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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 1

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Abstract—A series of 1-aryloxy-3-piperidinylpropan-2-ols possessing potent dual 5-HT_{1A} receptor antagonism and serotonin reuptake inhibition was discovered. 1-(1*H*-Indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols exhibited selective and high affinity at the 5-HT_{1A} receptor and serotonin reuptake inhibition at nanomolar concentrations for dual activities.

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) have become a standard treatment in recent years because of their safety profile and fewer side effects than the older tricyclic antidepressants. A major drawback of the now widely prescribed SSRIs is their slow onset of antidepressant activity. One hypothesis for this latency is that the initial SSRI-induced increase in extracellular 5-HT activates somatodendritic 5-HT_{1A} autoreceptors, thus, inhibiting the firing rate of the 5-HT neurons and limiting the rise in extracellular 5-HT.[1–3] With chronic SSRI treatment it is thought that the autoreceptors desensitize, allowing the serotonergic neurons to resume their normal firing rate and enabling extracellular levels of 5-HT to rise to levels sufficient to achieve antidepressant effects. Co-administration of a 5-HT_{1A} receptor antagonist and an SSRI has been shown to accelerate antidepressant effects by several groups.[4–7] A 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 emerged.[8,9]

In the course of our efforts to develop more efficacious antidepressants with a faster onset of action, we discovered a series of 1-aryloxy-3-piperidinylpropan-2-ols possessing dual 5-HT_{1A} receptor antagonism and serotonin reuptake inhibition (Fig. 1). We identified fused bicyclic aryl-substituted piperidines as an essential pharmacophore for 5-HT reuptake inhibition. Incorporation of an aryloxy group with a propanol chain linker which exhibited affinity at the 5-HT_{1A} receptor induced a combined 5-HT1A/SSRI activity in one single molecule. We report here the synthesis and initial structure–activity relationship (SAR) study of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols that exhibited selective and potent dual activities of 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibition.

Scheme 1 shows the synthesis of the target compounds. A substituted benzo[*b*]thiophene **1** in THF was deprotonated with *n*-butyllithium to add to *N*-Boc-protected

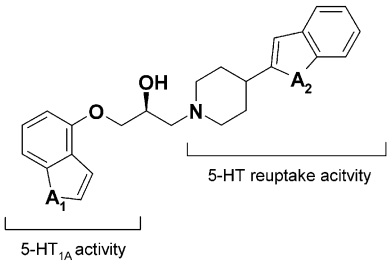

Figure 1. General structure of 1-aryloxy-3-piperidinylpropan-2-ols, new 5-HT1A/SSRIs.

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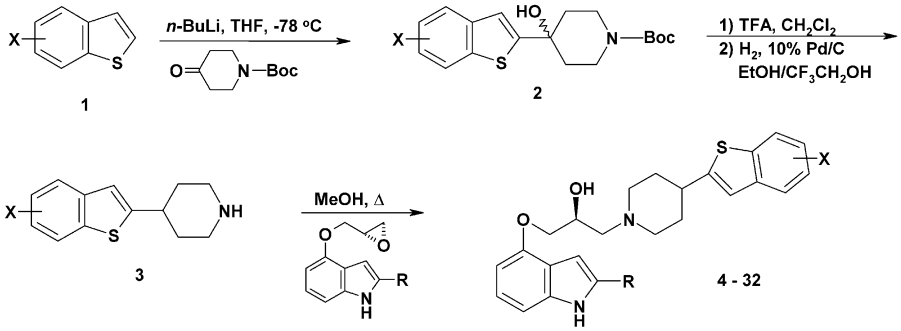


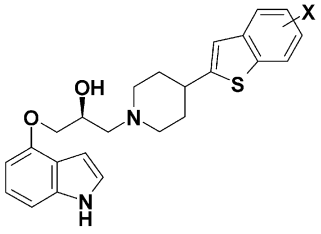
Scheme 1. Synthesis of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols.

4-piperidone. Dehydration of **2** with trifluoroacetic acid in CH_2Cl_2 followed by hydrogenation of the resultant olefin in $EtOH/CF_3CH_2OH$ afforded the 4-benzo[*b*]-thiophenylpiperidine **3**. Coupling of **3** with 4-oxiranylmethoxy-1*H*-indole in MeOH at reflux then provided 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ol derivatives **4**–**32**.

Compounds were evaluated in vitro to determine their affinity at the 5-HT_{1A} receptor and 5-HT transporter sites as well as their functional activity as an agonist or antagonist, according to the previously described methods.[10–12] Biological activities of the compounds explored are shown in Tables 1–3. The compound **4** (R, X = H) exhibited excellent dual activities in low nanomolar concentrations ($K_i = 3.70$ nM at the 5-HT_{1A} receptor and 16.75 nM at the 5-HT reuptake site). Table 1 shows the effect of electron donating group (EDG) on the binding affinity and in vitro functional activity of the 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols. Regiochemistry and the size of the EDG-substituents affected both the 5-HT_{1A} receptor affinity and reuptake inhibition, but more profoundly the latter, as compared to the unsubstituted **4**. Substitution at the 4-position of benzo[*b*]thiophene ring was most preferred (**5** and **14**). A bigger substituent such as isopropoxy (**9** and **10**) or polar hydroxy group (**11** and **12**) reduced the biological activity particularly at the reuptake site. Disubstitution (**16** and **17**) was also detrimental to the dual activities, compared to the unsubstituted analogue **4**.

Table 2 shows the effect of electron withdrawing group (EWG) on the binding affinity and in vitro functional activity of the series. Overall, the EWG-substituents provided potent and more balanced dual activities than the EDG substituents except the compounds **22** and **24**.

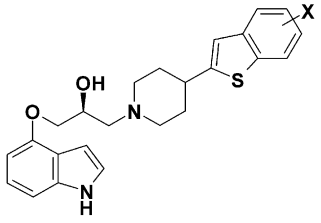
Table 1. Effect of EDG-substituted 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols



Compd	X	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT_{1A} GTPγS E_{max} (%)[c]
4	H	3.70±0.61	16.75±2.13	12.26
5	4-OMe	1.89±0.73	12.63±0.50	7.47
6	5-OMe	1.44±0.27	—	ND
7	6-OMe	3.13±1.48	68.67±15.43	4.92
8	7-OMe	6.13±1.94	94.32±16.21	9.32
9	4-O*i*Pr	7.45±2.15	—	ND
10	6-O*i*Pr	19.85±1.35	—	ND
11	6-OH	3.09±0.85	—	ND
12	7-OH	7.12±1.36	37.16±4.46	12.52
13	3-Me	6.28±2.44	24.05±1.08	ND
14	4-Me	4.70±0.64	3.69±0.99	16.99
15	6-Me	12.66±3.89	50.49±8.72	13.85
16	4,6-diMe	—	—	ND
17	6-OMe-3-Me	6.07±1.80	—	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] —denotes <50% inhibition at 100 nM, no K_i was generated.
[c]Maximal response of the compound as a result of 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding.[12] ND denotes 'not determined' due to the weak binding affinity at either one or both sites.

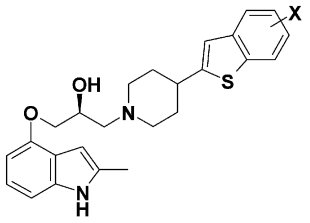
Table 2. Effect of EWG-substituted 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols



Compd	X	5-HT1A K_i (nM)[a]	Paroxetine K_i (nM)[b]	GTPγS E_{max} (%)[c]
4	H	3.70±0.61	16.75±2.13	12.26
18	4-F	6.79±0.27	15.89±0.20	11.17
19	5-F	29.40±7.90	11.81±7.16	13.23
20	6-F	9.31±1.29	1.99±0.14	11.65
21	4-Cl	9.12±0.20	15.63±4.88	ND
22	5-Cl	7.21±0.85	105.14±78.09	10.97
23	6-Cl	7.64±1.54	13.96±0.00	ND
24	5-F-3-Me	5.17±0.42	—	ND

[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] —denotes <50% inhibition at 100 nM, no K_i was generated.
[c]Maximal response of the compound as a result of 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding.[12] ND denotes 'not determined' due to the weak binding affinity at either one or both sites.

Table 3. Effect of 2-methylindole



Compd	X	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT_{1A} GTPγS E_{max} (%)[c]
25	4-OMe	4.83±0.80	51.16±12.93	9.05
26	4-Me	10.40±2.81	17.35±1.26	12.09
27	6-Me	22.60±2.30	—	ND
28	4,6-di-Me	27.83±7.05	52.13±4.76	13.38
29	4-F	14.15±2.55	34.17±4.71	11.62
30	5-F	7.50±1.14	5.27±0.25	12.06
31	6-F	15.35±1.85	11.27±0.31	12.61
32	5-Cl	—	60.63±7.58	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] —denotes <50% inhibition at 100 nM, no K_i was generated. [c]Maximal response of the compound as a result of 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding.[12] ND denotes 'not determined' due to the weak binding affinity at either one or both sites.

Regiochemistry or the size of the EWG-substituents did not affect the binding affinity and in vitro functional activity as profoundly as the EDG-substituents did, with the exception of substituents at the 5-position of benzo[*b*]thiophene being less favored especially at the 5-HT reuptake site (**22** and **24**). Anomaly with another 5-substituted benzo[*b*]thiophene compound **19** with fluorine in this case was that it was 3- to 8-fold less potent at the 5-HT_{1A} receptor site than other EWG-substituted compounds, though still showing respectable dual activities. Inactive reuptake inhibition of the compound **24** could also be due to the disubstitution as seen in the EDG-substituted cases (**8** and **9**).

Metabolic liability is an important consideration for the SAR study in the drug discovery efforts. We considered potential metabolic sites in our scaffold and how blocking such a site would affect the binding affinity and in vitro functional activity in order to avoid metabolic liabilities often encountered later in the development. Table 3 shows the effect of methyl substituent on the indole ring, which was incorporated to block a potential metabolic site of the indole at 2-position. Overall this substitution was detrimental to both the 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibition. Two exceptions were observed: 4,6-dimethyl derivative that was inactive without the 2-methyl group now showed modest activity (**16** vs **28**); and incorporation of methyl substituent at the 2-postion of indole in the 5-fluorobenzo[*b*]thiophene derivative improved and exhibited excellent equipotent dual activities, as compared to the desmethyl analogue (**30** vs **19**).

These compounds were also studied for their functional activity at the 5-HT_{1A} receptor in an in vitro GTPγS binding assay to determine their agonist/antagonist properties. By this sensitive measure, the compounds of this class appeared as very weak partial agonists (shown in the tables as the E_{max} values expressed as a percentage of the maximal activity of 5-HT). It was found that compounds having 15% or less maximal stimulation of the 5-HT_{1A} receptor measured in the in vitro GTPγS binding assay behaved only as functional antagonists in vivo, with no measurable agonist character (unpublished observations). Moreover, these compounds were tested against other cloned human 5-HT receptor subtypes in the radioligand binding assays and found to be inactive or very weak at other 5-HT receptors.

In conclusion, we have identified potent and selective dual acting 5-HT1A/SSRIs in a single chemical entity. Further SAR exploration to improve the overall biological activity profiles will be reported in due course.

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