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The Synthesis of Conformationally/Rotationally Restricted Analogs of the Neurotransmitter Serotonin

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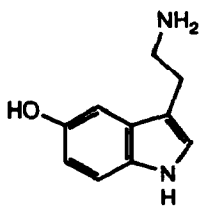
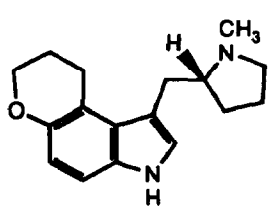
Abstract: *The syntheses of two novel conformationally/rotationally restricted analogs of the neurotransmitter serotonin which are modeled after the 5-HT$_2$ receptor selective agonist CP-132,484 [a dihydropyrano[3,2-e]indole] are described.*

The synthesis and study of conformationally restricted analogs of biologically relevant molecules can provide insight into the specific molecular recognition elements involved in the binding of those small biomolecules to receptor proteins. This approach can lead to a better understanding of the specific binding requirements within a family of receptors which all recognize a common natural substrate. Such is the case of the ubiquitous neurotransmitter serotonin [5-hydroxytryptamine, 5-HT]. Approximately a dozen different receptor proteins have been identified[1] which are activated by this indole derivative, and it is no wonder that dysfunction of serotonin receptors has been implicated with a wide variety of disease states in the central nervous system.[2] In order to better understand which 5-HT receptor can be directly linked to a particular disease state, molecular probes and tools need to be designed which can better differentiate receptor subtypes within the family of 5-HT receptors. Our laboratory has been extensively involved in such a pursuit via the synthesis and pharmacological study of conformationally restricted analogs of 5-HT.[3] Recently, this line of research led to the synthesis of a rotationally restricted phenolic analog (CP-132,484) of 5-HT in which the C5-OH had been incorporated into a dihydropyran ring.[3e] With this small modification, CP-132,484 could function only as a hydrogen bond acceptor within a 5-HT receptor with a directionality of interaction defined by the rotationally restricted lone pairs of electrons on the pyran oxygen. This compound was found to be a highly selective agonist for the 5-HT$_2$ family of receptors versus the 5-HT$_1$ family of receptors when compared to serotonin itself.[3f] With this finding in hand, we sought to further improve the 5-HT$_2$ receptor selectivity via additional conformationally restrictive modifications,



5-HT

CP-132,484



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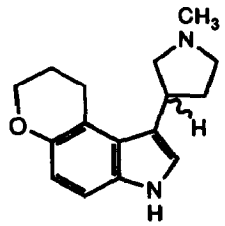
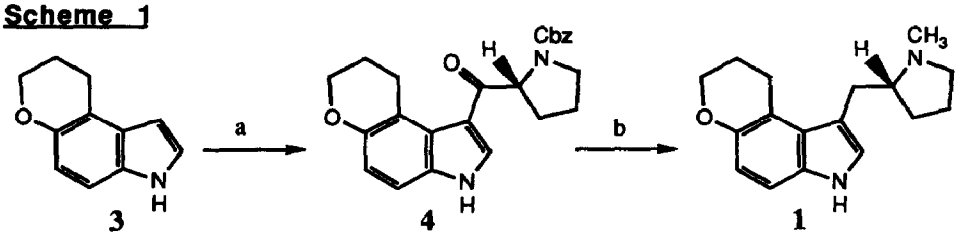


2

specifically involving the C3-(2-aminoethyl) sidechain of the tryptamine in CP-132,484. This line of thought led us to desire the 3-(pyrrolidin-2-ylmethyl)indole (**1**) and 3-(pyrrolidin-3-yl)indole (**2**) analogs of CP-132,484. Herein, we describe the synthesis of these targets.

The original synthesis of CP-132,484 proceeded through dihydropyrano[3,2-e]indole (**3**), which was made via a sequence of five steps in a 20% overall yield.[3e] Alkylation of 3-methyl-4-nitrophenol with allyl iodide was followed by a Claisen rearrangement. Hydroboration of the resulting olefin, followed by an intramolecular Mitsunobu reaction constructed the dihydropyran ring. Batcho-Leimgruber indolization led to **3**. Drawbacks to this synthesis included a lack of regiospecificity in the Claisen rearrangement and the tedious chromatographic separation of the resulting final dihydropyranoindoles [i.e. dihydropyrano[2,3-f]indole and the desired dihydropyrano[3,2-e]indole (**3**)]. Despite these limitations in the synthesis of **3**, this compound was still viewed as the most available starting material for the synthesis of the 3-(pyrrolidin-2-ylmethyl)indole (**1**, Scheme 1). The R-enantiomer of **1** contained the desired stereogenicity because previous studies[3g] have shown that that configuration was the more potent of the two antipodes at 5-HT receptors. Acylation of the preformed indole-magnesium chloride salt of **3** [formed via reaction of **3** with a solution of *t*-butyl magnesium chloride] with the acid chloride of Cbz-*d*-proline[4] afforded the 3-ketoindole (**4**, 88%).[5] As was the previous case with 5-methoxyindole,[3g] the use of two equivalents of the indole-Mg-halide salt was required for a satisfactory yield, since one equivalent was necessary as an equilibrating base for the more acidic NH found in the 3-ketoindole product (**4**). Reduction of the ketone to methylene and the carbamate to methyl were both accomplished with a single application of lithium aluminum hydride (LAH) to afford the desired conformationally restricted target analog of serotonin (**1**, 81%, 71% for two steps, Scheme 1).[6] Key to the success of this reaction was the order of addition of reagents. When LAH was added to a solution of **4**, a significant amount of alcohol (from ketone reduction) was seen, despite extensive heating and additional LAH. Alternatively, when **4** was added to a solution/mixture of LAH in tetrahydrofuran, complete reduction of the ketone and carbamate functionalities was observed affording **1** in high yield.

Scheme 1



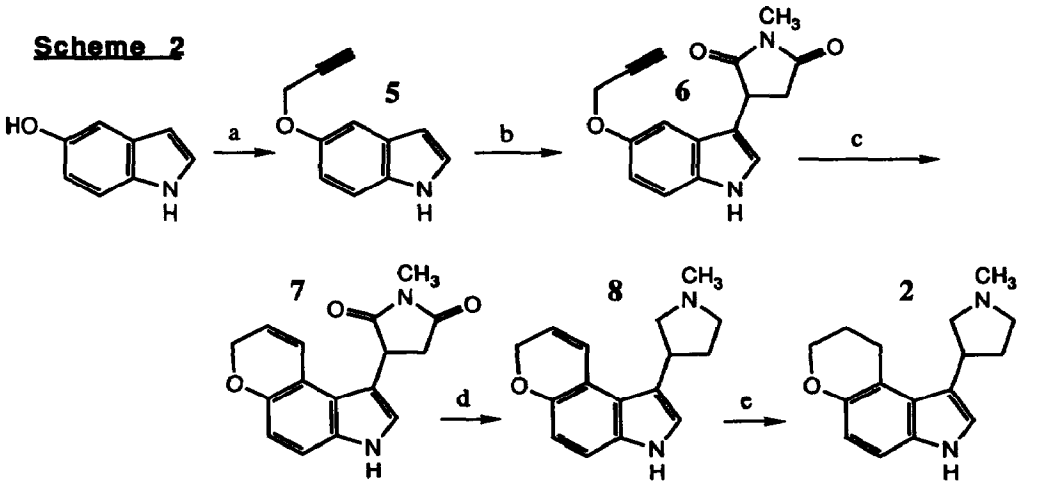
a = 1) 2.0 eq *t*-Bu-MgCl in diethyl ether, 0 °C
2) R-Cbz-proline, acid chloride, ether, 0 °C (88%)

b = LAH, THF, Δ (81%)

Keeping in mind the limitations of the synthesis of the dihydropyranoindole (**3**), we desired an approach to the 3-(pyrrolidin-3-yl)indole (**2**) which did not need to involve **3**. We envisioned utilizing a Claisen rearrangement of a 5-propargyloxyindole derivative, which others have shown[7] leads directly to the corresponding pyrano[3,2-e]indole. This would allow us to build our desired molecule with the requisite functionality at C3 of the indole already intact. Also, this approach to the dihydropyrano[3,2-e]indole portion of the molecule would require one less step than the procedure used to make **3**. Alkylation of 5-hydroxyindole with propargyl bromide in acetone using cesium carbonate as base led to a

high yield of 5-(2-propynoxy)indole (**5**, 87%, Scheme 2). Cesium carbonate was the base of choice because limited optimization studies of similar alkylation reactions showed that use of cesium carbonate (as opposed to sodium carbonate or sodium hydride) afforded little to no undesired nitrogen alkylation. A single attempt at cyclizing **5** directly at 180 °C afforded only decomposition, and we believed that the lack of substitution at C3 in **5** was responsible for our result. Accordingly, reaction of 5-(2-propynoxy)indole (**5**) with an excess of N-methylmaleimide (3 equivalents) in refluxing acetic acid afforded the succinimide (**6**, 31%) directly via a Michael-type reaction of the nucleophilic C3-position of the indole on the electrophilic maleimide. The yield of this particular reaction was low, and optimization of this reaction sequence is focused on the improvement of this step. This type of reaction for the synthesis of 3-(indol-3-yl)succinimides such as **6** has found very limited use in the literature,[8] despite the fact that it provides in a single step the framework for the ultimate production of 3-(pyrrolidin-3-yl)indoles, an important class of conformationally restricted tryptamine derivatives.[9] Claisen rearrangement of the succinimide (**6**) was successfully accomplished in refluxing bromobenzene (25 hours, 156 °C) to afford the pyranoindole (**7**, 72%), although monitoring the reaction by TLC was difficult due to the lack of separation of **6** from **7** in any solvent system tested.

Scheme 2



a = Cs_2CO_3, propargyl bromide, acetone, RT (87%)
b = N-methylmaleimide, acetic acid, Δ (31%)
c = bromobenzene, Δ (72%)
d = LAH, THF, Δ (100%)
e = H_2, Pd/C, EtOH, RT (91%)

Reduction of the succinimide (**7**) directly to the pyrrolidine (**8**, 100%) was accomplished quantitatively using an excess of lithium aluminum hydride in tetrahydrofuran. As was the case with the reduction of **4** to **1** (Scheme 1), the order of addition of reagents was absolutely crucial to the success of this reaction. Addition of LAH to a solution of the succinimide (**7**) led to a low yield of the desired pyrrolidine (**8**), and numerous other by-products could be observed by TLC. Reversing the order of addition (i.e. adding **7** to a solution/mixture of LAH in tetrahydrofuran) gave a striking contrast as the desired product was the only product seen in that reaction. Reduction of the olefin in the pyranoindole (**8**) was effected uneventfully using standard hydrogenation conditions (10% Pd/C, 3 atmospheres hydrogen) affording the second desired conformationally/rotationally restricted analog of serotonin (**2**, 91%, 18% from 5-hydroxyindole).[10]

The two dihydropyrano[3,2-3]indoles (1 and 2) are presently under evaluation for their affinity for receptor subtypes within the family of serotonin receptors. Both 1 and 2 appear to have a similar binding profile to CP-132,484; that is, both compounds appear to behave as selective agonists for the 5-HT_2 family of receptors when compared to serotonin itself. A full evaluation of the pharmacology of these novel conformationally/rotationally restricted analogs (1 and 2) of serotonin will be reported in due course.

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4] Aoyama, T.; Shiori, T. Chem. Pharm. Bull., **1981**, 29, 3249.

5] All new compounds disclosed in this communication have been thoroughly characterized including ^1H NMR, ^{13}C NMR, IR, LRMS, HRMS and/or elemental analysis.

6] The spectral and physical properties of 1 are as follows: mp, 152.0-154.5 °C; IR (KBr) 1620, 1586, 1505 cm^{-1} H NMR ($CDCl_3$) δ 8.50 (br s, NH), 7.07 (d, J=8.7 Hz, 1H), 6.91 (d, J=2.1 Hz, 1H), 6.72 (d, J=8.7 Hz, 1H), 4.20 (t, J= 5.1 Hz, 2H), 3.42 (dd, J= 3.2 and 14.4 Hz, 1H), 3.29-3.15 (m, 3H), 2.72 (dd, J=9.9 and 14.4 Hz, 1H), 2.57-2.49 (m, 1H), 2.49 (s, 3H), 2.34-2.23 (m, 1H), 2.15-2.05 (m, 2H), 1.99-1.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 148.5, 131.3, 125.9, 123.0, 114.5, 113.3, 110.0, 67.1, 65.8, 57.6, 40.8, 32.1, 31.3, 23.1, 22.7, 22.0; LRMS (m/z, relative intensity) 270 (M^+, 29), 239 (5), 170 (18), 84 (100); HRMS calculated for $C_{17}H_{22}N_2O$ 270.1734, found 270.1731; $[\alpha]^{25}_{Na}$ = +97° [c=1, $CHCl_3$]. Anal. calcd for $C_{17}H_{22}N_2O \cdot 1/8\ H_2O$: C, 74.90; H, 8.23; N, 10.29. Found: C, 74.81; H, 8.62; N, 10.26.

7] For example, see: Plug, J.P.M.; Koomen, G.-J.; Pandit, U.K. Tetrahedron Letters, **1992**, 33, 2179.

8] Colonna, M. and Monti, A. Gazz. Chim. Ital., **1962**, 92, 1401.

9] In our hands this reaction has been useful for the synthesis of a number of 3-(indol-3-yl)succinimides, especially when the indoles contain electron rich substituents. The utility of this reaction diminishes when indoles substituted with electron poor substituents are used. We are presently rigorously studying the scope and utility of this reaction.

10] The spectral and physical properties of 2 are as follows: mp, 173.0-176.0 °C; IR (KBr) 1605, 1600, 1585, 1510 cm^{-1}; ^1H NMR (CD_3OD) δ 7.05 (s, 1H), 7.01 (d, J=8.7 Hz, 1H), 6.54 (d, J=8.7 Hz, 1H), 4.89 (s, 1 exchangeable H), 4.08 (t, J=5.0 Hz, 2H), 3.94-3.83 (m, 1H), 3.16-3.04 (m, 3H), 2.87-2.78 (m, 1H), 2.65-2.57 (m, 1H), 2.54-2.47 (m, 1H), 2.38 (s, 3H), 2.36-2.25 (m, 1H), 2.05-1.84 (m, 3H); ^{13}C NMR (CD_3OD) δ 149.3, 133.4, 126.7, 122.0, 119.6, 113.7, 113.5, 111.2, 66.8, 65.4, 56.9, 42.6, 37.2, 35.2, 24.0, 24.0; FAB LRMS (m/z, relative intensity) 257 (MH^+, 100). Anal. calcd for $C_{16}H_{20}N_2O$: C, 75.03; H, 7.87; N, 10.94. Found: C, 75.13; H, 8.16; N, 10.82.

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