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Advances Toward New Antidepressants Beyond SSRIs: 1-Aryloxy-3-piperidinylpropan-2-ols with Dual 5-HT_{1A} Receptor Antagonism/SSRI Activities. Part 2

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Abstract—Potent 5-HT1A/SSRIs at low nanomolar and subnanomolar concentrations were identified in a series of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols. Incorporation of an α-Me group in the piperidine ring with its specific stereochemistry enhanced binding affinity at the 5-HT reuptake site and in vitro 5-HT_{1A} antagonist functional activity.
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Introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs) as antidepressants has revolutionized the treatment of depression. Not only have SSRIs become a standard treatment for depression, but they have also widened recognition of depression as a treatable disease among medical professionals and the general population. Depression has now been recognized as a debilitating disease with an overwhelming economic liability to society. A major drawback for the treatment of depression by the current SSRIs is the delayed onset of therapeutic benefit.[1,2] More recent efforts in developing newer antidepressants are targeted for a fast acting agent in a single molecule via a mechanism-based combination therapy. One such approach has stemmed from reports by several groups that co-administration of a 5-HT_{1A} receptor antagonist and an SSRI has been shown to accelerate antidepressant effects.[3–5] The concept of developing a dual-acting agent blocking both the 5-HT_{1A} receptor and the 5-HT reuptake sites in a single molecule (5-HT1A/SSRI) has been proposed by us and others.[6–9]

Previously we reported a series of 1-aryloxy-3-piperidinylpropan-2-ols possessing dual 5-HT_{1A} receptor antagonism and serotonin reuptake inhibition (Fig. 1).[6] In this report we describe a structure–activity relationship (SAR) study focusing on the piperidine ring of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols in order to optimize the dual activity for 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibition in the development of more efficacious antidepressants with a faster onset of action (Fig. 2).

We first explored the effects of a methyl substituent alpha to the piperidine nitrogen (R1 = Me and R2 = H) in Figure 2. Scheme 1 shows the synthesis of target compounds, similar to what we have already reported.[6] A substituted benzo[*b*]thiophene **1** was deprotonated with alkyllithium reagent to add to *N*-Boc protected

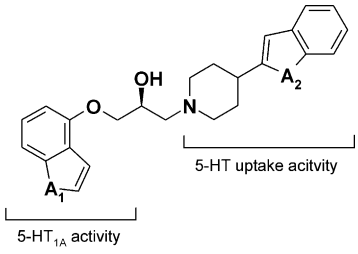

Figure 1. General structure of 1-aryloxy-3-piperidinylpropan-2-ols, new 5-HT1A/SSRIs.

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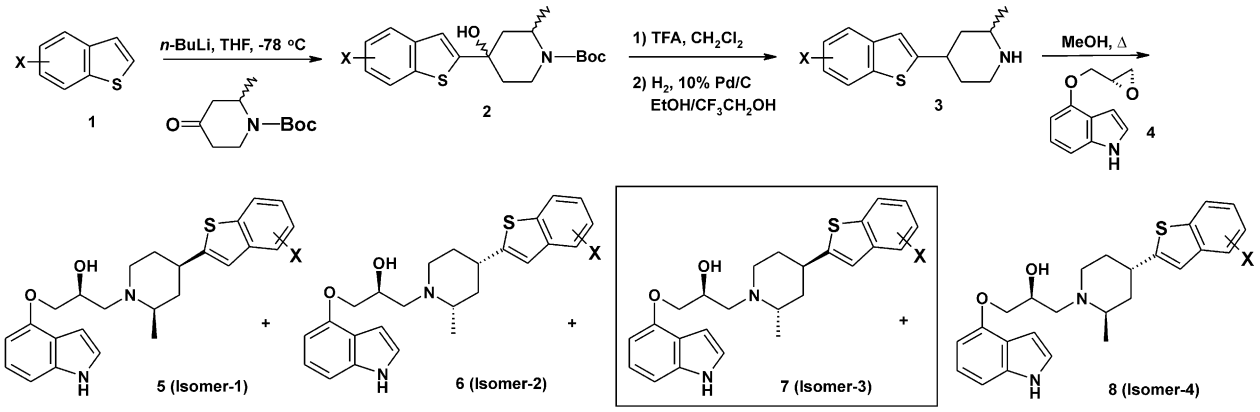


Scheme 1. Synthesis of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-yl-2-methylpiperidinyl)propan-2-ols.

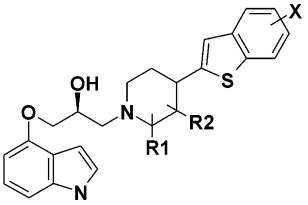
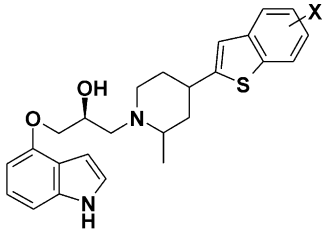


Figure 2. SAR study on 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols.

(±)-2-methyl-4-piperidone. Dehydration of **2** with TFA followed by hydrogenation of the resultant olefin afforded the chromatographically separable (*cis*)- and (*trans*)-4-(benzo[*b*]thiophen-2-yl)-2-methylpiperidine intermediates **3**. Reaction with indolyl glycidyl ether **4** then yielded four diastereomeric isomers of the target molecules **5–8** that were isolated by flash chromatography.[13]

Tables 1–3 show the results of biological assays on these molecules. Affinities at the 5-HT_{1A} receptor and serotonin transporter were measured using standard radioligand-binding assays.[10,11] Functional activity at the 5-HT_{1A} receptor was measured in vitro by the human cloned 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding to G proteins.[12] Compounds were first tested for potential agonist activity using a high concentration (1 μM). As can be seen in Tables 1–4, all compounds produced less than a 10% stimulation of [^{35}S]GTPγS binding compared to the maximal stimulation produced by the endogenous agonist 5-HT. To confirm 5-HT_{1A} receptor antagonism the compounds were evaluated for their ability to inhibit [^{35}S]GTPγS binding that was induced by 5-HT. Tables 1–4 show that tested compounds were able to inhibit the effects of 5-HT down to a level of 10% or less of that produced by 5-HT. K_i values calculated from these functional

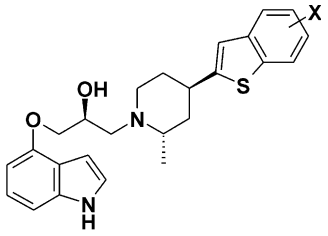
Table 1. SAR of 2-methylpiperidine: effects of ring stereochemistry



Compd	X	Isomer	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	GTPγS binding % Stim[c]	Inhibition of 5-HT-stimulated GTPγS binding	
						K_i (nM)[d]	E_{min} (%)[e]
5a	4-OMe	1 (2*R*,4*R*)	2.76±0.02	14.71±1.43	1.20	1.80	2.01
6a	4-OMe	2 (2*S*,4*S*)	14.45±1.55	13.59±1.12	1.38	16.45	1.43
7a	4-OMe	3 (2*S*,4*R*)	3.64±0.13	0.27±0.09	7.77	2.33	7.83 (5)
8a	4-OMe	4 (2*R*,4*S*)	8.47±2.03	1.15±0.21	4.41	8.37	5.97 (8)
5b	5-F	1 (2*R*,4*R*)	8.77±2.13	3.53±0.61	7.21	1.76	10.83
6b	5-F	2 (2*S*,4*S*)	36.80±0.80	4.22±1.04	3.24	16.48	7.87
7b	5-F	3 (2*S*,4*R*)	6.40±1.06	0.39±0.08	7.68	5.67	7.69
8b	5-F	4 (2*R*,4*S*)	11.75±0.75	0.99±0.22	6.35	16.71	10.54

[a]Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geq 2$).[10]
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geq 2$).[11]
[c]Stimulation by a 1 μM compound concentration expressed as a % of the maximal [^{35}S]GTPγS binding induced by 5-HT.
[d]K_i calculated from the inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding.
[e]Degree of maximal inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding expressed as % of the stimulation produced by 5-HT (300 nM)

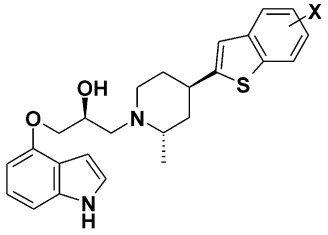
Table 2. Effects of EDG-substituted benzo[*b*]thiophene derivatives **7**



Compd	X	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	GTPγS binding % Stim[c]	Inhibition of 5-HT-stimulated GTPγS binding	
					K_i (nM)[d]	E_{min} (%)[e]
7a	4-OMe	3.64±0.13	0.27±0.09	7.77	2.33	7.83 (5)
7c	6-OMe	14.49±2.76	1.10±0.29	5.26	2.98	6.67
7d	4,5-di-OMe	1.30±0.22	10.83±1.66	8.38	0.98	4.80
7e	4-Me	6.85±1.03	0.44±0.04	8.48	8.75	4.96
7f	6-Me	—	2.24±0.14	nd	nd	nd
7g	4,6-di-Me	94.90±11.50	1.93±0.33	nd	nd	nd

[a]Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geq 2$).[10] – denotes <50% inhibition at 100 nM, no K_i was generated.
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geq 2$).[11]
[c]Stimulation by a 1 μM compound concentration expressed as a% of the maximal [^{35}S]GTPγS binding induced by 5-HT.
[d]K_i calculated from the inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding.
[e]Degree of maximal inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding expressed as % of the stimulation produced by 5-HT (300 nM) ($n=1$ unless noted otherwise in parentheses). nd denotes 'not determined' due to the weak binding affinity.

Table 3. Effects of EWG-substituted benzo[*b*]thiophene derivatives **7**



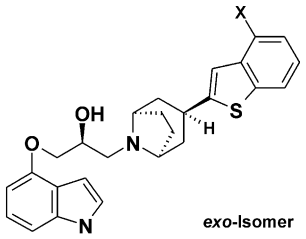
Compd	X	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	GTPγS binding % Stim[c]	Inhibition of 5-HT-stimulated GTPγS binding	
					K_i (nM)[d]	E_{min} (%)[e]
7h	H	3.09±0.18	0.51±0.06	6.32	3.28	7.50
7i	4-F	13.87±4.64	1.16±0.15	5.37	4.88	7.44
7b	5-F	6.40±1.06	0.39±0.08	7.68	5.67	7.69
7j	6-F	5.52±1.04	0.31±0.06	5.32	7.45	9.00
7k	7-F	21.95±4.55	3.47±2.20	2.66	4.23	6.80
7l	4-Cl	—	0.69±0.04	nd	nd	nd
7m	5-Cl	8.34±1.36	0.58±0.23	3.97	5.26	6.81
7n	6-Cl	24.85±0.65	1.10±0.42	8.49	11.66	7.99
7o	4-CF_3	24.23±2.31	3.46±0.38	nd	nd	nd

[a]Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geq 2$).[10] – denotes <50% inhibition at 100 nM, no K_i was generated.
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geq 2$).[11]
[c]Stimulation by a 1 μM compound concentration expressed as a % of the maximal [^{35}S]GTPγS binding induced by 5-HT.
[d]K_i calculated from the inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding.
[e]Degree of maximal inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding expressed as % of the stimulation produced by 5-HT (300 nM); ($n=1$). nd denotes 'not determined' due to the weak binding affinity.

inhibition curves were generally in good agreement with the K_i values determined from the radioligand-binding assays.

We found interesting stereochemical influences of the four isomers on the binding affinity and in vitro functional activity (Table 1). There was a stereochemical preference on both 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibition in the order of Isomer 3 (2*S*,4*R*) > Isomer 4 (2*R*,4*S*) > Isomer 1 (2*R*,4*R*) > Isomer 2 (2*S*,4*S*) in general (Scheme 1), though only two representative examples are shown in Table 1. Dual activities improved overall, compared to the desmethylpiperidine series reported earlier.[6] In particular this series exhibited excellent 5-HT reuptake inhibition and improved the 5-HT_{1A} antagonism functional activity. Both electron donating (EDG) and withdrawing (EWG) substituents (Tables 2 and 3) were well tolerated, which might provide metabolic advantages in the in vivo profile of this series of compounds. There was a

Table 4. Effects of rigidified stereocenter in the piperidine ring



Compd	X	Isomer	5-HT$_{1A}$ K_i (nM)[a]	Paroxetine K_i (nM)[b]	GTPγS binding % Stim[c]	Inhibition of 5-HT-stimulated GTPγS binding	
						K_i (nM)[d]	E_{min} (%)[e]
9	H	Unknown	30.55±3.75	0.07±0.01	9.26	70.08	9.40
10	OMe	*exo*	15.70±1.10	1.31±0.49	7.22	18.75	4.02
11	OMe	*endo*	—	0.17±0.04	nd	nd	nd

[a]Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geq 2$).[10] – denotes <50% inhibition at 100 nM, no K_i was generated.
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geq 2$).[11]
[c]Stimulation by a 1 μM compound concentration expressed as % of the maximal [^{35}S]GTPγS binding induced by 5-HT.
[d]K_i calculated from the inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding.
[e]Degree of maximal inhibition of 5-HT-mediated stimulation of [^{35}S]GTPγS binding expressed as a% of the stimulation produced by 5-HT (300 nM). ($n = 1$ unless). nd denotes 'not determined' due to the weak binding affinity.

regiochemical preference in the substitution patterns as seen in the des-methyl series:[6] preferences in EDG at 4-position (Table 2) and EWG at 5-position (Table 3) of benzo[*b*]thiophene. Another striking effect of 2-methylpiperidine was that di-substitution in the benzo[*b*]thiophene ring was well tolerated (**7d**, **7g**), especially in the 5-HT reuptake inhibition, in contrast to des-methyl series,[6] which were inactive.

With the stereochemical influence of the methyl substituent on the piperidine ring observed, we further explored the effects of di-substitution in the piperidine ring. The purposes of these substituents were (1) to remove the stereogenic center at the 2-position and (2) to fixate the piperidine ring. 2,2-*gem*-Dimethylpiperidines (Fig. 3) were inactive in both binding affinity assays at the 5-HT$_{1A}$ receptor and 5-HT reuptake site.

Interesting results were observed with rigidified piperidine, namely tropane derivatives (Table 4). The compound **9** without any substituent on the benzo[*b*]thiophene ring was a very potent 5-HT reuptake inhibitor with somewhat modest 5-HT$_{1A}$ receptor affinity. Two stereoisomers of the tropane ring compounds[14] showed distinctive differences in the 5-HT$_{1A}$ receptor affinity. The *exo*-isomer **10** showed respectable affinity at the 5-HT$_{1A}$ receptor, whereas the *endo*-isomer **11** was inactive. These results suggest the importance of a certain conformational bias at the receptor site interacting and relating to the stereochemistry of the piperidine middle ring of the molecule.

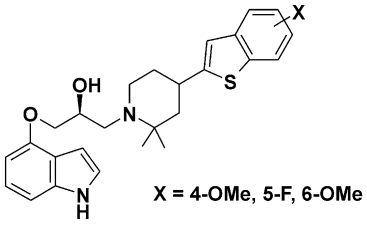


Figure 3. 2,2-Dimethylpiperidine derivatives.

In conclusion, we have identified potent 5-HT$_1$A/SSRIs in a series of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols. Incorporation of an α-Me group in the piperidine ring with its specific stereochemistry enhanced binding affinity at the 5-HT reuptake site and in vitro 5-HT$_{1A}$ antagonist functional activity. Further optimization of pharmacological profiles of this series of compounds will be reported in due course.

Acknowledgements

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13. Absolute stereochemistry of one of the 'Isomer 3' was determined by a single crystal X-ray determination, and then the relative stereochemistry of other three isomers were determined by ^{1}H NMR.
14. 3 - (4 - Methoxybenzo[*b*]thiophen - 2 - yl) - 8 - azabicyclo [3.2.1]octane was prepared from *N*-carboethoxy-4-tropinone and its stereochemistry was determined by the ^{1}H NMR, COSY, ROESY or 1D TOCSY, and eHSQC experiments. Details of the stereoselective synthesis of each isomer will be reported elsewhere.