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Novel benzofuran derivatives with dual 5-HT$_{1A}$ receptor and serotonin transporter affinity

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ABSTRACT

Several benzofuran derivatives linked to a 3-indoletetrahydropyridine through an alkyl chain were prepared and evaluated for serotonin transporter and 5-HT$_{1A}$ receptor affinities. Their design, synthesis and structure–activity relationships are described.

Selective serotonin reuptake inhibitors (SSRIs) have achieved great success in treating depression and related conditions. SSRIs act by blocking the neuronal reuptake of serotonin (5-HT), increasing the concentration of synaptic 5-HT and thus, increasing the activation of post synaptic 5-HT receptor; however, they suffer from a delayed onset of action.[1] This delay in antidepressant activity is speculated to be the result of acute stimulation of the somatodendritic 5-HT$_{1A}$ auto receptors that decrease neuronal firing to release 5-HT in the forebrain. Only after desensitization of these autoreceptors do the serotonergic neurons resume normal firing and eventually lead to an increase in 5-HT levels in the major forebrain areas.[2–4] It can take two to three weeks before the patient feels the full antidepressant effect. This delayed onset of action is a significant problem, especially in the patients with severe depression. It has been shown by Arborelius et al.[5] that acute administration of SSRIs reduces firing of 5-HT neurons of dorsal raphe nucleus in the rodent brain and sustained treatment of SSRIs leads to normalization of the firing activity of the 5-HT neurons. Furthermore, it has been shown by Invernizzi et al.[6] that the recovery of firing activity of the 5-HT neurons is linked to desensitization of somatodendritic 5-HT$_{1A}$ autoreceptors. Hence it has been suggested that simultaneous administration of an SSRIs and a 5-HT$_{1A}$ antagonist would lead to a rapid onset of antidepressant effect.[7]

Pre-clinical evidence has shown that acute SSRI-induced increases in forebrain 5-HT can be significantly augmented by co-treatment with either pindolol or the more selective 5-HT$_{1A}$ antagonist WAY-100635.[7,8] It has been shown by Dawson et al.[9] that the co-administration of fluoxetine and WAY-100635 produces an immediate increase in 5HT levels in rat frontal cortex, as evidenced by in vivo microdialysis, where this effect was not seen with fluoxetine treatment alone. This 'immediate' onset was strongly supported in the clinical trials conducted by Artigas et al[10] and Blier et al.[1] These researchers have demonstrated that combination of racemic pindolol, a non-selective 5-HT$_{1A}$ antagonist with the SSRI paroxetine shortened the onset of antidepressant action to a period of 3–7 days in contrast to the 2–3 weeks required with the SSRI alone. Therefore, incorporating both the antagonism of the 5-HT$_{1A}$ receptor and 5-HT reuptake inhibition of the 5-HT transporter within a single molecule should provide an immediate increase of 5-HT in the frontal cortex, resulting in a more rapid onset of antidepressant action.[9,10,1]

Previous reports from our laboratories have revealed four novel series (Fig. 1) capable of modulating both SSRI and 5-HT$_{1A}$ receptor activities by linking an aryloxy ethylamine **1** and **3** or a benz[1,4]oxazine **2** and **4** with a 3-indoletetrahydropyridine or a 3-indolealkylamine **1** and **2** through a common basic nitrogen.[11–13] In all these series, an aryloxy ethylamine moiety has been utilized to produce potent 5-HT$_{1A}$ ligands, while the indole tetrahydropyridine or indole alkyamine portion have served as the 5-HT uptake inhibitor substructure. In order to expand upon the type of structures that can potentially maintain both desired activities and to probe the

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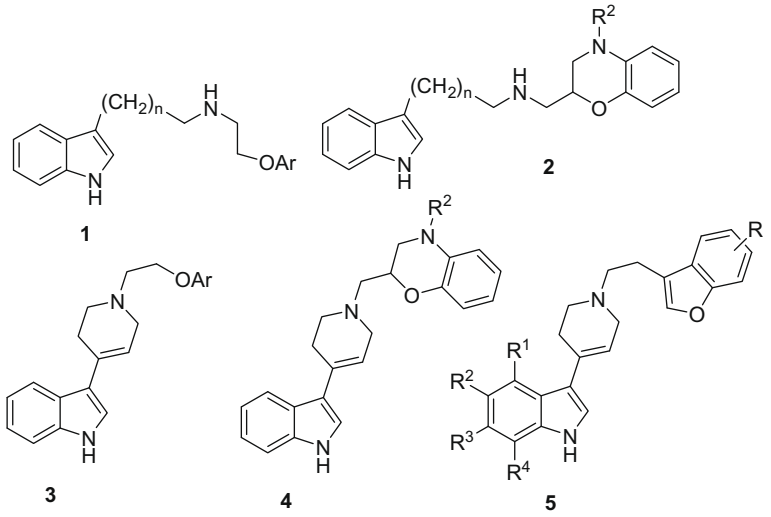
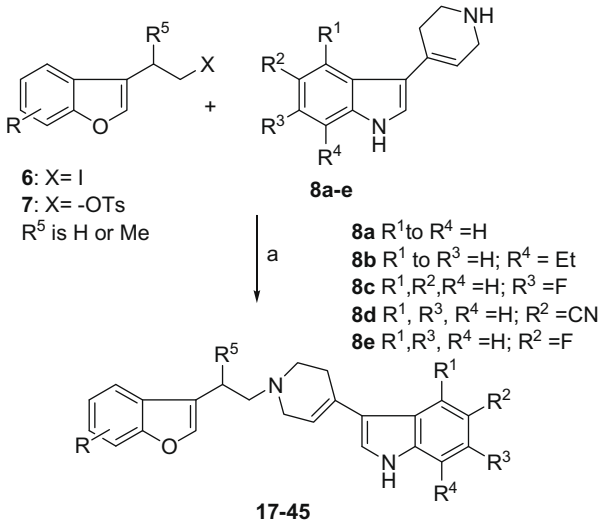


Figure 1.

structure–activity relationship (SAR), we replaced the benzoxazine portion of **4** with benzofuran moiety. We herein report the syntheses and SAR of this series **5** of dual-acting compounds.

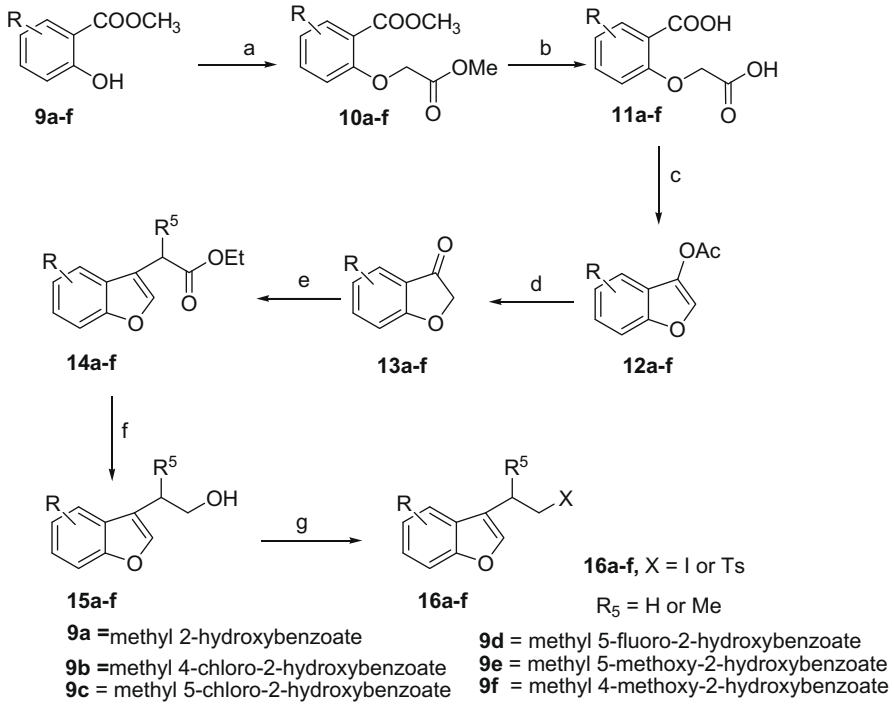
The 3-{1-[2-(1-benzofuran-3-yl)alkyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1*H*-substituted indole **5** were prepared by reacting the appropriately substituted benzofuran-3-yl-ethyl iodide **6** or the tosylate **7** with the corresponding substituted or unsubstituted (1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole derivative **8a–e** in DMSO at 150 °C in the presence of Hunig's base (Scheme 1). The intermediates **8a–e** were prepared according to literature procedure,[14] while the 3-alkyl-benzofuran derivatives **6a**–**f** were prepared starting from the commercially available substituted salicyclic acid derivatives as depicted in Scheme 2. The salicyclic acids were esterified to their corresponding methyl esters **9a–f**. Reaction of **9a–f** with bromoethyl acetate in the presence of potassium carbonate in refluxing acetone yielded **10a–f** in almost quantitative yields. The diesters **10a–f** were hydrolyzed to the diacids **11a–f** using sodium hydroxide. Cyclization to intermediate **12a–f** was carried out using acetic anhydride and fused sodium acetate in boiling acetic acid; subsequent conversion to the ketone derivatives **13a–f** was accomplished by boiling **12a–f** in 1N. HCl. Horner–Emmon's reaction of **13a–f** using (carbethoxymethylene)triphenylphosphorane or (carbethoxyethylidene)triphenylphosphorane in boiling toluene gave the ester derivatives **14a–f**, which were converted to **15a–f** using $LiAlH_4$. The alcohol derivatives were converted to their corresponding iodide **(16a–f)** using the I_2/imidazole/Ph_3P procedure. Some derivatives of **15a–f** were also converted to their respective tosylates using *p*-toluenesulfonyl chloride/pyridine at 0 °C. The proton NMR and ESMS spectra confirmed the structures of all newly prepared compounds. Analogues 43–**45** were tested as racemic mixtures.



Scheme 1. General method to prepare **17**–**45**. Reagents and conditions: (a) DMSO, Hunig's base, 150 °C, 4 h.

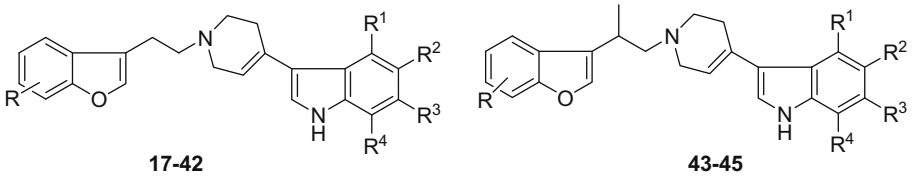
The 3-{1-[2-(1-benzofuran-3-yl)alkyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1*H*-substituted indole derivatives **17–45** were tested in vitro to determine affinity for the 5-HT_{1A} receptor and 5-HT transporter (5-HT-T). Human 5-HT_{1A} (h-5-HT_{1A}) receptor binding affinity was determined by the displacement of [^{3}H]-8-OH-DPAT from human 5-HT_{1A} receptors stably transfected into CHO cells according to Dunlop et al.[15] Assessment of the functional activity at the 5-HT_{1A} receptor for the most active compounds was determined using a [^{35}S]GTPγS assay.[16] A protocol similar to that of Cheetham et al.[17] was used to determine rat 5-HT transporter affinity (r5-HT-T). Biological data for all the 3-{1-[2-(1-benzofuran-3-yl)alkyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1*H*-substituted indole derivatives **17–45** are presented in Table 1.

Thus benzofuran-3-yl-ethyl iodide **16a** (R = H) was initially reacted with **8a** (R^1 to R^4 = H) to form **17** (Table 1) a compound with potent 5HT-T affinity with moderate 5-HT_{1A} affinity. This initial result encouraged us to probe the SAR more systematically. When R = H, introduction of 5-cyano **20**, 5-fluoro **21** or 7-ethyl **18** into the 1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole was proved to be detrimental to both transporter and 5-HT_{1A} receptor affinity. However, the 6-F derivative **19** gave potent transporter activity without increasing the 5-HT_{1A} receptor affinity. Similarly, when R = 5-Cl **25–27** or 6-Cl **22–24** in the benzofuran portion the 5-HT_{1A} acitivity was not improved. Replacement of the 5-Cl in the benzofuran portion of the molecule with 5-F gave potent transporter compounds **28–30** that still had moderate to poor 5-HT_{1A} activity. The effect of an electron releasing group (–OMe) in the benzofuran was investigated. As can be seen from Table 1, the introduction of the methoxy group at the 5 and 6-position of the benzofuran gave compounds **31–38** with generally good transporter activity, but poor to moder-



Scheme 2. General method to prepare **16a–f**. Reagents and conditions: (a) $BrCH_2COOMe$; K_2CO_3, acetone, reflux, 6 h; (b) NaOH,EtOH, THF, reflux, 24 h; (c) $(CH_3CO)_2O$ fused CH_3COONa, CH_3COOH, reflux/3 h; (d) 1 N HCl, MeOH, reflux, 1 h; (e) $Ph_3P{=}C(R_5)COOEt$, toluene, reflux, 24 h (R = H or Me); (f) $LiAlH_4$, THF, 0 °C: (g) when X = OTs, *p*-toluene sulfonylchloride, pyridine, 0 °C, 24 h: when X = I, I_2, imidazole, PPh_3, THF, rt, 4 h.

Table 1
In vitro data for compounds **17–44**



Compd #	R	R^1	R^2	R^3	R^4	h-5-HT_{1A} (K_i nM or% inh)	r-5-HT-T (K_i nM or% inh)
17	H	H	H	H	H	36.1	1.33
18	H	H	H	H	Et	1%*	156
19	H	H	H	F	H	56.3	2.55
20	H	H	CN	H	H	42%*	90.0
21	H	H	F	H	H	248.0	14.0
22	6-Cl	H	H	H	H	49%*	12.0
23	6-Cl	H	F	H	H	30%*	300.0
24	6-Cl	H	H	F	H	45%*	3.54
25	5-Cl	H	H	H	H	29%*	14.0
26	5-Cl	H	F	H	H	46%*	15.0
27	5-Cl	H	H	F	H	6%*	3.00
28	5-F	H	H	H	H	190.0	3.14
29	5-F	H	CN	H	H	41.5	4.13
30	5-F	H	F	H	H	300.0	9.25
31	5-OMe	H	H	H	H	23%*	11.0
32	5-OMe	H	F	H	H	44%*	54.0
33	5-OMe	H	H	F	H	8%*	5.50
34	5-OMe	H	H	H	Et	39%*	41.0
35	6-OMe	H	H	H	H	56.3	3.36
36	6-OMe	H	F	H	H	66.3	3.63
37	6-OMe	H	H	F	H	303.0	1.20
38	6-OMe	H	CN	H	H	12.7	3.36
39	7-OMe	H	H	H	H	8.46	2.85
40	7-OMe	H	H	F	H	11.0	0.76
41	7-OMe	H	F	H	H	10.1	3.17
42	7-OMe	H	CN	H	H	5.14	3.24
43	7-OMe	H	H	H	H	29.2	3.98
44	7-OMe	H	F	H	H	48%*	13.0
45	7-OMe	H	H	F	H	48%*	1.97

K_i values in nM.
* % Inhibition at 1 μM.

ate 5-HT_{1A} receptor affinity. The exception was compound **38**, which showed good affinity to both targets, (5-HT-T K_i = 3.36 nM; 5-HT_{1A} K_i = 12.7 nM) but subsequently found to be partial agonist at the 5-HT_{1A} receptor (I_{max} = 50%). Introduction of the -OMe group at the 7-position of the benzofuran gave potent compounds **39–42** with both transporter and 5-HT_{1A} affinity. Introduction of 6-F in the indole moiety **40** afforded a highly potent transporter compound (K_i = 0.76 nM). Moreover, this compound possesses potent 5-HT_{1A} affinity (K_i = 11.0 nM) but functions as a full agonist at the 5-HT_{1A} receptor (E_{max} = 100%). Compound **42** has balanced affinities for the two targets but is a partial 5-HT_{1A} agonist (I_{max} = 59%). Introduction of a methyl group in the linker chain of **39** gave compound **43** that has good affinity for the 5-HT transporter and moderate affinity for the 5-HT_{1A} receptor. Introduction of a fluorine at either the 5- **44** or 6- position **45** of the benzofuran further decreased the 5-HT_{1A} receptor affinity while having less affect on the transporter affinity.

In this Letter, we have disclosed a series of of novel 3-{1-[2-(1-benzofuran-3-yl)alkyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1*H*-substituted indole derivatives that generally posses potent affinity for the 5-HT-T and show good to moderate 5-HT_{1A} affinity. In addition, structure–activity relationships have been delineated such that these compounds can have 5-HT_{1A} antagonist functional activity via the optimization of the R^1 and R^3 groups in benzofuran and indole nucleus. Most interestingly, analog such as **40** possesses potent 5-HT-T and 5-HT_{1A} affinities. However, this compound functions as a full 5-HT_{1A} agonist. Further studies concerning agents that target the 5-HT_{1A} and 5-HT-T receptors will be reported in due course.

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