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1-Oxo-5-hydroxytryptamine: A Surprisingly Potent Agonist of the 5-HT_3 (Serotonin) Receptor

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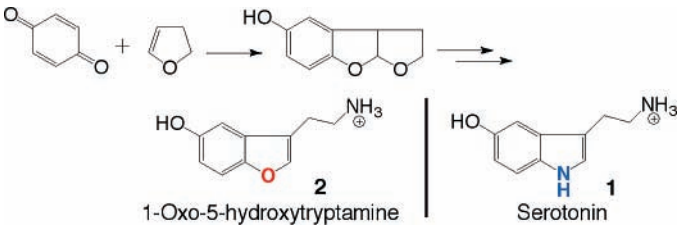
ABSTRACT



A novel synthetic route to 1-oxo-5-hydroxytryptamine, the benzofuran analogue of serotonin, has been developed. The new synthesis proceeds via the [3+2] cycloaddition of *p*-benzoquinone and 2,3-dihydrofuran, followed by a Lewis acid-catalyzed isomerization. This molecule proves to be a competent agonist (equipotent to serotonin) of the 5-HT_3 receptor, demonstrating that the indolic proton of serotonin is not essential to its activation of the receptor.

Following its isolation in 1948,[1] 5-HT (5-hydroxytryptamine, serotonin, **1**) was identified as a key signaling molecule throughout many areas of biology. Derived from the enzymatic hydroxylation−decarboxylation of tryptophan, it can be found in most multicellular organisms, although it is primarily known as a neurotransmitter. In the mammalian CNS (central nervous system), **1** is believed to play an important role in many fundamental processes, such as mood, sexuality, appetite, aggression, sleep, vomiting, and body temperature. Abnormal levels of **1** have been correlated with a variety of disorders, including obsessive−compulsive disorder (OCD), clinical depression, fibromyalgia, tinnitus, bipolar disorder, anxiety disorders, sudden infant death syndrome, and substance abuse.[2,3]

The network of known macromolecular targets of **1** is similarly broad and complex—seven families (and multiple subfamilies) of 5-HT receptors have been identified in humans. All but one of these receptor families are GPCRs (G-protein coupled receptors), with the 5-HT_3 class belonging to the Cys-loop superfamily of LGICs (ligand-gated ion channels).[4,5]

Cys-loop LGICs are characterized by five transmembrane protein subunits arranged symmetrically about an ion-conducting pore. The 5-HT_3 receptor is a cation selective channel that alters its conformation from the resting (non-

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(5) (a) Thompson, A. J.; Lummis, S. C. R. *Curr. Pharm. Des.* **2006**, *12*, 3615. (b) Reeves, D. C.; Lummis, S. C. R. *Mol. Memb. Biol.* **2002**, *19*, 11. (c) Maricq, A. V.; Peterson, A. S.; Brake, A. J.; Myers, R. M.; Julius, D. *Science* **1991**, *254*, 432−437. (d) Greenshaw, A. J. *Trends Pharmacol. Sci.* **1993**, *14*, 265−270. (e) Gyermek, L. *J. Clin. Pharmacol.* **1995**, *35*, 845−855.

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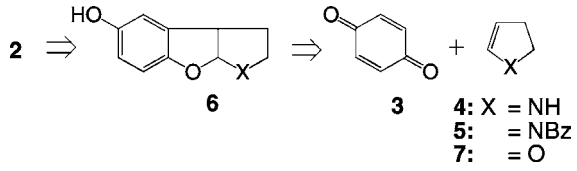
conductive) state to the active (cation-permeable) state upon binding to **1**. As part of our efforts to better understand this key process, we have been mapping out the binding site.[6] We thus became curious as to whether the protic indole nitrogen of **1** forms a hydrogen bond with the receptor as part of its binding interaction.[6a] A valuable probe of this putative interaction would be the benzofuran analogue of **1**, in which an aprotic oxygen replaces the indole nitrogen.

The target molecule is 3-(2-aminoethyl)benzofuran-5-ol, which we will refer to as 1-OT (1-oxo-5-hydroxytryptamine, **2**), for consistency with 5-HT and related compounds. Structure **2** has been synthesized once before,[7] but it has never been explicitly tested on any of the known 5-HT receptors.[8,9] In considering this molecule for our own studies, we felt that the published synthesis (10 steps and <3% yield) was cumbersome, and we chose to pursue a novel synthetic strategy that could provide more ready access to **2**. Identification of the quinone synthon within the target molecule suggested a synthetic route utilizing a [3+2] cycloaddition between *p*-benzoquinone and an electron-rich olefin,[10,11] yielding the properly substituted benzofuran core in a single step (Scheme 1).

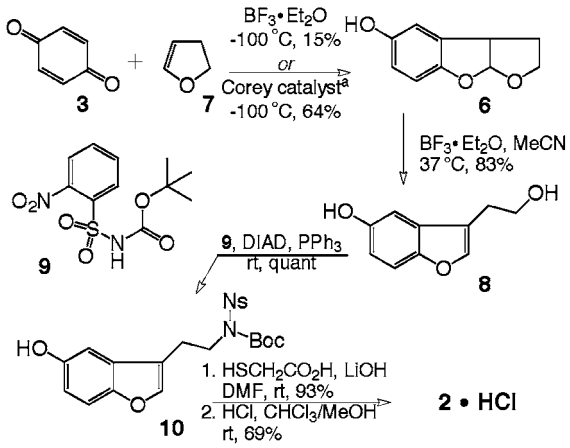
Scheme 1. Retrosynthetic Analysis of 1-oxo-5-hydroxytryptamine



To realize this strategy, we first attempted the cycloaddition of *p*-benzoquinone (**3**) with enamine **4**, which, when subjected to acidic workup conditions, was expected to give ring-opened product **2**. However, consistent with previous reports,[12] we found pyrroline (**4**) very difficult to work with due to its high reactivity (**4** readily forms trimers at room temperature), and we were never able to isolate the desired product from the reaction mixture. We then considered protection of **4** with an electron-withdrawing carbamate or amide to reduce its reactivity; however, the *N*-benzoyl compound **5** failed to react with **3**.

We then considered installing the amine subsequent to the formation of the heterocyclic framework (Scheme 2). Tricycle **6** is a known compound that can be prepared enantioselectively by the formal [2+3] cycloaddition of **3** with 2,3-dihydrofuran (**7**) by using an oxazaborolidine catalyst developed by Corey.[11] We discovered that the same transformation can be accomplished racemically by $BF_3{\cdot}Et_2O$, albeit in much poorer yield. Treatment of the cycloaddition product **6** with concentrated HCl or HBr failed to give **8** or the corresponding primary halide. However, $BF_3{\cdot}Et_2O$ was able to accomplish this transformation in good yield at slightly elevated temperatures. Neither $BF_3{\cdot}Et_2O$ nor a variety of other Lewis acids ($MgBr_2$, $AlCl_3$, $InCl_3$, $ZnBr_2$) proved capable of executing the cycloaddition−isomerization sequence in a single pot.[13]

Scheme 2. Synthesis of 1-Oxo-5-hydroxytryptamine



[a] Reference 11.

Installation of the primary amine by using Fukuyama's modified Mitsunobu protocol[14] worked well, giving the protected amine **10** in quantitative yield. Double deprotection of **10** with basic thioglycolic acid, followed by HCl in

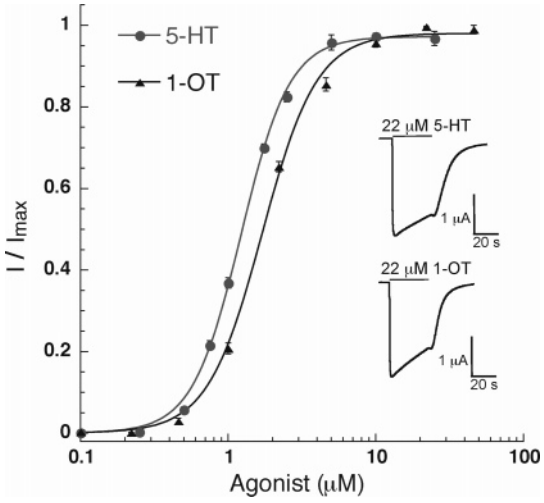


Figure 1. Dose−response curves for 5-HT and 1-OT with sample current traces inset.

(6) (a) Beene, D. L.; Price, K. L.; Lester, H. A.; Dougherty, D. A.; Lummis, S. C. R. *J. Neurosci.* **2004**, *24*, 9097−9104. (b) Bower, K. S.; Price, K. L.; Sturdee, L. F.; Dougherty, D. A.; Lummis, S. Submitted for publication.

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(8) There is one published pharmacological experiment on 1-OT (ref 9): the drug was assayed by measuring the rate of muscular contraction following drug application to surgically removed rat fundus strips.

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chloroform−methanol gave **2**, which could be crystallized from anhydrous ether as its hydrochloride salt in 65% yield from **10**.

The pharmacology of **2** on the 5-HT_3 receptor proved very interesting, as its EC_{50} (effective concentration for half-maximal response) value is nearly identical with that of the native agonist, **1** (1.7 ± 0.06 vs 1.2 ± 0.03 μM, respectively; Figures 1 and 2). Furthermore, **2** is essentially a full agonist,

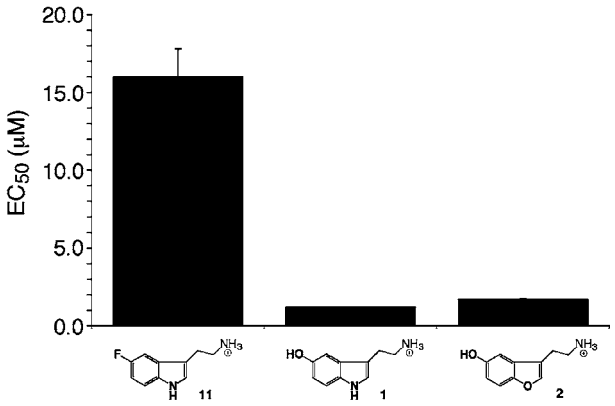

Figure 2. Pharmacology of 5-HT, 1-OT, and 5-FT on the 5-HT_3 receptor.

with an efficacy that is (94 ± 4)% of **1**. Surprisingly, the indole NH of **1** is not required for effective receptor activation. In sharp contrast, another subtle variant of **1**, 5-FT (5-fluorotryptamine, **11**), is a partial agonist with an efficacy of only 30% that of **1** and an EC_{50} that is 10-fold shifted (16 ± 1.8 μM).[6b]

In conclusion, we have established an efficient new route to 1-oxo-5-hydroxytryptamine, the benzofuran analogue of serotonin. We have further shown that this molecule is a competent agonist of the 5-HT_3 receptor, suggesting that the indole nitrogen of **1** does not donate a hydrogen bond to the receptor. The increased availability of **2** afforded by the synthetic route described here will enable similar studies to elucidate agonist binding in the other six classes of 5-HT receptors. In addition, this route should be easily modifiable (through the use of substituted benzoquinones and dihydrofurans) to synthesize more substituted 1-OT derivatives for further elucidation of 5-HT receptor binding sites.

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Supporting Information Available: Full experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR for all synthesized compounds, procedures for the experiments on the 5-HT_3 receptor, and dose−response curves for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) It is further worth noting that when pure **6** was subjected to the isomerization conditions in the presence of quinone **3**, no product **8** could be observed.

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