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Ring Substituted Analogues of 5-Aminomethyl-10,11-dihydro-dibenzo[*a*,*d*]cycloheptene (AMDH): Potential Modes of Binding to the 5-HT_{2A} Receptor

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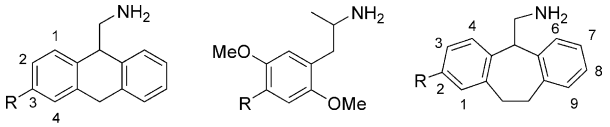
Abstract—The synthesis and 5-HT_{2A} receptor affinities of 2-substituted-5-aminomethyl-10,11-dihydrodibenzo[*a*,*d*]cycloheptene (AMDH) derivatives are described. Comparison of the effects of substitution on affinities allowed assignment of potential binding modes in comparison with DOB-like agonists/antagonists and 3-substituted 1-(aminomethyl)-9,10-dihydroanthracene structures.

We have recently found that the phenylethylamine containing tricyclic compound 1-(aminomethyl)-9,10-dihydroanthracene (AMDA, **1a**, Table 1), is a selective, high affinity 5-HT_2 antagonist.[1–5] Despite having a structural similarity to nonselective classical tricyclic antidepressant and antipsychotic agents, SAR and receptor modeling studies have suggested that AMDA and the classical tricyclic compounds interact differently with the 5-HT_{2A} receptors.[2,3] It has also been suggested that the symmetrically folded aromatic geometry of the parent in the series, AMDA, is nearly optimal for 5-HT_{2A} receptor affinity.[4] In a previous publication, aromatic ring substituted AMDA analogues (**1a–e**, Table 1)[5] were evaluated and compared with 4-substituted 1-(2,5-dimethoxyphenyl)-2-aminopropane analogues of the agonist DOB (**2a–e**, Table 1).[6,7] The SAR data, results of receptor mutagenesis, and computer modeling of potential ligand–receptor binding modes for a variety of 5-HT_{2A} agents suggests that ligands can bind in either of two overlapping sites: Site 1 and Site 2. All data suggest that DOB analogues can bind in either an agonist (interacting with TM3, TM5, and TM6; Site 1) or an antagonist mode (interacting with TM3, TM6 and TM7; Site 2) (Fig. 1) depending on the nature of the substituent.[5,7] AMDA and derivatives are thought to share a binding mode with the antagonist phenylethylamines regardless of the nature of the substituent.[5] The [*a*,*d*] dibenz fused cycloheptane **3a** (AMDH) has an altered aromatic ring geometry compared with AMDA in that AMDH has a pronounced twist in addition to a fold between the two aromatic rings. Given that **3a** has reasonably high affinity for the 5-HT_{2A} receptor and would probably have superior in vivo stability, we evaluated a series of aromatic ring 2-substituted derivatives (**3b–3e**) to examine the generality of the relationships between substituent structure and ligand–receptor binding modes as well as to provide a preliminary estimate of the suitability of AMDH for further optimization.



1a–1e **2a–2e** **3a–3e**

The data in Table 1 indicates that the affinities are much more sensitive to the nature of the substituent within the DOB-like series (**2a–e**; 21,000-fold) than either the AMDA series (**1a–e**; 15-fold) or the AMDH series (**3b–e**; 7-fold). There is no quantitative correlation between the pK_i values for the **3b–3e** series and those in the DOB-like series ($r^2 = 0.0004$) and little correlation between the AMDA series and the DOB-like series

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Table 1. K_i values for compounds **1a–e**, **2a–e**, and **3a–e** at ketanserin labeled 5-HT_{2A} sites

R	Compd	K_i, nM[a]	Compd	K_i, nM[b]	Compd	K_i, nM[c]
–H	**1a**	20	**2a**	5,200	**3a**	110
–Br	**1b**	1.3	**2b**	41	**3b**	37
$-(CH_2)_3Ph$	**1c**	3.2	**2c**	10	**3c**	81
$-C_6H_{13}$	**1d**	7.0	**2d**	2.5	**3d**	630
$-OCH_3$	**1e**	7.5	**2e**	1,200	**3e**	800

[a][^{3}H]Ketanserin labeled cloned 5-HT_{2A} sites. Data from ref 5.
[b][^{3}H]Ketanserin labeled cloned 5-HT_{2A} sites. Data from ref 6.
[c][^{3}H]Ketanserin labeled cloned 5-HT_{2A} sites. Values represent the mean of computer-derived K_i estimates (using LIGAND) of quadruplicate determinations. Standard errors typically range between 15–25% of the K_i value.

($r^2 = 0.32$) suggesting that the tricyclic compounds and the phenylethylamines interact with the receptor in different fashions. The affinity data for the AMDA and AMDH series are not quantitatively parallel by virtue of the parent unsubstituted members of each series, however the limited sensitivity to substitution by a range of substituents with greatly different steric and electronic characteristics is a property shared by both the AMDA and AMDH series. Phenylethylamines with small substituents at the 4-position are 5-HT_{2A} agonists (e.g., **2b**) whereas those with long, bulky substituents (**2c**) are antagonists.[6,7] One possible explanation for the crossover in functional properties is simply that the two classes of phenylethylamines bind with the receptor in different modes. Computational exploration of this possibility has been described.[5] Briefly, binding modes that correspond to multiple superimposition's of agonists such as serotonin and LSD place the aromatic ring of phenylethylamines in proximity with TM5 (Site 1, Fig. 1) where halogens, methyl, ethyl, and propyl substituents are sterically tolerated. Computationally, using both minimization and dynamics simulation methods, phenylethylamines with 4-substituents larger than propyl cause a displacement of the ligand from the site. In fact the longer chain phenylalkylamines are functional antagonists, not agonists.[7] When docked into the ligand binding site, the tricyclic compounds place one phenyl carbon (C3 and C2 for AMDA and AMDH respectively; Site 2) near TM7 and the other (C6 and C8 for AMDA and AMDH respectively; Site 1) very near TM5. Examination of ligand–receptor complex models for both AMDA and AMDH indicates that steric tolerance for C6 and C8 substitution is much less than tolerance for C3 and C2 substitution. In fact, because its central ring is seven membered as opposed to six-membered, AMDH has even less steric tolerance near TM5 than AMDA (Fig. 1).

Because it has smaller dimensions than the tricyclic compounds, small substituents are tolerated when the DOB-like compounds are bound with the 4-substituent in Site 2. But even within the less sterically demanding DOB-like series, large aromatic substituents produce unstable ligand–receptor complex models when the ligand occupies Site 1. AMDH can be docked to the 5-HT_{2A} receptor in a fashion similar to AMDA.

Despite differences in the geometry of central ring, it appears that the 2-substituted-5-aminomethyl-10,11-dihydrodibenzo[*a,d*]cycloheptenes may bind to the 5-HT_{2A} receptor in a fashion similar to that of 5-(aminomethyl)-9,10-dihydroanthracenes with bulky substituents located in the Site 2 defined by TM6 and TM7 of the helical aggregate. This binding mode is distinct from agonist phenylethylamines but similar to antagonist phenylethylamine ligands. These observations strengthen the notion that occupation of Site 2 versus Site 1 may be a characteristic feature determining the functional properties of 5-HT_{2A} ligands and may prove to be a general design principle.

Experimental

Ligand synthesis

The target amine **3a** was prepared as previously described.[8] The ketone precursor (**6b**) of **3b** was obtained as described for the 2-chloro-10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one.[9] The ketone precursor **4** was prepared according a literature method.[10] 2-(Trifluoromethylsulfonyl)oxy-10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one **5** was synthesized from 2-hydroxy-10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one[10] and triflic anhydride in pyridine in 96% yield based on a literature method.[11] Ketones **6c** and **6d** were obtained through a palladium catalyzed cross coupling reaction of the triflate **5** with the 9-BBN derivatives of allylbenzene and 1-hexene respectively in anhydrous THF using K_3PO_4 as the base and $PdCl_2$(dppf) as the

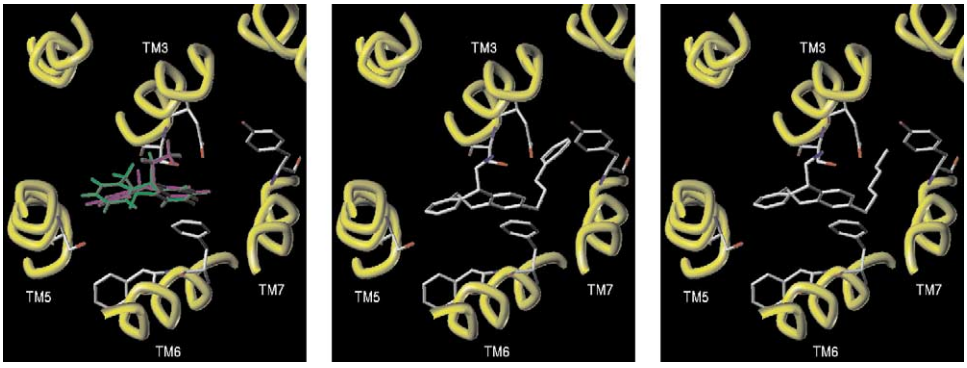


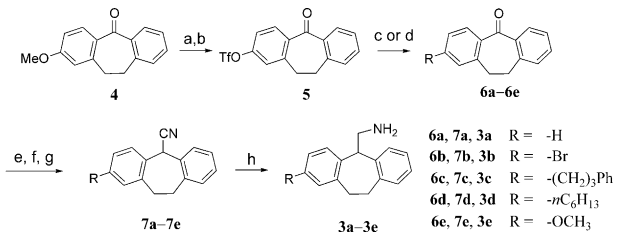
Figure 1. AMDA (**1a**, purple) and AMDH (**3a**, green) bound to the 5-HT_{2A} receptor model (left); compound **3c** with substituent bound in Site 2 (center); Compound **3d** with substituent bound in Site 2 (right).

cross-coupling catalyst in 85% yield based on general cross-coupling methods.[12] Conversion of the ketones to the amines **3b–e** was accomplished through reduction ($NaBH_4$) followed by chlorination ($SOCl_2$) and cyanation (AgCN) to give the respective nitriles **7a–e**. The nitriles were subsequently reduced to the amines using BH_3–THF (Scheme 1).

General method for the synthesis of 2-substitited-5-cyano-10,11-dihydrodibenzo[*a,d*]cycloheptenes. 2-(substituted)-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-one (2.0 mmol) was dissolved in anhydrous CH_3OH (15 mL) and cooled (0 °C). $NaBH_4$ (10.0 mmol) was added in portions and the reaction mixture brought to room temperature and heated at reflux ($1\frac{1}{2}$ h). The solvent was removed under reduced pressure, water (20 mL) added to the residue and the resulting solution was acidified (dil HCl) to pH 4.0 and extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an oil which was dissolved in anhydrous C_6H_6 (15 mL). $SOCl_2$ (10.0 mmol) was added dropwise with stirring and the reaction mixture was heated at reflux ($1^1/_2$ h) and cooled. The solvent was removed under reduced pressure to give a brown oil which was redissolved in anhydrous C_6H_6 (10 mL) and added dropwise to a suspension of AgCN (2.5 mmol) in anhydrous C_6H_6 (20 mL). The reaction mixture was heated at reflux overnight, cooled and filtered. The residue was washed with CH_2Cl_2 and the filtrate was evaporated to dryness under reduced pressure to give a dark brown oil. The oil was purified by mplc using petroleum ether–EtOAc (9:1) as eluent.

2-Bromo-5-cyano-10,11-dihydrodibenzo[*a,d*]cycloheptene (7b). Yield (84%), mp 68–69 °C. ^{1}H NMR ($CDCl_3$) δ 3.13–3.28 (bm, 4H, CH_2), 5.41 (s, 1H, CH), 7.13–7.47 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 31.95, 32.14, 40.88, 119.22, 123.05, 127.61, 127.94, 129.46, 129.46, 129.64, 130.37, 131.20, 134.00, 138.41, 140.91.

5-Cyano-2-(3-phenylpropyl)-10,11-dihydrodibenzo[*a,d*]-cycloheptene (7c). Yield (66%), oil. ^{1}H NMR ($CDCl_3$) δ 1.97–2.05 (m, 2H, CH_2), 2.64–2.74 (m, 4H, CH_2), 3.22–3.42 (m, 4H, CH_2–CH_2), 5.48 (s, 1H, CH), 7.06–7.58 (m, 7H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 32.41, 32.50, 33.42, 35.51, 36.08, 41.23, 119.99, 126.49, 127.44, 128.08, 128.17, 128.28, 129.01, 129.11, 129.23, 131.19, 131.28, 131.46, 134.18, 138.73, 142.73, 143.48.



Scheme 1. (a) $AlCl_3$, C_6H_6; (b) $(CF_3SO)_2O$, C_5H_5N; (c) 9-BBN, allylbenzene, $PdCl_2$(dppf), K_3PO_4, THF; (d) 9-BBN, 1-hexene, $PdCl_2$(dppf), K_3PO_4, THF; (e) $NaBH_4$, CH_3OH; (f) $SOCl_2$, C_6H_6; (g) AgCN, C_6H_6; (h) BH_3–THF, 6.0 M HCl.

5-Cyano-2-n-hexyl-10,11-dihydrodibenzo[*a,d*]cycloheptene (7d). Yield (50%), oil. ^{1}H NMR ($CDCl_3$) δ 1.30–1.35 (t, 3H, CH_3), 1.51–2.29 (brm, 8H, CH_2), 2.55–2.59 (t, 2H, CH_2), 3.16–3.35 (m, 4H, CH_2), 5.47 (s, 1H, CH), 7.13–7.49 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 26.66, 27.44, 27.98, 28.83, 29.97, 30.47, 32.33, 41.45, 124.67, 127.40, 128.06, 129.22, 131.19, 133.80, 138.82.

5-Cyano-2-methoxy-10,11-dihydrodibenzo[*a,d*]cycloheptene (7e). Yield (96%), mp 106–107 °C. ($CHCl_3$-pet.ether). lit.[13] mp 87–88 °C. ^{1}H NMR ($CDCl_3$) δ 3.16–3.36 (m, 4H, CH_2), 3.78 (s, 3H, OCH_3), 5.39 (s, 1H, CH), 6.73–7.48 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 32.30, 32.68, 40.91, 55.86, 112.25, 116.83, 126.02, 127.40, 128.12, 129.17, 129.58, 131.17, 134.21, 139.02, 140.39. Anal. ($C_{17}H_{15}NO$): C, H, N.

General method for the synthesis of 5-aminomethyl-2-(substituted)-10,11-dihydrodibenzo[*a,d*]cycloheptenes. 2-(Substituted)-5-cyano-10,11-dihydrodibenzo-[*a,d*]cycloheptene (1.0 mmol) was dissolved in anhydrous THF (1 mL) and cooled (0 °C). Borane–THF complex (1.0 M soln., 5.1 mmol) was added dropwise with stirring and the mixture was slowly warmed to room temperature and then heated at reflux (8 h). The reaction mixture was cooled and HCl (6.0 M, 3 mL) was added dropwise and the mixture was heated at reflux for another hour, cooled and the solvent was removed under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (20 mL). The aqueous portion was made basic with 10% NaOH and extracted with Et_2O (3×25 mL). The combined Et_2O extracts were washed with water, brine, dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil which was purified by mplc using CH_2Cl_2–CH_3OH (9.5:0.5) as eluent. The products were isolated as their respective salts by treatment with either oxalic or fumaric acid in anhydrous acetone.

5-Aminomethyl-2-bromo-10,11-dihydrodibenzo[*a,d*]cycloheptene fumarate (3b). Yield (82%), mp 204–205 °C (EtOAc-CH_3OH). ^{1}H NMR (DMSO-d_6) δ 2.95–3.32 (brm, 6H, CH_2), 4.36 (brs, 1H, CH), 6.43 (s, 2H, CH), 7.14-7.38 (m, 7H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 32.33, 32.43, 120.30, 126.63, 127.42, 129.19, 130.77, 132.98, 135.93, 142.84, 169.19. Anal. ($C_{16}H_{16}NBr$ 0.50 $C_4H_4O_4$): C, H, N.

5-Aminomethyl-2-(3-phenylpropyl)-10,11-dihydrodibenzo [*a,d*]cycloheptene fumarate (3c). Yield. (62%), mp 159–160 °C (EtOAc–CH_3OH). ^{1}H NMR (DMSO-d_6) δ 1.78–1.86 (m, 2H, CH_2), 2.49–2.60 (m, 4H, CH_2), 2.96–3.26 (m, 4H, CH_2–CH_2), 3.40–3.42 (d, J=6 Hz, 2H, CH_2), 4.40 (bs, 1H, CH), 6.48 (s, 2H, CH), 6.94-7.29 (m, 7H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 32.64, 32.83, 34.57, 35.18, 39.06, 126.07, 126.49, 126.63, 127.56, 128.64, 130.78, 135.33, 141.13, 168.10. Anal. ($C_{25}H_{27}N$·$C_4H_4O_4$) : C, H, N.

5-Aminomethyl-2-*n*-hexyl-10,11-dihydrodibenzo[*a,d*]cycloheptene fumarate (3d). Yield (64%), mp 170–171 °C (EtOAc–CH_3OH). ^{1}H NMR (DMSO-d_6) δ 0.81–0.85 (t, J=6 Hz, 2H, CH_2), 1.17–1.50 (brm, 6H, CH_2), 2.45–2.50

(t, $J = 7.5$ Hz, 2H, CH_2), 2.95-3.42 (brm, 6H, CH_2), 4.44 (bs, 1H, CH), 6.47 (s, 2H, CH), 6.94–7.26 (m, 7H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 14.33, 22.42, 28.80, 31.21, 31.48, 32.61, 35.02, 126.46, 126.61, 127.51, 130.73, 135.62, 141.51, 168.56. Anal. ($C_{17}H_{19}NO.C_4H_4O_4.0.25H_2O$): C, H, N.

5-Aminomethyl-2-methoxy-10,11-dihydrodibenzo[*a*,*d*]cycloheptene oxalate (3e). Yield (82%), mp 197–198 °C (EtOAc–CH_3OH). ^1H NMR (DMSO-d_6) δ 2.96–3.25 (brm, 4H, CH_2), 3.42 (brs, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.41 (s, 1H, CH), 6.72-7.47 (m, 7H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 32.65, 32.79, 55.36, 111.93, 116.12, 126.69, 127.62, 130.91, 139.95, 141.33, 158.75, 165.14. Anal. ($C_{17}H_{19}NO.C_2H_2O_4.\ 0.25H_2O$) : C, H, N.

Molecular modeling. Investigations were conducted using the SYBYL molecular modeling package (version 6.6, 1999, Tripos Associates, Inc., St. Louis, MO). Molecular mechanics minimizations were performed using the Tripos force field with Gasteiger-Huckel charges (distance dependant dielectric constant = 4, non-bonded cutoff = 8) with or without constraints as specified and were terminated at an energy gradient of 0.01 kcal/mol/Å. Typically, initial ligand–receptor complexes were minimized first with backbone atoms constrained to their original positions followed by dynamics equilibration (100 ps), also with fixed backbone constraints. Sample trajectories from dynamics simulations were averaged and the average structures were minimized, first with backbone constraints then with all constraints removed. Unless specified otherwise, sequence numbers for the rat receptor 5-HT_{2A} are listed followed by the bovine rhodopsin numbers in parentheses. An unambiguous alignment of the rhodopsin and 5-HT_{2A} receptor sequences was performed manually by matching the highly conserved residues previously identified.[14,15] The transmembrane (TM) helical segments were extracted from the experimental bovine rhodopsin structure (a chain of 1F88.pdb)[16] retaining the following segments (helix number, 5-HT_{2A} sequence range, rhodopsin sequence range): TM1 72-101(35-64); TM2, 108-137(71-100); TM3, 145-177(107-139); TM4, 190-212(151-173); TM5, 231-225(200-225); TM6, 318-348(247-277); TM7, 360-380(286-306). Mutation of the rhodopsin sequence to that of the 5-HT_{2A} receptor was accomplished using the BIOPOLYMER within SYBYL. Amino acid side-chain geometries for the 5-HT_{2A} receptor model were established from backbone-dependent libraries of rotomer preference using the program SCWRL.[17] The helix backbone geometry of rhodopsin is transferred without change in this procedure. The PROTABLE facility within SYBYL was used to identify sites of unusual geometries.

Affinity determinations. Radioligand binding assays using [^3H]-ketanserin and cloned 5-HT_{2A} receptors were performed as previously described. Data were analyzed with the LIGAND program as previously detailed.[18]

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