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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 5

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Dedicated to the memory of David W. Robertson, mentor, colleague and friend.

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 affinities at the 5-HT$_{1A}$ receptor and serotonin reuptake site in vitro. In vivo evaluation of this series of compounds demonstrated elevated extracellular serotonin levels from the basal and quick recovery of neuron firing that was presumably suppressed by the initial acute activation of 5-HT$_{1A}$ somatodendritic autoreceptors.
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Selective serotonin (5-HT) reuptake inhibitors (SSRIs) have become a standard treatment over the past decade because of their safety profile and fewer side effects than the older tricyclic antidepressants. In spite of their wide acceptance and over a decade of treatment of depression, however, the need for the new generation of more efficacious antidepressant therapies with faster onset of action and a more favorable side-effect profile is now widely recognized because of their drawbacks and limited benefits.[1] Major drawbacks of SSRIs in the pharmacological treatment of depression are a latency in the onset of clinically meaningful effects for at least 3–4 weeks and the lack of consistent response in 30–40% of refractory patients. Furthermore, adverse events such as sexual dysfunction, gastrointestinal intolerance, and activating effects (nervousness, anxiety, and insomnia) are associated with all available SSRIs and remain as considerable barriers to effective therapy. Finding the next generation of antidepressants with a new mechanism of action or a combination therapy with an SSRI has spurred a flurry of research efforts in order to accelerate the onset of effective antidepressant activity, while offsetting the undesirable side effects.[2]

One hypothesis for the delayed onset of therapeutic benefits by SSRIs is that the initial SSRI-induced increase in extracellular 5-HT activates somatodendritic 5-HT$_{1A}$ autoreceptors, which in turn inhibit the firing rate of the 5-HT neurons and limit the rise in extracellular 5-HT.[3,4] 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,[5–8] although the unsuccessful results are also reported.[9,10] 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.[11]

Keywords: 5-HT$_{1A}$/SSRI; Serotonin; 5- HT$_{1A}$ receptor antagonist; Selective serotonin reuptake inhibitor; Antidepressants; 1-Aryloxy-3-piperidinylpropan-2-ols.
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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-(4-arylpiperidin-1-yl)propan-2-ols possessing dual 5-HT_{1A} receptor antagonism and serotonin reuptake inhibition.[12] We identified fused bicyclic aryl-substituted piperidines as an essential pharmacophore for 5-HT reuptake inhibition. Incorporation of an aryloxy group with a propanolamine chain linker that exhibited affinity at the 5-HT_{1A} receptor induced a combined 5-HT1A/SSRI activity in one single molecule (Fig. 1).

Subsequently, we reported in a series of papers[13] the synthesis and development of structure–activity relationship (SAR) of this series of compounds that exhibited selective and potent dual activities of 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibition in vitro. In this report, we present in vivo study results of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidin-1-yl)propan-2-ols (Fig. 2) and discuss findings of how the in vitro profiles of selected compounds from this series translated into the in vivo profiles.

Inhibition of ex vivo binding: Having identified potent dual-acting 5-HT1A/SSRI compounds in vitro as previously reported,[12,13] we investigated the ability of compounds to be absorbed after oral administration, to penetrate into the brain and to occupy these binding sites and receptors using the ex vivo binding technique. For occupancy of 5-HT_{1A} receptors, ex vivo binding of [^{3}H]-8-OH-DPAT in frontal cortex homogenates was examined. Inhibition of [^{3}H]-paroxetine (or [^{3}H]-citalopram) ex vivo binding was used to determine occupancy of the 5-HT reuptake site or transporter in frontal cortex homogenates. Briefly, Sprague–Dawley male rats

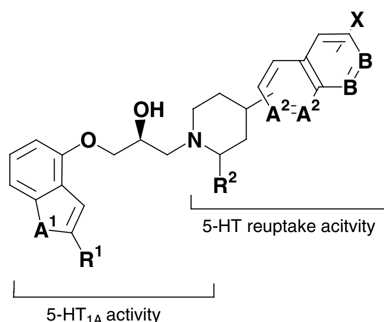


Figure 1. General structure of 1-aryloxy-3-(4-arylpiperidin-1-yl)propan-2-ols, new 5-HT1A/SSRIs.

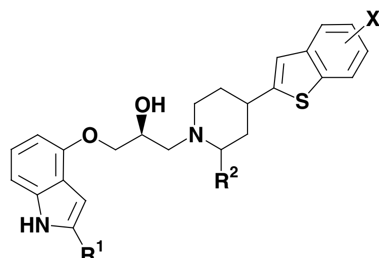


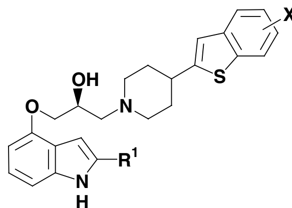
Figure 2. Variation of substituents on 1-(1*H*-indol-4-yloxy)-**3**-(**4**-benzo[*b*]thiophen-2-yl)propan-2-ols for SAR development.

(50–80 g) in groups of five were administered vehicle or a test compound by oral administration (30 mg/kg po) and the rats were killed 1 h after drug administration. The brains were rapidly removed, the frontal cortex brain region was dissected and then frozen on dry ice. The tissues were homogenized in 10 volumes of buffer, frozen overnight, preincubated, and then ex vivo binding of [^{3}H]-paroxetine (0.1 nM) and [^{3}H]-8-OH-DPAT (1 nM) in the whole homogenate was determined using standard binding techniques.

The ex vivo binding occupancy did not always correspond to the in vitro binding affinity K_i values, especially at the 5-HT reuptake site (Tables 1 and 2). Compounds **1** and **2** did not occupy the reuptake site to inhibit the ligand binding, though the 6-fluorobenzo[*b*]thiophene derivative **4** effectively inhibited the ex vivo binding of the tritiated ligand (Table 1). Compounds **1**, **2**, **5**, and **6** did not inhibit [^{3}H]-paroxetine (or [^{3}H]-citalopram) ex vivo binding at the reuptake site anymore than 35% even though they exhibited potent in vitro binding affinity with K_i values <20 nM. It appears that a methyl substituent and its stereochemistry on the piperidine ring significantly affect the ex vivo occupancy. The stereochemical preference observed in the in vitro binding affinities[13] in the order of (2*S*,4*R*) isomer-3 > (2*R*,4*S*) isomer-4 > (2*R*,4*R*) isomer-1 > (2*S*,4*S*) isomer-2 was translated into the ex vivo binding affinities as exemplified by the diastereomers **5**–**8** (Table 2). The (2*S*,4*R*) isomer-3 with both electron-donating and electron-withdrawing substituents on the benzo[*b*]thiophene ring effectively occupied both the 5-HT_{1A} receptor and reuptake sites (**7**, **9**–**16**). There were a few instances where the (2*R*,4*R*) isomer-1 (example not shown) or the (2*R*,4*S*) isomer-4 (e.g., the compound **8**) also showed good occupancy, reflecting their potent in vitro efficacy. Overall good occupancy at the 5-HT reuptake site appears to require low to sub-nanomolar binding affinities, while occupancy at the 5-HT_{1A} receptor was adequately demonstrated with binding affinity K_i < 20 nM.

Microdialysis: The compounds **4** and **7**–**16** that occupied more than 50% (i.e., <50% of control in inhibition in Table 2) of the 5-HT_{1A} receptors and reuptake sites in the ex vivo binding assays were then examined for their ability to increase 5-HT levels in rat hypothalamus. Microdialysis was performed as previously described.[14,15] In brief, rats (male, Harlan Sprague–Dawley, 260–300 g) were implanted with a microdialysis probe in the hypothalamus under anesthesia. After a 48-h washout and recovery period, artificial cerebrospinal fluid was perfused through the probe, and microdialysates were collected and analyzed using HPLC with electrochemical detection. 5-HT and 5-HIAA concentrations were calculated by comparing peak heights using 50 pmol/ml standards. Basal values were converted to percent of basal, and data are presented as percent of basal. For comparison purposes, a bolus dose administration of fluoxetine (10 mg/kg ip), followed by a dose of the selective 5-HT_{1A} antagonist WAY100635 (1 mg/kg sc), was also carried out in this experiment, and the data are shown in Table 3. Our goal was to achieve extracellular 5-HT level

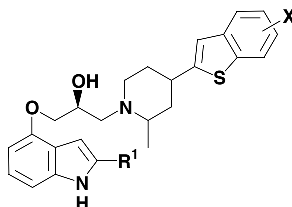
Table 1. In vitro affinity and ex vivo occupancy of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols



Compound	X	R[1]	5-HT_{1A} K_i (nM)[a]	5-HT reuptake K_i (nM)[b]	Inhibition of ex vivo binding % of control (100%)	
					5-HT_{1A}[c]	Reuptake[d]
1	H	H	3.70 ± 0.61	16.75 ± 2.13	6	80
2	4-OMe	H	1.89 ± 0.73	12.63 ± 0.50	4	100
3	4-OMe	Me	4.83 ± 0.80	51.16 ± 12.93	nd	nd
4	6-F	H	9.31 ± 1.29	1.99 ± 0.14	9	13

nd, denotes not determined.
[a] Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geq 2$).[12]
[b] Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geq 2$).[12] Values represent means ± SEM where $n \geq 3$ or ±1/2 the range when $n = 2$.
[c] Inhibition of ex vivo binding of [^{3}H]-8-OH-DPAT (1 nM) in the frontal cortex homogenates at 30 mg/kg po.
[d] Inhibition of ex vivo binding of [^{3}H]-paroxetine (0.1 nM) in the frontal cortex homogenates at 30 mg/kg po.

Table 2. In vitro affinity and ex vivo occupancy of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-yl-2-methylpiperidinyl)propan-2-ols



Compound	X	R[1]	Piperidine ring stereoisomer	5-HT_{1A} K_i (nM)[a]	5-HT reuptake K_i (nM)[b]	Inhibition of ex vivo binding % of control (100%)	
						5-HT_{1A}[c]	Reuptake[d]
5	4-OMe	H	1 (2*R*,4*R*)	2.76 ± 0.02	14.71 ± 1.43	28	70
6	4-OMe	H	2 (2*S*,4*S*)	14.45 ± 1.55	13.59 ± 1.12	40	88
7	4-OMe	H	3 (2*S*,4*R*)	3.64 ± 0.13	0.27 ± 0.09	13	11
8	4-OMe	H	4 (2*R*,4*S*)	8.47 ± 2.03	1.15 ± 0.21	33	8
9	H	H	3 (2*S*,4*R*)	3.09 ± 0.18	0.51 ± 0.06	1	−2
10	6-F	H	3 (2*S*,4*R*)	5.52 ± 1.04	0.31 ± 0.06	23	8
11	5-Cl	H	3 (2*S*,4*R*)	8.34 ± 1.36	0.58 ± 0.23	47	39
12	4-Me	H	3 (2*S*,4*R*)	6.85 ± 1.03	0.44 ± 0.04	20	9
13	6-OMe	H	3 (2*S*,4*R*)	14.49 ± 2.76	1.10 ± 0.29	14	29
14	H	Me	3 (2*S*,4*R*)	7.11 ± 0.07	0.53 ± 0.00	5	17
15	5-F	Me	3 (2*S*,4*R*)	5.65 ± 0.93	0.24 ± 0.03	6	30
16	4-OMe	Me	3 (2*S*,4*R*)	14.35 ± 0.05	0.86 ± 0.12	−3	26

[a] Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geq 2$).[12]
[b] Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geq 2$).[12] Values represent means ± SEM where $n \geq 3$ or ±1/2 the range when $n = 2$.
[c] Inhibition of ex vivo binding of [^{3}H]-8-OH-DPAT (1 nM) in the frontal cortex homogenates at 30 mg/kg po.
[d] Inhibition of ex vivo binding of [^{3}H]-paroxetine (0.1 nM) in the frontal cortex homogenates at 30 mg/kg po.

from basal by the dual 5-HT1A/SSRI in a single chemical entity greater than that by the combination of fluoxetine and WAY100635. The data show that compounds **7**, **8**, **10**, **15**, and **16** demonstrated greater efficacies at the doses administered via an oral route than fluoxetine alone or fluoxetine–WAY100635 combination regimen. The 2-methyl group on the piperidine ring appears to have a profound effect on the 5-HT level increase. The desmethyl compound **4** effected a modest increase in 5-HT levels, whereas 2-methyl compound **10** showed robust 5-HT elevation (130% vs 479% at 30 mg po). The substituent on the benzo[*b*]thiophene ring also affected the 5-HT elevation. 4-Methoxy group exhibited the most favorable effects among the electron-donating groups (**7**, **8**, and **16** vs **12** and **13**) and fluoro substituent is favored over chloro (**10**

Table 3. Results of microdialysis, neurochemistry, and neuroendocrinology studies

Compound	Microdialysis % of basal[a] at mg/kg (route)	5-HT_{1A}		5-HT reuptake	
		In vitro K_i (nM)[d]	In vivo (corticosterone)[b] ED_{50} mg/kg (route)	In vitro K_i (nM)[d]	In vivo (PCA)[c] ED_{50} mg/kg (route)
4	130 at 30 (po)	9.31 ± 1.29	nd[e]	1.99 ± 0.14	nd
7	368 at 30 (po)	3.64 ± 0.13	21.1 (po)	0.27 ± 0.09	3.71 (po)
8	330 at 20 (po)	8.47 ± 2.03	>30 (po)	1.15 ± 0.21	>10 (po)
9	264 at 20 (sc)	3.09 ± 0.18	2.83 (sc)	0.51 ± 0.06	0.28 (sc)
10	479 at 30 (po)	5.52 ± 1.04	>30 (po) (5.08 (sc))	0.31 ± 0.06	0.69 (po)
11	287 at 20 (po)	8.34 ± 1.36	~26 (po)	0.58 ± 0.23	3.65 (po)
12	210 at 30 (po)	6.85 ± 1.03	>30 (po)	0.44 ± 0.04	1.65 (po)
13	140 at 30 (po)	14.49 ± 2.76	nd	1.10 ± 0.29	1.07 (sc)
14	119 at 10 (po)	7.11 ± 0.07	nd	0.53 ± 0.00	nd
15	315 at 30 (po)	5.65 ± 0.93	nd	0.24 ± 0.03	nd
16	713 at 10 (po)	14.35 ± 0.05	3.2 (po)	0.86 ± 0.12	3.79 (po)
Fluoxetine	160 at 10 (ip)				
Fluoxetine+WAY100635	292 at 10 (ip) FLX+1 (sc) WAY				

[a] Single point increase <4 h after dose ($n = 3$–7, except for compounds **8** and **10** where $n = 2$).
[b] Effective dose producing 50% blockage of 1 h after 0.3 mg/kg sc 8-OH-DPAT-induced increase in rat serum corticosterone concentrations ($n = 3$–5).
[c] Effective dose producing 50% blockade of rat brain 5-HT 2 h after 5 mg/kg ip *p*-chloroamphetamine (PCA) ($n = 3$–5).
[d] see the footnotes a and b in Table 2.
[e] nd = not determined.

and **15** vs **11**). The compound **16** was the most efficacious for elevating the 5-HT levels with over 700% increase from the basal at 10 mg/kg po. Differences in the in vivo efficacy could be attributed to the metabolic stability or exposure of these compounds. Combined effects of substituents on the piperidine, indole, and benzo[*b*]thiophene rings as well as their stereochemical, regiochemical, and electronic properties may be playing a role in the pharmacokinetic profile of this series of compounds.

In vivo pharmacology in rats: The compounds were also examined for their abilities to block the 8-OH-DPAT-induced increase in rat serum corticosterone and the PCA-induced depletion of rat brain 5-HT in order to confirm their mechanism of action and determine their in vivo potency as dual-acting 5-HT_{1A} receptor antagonist and 5-HT reuptake inhibitor, respectively. According to the previously described methods,[15] effects of a compound as a 5-HT_{1A} receptor antagonist were determined by blockade of 8-OH-DPAT-induced increase in rat serum corticosterone concentrations and the potency of the compound in blockade of 5-HT_{1A} receptors was determined by the dose-dependent antagonism of the increase in rat serum corticosterone elicited by 8-OH-DPAT. The effects and potency of a compound as a 5-HT reuptake inhibitor were determined by blockade of the *p*-chloroamphetamine (PCA)-induced depletion of rat brain 5-HT concentrations.[16] The data in Table 3 show that these compounds are indeed acting as 5-HT1A/SSRI in single chemical entity. The compound **16** was the most potent and balanced dual 5-HT_{1A} antagonist (ED_{50} 3.2 mg/kg po) and SSRI (ED_{50} 3.8 mg/kg po) via an oral route. The combined effects appear to be reflected in the high 5-HT level increase from the basal in the microdialysis assay.

Electrophysiology: Selective serotonin reuptake inhibitors (SSRIs) enhance serotonergic neurotransmission by blocking the reuptake of 5-HT from the synapse.[17] Upon acute administration, SSRIs block the 5-HT reuptake site leading to increased synaptic levels of 5-HT in terminal regions.[18] Simultaneously, however, the amount of 5-HT released in the vicinity of the 5-HT cell body is increased.[4] The 5-HT released near the cell bodies and dendrites acts on 5-HT_{1A} somatodendritic autoreceptors to inhibit the activity of the neurons.[19] This increased activity at the cell body autoreceptor leads to a decreased firing rate of the serotonergic neurons, thus limiting the amount of 5-HT released into the terminal synapse. This negative feedback on 5-HT cells, and subsequent limitation of 5-HT terminal output, has been hypothesized to play a role in the delayed therapeutic onset of SSRIs.[20] Blocking the activation of 5-HT_{1A} autoreceptors then should maintain the normal neuronal activity. We examined the activity of serotonergic neurons in the dorsal raphe nucleus (DRN) of the anesthetized rat during a 3-day sub-chronic administration of compounds that showed robust 5-HT elevation according to the previously described method.[21]

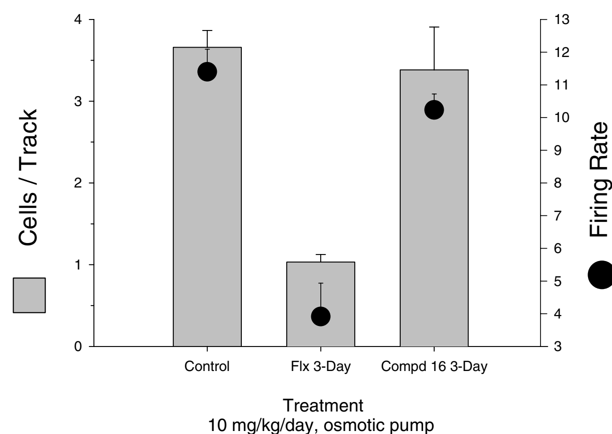


Figure 3. Effect of three-day sub-chronic treatment with fluoxetine versus the compound **16** on the serotonergic neurons in the dorsal raphe nucleus (DRN).

Figure 3 shows the results obtained from the 3-day administration of the compound **16** in comparison to fluoxetine. Fluoxetine reduced both the serotonergic neuron population and firing rate in the 3-day treatment, while the compound **16** had no effect on the 5-HT neuronal activity. This seems to confirm that blockade of 5-HT_{1A} receptors maintains the normal neuronal activity and elevates synaptic levels of 5-HT in terminal regions as seen in Table 3. These results suggest that a dual 5-HT1A/SSRI agent could effect fast onset of therapeutic effects in the clinical setting as compared to the treatment by fluoxetine or other SSRIs alone.

In conclusion, we have discovered 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols as selective and potent dual-acting 5-HT1A/SSRIs in the course of our efforts to develop more efficacious and fast-acting antidepressants. We identified compounds with balanced 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibition at low nanomolar concentrations in vitro that also demonstrated excellent in vivo efficacy via an oral administration. Among the compounds reported here the compound **16** also demonstrated that the combined 5-HT1A/SSRI in a single molecule had no negative feedback effect on the 5-HT neuronal activity that was elicited by an SSRI alone via activation of somatodendritic 5-HT_{1A} autoreceptors. These results indicate that the dual-acting 5-HT1A/SSRI in a single molecule may provide more efficacious therapeutic benefits with faster onset of action for the treatment of depression than the widely used current SSRI regimen.

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