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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 4

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Abstract—A series of 1-(1*H*-indol-4-yloxy)-3-(4-arylpiperidinyl)propan-2-ols possessing potent dual 5-HT$_{1A}$ receptor antagonism and serotonin reuptake inhibition was discovered. The fused aryl ring moiety contributed to the robust dual activities irrespective of the regiochemistry associated with its connectivity to the piperidine central ring.

The need for more efficacious antidepressant therapies with faster onset of action and a more favorable side effect profile is now widely acknowledged after decades of the SSRI treatment of depression with limited benefits due to its drawbacks.[1] Finding the next generation of antidepressant with a new mechanism of action or a combination therapy with an SSRI has spurred a flurry of research efforts in recent years.[2] One of the emerging approaches is a combined therapeutic intervention through blocking 5-HT$_{1A}$ somatodendritic autoreceptor activation and 5-HT reuptake. The hypothesis behind this approach is based on observations that the activation of 5-HT$_{1A}$ somatodendritic autoreceptors inhibits the firing of serotonergic neurons.[3] Co-administration of a 5-HT$_{1A}$ antagonist and an SSRI has been shown to accelerate antidepressant effects.[4,5]

We have reported that a series of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols possesses dual action against the 5-HT$_{1A}$ receptor and 5-HT reuptake sites.[6] Our initial exploration of regiochemical preference for the connectivity of the benzo[*b*]thiophene moiety to the piperidine ring indicated that the 2-position of benzo[*b*]thiophene was favored over the 3-position particularly for the 5-HT reuptake inhibition (Table 1). Based on this premise, optimization with various substituents on the benzo[*b*]thiophene, piperidine, and indole rings led us to discover a series of potent and balanced dual acting benzo[*b*]thiophen-2-yl compounds.[7]

In the course of our SAR exploration, we explored various aromatic rings in place of benzo[*b*]thiophene. The most logical alternative, the naphthalene ring was first explored but metabolic liability of the unsubstituted naphthalene ring and a less amenable synthetic route to incorporate substituents at various positions on a naphthalene ring thwarted our efforts. We observed, however, that the compounds with a benzo[*b*]thiophene or naphthalene moiety exhibited comparable dual binding affinities at the 5-HT$_{1A}$ receptor and 5-HT reuptake sites (Table 2: **3** vs **4**; **5** vs **6**).

The results prompted us to examine if the phenyl and thiophene regions of the fused aromatic ring might be interchangeable. This can be carried out by connecting the phenyl side of benzo[*b*]thiophene to the piperidine ring. Figure 1 depicts further structure–activity relationship exploration of the aromatic ring connected to piperidine in the 1-(1*H*-indol-4-yloxy)-3-(4-arylpiperidinyl)propan-2-ols. In this paper, we report the influence of the positional difference of a heteroaryl group (Fig. 1 where A=A=heteroatom; B=B=C=C) on the binding affinity and in vitro functional activity of

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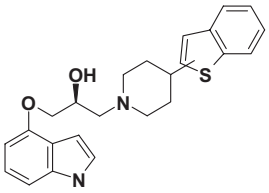
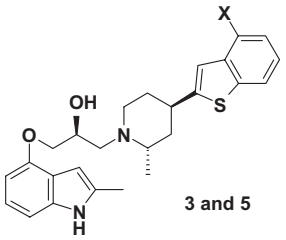
Table 1. Effects of regiochemistry of benzo[*b*]thiophene ring moiety connected to piperidine[8]

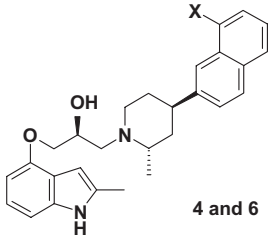


Compound	Connectivity at benzo[*b*]thiophene	5-HT$_{1A}$ K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT$_{1A}$ GTPγS E_{max} (%)[c]
1	2-	3.70 ± 0.61	16.75 ± 2.13	12
2	3-	1.84 ± 0.30	—	nd

[a] Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$).[9]
[b] Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[10]
[c] Stimulation by a 1 μM compound concentration expressed as a % of the maximal [^{35}S]GTPγS binding induced by 5-HT.[11]
Values represent the mean ± SEM where $n \geqslant 3$ or ±1/2 the range when $n = 2$. — denotes <50% inhibition at 100 nM, no K_i was generated. nd denotes 'not determined' due to the weak binding affinity at either one or both sites.

Table 2. Comparison between the benzo[*b*]thiophene and naphthalene moiety of 1-indol-4-yloxy-3-(4-arylpiperidinyl)propan-2-ols[8]





Compound	X	Aryl group	5-HT$_{1A}$ K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT$_{1A}$ GTPγS E_{max} (%)[c]
3	H	Benzothiophen-2-yl	7.11 ± 0.08	0.53 ± 0.00	6
4	H	Naphthalen-2-yl	5.11 ± 0.41	0.40 ± 0.03	9
5	4-OMe	Benzothiophen-2-yl	14.35 ± 0.05	0.86 ± 0.12	3
6	8-OMe	Naphthalen-2-yl	10.91 ± 1.29	0.34 ± 0.00	11

[a] Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$).[9]
[b] Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[10]
[c] Stimulation by a 1 μM compound concentration expressed as a % of the maximal [^{35}S]GTPγS binding induced by 5-HT.[11]
Values represent the mean ± SEM where $n \geqslant 3$ or ±1/2 the range when $n = 2$.

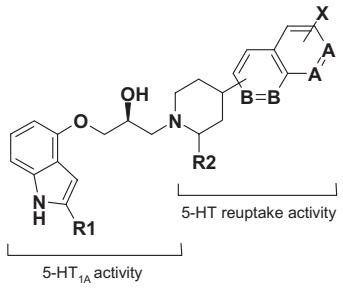
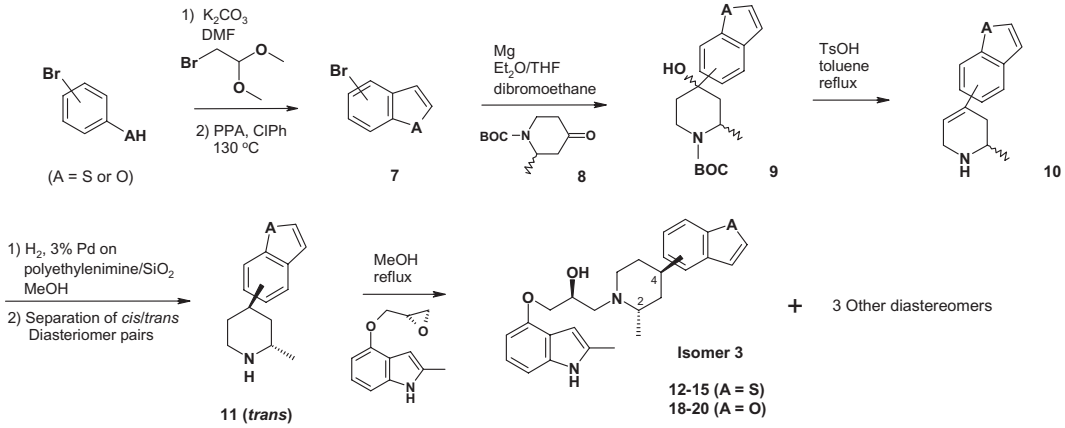


Figure 1. SAR study on 1-indol-4-yloxy-3-(4-arylpiperidinyl)propan-2-ols.

this series of compounds, while taking advantage of the SAR already established (with A=A=C=C; B=B=S) in our earlier work.[6,7]

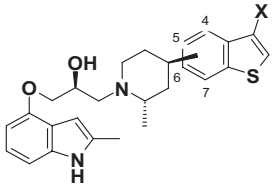
Scheme 1 shows the synthesis of target compounds. An appropriately brominated benzo[*b*]thiophene **7** (where A=S) was prepared from a corresponding bromobenzenethiol according to a known literature method.[12] Grignard's reagent formation followed by its nucleophilic addition to the piperidone **8** provided the intermediate **9**. Dehydration with *p*-TsOH in toluene at reflux and hydrogenation of the resultant olefin afforded the chromatographically separable *cis*- and *trans*-diastereomers **11** (only *trans*-isomer shown). Each isomer was then treated with (2*S*)-2-methylindol-4-yl glycidyl ether to yield chromatographically separable target molecules as four diastereomers.

Table 3 shows the results of the SAR exploration. There was a stereochemical preference among the four diastereomers similar to what we already reported.[7] However, we have noticed the following differences: (1) the potencies in the dual activities have narrowed down considerably among the isomers and (2) the so-called isomers **2** and **4** reversed its order with isomer **3** still exhibiting the most potent dual activities; namely, the order of preference was isomer **3** (2*S*,4*R*) > isomer **2** (2*R*,4*R*) ⩾ isomer **4** (2*R*,4*S*) > isomer **2** (2*R*,4*S*). We therefore report here the results of the most preferred (2*S*,4*R*)-isomer **3**. Remarkably all four benzo[*b*]thio-



Scheme 1. Preparation of 1-(2-methyl-1*H*-indol-4-yloxy)-3-(4-aryl-2-methylpiperidinyl)propan-2-ols.

Table 3. Effects of regiochemical connectivity difference in the benzo[*b*]thiophene moiety of (2*S*)-1-(2-methyl-1*H*-indol-4-yloxy)-3-((2*S*,4*R*)-4-aryl-2-methylpiperidinyl)propan-2-ols



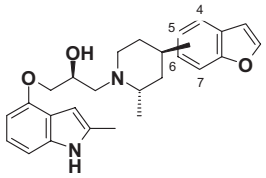
Compound	X	Connectivity at benzo[*b*]thiophene	5-HT$_{1A}$ K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT$_{1A}$ GTPγS E_{max} (%)[c]
12	H	4-	1.82 ± 0.51	4.35 ± 0.66	15
13	H	5-	1.43 ± 0.05	0.30 ± 0.02	12
14	H	6-	4.45 ± 0.57	0.75 ± 0.03	12
15	H	7-	0.91 ± 0.23	9.24 ± 1.40	8
16	Me	5-	3.12 ± 0.68	0.54 ± 0.06	8
17	Me	6-	7.82 ± 1.36	0.58 ± 0.01	4

[a] Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$).[9]
[b] Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[10]
[c] Stimulation by a 1 μM compound concentration expressed as a % of the maximal [^{35}S]GTPγS binding induced by 5-HT.[11]
Values represent the mean ± SEM where $n \geqslant 3$ or ±1/2 the range when $n = 2$.

phene regioisomers on the phenyl ring side (**12**–**15**) exhibited excellent in vitro binding affinities at both the 5-HT$_{1A}$ receptor and 5-HT reuptake sites. As before, these compounds showed <15% agonist activity in the GTPγS functional assay. This is a level of in vitro agonist activity that did not translate into measurable in vivo agonist activity. Among the four benzo[*b*]thiophene regioisomers, 5-regioisomer **13** showed the most potent dual activities. 4- and 7-Regioisomers (**12** and **15**) were over 10-fold less potent than the 5- and 6-regioisomers (**13** and **14**) at the 5-HT reuptake site, respectively, whereas the difference was not so pronounced at the 5-HT$_{1A}$ receptor site. 5- and 6-Benzo[*b*]thiophenyl regioisomers correspond to the 2-naphthyl regioisomer, whereas 4- and 7-benzo[*b*]thiophenyl regioisomers correspond to the 1-naphthyl regioisomer. Interestingly, without the methyl substituent on the piperidine or indole ring, the 2-naphthalenyl regioisomer exhibited more potent activities than the 1-naphthalenyl regioisomer at both the 5-HT$_{1A}$ receptor and 5-HT reuptake sites, and the negative regiochemical effect of the 1-naphthalenyl regioisomer was more pronounced at the 5-HT reuptake site ($K_i = 8$ vs 20 nM). The trends observed therefore appear to agree with the regiochemistry of each series. We also examined what effect a substituent on the thiophene side would manifest. In Table 2, we observed that the 8-methoxynaphthalene derivative **6** exhibited good dual activities. The substituent at the 8-position of the naphthalene derivative **6** could correspond to 3-position of 5-regioisomer **13**. The 3-methylthio[*b*]phen-5-yl regioisomer **16** maintained the excellent dual activity as compared to **6** and **13**. Interestingly, the 3-methylthio[*b*]phen-6-yl regioisomer **17**, which could correspond to the 7-substituted benzo[*b*]thiophen-2-yl[13] or 5-substituted naphthalen-2-yl derivative, also maintained virtually the same potency as **14**. The 3-methyl substituent in these molecules might serve to block potential metabolism in vivo.

Encouraged by these results, we explored modification of the aryl moiety from benzo[*b*]thiophene to a benzofuran bioisostere. Table 4 shows the results of benzofuran ring replacement that can be compared to compounds **12**–**14** and **4**. The compounds **18**–**20**

Table 4. Replacement and regiochemical effects of the benzofuranyl moiety in the (2*S*)-1-(2-methyl-1*H*-indol-4-yloxy)-3-((2*S*,4*R*)-4-aryl-2-methylpiperidinyl)propan-2-ols



Compound	Connectivity at benzofuran	5-HT$_{1A}$ K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT$_{1A}$ GTPγS E_{max} (%)[c]
18	4-	1.23 ± 0.25	7.18 ± 1.17	8
19	5-	1.39 ± 0.30	1.69 ± 0.85	9
20	6-	1.05 ± 0.20	3.77 ± 0.12	6

[a] Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$).[9]
[b] Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[10]
[c] Stimulation by a 1 μM compound concentration expressed as a % of the maximal [^{35}S]GTPγS binding induced by 5-HT.[11]
Values represent the mean ± SEM where $n \geqslant 3$ or ±1/2 the range when $n = 2$.

exhibited excellent 5-HT$_{1A}$ antagonism and very good reuptake inhibition, even though the latter appears somewhat less potent than the benzo[*b*]thiophene or naphthalene counterpart. Once again 5-regioisomer **19** showed the most potent and balanced dual activities.

In conclusion, we have discovered potent and well-balanced dual acting (2*S*)-1-(2-methyl-1*H*-indol-4-yloxy)-3-((2*S*,4*R*)-2-methyl-4-arylpiperidinyl)propan-2-ols at both the 5HT$_{1A}$ receptor and 5-HT reuptake sites. The aryl group well accommodates regiochemistry of both the connectivity to the piperidine ring and aryl substituents. The comprehensive in vivo studies of these compounds will be reported elsewhere.

Acknowledgements

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8. The synthesis of the compounds **1**, **3**, and **5** has already been reported.[6,7] Compounds **2**, **4**, and **6** were prepared from 3-bromobenzo[*b*]thiophene or appropriately substituted 2-bromonaphthalenes by the same protocol after the metal–halogen exchange.
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13. We earlier reported[7b] that the 7-fluorobenzo[*b*]thiophen-2-yl derivative was a potent dual acting compound (K_i for 5-HT$_{1A}$, 1.34 nM; for 5-HT reuptake, 1.29 nM; E_{max} 4.1% in GTPγS functional assay).