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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 3

Kumiko Takeuchi,* Todd J. Kohn, Nicholas A. Honigschmidt, Vincent P. Rocco, Patrick G. Spinazze, Steven T. Atkinson, Larry W. Hertel, David L. Nelson, D. Bradley Wainscott, Laura J. Ahmad, Janice Shaw, Penny G. Threlkeld and David T. Wong

Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA

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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. Modification of potential metabolic sites of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols further improved the in vitro binding affinities and functional antagonism.

The selective 5-HT reuptake inhibitors (SSRIs) are effective antidepressants with fewer side effects than the older tricyclics. 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.[1] 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. The need for the next generation of antidepressants to overcome these drawbacks associated with SSRIs has spurred flurries of research activities.[2] An approach that has drawn attention has been an effort to develop therapeutic agents with a faster onset of action that might also mitigate undesirable side effects. One of the hypotheses for the delayed onset of therapeutic benefits by SSRIs is that acute activation of 5-HT_{1A} somatodendritic autoreceptors inhibits the firing of serotonergic neurons until desensitization occurs.[3] Coadministration of a 5-HT_{1A} antagonist and an SSRI has been shown to accelerate antidepressant effects,[4,5] although the unsuccessful results are also reported.[6,7]

We and others have taken an approach to developing a therapeutic agent that exhibits dual activity blocking both the 5-HT_{1A} receptor and 5-HT reuptake site in a single chemical entity (5-HT1A/SSRI).[8–11]

Previously we reported 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols possessing dual activity as a 5-HT_{1A} receptor antagonist and a 5-HT reuptake inhibitor (Fig. 1, A = NH).[8,9] Even though we identified potent dual-acting compounds having low nanomolar affinities in this series, we found that the in vitro activity did not always translate into ex vivo or in vivo efficacy (unpublished results). Earlier we briefly considered potential metabolic sites in our scaffold and how blocking such sites would affect the binding affinity and in vitro functional activity in order to avoid metabolic liabilities often encountered later in the development.[8] In this study we report further optimization of this series of compounds, focusing on the indole ring modification while taking advantage of the structure–activity relationship already established (Fig. 1).

Target molecules were prepared as previously reported.[9] The requisite functionalized indolyl or benzofuranyl glycidyl ethers were prepared by functionalization of 4-hydroxy-indole or-benzofuran via conventional methods, followed by 4-alkoxide formation and its addition to (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (Scheme 1).

*Corresponding author. Tel.: +1-317-276-6771; fax: +1-317-433-0715; e-mail: ktak@lilly.com

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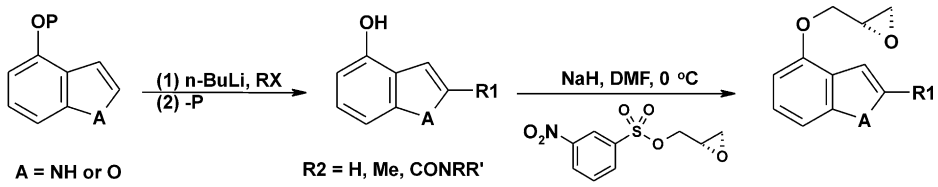


Scheme 1. Preparation of aryl (2S)-glycidyl ether.

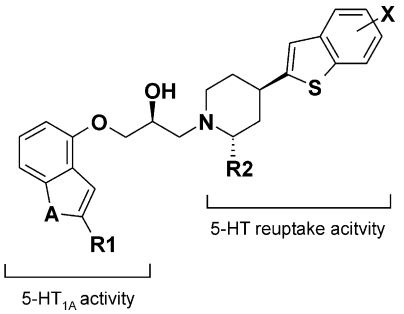


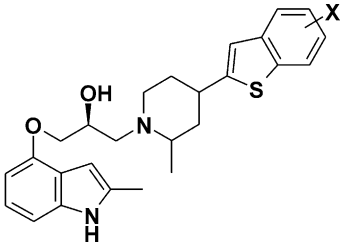
Figure 1. SAR study on 1-heteroayloxy-3-(4-benzo[*b*]thiophen-2-yl-piperidinyl)propan-2-ols.

Tables 1–3 show the results of the SAR findings. We reported earlier that the methyl substituent at the 2-position of indole was detrimental to the binding affinities at both the 5-HT_{1A} receptor and 5-HT reuptake site (Fig. 1: A = NH; R_1 = Me; R_2 = H).[8] On the other hand, the α-methyl substituent on the piperidine ring was beneficial with certain stereochemical preference at the 2- and 4-positions of the piperidine ring (Fig. 1: A = NH; R_1 = H; R_2 = Me).[9] In contrast, two different phenomena were observed in the present study. First of all, we found that the methyl group on the indole neither negatively impacted the binding affinity, nor did it change the stereochemical preference for the piperidine substituents. The stereochemical preference was carried over to this series with the (2*S*,4*R*)-isomer being the most preferred, as seen before[9] (Table 1). Secondly, and more importantly, the combination of 2-methylindole and 2-methylpiperidine not only canceled out the detrimental effects previously seen, but also improved overall binding affinities and in vitro functional activity, possibly with a synergistic effect (Table 2). Among them fluorobenzo[*b*]thiophene derivatives (e.g., **7** and **15**) were the most potent and balanced dual agents.

Encouraged by these results, we explored further modifications of the indole ring (Table 3). 2-Indolecarboxamide derivatives showed binding affinities comparable to the 2-methylindole series with the same stereochemical preference (**1**–**4** vs **19**–**22**). The difference between the two series was observed with respect to the in vitro functional agonist effect, albeit modest, where the methyl substituent was preferred. When the indole ring was replaced with benzofuran in the 2-methyl series, the compounds lost considerable activity for the 5-HT reuptake inhibition, while 5-HT_{1A} binding affinity was improved (**1**–**4** vs **23**–**26**).

The effect of 2-substitution on the indole ring was more profound than expected when the piperidine ring was

Table 1. Effects of 2-methylindole on the 2-methylpiperidine series relative to the piperidine ring stereochemistry



Compd	X	Isomer	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT_{1A} GTPγS E_{max} (%)[c]
1	4-OMe	1 (2*R*,4*R*)	20.20±2.70	28.98±3.82	1.80
2	4-OMe	2 (2*S*,4*S*)	—	—	nd
3	4-OMe	3 (2*S*,4*R*)	14.35±0.05	0.86±0.12	4.76
4	4-OMe	4 (2*R*,4*S*)	28.10±1.10	3.30±0.76	2.38
5	7-F	1 (2*R*,4*R*)	2.12±0.22*	34.35	nd
6	7-F	2 (2*S*,4*S*)	19.38±0.57*	47.52	nd
7	7-F	3 (2*S*,4*R*)	1.34±0.06*	1.29±0.41	4.09
8	7-F	4 (2*R*,4*S*)	9.80±0.10*	6.06±0.09	6.35

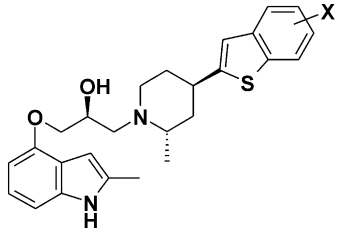
[a]Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$),[12] *determined in our laboratories.
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[13]
[c]Maximal response of the compound as a result of 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding.[14]

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.

further modified. Fine-tuning of piperidine substitution by adding another substituent at 2- or 6-position of the ring produced interesting results (Table 4). The purpose of this di-substitution was 2-fold: (1) to remove the stereogenic center at the 2-position; and (2) to fix the piperidine ring with its stereochemistry.[9] *gem*-Dimethylpiperidine series (**28** and **29**) showed modest but respectable binding affinities with 2-methyl incorporation in the indole ring, in contrast to the desmethylindole (**27**), which was inactive at both 5-HT_{1A} receptor and 5-HT reuptake site.

Two things were noted with the rigidified piperidine stereochemistry at 2,6-position. The *exo*-isomer, where 2- and 4-substituents are in the *trans* orientation, affected favorably 5-HT_{1A} receptor antagonism as before[9] (**32** vs **33**, as seen with **30** vs **31**). Moreover, both methyl and carboxamide substituents at the 2-position of indole improved dual binding affinities in both *exo*- and *endo*-stereoisomers, as compared to the corresponding desmethylindoles (**30** vs **32** or **34**; **31** vs **33**). These results reinforce the notion of a synergistic effect of substituents at the 2-position of indole and piperidine rings.

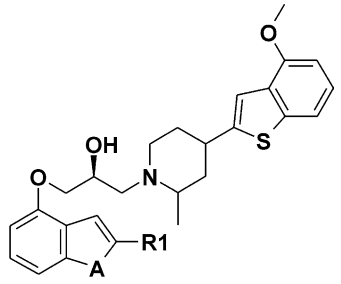
Table 2. Effects of 2-methylindole on the (2*S*,4*R*)-2-methylpiperidine series relative to the substituents on the benzo[*b*]thiophene ring



Compd	X	5-HT$_{1A}$ K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT$_{1A}$ GTPγS E_{max} (%)[c]
9	H	7.11±0.08	0.53±0.00	6.09
3	4-OMe	14.35±0.05	0.86±0.12	4.76
10	6-OMe	13.48±0.82	2.37±0.26	3.21
11	4,6-di-OMe	23.15±6.25	2.79±0.28	7.62
12	4-Me	10.52±0.39	0.62±0.10	6.32
13	6-Me	—	1.28±0.14	nd
14	4,6-di-Me	104.63±60.60	1.99±0.17	nd
15	4-F	0.75±0.21*	0.92±0.23	3.15
16	5-F	5.65±0.93	0.24±0.03	9.05
17	6-F	12.35±1.85	0.39±0.04	7.26
7	7-F	1.34±0.06*	1.29±0.41	4.09
18	5-Cl	15.65±2.35	1.02±0.15	8.42

[a]Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$),[12] *determined in our laboratories.
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[13]
[c]Maximal response of the compound as a result of 5-HT$_{1A}$ receptor-mediated stimulation of [^{35}S]GTPγS binding.[14]
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 3. Modification of the indole ring

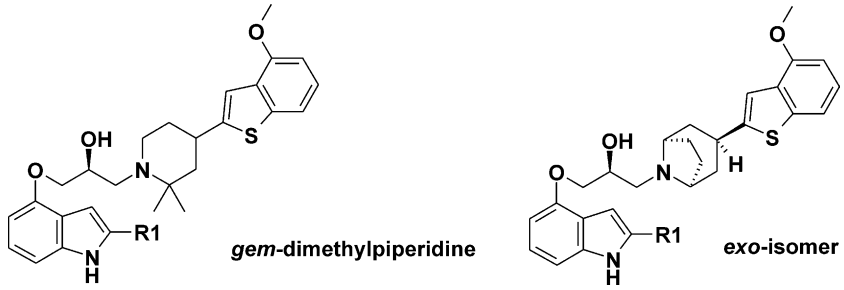


Compd	A	R1	Isomer	5-HT$_{1A}$	Paroxetine	5-HT$_{1A}$ GTPγS
				K_i (nM)[a]	K_i (nM)[b]	E_{max} (%)[c]
19	N	$CONH_2$	1 (2*R*,4*R*)	12.65±2.65	16.25±0.61	7.21
20	N	$CONH_2$	2 (2*S*,4*S*)	—	6.61±1.30	nd
21	N	$CONH_2$	3 (2*S*,4*R*)	6.36±0.46	0.56±0.06	12.75
22	N	$CONH_2$	4 (2*R*,4*S*)	32.00±3.40	1.22±0.10	nd
23	O	Me	1 (2*R*,4*R*)	4.84±0.34*	110.25±15.76	nd
24	O	Me	2 (2*S*,4*S*)	—	76.07±47.57	nd
25	O	Me	3 (2*S*,4*R*)	4.06±0.28*	38.45±28.02	8.76
26	O	Me	4 (2*R*,4*S*)	26.77±0.65*	15.22±4.66	6.49

[a]Binding affinity at 5-HT$_{1A}$ receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$),[12] *determined in our laboratories.
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[13]
[c]Maximal response of the compound as a result of 5-HT$_{1A}$ receptor-mediated stimulation of [^{35}S]GTPγS binding.[14]
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.

In conclusion, we have found that incorporation of substituents in both the indole and piperidine rings at their potential metabolic sites of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols improved the binding affinities at both 5HT$_{1A}$ receptor and 5-HT reuptake sites. These compounds were all antagonists or very weak partial agonists based on the fact that they produced no more than 10–12% stimulation of GTPγS binging relative to serotonin. The in vivo efficacy study of these compounds will be reported elsewhere in due course.

Table 4. Effects of 2-substituted indoles on other piperidine substituents



Compd	R1	Isomer	5-HT_{1A} K_i (nM)[a]	Paroxetine K_i (nM)[b]	5-HT_{1A} GTPγS E_{max} (%)[c]
27	H	*gem*-diMe, mixture	—	—	nd
28	Me	*gem*-diMe, isomer-1	9.42±1.28	118.42±0.00	nd
29	Me	*gem*-diMe, isomer-2	42.76±3.26	20.51	nd
30	H	*exo*	15.70±1.10	1.31±0.49	7.22
31	H	*endo*	—	0.17±0.04	nd
32	Me	*exo*	9.20±0.46	0.69±0.21	2.98
33	Me	*endo*	20.90±1.00	0.45±0.16	7.92
34	$CONH_2$	*exo*	12.36±3.24	0.37±0.00	11.26

[a]Binding affinity at 5-HT_{1A} receptors labeled with [^{3}H]-8-OH-DPAT ($n \geqslant 2$).[12]
[b]Affinity at the 5-HT reuptake site labeled with [^{3}H]-paroxetine ($n \geqslant 2$).[13]
[c]Maximal response of the compound as a result of 5-HT_{1A} receptor-mediated stimulation of [^{35}S]GTPγS binding.[14]
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.

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