Synthesis of Hexahydrobenzodipyrans as Ring-Expanded Analogues of Potent Serotonin 5-$HT_{2A/2C}$ Receptor Probes

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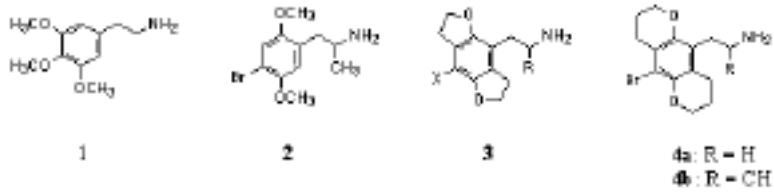
Substituted hexahydrobenzodipyrans were designed as molecular probes for determining the steric restrictions of the agonist binding site of serotonin 5-HT_{2A} and 5-HT_{2C} receptors. The rationale for the design of these novel receptor ligands, and their chemical synthesis, is described here. Upon completion of their synthesis, these compounds will be evaluated for their *in vivo* behavioral activity in rats and for their affinity for cloned human 5-$HT_{2A/2C}$ receptors *in vitro*. The results of these studies will provide information about the three-dimensional structure of the 5-$HT_{2A/2C}$ receptor binding site. Ultimately, this work may provide a better understanding of serotonin-related mental disorders.

INTRODUCTION

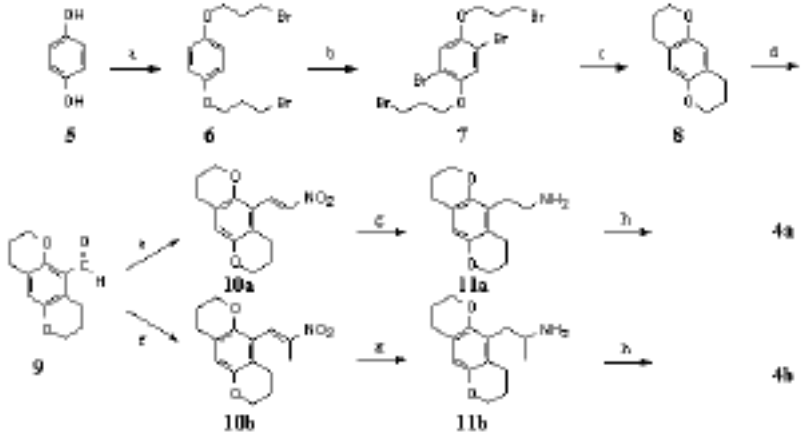
Peyote, a constituent of the *Lophophora* cactus, has been used as a religious sacrament by many Native American tribes in search of religious insight unattainable under normal circumstances. The main psychoactive ingredient in peyote, mescaline (1,3,5-trimethoxy-β-phenethylamine, **1**), was first isolated by Heffter in 1896.[1] Its synthesis in 1919[2] began a series of studies relating hallucinogenic activity to molecular structure.[3,4] The subsequent identification of mescaline's affinity for the serotonin 5-HT_{2A} and 5-HT_{2C} receptor subtypes has lead to its use as a natural template for the design of compounds of modified structures that probe these receptors in order to obtain a better idea as to their functional topography. Successive structure activity relationship (SAR) studies have lead to the synthesis of compounds with the general structure **2**, (R = H, CH_3; X = alkyl, halo, alkylthio, alkoxy, etc.) which contain three major structural features that have been shown to lead to compounds with high affinity for the 5-$HT_{2A/2C}$ receptors.[5] These include; 1) a primary ethyl amine located two carbons from the central aromatic ring, 2) aromatic methoxy groups at the 2 and 5 positions, and 3) a hydrophobic substituent, X, at the aromatic position 4) The presence of a methyl group α to the amine serves to inhibit the ability of monoamine oxidase (MAO) to degrade the molecule, thereby prolonging its action at the receptor site.[6,7] From this general structure, compounds that further characterize the 5-HT_{2A} and 5-HT_{2C} receptors have been designed. The benzodifurans (**3a-b**) were designed as rigid analogues of **2**, with heterocyclic rings that lock the methoxy groups into a specific conformation. These molecular probes served to reveal information concerning the correct binding orientation of the oxygen lone electron pairs.[8] Furthering this rigid analogue approach, the benzodipyrans (**4a-b**) were designed as ring-expanded analogues of **3**. The increased steric bulk of these compounds was predicted to alter their ability to bind to the receptor. Thus, the benzodipyrans were designed to probe the size of the binding pockets within the receptor. We report here the synthesis of 10-bromo-5-(2-aminoethyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran **4a**, and 10-bromo-5-(2-aminopropyl)-2,3,4,7,8,9-hexahydro[1,2b:4,5b']dipyran **4b**.



CHEMISTRY

The synthesis of target molecules **4a** and **4b** is outlined in Scheme 1. Commercially available hydroquinone **5** was alkylated with 1,3-dibromopropane using K_2CO_3 in acetone, and the resulting diether **6** was brominated in methylene chloride using iron catalysis. Tandem cyclization of the tetrabromo compound **7** was accomplished by the addition of *n*-butyllithium at -78ºC, providing the key hexahydrobenzodipyran intermediate **8**. The dipyran **8** was then formylated by reaction with dichloromethyl methyl ether and tin (IV) chloride to provide the aldehyde **9**, which, in turn, was condensed with either nitromethane or nitroethane to give the respective nitroalkenes **10a** and **10b**. Lithium aluminum hydride was then used to reduce the nitroalkenes to their respective amines **11a** and **11b**, which were brominated to form the final target compounds **4a** and **4b**.

Scheme 1[a]



[a] **(a) 1,3-dibromopropane, K_2CO_3, acetone; (b) Br_2, CH_2Cl_2,Fe; (c) n-butyllithium, THF; (d) dichloromethyl methyl ether, $SnCl_4$, CH_2Cl_2; (e) nitromethane, $NH_4^{+-}OAc$; (f) nitroethane, $NH^{+-}OAc$: (g) $LiAlH_4$,THF; (h) Br_2,CH_2Cl_2**

CONCLUSIONS

The described target compounds have been successfully synthesized and are currently undergoing pharmacological evaluation. Preliminary results from the rat, two-lever, drug discrimination assay in which the effects of the test compound are compared with those of LSD, show at least partial activity at the 5-$HT_{2A/2C}$ receptor. Further testing will include radioligand binding data where the test compound will compete directly with the known 5-$HT_{2A/2C}$ receptor agonist, DOI.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded using a Bruker AC300 300 MHz NMR spectrometer, with chemical shifts reported in δ values (ppm) relative to tetramethylsilane (TMS) as an internal reference. Abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, ArH = aromatic hydrogen. IR spectra were taken with a MIDAC Prospect IR, and are reported in cm^{-1}. Thin layer chromatography was performed using silica gel IB2-F (2.5 X 7.5 cm) plates from J. T. Baker Inc.

1,4-bis-(3-bromopropoxy)benzene (6)[9]: Hydroquinone **5** (80 g, 0.7265 moles), 222 mL (3.0 equiv.) of 1,3-dibromopropane, 425g (4.5 equiv.) of K_2CO_3, and 1300 mL of acetone were added to a three liter, three-neck, round-bottom flask equipped with a condenser and mechanical stirrer and stirred at reflux for 24 h. The K_2CO_3 was removed by filtration through celite, and the solvent was removed on the rotary evaporator. The resulting brown solid was taken up in methylene chloride and washed with HH_2O (3 x 100 mL), 3 N NaOH (3 x 100 mL), 3 M HCl (3 x 100 mL), and brine (3 x 100 mL) and dried ($MgSO_4$). The solvent was removed on the rotary evaporator to yield a brown solid, which was crystallized from ethyl acetate and hexane to yield 124.34 g (49%) of 6 as powdery white crystals: mp 68-69 ˚C (lit. mp 71-72˚C); IR: Ar-O-R (1220, 1031); ^{1}H NMR ($CDCl_3$) δ 2.30 (p, 4, $ArOCH_2C\mathit{H}_2C\mathit{H}_2Br$, J=6.0 Hz), 3.52 (t, 4, $ArOC\mathit{H}_2CH_2CH_2Br$, J=7.5 Hz), 4.15 (t, 4, $ArOCH_2CH_2C\mathit{H}_2Br$, J=7.5 Hz

1,4-bis-(3-bromopropoxy)-2,5-dibromobenzene (7): A two liter, three-neck round-bottom flask was equipped with an addition funnel, condenser, N_2 inlet, and magnetic stir bar, and 50.76 g (0.144 moles) of **6**, followed by 600 mL of methylene chloride. A mixture of 15.8 mL (2.14 equiv) of Br_2 and 100 mL of methylene chloride was placed in the addition funnel and added to the reaction vessel dropwise, with stirring, over approximately 1 h. After stirring for an additional 24 h, the mixture was poured into a separatory funnel and washed with 5% $Na_2S_2O_3$ (3 x 75 mL), saturated $NaHCO_3$ (3 x 75 mL), and brine (3 x 75 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed on the rotary evaporator. The resulting dark brown oil solidified when dried under high vacuum, and the solid was recrystalized from ethyl acetate to yield 52.46 g (71%) of **7** as a white powder: mp 115-117 ˚C; IR: Ar-O-R (1216,1066), Ar-Br (1028); ^{1}H NMR (CDCl3) δ 7.4 (s, 2, Ar*H*), 4.0 (t, 4, $ArOCH_2C\mathit{H}_2CH_2Br$), 3.6 (t, 4, $ArOCH_2CH_2C\mathit{H}_2Br$), 2.3 (p, 4, $ArOCH_2C\mathit{H}_2CH_2Br$). Anal. ($C_{12}H_{14}O_2Br_4$) C, H.

2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran (8):[10] The tetrabromo compound, **7**, (30.45 g, 60.00 mmoles) was added to a one liter, three-neck round-bottom flask equipped with a N_2 inlet, and a magnetic stir bar. Approximately 450 mL of anhydrous tetrahydrofuran (THF) was then added, and the mixture was cooled to -100 ˚C. Next, 27.0 mL (5.34 equiv) of 10 M n-butyllithium in hexanes was added slowly so the solution did not warm above -80 ˚C. After holding the reaction mixture at -100 ˚C for 45 min, the solution was warmed to -78 ˚C, and stirred for an additional 4.5 h before being quenched with 75 mL of H_2O. The THF was removed on the rotary evaporator, and the remaining liquid was taken up in ether, placed in a separatory funnel, and washed with H_2O (3 x 50 mL). The organic phase was dried ($MgSO_4$), and the ether was removed to yield a light yellow solid that was recrystallized from ethyl acetate to give 7.63 g (67%) of **8** as white needles: mp 104-106 ˚C (lit mp 105-106 ˚C); IR: Ar-O-R (1235); ^{1}H NMR ($CDCl_3$) δ6.4 (s, 2, Ar*H*), 4.1 (t, 4, ArOCH_2), 2.7 (t, 4, ArOCH$_2$CH$_2$CH_2), 1.9 (p, 4, ArOCH$_2$CH_2CH$_2$). Anal. ($C_{12}H_{14}O_2$) C, H.

5-formyl-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran (9): A 3.277 g (17.2 mmoles) sample of **8** was placed in a 250 mL, three-neck, round-bottom flask equipped with a N_2 inlet and a magnetic stir bar. Approximately 100 mL of methylene chloride was added, and the solution was cooled on an ice bath. Tin (IV) chloride (3.00 mL, 1.5 equiv.) was introduced to the stirred solution via syringe, whereupon the solution turned reddish-brown. Approximately 15 min later, 2.34 mL (1.5 equiv.) of dichloromethyl methyl ether was added, changing the color of the solution to bright pink. After 45 min, the solution was poured into a separatory funnel containing approximately 25 mL of ice and water. The layers were separated and the organic phase was washed with 3 M HCl (2 x 20 mL), H_2O (2 x 20 mL), and brine (1 x 50 mL). The organic layer was dried ($MgSO_4$), and the solution was run through a short flash column of silica gel (100-200 mesh), eluting with methylene chloride. The solvent was then evaporated on the rotary evaporator, yielding a light yellow solid that was recrystalized from ethyl acetate and hexane to yield 3.363 g (90%) of **9** as yellow needles: mp 79-80 ˚C; IR: C=O (1681), ; ^{1}H NMR ($CDCl_3$) δ 10.5 (s, 1, ArCO*H*), 6.7 (s, 1, Ar*H*), 4.1 (t, 2, ArOCH_2, J = 5.1 Hz), 4.05 (t, 2, ArOCH$_2$, J = 5.1 Hz), 3.0 (t, 2, ArOCH$_2$CH$_2$CH$_2$, J = 6.6 Hz), 2.7 (t, 2, ArOCH$_2$CH$_2$CH_2, J = 6.5 Hz), 2.0 (m, 4, ArOCH$_2$CH_2CH$_2$). Anal. ($C_{13}H_{14}O_3$) C, H.

5-(2-nitroethenyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran (10a): The aldehyde **9** (6.51 g, 29.80 mmoles) was placed in a 100 mL, three-neck, round-bottom flask equipped with a N_2 inlet and a magnetic stir bar. Ammonium acetate (3.19 g, 1.39 equiv.) was added to the flask, followed by 30.0 mL of nitromethane. The mixture was stirred at 80 ˚C for 4.5 h before the volatiles were removed under vacuum. The residue was taken up in methylene chloride and washed with 3 N HCl (3 x 25 mL), H_2O (2 x 25 mL), and brine (1 x 25 mL). The product was dried ($MgSO_4$), and the solvent was removed on the rotary evaporator. The crude product was recrystalized from methanol to yield 6.55 g (84 %) of **10a** as orange needles: mp 139-140 ˚C; IR: Ar-O-R (1247), R-NO_2 (1515); ^{1}H NMR ($CDCl_3$) δ 8.1 (d, 1, ArC*H*=C*H*, J = 13.4 Hz), 8.0 (d, 1, ArC*H*=CH, J = 13.5 Hz), 6.6 (s, 1, Ar*H*), 4.24 (t, 2, ArOCH_2, J = 5.2 Hz), 4.0 (t, 2, ArOCH_2, J = 5.1 Hz), 2.8 (t, 2, ArOCH$_2$CH$_2$CH_2, J = 6.7 Hz), 2.7 (t, 2, ArOCH$_2$CH$_2$CH_2, J = 6.4 Hz), 2.0 (m, 4, ArOCH$_v$CH_2CH$_2$). Anal. ($C_{14}H_{15}NO_4$) C, H, N.

5-(2-nitro-1-propenyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran (10b): The aldehyde **9** (10.16 g, 46.50 mmoles) was placed in a 100 mL, three-neck, round-bottom flask equipped with a magnetic stir bar and a N_2 inlet. Ammonium acetate (3.9 g, 1.08 equiv.) was then added, followed by 40 mL of nitroethane. The mixture was stirred at 80 ˚C for 4.5 h before the nitroethane was removed on the rotary evaporator. The remaining residue was taken up in methylene chloride, placed in a separatory funnel, washed with 3 N HCl (2 x 25 mL), H_2O (2 x 25 mL), brine (1 x 25 mL), and dried ($MgSO_4$). After solvent removal under vacuum, the resulting orange solid was recrystalized from methanol to yield 10.68 g (83%) of **10b** as yellow crystals: mp 91-92 ˚C; IR: Ar-O-R (1235), R-NO_2 (1524); ^{1}H NMR ($CDCl_3$) δ 7.8 (s, 1, ArC*H*=C), 6.5 (s, 1, Ar*H*), 4.1 (m, 4, $ArOCH_2CH_2CH_2$), 2.7 (t, 2, $ArOCH_2$, J = 6.5 Hz), 2.5 (t, 2, $ArOCH_2$, J = 6.5), 2.1 (s, 3, ArC*H*=CCH_3), 1.9 (m, 4, $ArOCH_2CH_2CH_2$). Anal. ($C_{15}H_{17}NO_4$) C, H, N.

5-(2-aminoethyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran hydrochloride (11a): $LiAlH_4$ (1.5 g, 39.5 mmoles) was placed in a 500 mL 3-necked round-bottom flask equipped with a condensor, addition funnel, and a mechanical stirrer. A needle was used to transfer 250 mL of anhydrous THF from the original bottle to the flask, creating a grey suspension of $LiAlH_4$. The addition funnel was used to for the dropwise addition of 4.90 g (18.8 mmoles) of the nitrostyrene **10a** dissolved in 200 mL of THF. The mixture was then heated to reflux for 10 hours before being quenched by the addition of 100 mL of 5 M NaOH. A small amount of Celite was added to the mixture before vacuum filtration through Celite. The volatiles were removed *in vacuo* and the residue was taken up in ether and amine was extracted with 3 M HCl (4 x 25 mL). The aqueous solution was then made strongly basic with the addition of 100 mL 5 M NaOH, and the free amine was extracted with CH_2Cl_2 (4 x mL). The organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and the CH_2Cl_2 was removed on the rotary evaporator. The residue was taken up in ether, and the hydrochloride salt was precipitated with the addition of 1 equivalent of a 1.0 M solution of HCl in EtOH. The salt was recrystallized form EtOH and ether yielding 1.172 g (23.12%) of **11a** as a white salt. Anal. ($C_{14}H_{19}NO_2$) C, H, N.

5-(2-aminopropyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran hydrochloride (11b): A double tipped needle was used to transfer 400 mL of anhydrous THF to a 1 L, three-neck, round-bottom flask equipped with a magnetic stir bar, a water cooled condenser, and an addition funnel containing 5.006 g (18.2 mmoles) of **10b** dissolved in 150 mL of anhydrous THF. An ice bath was used to cool the system before an excess of $LiAlH_4$ (4.165 g, 0.110 mmoles) was funneled into the stirring THF. The nitropropene was then added dropwise over the next 1.5 h after which the reaction was heated to reflux for an additional 4.5 h. The reaction was then cooled to approximately room temperature, and quenched by the careful addition of 200 mL of 5 N NaOH. A small portion of Celite was added to the mixture before the solids were filtered off. The filter cake was thoroughly washed with methylene chloride, and the solvents were removed on the rotary evaporator, and the free amine was taken up in ether and washed with 3 M HCl (4x 100 mL). The aqueous extracts were combined and basified with the addition of 100 mL of 5 N NaOH. The amine was extracted by washing with CH_2Cl_2 (4x 100 mL). The organic fractions were combined and washed with brine (2x 200 mL), dried ($MgSO_4$), and the volatiles were removed on the rotary evaporator. The amine was taken up in ether and precipitated as the hydrochloride salt by adding 1

equivalent of a 1.0 M solution of HCl in ethanol, yielding 2.144 g (42%) of **11b** as a white, powder salt. Anal. ($C_{15}H_{20}NO_2$) C, H, N.

10-bromo-5-(2-aminoethyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran hydrochloride (4a): A 0.536 g (1.99 mmoles) sample of the unsubstituted hydrochloride salt **11a** was placed in a 100 mL round-bottom flask, followed by the addition of 40 mL glacial acetic acid as solvent. A magnetic stir bar was used to mix the solution until all of the hydrochloride salt was dissolved. A pipette was then used to add 9.0 mL of a pre-made 0.266 M solution of bromine in acetic acid to the stirring solution. The bromine color slowly disappeared as a white salt gradually precipitated over the next four hours. The acetic acid was then removed *in vacuo*, and the residue was taken up in 3 M HCl and washed with ether (2 x 50 mL). The aqueous layer was made strongly basic with the addition of 5 M NaOH, and the free amine was extracted with CH_2Cl_2 (5 x 20 mL). The organics were then washed with brine (2 x 20 mL), dried ($MgSO_4$), and filtered through Celite. The volatiles were removed on the rotary evaporator, and the free amine was taken up in ether. The product was then precipitated as the hydrochloride salt with the addition of one equivalent of a 1.0 M solution of HCl in EtOH. The salt was recrystallized from EtOH and ether yielding 0.20 g (28.8 %) of **4a** as a white salt. Anal. ($C_{14}H_{19}BrClNO_2$) C, H, N.

10-bromo-5-(2-aminopropyl)-2,3,4,7,8,9-hexahydrobenzo[1,2b:4,5b']dipyran hydrochloride (4b): A portion (1.033 g, 3.64 mmoles) of the unsubstituted hydrochloride salt **11b** was placed in a 100 mL round-bottom flask, followed by the addition of 20 mL glacial acetic acid as solvent. The mixture was stirred with a magnetic stir bar until the solution was almost entirely clear before 7.2 mL of a 0.716 M solution of Br_2 in acetic acid was slowly added. The bromine color slowly disappeared, and a white precipitate was evident over the next 3.5 h. The acetic acid was removed under high vacuum before the residue was taken up in 3 M HCl and washed with ether (2x 50 mL). The aqueous layer was made strongly basic with the addition of 200 mL of 5 N NaOH, and the amine was extracted with CH_2Cl_2 (5x 50 mL). The organics were then washed with brine (2x 50 mL), dried ($MgSO_4$), and the volitiles were removed and the free amine was taken up in ether. The hydrochloride salt (1.034 g, 78%) of **4b** was precipitated as a white salt by the addition of 1.5 equivalents of a 1.0 M solution of HCl in ethanol. Anal. ($C_{15}H_{21}BrClNO_2$) C, H, N.

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