] Each determination lies within 0.3 log units of the mean with a minimum of three replicates. See text for radioligands and assay details.
[c] Compounds were characterized and purity assessed using ^{1}H NMR and LCMS.

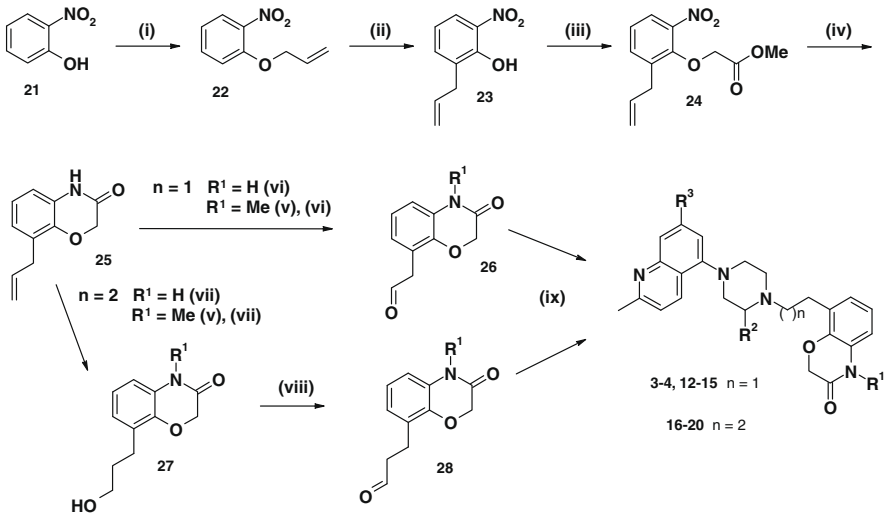
ful strategy to this end and further exploration of the structure-activity relationships (SAR) in this novel series.

The synthesis of the 6-substituted compounds **1** and **2** has been previously described.[6] The 8-substituted ethyl linked analogues **3, 4**, **12–15** (Tables 1 and 3) were prepared according to Scheme 1 by Claisen rearrangement of **22** (CARE—violently exothermic on large scale >5 g) followed by construction of the benzoxazinone ring and then osmylation of **25** to the key aldehyde **26** followed by reductive amination with the appropriate quinolinyl piperazine.[10] The homologated analogues **16–20** were prepared similarly from the NH– or *N*-methylbenzoxazinone-8-(3-propanal) **28** itself prepared by hydroboration of **25** to the primary alcohol **27** followed by Dess–Martin oxidation.

Compounds **7**, **8** and **10** (Table 2) were prepared as **4** according to Scheme 1 by alkylation of **25** with the appropriate alkylating agent in place of MeI at room temperature (41–77% yield). The difluoromethyl analogue **11** was prepared similarly using chlorodifluoromethane at −60 °C for 5 h then 16 h at room temperature (28% yield).[11] The cyclopropyl analogue **9** was prepared by the alternative procedure outlined in Scheme 2 in which the cyclopropyl group was introduced prior to the formation of the benzoxazinone system.

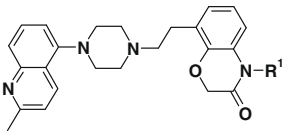
The 7-substituted compounds **5** and **6** (Table 1) were prepared according to Scheme 3. Thus, commercially available 3-hydroxy-4-nitrobenzaldehyde was alkylated with methyl bromoacetate to afford **32** which was converted to the enol ether **33**. Reduction of the nitro moiety and concomitant cyclisation afforded the benzoxazinone **34** which was hydrolysed directly to the key aldehyde **35** or alternatively methylated and then hydrolysed to afford the corresponding *N*-methyl analogue **36**. Reductive amination of **35** and **36** with 2-methyl-5-(1-piperazinyl)-quinoline afforded the target compounds **5** and **6**.

The affinities of the compounds for the reuptake site of the hSerT, stably expressed in epithelial pig kidney (LLCPK) cells, were assessed by displacement of [^{3}H]-citalopram binding either by filtration or proximity assays.[10] The affinities of the compounds for hERG potassium channels, stably expressed in Chinese hamster ovary (CHO) cells, were assessed by displacement of [^{3}H]-dofetilide



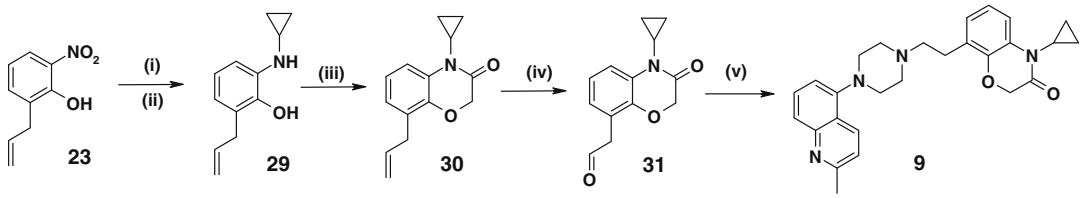
Scheme 1. Reagents and conditions: (i) allyl bromide, K_2CO_3, acetone, reflux, overnight (100%); (ii) 200 °C, 3 h (45%); (iii) $BrCH_2CO_2Me$, K_2CO_3, acetone, reflux, 4 h (100%); (iv) iron powder, NH_4Cl, MeOH/H_2O, 80 °C, 5 h (68%); (v) 60% NaH, MeI, DMF, 0 °C to rt, 4 h (66%); (vi) 4% OsO_4 aq solution, $NaIO_4$, THF/H_2O, rt, 4 h (52–67%); (vii) Sia_2BH, THF, 0 °C, 3 h; 3 N NaOH, 30% H_2O_2, THF/EtOH, 0 °C to 50 °C, 2 h (30%); (viii) Dess–Martin, DCM, rt, 3 h (54%) (ix) 7-R_1-2-methyl-5-[3-R_2-1-piperazinyl]quinoline, $NaHB(OAc)_3$, 1,2-DCE, rt, 6 h (26–83%).

Table 2
Functional activity (*f*-pK_i or pEC_{50})[a,b] for human 5-$HT_{1A/B/D}$ receptors with intrinsic activity (IA) and SerT and hERG binding affinities (pK_i)[b]: N-substitution of the benzoxazinone ring of **4**

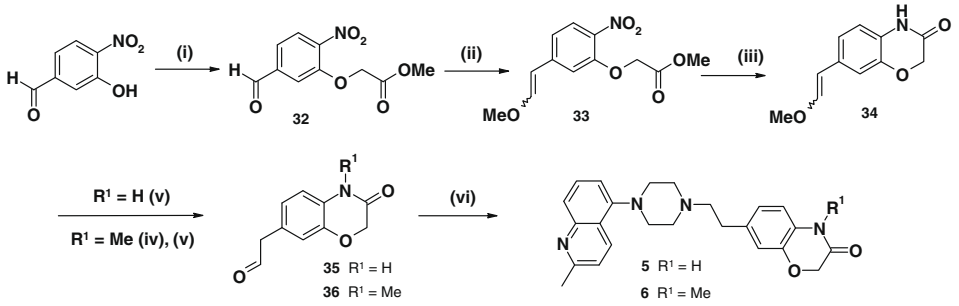


Compd[c]	R^1	*f*-pK_i[a,b]			pK_i[b]	
		5-HT_{1A} (I.A.)	5-HT_{1B} (I.A.)	5-HT_{1D} (I.A.)	hSerT	hERG
4	Me	9.8 (0.0)	8.4 (0.0)	9.5 (0.0)	8.0	5.4
7	Et	9.9 (0.3)	8.4 (0.0)	9.7 (0.0)	7.7	5.1
8	iPr	9.2 (0.0)	8.3 (0.0)	9.6 (0.0)	6.8	5.3
9	cPr	10.0 (0.0)	8.3 (0.0)	9.8 (0.0)	6.9	5.8
10	$CH_2{}^cPr$	9.2 (0.0)	8.2 (0.0)	9.5 (0.0)	6.7	5.8
11	CHF_2	9.3 (0.0)	7.8 (0.0)	9.4 (0.0)	7.2	6.4

[a–c] see Table 1.



Scheme 2. Reagents and conditions: (i) Fe, CH_3COOH, reflux 1 h, 69%; (ii) [(1-ethoxycyclopropyl)oxy]trimethylsilane, CH_3COOH, $NaBH(OAc)_3$, MeOH, reflux 3 h, 37%; (iii) (a) chloroacetyl chloride, sodium bicarbonate, water/MEK (1:1), from 0 °C to reflux 4.5 h; (b) K_2CO_3, DMF, reflux overnight, 63%; (iv) OsO_4 4% sol. in H_2O, $NaIO_4$, THF/ H_2O, rt 3 h, 52%; (v) 2-methyl-5-(1-piperazinyl)quinoline, $NaBH(OAc)_3$, 1,2-DCE, rt, overnight, 100%.



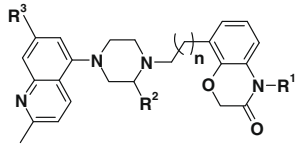
Scheme 3. Reagents and conditions: (i) $BrCH_2CO_2Me$, K_2CO_3, MEK, reflux, 6 h (72%); (ii) $Ph_3P^+CH_2OMeCl^-$, 18-Crown-6, THF, reflux, 6 h (71%, *E*/*Z*: 80:20); (iii) iron powder, NH_4Cl, MeOH/water, reflux, 2 h (66%); (iv) NaH 60%, MeI, THF, rt, 3 h (88%); (v) 10% HCl , THF, rt, overnight (80%); (vi) 2-methyl-5-(1-piperazinyl)quinoline, $NaBH(OAc)_3$, 1,2-DCE, from 0 °C to rt, overnight, (70%).

binding by proximity assays.[12] Compounds were screened against human-5-$HT_{1A/B/D}$ receptors in a dose response GTPgS functional assay using Scintillation Proximity Detection (LEADSeeker™) in both agonist and antagonist mode, that is, in absence and presence of 5-HT, respectively. Compounds with intrinsic activity (IA) in the agonist mode $\geqslant$ 0.4 relative to 5-HT were classified as partial or full agonists and only the agonist data is reported (pEC_{50}) whereas compounds with IA <0.4 in the agonist mode were classified as antagonists and data from the antagonist mode is reported as a functional pK_i (*f*-pK_i).[13] In general, the data from the 5-$HT_{1A/1D}$ functional assays correlated well with displacement binding data[6] which we had previously employed, however, for the 5-HT_{1B} assays the *f*-pK_i values were generally 0.5–1.0 log lower although the rank order was in general maintained.[14]

We previously concluded that the lactam N–H of **1** was a key pharmacophoric requirement for hSerT binding since the corresponding *N*-methyl analogue **2**, despite potent 5-$HT_{1A/B/D}$ antagonist potencies and low IA, had 15-fold reduced hSerT affinity relative to **1** (Table 1).[6b] Interestingly, **2** also showed 10-fold reduced hERG affinity relative to **1** which was somewhat surprising since the increased lipophilicity of **2** might be expected to result in higher hERG affinity.[15] This finding led us to hypothesise a specific binding interaction between the lactam N–H and the hERG channel and to investigate the effect of transposing the substitution point of the linker to different positions of the benzoxazinone ring in an attempt to selectively disrupt interaction with the hERG channel whilst maintaining the key target interactions.

Encouragingly, the 8-substituted analogues **3** and **4** were found to have similar or improved pan 5-$HT_{1A/B/D}$ antagonist potencies with no intrinsic activity (IA) relative to **1** and **2** with significantly reduced hERG affinities (40- and 5-fold, respectively). Unexpectedly, the SAR for hSerT was reversed in the 8-substituted compared to the 6-substituted series. Thus, whereas the 6-substituted NH analogue **1** had 15-fold higher hSerT affinity than the corresponding

Table 3
Functional activity (f-pK_i or pEC$_{50}$)[a,b] for human 5-HT$_{1A/B/D}$ receptors with intrinsic activity (IA) and SerT and hERG binding affinities (pK_i)[b]: SAR studies on **4**



Compd[c]	n	R^1	R^2	R^3	f-pK_i or *pEC$_{50}$[a,b]			pK_i[b]	
					5-HT$_{1A}$ (I.A.)	5-HT$_{1B}$ (I.A.)	5-HT$_{1D}$ (I.A.)	hSerT	hERG
4	1	Me	H	H	9.8 (0.0)	8.4 (0.0)	9.5 (0.0)	8.0	5.4
12	1	Me	*R*-Me	H	9.5 (0.0)	8.6 (0.0)	9.4 (0.0)	8.3 (1)	5.0
13	1	Me	*S*-Me	H	9.4 (0.0)	7.8 (0.0)	8.8 (0.0)	7.9 (1)	4.9
14	1	Me	H	F	9.7 (0.0)	8.6 (0.0)	10.1 (0.0)	8.1	5.4
15	1	Me	*R*-Me	F	9.7 (0.0)	8.7 (0.0)	9.5 (0.0)	8.7	5.5
16	2	Me	H	H	8.8 (0.0)	*7.2 (0.5)	8.5 (0.0)	9.4 (1)	5.3
17	2	Me	*R*-Me	H	8.7 (0.0)	*7.6 (0.4)	9.2 (0.0)	9.3 (1)	5.2
18	2	Me	H	F	8.2 (0.0)	6.1 (0.0)	7.8 (0.0)	9.5	5.2
19	2	Me	*R*-Me	F	8.8 (0.0)	6.8 (0.0)	8.4 (0.0)	9.1	5.5
20	2	H	H	H	8.5 (0.3)	*7.8 (0.4)	9.4 (0.3)	7.4	6.2

[a–c] see Table 1.

NMe analogue **2**, the 8-substituted NH analogue **3** showed 30-fold lower hSerT affinity compared to its corresponding NMe analogue **4**. Therefore, **3** and **4** have distinct pharmacological profiles (5-HT$_{1A/B/D}$ antagonists with an additional hSerT component in the case of the latter) both of which are of potential therapeutic utility with low potential hERG/QT risk.

Results in the 7-substituted series were less promising. The 7-substituted NH-benzoxazinone **5** demonstrated potent 5-HT$_{1A/D}$ antagonism, partial agonism at 5-HT$_{1B}$ and comparable hERG affinity to **1** but 100-fold reduced hSerT affinity. In contrast, the corresponding NMe analogue **6** demonstrated low hERG and hSerT affinities and although some 5-HT$_{1B/D}$ activity was maintained 5-HT$_{1A}$ activity was lost.

On the basis of the very encouraging results obtained for the 8-substituted analogue **4** we undertook a limited targeted exploration at several key positions in the molecule. Increasing the size of the benzoxazinone *N*-alkyl substituent **7–11** in general maintained potent 5-HT$_{1A/B/D}$ antagonist activities and similar or slightly increased hERG affinities but reduced hSerT activity (Table 2).

Methyl substitution at the alpha position of piperazine ring was undertaken to probe the effect on hERG and hSerT activities (Table 3). Introduction of *R*-Me into alpha position of piperazine **12** had minimal effect on 5-HT$_{1A/B/D}$ antagonist potencies, relative to **4**, but afforded a modest increase in hSerT affinity together with a modest reduction in hERG affinity thereby further enhancing selectivity. The corresponding *S*-enantiomer **13** maintained a reasonable overall profile but had reduced 5-HT$_{1B/D}$ potencies and hSerT compared to **12** and consequently lower selectivity over hERG. Introduction of F into the 7-position of the quinoline **14** was well tolerated and in combination with the *R*-Me piperazine **15** gave a potent and balanced target profile with >1000-fold selectivity over hERG affinity.

Extending the ethyl linker to propyl afforded interesting pharmacological profiles with a very distinct balance of target activities (**16**, **17**, **18** and **19**). In general, 5-HT$_{1A/D}$ antagonist potencies were reduced by an order of magnitude (IA = 0) whilst 5-HT$_{1B}$ potencies were more dramatically reduced and in some cases partial agonism emerged (**16**, **17**). Conversely, hSert affinities were significantly increased to subnanomolar levels with consistently low hERG affinities. Interestingly, the NH analogue **15** afforded a similar 5-HT$_{1A/B/D}$ profile to the corresponding NMe analogue **11** with 100-fold reduced hSerT but 10-fold increased hERG affinity.

A number of compounds with a range of interesting pharmacological profiles and acceptable selectivity over hERG were progressed to in vivo rat pharmacokinetic studies (Table 4). The 'selective' 5-HT$_{1A/B/D}$ antagonist **3** demonstrated good oral bioavailability combined with low blood clearance, a good half-life and high brain exposure. Compounds with additional hSerT activity were also identified which were suitable for further in vivo study (e.g., **4**, **13**, **14** and **16**). However, although these gave good brain exposure, they were more rapidly cleared in rat than **3** resulting in modest half-lives and in addition demonstrated higher intrinsic clearance in human liver microsomes. The metabolic stabilization of these compounds will be the subject of future publications.

In conclusion, 8-[2-(4-aryl-1-piperazinyl)alkyl]benzoxazinones have been identified as potent 5-HT$_{1A/B/D}$ receptor antagonists with

Table 4
Rat pharmacokinetic profile for compounds **1–4**, **13**, **14** and **16**

Compound	Cli rat; hum[a] mL/min/g liver	CLb[b] (mL/min/kg)	Vss (L/kg)	$t_{½}$ (h)	Fpo (%)	Br:Bl
1	1.3; <0.5	5	2.0	5.1	68	1.6
2	0.8; 1.1	8	2.7	4.4	59	2.2
3	0.7; 1.0	8	3.4	5.2	63	0.7
4	1.0; 2.4	29	1.7	1.0	26	1.5
13	1.1; 3.5	44	1.9	0.8	31	1.9
14	0.8; 3.2	21	2.1	1.4	41	1.1
16	1.4; 2.1	55	5.2	1.5	ND	2.9

[a] Intrinsic clearance in liver microsomes.
[b] In vivo data determined by 0.5 mg/kg iv and 1 mg/kg po administration in rat.

and without additional SerT activity and a high degree of selectivity over hERG potassium channels (e.g., **3**, **4**, **14** and **16**). Modulation of the balance between the different target affinities allowed us to identify tool compounds for in vivo comparison of efficacy versus side-effect profiles with the ultimate aim to identify faster acting anti-depressants with reduced side-effect burden.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.02.056.

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