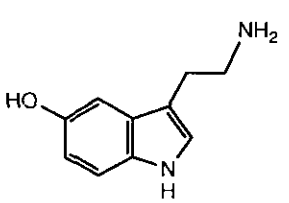
A SHORT SYNTHESIS OF A CONFORMATIONALLY RESTRICTED ANALOG OF THE NEUROTRANSMITTER SEROTONIN WITH REDUCED BASICITY[1]

John E. Macor and Kevin Ryan[2]
Department of Medicinal Chemistry, Central Research Division,
Pfizer Inc, Groton, CT 06340, U. S. A.

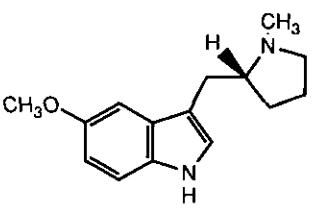
Abstract - The synthesis of a less basic, conformationally restricted analog of serotonin is described [2-(5-methoxyindol-3-ylmethyl)imidazole (**1**)]. The crucial carbon-carbon bond formation step in this synthesis involves the attack of a 2-lithioimidazole anion on an indole-3-carboxaldehyde derivative.

Recently, our laboratory has been engaged in the synthesis and study of conformationally and rotationally restricted analogs of the neurotransmitter serotonin [5-hydroxytryptamine, 5-HT].[3] This line of research has led to a better understanding of the molecular recognition elements between the substrate [i.e. 5-HT] and the neuronal receptors which are activated by that molecule. Since the discovery of additional serotonin receptors continues,[4] our research is especially relevant for understanding specific binding requirements between 5-HT and individual serotonin receptor subtypes. This work has led to the discovery of a rotationally restricted phenolic analog of serotonin [CP-93,129] which is selective for the 5-HT_{1B} receptor[3a,b] and a tryptamine [CP-132,484] which is selective for 5-HT_2 receptors versus 5-HT_1 receptors.[3d-f]

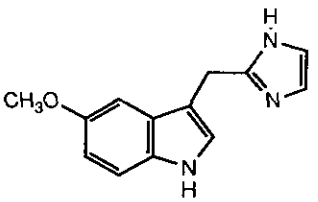
During the course of these studies, we also discovered that the C3-(2-aminoethyl) sidechain of serotonin could be replaced with a 3-(*N*-methylpyrrolidin-2*R*-ylmethyl) group with essentially no loss of binding affinity among 5-HT receptors. This led to CP-108,509 in which the C-N bond of the C3-(2-aminoethyl) sidechain of serotonin was restricted into a pyrrolidine ring. Upon seeing that the conformational restriction in CP-108,509 did not have an appreciable deleterious effect on the binding of that compound to 5-HT receptors [when compared to 5-HT], we wished to further ex-



serotonin



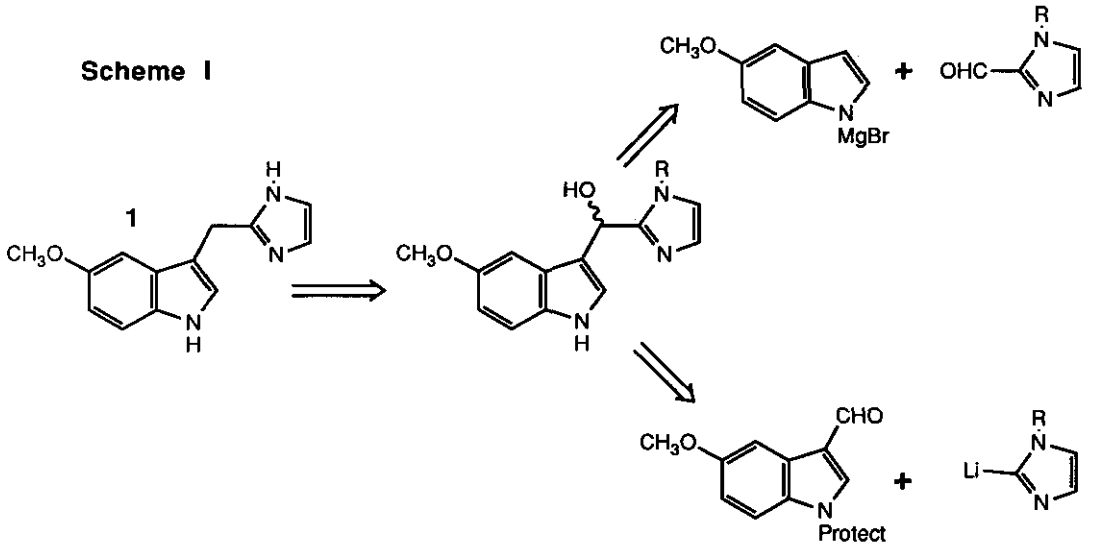
CP-108,509



1

plore this discovery with the examination of a less basic version of CP-108,509. Our goal was to replace the pyrrolidine basic amine with a less basic site, and study the basicity requirements and degree of amine protonation of 5-HT within serotonin receptors. Following this line of reasoning, we sought to replace the pyrrolidine in CP-108,509 with an imidazole, since at physiological pH, a 2-methylimidazole would be only partially protonated in comparison with the amine contained in 5-HT, which would be almost completely protonated at physiological pH. This line of reasoning led us to desire **1**, the imidazole analog of CP-108,509.

Scheme I

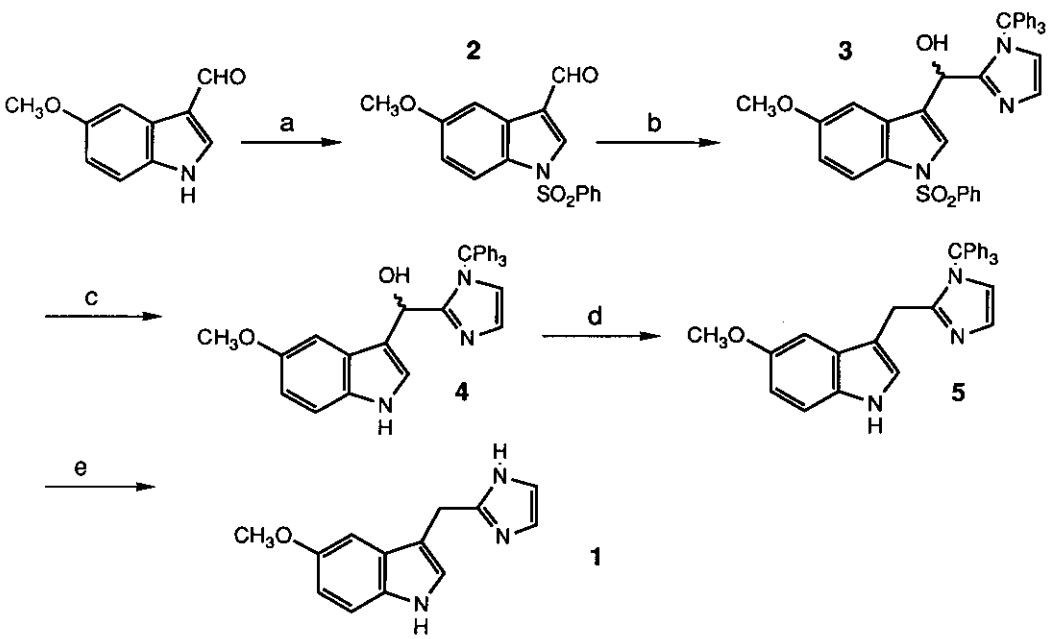


Two approaches to 2-(5-methoxyindol-3-ylmethyl)imidazole (**1**) were envisioned (Scheme I), both involving the attack of a carbanion on a carboxaldehyde. While the attack of an indole magnesium halide on a *N*-protected imidazole-2-carboxaldehyde initially appeared to be the simplest approach, literature on this type of reaction indicated otherwise.[5] Instead, we chose to pursue the alternative because of the ready availability of the indole-3-carboxaldehyde and imidazole starting materials. This approach required the attack of an *N*-protected 2-lithioimidazole on an *N*-protected indole-3-carboxaldehyde. Reaction of commercially available 5-methoxyindole-3-carboxaldehyde with sodium hydride in anhydrous tetrahydrofuran followed by phenylsulfonyl chloride succinctly provided the protected indole (**2**) in high yield (88%, Scheme II).

Following a report by Kirk[6] on the synthesis of 2-substituted imidazoles, 1-tritylimidazole[7] was deprotonated with a slight excess of butyllithium in tetrahydrofuran at room temperature (addition of BuLi at -78 °C, then warming to room temperature) to form the 2-lithioimidazole carbanion as a red solution. Addition of the indole-3-carboxaldehyde (**2**) to this solution at 0 °C led to a solution color change to yellow, and upon quenching and work-up, the desired alcohol (**3**, 66%, Scheme II) was isolated.[8] Clearly visible in the ^{1}H nmr were single proton doublets (J=7.3 Hz) at δ 5.51 and δ 5.10 for the alcohol proton and the methine proton α to the two aromatic rings, respectively. Addition of D_2O to this nmr sample led to a disappearance of the doublet at δ 5.51 and appearance of only a singlet for one proton at δ 5.10.

With the crucial C-C bond formed, only reduction of the hydroxy function and deprotection of the indole and imidazole heterocycles remained. Attempted reduction of the hydroxy group via hydrogenation only removed the trityl group from the imidazole. Since literature precedent showed that metal hydrides can reduce a C3-keto group on an indole ring directly to the methylene,[9] we assumed that similar reaction conditions would reduce the hydroxy group. This approach required the removal of the *N*-phenylsulfone first, and this was accomplished using sodium hydroxide in refluxing ethanol to afford the NH-indole (**4**, 32%). The low yield in this reaction was attributed to the lability of the resulting alcohol due to the resonance delocalization of the indole nitrogen lone pair of electrons.[10] Optimization of this step would be the priority upon re-examination of the reaction sequence.

Scheme II



a = 1) NaH; 2) $PhSO_2Cl$, THF, 5 °C
b = 1) trityimidiazole, THF, -78 °C; 2) C_4H_9Li, -78 - 25 °C; 3) **3** in THF
c = NaOH, C_2H_5OH, Δ
d = $LiBH_4$, THF, Δ
e = 5% glacial acetic acid in C_2H_5OH, Δ

Use of lithium borohydride reduced the alcohol to methylene in refluxing tetrahydrofuran to afford **5** (65%, Scheme II), and the trityl group was removed uneventfully from the imidazole employing 5% glacial acetic acid in refluxing ethanol to yield 2-(5-methoxyindol-3-ylmethyl)imidazole[11] (**1**, 66% last step, 8% overall from 5-methoxyindole-3-carboxaldehyde). Initial binding pharmacology revealed reduced affinity of **1** for 5-HT receptors when compared to serotonin. This result

has led us to conclude that the 5-HT receptors studied require a ligand with a greater degree of protonation of the basic amine than could be achieved by the imidazole found in **1**. Synthesis and examination of a more basic imidazole is being pursued to further address the basicity requirments of ligands for 5-HT receptors.

REFERENCES

1. This paper is dedicated to Professor Katritzky on the occasion of his 65th birthday.
2. Present Address: Department of Chemistry, University of Rochester, Rochester, NY 14627.
3. a) J. E. Macor, C. A. Burkhart, J. H. Heym, J. L. Ives, L. A. Lebel, M. E. Newman, J. A. Nielsen, K. Ryan, D. W. Schulz, L. K. Torgersen, and B. K. Koe, *J. Med. Chem.*, 1990, **33**, 2087; b) J. E. Macor and M. E. Newman, *Heterocycles*, 1990, **31**, 805; c) J. E. Macor and K. Ryan, *Heterocycles*, 1990, **31**, 1497; d) J. E. Macor and M. E. Newman, *Tetrahedron Letters*, 1991, **32**, 3345; e) J. E. Macor, K. Ryan, and M. E. Newman, *Tetrahedron*, 1992, **48**, 1039; f) J.E. Macor, C.B. Fox, C. Johnson, B.K. Koe, L.A. Lebel, and S.H. Zorn, *J. Med. Chem.*, 1992, **35**, 3625; g) J. E. Macor, J. Blake, C. A. Fox, C. Johnson, B. K. Koe, L. A. Lebel, J. M. Morrone, K. Ryan, A. W. Schmidt, D. W. Schulz, and S. H. Zorn, *J. Med. Chem.*, 1992, **35**, 4503; h) J. E. Macor, R. J. Post, D. H. Blank, and K. Ryan, *Tetrahedron Letters*, 1992, **33**, 8011.
4. C. Gluchowski, T. A. Branchek, R. L. Weinshank, and P. R. Hartig, 'Annual Reports in Medicinal Chemistry,' Vol. 28, ed. by J. A. Bristol, Academic Press, Inc. New York, 1993, pp. 29-38.
5. W. A. Reimers, 'Properties and Reactions of Indoles,' Vol. 25, Part 1 (ed. by W.J. Houlihan) of 'The Chemistry of Heterocyclic Compounds,' ed. by A. Weissberger and E. C. Taylor, John Wiley & Sons, Inc., New York, 1972, pp. 126-133.
6. K. L. Kirk, *J. Org. Chem.*, 1978, **43**, 4381.
7. D. P. Davis, K. L. Kirk, and L. A. Cohen, *J. Heterocyclic Chem.*, 1982, **19**, 253.
8. All new compounds disclosed in this communication have been thoroughly characterized including ^{1}H nmr, ^{13}C nmr, lrms, hrms and/or elemental analysis.
9. T. F. Spande, 'Hydroxyindoles, Indole Alcohols, and Indolethiols,' Vol. 25, Part III (ed. by W. J. Houlihan) of 'The Chemistry of Heterocyclic Compounds,' ed. by A. Weissberger and E. C. Taylor, John Wiley & Sons, Inc., New York, 1979, pp. 174-175.
10. For a discussion of the instability of 3-hydroxymethylindoles, see reference 9.
11. The spectral and physical properties of 2-(5-methoxyindol-3-ylmethyl)imidazole (**1**) are as follows: mp 149.0-151.0 °C (decomp.); IR (KBr) 1586, 1570, 1489, 1459, 1441, 1428 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 10.70 (br s, 1H), 7.21 (d, J=8.8 Hz, 1H), 7.09 (s, 1H), 6.94 (d, J=2.3 Hz, 1H), 6.86 (s, 2H), 6.69 (dd, J=2.4 and 8.8 Hz, 1H), 4.01 (s, 2H), 3.70 (s, 3H); ^{13}C nmr (DMSO-d_6) δ 152.9, 146.9, 131.3, 127.2, 123.9, 123.7, 121.2, 111.9, 110.9, 100.5, 55.3, 24.6; lrms (m.z, relative intensity) 228 (18), 227 (M^+, 100), 212 (47), 196 (5), 184 (16), 160 (11); hrms calc for $C_{13}H_{13}N_3O$ 227.1060, found 227.1040

Received, 24th September, 1993