Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 7, pp. 763-768, 1997

0960-894X/97 $17.00 + 0.00

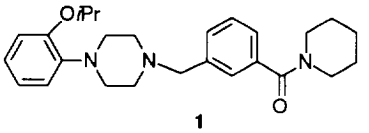
PII: S0960-894X(97)00074-7

HINDERED ROTATION CONGENERS OF MAZAPERTINE: HIGH AFFINITY LIGANDS FOR THE 5-HT$_{1A}$ RECEPTOR

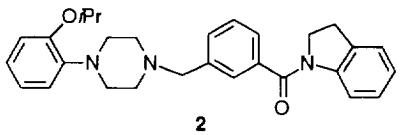
Ellen W. Baxter* and Allen B. Reitz
The R. W. Johnson Pharmaceutical Research Institute, Drug Discovery, Welsh and McKean Roads, Spring House, PA 19477

Abstract. Hindered rotation analogs of the antipsychotic mazapertine (**1**) were prepared. These compounds exhibited high affinity for the 5-HT$_{1A}$ receptor, but not for other serotonin or dopamine receptors. The related β-carboline structures were also synthesized and were found to be potent 5-HT$_{1A}$ ligands. © 1997 Elsevier Science Ltd.

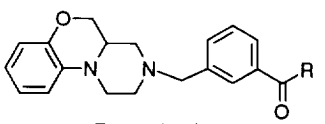
Introduction. Mazapertine (**1**) is currently in advanced clinical trials for the treatment of schizophrenia.[1] This novel antipsychotic has minimal extrapyramidal side effects and has a unique receptor binding profile characterized by nanomolar affinity to D_2, D_3, 5-HT$_{1A}$, and α_{1A} receptors. This multireceptor affinity can be attributed to the ability of **1** to adopt a variety of low energy conformations. In addition, **2**, the indoline analog of **1**, lacks dopamine receptor affinity, but retains 5-HT$_{1A}$ and α_{1A} binding. To probe the bioactive conformations of **1**, compounds **3** and **4** in which the 2-isopropoxyphenyl and piperazine rings are constrained as well as the analogous β-carbolines **5** and **6** were prepared.



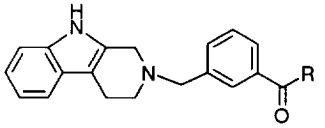
1



2

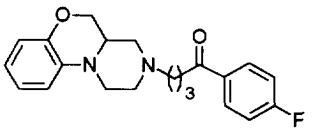


3 R = 1-piperidino
4 R = 1-indolinyl

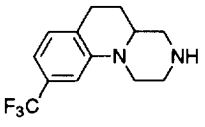


5 R = 1-piperidino
6 R = 1-indolinyl

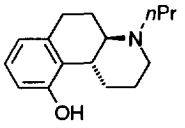
Prior to these efforts, the related pyrazino-1,4-benzoxazine **7** had been prepared and shown to have weak CNS activity,[2] and pyrazinotetrahydroquinoline **8** was found to have modest serotonin affinity (K_i = 67 nM).[3] Furthermore, octahydrobenzoisoquinoline **9**,[4] hexahydrobenzindoles **10**[5] and **11**[6] and hexahydroindenopyridine **12**[7] exhibit potent binding to the 5-HT$_{1A}$ receptor with K_is of 3.87, 0.1, 1.9 and 0.89 nM, respectively. Tetrahydropyrazinoindole **13** has modest affinity at the 5-HT$_{1A}$ receptor (K_i = 74 nM),[8] and tetrahydropyrazinoindole **14** has weak serotonergic properties.[9] Moreover, β-carboline **15** has antiserotonin activity,[10] and **16** has 5-HT$_{1A}$ receptor affinity (K_i = 79 nM).[11] The 5-HT affinity of these tricyclic structures suggests that the 5-HT binding of **1**, **2**, and related structures may be due to a conformation in which the 2-isopropoxyphenyl and piperazine rings approximates that found in the constrained tricyclic systems. Because 5-HT agents have potential in a variety of therapeutic areas such as anxiety, depression, schizophrenia, and emesis,[12] the effect of the tricyclic nucleus was explored in our series.



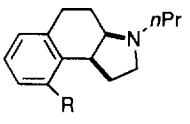
7



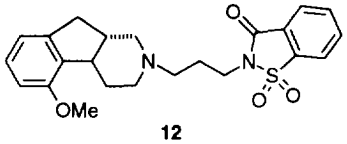
8



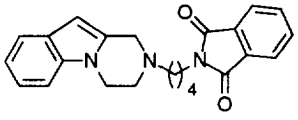
9



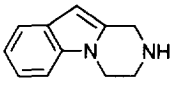
10 R = OH
11 R = $CONH_2$



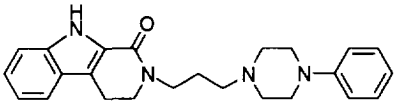
12



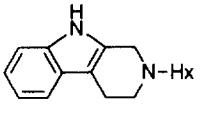
13



14

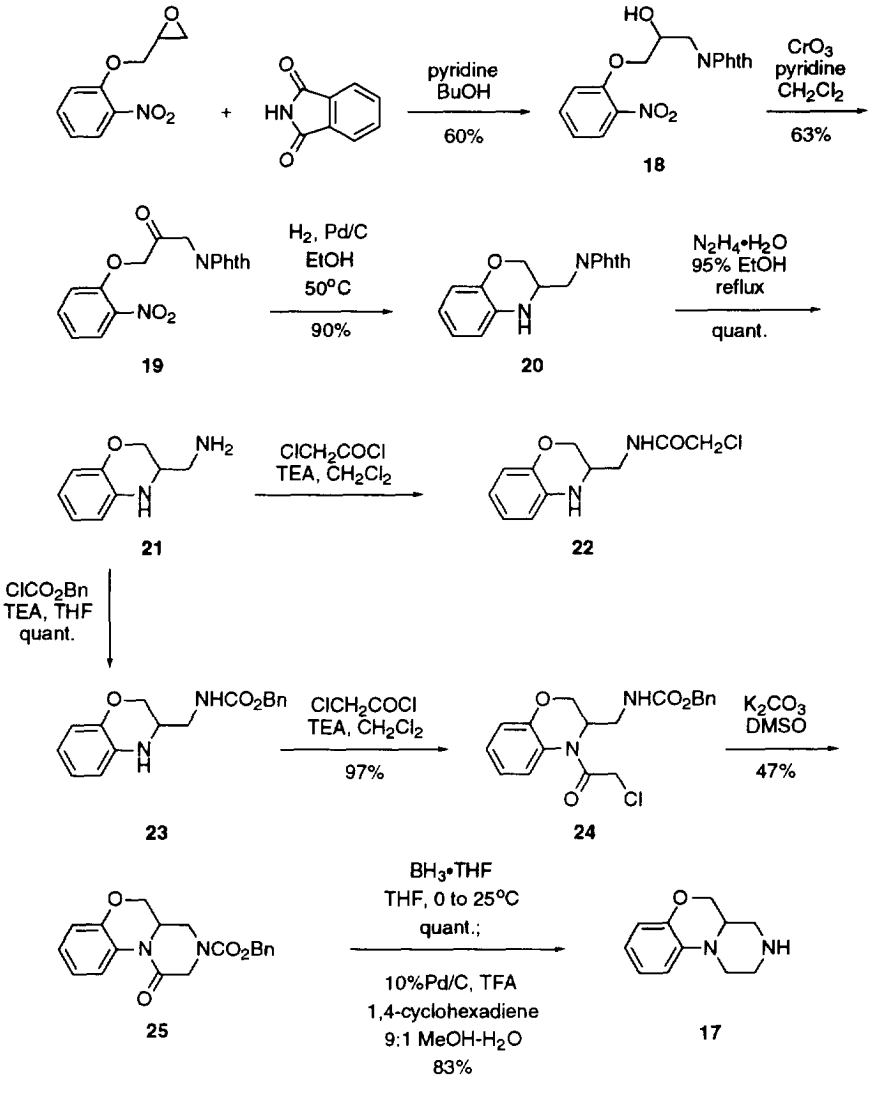


15

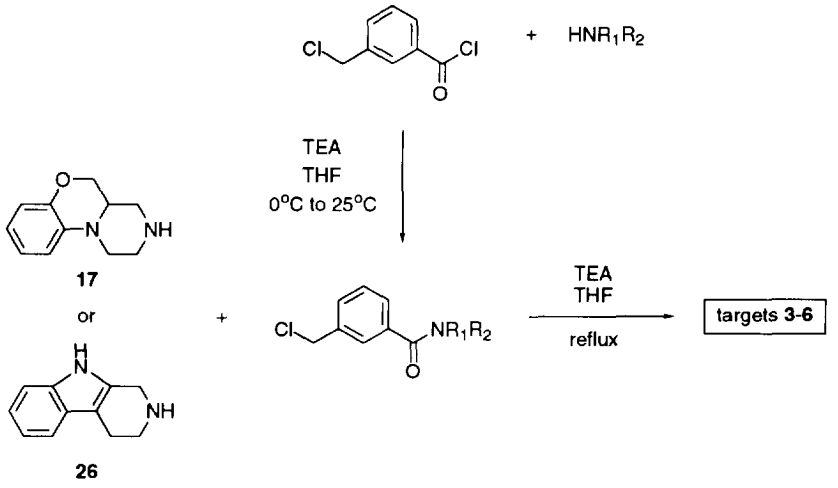


16

Chemistry. For the synthesis of targets **3** and **4**, pyrazinobenzoxazine **17** had to be prepared. This end was achieved using a modification of Gupta's procedure[2] for the preparation of **7**.[9,13] Condensation of 1-(2-nitrophenoxy)-2,3-epoxypropane and phthalimide afforded intermediate **18** which was oxidized to ketone **19**. Catalytic hydrogenation effected nitro group reduction and subsequent reductive amination to provide benzoxazine **20**. Removal of the phthalamido group afforded diamine **21**. Conversion of **21** to a tricyclic moiety was attempted with a variety of biselectrophiles. For example, reaction of **21** with chloroacetyl chloride resulted in acylation of the primary amino group to give **22**, but all attempts to effect ring closure were unsuccessful. Use of other reagents, such as bromoacetyl bromide, diethyl oxalate, or oxalyl chloride afforded only monoacylated materials or extensive decomposition. These difficulties were circumvented using a procedure reported by Nate and coworkers.[14] Compound **21** was converted to carbamate **23** which was subsequently reacted with chloroacetyl chloride to provide **24**. Treatment of **24** with base effected cyclization to tricyclic lactam **25**. Reduction of the lactam followed by removal of the carbobenzyloxy group afforded pyrazino-1,4-benzoxazine **17**.



Pyrazinobenzoxazine **17** and commercially available pyridoindole **26** were converted to targets **3-6** by alkylation with the appropriate chloromethyl benzamides. The benzamides were prepared by condensation of either piperidine or indoline with 3-(chloromethyl)benzoyl chloride.



Pharmacology. Tricyclic compounds **3-6** were tested in a number of receptor binding assays and were also evaluated for their in vivo properties. Unlike mazapertine (**1**), which has high affinity for D_2, D_3, 5-HT_{1A}, and α_{1A} receptors, **3-6** generally show high affinity for the 5-HT_{1A} receptor only (Table 1). With the exception of compound **5**, these tricycles do not have appreciable binding to the D_2 receptor. Compounds **5** and **6** show α_{1A} receptor affinity while **3** and **4** exhibit weak or no binding respectively. Furthermore, **3-6** were also tested for their affinity to a number of other serotonergic receptors as well as the D_1 receptor as outlined in Table 2. The tricyclics have little affinity for these receptors. Finally, compounds **3-6** were weakly active in the rat conditioned avoidance test, a predictor of antipsychotic activity.

Table 1

Compound	5-HT_{1A} Ki (nM)	α_1 Ki (nM)	D_2 Ki (nM)	D_3 Ki (nM)	D_3 % Inhibition at 100 nM	Rat Conditioned Avoidance % Inhibition[15] (dose, mg/kg, po)
1	1.7	1.3	2.2	1.8		-92 (5)
2	3.4	1.7	>1000	not determined		-96 (15)
3	12	200	>1000		64	-49 (15)
4	6.5	>1000	>1000		54	-20 (15)
5	13	36	374		27	-74 (15)
6	9.2	2.9	>1000		56	-37 (15)

Ligands employed for binding assays:[16] **5-HT_{1A}:** ^{3}H-8-OH-DPAT; α_1: ^{3}H-prazosin; **D_2:** ^{3}H-spiperone; **D_3:** ^{3}H-YM-09151-2

Table 2

% Inhibition (Concentration)

Compound	5-HT$_{1B}$ (100 nM)	5-HT$_{1C}$ (100 nM)	5-HT$_{1D}$ (10 μM)	5-HT$_2$ (10 μM)	5-HT$_3$ (10 μM)	D$_1$ (10 μM)
3	3.4	5.6	63.8	7.5	5.1	14.7
4	8.1	-2.8	58.9	7.5	12.5	42.4
5	1.0	5.5	74.7	18.0	13.6	23.7
6	8.8	8.7	86.1	29.9	22.6	40.8

Ligands employed for binding assays: **5-HT$_{1B}$**: ^{125}I-CYP;[17] **5-HT$_{1C}$**: ^{3}H-mesulergine;[18] **5-HT$_{1D}$**: ^{3}H-serotonin;[19] **5-HT$_2$**: ^{3}H-ketanserin;[20] **5-HT$_3$**: ^{3}H-BRL-43694;[21] **D$_1$**: ^{3}H-SCH-23390[22]

Discussion. From the binding data, constraining the phenyl and piperazine rings of **1** leads to a loss of affinity at all receptors except the 5-HT$_{1A}$. Energy minimization studies did not show an appreciable difference in the low energy conformations of **1** and **3**. However, energy calculations of N-(2-methoxyphenyl)piperazine as a function of the torsional angle between the aromatic and piperazine rings indicate that several minima are possible, for example when the angle is ca. 0°, 30-50°, and 130°.[23] Furthermore, conformational analysis of N-(2-alkoxyphenyl)piperazines suggest that a dihedral angle of either 30° or 150° is optimal for 5-HT$_{1A}$ receptor binding.[24] That compounds **1** and **2** can adopt a variety of low energy conformations could explain their ability to bind to a number of receptors. However, compounds **3** and **4** as well as **5** and **6** can not exist in a conformation in which the dihedral angle is 150°, but could readily adopt an angle of 30-50° between the rings which suggests that their high affinity to the 5-HT$_{1A}$ receptor is due to a conformation in which the dihedral angle is ca. 30°.

Conclusions. Structures **3** and **4**, analogs of mazapertine in which the 2-isopropoxyphenyl and piperazine rings are constrained, have high affinity for the 5-HT$_{1A}$ receptor, but, unlike mazapertine, bind to D$_2$, D$_3$, and α_{1A} receptors to a much lower extent.

Acknowledgements. We gratefully acknowledge the efforts of D. J. Bennett, E. E. Codd, M. E. Ortegon, M. J. Renzi, and R. P. Shank (CNS Pharmacology, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA) in obtaining D$_2$, 5-HT$_{1A}$, and α_{1A} receptor binding data as well as the in vivo test results. We also thank B. E. Maryanoff, J. D. Rodgers, H. R. Almond, and D. A. Demeter for helpful suggestions. In addition, Cerep (Celle L'Evescault, France) conducted the D$_1$, D$_3$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$, 5-HT$_2$, 5-HT$_3$ receptor binding assays.

References and Notes

1. Reitz, A. B.; Bennett, D. J.; Blum, P. S.; Codd, E. E.; Maryanoff, C. A.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1994**, *37*, 1060.
2. Gupta, S. P.; Chatterjee, S. S.; Bindra, J. S.; Jain, P. C.; Anand, N. *Ind. J. Chem.* **1975**, *13*, 462.
3. Huff, J. R.; King, S. W.; Saari, W. S.; Springer, J. P.; Martin, G. E.; Williams, M. *J. Med. Chem.* **1985**, *28*, 945.
4. (a) Mellin, C.; Vallgarda, J.; Nelson, D. L.; Bjork, L.; Yu, H.; Anden, N.-E.; Csoregh, I.; Arvidsson, L.-E., Hacksell, U. *J. Med. Chem.* **1991**, *34*, 497. For related benzooctahydroquinolines, see (b) Cannon, J. G.; Amoo, V. E. D.; Long, J. P.; Bhatnagar, R. K.; Flynn, J. R. *J. Med. Chem.* **1986**, *29*, 2529 and (c) Wikstrom, H.; Andersson, B.; Elebring, T.; Jacyno, J.; Allinger, N. L.; Svensson, K.; Svensson, K.; Carlsson, A.; Chidester, C. G.; Von Voigtlander, P. F. *J. Med. Chem.* **1993**, *36*, 2208.
5. Lin, C.-H.; Haadsma-Svensson, S. R.; Lahti, R. A.; McCall, R. B.; Piercey, M. F.; Schreur, P. J. K. D.; Von Voigtlander, P. F.; Smith, M. W.; Chidester, C. G. *J. Med. Chem.* **1993**, *36*, 1053.
6. Lin, C.-H.; Haadsma-Svensson, S. R.; Phillips, G., McCall, R. B.; Piercey, M. F.; Smith, M. W.; Svensson, K.; Carlsson, A.; Chidester, C. G.; Von Voigtlander, P. F. *J. Med. Chem.* **1993**, *36*, 2208.
7. Meyer, M. D.; DeBernardis, J. F.; Hancock, A. A. *J. Med. Chem.* **1994**, *37*, 105.
8. Mokrosz, M. J.; Chojnacka-Wojcik, E.; Tatarczynska, E.; Klodzinska, A.; Filip, M.; Boksa, J.; Charakchieva-Minol, S. Mokrosz, J. L.; *Med. Chem. Res.* **1994**, *4*, 161 and references cited therein.
9. Rajur, S. B.; Merwade, A. Y.; Hendi, S. B.; Basanagoudar, L. D. *Ind. J. Chem.* **1989**, *28B*, 1065.
10. Boksa, J.; Misztal, S.; Chojnacka-Wojcik, E.; Gastol-Lewinska, L.; Grodecka, A.; Mokrosz, J. L. *Pharmazie* **1992**, *47*, 254.
11. Bojarski, A. J.; Cegla, M. T.; Charakchieva-Minol, S.; Mokrosz, M. J.; Mackowiak, M.; Misztal, S.; Mokrosz, J. L. *Pharmazie* **1993**, *48*, 289.
12. (a) Romero, A. G.; McCall, R. B. *Annu. Rept. Med. Chem.* **1992**, *27*, 21. (b) Saxena, P. R. *Pharmac. Ther.* **1995**, *66*, 339.
13. Banzatti, C.; Della Torre, A.; Melloni, P.; Pieraccioli, D.; Salvadori, P. *J. Heterocycl. Chem.* **1983**, *20*, 139.
14. Nate, H.; Watanabe, A.; Matsuki, K.; Inoue, I.; Ohtsuka, H.; Sekine, Y.; Oda, K.; Honma, Y.; Ishida, A.; Kanno, T.; Konda, M.; Nakai, H.; Wada, H.; Takeda, M.; Yabana, H.; Nagao, T. *Chem. Pharm. Bull.* **1987**, *35*, 2825.
15. Martin, G. E.; Elgin, R. J., Jr.; Kesslick, J. M.; Baldy, W. J.; Mathiasen, J. R.; Shank, R. P.; Scott, M. K. *Eur. J. Pharmacology* **1988**, *156*, 223.
16. Martin, G. E.; Elgin, R. J., Jr.; Mathiasen, J. R.; Davis, C. B.; Kesslick, J. M.; Baldy, W. J.; Shank, R. P.; DiStefano, D. L.; Fedde, C. L.; Scott, M. K. *J. Med. Chem.* **1989**, *32*, 1052.
17. Hoyer, D.; Engel, G.; Kalkman, H. O. *Eur. J. Pharmacology* **1985**, *118*, 1.
18. Pazos, A.; Hoyer, D.; Palacios, J. M. *Eur. J. Pharmacology* **1984**, *106*, 539.
19. Heuring, R. E.; Peroutka, S. J. *J. Neurosci.* **1987**, *7*, 894.
20. Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301.
21. Hoyer, D.; Neijt, H. C. *Mol. Pharmacol.* **1988**, *33*, 303.
22. Trampus, M.; Ongini, E.; Varani, K.; Borea, A. *Eur. J. Pharmacology* **1991**, *194*, 17.
23. Dijkstra, G. D. H. *Rec. Trav. Chim. Pays-Bays* **1993**, *112*, 151.
24. Mokrosz, J. L.; Duszynska, B.; Bojarski, A. *Pol. J. Pharmacol. Chem.* **1992**, *44*, 87.

(*Received in USA* 13 *January* 1997; *accepted* 28 *January* 1997)