Geometry−Affinity Relationships of the Selective Serotonin Receptor Ligand 9-(Aminomethyl)-9,10-dihydroanthracene

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With the exception of its two aromatic rings and basic nitrogen atom, 9-(aminomethyl)-9,10-dihydroanthracene (AMDA; **1**) is remarkably devoid of the pharmacophore features usually associated with high-affinity receptor ligands such as the heteroatom hydrogen bonding features of the endogenous ligand serotonin. AMDA does contain a phenylethylamine skeleton within a tricyclic ring system, and the presence of the second aromatic group is necessary for optimal receptor affinity. The structural requirements for the binding of AMDA at 5-HT_{2A} receptors were investigated with respect to the geometric relationship between the two aromatic rings. It appears that the geometry of the AMDA parent is in the optimal range for fold angle between aromatic moieties. Evaluation of conformationally constrained derivatives of AMDA suggests that a chain extended trans, gauche form is most likely responsible for high affinity.

Introduction

The serotonin (5-hydroxytryptamine; 5-HT) receptor family consists of a large number (>14) of distinct entities that have been identified using cloning technology. Many therapeutically useful drugs have 5-HT receptors as their targets.[1,2] Specifically, 5-hydroxytryptamine$_2$ (5-HT_2) receptors have been implicated as the site of action for hallucinogens, atypical antipsychotic drugs, and certain atypical antidepressants.[1,2] For these reasons, generation of structurally novel agents that interact with 5-HT_2 receptors is of considerable current interest.[3] Typically, simple unsubstituted phenylethylamines show very low affinity for 5-HT_2 receptors (e.g., phenylethylamine, 5-HT_{2A} K_i > 10 000 nM).[4] Some time ago, examination of receptor models suggested that the affinity of structures containing a phenylethylamine skeleton could be enhanced by introducing a second aromatic moiety, perhaps by participating in additional aromatic−aromatic interactions between ligand and receptor.[5] This prompted us to prepare and evaluate 9-(aminomethyl)-9,10-dihydroanthracene (AMDA, **1**, Figure 1) which has proven to be a unique 5-HT_2 selective antagonist that most likely binds to the receptor in a fashion different from that of structurally related, nonselective tricyclic antidepressants.[4,6,7] In fact, AMDA fails to conform[7] to existing pharmacophore models for 5-HT_{2A} antagonists.[8,9] Because of its remarkably simple structure and impressive selectivity,[7] we explored a series of AMDA analogues to determine the importance of the tricyclic ring system, the effects of altering the tricyclic aromatic ring fold angle, and the consequences of restricting conformational freedom of the ligand ammonium ion on 5-HT_2 receptor affinity.

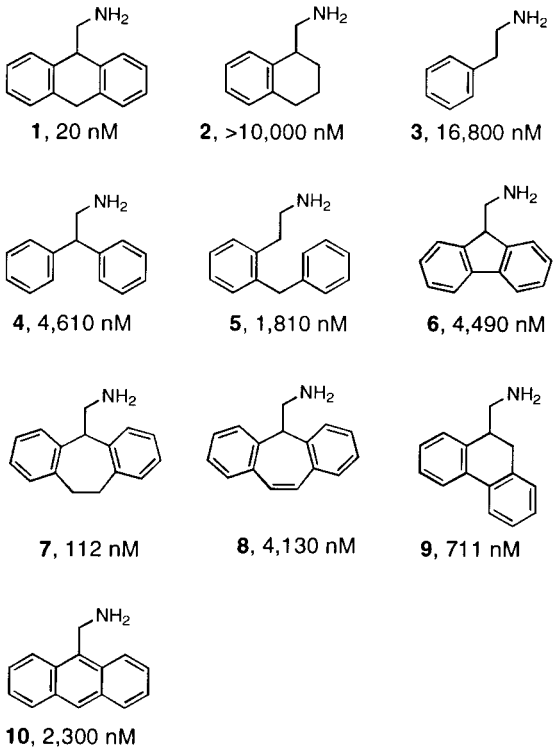

Figure 1. Structures and receptor affinities of compounds **1**−**10** at [^{3}H]ketanserin-labeled cloned 5-HT_{2A} sites. Values represent the mean of computer-derived K_i estimates (using LIGAND) of quadruplicate determinations. Standard errors typically range between 15 and 25% of the K_i value. The K_i values for compounds **1**−**3** (ref 4) and **8** (ref 6) were previously reported.

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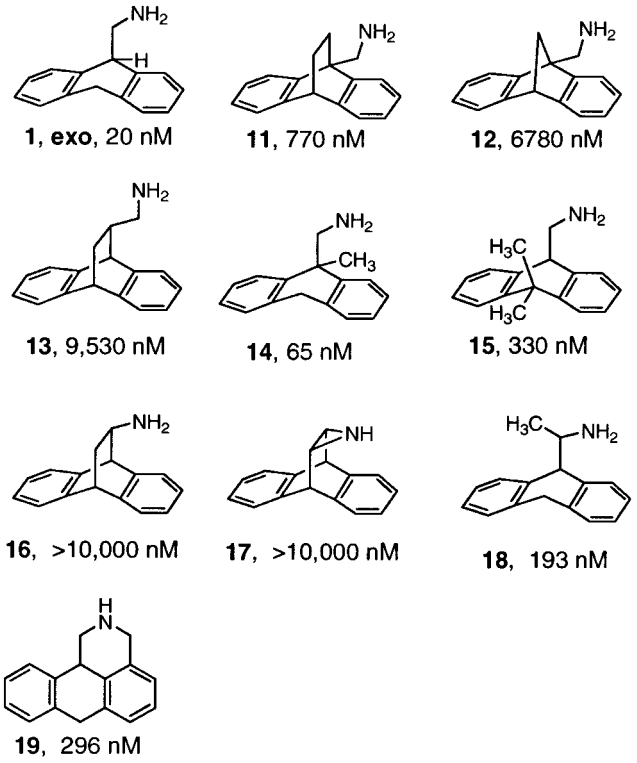
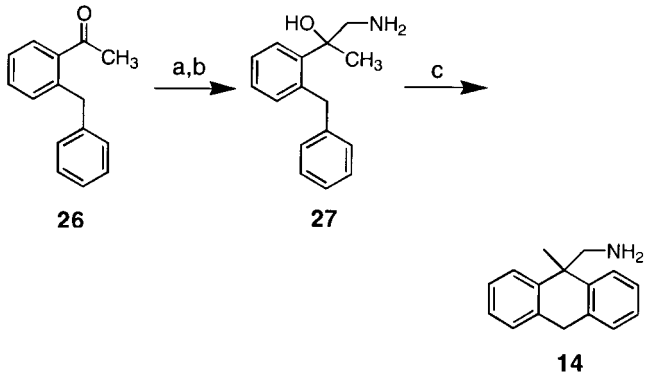


Figure 2. Structures and receptor affinities of compounds **1** and **11**−**19** at 5-HT_{2A} represent the mean of computer-derived K_i estimates (using LIGAND) of quadruplicate determinations at [^{3}H]ketanserin-labeled cloned 5-HT_{2A} sites. Standard errors typically range between 15 and 25% of the K_i value.

Chemistry

All target compounds (**1**−**19**) are shown in Figures 1 and 2. Compounds **3**, **4**, and **13** are commercially available; compound **4** was purchased as a free base and subsequently converted to its HCl salt[10] using ethereal HCl and anhydrous ether. Compounds **1**,[4] **2**,[4] **6**,[11] **7**,[5] **8**,[6] **10**,[12] and **17**,[13] were prepared as previously reported. The preparation of phenylalkyamine **5** was initiated with a BH_3 reduction of commercially available 2-(benzyl)benzoic acid followed by PCC oxidation to provide 2-(benzyl)benzaldehyde in good overall yield. A Henry reaction was then employed to generate 2-(2-benzylphenyl)-*trans*-nitroethene from 2-(benzyl)benzaldehyde and nitromethane. Reduction of the nitrostyrene was accomplished using AlH_4 in THF to provide the target amine **5**. Compounds **9**, **11**, and **12** were all prepared in an analogous manner starting from the reported carboxylic acids (**23**−**25**).[14−16] The desired amides were prepared from the respective acid chlorides via the addition of anhydrous ammonia in THF. The target amines **9**, **11**, and **12** were obtained in good yield following reduction of the amides using either BH_3 or $LiAlH_4$ in THF. The preparation of compound **14** began (Scheme 1) with the formation 2-(benzyl)benzoyl chloride from 2-(benzyl)benzoic acid and $SOCl_2$ in benzene; 2-(benzyl)benzoyl chloride was then treated with CH_3-MgCl in THF to provide 2-(benzyl)acetophenone (**26**) in moderate yield. The conversion of 2-(benzyl)acetophenone (**26**) to 3-amino-2-(2-benzylphenyl)-2-propanol (**27**) was accomplished using trimethylsilyl cyanide and ZnI_2 followed by $LiAlH_4$ reduction. This product was cyclodehydrated to 9-methyl-9-aminomethyl-9,10-dihydroanthracene oxalate (**14**) using Eaton's reagent.

Scheme 1[a]



[a] Reagents and conditions: (a) trimethylsilyl cyanide, ZnI_2, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) Eaton's reagent RT.

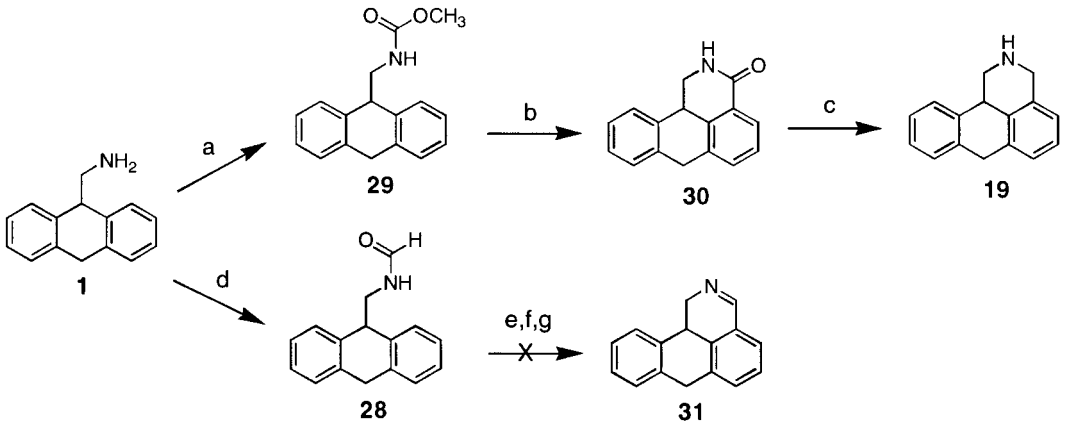
Compound **16** was prepared through catalytic hydrogenation of 9,10-dihydro-9,10-ethanoanthracene-11-one oxime[13] using 10% Pd/charcoal. Synthesis of compound **19** (Scheme 2) was initially attempted through the conversion of **1** to the *N*-formyl derivative **28** with the hope of subsequent cyclization to the dihydroisoquinoline **31**. This route proved unsuccessful under several cyclization conditions. Compound **19** was successfully prepared using the method reported by Grunewald et al. (Scheme 2).[17] Compound **1** was converted into the carbamate **29** using methyl chloroformate followed by cyclization to the amide **30** with $POCl_3$ and $SnCl_4$. The resulting amide **30** was reduced to the amine **19** using BH_3 in THF. Compound **18** was prepared from 9-acetyl-9,10-dihdroanthracene[18] via the reductive amination procedure of Barney et al.[19]

Results and Discussion

With the exception of its two aromatic rings and basic nitrogen atom, AMDA is remarkably devoid of the pharmacophore features usually associated with high-affinity receptor ligands such as the heteroatom hydrogen bonding features of the endogenous ligand serotonin. AMDA (**1**, Figure 1) contains a phenylethylamine skeleton within a tricyclic ring system. The structural requirements for the binding of AMDA (**1**) at 5-HT_{2A} receptors were investigated with respect to the necessity of, and relationship between, the two aromatic rings as well as the effects of altering the aminoalkyl side chain conformation by molecular dissection and elaboration of conformationally constrained derivatives.

Nature of the Tricyclic Ring System. Removing one aromatic ring from AMDA (**1**; K_i = 20 nM) drastically reduces affinity as indicated by the tetrahydronaphthalene **2** (K_i > 10 000 nM). This suggests that the enhanced affinity of AMDA (**1**) over phenylethylamine (**3**; K_i = 16 800 nM) is not due solely to the presence of the central ring. The simple presence of two aromatic rings is also not sufficient for optimal affinity as demonstrated by compounds **4**−**10**. The 2,2-diphenylethylamine **4** (K_i = 4610 nM), while enhanced in affinity compared to phenylethylamine (**3**), has 240-fold lower affinity than AMDA (**1**). Similarly, 2-(2-benzylphenyl)-ethylamine (**5**; K_i = 1810 nM) has a 9-fold greater affinity than phenylethylamine (**3**) but has a 90-fold lower affinity than AMDA (**1**). Thus, it appears that the high affinity of AMDA (**1**) could be attributable to its

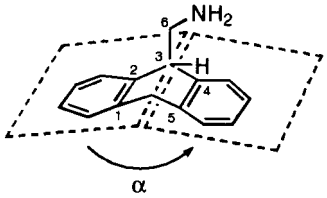
Scheme 2[a]



[a] Reagents and conditions: (a) methyl chloroformate, triethyl amine, CH_2Cl_2; (b) $POCl_3$, reflux 24 h, $SnCl_4$, 6 h; (c) BH_3−THF reflux; (d) formic acid, acetic anhydride; (e) $POCl_3$; (f) PPA; (g) $TiCl_4$.

Table 1. Geometric Parameters and 5-HT_{2A} Receptor Affinities

compd	α (deg)[a]	T_1 (deg)[b]	Ar−N (Å)[c]	N-plane (Å)[d]	T_2 (deg)[e]	K_i (nM)[f]
12	111	0.6	5.3	0.6	172	6780
11	118	2.4	5.3	0.2	173	770
17	120	0	4.7	1.3	122	>10000
16	121	0.7	5.1	1.3	177	>10000
13	121	1.3	5.9	1.3	137	9530
8	123	2.0	5.2	1.3	174	4130
19	137	1.7	5.2	−0.6	170	296
14	142	3.7	5.1	1.8	178	65
18	144	0.9	5.2	1.6	173	193
1	147	1.8	5.2	1.6	177	20
15	155	2.2	5.1	2.0	169	330
10	164	0	4.8	1.8	123	2300
6	174	0	5.1	1.7	169	4490
7	131	31	5.2	1.2	176	112
4		88	5.3	0.3	175	4610



[a] Fold angle α as defined by Rabideau (ref 20). [b] Twist angle C1−C2−C4−C5. [c] Distance between aromatic ring centroid and amine nitrogen. [d] Distance between aromatic ring plane and amine nitrogen. [e] Side chain torsion angle C2−C3−C5−N. [f] [^{3}H]Ketanserin radioligand with cloned 5-HT_{2A} receptors.

tricyclic configuration. However, incorporation of two aromatic rings fused to a central cyclopentane ring produces a compound (**6**; K_i = 4490 nM) that has very low 5-HT_{2A} affinity. The [*a*,*d*]dibenz-fused cycloheptane **7** (K_i = 112 nM) has a lower affinity than AMDA (**1**) but binds reasonably well. The [*a*,*d*]dibenz-fused cycloheptene **8** (K_i = 4130 nM) is reduced in affinity by 37-fold compared to the saturated cycloheptane **7**. The position of the fused aromatic ring is important; the [*a*,*d*]dibenz-fused cyclohexane AMDA (**1**) has 36-fold higher affinity than the [*a*,*c*]dibenz-fused cyclohexane **9** (K_i = 710 nM). The fully aromatic derivative of AMDA, anthracene **10** (K_i = 2300 nM), has 100-fold lower affinity than the dihydro derivative AMDA (**1**). Consideration of the binding data in Figure 1 and Table 1 invites a simple conclusion: Compounds with a nearly coplanar (**6**, **10**) or orthogonal (**4**) orientation of the two necessary aromatic rings have low affinity while compounds with a substantial symmetrical aromatic fold can bind to the receptor with high affinity (Figure 1, Table 1).

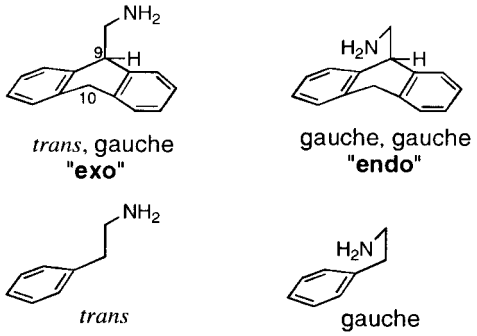


Figure 3. Rotational conformers on AMDA (**1**) and phenylethylamine (**3**).

Conformational Properties of AMDA and Related Tricyclic Compounds. Unsubstituted dihydroanthracene adopts a symmetrical folded structure with 9- and 10-position hydrogens in either a pseudoaxial or pseudoequatorial configuration.[20] Structural information from crystallographic,[21] ^{1}H NMR,[22] and molecular mechanics based conformational analysis[23] indicates that 9-position substituents of 9,10-dihydroanthracene derivatives preferably adopt the pseudoaxial configuration (Figure 3). Molecular mechanics based conformational analysis of the 9,10-dihydroanthracene AMDA performed by ourselves and of 10-aminomethyl-9,10-dihydro-1,2-dihydroxyanthracene[24] in vacuo also suggest the dihydroaromatic system is most likely folded with the aminoalkyl substituent in the pseudoaxial position. The aminomethyl substituent is capable of adopting a trans, gauche (exo) or a gauche, gauche (endo) conformation of nearly equal energies calculated for either the free base or the protonated amine using molecular mechanics. The apparent slight stability of the endo conformer (6.8 kcal/mol; two 1,4 interactions) compared to the exo form (8.0 kcal/mol; one 1,4 interaction) is somewhat unexpected, even though the same behavior was observed with 10-aminomethyl-9,10-dihydro-1,2-dihydroxyanthracene.[24] Since molecular mechanics energy minimizations tend to overemphasize van der Waals interactions when performed in vacuo, often producing artificially compact, folded structures, the conformational analysis using molecular mechanics

in the presence of explicit water and by using semi-empirical molecular orbital methods (AM1, $\Delta E = 2.4$ kcal/mol; MNDO, $\Delta E = 1.2$ kcal/mol) in vacuo were also conducted. In all cases, the endo and exo forms again have similar calculated energies, with the endo form having slightly lower energy, providing further support for conformational flexibility of the aminomethyl substituent of AMDA and the existence of both exo and endo minima. While it is not known which, or if both, rotomers of AMDA contribute to 5-HT_{2A} binding, the CNS activity of arylethylamines is usually attributed to the trans form.[25] Thus, AMDA has a significant symmetrical aromatic fold with relatively free rotation about the aminomethyl−dihydroanthracene bond producing both exo and endo minima (Figure 3). As previously noted, compounds with less than optimal affinity at 5-HT_{2A} receptors have either a nearly planar (**6**, **10**), folded but twisted (**7**), or orthogonal arrangement (**4**) of two aromatic rings (Figure 1). The relationship between biological activity and the nature of a folded tricyclic aromatic ring system has also been noted for tricyclic antipsychotics (phenothiazine and thioxanthene derivatives) and antidepressants (dibenzazepine and cyclopheptadiene derivatives).[26] Phenothiazines and thioxanthenes that have a symmetrical fold of nearly 133−139° (α) and fused ring torsion angle $\tau_1 \sim 0°$ tend to be antipsychotics (presumably D_2 antagonists) while dibenzazepine and dibenzocycloheptadienes that have a folded aromatic configuration (α = 125°) with a distinct twist ($\tau_1 \sim 10°$) tend to be antidepressants (presumably by inhibition of neurotransmitter uptake).[26] Thus, the geometric characteristics of AMDA and AMDA analogues are reminiscent of classical tricyclic agents. The major difference between AMDA and AMDA analogues and classical tricyclic agents is simply that the former contain a phenylethylamine skeleton while the later have a "phenylbutylamine" skeleton.[7]

Variation of the Aromatic Fold Angle (Unrestricted Aminomethyl Rotation). Since AMDA has a significantly folded aromatic tricyclic system with free rotation about the aminomethyl bond, we synthesized and evaluated several AMDA derivatives with varying fold angles α (α as defined by Rabideau[23]) while maintaining a rotatable alkylamine (Figure 2, Table 1). In this series, the fold angle α falls between a maximum of 174° and a minimum of 111°. Some of the compounds in Table 1 have multiple ring conformations; the geometric parameters listed in Table 1 are for the most energetically stable and most exo AMDA-like conformer. Introduction of the ethano (**11**; K_i = 770 nM) and methano (**12**; K_i = 6780 nM) bridges effectively decreases the fold angle (Table 1) but also introduces steric bulk. Since the ethano bridge is tolerated, and **11** has higher affinity than the methano-bridged compound **12**, it is not likely that steric effects are overwhelming. In addition, 9-mono- (**14**) and 10,10-dimethylated (**15**) compounds bind with reasonable affinity (K_i = 65 and 330 nM, respectively), indicating that alkylation at the positions of bridge attachment is sterically tolerated (Figure 1, Table 1). Introduction of the alkyl bridge, as in **11** and **12**, also effectively "inverts" the aminomethyl group to the pseudoequatorial position but still places the amine in reasonable proximity to the amino group of exo AMDA. Similarly, 9- and 10-methylation (**14** and **15**) produce decreased aromatic folding and introduce steric bulk, but methylation produces compounds with reasonable receptor affinity. It should be noted that 9- and 10-alkylation tend to render an energetically reasonable flattened-central-ring conformer as well as the typical boat form. Taken together, the data in Table 1 suggest that there may be some optimum aromatic fold angle near the value for AMDA in the 137−155° range. For compounds with a nearly symmetrical fold ($\tau_1 < 4°$), there appears to be a parabolic relationship between receptor affinity and the fold angle α (for compounds **1**, **6**, **8**, **10**−**15**, **18**, and **19**, $y = yo + ax + bx^2$, $r^2 = 0.65$; this list excludes the "twisted" compounds **4**, **7** and compounds **16**, **17** (which do not have finite K_i values)). Since the AMDA parent is the highest affinity member in the series, it is not yet known whether AMDA has the optimal aromatic ring fold. There is no quantitative relationship (linear or parabolic) between affinity and any of the other geometric parameters listed in Table 1 ($r^2 < 0.3$) and, in most cases, the range of values is small. It is rather remarkable that affinity appears to be sensitive to relatively small changes in aromatic fold angle.

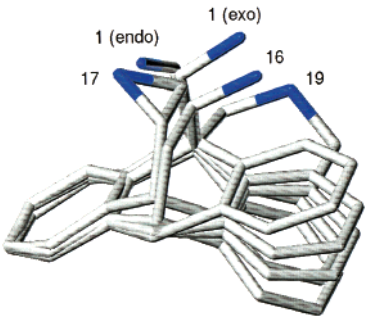


Figure 4. Superimposition of a single aromatic ring from compounds **1** (endo conformation), **1** (exo conformation), and the conformationally restricted AMDA analogues **16**, **17**, and **19**.

Conformationally Restricted AMDA Analogues. Of course, the conformational disposition of all substances is not static, and AMDA most certainly exists as a rapidly interconverting population of species. We have synthesized and evaluated a number of conformationally restricted AMDA variants in an attempt to delineate the "AMDA pharmacophore" (Figure 2). As with any such study, results are complicated by the necessity of introducing additional steric bulk to accomplish a decrease in rotational degrees of freedom, as well as changing other features that may be important (i.e., aromatic ring fold angle). The [2.2.2]bicyclo derivatives **16** and **17** (K_i > 10,000 nM) are both reasonable approximations of the exo and endo aminomethyl-axial AMDA conformers, respectively (Figures 3 and 4), but have no measurable 5-HT_{2A} affinity. Since compound **18** (K_i = 193 nM) does have measurable affinity and binds with only 10-fold lower affinity than AMDA, the α-carbon bridge should be sterically tolerated. It appears that, while reasonable placement of the nitrogen can be achieved, the aromatic fold angle may be too acute (α ∼ 120°) to be compatible with good receptor affinity. The aromatic fold angle of compound **19** is closer to the presumed optimum, and it has reasonably good receptor affinity (K_1 = 296 nM). The

fused piperidine ring of 2,3,7,11*b*-tetrahydrodibenzo-[*d*,*e*,*h*]isoquinoline (**19**) has two possible orientations that place the nitrogen atom either above or below the aromatic plane. On the basis of the geometric considerations discussed above, we suspect that one of the aminomethyl axial conformers may be responsible for the reasonable affinity of the compound although all conformers are accessible and will likely bind to the receptor. It should be noted that none of the conformers of **19** closely resemble the endo form of AMDA. Compound **19** (K_i = 296 nM) has the highest affinity of any conformationally constrained analogue in the AMDA class. This observation is particularly interesting given that 9-methyl AMDA (**14**, K_i = 65 nM, i.e., an equatorial methyl is tolerated) has modest affinity as does *N*-methyl AMDA[7] (K_i = 52 nM), suggesting that methylation is tolerated but decreases affinity. Compound **19** can exist in one of two conformational minima with the aminoalkyl chain either pseudoequitorial ($\alpha = 137°$, $\tau_1 = 1.7°$, $\tau_2 = 170°$; E =14.2 kcal/mol, as shown in Table 1) or a pseudoaxial ($\alpha = 0°$, $\tau_1 = 5°$, $\tau_2 = 157°$, E = 16.8 kcal/mol). While both conformers should be energetically accessible, the former is energetically more stable by about 3 kcal/mol and is most likely the form bound to the receptor. Since compound **19** more closely resembles the exo form of **1** than the endo form, we speculate that the exo conformer of AMDA may be the bound form. It should be noted that while compounds **2**, **9**, **13**, and **16**−**19** are chiral, all were evaluated as their racemates. While **2**, **13**, **16**, and **17** do not show significant affinity, the K_i values for **9**, **18**, and **19** may be underestimated due to evaluation of the racemate.

Conclusion

AMDA is a high-affinity, 5-HT_2 selective antagonist that possesses a geometry inconsistent with previously reported 5-HT_2 antagonist pharmacophore models.[8,9] On the basis of the present studies, it is expected that structural variations that retain a phenylethylamine skeleton in a configuration similar to that of exo AMDA, within a tricyclic system containing two symmetrically folded aromatic rings (fold angle, $\alpha = 137° - 155°$), should have high 5-HT_{2A} affinity. On the basis of the pharmacological properties of AMDA, compounds in this class are expected to function as 5-HT, selective antagonists.

Experimental Section

Synthesis. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained with a Varian Gemini 300 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet Avatar 360 E.S.P. FT-infrared spectrometer. Elemental analysis was performed by Atlantic Microlab, Inc., and determined values are within 0.4% of theory. Thin-layer chromatography (TLC) was performed using silica gel-coated GHLF plates (250 μm, 2.5 × 10 cm, Analtech, Inc., Newark, DE). Anhydrous solvents were purchased and stored under nitrogen over Molecular Sieves. Medium-pressure column chromatography was carried out using silica gel 60, 0.040−0.063 mm (230−400 mesh), Lancaster Synthesis.

2-(2-Benzylphenyl)ethylamine Hydrochloride (5). A solution of 2-(2-benzylphenyl)-*trans*-nitroethene (**22**, 0.50 g, 2.09 mmol) in anhydrous THF (5 mL) was added at 0 °C under N_2 to a stirred suspension of $LiAlH_4$ (0.15 g, 4.18 mmol) and $AlCl_3$ (0.31 g, 2.30 mmol) that was maintained at 0 °C. The suspension was warmed to room temperature and heated at reflux (6 h). The suspension was allowed to cool, and water (0.25 mL), 10% NaOH (0.25 mL), and Celite (1.0 g) were cautiously added. The suspension was filtered through a sintered glass filter, and the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to provide a pale yellow oil (0.43 g). The oil was dissolved in anhydrous Et_2O (55 mL), and 2 mL of anhydrous HCl (1.0 M in Et_2O) was added. The resulting precipitate was collected by filtration, washed with anhydrous Et_2O, and recrystallized from 2-propanol to provide **5** (0.38 g, 75%) as a white powder: mp 167−168 °C (lit.[29] mp 169−170 °C). ^{1}H NMR (DMSO-d_6): δ 2.85−2.96 (m, 4H, CH_2), 4.02 (s, 2H, Ar−CH_2−Ar), 7.15−7.30 (brm, 9H, Ar−H). ^{13}C NMR (DMSO-d_6): δ 30.42, 38.06, 126.32, 127.06, 127.35, 128.75, 129.01, 130.01, 130.79, 136.10, 139.47, 141.03.

9-Aminomethyl-9,10-dihydrophenanthrene Hydrochloride (9). Borane−THF complex (1.0 M in THF, 7.87 mL, 7.87 mmol) was added in a dropwise manner to a stirred solution of 9,10-dihydrophenanthrene-9-carboxamide (**23**, 0.35 g, 1.57 mmol) in anhydrous THF (2 mL) under N_2 at 0 °C. The mixture was slowly warmed to room temperature and then heated at reflux (8 h). The reaction mixture was allowed to cool to room temperature, and HCl (6.0 M, 4 mL) was added with caution. The mixture was heated at reflux (1 h) and allowed to cool to room temperature, and the solvent was removed under reduced pressure. Water (20 mL) was added, and the residue was extracted with EtOAc (20 mL). The aqueous portion was made basic with 10% NaOH and extracted with EtOAc (3 × 25 mL). The combined EtOAc extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.30 g (89%) of the amine as a colorless oil. The oil was dissolved in anhydrous Et_2O (30 mL), and HCl (1.0 M in Et_2O ≈ 1.46 mmol) was added. The precipitate was collected by filtration, dried, and recrystallized (EtOAc/MeOH) to provide **9** (0.18 g) as colorless needles: mp 263−264 °C. ^{1}H NMR (DMSO-d_6): δ 2.69 (brs, 2H, CH_2), 2.98−3.11 (m, 2H, CH_2), 3.33−3.37 (t, J = 7.5 Hz, 1H, CH), 7.29−7.9 (brm, 8H, Ar−H), 8.3 (brs, 2H, NH2). ^{13}C NMR (DMSO-d_6): δ 30.53, 36.06, 41.28, 123.90, 124.53, 127.78, 128.29, 128.46, 128.53, 128.93, 129.96, 133.79. Anal. ($C_{15}H_{15}N$·HCl) C, H, N.

1-(Aminomethyl)dibenzo[*b*,*e*]bicyclo[2.2.2]octadiene Hydrochloride (11). Borane−THF complex (1.0 M in THF) (15 mL, 15.0 mmol) was added under N_2 at 0 °C to a stirred solution of dibenzo[*b*,*e*]bicyclo[2.2.2]octadiene-1-carboxamide (**24**, 1.0 g, 3.74 mmol) in anhydrous THF (5.0 mL). The solution was allowed to warm to room temperature and heated at reflux (10 h). The solution was allowed to cool, HCl (6.0 M, 10 mL) was cautiously added, and the solution was heated at reflux (0.5 h). The solution was allowed to cool to room temperature, made basic with 10% NaOH (≈40 mL), and extracted with CH_2Cl_2 (3 × 45 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a colorless oil. The oil was dissolved in anhydrous Et_2O (40 mL), and ethereal HCl was added until no further precipitate formed. The preciptitate was collected by filtration and washed with anhydrous Et_2O (10 mL) to provide a white solid. The solid was recrystallized from 2-propanol/Et_2O to provide 0.70 g (63%) of **11** as white needles: mp 310−313 °C (lit.[15] mp 313−315 °C). ^{1}H NMR (DMSO-d_6): δ 1.56−1.61 (m, 2H, CH_2), 1.72−1.75 (m, 2H, CH_2), 3.97 (s, 2H, CH_2−NH2), 4.44 (s, 1H, CH), 7.15−7.39 (brm, 8H, Ar−H). Anal. ($C_{17}H_{17}N$·HCl) C, H, N.

9-Aminomethyl-9,10-dihydro-9,10-methanoanthracene Hydrochloride (12). A solution of 9,10-dihydro-9,10-methanoanthracene-9-carboxamide (**25**, 0.50 g, 2.13 mmol) in anhydrous THF (3 mL) was cooled (0 °C), and borane−THF complex (1.0 M in THF) (6.39 mL, 6.39 mmol) was added under N_2. The solution was warmed to room temperature and heated at reflux (6 h). The solution was cooled (0 °C), HCl (6.0 M, 5 mL) was cautiously added, and the mixture was again heated at reflux (0.5 h). The solution was allowed to cool, made basic (10% NaOH, ≈40 mL), and extracted with CH_2Cl_2 (3 × 35 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide an opaque semisolid. The semisolid was dissolved in anhydrous Et_2O (35

mL), and ethereal HCl was added until no more precipitate formed. The white suspension was filtered and the filter cake washed with anhydrous Et_2O (10 mL). The white solid was recrystallized from MeOH/2-propanol to provide **12** (0.28 g, 51%) as white crystals: mp 315−318 °C dec. ^{1}H NMR (CD_3OD): δ 2.37−2.38 (d, J = 1.5 Hz, 2H, CH_2), 3.88 (s, 2H, CH_2−NH_2), 4.19 (s, 1H, CH), 6.77−6.82 (brm, 4H, Ar−H), 7.02−7.11 (brm, 4H, Ar−H). ^{13}C NMR (CD_3OD): δ 39.33, 51.45, 59.35, 69.06, 121.19, 123.61, 126.95, 127.43, 149.80, 153.17. Anal. ($C_{16}H_{15}N$·HCl) C, H, N.

9-Methyl-9-aminomethyl-9,10-dihydroanthracene Oxalate (14). 3-Amino-2-(2-benzylphenyl)-2-propanol (**27**, 0.50 g, 2.07 mmol) was added under N_2 to a stirred solution of Eaton's reagent (10 mL). The mixture was allowed to stir for 3 h at room temperature. The reaction was terminated by gradual addition of water (150 mL). The solution was made basic by addition of 10% NaOH (≈50 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide (0.32 g, 1.43 mmol, 69%) a pale yellow oil. The oil was dissolved in anhydrous acetone (50 mL), and anhydrous oxalic acid (0.14 g, 1.43 mmol) was added. The solution was heated until the solid dissolved, allowed to cool, and filtered. The salt was recrystallized from MeOH/2-propanol to provide **14** (0.28 g) as white flakes: mp 210−211 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (s, 3H, CH_3), 3.20 (s, 2H, CH_2), 4.01−4.08 (d, J = 19 Hz, 1H, Ar−CH_2-Ar) 4.14−4.19 (d, J = 19 Hz, 1H, Ar−CH_2−Ar), 7.25−7.61 (brm, 8H, Ar−H). ^{13}C NMR (DMSO-d_6): δ 24.48, 34.96, 42.28, 46.80, 125.96, 127.08, 127.30, 128.49, 136.53, 139.08, 165.02. Anal. ($C_{16}H_{17}N$·$C_2H_2O_4$) C, H, N.

9-Aminomethyl-10,10-dimethyl-9,10-dihydroanthracene Oxalate (15). A solution of 10,10-dimethyl-9,10-dihydroanthracene-9-carboxamide[34] (**31**, 0.45 g, 1.78 mmol) in anhydrous THF (2 mL) was cooled (0 °C), and 1.0 M borane−THF complex (8.90 mL, 8.90 mmol) was added under N_2. The solution was allowed to warm to room temperature and then heated at reflux (8 h). The suspension was cooled (0 °C), and HCl (6.0 M, 4 mL) was cautiously added to the reaction mixture. The reaction mixture was heated at reflux (1 h), allowed to cool to room temperature, and concentrated under reduced pressure. Water (20 mL) was added, and the resulting white suspension was extracted with EtOAc (20 mL). The aqueous phase was made basic with 10% NaOH and then extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide (0.35 g, 82%) a viscous oil. Oxalic acid (0.15 g, 1.61 mmol) was added to the amine in anhydrous acetone (40 mL), and the suspension was heated until the oxalic acid dissolved. The solution was allowed to cool and was filtered, and the filter cake was washed with anhydrous acetone. The solid was recrystallized from acetone to provide **15** as a white powder: mp 187−189 °C. ^{1}H NMR (DMSO-d_6): δ 1.50 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.87−2.90 (d, J = 9 Hz, 2H, CH_2), 4.21−4.26 (t, J = 9 Hz, 1H, CH), 7.24−7.69 (brm, 8H, Ar−H). ^{13}C NMR (DMSO-d_6): δ 30.58, 36.85, 38.29, 43.80, 49.43, 126.67, 126.76, 127.71, 128.87, 134.41, 144.38. Anal. ($C_{17}H_{19}N$·$C_2H_2O_4$) C, H, N.

11-Amino-9,10-dihydro-9,10-ethanoanthracene Oxalate (16). 10% Pd on charcoal (0.10 g) was added to 9,10-dihydro-9,10-ethanoanthracen-11-one oxime[13] (0.30 g, 1.27 mmol) in MeOH (20 mL). The resulting suspension was hydrogenated at 55 psi. (12 h). The catalyst was removed by filtration through Celite, and solvent was evaporated under reduced pressure to provide an oily solid. Water (10 mL) was added, and the solution was made basic with 10% NaOH and extracted with Et_2O (3 × 25 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide an oily solid. The oily solid was purified by medium-pressure column chromatography using $CHCl_3$/MeOH (9:1) to provide **16** (0.20 g, 71%) as a viscous oil. The oil was dissolved in anhydrous acetone (35 mL), and oxalic acid (0.09 g, 1.00 mmol) was added. The suspension was heated until the solid dissolved, and the solution was allowed to cool; the precipitate was collected by filtration and washed with anhydrous acetone. The solid was recrystallized (anhydrous acetone) to provide **16** (0.09 g) as a white solid: mp 228−229 °C. ^{1}H NMR (DMSO-d_6): δ 1.45−1.49 (d, J = 12 Hz, 1H, CH), 2.13−2.21 (t, J = 12 Hz, 1H, CH), 3.49−3.52 (d, J = 9 Hz, 1H, CH), 4.42 (s, 1H, CH), 4.62 (s, 1H, CH), 7.10−7.39 (brm, 8H, Ar−H). ^{13}C NMR (DMSO-d_6): 833.46, 42.53, 46.81, 49.04, 124.00, 124.79, 126.25, 126.41, 126.62, 126.87, 127.12, 164.93. Anal. ($C_{16}H_{15}N$·$C_2H_2O_4$) C, H, N.

9-(1-Aminoethyl)-9,10-dihydroanthracene Hydrochloride (18). Hexamethyldisilazane (2.17 g, 13.49 mmol), 9-acetyl-9,10-dihydroanthracene[18] (1.0 g, 4.49 mmol), and anhydrous CH_2Cl_2 (40 mL) were placed in a flask equipped with a septum inlet and cooled (0 °C) under N_2. $TiCl_4$ solution (1.0 M in CH_2Cl_2, 2.25 mL, 2.25 mmol) was added in a dropwise manner, and the reaction mixture was allowed to warm to room temperature and stirred (18 h). The reaction was carefully quenched by the dropwise addition of $NaCNBH_3$ (1.7 g, 27.0 mmol) in MeOH (10 mL), and the suspension was allowed to stir for an additional 1 h. The reaction mixture was then made basic with NaOH (5 M) to pH 13 and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide a dark brown oil. The oil was purified with medium-pressure column chromatography using $CHCl_3$/MeOH (9:1) to provide (0.40 g, 40%) a colorless oil. The oil was dissolved in anhydrous Et_2O, and HCl (1.0 M in Et_2O) (1.46 mL) was added. The precipitate was collected by filtration, washed with anhydrous Et_2O, and recrystallized (EtOAc/MeOH) to provide **18** as colorless needles: mp 292−293 °C. ^{1}H NMR (DMSO-d_6): δ 1.03−1.05 (d, J = 6 Hz, 3H, CH_3), 2.99−3.06 (q, J = 13.5 Hz, 1H, CH), 3.85−4.13 (dd, J = 18 Hz, 2H, CH_2), 4.36−4.34 (d, J = 6 Hz, 1H, CH), 7.31−7.7.69 (m, 8H, Ar−H). ^{13}C NMR (DMSO-d_6): δ 16.45, 35.17, 49.61, 50.81, 126.54, 126.86, 127.44, 128.36, 129:24, 129.72, 135.25, 136.21, 137.36, 137.60. Anal. ($C_{17}H_{19}N$·HCl) C, H, N.

2,3,7,11*b*-Tetrahydrodibenzo[*d*,*e*,*h*]isoquinoline Oxalate (19). 2,3,7,11*b*-Tetrahydrodibenzo[*d*,*e*,*h*]isoquinolin-3-one (**30**, 0.30 g, 1.42 mmol) in anhydrous THF (2 mL) was cooled (0 °C) under N_2. A 1.0 M solution of borane−THF complex (7.10 mL, 7.10 mmol) was added in a dropwise manner to the reaction mixture with constant stirring. The reaction mixture was heated at reflux (6 h) and cooled to room temperature. HCl (6.0 M, 4 mL) was cautiously added, and the reaction mixture was heated at reflux (1 h), cooled to room temperature, and concentrated under reduced pressure to provide a white solid. Water (20 mL) was added, and the suspension was extracted with Et_2O (25 mL). The aqueous layer was made basic with 10% NaOH and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide (0.23 g, 83%) a colorless oil. The oil was dissolved in anhydrous acetone (30 mL), and oxalic acid (0.10 g, 1.15 mmol) was added. The suspension was heated until the solid dissolved, it was cooled and filtered, and the filter cake was washed with anhydrous acetone. The solid was then recrystallized (EtOAc/MeOH) to provide **19** as white crystals: mp 196−198 °C. ^{1}H NMR (DMSO-d_6): δ 3.38−3.46 (t, J = 12 Hz, 1H, CH), 3.81−4.10 (brm, 4H, CH_2), 4.36 (brs, 2H, CH_2), 7.10−7.41 (brm, 7H, Ar−H). ^{13}C NMR (DMSO-d_6): δ 33.73, 35.76, 43.64, 44.28, 124.02, 124.60, 126.44, 126.94, 127.60, 128.65, 131.99, 136.38, 137.322, 165.18. Anal. ($C_{16}H_{15}N$·$C_2H_2O_4$) C, H, N.

2-(Benzyl)benzyl Alcohol (20). A solution of 2-(benzyl)-benzoic acid (2.0 g, 9.40 mmol) in anhydrous THF (5 mL) was added under N_2 at 0 °C to a stirred suspension of $LiAlH_4$ (0.70 g, 18.8 mmol) in anhydrous THF (15 mL). The reaction mixture was warmed to room temperature and heated at reflux (4 h). The solution was cooled to room temperature, and water (0.75 mL), 10% NaOH (0.75 mL) and Celite (1.0 g) were cautiously added. The mixture was filtered through a sintered glass filter, and the filter cake was washed with CH_2Cl_2 (75 mL). The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to provide **20** (1.8 g, 97%) as a colorless oil.[27] The oil

was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.87 (brs, 1H, OH), 4. 10 (s, 2H, CH_2), 4.65 (s, 2H, CH_2), 7.15−7.44 (brm, 9H, Ar−H). ^{13}C NMR ($CDCl_3$): δ 39.07, 63.72, 126.77, 127.41, 128.55, 128.93, 129.16, 129.29, 131.17, 139.5, 140.54. IR (KBr): 3353 cm^{-1}.

2-(Benzyl)benzaldehyde (21). A solution of 2-(benzyl)-benzyl alcohol (**20**, 1.8 g, 8.82 mmol) in anhydrous CH_2Cl_2, (20 mL) was added over 30 min to a suspension of PCC (2.2 g, 10.1 mmol) and Celite (2.0 g) in anhydrous CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for an additional 2 h. Anhydrous Et_2O (150 mL) was added, and the dark solution was filtered through a Florisil column. The brown solution was concentrated under reduced pressure and purified by medium-pressure column chromatography using petroleum ether/acetone (9.5/0.5) to provide **21** as a colorless oil[28] (1.40 g, 82%). ^{1}H NMR ($CDCl_3$): δ 4.48 (s, 2H, CH_2), 7.17−7.90 (brm, 9H, Ar−H), 10.28 (s, 1H, COH). ^{13}C NMR ($CDCl_3$): δ 38.62, 126.9, 127.61, 129.19, 129.4, 132.27, 132.66, 134.54, 140.89, 143.60, 193.03. IR (KBr): 1699 cm^{-1}.

2-(2-Benzylphenyl)-*trans*-nitroethene (22). Ammonium acetate (0.39 g, 5.10 mmol) was added to a stirred solution of 2-(benzyl)benzaldehyde (**21**, 1.0 g, 5.10 mmol) in nitromethane (20 mL). The solution was heated at reflux (40 min), and the yellow solution was cooled and concentrated under reduced pressure to provide a yellow solid. The solid was recrystallized from absolute EtOH to provide **22** (0.77 g, 63%) as yellow needles: mp 98−100 °C. ^{1}H NMR ($CDCl_3$): δ 4.14 (s, 2H, CH_2), 7.10−7.54 (brm, 10H, Ar−H, C**H**=CH), 8.29−8.33 (d, J = 14 Hz, 1H, C**H**=CH). ^{13}C NMR ($CDCl_3$): δ 39.90, 127.14, 127.96, 128.15, 129.16, 129.36, 132.05, 132.59, 137.23, 138.47, 140.07, 142.15. IR (KBr): 1512, 1351 cm^{-1}.

9,10-Dihydrophenanthrene-9-carboxamide (23). 9,10-Dihydrophenanthrene-9-carboxylic acid[14] (0.50 g, 2.21 mmol) was dissolved in anhydrous benzene (10 mL) under N_2 and cooled (0 °C) in an ice bath. Thionyl chloride (0.79 g, 6.65 mmol) was added in a dropwise manner with continuous stirring, the reaction mixture was heated at reflux (2 h) and cooled to room temperature, and the solvent was removed under reduced pressure to provide an oil. The oil was dissolved in anhydrous THF (20 mL) and cooled (0 °C) in an ice bath. Anhydrous NH_3 was slowly bubbled into the stirred solution for 0.5 h, and the mixture was stirred at room temperature (2 h). The solvent was removed under reduced pressure to give an oil. Water (20 mL) was added, and the suspension was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil that solidified on standing. The solid was purified by medium-pressure column chromatography using CH_2Cl_2/acetone (8:2) to give a colorless solid. The solid was then recrystallized from toluene to give **23** (0.40 g, 80%) as colorless crystals: mp 144−145 °C. ^{1}H NMR ($CDCl_3$): δ 3.01−3.08 (m, 1H, CH), 3.31−3.38 (m, 1H, CH), 3.63−3.67 (t, J = 6 Hz, 1H, CH), 7.21−7.80 (brm, 8H, Ar−H). ^{13}C NMR ($CDCl_3$): δ 32.36, 46.30, 124.18, 125.01, 127.97, 128.59, 128.73, 128.89, 129.58, 176.04.

Dibenzo[*b*,*e*]bicyclo[*2.2.2*]octadiene-1-carboxamide (24). Thionyl chloride (1.9 g, 16.0 mmol) was added under N_2 to a stirred solution of dibenzo[*b*,*e*]bicyclo[*2.2.2*]octadiene-1-carboxylic acid[15] (2.0 g, 8.00 mmol) in anhydrous toluene (10 mL). The solution was heated at reflux (2 h), cooled, and concentrated under reduced pressure to provide a pale yellow oil. The oil was dissolved in anhydrous THF (50 mL), cooled (0 °C) in an ice bath, and NH_3 was bubbled into the solution for 0.5 h. The solution was allowed to warm to room temperature (2 h). The white suspension was poured into water (50 mL) and extracted with $CHCl_3$ (3 × 45 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a white solid. The solid was recrystallized from absolute EtOH to provide **24** (1.6 g, 75%) as white crystals: mp 259−261 °C. ^{1}H NMR ($CDCl_3$): δ 1.75−1.80 (m, 2H, CH_2), 1.89−1.93 (m, 2H, CH_2), 4.39 (s, 1H, CH), 6.00 (brs, 1H, NH_2), 6.19, (brs, 1H, NH_2), 7.17−7.56 (brm, 8H, Ar−H). IR (KBr): 3440, 3179, 1655, cm^{-1}. Compound **24** was used without further characterization in the preparation of **11**.

9,10-Dihydro-9,10-methanoanthracene-9-carboxamide (25). Thionyl chloride (1.0 g, 8.48 mmol) was added under N_2 to a stirred solution of 9,10-dihydro-9,10-methanoanthracene-9-carboxylic acid[16] (1.0 g, 4.24 mmol) in anhydrous toluene (5 mL). The solution was heated at reflux (2 h), cooled to room temperature, and concentrated under reduced pressure to provide a pale yellow oil. Anhydrous THF (45 mL) was added, and the solution was cooled (0 °C). NH_3 was slowly bubbled into the solution (0.5 h), and the solution was allowed to warm to room temperature (1 h). Water (100 mL) was added, and the suspension was extracted with $CHCl_3$ (3 × 40 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a white solid. The solid was recrystallized from absolute EtOH to provide **25** (0.80 g, 85%) as white needles: mp 310−313 °C dec. ^{1}H NMR ($CDCl_3$): δ 2.77−2.78 (d, J = 1.6 Hz, 2H, CH_2), 4.35 (s, 1H, CH), 5.80 (brs, 2H, $CONH_2$), 6.95−7.58 (brm, 8H, Ar−H). IR (KBr): 3421 cm^{-1}. Compound **25** was used without further characterization in the preparation of **12**.

2-(Benzyl)acetophenone (26). Thionyl chloride (2.8 g, 23.6 mmol) was added under N_2 to a stirred solution of 2-(benzyl)-benzoic acid (2.5 g, 11.8 mmol) in anhydrous benzene (50 mL). The solution was heated at reflux (2 h), allowed to cool, and the excess benzene and thionyl chloride were removed under reduced pressure. The resulting yellow oil in anhydrous THF (50 mL) was cooled (−78 °C), and methylmagnesium chloride (3.0 M solution in THF) (4.0 mL, 12 mmol) was slowly added under N_2. The stirred mixture was allowed to warm to room temperature (8 h). The solution was poured into water (100 mL) and extracted with EtOAc (3 × 75 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by Kuhgelrohr distillation to provide a solid (bp 153 °C, 0.02 mmHg). The solid was recrystallized from EtOAc/petroleum ether to provide **26** (1.5 g, 59%) as white needles: mp 47−49 °C (lit.[30] mp 48−49 °C). ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.13−7.67 (brm, 9H, Ar−H). ^{13}C NMR ($CDCl_3$): δ 30.36, 39.79, 126.51, 126.77, 128.88, 129.54, 129.68, 131.95, 132.36. IR (KBr): 1683 cm^{-1}.

3-Amino-2-(2-benzylphenyl)-2-propanol (27). Trimethylsilyl cyanide (0.57 g, 5.71 mmol) was added under N_2 to a suspension of 2-(benzyl)acetophenone (**26**, 1.0 g, 4.76 mmol) and ZnI (cat. amt.) in anhydrous CH_2Cl_2 (5 mL). The solution was heated at reflux (3 h), allowed to cool to room temperature, and poured into water (100 mL). The resulting suspension was extracted with CH_2Cl_2 (3 × 60 mL), and the organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a pale yellow oil. The oil in anhydrous THF (5 mL) was added to an ice-cold suspension of $LiAlH_4$ (0.54 g, 14.3 mmol) in anhydrous THF (25 mL). The reaction mixture was allowed to warm to room temperature and heated at reflux (8 h). The solution was cooled (0 °C), and water (0.54 mL), 10% NaOH (0.54 mL), and Celite (1.25 g) were added cautiously. The suspension was filtered through a sintered glass filter and the filter cake washed with CH_2Cl_2 (100 mL). The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to provide a white solid. The solid was recrystallized (toluene) to provide **27** (0.70 g, 61%) as fine white needles: mp 114−116 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3H, CH_3), 2.72−2.77 (d, J = 13 Hz, 1H, CH_2−NH_2), 3.25−3.28 (d, J = 13 Hz, 1H, CH_2-NH_2), 4.30−4.36 (d, J = 16 Hz, 1H, Ar−CH_2−Ar), 4.40−4.46 (d, J = 16 Hz, 1H, Ar−CH_2-Ar), 7.08−7.45 (brm, 9H, Ar−H). ^{13}C NMR ($CDCl_3$): δ 28.48, 40.40, 52.24, 75.24, 126.29, 126.76, 127.00, 127.6, 128.89, 129.34, 133.91. IR (KBr): 3123 cm^{-1}. Compound **27** was used without further characterization in the preparation of **14**.

***N*-(Methoxycarbonyl)-9-aminomethyl-9,10-dihydroanthracene (29).** 9-(Aminomethyl)-9,10-dihydroanthracene (**1**,[1] 1.3 g, 6.00 mmol) and triethyl amine (1.25 mL, 9.01 mmol) in anhydrous CH_2Cl, (25 mL) were cooled (0 °C) under N_2. Methyl chloroformate (0.62 g, 6.61 mmol) was added to the reaction mixture in a dropwise manner with constant stirring over 5

min. The reaction mixture was gradually allowed to warm to room temperature and then heated at reflux (0.5 h). The reaction was allowed to cool to room temperature, and the solvent was removed under reduced pressure to provide an oily solid. Water (20 mL) was added, and the suspension was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide a pale white solid. The solid was recrystallized (EtOAc/petroleum ether) to provide **29** (1.4 g, 86%) as colorless crystals: mp 96−97 °C. ^{1}H NMR ($CDCl_3$): δ 3.27−3.31 (t, J = 6 Hz, 1H, CH), 3.66 (s, 3H, CH_2), 3.87−4.13 (m, 4H, Ar−CH_2−Ar, CH, NH_2), 4.69 (s, 1H, NH), 7.19−7.49 (m, 8H, Ar−H). ^{13}C NMR ($CDCl_3$): δ 35.53, 44.89, 125.18, 126.79, 127.38, 127.68, 128.73, 132.14, 135.01, 136.08, 167.83. Compound **29** was used without further characterization in the preparation of **30**.

2,3,7,11*b*-Tetrahydrodibenzo[*d*,*h*,*e*]isoquinolin-3-one (30). *N*-(Methoxycarbonyl)-9-amino-methyl-9,10-dihydroanthracene (**29**, 0.65 g, 2.43 mmol) was added to ice cold $POCl_3$ (11 mL) under N_2. The solution was allowed to warm to room temperature and heated at reflux (24 h). The solution was cooled (0 °C), and $SnCl_4$ (0.94 g, 3.64 mmol) was added in a dropwise manner. The reaction mixture was held at 0 °C for 4 h and slowly allowed to warm to room temperature (2 h). The reaction mixture was poured onto ice (50 g), and the suspension was allowed to stir (0.5 h). The suspension was extracted with EtOAc (3 × 25 mL), and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide a brown solid that was purified by medium-pressure column chromatography (CH_2Cl_2/acetone, 9:1). The resulting yellow solid was recrystallized (EtOAc/petroleum ether) to provide **30** (0.38 g, 73%) as pale white crystals: mp 112−113 °C. ^{1}H NMR ($CDCl_3$): δ 3.61−3.70 (t, J = 12 Hz, 1H, CH), 4.04 (brs, 2H, CH_2), 4.24−4.26 (d, J = 6 Hz, 1H, CH_2), 4.27−4.29 (d, J = 6 Hz, 1H, CH_2), 7.21−8.07 (brm, 7H, Ar−H). ^{13}C NMR ($CDCl_3$): δ 35.53, 44.89, 125.18, 126.79, 127.38, 127.68, 128.73, 132.14, 135.01, 136.08, 167.83. Compound **30** was used without further characterization in the preparation of **19**.

Molecular Modeling. 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 dependent dielectric constant ϵ = 4, nonbonded cutoff = 8Å) without constraints and were terminated at an energy gradient of 0.005 kcal/mol. Systematic conformational analysis was performed for structures having free rotation about single bonds. Conformational analysis of cyclic systems was performed using molecular dynamics based simulated annealing followed by minimization of the resulting structures.

Affinity Determinations. Binding assays and data analysis were performed as previously described using [^{3}H]-ketanserin as the radioligand and stably transfected NIH3T3 cells expressing the 5-HT_{2A} receptor (GF-62 cells).[32] All compounds were tested as the water soluble salts except **17**. The test compound was introduced into buffered assay mixtures from DMSO stock solutions. Under these conditions, homogeneous aqueous solutions of **17** were generated without subjecting the aziridine to acidic conditions.

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