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Synthesis and activity of functionalizable derivatives of the serotonin (5-HT) 5-HT_{2A} receptor (5-HT_{2A}R) antagonist M100907

Scott R. Gilbertson [a,b,*], Ying-Chu Chen [a], Claudia A. Soto [b], Yaxing Yang [a], Kenner C. Rice [d], Kathryn A. Cunningham [b,c], Noelle C. Anastasio [b,c]

[a] Department of Chemistry, University of Houston, Houston, TX, United States
[b] Center for Addiction Research, United States
[c] Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX, United States
[d] Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse, Bethesda, MD, United States

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ABSTRACT

The approach of tethering together two known receptor ligands, to be used as molecular probes for the study of G protein-coupled receptor (GPCR) systems, has proven to be a valuable approach. Selective ligands that possess functionality that can be used to link to other ligands, are useful in the development of novel antagonists and agonists. Such molecules can also be attached to reporter molecules, such as fluorophores, for the study of GPCR dimerization and its role in signaling. The highly selective serotonin (5-HT) 5-HT_{2A} receptor (5-HT_{2A}R) antagonist M100907 (volinanserin) is of clinical interest in the treatment of neurological and mental health disorders. Here, we synthesized the most active (+)-M100907 enantiomer as well as a series of derivatives that possessed either an alkyne or an azide. The triazole resulting from the dipolar cycloaddition of these groups did not interfere with the ability of the bivalent ligand to act as an antagonist. Thus, we have synthesized a number of compounds which will prove useful in elucidating the role of the 5-HT_{2A}R in the central nervous system.

M100907 (**1**), also known as volinanserin, is a highly selective 5-HT_{2A}R receptor antagonist developed initially by Sanofi-Aventis for the treatment of schizophrenia[1] and sleep disorders.[2] Our group reported that M100907 derivatives substituted at the methoxy group of the catechol ring retain the 5-HT_{2A}R antagonist activity with either the ketone (**2**) or racemic hydroxyl group (**3**) at the benzylic position.[3,4] Reported here is the installation of a polyethylene glycol (PEG) linker substituted at the methoxy group of M100907 and the chiral resolution of the molecule to provide a version of M100907 possessing an ether tether that is terminated with an azide (**4**) or an alkyne (**5**). The azide on (**4**) will be used for future connection to other molecules such as fluorophores, affinity tags and other receptor ligands (Fig. 1).[5,6]

The synthetic route to M100907 developed by Rice[7] was utilized, however, the chiral resolution was carried out at an earlier stage to provide the possibility of introducing different substituents onto the piperidinyl group. The conditions for this resolution were different from previously reported.[7]

The route to M100907-azide **4**, began with the protection of commercially available guaiacol (Scheme 1). Guaiacol was reacted with TBDPSCl, imidazole and catalytic amount of DMAP at room temperature for 24 h to generate compound **6** in 98% yield. The silyl protected **6** was regioselectively *ortho*-lithiated by *n*-butyl lithium with TMEDA for 2 h at room temperature. Then Weinreb amide **7** was added at -70 °C and the mixture was stirred at room temperature for 21 h to produce the ketone **8**. Following reaction with the lithiated **6**, the Boc group of **8** was removed with TFA to give **9**. Sodium borohydride reduction then provided the racemic alcohol **10** (Scheme 1).

Weinreb amide **7** was synthesized from isonipecotic acid (Scheme 2). BOC protection of isonipecotic acid by reaction of ditertbutyldicarbonate, in a mixed solvent of 1,4-dioxane, acetonitrile and water in the presence of 1 N NaOH gave compound **12** which was then reacted with *N,O*-dimethylhydroxylamine hydrochloride, and the coupling reagent HBTU, in the presence of DIPEA to give the desired Weinreb amide **7** in ~80% yield over the two steps.

For the chiral resolution of a later synthetic intermediate by the Rice group,[7] methanol was used as the solvent to obtain the resolved salt with (*R*)-mandelic acid. However, the solubility of the diastereomeric salt formed from compound **10** and (*R*)-mandelic acid was sufficiently high in methanol that the yield of recovered material was low. Using a 1:1 ratio of acetonitrile:methanol for the first recrystallization and 1:2 ratio for the second

* Corresponding author at: Department of Chemistry, University of Houston, Houston, TX, United States.
E-mail address: srgilbe2@central.uh.edu (S.R. Gilbertson).

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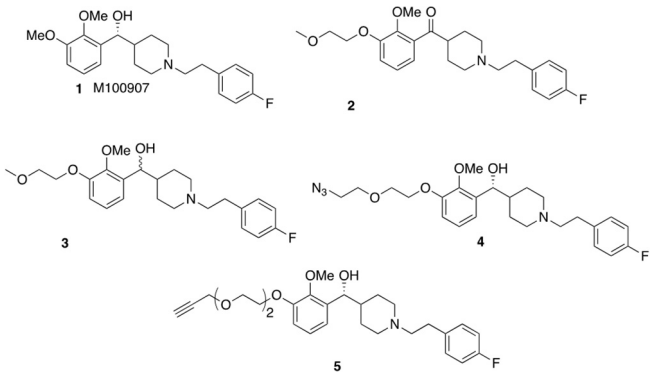


Fig. 1. Structures of M100907 (**1**) and derivatives (**2**–**5**) which retained 5-HT_{2A}R antagonist properties.

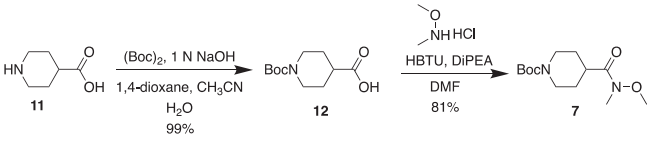
recrystallization, provided one diastereomeric salt in 36% overall yield as white crystals (Scheme 3). Aqueous workup of the diastereomeric salt with ammonium hydroxide afforded the enantiomer in a purity of >95% *ee* (Fig. 2).

The optical purity was evaluated with (*R*)-(−)-1,10- binaphthyl-2,2′-diyl hydrogen phosphate [(−)-BNP] as a ^{1}H NMR shift reagent (Fig. 2).[8] The benzylic proton adjacent to the hydroxyl group gave a doublet near 4.6 ppm that was resolved from all other aliphatic signals. This peak was followed on adding (−)-BNP. When one equivalent of (−)-BNP was added to the racemic **10** in $CDCl_3$, the benzylic signal separated into 2 doublets, with *R*-enantiomer at 4.4 ppm and the S-enantiomer at 4.5 ppm. Chemical shift changes of this signal were linear relative to the concentration of amine and (−)-BNP. Higher concentrations of (−)-BNP resulted in more significant proton shifting but with broadening of the proton signal.[8]

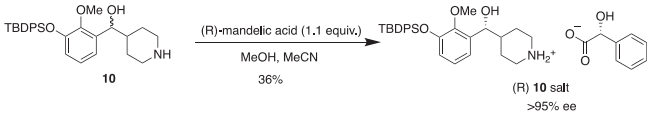
The resolved diastereomeric salt was partitioned between ammonium hydroxide and dichloromethane to obtain a single enantiomer amine (***R*)-10**, which underwent *N*-alkylation with (2-tosylethyl)-4-fluorobenzene **11** to generate compound **12**. Removal of the TBDPS group and reaction with linker **13** provided azide-terminated M100907 (**4**) (Scheme 4).

The alkyne needed to form the homobivalent **15** was synthesized from intermediate **12** through cleavage of the silyl group and alkylation with the tosylated PEG-alkyne **14** (Scheme 5). The bivalent was then synthesized by formation a 1,2,3-triazole ring generated from the dipolar cycloaddition between the azide and the alkyne.[5] This reaction was carried out by adding copper sulfate with sodium ascorbate in a mixture of **4** and **5** DMF and water at room temperature to form the triazole homodimer **15**.

Inhibition of 5-HT_{2A}R-mediated signaling was determined by measuring the reduction of 5-HT (1 μM) stimulated intracellular calcium (Ca^{2+}) release in CHO-K1 cells stably expressing the 5-



Scheme 2. Synthesis of compound **7**.



Scheme 3. Chiral resolution of compound **10**.

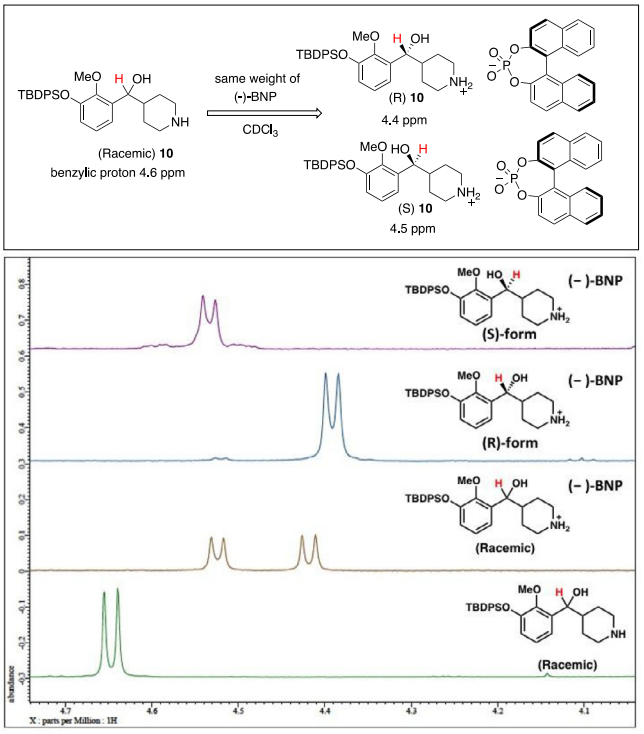
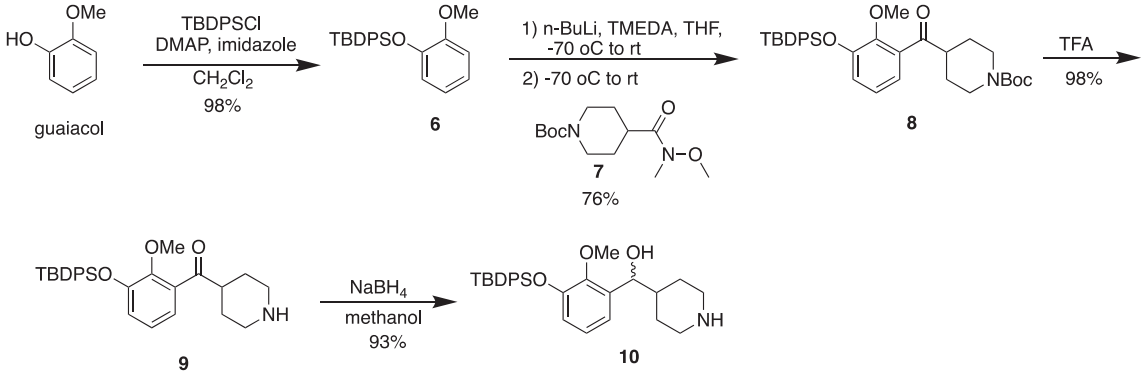


Fig. 2. Determination of the optical purity of **10**. The proton NMR shift of benzylic proton of compound **10** after mixing with same weight of (−)-BNP in $CDCl_3$.

HT_{2A}R.[3,4] Serotonin induces a concentration-dependent increase in Ca_i^{2+} release with an EC_{50} of 4.2 nM ($pEC_{50} = 8.38 \pm 0.10$) and 1 μM of 5-HT exhibited maximal intracellular Ca_i^{2+} release



Scheme 1. Synthesis of the precursor **10** of M100907 derivative **4**.