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Structural determinants for high 5-HT$_{2A}$ receptor affinity of spiro[9,10-dihydroanthracene]-9,3′-pyrrolidine (SpAMDA)

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Abstract—The synthesis and 5-HT$_{2A}$ receptor affinities of ring altered derivatives of spiro[9,10-dihydroanthracene]-9,3′-pyrrolidine (**4**), a structurally unique tetracyclic 5-HT$_{2A}$ receptor antagonist, are described. The characteristics of the parent compound prove to be necessary for optimal 5-HT$_{2A}$ receptor affinity. However, expansion of the size of the pyrrolidine and central rings produce compounds with reasonably high 5-HT$_{2A}$ receptor affinities. In addition, the parent compound is shown to have high 5-HT$_2$ receptor selectivity.

We have previously found that the phenylethylamine-containing tricyclic compound 1-(aminomethyl)-9,10-dihydroanthracene (AMDA, **1**, Fig. 1) is a selective, high affinity 5-HT$_2$ antagonist.[1–5] In the course of investigating the structure–affinity relationships for derivatives based on the AMDA skeleton, we demonstrated that both 9-methylation and N-methylation (**2**, **3**, Fig. 1) decrease affinity only slightly. We have recently found that the tetracyclic compound spiro[9,10-dihydro-anthracene]-9,3′-pyrrolidine (SpAMDA, **4**, Fig. 1) conceptually derived by homologation and cyclization of either **2** or **3**, is a high affinity 5-HT$_{2A}$ antagonist.[6] It has been demonstrated that both aromatic rings of AMDA are necessary for optimal activity and that compounds with the highest affinity have a symmetrical fold between the aromatic moieties. The aminoalkyl side chain of AMDA most likely adopts an axial configuration with two energetically accessible side chain rotomers, one folded (*endo*) and the other extended (*exo*).[4] Receptor modeling, ligand structure–affinity relationships, and site-directed mutagenesis studies suggest that AMDA and AMDA derivatives bind 5-HT$_{2A}$ receptors at a site that may be overlapping with but is distinct from the site for typical 5-HT$_{2A}$ receptor antagonists.[5] As demonstrated for AMDA, SpAMDA does not conform to existing pharmacophore models for 5-HT$_{2A}$ receptor antagonists.[6] SpAMDA can exist as any of four energetically equivalent minima, all of which resemble the *exo* form of AMDA more closely than the *endo* form.[6] Although AMDA (**1**) and SpAMDA (**4**) share a

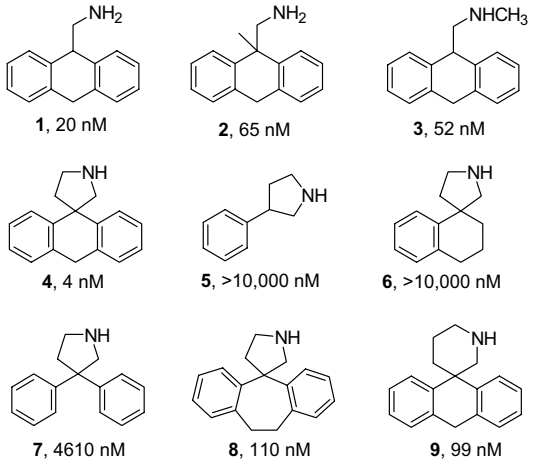

Figure 1. Structures and receptor affinities of compounds **1**–**9** at [^{3}H]ketanserin-labeled cloned 5-HT$_{2A}$ sites. Values represent the mean of computer-derived K_i estimates (using LIGAND) of quadruplicate determinations. Standard errors typically range between 15 and 25% of the K_i values. The K_i values for compounds **1**–**4** were previously reported (Refs. 3, 4, and 6).

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common tricyclic amine fragment, it was necessary to evaluate the dependence of receptor affinity on structural features common to the tricyclic AMDA and the tetracyclic SpAMDA compounds before optimization of SpAMDA like compounds could be carried out in a rational way.

The fact that **5** has no measurable affinity for 5-HT_{2A} receptors (**5**; $K_i > 10,000$ nM) suggests that the phenylpyrrolidine fragment of SpAMDA is not sufficient for binding. Removing one aromatic ring from SpAMDA (**4**; $K_i = 4$ nM) drastically reduces affinity as indicated by the tetrahydronaphthalene **6** ($K_i > 10{,}000$ nM). This suggests that the enhanced affinity of SpAMDA (**4**) over phenylethylamine ($K_i = 16{,}800$ nM), and the phenylpyrrolidine 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 compound **7**. The 3,3-diphenyl-pyrrolidine **7** ($K_i = 4610$ nM), while enhanced in affinity compared to phenylethylamine, has 1200-fold lower affinity than SpAMDA (**4**). The [*a*,*d*]dibenz-fused cycloheptane **8** ($K_i = 110$ nM) has a lower affinity than SpAMDA (**4**) but binds reasonably well suggesting that with SpAMDA, as has been demonstrated with AMDA, compounds with a substantial symmetrical aromatic fold can bind to the receptor with high affinity. Expansion of the spiropyrrolidine of SpAMDA to a spiropiperidine **9** results in a modest decrease in affinity (25-fold). Thus, it appears that both the presence and orientation of two aromatic rings in a tricyclic configuration, and a basic amine constrained within a spiropyrrolidine system, are necessary for optimal affinity. Although there is a superficial similarity between SpAMDA and classical tricyclic antidepressants, the lack of a common pharmacophore between AMDA and SpAMDA and classical agents suggests that SpAMDA may bind to 5-HT_{2A} receptors in a different manner. The difference between SpAMDA and other tricyclic agents is further supported by selectivity data (Table 1). Given the high degree of receptor sequence homology between the 5-HT_{2A} and 5-HT_{2C} receptors, it is not surprising that SpAMDA shows little selectivity (6-fold) between the subtypes. SpAMDA is, however, remarkably selective for 5-HT_{2A} receptors versus dopamine D_2 receptors and serotonin (SERT) and norepinephrine (NET) transporters, sites at which many tricyclic antidepressants bind.

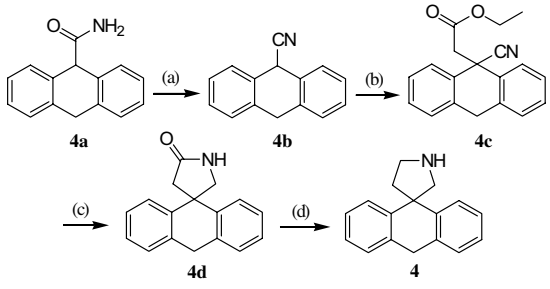
1. Ligand synthesis

9,10-Dihydroanthracene-9-carboxamide[7] (**4a**) on treatment with $POCl_3$ gave 9-cyano-9,10-dihydro anthracene (**4b**), which was alkylated using $C_2H_5OCOCH_2Br$ in presence of C_2H_5ONa/C_2H_5OH to give (9-cyano-9,10-dihydroanthracen-9-yl)-acetic acid ethyl ester (**4c**). The ester **4c** was then subjected to reductive cyclization using 10% Pd/C in presence of HCl in CH_3OH to give spiro[9,10-dihydroanthracene]-9,4′-pyrrolidin-2′-one (**4d**), which was further reduced to spiro[9,10-dihydroanthracene]-9,3′-pyrrolidine (**4**) using BH_3–THF complex (Scheme 1).

3-Phenyl pyrrolidine (**5**) was synthesized starting from phenyl-succinonitrile according to a literature method.[8] Spiro[1,2,3,4-tetrahydronaphthalenyl)-1,3′-pyrrolidine (**6**), 3,3-diphenylpyrrolidine (**7**), and spiro(10,11-dihydro-dibenzo[*a*,*d*]cycloheptene)-5,3′-pyrrolidine (**8**), were synthesized by the method adopted for **4** starting from 1-cyano-1,2,3,4-tetrahydronaphthalene,[9] diphenyl acetonitrile, and 5-cyano-10,11-dihydrodibenzo[*a*,*d*]-cycloheptene[10], respectively. Spiro[9,10-dihydroanthra-cene]-9,3′-piperidine (**9**) was synthesized from **4b** using $C_2H_5OCO(CH_2)_2Br$ as the alkylating agent.

1.1. 9-Cyano-9,10-dihydroanthracene (4b)

$POCl_3$ (5.5 mL, 59 mmol) was added to crystalline 9,10-dihydroanthracene carboxamide (0.54 g, 2.43 mmol)



Scheme 1. (a) $POCl_3$, NH_4OH (b) $EtOCOCH_2Br$, EtONa/EtOH; $EtOCOCH_2CH_2Br$, EtONa/EtOH for (**9**) (c) 10% Pd/C, H_2, MeOH, HCl (d) BH_3–THF, 6.0 M HCl.

Table 1. Receptor and transporter selectivities of SpAMDA (**4**) and classical tricyclic agents

Compound	K_i, nM				
	5-HT_{2A}[a]	5-HT_{2C}[b]	D_2[c]	SERT[d]	NET[e]
SpAMDA (**4**)	4	24	5,000	3,900	10,000
imipramine	94	160	726	5	16
cyproheptadine	3	11	112	4100	290

[a] [^{3}H]ketanserin.
[b] [^{3}H]mesulergine.
[c] [^{3}H]spiperone.
[d] [^{3}H]paroxitine.
[e] [^{3}H]nisoxitine radioligands.

with stirring. The solution was then heated at reflux (45 min) and poured into a mixture of crushed ice/NH_4OH with vigorous stirring (15 min). Excess of NH_4OH was added to keep the solution alkaline. The solid formed was extracted with Et_2O (3×50 mL). The combined Et_2O extracts were washed with water, brine, dried ($MgSO_4$), and removal of Et_2O under reduced pressure gave a yellow oil, which crystallized immediately. The product was purified by MPLC using hexanes/EtOAc (9:1) as eluent to give 0.3 g (60%) of pure 9-cyano-9,10-dihydro-anthracene as colorless crystals mp 106–108 °C. lit.[11] mp 101–102 °C. IR cm^{-1} 2215. ^1H NMR ($CDCl_3$) δ 3.87–3.93 (d, $J = 18$ Hz, 1H, CH_2), 4.05–4.11 (d, $J = 18$ Hz, 1H, CH_2), 5.02 (s, 1H, CH), 7.28–7.79 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 36.14, 37.60, 119.54, 125.88, 127.12, 127.60, 128.53, 128.82, 129.56, 131.34, 136.65.

2. Methods for the synthesis of spiro-pyrrolidines (4, 6–9)

2.1. General method for the synthesis of the cyano acetic acid ethyl esters

Nitrile (6.09 mmol) was added to sodium ethoxide prepared from Na (8.53 mmol) and EtOH (10 mL) and heated at reflux (1 h). The solution was then cooled in an ice bath and $C_2H_5OCOCH_2Br$ (8.53 mmol) or $C_2H_5OCO(CH_2)_2Br$ (8.53 mmol) was added dropwise via a syringe. The resulting mixture was heated at reflux (4 h) cooled and filtered. The residue was washed with Et_2O (25 mL). Water (25 mL) was added to the filterate and the organic layer was separated. The aqueous layer was once again extracted with ether (25 mL). The combined Et_2O extracts were washed with water, brine, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil, which was purified by MPLC using hexanes/EtOAc (9:1) as eluent to give the respective cyano acetic or propionic acid ethyl esters.

2.1.1. (9-Cyano-9,10-dihydroanthracen-9-yl)-acetic acid ethyl ester (4c). Yield (70%); mp 69–70 °C (EtOAc/petroleum ether). ^1H NMR ($CDCl_3$) δ 1.10–1.15 (t, $J = 7.5$ Hz, CH_3), 2.85 (s, 2H, CH_2), 3.97–4.14 (m, 4H, CH_2), 7.33–7.89 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.53, 35.27, 46.05, 46.28, 61.63, 121.89, 127.58, 127.70, 128.93, 134.21, 135.10, 167.96.

2.1.2. (1-Cyano-1,2,3,4-tetrahydronaphthalen-1-yl)-acetic acid ethyl ester. Yield (61%); golden yellow oil. ^1H NMR ($CDCl_3$) δ 1.20–1.26 (t, $J = 9$ Hz, 3H, CH_3), 1.89–1.97, (m, 2H, CH_2), 2.28–2.32 (t, $J = 6$ Hz, 2H, CH_2), 2.79–3.06 (m, 4H, CH_2), 4.11–4.20 (q, 2H, CH_2), 7.10–7.47 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.65, 19.46, 29.44, 33.20, 38.18, 44.82, 61.61, 123.78, 127.39, 128.24, 128.72, 130.51, 134.48, 136.85, 169.20.

2.1.3. 3-Cyano-3,3-diphenyl-propionic acid ethyl ester. Yield (75%); mp 99–10 °C (EtOAc/petroleum ether). ^1H NMR ($CDCl_3$) δ 1.08–1.13 (t, $J = 7.5$ Hz, 3H, CH_3), 3.41 (s, 2H, CH_2), 4.03–4.10 (q, $J = 15$ Hz, 2H, CH_2), 7.21–7.39 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.45, 44.73, 48.97, 61.76, 127.31, 128.76, 129.54, 139.78, 168.71.

2.1.4. 5-(Cyano-10,11-dihydrodibenzo[*a,d*]cycloheptene-5-yl)-acetic acid ethyl ester. Yield (55%); colorless oil. ^1H NMR ($CDCl_3$) δ 1.01–1.06 (t, $J = 7.5$ Hz, 3H, CH_3), 3.04–3.47 (m, 4H, CH_2), 3.50 (s, 2H, CH_2), 3.91–3.98 (q, $J = 13.5$ Hz, 2H, CH_2), 7.13–8.07 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.39, 34.21, 48.21, 52.36, 61.59, 122.42, 127.34, 129.27, 129.54, 132.17, 135.29, 139.46, 168.23.

2.1.5. 3-(9-Cyano-9,10-dihydroanthracen-9-yl)-propionic acid ethyl ester. Yield (82%); colorless oil. ^1H NMR ($CDCl_3$) δ 1.15–1.20 (t, $J = 7.5$ Hz, 3H, CH_3), 2.20–2.44 (m, 4H, CH_2), 3.94–4.16 (m, 4H, CH_2), 7.32–7.79 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.67, 31.27, 35.20, 37.36, 48.77, 61.24, 121.78, 127.26, 127.66, 128.75, 129.05, 134.57, 135.01, 172.30.

2.2. General method for the synthesis of spiro-pyrrolidin-2′-ones

A mixture of the cyanoester (2.06 mol), 10% Pd/C (0.15 g) in methanol (40 mL), and HCl (1 mL) was hydrogenated at 50 kg/cm^3 (3 days). The catalyst was removed and the solvent was evaporated under reduced pressure to give a white semisolid. Water (25 mL) was added and the solution was made basic with 10% NaOH and extracted with EtOAc (3×25 mL). The combined EtOAc extracts were washed with water, brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil. The oil was purified by mplc using hexane/EtOAc (9:1) as eluent to give the respective spiro-pyrrolidin-2′-ones.

2.2.1. Spiro[9,10-dihydroanthracene]-9,4′-pyrrolidin-2′-one (4d). Yield (68%); mp 189–190 °C ($CHCl_3$/petroleum ether). ^1H NMR ($CDCl_3$) δ 3.06 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 4.00–4.06 (d, $J = 18$ Hz, 1H, CH_2), 4.09–4.15 (d, $J = 18$ Hz, 1H, CH_2), 6.15 (s, 1H, NH), 7.24–7.58 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 36.37, 43.20, 47.49, 55.66, 125.04, 127.50, 128.73, 136.35, 141.36, 178.40.

2.2.2. Spiro[1,2,3,4-tetrahydronaphthalenyl)-1,4′-pyrrolidin-2-one. Yield (70%); mp 152–153.5 °C ($CHCl_3$/petroleum ether) lit. mp 148–158 °C[12]. ^1H NMR ($CDCl_3$) δ 1.77–2.03 (m, 4H, CH_2), 2.44–2.73 (m, 2H, CH_2), 2.79–2.83 (t, $J = 6$ Hz, 2H, CH_2), 3.43–3.46 (d, $J = 9$ Hz, 1H, CH_2), 3.61–3.64 (d, $J = 9$ Hz, 1H, CH_2), 7.06–7.38 (m, 4H, Ar-H), 7.56 (s, 1H, NH); ^{13}C NMR

($CDCl_3$) δ 20.64, 30.60, 37.72, 42.39, 48.06, 57.97, 126.93, 127.22, 129.90, 137.22, 142.38, 178.51.

2.2.3. 4,4-Diphenylpyrrolidin-2-one. Yield (75%); mp 160–161 °C ($CHCl_3$/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 3.04–3.05 (d, $J = 3$ Hz, 2H, CH_2), 4.01–4.03 (d, $J = 6$ Hz, 2H, CH_2), 6.92 (br s, 1H, NH), 7.18–7.34 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 44.69, 51.64, 54.54, 127.20, 127.35, 129.21, 146.64, 177.46.

2.2.4. Spiro[10,11-dihydrodibenzo[*a,d*]cycloheptene-5,4′-pyrrolidin]-2′-one. Yield (55%); mp 198–199 °C ($CHCl_3$/petroleum ether). lit. mp 201–202 °C.[7] ^{1}H NMR ($CDCl_3$) δ 3.18–3.48 (m, 6H, CH_2), 4.15 (s, 2H, CH_2), 7.08–7.31 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 32.80, 40.44, 44.37, 55.24, 93.06, 125.28, 125.71, 126.79, 127.224, 127.98, 128.29, 129.93, 131.98, 138.88, 142.92, 177.37.

2.2.5. Spiro[9,10-dihydroanthracene]-9,5′-piperidin-2′-one. Yield (66%); mp 189–190 °C. ($CHCl_3$/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 2.04–2.18 (m, 4H, CH_2), 3.93–4.25 (m, 4H, CH_2), 7.31–7.61 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 30.25, 31.36, 37.32, 41.22, 49.16, 124.89, 127.33, 129.04, 137.34, 141.36, 172.60.

2.3. General method for the reduction of the spiropyrrolidin-2-ones to spiro pyrrolidines

A 1.0 M solution of BH_3–THF complex (7.00 mol) was added at 0 °C to a well stirred solution of 4-spiro-pyrrolidin-2-ones (1.40 mmol) in anhydrous THF (2 mL). The solution was brought to room temperature and then heated at reflux (8 h) and cooled. HCl (4 mL) of 6.0 M solution was added cautiously to the reaction mixture, heated at reflux (1 h), cooled, and the solvent was removed under reduced pressure, resulting in a white suspension. Water (20 mL) was added and extracted with EtOAc (20 mL). The aqueous phase was made basic with 10% NaOH and extracted with CH_2Cl_2 (3×25 mL). The combined CH_2Cl_2 extracts were washed with water, brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the respective amines as oils.

2.3.1. Spiro[9,10-dihydroanthracene]-9,3′-pyrrolidine fumarate (4). Yield (94%); mp 190.5–191.5 °C (EtOAc/CH_3OH). ^{1}H NMR (DMSO-d_6) δ 2.25–2.30 (t, $J = 7.5$ Hz, 2H, CH_2), 3.21–3.26 (t, $J = 7.5$ Hz, 2H, CH_2), 3.55 (s, 2H, CH_2), 4.06 (s, 2H, CH_2), 6.44 (s, 1H), 7.20–7.56 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 36.22, 36.67, 45.18, 51.09, 54.10, 124.43, 126.69, 126.76, 128.17, 135.84, 137.08, 141.44, 168.96. Anal. Calcd for ($C_{17}H_{17}N.1/2C_4H_4O_4$): C, 77.79; H, 6.52; N, 4.77. Found: C, 77.12; H, 6.56; N, 4.78.

2.3.2. Spiro[1,2,3,4-tetrahydronaphthalenyl)-1,3′-pyrrolidine oxalate (6). Yield (80%); mp 197–198 °C (EtOAc/CH_3OH). ^{1}H NMR ($CDCl_3$) δ 1.71–2.27 (m, 6H, CH_2), 2.72 (s, 2H, CH_2), 3.30–3.50 (m, 4H, CH_2), 7.06–7.47 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 20.00, 29.89, 34.20, 44.54, 45.35, 57.56, 126.71, 126.79, 127.05, 129.51, 137.99, 139.26, 164.93. Anal. Calcd for ($C_{13}H_{17}N.C_2H_2O_4$): C, 64.96; H, 6.90; N, 5.05. Found: C, 64.99; H, 6.93; N, 4.96.

2.3.3. 3,3-Diphenylpyrrolidine oxalate (7). Yield (91%); mp 184–185 °C (EtOAc/CH_3OH). ^{1}H NMR (DMSO-d_6) δ 2.68–2.72 (t, $J = 6$ Hz, 2H, CH_2), 3.13–3.17(t, $J = 6$ Hz, 2H, CH_2), 3.92 (s, 2H, CH_2), 7.18–7.43 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 35.98, 43.72, 53.18, 54.86, 126.90, 127.07, 128.99, 144.48, 165.37. Anal. Calcd for ($C_{16}H_{17}N.C_2H_2O_4$): C, 68.99; H, 6.11; N, 4.46. Found: C, 69.07; H, 6.13; N, 4.53.

2.3.4. Spiro(10,11-dihydrodibenzo[*a,d*]cycloheptene)-5,3′-pyrrolidine fumarate (8). Yield (77%); mp 169–170 °C (EtOAc/CH_3OH). ^{1}H NMR(DMSO-d_6) δ 2.70–2.75 (t, $J = 7.5$ Hz, 2H, CH_2), 3.14–3.19 (t, $J = 7.5$ Hz, 2H, CH_2), 3.29–3.37 (m, 4H, CH_2), 3.73 (s, 2H, CH_2), 7.07–7.29 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 32.74, 38.25, 45.76, 58.14, 125.66, 126.54, 127.35, 131.98, 138.79, 144.67. Anal Calcd for ($C_{19}H_{21}N.C_4H_4O_4.1/4H_2O$): C, 71.42; H, 6.40; N, 3.78. Found: C, 71.35; H, 6.61; N, 3.65.

2.3.5. Spiro[9,10-dihydroanthracene]-9,3′-piperidine oxalate (9). Yield (77%); mp 193–194 °C (EtOAc/CH_3OH). ^{1}H NMR ($CDCl_3$) δ 1.72–1.81 (t, $J = 3$ Hz, 2H, CH_2), 2.09–2.18 (m, 2H, CH_2), 2.94–2.98 (m, 2H, CH_2), 3.45 (s, 2H, CH_2), 4.00–4.06 (d, $J = 18$ Hz, 1H, CH_2), 4.10–4.16 (d, $J = 18$ Hz, 1H, CH_2), 7.19–7.89 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 24.79, 33.45, 38.07, 42.18, 47.60, 54.09, 126.23, 123.32, 123.61, 128.69, 138.18, 144.57. Anal. Calcd for ($C_{18}H_{19}N.C_2H_2O_4$): C, 70.77; H, 6.23; N, 4.12. Found: C, 70.93; H, 6.19; N, 4.05.

2.3.6. Affinity determinations. Radioligand binding assays using [^{3}H]-ketanserin and cloned $5HT_{2A}$ receptors were performed as previously described. Data were analyzed with the LIGAND program as previously detailed.[13,14]

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