Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 307–310

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Studies Toward the Discovery of the Next Generation of Antidepressants. Part 2: Incorporating a 5-HT_{1A} Antagonist Component into a Class of Serotonin Reuptake Inhibitors

Richard E. Mewshaw,* Kristin L. Meagher, Ping Zhou, Dahui Zhou, Xiaojie Shi, Rosemary Scerni, Deborah Smith, Lee E. Schechter and Terrance H. Andree

Global Chemical Sciences and Neuroscience Departments, Wyeth-Ayerst Research Laboratories, PO Box 42528, Philadelphia, PA 19101-2528, USA

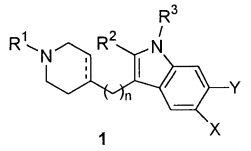
Received 14 September 2001; accepted 31 October 2001

Abstract—The design and synthesis of a novel series of indole derivatives (**9**) having dual 5-HT transporter reuptake and 5-HT_{1A} antagonist activity are described.

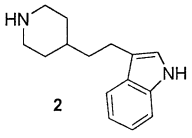
Depression is a chronic illness that affects people of all ages with far-reaching social and economic implications.[1] Although serotonin (5-HT) selective reuptake inhibitors (SSRIs) are currently first-line therapy for depression, a major problem associated with SSRIs is their delayed onset of action.[2] Given antidepressant activity is generally believed to be exerted by increased 5-HT neurotransmission,[3] therapeutic efficacy of SSRIs is thought to be compromised acutely due to their inhibitory effect on 5-HT cell firing, which suppresses the antidepressant effect. However, upon chronic administration of SSRIs a desensitization of the somatodendritic 5-HT_{1A} autoreceptors occurs, allowing serotonergic neurons to resume their normal firing which is manifested as an antidepressant effect after 2–6 weeks.[4]

According to this hypothesis, blockade of the 5-HT_{1A} autoreceptors should result in an advanced therapeutic action of the SSRI, allowing a more rapid onset of efficacy.[5] Interestingly, independent studies by Artigas[5–7] and Blier[8,9] recently reported that pindolol, the mixed 5-HT_{1A}/β-adrenoceptor antagonist, when co-administered with SSRIs accelerates their antidepressant effects. Further support of this hypothesis was later observed when the 5-HT_{1A} antagonist WAY 100635 was found to potentiate the antidepressant effects of several SSRIs.[10,11] Consequently, there has been considerable interest by several groups to identify drug design strategies focusing on incorporating a 5-HT_{1A} antagonist component into a 5-HT reuptake inhibitor to bring about a more immediate and complete antidepressant effect (Fig. 1).[12,13]

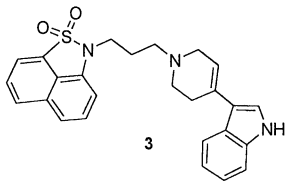
As one of our preliminary examinations of this hypothesis,[14] our group focused on modifying a known class of indoles (**1**) which embrace the known 5-HT uptake inhibitor indalpine (**2**).[15] This series of indoles was reported as being potent 5-HT uptake inhibitors and later derivatized without any significant loss of 5-HT reuptake activity (e.g., **3**[16] and **4**[17]). Due to the inherent robust 5-HT reuptake activity of this class of indoles, they appeared to be an excellent starting point to attempt to incorporate 5-HT_{1A} antagonistic activity within a class of 5-HT reuptake inhibitors. From recent reports in the literature,[17–21] our group believed the 5-HT_{1A} pharmacophore requirements[22] could be met by



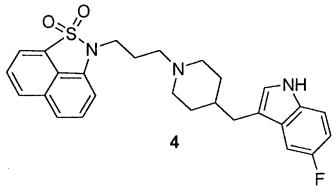
1



2



3



4

*Corresponding author. Fax: +1-484-865-9399; e-mail: mewshar@war.wyeth.com

0960-894X/02/$ - see front matter
PII: S0960-894X(01)00746-6

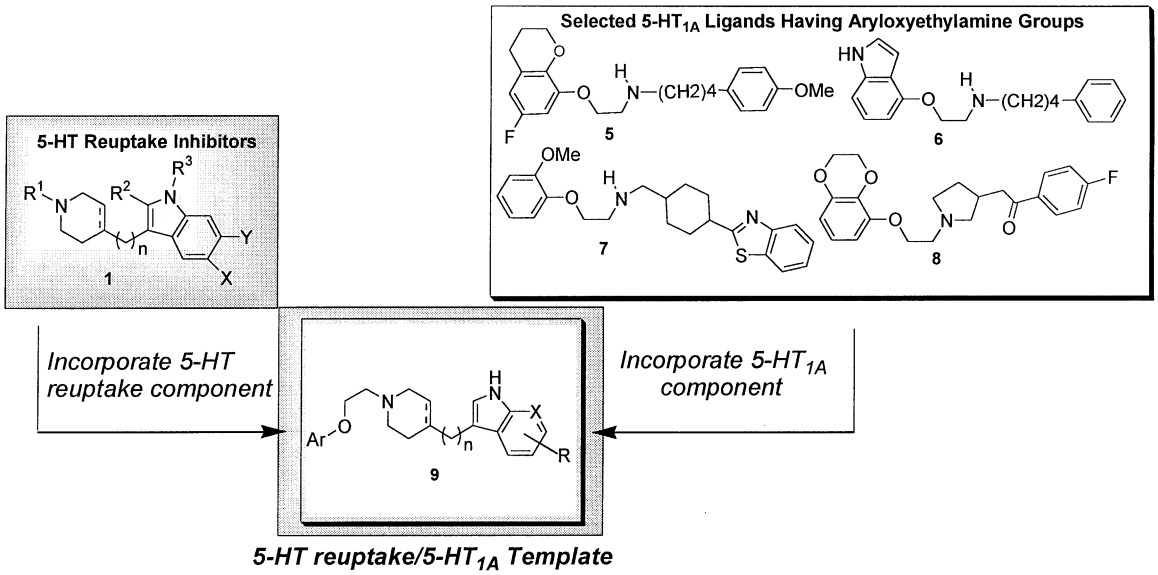
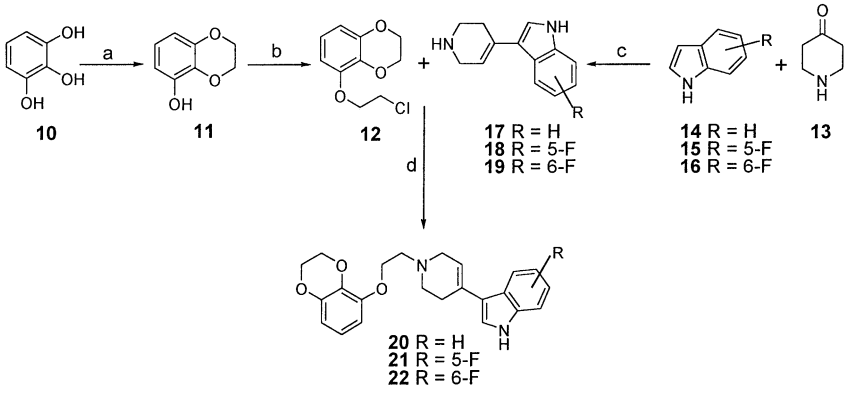


Figure 1. Design strategy: incorporation of the 5-HT_{1A} component within a 5-HT uptake inhibitor.



Scheme 1. Reagents and conditions: (a) $BrCH_2CH_2Br$/MEK; (b) $ClCH_2CH_2OH/PPh_3$/DIAD/PPh_3; (c) 2 N KOH/MeOH; (d) DMSO/Et_3N/80 °C.

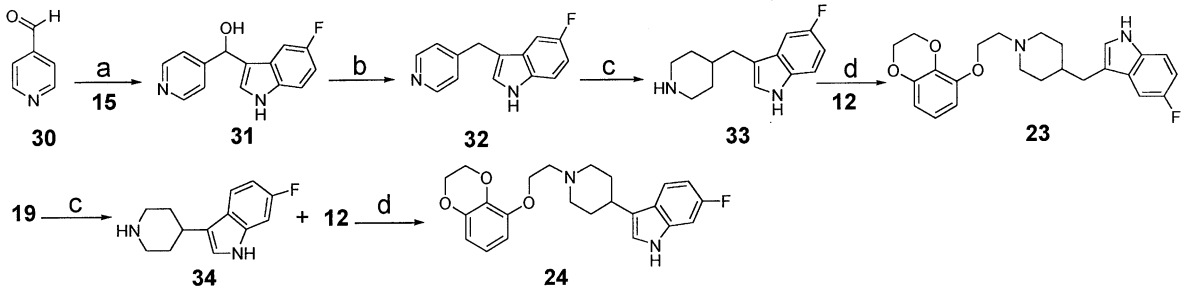
tethering an appropriate aryloxyethyl moiety from the basic nitrogen. Recently aryoxyethylamines have been successfully utilized to produce potent 5-HT_{1A} ligands such as compounds **5**–**8**.[18–21] In this paper the preparation and structure–activity relationships of a series of aryloxyethylamines (**9**), which represent our laboratories' initial attempts to discover a potentially new class of antidepressant agents, will be discussed.

Schemes 1–3 show the syntheses of target molecules **20**–**29**. The condensation of pyrogallol (**10**) and 1,2-dibromoethane afforded 5-hydroxy-benzodioxan **11** in good yield. The hydroxy benzodioxan was alkylated under Mitsunobu conditions[23] to afford the aryloxyethyl chloride **12**. Tetrahydropyridines **17**–**19** were prepared by the addition of the indoles **14**–**16** to 4-piperidone under basic conditions in yields ranging from 50 to 80%.[24] Treatment of indole tetrahydropyridines **17**–**19** with **12** afforded the desired compounds **20**–**22**. Shown in Scheme 2 is the preparation of the piperidine analogues **23** and **24**. Reaction of 4-pyridinecarboxaldehyde **30** with 5-fluoroindole (**15**) affords **32** in good yield.[25] Hydrogenation of indoles **32** and **19** over platinum oxide under acidic conditions provided piperidines **33** and **34**, respectively. Alkylation of **33** and **34** with **12** gave target molecules **23** and **24**, respectively. The 4-indolyl- and 5-quinolyl-oxyethyltetrahydropyridines (i.e., **26** and **28**; Scheme 3) were prepared using similar chemistry as described in Schemes 1 and 2. The azaindole tetrahydropyridines (i.e., **25**, **27**, and **29**) were prepared from commercially available 7-azaindole (**35**) using analogous chemistry as depicted in Scheme 1.

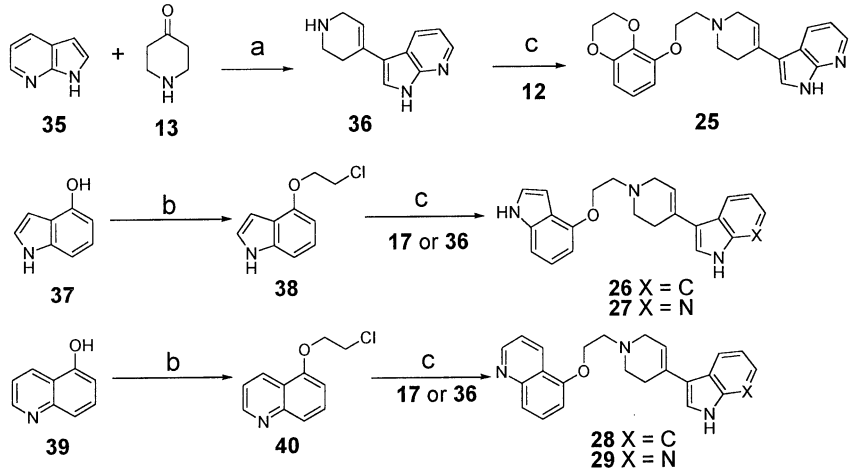
Compounds were evaluated in vitro to determine activity at the 5-HT transporter, 5-HT_{1A} receptor, and α_1 receptor. A binding assay protocol similar to that used by Cheetham employing [^{3}H]-paroxetine was used to determine the affinity of compounds for the 5-HT transporter (RB5-HT-T).[26] Affinity for the human transporter was determined by incubating test compound and [^{3}H]-5-HT with human carcinoma (Jar cells), previously treated with staurosporine to enhance transporter expression, and measuring specific uptake (HC5-HT-T).[27] Human 5-HT_{1A} binding (HC5-HT_{1A}) was determined with [^{3}H]-8-OH-DPAT,[28] and α_1 affinity was determined with [^{3}H]-prazosin.[29] Antagonism at the 5-HT_{1A} receptor was determined using a [^{35}S]-GTPγS binding assay similar to that of Larenzo[30] and a cAMP

assay reported by Dunlop.[31] E_{max} refers to the maximum agonist effect observed. Since 5-HT_{1A} antagonism is of interest in this study, the IC_{50} values were calculated.

Shown in Table 1 are the biological results of target molecules **20**–**29**. Comparing tetrahydropyridinyl-indoles **20**–**22**, revealed the 5-fluoro substituent had a detrimental effect for the 5-HT reuptake site. Reducing the double bond of **22** (i.e., **24**) led to a 4-fold higher 5-HT_{1A} affinity at the expense of a 31-fold loss of 5-HT transporter affinity. Replacing the piperidinyl moiety with a piperidinylmethyl group (i.e., **21** vs **23**) resulted in a 2-fold loss in 5-HT_{1A} affinity while having a beneficial effect on 5-HT uptake affinity. Indole derivative **26** was found to have much higher 5-HT_{1A} and 5-HT transporter affinity than both its benzodioxan (**20**) and

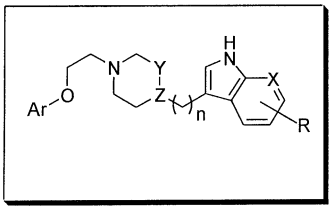


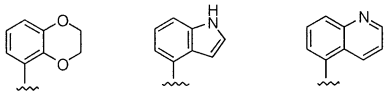
Scheme 2. Reagents and conditions: (a) MeOH/50% NaOH/5-F-indole; (b) $Et_3SiH/TFA/CH_2Cl_2$; (c) $Pt_2O/AcOH/H_2$; (d) $DMSO/Et_3N$/80 °C.



Scheme 3. Reagents and conditions: (a) 2 N KOH in MeOH; (b) $ClCH_2CH_2OH/PPh_3/DIAD/THF$; (c) $DMSO/Et_3N$/80 °C.

Table 1. Aryoxylethylamine indole derivatives (**20**–**29**)[32]





Compd	Ar	X	Y–Z	R	*n*	HC5-HT-T K_i (nM)	RB5-HT-T K_i (nM)	HC5-HT_{1A} K_i (nM)	GTPgS E_{max} (IC_{50}, nM)	cAMP E_{max} (IC_{50}, nM)	RBα_1 K_i (nM)
20	A	C	C=C	H	0	45.0	0.17	78.3	21.0 (222)	0.0 (115)	4.7
21	A	C	C=C	5-F	0	46.9	1.17	83.3	11.0 (684)	0.0 (1036)	30
22	A	C	C=C	6-F	0	19.8	0.15	83.6	53.0 (nd)	nd	4.1
23	A	C	CH_2CH_2	5-F	1	nd	0.01	168.2	nd	nd	nd
24	A	C	CH_2CH_2	6-F	0	127.8	4.7	19.6	29.5 (666)	0.0 (920)	2.8
25	A	N	C=C	H	0	276	18.0	43.9	30.0 (nd)	0.0 (969)	33
26	B	C	C=C	H	0	41.2	0.03	21.6	7.5 (115)	0.0 (33)	0.19
27	B	N	C=C	H	0	175	1.46	10.9	7.0 (38.9)	0.0 (12)	0.90
28	C	C	C=C	H	0	93.6	0.23	92.6	14 (524)	0.0 (686)	3.6
29	C	N	C=C	H	0	387	6.89	71.6	0.0 (181)	0.0 (90)	78.0

nd, no data.

quinoline analogues (**28**). When comparing the azaindoles to their indole analogues higher affinity for the 5-HT_{1A} receptor and lower affinity for the 5-HT transporter was observed (**25** vs **20**; **27** vs **26**; **29** vs **28**). To our delight, all the compounds in this study were found to be 5-HT_{1A} antagonists. In general, a major limitation of the compounds discussed in this investigation was their high affinity for the α_1 receptor. Due to this shortcoming this particular class of molecules was not further pursued.

In conclusion, we have demonstrated that a known class of 5-HT reuptake inhibitors can be modified to incorporate both 5-HT_{1A} affinity and antagonist activity. Though this class of molecules was not selective due to their α_1 receptor affinity, this study clearly demonstrates the potential of creating a new class of antidepressants embracing both 5-HT reuptake and 5-HT_{1A} antagonist activity. Investigations are currently underway in our laboratories to improve upon these findings by creating molecules which are both more selective and potent at the 5-HT_{1A} receptor.

References and Notes

1. Greenberg, P. E.; Stiglin, L. E.; Finkelstein, S. N. *J. Clin. Psy*. **1993**, *54*, 405.
2. Blier, P.; Bergeron, R. *J. Clin. Psy*. **1998**, *59* (Suppl. 5), 16.
3. Feighner, J. P. *J. Clin. Psy*. **1999**, *60* (Suppl. 4), 4.
4. Blier, P.; De Montigny, C.; Chaput, Y. *J. Clin. Pyschopharmacol*. **1987**, *7* (Suppl. 6), 24.
5. Artigas, F. *Trends Pharmacol. Sci*. **1993**, *14*, 263.
6. Artigas, F.; Perez, V.; Alvarez, E. *Arch. Gen. Psychiatry* **1994**, *51*, 248.
7. Artigas, F.; Romero, L.; de Montigny, C.; Blier, P. *Trends Neurosci*. **1996**, *19*, 378.
8. Blier, P.; Bergeron, R. *J. Clin. Psychopharmacol*. **1995**, *15*, 217.
9. Blier, P.; Bergeron, R. *J. Clin. Psy*. **1998**, *59* (Suppl. 5), 16.
10. Romero, L.; Hervas, I.; Artigas, F. *Neurosci. Lett*. **1996**, *219*, 123.
11. Romero, L.; Artigas, F. *J. Neurochem*. **1997**, *68*, 2593.
12. Perez, M.; Pauwels, P. J.; Paooard-Sigogneau, I.; Fourrier, C.; Chopin, P; Palmier, C.; Colovray, V.; Halazy, S. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3423.
13. (a) Oficialdegui, A. M.; Martinez, J.; Perez, S.; Heras, M.; Irurzun, M.; Palop, J. A.; Tordera, R.; Lasheras, B.; del Rio, J.; Monge, A. *Il Farm*. **2000**, *55*, 345. (b) Esparza, J. M.; Oficialdegui, A. M.; Perez-Silanes, S.; Heras, B.; Orus, L.; Palop, J. A.; Lasheras, B.; Roca, J.; Mourelle, M.; Bosch, A.; Del Castillo, J. C.; Tordera, R.; Del Rio, J.; Monge, A. *J. Med. Chem*. **2001**, *44*, 418.
14. Meagher, K. L.; Mewshaw, R. E.; Evrard, D. A.; Zhou, P.; Smith, D. L.; Scerni, R.; Spangler, T.; Abulhawa, S.; Shi, X.; Schechter, L. E.; Andree, T. H. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1885.
15. Gueremy, C.; Audiau, F.; Champseix, A.; Uzan, A.; Le Fur, G.; Rataud, J. *J. Med. Chem*. **1980**, *23*, 1306.
16. Malleron, J. L.; Gueremy, C.; Mignani, S.; Peyronel, J. F.; Truchon, A.; Blanchard, J. C.; Doble, A.; Laduron, P.; Piot, O.; Zundel, J. L.; Betschart, J.; Canard, H.; Chaillou, P.; Ferris, O.; Huon, C.; Just, B. I.; Kerphirique, R.; Martin, B.; Mouton, P.; Renaudon, A. *J. Med. Chem*. **1993**, *36*, 1194.
17. Mignani, S.; Damour, D.; Doble, A.; Labaudiniere, R.; Malleron, J.-L.; Piot, O.; Gueremy, C. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1913.
18. Yasunaga, T.; Naito, R.; Kontani, T.; Tsukamoto, S.; Nomura, T.; Yamaguchi, T.; Mase, T. *J. Med. Chem*. **1997**, *40*, 1252.
19. Dabire, H.; Bajjou, R.; Chaouche-Teyera, K.; Fournier, B.; De Nanteuil, G.; Laubie, M.; Safar, M.; Schmitt, H. *Eur. J. Pharmacol*. **1991**, *203*, 323.
20. Mewshaw, R. E.; Kavanagh, J.; Stack, G.; Marquis, K.; Shi, X.; Kagan, M. Z.; Webb, M. B.; Katz, A. H.; Park, A.; Kang, Y. H.; Abou-Gharbia, M.; Wasik, T.; Cortes-Burgos, L.; Scerni, R.; Spangler, T.; Brennan, J. A.; Piesla, M.; Mazandarani, H.; Coupet, J.; Andree, T. H. *J. Med. Chem*. **1997**, *40*, 4235.
21. Millan, M. J.; Schreiber, R.; Monneyron, S.; Denorme, B.; Melon, C.; Queriaux, S.; Dekeyne, A. *J. Pharmacol. Exp. Ther*. **1999**, *289*, 427, and references therein.
22. Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *J. Med. Chem*. **1988**, *31*, 1087.
23. Mitsunobu, O. *Synthesis* **1981**, 1.
24. Taylor, E. W.; Nikam, S. S.; Lambert, G.; Martin, A. R.; Nelson, D. L. *Mol. Pharmacol*. **1988**, *34*, 42.
25. Zhou, P.; Yanfang, L.; Meagher, K. L.; Mewshaw, R. E.; Harrison, B. L. *Tetrahedron Lett*. **2001**, *42*, 7333.
26. Cheetham, S. C.; Viggers, J. A.; Slater, N. A.; Heal, D. J.; Buckett, W. R. *Neuropharmacology* **1993**, *32*, 737.
27. Ramamoorthy, J. D.; Ramamoorthy, S.; Papapetropoulos, A.; Catravas, J. D.; Leibach, F. H.; Ganapathy, V. *J. Biol. Chem*. **1995**, *270*, 17189.
28. Hall, M. D.; El Mestikawy, S.; Emerit, M. B.; Pichat, L; Hamon, M.; Gozlan, H. *J. Neurochem*. **1985**, *44*, 1685.
29. Morrow, A.; Creese, I. *Mol. Pharmacol*. **1986**, *29*, 321.
30. Lazareno, S.; Birdsall, N. J. M. *Br. J. Pharmacol*. **1993**, *109*, 1120.
31. Dunlop, J.; Zhang, Y.; Smith, D. L.; Schechter, L. E. *J. Pharmacol. Toxicol. Methods* **1998**, *40*, 47.
32. K_i values are the mean of 2–3 experiments run at six different concentrations. Each experiment was carried out in triplicate. 95% confidence limits were generally ±15% of the mean value.