Synthesis and Evaluation of 6,7-Dihydroxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*ef*][3]benzazepine, 6,7-Dihydroxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine, and 10-(Aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene as Conformationally Restricted Analogs of β-Phenyldopamine

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The present study was designed to define the geometry of the hydrophobic accessory region for binding of dopamine D_1 receptor ligands and to assess the relative importance of ethylamine side chain conformation for receptor affinity. Three compounds, 6,7-dihydroxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*ef*][3]benzazepine, **4**, 6,7-dihydroxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine, **5**, and 10-(aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene, **6**, were synthesized as conformationally restricted analogs of β-phenyldopamine. Molecular modeling studies were performed to compare these three compounds with the high-affinity D_1 agonists dihydrexidine (DHX), **2**, and SKF 38393, **3**. The β-phenyl moieties in the target compounds are constrained by means of either an ethyl (**4**) or methylene (**5** and **6**) bridge. The compounds adopt minimum-energy conformations in which the β-phenyl group is approximately −22° (**4**), −12° (**5**), and −30° (**6**) from coplanarity with the catechol ring. These compounds also embody either a freely rotating (**6**) or a rigidified gauche (**4** and **5**) rotameric conformation of the dopamine ethylamine side chain, the latter nearly perfectly superimposible on the benzazepine portion of SKF 38393. Radioligand competition experiments showed that compounds **4**, **5**, and **6** have only micromolar affinity for both the D_1 and D_2 dopamine receptor subtypes. The low affinity of **4**–**6**, relative to **2** and **3**, may be due to improper orientation of the β-phenyl moiety and provides important information about the three-dimensional orientation of the hydrophobic accessory binding domain of the dopamine D_1 receptor. In addition, the negligible affinity of **6**, as compared to **2** and **3**, indicates that the rotameric positioning of the ethylamine side chain may not be a primary determinant of receptor affinity.

Dopamine mediates a number of neuronal processes in both the central nervous system and in peripheral tissues. Abnormalities in, or perturbation of, dopamine-mediated neurotransmission are involved in the etiology or pharmacotherapy of central disorders including Parkinson's disease and schizophrenia.[1] In addition, dopamine has recently been implicated in the reinforcing effects of several psychotropic agents, making the study of dopamine neurotransmitter systems important in understanding the biochemical mechanisms of substance abuse.[2]

The involvement of dopamine in such physiological processes and pathologies has made all aspects of dopamine neurotransmission of great interest. One major focus has been to elucidate the structure and function of the various dopamine receptors and the mechanisms of their interaction with ligands. Five genes encoding dopamine receptors have been identified and characterized, and the cloned receptors are under intensive study.[3–5] At present a number of research groups (including our own) are using these and other data to develop three-dimensional models of the binding sites on these receptor proteins. One source of information necessary to create and validate these models has been structure–activity relationship (SAR) data, compiled by pharmacological evaluation of compounds from both natural and synthetic sources.

One of our major foci has been on designing ligands with high affinity for the dopamine D_1 receptor subtype. The pharmacological data from such compounds provide key structure–activity data that can aid in refining the three-dimensional binding model of the dopamine D_1 receptor. Several dopamine analogs that contain a bulky hydrophobic substituent (*e.g.*, phenyl, thiophenyl, or adamantyl moieties) attached to the β-carbon of the ethylamine side chain have high affinity for the dopamine D_1 receptor, and often (but not always) selectivity, for D_1 relative to D_2. It has been postulated that the increased affinity of these β-phenyldopamine (**1**) analogs may be due to a direct interaction of the β-phenyl moiety with an accessory hydrophobic binding domain at the receptor active site.[6] Furthermore, Brewster *et al.*[7] have postulated, based on the affinity and full efficacy of the benzo[*a*]phenanthridine dihy-

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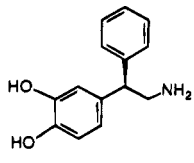
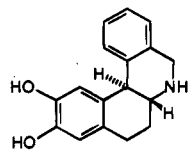
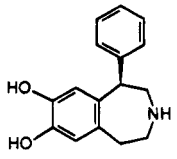
drexidine (DHX, **2**) at the D_1 receptor, that this putative accessory region for full agonists favors an orientation in which an accessory phenyl moiety, for example, is relatively coplanar with the binding plane of the dopamine catechol ring. This coplanar orientation is similar to the minimum-energy conformation calculated for **2**.



β-Phenyldopamine, 1



Dihydrexidine, 2

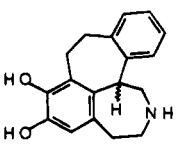


SK&F 38393, 3

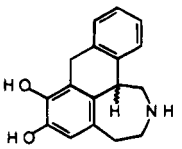
The 1-phenyl-1,2,4,5-tetrahydro-3-benzazepines, another class of β-phenyldopamine analogs, represent a group of high-affinity ligands for D_1 receptors. One member of this class, SKF 38393 (**3**), was the prototype D_1 selective dopamine agonist, possessing low nanomolar affinity for D_1 receptors and a 100-fold selectivity for binding to the D_1 *vs* D_2 receptor subtypes.[8,9] Unlike **2**, the β-phenyl moiety in **3** has been postulated, based on both X-ray crystal structure determinations and computer-assisted modeling studies, to adopt a conformation perpendicular to the plane of the catechol ring.[8,10] It should be noted, however, that the β-phenyl in **3** is freely rotating and is constrained in this conformation only by its rotational energy barrier. Another difference is that the dopamine ethylamine side chain in **3** is rigidified into a gauche rotameric conformation, where the side chain of **2** is constrained into the *trans*-β rotamer. This latter difference has been suggested as one explanation for the fact that **3**, unlike **2**, is only a partial agonist.[7,9]

The fact that two compounds with distinctly different conformational characteristics possess high affinity for the dopamine D_1 receptor subtype raises interesting questions as to the three-dimensional conformation of the receptor active site. Is the coplanar orientation of the β-phenyl moiety in **2** the optimal conformation? Or perhaps, is any deficiency in overlap at this region compensated for by the improved interaction of the rigid *trans*-β conformer of the ethylamine side chain in **2** *vs* the gauche rotameric conformation of the azepine ring in **3**?

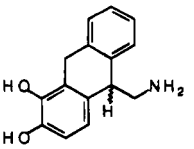
The present studies sought to probe the three-dimensional orientation of the putative hydrophobic accessory binding domain of the D_1 receptor and thus determine the relative importance of the rotameric conformation of the ethylamine side chain of dopamine. Compounds **4**, **5**, and **6** were designed to provide this information. All three compounds contain the β-phenyldopamine pharmacophore with the unsubstituted phenyl ring tethered by means of either an ethyl or a methylene bridge into a dibenzocycloheptene or dihydroanthracene ring system. The side chain in compound **4** (6,7-dihydroxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*ef*][3]benzazepine) and compound **5** (6,7-dihydroxy-1,2,3,4,8,12b-hexahydroanthr-[10,4a,4-*cd*]azepine) has then been tethered into the catechol ring. These compounds may be thought of as constrained structural analogs of the prototype D_1-selective dopamine agonist SKF 38393, **3**, differing only in the presence of the hydrocarbon bridge. Conversely, the side chain in 10-(aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene, **6**, has been left freely rotating such that several possible conformations are accessible.



4



5



6

On the basis of the conformational studies of substituted 9,10-dihydroanthracenes by Rabideau and coworkers,[11-15] it was anticipated that both of the target compounds **5** and **6** would adopt a minimum-energy conformation in which the β-phenyl moiety is held only slightly out of plane with respect to the catechol, similar to the proposed minimum-energy conformation of **2**.[7] It was also expected that little or no twisting between the two aromatic rings would be possible due to this ring fusion. Compound **4** was predicted to be less conformationally restricted than the dihydroanthracenes, **5** and **6**, due to the longer hydrocarbon tether. This would allow the β-phenyl moiety of **4** to adopt a more perpendicular orientation with respect to the catechol ring, similar to that proposed for **3**. These assumptions were tested through computer-assisted molecular modeling studies performed for **4**–**6**. In order to validate these procedures and enable direct comparison among the conformational data obtained, **2** and **3** were also modeled as compounds of known conformation and receptor affinity.[7,8,10]

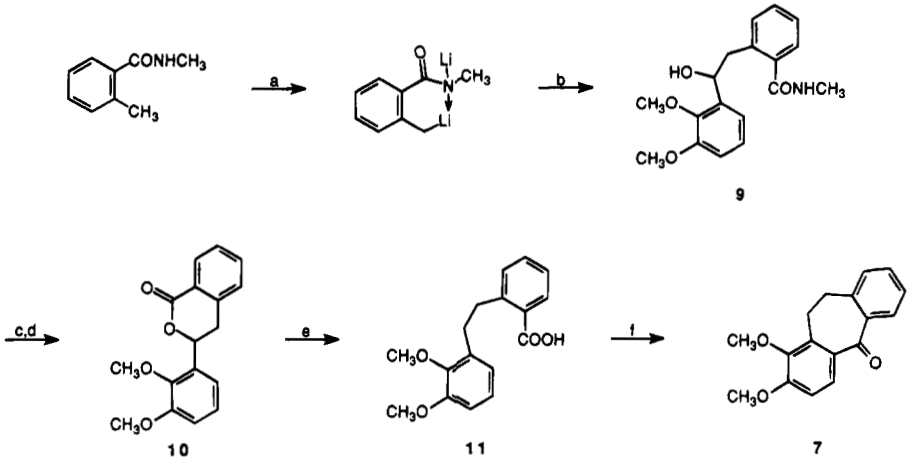
No detrimental effects on receptor affinity due to the hydrocarbon bridges themselves were expected for **4**–**6** as substitution at the position *ortho* to the ethylamine side chain seems to be well-tolerated. In fact, 2-phenyldopamine and 9-(aminomethyl)fluorene analogs have been synthesized and are active D_1 agonists with affinities in the 400 nM range.[16,17] Apomorphine, which has a considerable amount of steric bulk in this area, also binds with high affinity to dopamine receptors.[18]

Chemistry

Synthesis of 1,2-Dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, 7. When examined by retrosynthetic analysis, compound **4**, containing the dibenzo[*a*,*d*]cycloheptene ring system, was envisioned as being accessible through intermediate ketone **7** (Scheme 1). This ketone could be transformed *via* several steps into acetal **8** (Scheme 2) which can subsequently be cyclized to provide benzazepine **4**. The synthesis of **7** was accomplished starting from hydroxy amide **9** (Scheme 1), which in turn was prepared following a heteroatom-facilitated lithiation procedure developed by Vaulx *et al.*[19] Treatment of *N*-methyl-*o*-toluamide with 2 equiv of *n*-butyllithium in tetrahydrofuran formed a dilithio amide intermediate which was then condensed with 2,3-dimethoxybenzaldehyde and quenched to form **9**. Base hydrolysis of the amide, followed by acidification, gave lactone **10**. Catalytic hydrogenation in ethanol then afforded the reduced acid **11**. Friedel–Crafts cycliacylation was accomplished using Eaton's reagent[20] to afford the key intermediate ketone **7** in an overall yield for four steps of 42%.

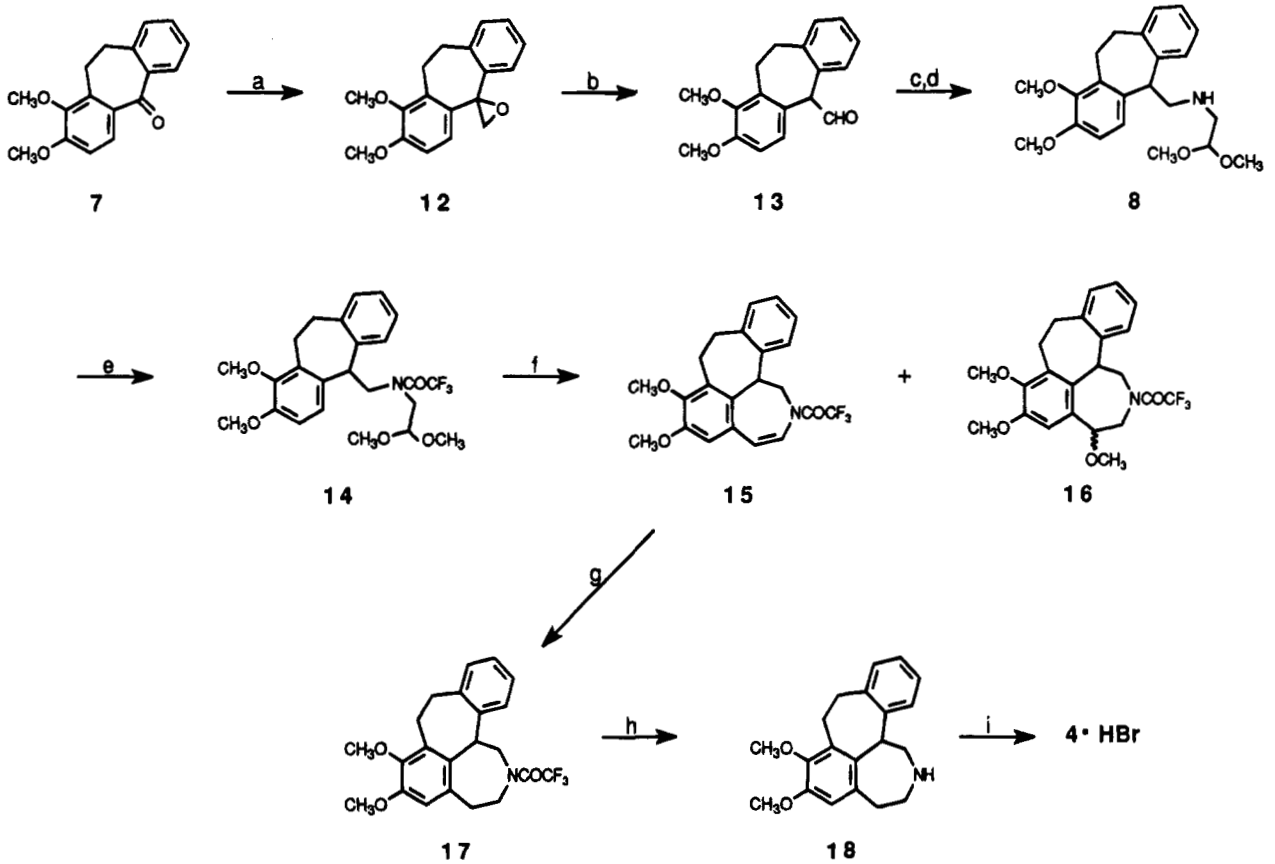
Synthesis of 6,7-Dihydroxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*ef*][3]benzazepine Hydrobromide, 4·HBr. The first step in the synthesis of **4** from key intermediate **7** is homologation of the ketone. Several potential approaches were examined to effect this transformation using both the Wittig[21,22] and Wittig–Horner[23] reactions, but neither

Scheme 1. Synthesis of 1,2-dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, **7**[a]



[a] (a) *n*-Butyllithium (2 equiv); (b) 2,3-dimethoxybenzaldehyde; (c) NaOH; (d) HCl; (e) H_2 (50 psi), Pd/C, $HClO_4$, ethanol; (f) P_2O_5/methanesulfonic acid.

Scheme 2. Synthesis of 6,7-dihydroxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*ef*][3]benzazepine hydrobromide, **4**[a]

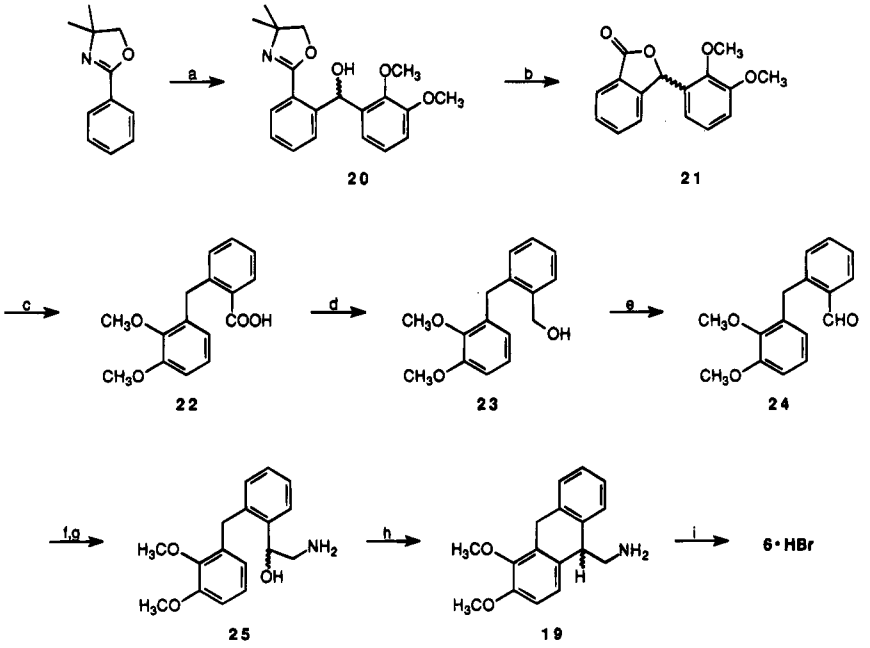


[a] (a) NaH, trimethylsulfonium iodide; (b) zinc iodide; (c) aminoacetaldehyde dimethyl acetal; (d) sodium cyanoborohydride; (e) acetic anhydride; (f) methanesulfonic acid; (g) H_2 (50 psi), Pd/C; (h) KOH, methanol; (i) boron tribromide.

of these methods gave satisfactory results in the present synthesis. The approach that was finally successful involved formation of the spiroepoxide **12** using dimethylsulfonium methylide, as first described by Corey[24] (Scheme 2). This transformation proceeded without difficulty following the procedure of Ackermann,[25] although large amounts of the ylide were necessary to drive the reaction to completion. The epoxide partially rearranged to the aldehyde **13** over silica, as evident by TLC, and could be completely converted to **13** by treatment with zinc iodide.[26]

Aldehyde **13** was readily condensed with aminoacetaldehyde dimethyl acetal to form the corresponding imine, as monitored by the disappearance of the aldehyde C=O band (IR 1730 cm^{-1}). This imine was selectively reduced using sodium cyanoborohydride under weakly acidic conditions to provide the corresponding amine **8**, but could not be reduced either by sodium borohydride or under neutral catalytic hydrogenation conditions. Further inspection of the IR spectrum of the crude imine revealed a peak at 3400 cm^{-1}, characteristic of an NH functionality. These latter observations indicated the imine to be in equilibrium with the highly stable enamine, where the double bond is conjugated to both of the two aromatic rings. Apparently, the equilibrium is shifted toward the

Scheme 3. Synthesis of 10-(Aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene, **6**[a]



[a] (a) 1. secbutyllithium, tetrahydrofuran, −78 °C; (2) 2,3-dimethoxybenzaldehyde; (b) 5% HCl(aq), reflux; (c) H_2 (50 psi), Pd/C, acetic acid, 80 °C; (d) borane−tetrahydrofuran complex; (e) pyridinium chlorochromate, sodium acetate; (f) trimethylsilyl cyanide, ZnI_2 (cat.); (g) borane−tetrahydrofuran complex; (h) sulfuric acid/trifluoroacetic acid (1:1), dichloromethane; (i) boron tribromide.

iminium form only in the presence of acid, when the nitrogen is protonated, allowing reduction with $NaCNBH_3$.[27]

At this point, cyclization of amino acetal **8** was attempted with a variety of acids, none of which gave appreciable amounts of any of the anticipated possible products. We reasoned that protonation of the amine was unfavorable to formation of the necessary nearby carbocation. It was therefore decided to protect the amine functionality by reaction of **8** with trifluoroacetic anhydride, affording a nearly quantitative yield of amido acetal **14**. This was subsequently cyclized by treatment with methanesulfonic acid in benzene at ambient temperature to form a mixture of **15** and **16**, as evidenced by both ^1H NMR and CIMS data. This mixture resisted all attempts at chromatographic separation. Prolonged reaction times or increased temperature failed to drive the reaction to completion. Further, treatment of pure **16**, ultimately obtained later, with acid did not lead to **15**, suggesting **16** to be the diastereomer with the pseudoequatorial benzylic methoxy group. Direct catalytic hydrogenation of this mixture gave two spots by TLC. Chromatographic separation provided pure unchanged **16** and trifluoroacetamide **17**, the latter being subsequently hydrolyzed under basic conditions to give amine **18**. Demethylation of this compound with boron tribromide, followed by recrystallization from ethanol/ethyl acetate, afforded the target compound **4** as the hydrobromide salt.

Synthesis of 10-(Aminomethyl)-9,10-dihydro-1,2-dimethoxyanthracene, 19. Target compounds **5** and **6** both contain the same basic parent structure, 10-(aminomethyl)-9,10-dihydroanthracene, and thus are synthetically accessible through a common intermediate, 10-(aminomethyl)-9,10-dihydro-1,2-dimethoxyanthracene (**19**). As with compound **7**, the two key steps in the synthesis of **19** are both reactions involving carbon−carbon bond formation. The first step, as shown in Scheme 3, is a condensation of 2,3-dimethoxybenzaldehyde and 4,4-dimethyl-2-phenyl-1,3-oxazoline[28] *via* heteroatom facilitated *ortho* lithiation to afford the diphenylmethanol **20**.[29] This compound proved to be inconvenient to purify as it required repeated column chromatography. Thus, the crude reaction product **20** was subjected to acidic hydrolysis of the oxazoline ring with concomitant lactonization. This formed 3-(2,3-dimethoxyphenyl)isobenzofuran-1-one, **21**, that was easily recrystallized from methanol to give a yield of 63% from the phenyloxazoline.[30]

The next task was to remove the undesired dibenzylic oxygen. This was accomplished with a procedure used by deSilva and Snieckus[31] to reduce similar phthalide derivatives to the corresponding (phenylmethyl)benzoic acids. Thus, **21** was subjected to catalytic hydrogenation at elevated temperature in acetic acid providing a nearly quantitative yield of 2-((2,3-dimethoxyphenyl)-methyl)benzoic acid, **22**.

It was first thought that a direct cyanation of the corresponding acid chloride of **22** followed by reduction would give the desired β-hydroxyphenylethylamine precursor (**25**) for **19**. Unfortunately this proved to be impossible due to the acid sensitive nature of **22**. That is, it was discovered that treatment of **22** with acid, even a relatively weak Lewis acid like zinc iodide, readily led to intramolecular Friedel−Crafts cycliacylation to form the corresponding dihydroanthrone that can subsequently undergo spontaneous aromatization to form 1,2-dimethoxy-10-hydroxyanthracene. Synthetically, both the anthrol and anthrone are dead ends. The ease of this cyclialkylation is probably due both to activation of the benzene nucleophile by the *p*-methoxy substituent and to the stability of the anthrone product. Thus it was impossible to form either the acid chloride of **22** or any of the variety of activated acyl derivatives such as mixed anhydrides.

It was necessary, therefore, to perform a functional group interconversion of the acid to the corresponding aldehyde. Reduction of benzoic acid **22** with borane−tetrahydrofuran complex gave a quantitative yield of 2-((2,3-dimethoxyphenyl)methyl)benzenemethanol, **23**,

which was reoxidized using pyridinium chlorochromate[32] to 2-((2,3-dimethoxyphenyl)methyl)benzaldehyde, **24**. The aldehyde product **24**, like its acid precursor **22**, was extremely acid sensitive. The treatment of **24** with acid would lead directly to the fully aromatic 1,2-dimethoxyanthracene. This was prevented by buffering the oxidation reaction with sodium acetate, thus providing aldehyde **24** in a 95% yield after chromatographic purification.

Condensation of aldehyde **24** with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide followed by borane reduction of the intermediate α-(silyloxy)nitrile gave 2-amino-1-(2-((2,3-dimethoxyphenyl)methyl)phenyl)ethanol, **25**, in an overall 91% yield from the aldehyde. This finally provided the precursor for the key dihydroanthracene intermediate **19**.

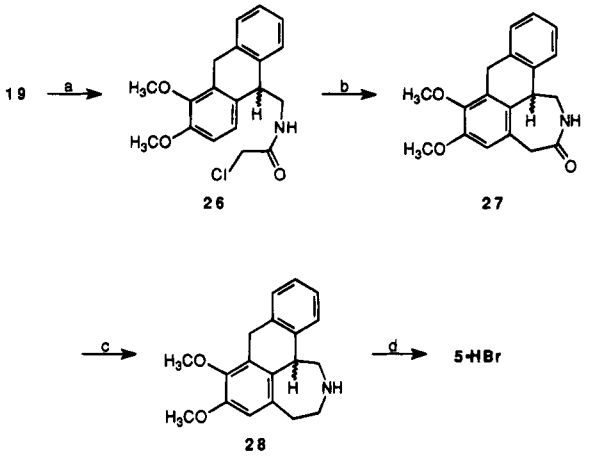
Pridgen *et al.*[33] have reported the synthesis in good yields of a number of isoquinolines and benzazepines from the corresponding β-hydroxyethylamines using a 1:1 mixture of sulfuric acid (H_2SO_4) and trifluoroacetic acid (TFA) in dichloromethane. Since **25** is merely a regioisomer of the type of compound used by Pridgen *et al.*,[33] it was anticipated that these cyclization conditions might be effective in the present case. Thus as shown in Scheme 3, treatment of a dichloromethane solution of the free base of **25** with an excess of a 1:1 mixture of sulfuric and trifluoroacetic acids gave, after the appropriate workup, a 67% yield of the desired product, 10-(aminomethyl)-9,10-dihydro-1,2-dimethoxyanthracene, **19**.

This compound proved to be somewhat unstable. In fact, after purification, the free base of **19** became very darkened after only 1 day at room temperature, even under a nitrogen atmosphere. Also, the hydrochloride salt was extremely hygroscopic and could not be isolated as a solid. Likewise, difficulties were encountered in trying to form and isolate organic acid salts of **19**. Thus, for ease of handling and storage, the stable hydrochloride salt of aminoethanol **25** was stored and only converted into **19** as needed shortly before use in subsequent reactions. Nonetheless, with the key intermediate finally in hand the divergent syntheses of the target compounds **5** and **6** could proceed.

Synthesis of 10-(Aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene, 6. Catechol **6** was synthesized very easily from the key intermediate **19** *via* boron tribromide cleavage of the methoxy groups (Scheme 3). This compound, as with **4**, was isolated as the crystalline hydrobromide salt in a yield of 51%.

Synthesis of 6,7-Dihydroxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine, 5. Similar to compound **4**, the initial plan for the synthesis of **5** was to *N*-alkylate **19** with a two-carbon fragment that could subsequently serve as an electrophile for acid-catalyzed alkylation or acylation of the oxygenated ring of the dihydroanthracene. It was anticipated that ethyl or methyl bromoacetate or bromoacetaldehyde dimethyl acetal could be used as an alkylating reagent to derivatize **19**. We reasoned, however, that the bromoacetate esters would require saponification and conversion to their acid chlorides before cyclization. Also, the intermediate aminoacids would likely prove inconvenient to handle. Thus, it was initially decided to attempt alkylation of **19** with bromoacetaldehyde dimethyl acetal. In this case, the usual *N*-alkylation conditions of

Scheme 4. Synthesis of 6,7-dihydroxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine, **5**[a]



[a] (a) 2-Chloroacetyl chloride, triethylamine, dichloromethane, 0 °C; (b) *hν*, methanol; (c) borane–tetrahydrofuran complex; (d) boron tribromide.

alkyl halide and potassium carbonate in warm dimethylformamide (DMF) gave no reaction. Likewise, the use of cesium carbonate as the base, despite its greater solublility in DMF, was no improvement. Alkylation was finally accomplished in warm DMF using triethylamine (TEA) as the base. This reaction, however, gave only a 36% yield of the desired product, in addition to several minor side products and some unreacted starting material. Alkylation of **19** using methyl bromoacetate under similar reaction conditions gave two major products, again with unreacted starting material. These unfavorable initial results, and the additional saponification and activation steps necessary for this approach, led us to select another route.

A search of the literature identified procedures by Yonemitsu *et al.*[34,35] for the preparation of a series of azepinoindoles and benzazepinones by photocyclization of the corresponding α-chloro amide precursors. Several other reports used similar methods with slightly varying reaction conditions.[17,36–39] Unfortunately, these procedures all suffered from low yields, in the range of 25 to 40%. This was attributed to side reactions that formed bicyclic compounds or undesired azepinone regioisomers. In our system, however, it was reasoned that the dihydroanthracene ring system would constrain the α-chloro amide and might prevent reaction at any position other than the one desired.

First, **19** was *N*-acylated with chloroacetyl chloride (Scheme 4) to afford 10-((2′-chloroacetamido)methyl)-9,10-dihydro-1,2-dimethoxyanthracene, **26**, in 85% yield. A millimolar solution of **26** in methanol was then cyclized *via* photoirradiation for 1 h with a 450-W medium-pressure mercury vapor lamp[17] to provide the corresponding azepinone **27** in a modest 36% yield. These were the optimum conditions found for this reaction. None of the side products were isolated since **27** crystallized readily from the crude reaction mixture. Although this yield was still low, it was in the high range of those reported for this type of transformation.

Finally, reduction of lactam **27** with borane–tetrahydrofuran complex provided 6,7-dimethoxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine, **28**, in 88% yield. Subsequent cleavage of the methyl ethers with boron tribromide yielded catechol **5** which was isolated in 45% yield as the crystalline hydrobromide salt.

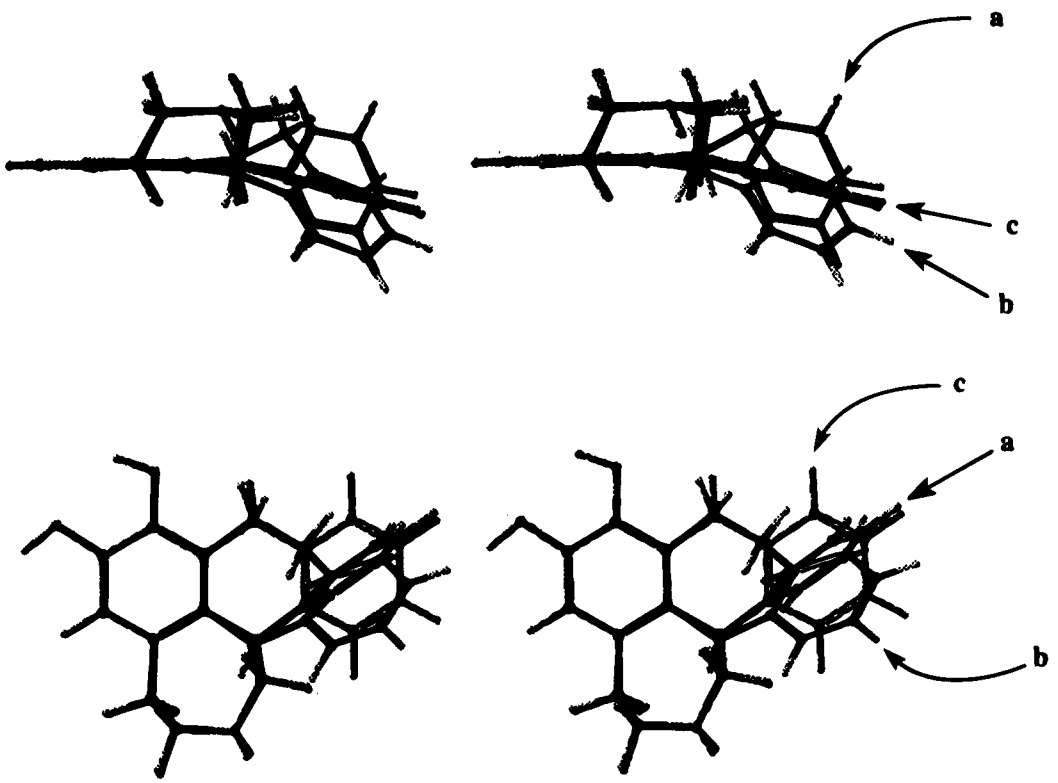


Figure 1. Three point superposition (using the phenyl ring C1 and both catechol oxygens) of (a) SKF 38393, **3**; (b) **4**; and (c) **5** (stereopair illustration).

Molecular Modeling

One of the objectives of this research was to attempt to determine the three-dimensional orientation of the proposed hydrophobic accessory binding domain of the dopamine D_1 receptor. Toward this end, the minimum-energy conformations for the free amines of **2**–**6** were calculated using a Tektronix CAChe work system running Tektronix proprietary software (CAChe Version 2.8, Tektronix, Inc., 1991). Compounds **2** and **3** were included in this study for the sake of comparison, and the conformations obtained were consistent with those reported previously.[7,8,10] The azepine rings of **4** and **5** adopt minimum-energy conformations similar to **3**. The major difference among these molecules is the orientation of the β-phenyl moiety. This can be seen clearly in the superposition of **3**, **4**, and **5** shown in Figure 1. In compound **6**, the (aminomethyl) side chain is freely rotating and has two conformations of nearly equal energy. The orientation of the gauche conformation compares closely to **3**, whereas the *trans*-β conformation of the side chain is more similar to the nitrogen position in **2**. However, the orientation of the β-phenyl moiety is different from both **2** and **3**.

Both **2** and **3** have high affinity for the dopamine D_1 receptor and are selective for this receptor subtype. However, in their lowest energy conformations they express completely different positioning of the β-phenyl moiety, relative to the plane of the catechol ring. For this reason it was decided to perform a fairly extensive study of the conformational mobility of these two molecules as well as the target molecules **4**–**6**.

In order to make accurate comparisons among these diverse structures, the position of the β-phenyl moiety in each compound was determined, relative to the catechol ring, in terms of an out-of-plane angle θ and a twist angle φ. Both θ and φ were defined based on the β-phenyldopamine skeleton which is present in all of the molecules studied. As depicted in Figure 2a, the out-of-plane angle θ was defined as the dihedral angle given by carbons C2′, C1′, C2, and C1″ of β-phenyldopamine. A positive value of θ corresponds to a clockwise rotation, viewed from C1′ to C2, and indicates that the β-phenyl moiety is "above" the plane of the catechol ring. Likewise, a negative value of θ indicates that the β-phenyl is "below" the plane of the catechol ring. The twist angle φ was defined as the dihedral angle given by carbons C1′, C2, C1″, and C2″ of β-phenyldopamine. A positive value of φ corresponds

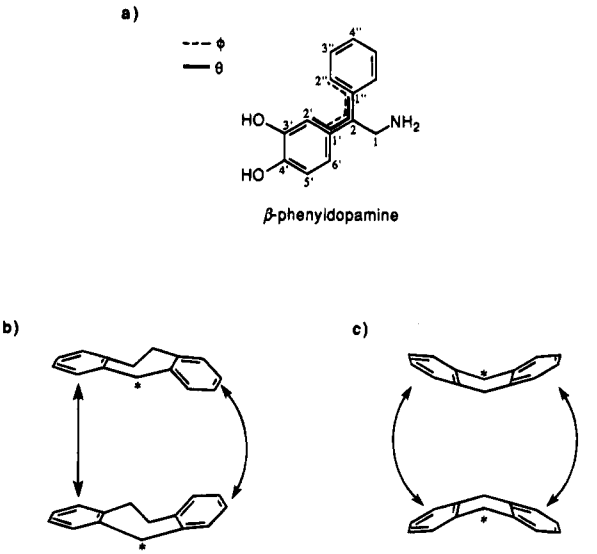


Figure 2. (a) Definition of dihedral angles φ and θ based on the β-phenyldopamine pharmacophore (φ = C2″–C1″–C2–C1′ and θ = C1″–C2–C1′–C2′). (b) Two possible conformations of the dibenzocycloheptene ring system resulting from inversion of the ethylene bridge (an asterisk (*) represents C5 on each conformer). (c) Two conformations resulting from the boat-to-boat inversion of the dihydroanthracene ring system (an asterisk (*) represents C9 on each conformer).

Table 1. Conformational Data from Energy-Minimized Structures

compd	ring[a]/chain[b] conformation	angles (deg) θ	angles (deg) φ	N–O[c] (Å)	ΔH°f[d] (kcal/mol)	ring inversion barrier (kcal/mol)
2	up	58 (43)[e]	−11 (0)	7.4	−41.2	3.4
	down	−0.66 (6)	−55 (−59)	7.1	−42.5	4.7
3	up	86	31	6.2	−42.3	7.3
	down	−9	82	6.7	−44.2	9.2
4	up/8-up[f]	67	−78	6.4	−41.7	2.5[g]
	up/8-down	75	−67	6.3	−41.9	7.5
	down/8-down	−22	54	6.7	−43.7	9.3
	down/8-up	−29	5.6	6.6	−41.1	2.5[g]
5	up	45	−46	6.6	−42.0	3.3
	down	−12	13	6.7	−47.5	8.8
6	up/*trans*-β	47	−48	7.4	−45.5	3.8[h]
	up/gauche	48	−47	6.8	−45.5	1.5
	down/gauche	−27	−27	6.2	−49.9	5.9
	down/*trans*-β	−27	27	6.9	−50.0	2.3[h]

[a] Position of the β-phenyl moiety relative to the plane of the catechol ring. [b] Rotameric conformation of the ethylamine side chain, where applicable. [c] Straight-line distance from the amine nitrogen to the *m*-hydroxyl oxygen. [d] Relative heat of formation. [e] Data in parentheses for **2** are from ref 7. [f] The 8-up and 8-down designate conformations in which carbon 8 of **4** is directed above or below the plane of the catechol ring (see Figure 3b). [g] Transition between 8-up and 8-down. [h] Transition between gauche and *trans*-β.

to a clockwise rotation viewed from C2 to C1″. Small values of θ and φ indicate near coplanarity of the two aromatic rings. Also, the effects of rotation about these two angles tend to be additive. That is, when values of both θ and φ have the same sign (+ or −) the molecule tends to be less planar, overall, than when θ and φ have opposite signs.

Kaiser *et al.*[8] have observed that SKF 38393, **3**, can exist in two different azepine ring-inversion conformations with the pendant phenyl ring in either an axial or equatorial conformation. Further, they have suggested that the equatorial phenyl ring conformation is preferred for receptor binding. The existence of two minimum-energy conformations for **3** has been confirmed by Berger *et al.*[10] who report a slight energetic preference (<1 kcal/mol) for the axial conformation in molecular mechanics calculations. Brewster *et al.*[7] have suggested a similar conformational mobility for DHX, **2**, which can exist in two minimum-energy conformations resulting from inversion of the B and C rings. These two conformations were reported to differ by only about 0.5 kcal/mol.

Likewise, each of the target molecules **4**–**6** should be capable of some sort of ring inversion that may result in a significantly different conformation for the β-phenyl moiety. Thus, in addition to the global minimum-energy conformation, there should be at least one secondary local minimum for each of these five molecules, producing a "β-phenyl-up" and a "β-phenyl-down" conformation for each. In order to determine the structure and accessibility, under physiological conditions, of these secondary minima, an optimized search was performed of dihedral angle θ for **2**–**6**. In this search the dihedral angle was locked at a particular value and the remainder of the molecule was energy minimized. The dihedral angle was then changed by a fixed increment, locked at the new value, and the structure again minimized. Repetitions of this operation resulted in the generation of an energy profile for rotation about θ, as well as providing the minimum-energy conformation for each point along the rotation coordinate.

The energy profiles generated for **2**–**6** are not shown, but all exhibited two energy minima corresponding to the two ring-inverted conformations and an intervening maximum corresponding to the least stable inversion intermediate. The secondary local minima identified from these energy profiles were reminimized without constraint of θ to give the minimum-energy conformations resulting from ring inversion. The difference between the heats of formation ($\Delta H°_f$) of the maximum and one of the minima is an approximation of the energy barrier to ring inversion in that given direction, thus providing some estimate of the availability of both conformations, under physiological conditions, for each molecule. The relative positioning of the two phenyl rings, in terms of θ and φ, for both conformational minima of each structure is represented in Table 1. Also included are the heats of formation ($\Delta H°_f$) calculated using MOPAC and the approximate energy barrier to inversion for each pair of conformations.

As shown in Table 1, the values of θ and φ calculated for both the β-phenyl-up and β-phenyl-down conformations of **2** in this study are consistent with those reported by Brewster *et al.*[7] Likewise, these two conformations differ by only about 1 kcal in $\Delta H°_f$, similar to the 0.5 kcal calculated previously. However, in contrast to the previous studies, the β-phenyl-down conformation is slightly favored. Also, the present calculations reveal an energy barrier for the transition between the β-phenyl-up and β-phenyl-down conformations for **2** of approximately 3–5 kcal/mol. Nevertheless, the minimum-energy conformation found here reproduced the β-phenyl-up conformer reported by Brewster *et al.*[7]

Similarly, the two minimum-energy conformations calculated for **3** are consistent with those reported previously by Kaiser *et al.*[8] and later confirmed by Berger *et al.*[10] Again the β-phenyl-down conformation is slightly favored and the energy difference between the two conformations is small (<2 kcal/mol), although somewhat larger than the value of <1 kcal/mol reported by Berger *et al.*[10] In fact, even the larger value may be somewhat deceiving in that the barrier to transition between the β-phenyl-up and β-phenyl-down conformations for **3** is approximately 7–9 kcal/mol.

There were actually four different conformational extremes identified for compound **4**, listed in Table 1, which can be envisioned as arising from two separate ring inversions. First, inversion of the azepine ring resulted in the expected "β-phenyl-up" and a "β-phenyl-down" conformations. The conformational effects of this inversion were exhibited as variation in the values of both φ and θ. Second, for each of these conformational extremes there were two possible rotameric conforma-

Table 2. Receptor Affinities for Target Compounds **4**–**6**

compd	D1 affinity[a] $K_{0.5}$[b] (nM) ± SD	Hill coeff	D2 affinity $K_{0.5}$ (nM) ± SD	Hill coeff
(+)-DHX, **2**	2.4 (1); 2.8[c]	0.69	29 (1); 44[c]	0.76
SKF 38393, **3**	11.1 (1); 17[d]	0.76	1870 (1); 1880[d]	0.81
4	372 ± 16 (3)	1.03 ± 0.04	2150 ± 630 (3)	0.95[f]
5	590 ± 156 (2)	0.81 ± 0.55	1250 ± 210 (2)	0.67 (1)[f]
6	>2500 (3)	–[e]	>2500 (3)	–[e]

[a] All assays were performed as described in the Experimental Section on rat striatal membranes, using [^{3}H]SCH 23390 as the D1 radioligand and [^{3}H]spiperone as the D2 ligand. The number of determinations on separate days is listed in parentheses. [b] See Experimental Section for details on $K_{0.5}$ values. [c] Data from ref 40. [d] Data from ref 7. [e] Data not applicable. [f] Because of the low affinity of these drugs for the D2 receptor, the concentrations used were not high enough to cause complete competition and allow an accurate determination of n_H.

tions of the ethyl bridge, depicted in Figure 2b and designated as 8-down and 8-up in Table 1, inversion between which was exhibited mostly as variation in the value of ϕ. In compounds **5** and **6**, the two conformational extremes result from a boat-to-boat inversion of the dihydroanthracene center ring (Figure 2c). Due to the fairly rigid nature of the ring fusions in tetracycle **5**, this dihydroanthracene inversion induced a concomitant inversion of the azepine ring, thus giving rise to large differences in both ϕ and θ.

Another objective of this research was to determine the relative importance of side chain conformation to affinity for the D_1 receptor. The major effect of side chain conformation is to position the *m*-hydroxyl and amine moieties at the proper relative position for optimal interaction with the receptor. Thus, the linear N–O atom-to-atom distance can be used as an approximate measure of this goodness of fit. The fully extended *trans*-β rotameric conformation of dopamine, which has an N–O distance of ~7.3 Å, has been postulated as optimal for receptor activation, based on the full agonist properties of 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (DHPT), **2**, and 6,7-dihydroxy-2-aminotetralin (ADTN) *vs* SKF 38393, **3**, which is only a partial agonist.[7]

Therefore, optimized searches, similar to those described above, were performed on the minimum-energy conformation of **3**–**6** to locate the accessible range of N–O distances. The amine to *m*-hydroxyl, N–O distance, in Angstroms (Å), for each minimum-energy conformation is given in Table 1. In **3**–**5**, variance of the N–O distance represents deformation of the azepine ring. Thus, as expected, the energy profiles generated by varying the N–O distance from 6.0 to 7.5 Å for each of the compounds exhibited a minimum at the optimal N–O distance for each molecule with steep increases in both directions. The proposed optimal N–O distance for receptor binding of 7.3 Å lies >12 kcal above the minimum-energy conformation for all three azepines **3**–**5** and thus is not easily accessible under physiological conditions.

Alteration of the N–O distance in **6** is accomplished merely by rotation of the (aminomethyl) side chain. Thus, an energy profile for this molecule, plotted as rotational angle *vs* $\Delta H°_f$, exhibits two minima corresponding to the gauche and *trans*-β rotameric conformation. As with the ring inversions discussed previously, the rotational energy barrier of approximately 2.3 kcal/mol between either the gauche or *trans*-β minimum and the intermediate maximum is an estimate of the accessibility of these two conformations under physiological conditions. Thus, virtually any conformation of the (aminomethyl) side chain in **6** is accessible to the receptor; however, the N–O distance during this conformational rotation never exceeds 7.1 Å.

Pharmacology

Radioligand competition assays were performed for **4**–**6** using [^{3}H]SCH 23390 and [^{3}H]spiperone as radioligands for the dopamine D_1 and D_2 receptors, respectively. These compounds were tested concurrently with (+)-DHX, **2**, and SKF 38393, **3**, as standard ligands and IC_{50} values were compared to those reported previously.[7,40] The results of the competition assays are given in Table 2.

None of the target compounds had high affinity for dopamine receptors. The binding affinity of compound **4** was the highest of the three test compounds, although its affinity was over 30-fold lower relative to **3** and 150-fold lower relative to (+)-**2**. Compound **5** exhibited an affinity at the D_1 receptor 50-fold lower than **3** and 250-fold lower than (+)-**2**. Both **4** and **5** possessed only a modest selectivity for D_1 *vs* D_2. Compound **6** showed no appreciable affinity or selectivity for either receptor subtype. As the test compounds showed very low affinity for both receptor subtypes, none was tested for intrinsic activity, *i.e.*, stimulation of adenylate cyclase.

Results and Discussion

None of the target agonists **4**–**6** had high affinity for dopamine receptors as compared either to DHX, **2**, and the prototype D_1 dopamine agonist SKF 38393, **3**. The attenuated affinity of **4**–**6** was not thought to be due to substitution at the position *ortho* to the ethylamine side chain for the reasons stated previously. Also, as a point of reference, 2-benzyldopamine, a flexible analog of compounds **5** and **6**, had IC_{50} values of 1.12 μM for D_1 and 2.5 μM for D_2 (data not shown). This compound, having more conformational degrees of freedom, would be expected to have lower affinity than **5** and **6** if *ortho* substitution were a factor. In fact, 2-benzyldopamine exhibited affinities for the dopamine receptors nearly identical to that for **5** and much higher than that for **6**.

One possible explanation for the attenuated affinity of **4**–**6** is that the dibenzocycloheptene and dihydroanthracene ring systems may be too rigid to allow these molecules to adopt the amine to *m*-hydroxyl N–O distance optimal for receptor interaction. It has been suggested that the conformation of the dopamine ethylamine side chain, represented by the amine to *m*-hydroxyl distance, is an important determinant of *agonist activity* at the D_1 receptor. The fully extended *trans*-β rotameric conformation seems to be optimal for receptor activation. This is evidenced by the observation that **3** (amine to *m*-hydroxyl distance = 6.7 Å) is only a partial agonist whereas **2** (amine to *m*-hydroxyl

distance = 7.3 Å) is a full agonist at the D_1 receptor subtype. It is unclear, however, whether side chain conformation makes a significant contribution to D_1 *binding affinity* as both **2** and **3** exhibit low nanomolar affinity for the D_1 receptor.

In the present ligand series, compound **6** has a side chain constrained only slightly by incorporation of the β-carbon into a tricyclic system. The maximum amine to *m*-hydroxyl distance calculated for this molecule was 7.1 Å. The ethylamine side chain in **4** and **5**, however, has been tethered into a gauche conformation by incorporation into an azepine ring. In fact, **4** and **5** are direct structural analogs of **3**, and all three possess nearly identical minimum-energy conformations for the 3-benzazepine moiety. Likewise, there is little difference between **4**, **5**, and **3** with regard to the energy required for deformation of the azepine ring. In fact, the azepine ring in all three compounds is quite rigid and the energy required to deform the azepine ring sufficiently to attain an N−O distance of 7.3 Å varies only between approximately 13 and 15 kcal/mol for **3** and **5**, respectively (data not shown). Thus the extra rigidity introduced by incorporating the azepine ring into a tetracyclic system does not adequately account for the attenuation in binding affinity of **4** and **5** *vs* **3**. Similarly, the lower binding affinity of **6** *vs* **4** and **5** would seem to indicate that the ability of **6** to adopt the *trans*-β rotameric conformation does not compensate for the additional degree of freedom introduced by the untethered side chain. Thus, the ability of a ligand to attain the longer amine to *m*-hydroxyl distance does not seem to be the primary factor in determining receptor affinity. It is worth noting, however, that all calculations in this study were performed *in vacuo* and thus do not take into account solvent effects which may lend a significant degree of stability to an energetically less favorable conformation.

The other obvious possible explanation for the attenuated affinity of **4**−**6** is that the dibenzocycloheptene and dihydroanthracene ring systems do not allow the proper orientation of the β-phenyl moiety necessary for optimal receptor complementarity. Dibenzocycloheptene **4** is the most conformationally mobile of the molecules studied, although less so than either **2** or **3**. The two conformations of the azepine ring and mobility of the ethyl bridge between the phenyl moieties in this compound give rise to values ranging from −29° to 75° for angle θ and 54° to −78° for angle φ. The conformational mobility of **4** is somewhat less than that reported by Weissensteiner *et al.*[41] for 5-substituted 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes, however, presumably due to the added rigidity of fusion to the azepine ring. This is reflected in the much larger barrier to inversion of the azepine ring (~7−9 kcal/mol) versus inversion of the ethyl bridge in the cycloheptene ring (2.5 kcal/mol) for **4** (Figure 2b and Table 1). The global minimum-energy conformation calculated for **4** is in good agreement with reported conformations for both 5-hydroxy- and 5-(3-(*N*,*N*-dimethylamino)propyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene based on NMR and X-ray data (including a preference of the 5-substituent for the pseudoaxial conformation).[41−43]

The dihydroanthracenes **5** and **6** are the most conformationally rigid series of molecules with respect to β-phenyl orientation reported to date. Both exhibit a puckered central ring which exists in the boat conformation. This places the β-phenyl moiety either slightly above or slightly below the plane of the catechol ring. This ring system, as expected, is rigidly planar with respect to twisting between the two aromatic ring planes (*i.e.*, $\theta \approx -\phi$ in all dihydroanthracene derivatives). The (aminomethyl) moiety in compounds **5** and **6** seems to prefer the axial orientation, presumably due to peri interactions with the hydrogens on the adjacent aromatic rings. This explanation is evidenced by the fact that the energy profile of **5**, generated from inversion of the dihydroanthracene, exhibits only a small maximum at $\theta = 0°$, where the ring strain is highest. The global maximum occurs at $\theta = 35°$, where the distance between the α-methylene hydrogens of the (aminomethyl) side chain and the hydrogens on the two adjacent phenyl rings is smallest.

These data are in agreement with studies by Rabideau and co-workers[11−15] in which it was shown that the central ring of the dihydroanthracenes exists primarily in a somewhat flattened boat conformation. Both the degree of bending and the ease of ring inversion were shown in those studies to depend on substitution at the 9- and 10-positions of the dihydroanthracenes, with unsubstituted compounds being less planar and undergoing inversion more easily than mono- or disubstituted compounds. These studies also demonstrated the preference of alkyl substituents to occupy the axial conformation, presumably due to peri interactions. This preference was evidenced by NOE data showing an interaction between the methyl groups of 9-*tert*-butyl-9,10-dihydroanthracene and one of the hydrogens at position 10.[12,13]

Except for angle φ, the minimum-energy conformation of **3** is quite similar to the three test compounds, and to compound **5** in particular. The β-phenyl moiety lies slightly out of plane with respect to θ and the azepine ring adopts a conformation nearly identical to the conformation of the azepine or (aminomethyl) moieties in **4**−**6**. These data are in agreement with the published crystal structure of **3**.[8] It is apparent from the energy profile data for rotation about θ, that the most likely conformation of all four compounds, **3**−**6**, is one in which the β-phenyl moiety is below the plane of the catechol ring (*i.e.* $\theta < 0°$). In all four cases the ring-up conformation is less stable and there is a moderate (6−9 kcal) energy barrier to inversion. The dihydroanthracenes are, however, somewhat more amenable to inversion than is **3**.

The only obvious difference between the minimum-energy conformations of **3**, **4**, and the dihydroanthracenes **5** and **6** is the value of the twist angle φ. As mentioned, φ in the dihydroanthracenes is constrained to small values and $\theta \approx -\phi$ in both **5** and **6** adding to the overall planarity of the molecule. The ethylene bridge in **4** allows this compound much greater rotational freedom with respect to φ. However, even here φ is constrained to values less than ~60° from coplanarity with the catechol ring. In contrast, the β-phenyl ring in **3** lies nearly perpendicular to the plane of the catechol ring ($\phi = 82°$). This would seem to indicate that the hydrophobic accessory binding domain of the D_1 receptor lies out of the plane of the catechol and is possibly perpendicular to it. This orientation would allow high-affinity binding of **3** but not the dihydroanthracenes **5** and **6**, and only low-affinity binding of **4** would be expected.

Given that the proposed binding conformation of **2** has the β-phenyl moiety *above* the plane of the catechol ($\theta = 58°$) and somewhat twisted ($\phi = -11°$), it seems likely that the torsion angle ϕ is a more important determinant of binding affinity than the bending angle θ. However, as noted by Brewster *et al.*[44] and confirmed here (Table 1), **2** does have some conformational mobility and has accessible conformations which are nearly planar with respect to both θ and ϕ. It can also adopt conformations in which $\theta < 0°$, as with **3**. In fact, the β-phenyl down conformation was found, in the studies described here, to be the actual minimum-energy conformation. Thus the *binding* conformation of **2** may not be equivalent to its minimum-energy conformation.

Conclusions

The structural classes examined, the dibenzocycloheptenes and the dihydroanthracenes, represent variations of two features of a dopamine D_1 receptor binding model: the conformation of the ethylamine side chain and the three-dimensional orientation of the hydrophobic accessory binding domain. Molecular modeling studies and radioligand displacement data for the three test compounds provide useful information regarding the effect and relative importance of both of these features on the binding of ligands to the dopamine D_1 receptor subtype. First, based on the absence of any appreciable D_1 or D_2 affinity of **6** and the low nanomolar affinity of both **2** and **3**, the ethylamine side chain conformation does not seem to be the primary determinant of receptor affinity. Second, the results of these studies do not support the idea of a hydrophobic accessory binding domain coplanar with the binding plane of the catechol ring. In addition, in light of the highly attenuated affinity of **4** and **5**, and again the low nanomolar affinity of both **2** and **3** (molecules of vastly disparate minimum-energy conformation with respect to the β-phenyl moiety) it appears that optimal receptor overlap in this region is dependent mostly on large values of the twist angle ϕ and to a lesser degree on small values of the out-of-plane angle θ.

Experimental Section

Chemistry. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian XL-200 (200 MHz) or VXR-5000S (500 MHz) NMR instrument in $CDCl_3$, CD_3OD or DMSO-d_6 and chemical shifts are reported in δ values (parts per million) relative to an internal reference of $CHCl_3$ (δ 7.24), CD_2HOD (δ 3.30), or DMSO-d_5 (δ 2.49), respectively. Abbreviations used in NMR analysis are as follows: br s = broad singlet, br d = broad doublet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dq = doublet of quartets, m = multiplet, p = pentet, q = quartet, s = singlet, t = triplet, td = triplet of doublets. Chemical ionization (CI) and electron ionization (EI) mass spectra were obtained with a Finnegan 4000 quadrupole mass spectrometer. High-resolution CI and EI mass spectra were obtained on a Kratos MS 50 spectrometer and are within 0.0015 m/z, unless otherwise noted. Ionization gas for CIMS and high-resolution CIMS was isobutane, unless otherwise noted. Elemental analyses were performed by the Purdue University Microanalysis Laboratory, West Lafayette, IN, or the Galbraith Laboratories, Knoxville, TN, and were within 0.4% of the calculated values, unless otherwise noted.

2-(2-(2,3-Dimethoxyphenyl)-2-hydroxyethyl)-*N*-methylbenzamide (9).[19] To a stirred solution of *N*-methyl-*o*-toluamide (4.49 g, 30 mmol) in 50 mL of tetrahydrofuran at ambient temperature, under nitrogen, was slowly added 30 mL of *n*-butyllithium (2.5 M solution in hexanes, 75 mmol). During the addition the mixture refluxed spontaneously, finally giving a red solution. After reflux for an additional 15 min, the reaction mixture was cooled to −10 °C (ice–acetone bath), and a solution of 2,3-dimethoxybenzaldehyde (7.98 g, 48 mmol) in 30 mL of tetrahydrofuran was added. The mixture was stirred for 20 min at −10 °C and then 45 min at ambient temperature The reaction was poured into 6 g of ice, stirred, and extracted with diethyl ether (3 × 50 mL). After the organic extracts were combined and washed with saturated aqueous NaCl (brine), a yellowish-white solid began to precipitate. This mixture was left overnight, and the solid was collected by filtration. The product was recrystallized from 95% ethanol, yielding 6.02 g (63%): mp 140–142 °C; IR (KBr pellet) 3300–3100 (br), 1600 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.01 (3H, d, J = 5 Hz), 3.06–3.11 (2H, m), 3.89 (3H, s), 3.93 (3H, s), 5.17–5.24 (1H, m), 5.84 (1H, d, J = 5 Hz), 6.79–6.81 (1H, m), 6.85 (1H, dd, J = 1.5 and 8 Hz), 7.08 (1H, t, J = 8 Hz), 7.17 (1H, dd, J = 1.5 and 8 Hz), 7.23–7.30 (1H, m), 7.31–7.46 (2H, mm; CIMS m/z (relative intensity) 316 (MH^+, 3.52), 299 (19.86), 298 (100); high-resolution EIMS 315.1465 (calcd 315.1476). Anal. Calcd ($C_{18}H_{21}NO_4$): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.06; H, 6.64; N, 4.39.

3-(2,3-Dimethoxyphenyl)-3,4-dihydro-2(1*H*)-benzopyran-1-one (10). The hydroxy amide **9** (4.76 g, 15 mmol) in 45 mL of 95% ethanol and 45 mL of 6 N NaOH was heated at reflux for 18 h. The mixture was cooled to ambient temperature, most of the alcohol was removed under reduced pressure, and the residue was dissolved in 50 mL of water. The aqueous solution was extracted with ether (2 × 15 mL), and the organic washes were discarded. The aqueous solution was cooled in an ice bath and acidified. The product was extracted with a 1:1 mixture of diethyl ether/ethyl acetate (3 × 100 mL), and the combined organic extracts were washed with brine and dried (Na_2SO_4). Filtration and removal of solvent afforded a viscous oil, which solidified on standing: total product 3.55 g (83% yield); recrystallization from tetrahydrofuran/hot hexane gave mp 98–100 °C; IR (KBr) 1730, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10–3.14 (1H, m), 3.25–3.31 (1H, m), 3.87 (3H, s), 3.90 (3H, s), 5.87–5.90 (1H, dd, J = 3 and 12 Hz), 6.93–6.95 (1H, dd, J = 1.5 and 8 Hz), 7.14 (1H, t, J = 8 Hz), 7.18–7.20 (1H, dd, J = 1.5 and 8 Hz), 7.28 (1H, d, J = 7.6 Hz), 7.44 (1H, t, J = 7.6 Hz), 7.55–7.59 (1H, m), 8.17 (1H, d, J = 9 Hz); CIMS m/z (relative intensity) 285 (MH^+, 100), 284 (M^+, 22.62), 267 (83.43), 118 (12.88); high-resolution EIMS 284.1042 (calcd 284.1049). Anal. Calcd ($C_{17}H_{16}O_4$): C, 71.82; H, 5.67. Found: C, 71.39; H, 5.62.

2-(2-(2,3-Dimethoxyphenyl)ethyl)benzoic Acid (11). The lactone **10** (7.10 g, 25 mmol) was, dissolved in 200 mL of 100% ethanol, several drops of 70% $HClO_4$ was added and the mixture was shaken at ambient temperature with 1.42 g of 10% Pd/C under 50 psi of H_2. After 48 h hydrogen uptake was complete and the catalyst was removed by filtration. Removal of solvent afforded the acid as a yellowish oil, which solidified on standing: total product 7.07 g (90% yield); recrystallization from tetrahydrofuran/hot hexane gave mp 67–69 °C; IR (KBr) 3000, 1680, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.95–2.99 (2H, m), 3.30–3.33 (2H, m), 3.82 (3H, s), 3.85 (3H, s), 6.79 (1H, t, J = 8 Hz), 7.27–7.32 (2H, m), 7.45–7.48 (1H, m), 8.06 (1H, dd, J = 1.4 and 8 Hz); CIMS m/z (relative intensity) 287 (MH^+, 2.99), 286 (M^+, 12.38), 269 (100). Anal. ($C_{17}H_{18}O_4$) C, H.

1,2-Dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (7). P_2O_5 (8.77 g) was added portionwise to 60 mL of CH_3SO_3H in a 100-mL two-necked flask equipped with a stopper and a $CaSO_4$ guard tube, and the mixture was stirred at ambient temperature for 24 h. Acid **11** (3.54 g, 12 mmol) was then added portionwise. The reaction was stirred for 1.5 h and poured over ice (60 g). This mixture was stirred overnight. The reaction was then extracted with diethyl ether (3 × 100 mL), and the organic extracts were combined and washed with ice-cold 2% NaOH (2 × 25 mL) and brine and were dried (Na_2SO_4). Filtration and removal of solvent afforded the ketone as a solid. Recrystallization from methanol afforded 3.00 g (90% yield) of the product: mp 77 −79 °C; IR (KBr) 1620–1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.13–3.16 (2H, m), 3.25–3.28 (2H, m), 3.79 (3H, s), 3.93 (3H, s), 6.90 (1H, d, J = 8 Hz), 7.22 (1H, d, J = 8 Hz), 7.31 (1H, t, J = 8 Hz), 7.40–

7.43 (1H, m), 7.90–7.93 (2H, m); CIMS *m/z* (relative intensity) 269 (MH^+, 100), 268 (M^+, 22.31). Anal. ($C_{17}H_{16}O_3$) C, H.

1,2-Dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxaldehyde (13). NaH (0.86 g of a 60% dispersion in mineral oil, 21.4 mmol) was placed in a two-necked flask under nitrogen and washed three times with hexane to remove the mineral oil. It was vacuum-dried, and then 125 mL of DMSO and the ketone **7** (1.5 g, 5.6 mmol) were added, after which trimethylsulfonium iodide (2.57 g, 12.6 mmol) was also added, all at once. The reaction mixture was stirred at ambient temperature for 3.5 h and then was poured over ice (100 g) and extracted with 1:1 diethyl ether/ethyl acetate (3 × 100 mL). The combined extracts were washed with water (100 mL) and dried (Na_2SO_4). Removal of the solvent afforded 1.81 g of crude epoxide **12**, which was used without purification for the next step.

The crude epoxide was dissolved in 35 mL of benzene, 0.61 g (1.9 mmol) of ZnI_2 was added, and the reaction mixture was heated at reflux under nitrogen for 1.5 h. The reaction was then diluted with ethyl acetate (35 mL) and washed with water (35 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated to afford 1.58 g of the pure aldehyde as an oil (93% yield): IR (neat) 2700, 1750–1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.84–2.90 (1H, m), 3.01–3.13 (3H, m), 3.79 (3H, s), 3.85 (3H, s), 4.53 (1H, s), 6.79 (1H, d, J = 8 Hz), 6.97 (1H, d, J = 8 Hz), 7.18–7.24 (4H, m), 9.89 (1H, s); CIMS *m/z* (relative intensity) 283 (MH^+, 100), 265 (70), 253 (93); high-resolution EIMS 282.1255 (calcd 282.1256). Anal. Calcd ($C_{18}H_{18}O_3$): C, 76.57; H, 6.43. Found: C, 75.68; H, 6.09.

5-((*N*-(β,β-Dimethoxyethyl)amino)methyl)-1,2-dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (8). A mixture of the aldehyde **13** (1 g, 3.5 mmol) and aminoacetaldehyde dimethyl acetal (0.4 g, 3.9 mmol) in benzene (50 mL) was heated at reflux using a Dean–Stark trap for 4 h. The mixture was cooled to ambient temperature, and the solvent was evaporated. The crude material (IR 1640 cm^{-1}) was taken up in methanol (20 mL), $NaBH_3CN$ (1.34 g, 21 mmol) was added portionwise, and the solution was brought to pH 5 by the addition of 5% HCl in methanol. The mixture was stirred for 6 h at ambient temperature, and the solution was made basic by the addition of 6 N NaOH. Most of the solvent was removed *in vacuo*, water (20 mL) was added, and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and the solvent was evaporated. The crude product was then purified on the chromatotron (4 mm silica gel rotor; eluent: 50% hexane/ethyl acetate) to afford 1.09 g of the amino acetal (83%) as an oil: ^1H NMR ($CDCl_3$) δ 1.47 (1H, br s), 2.76 (2H, d, J = 5.5 Hz), 3.00–3.45 (12H, m), 3.77 (3H, s), 3.83 (3H, s), 4.21 (1H, m), 4.42 (1H, t, J = 5.5 Hz), 6.71 (1H, d, J = 8.5 Hz), 6.94 (1H, d, J = 8.5 Hz), 7.10–7.20 (4H, m); CIMS *m/z* (relative intensity) 372 (MH^+, 100), 340 (22.78); high-resolution CIMS 372.2168 (calcd 372.2175). Anal. Calcd ($C_{22}H_{29}NO_4$): C, 71.13; H, 7.87; N, 3.77. Found: C, 69.69; H, 7.73; N, 3.71.

5-((*N*-(β,β-Dimethoxyethyl)-*N*-(trifluoroacetyl)amino)methyl)-1,2-dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (14). A mixture of the amino acetal **8** (0.53 g, 1.4 mmol) and trifluoroacetic anhydride (1.5 g, 7.15 mmol) was stirred in benzene under nitrogen for 30 min at ambient temperature, after which the solvent was evaporated. The remaining oil was dissolved in dichloromethane and filtered through silica gel to afford, after solvent evaporation, 0.65 g (97%) of pure amidoacetal as an oil, which solidified after 2 days at 0 °C: recrystallization from methanol gave mp 89–91 °C; IR (neat) 1690 cm^{-1}; ^1H NMR (DMSO-d_6, 100 °C) δ 2.86–3.10 (4H, m), 3.28 (6H, s), 3.32–3.44 (2H, m), 3.69 (3H, s), 3.78 (3H, s), 4.01 (2H, d, J = 8 Hz), 4.24–4.34 (1H, m) 6.84 (1H, d, J = 8.4 Hz), 6.89 (1H, d, J = 8.4 Hz), 7.10–7.22 (4H, m); CIMS *m/z* (relative intensity) 468 (MH^+, 2.94), 436 (85), 253 (100). Anal. ($C_{24}H_{28}F_3NO_5$) C, H, N.

***N*-(Trifluoroacetyl)-6,7-dimethoxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*e*,*f*][3]benzazepine (17).** The amido acetal **14** (2.05 g, 4.39 mmol) in benzene (10 mL) was added slowly to ice-cold CH_3SO_3H (7.5 mL) under nitrogen with stirring. After the addition was complete, the mixture was stirred at ambient temperature for 20 min. It was then poured into cold water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4), and the solvent was evaporated. The crude product gave two spots on TLC; the higher R_f spot was isolated by column chromatography (silica gel; eluent: 85% petroleum ether/ethyl acetate). The product weighed 0.78 g and was a mixture of two products which could not be separated chromatographically; CIMS *m/z* (relative intensity) 436 (34.51), 404 (100).

This mixture of cyclized products was taken up in ethanol (150 mL) and shaken with 0.25 g of 10% Pd/C under 50 psi H_2 for 16 h. The catalyst was filtered off and the solvent was evaporated. The crude product gave two spots on TLC: the slower moving material was isolated by Chromatotron separation (4 mm silica gel rotor; eluent: 85% petroleum ether/ethyl acetate) to afford 0.60 g of **17** (34%): recrystallization from methanol gave mp 197–199 °C; IR (KBr pellet) 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50–3.62 (8H, m), 3.64–3.90 (8H, m), 4.30–4.50 (1H, m), 6.50–6.70 (1H, m), 7.12–7.25 (4H, m); CIMS *m/z* (relative intensity) 406 (MH^+, 100); high-resolution EIMS 405.1551 (calcd 405.1552). Anal. Calcd ($C_{22}H_{22}F_3NO_3$): C, 65.18; H, 5.47; N, 3.45. Found: C, 63.52; H, 5.48; N, 3.42.

6,7-Dimethoxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*e*,*f*][3]benzazepine (18). The amide **17** (0.53 g, 1.3 mmol) in a mixture of methanol (15 mL) and 4 N KOH (15 mL) was stirred at reflux for 4 h. Most of the methanol was evaporated, water (10 mL) was added, and the aqueous mixture was extracted with dichloromethane (3 × 20 mL). The organic extracts were combined, washed with brine (15 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated to afford the amine as an oil. Purification on the Chromatotron (2 mm silica gel rotor; eluent: 10% methanol in dichloromethane) afforded 0.39 g (97% yield) of the product. The free base was converted to the HCl salt and recrystallized from methanol/ethyl acetate: mp 249–251 °C dec; ^1H NMR ($CDCl_3$, free base) δ 1.99 (1H, br s), 2.50–3.09 (7H, m), 3.17 (1H, t, J = 13 Hz), 3.28–3.48 (1H, m), 3.57 (1H, dd, J = 6, 17 Hz), 3.72 (3H, s), 3.86 (3H, s), 4.38–4.54 (1H, m), 6.67 (1H, s), 7.10–7.26 (4H, m); CIMS *m/z* (relative intensity) 310 (MH^+, 100). Anal. ($C_{20}H_{23}NO_2$·HCl) C, H, N.

6,7-Dihydroxy-2,3,4,8,9,13b-hexahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*e*,*f*][3]benzazepine (4). To a solution of **18** (free base) (0.48 g, 1.55 mmol) in dichloromethane (20 mL) was added BBr_3 (0.58 mL, 6.2 mmol) dropwise at −78 °C. The temperature was raised to ambient temperature over a period of 2 h, and stirring was continued for 5 h. The reaction mixture was then cooled to −78 °C, decomposed by addition of methanol (15 mL), and concentrated *in vacuo*. The process of addition of methanol and evaporation was repeated three times to remove all boric acid formed as methyl borate. The crude hydrobromide salt was dried *in vacuo* (0.56 g, 99% yield). Recrystallization from ethanol/ethyl acetate afforded 0.42 g (74% yield): mp 242–245 °C dec; ^1H NMR (CD_3OD) δ 2.30–2.45 (2H, m), 2.70–2.88 (2H, m), 2.95–3.10 (2H, m), 3.30–3.45 (4H, m), 4.51 (1H, m), 6.56 (1H, s), 7.02–7.13 (3H, m), 7.25 (1H, d, J = 7 Hz); CIMS *m/z* (relative intensity) 282 (M + 1); high-resolution EIMS 281.1415 (calcd 281.1416). Anal. Calcd ($C_{18}H_{19}NO_2$·HBr): C, 59.68; H, 5.56; N, 3.87. Found: C, 59.01; H, 6.08; N, 3.62.

3-(2,3-Dimethoxyphenyl)-3H-isobenzofuran-1-one (21). In a dry 500 mL, three-neck flask under a nitrogen atmosphere was placed 20 g (0.114 mol) of 4,4-dimethyl-2-phenyl-1,3-oxazoline in 120 mL of dry tetrahydrofuran. Following the procedure of Gschwend and Hamdan,[29] this solution was cooled for 45 min in a dry ice–acetone bath (−78 °C) before dropwise addition of 0.130 mol of secbutyllithium (100 mL of 1.3 *M* solution in cyclohexane) *via* syringe. The reaction mixture was allowed to warm to 0 °C before the addition of 24 g (0.144 mol) of 2,3-dimethoxybenzaldehyde as a solution in 60 mL of dry tetrahydrofuran. The reaction mixture was then stirred at ambient temperature for 6 h and then was poured into 600 mL of H_2O and stirred vigorously for 15 min. The tetrahydrofuran was removed by rotary evaporation, and the resulting aqueous mixture was extracted with ethyl ether (3 × 200 mL). The ethereal solution was dried ($MgSO_4$) and filtered, and the solvent was again removed by rotary evaporation. The crude

condensation product was then redissolved in 500 mL of 5% HCl(aq) and heated at reflux for 8 h.[30] The acidic mixture was extracted with dichloromethane (3 × 200 mL), the organic solution was dried ($MgSO_4$) and filtered, and the solvent was removed to give a dark, viscous oil. Recrystallization from methanol gave 19.61 g (63%) of pure **21** as white prisms: mp 99–99.5 °C; ^1H NMR ($CDCl_3$) δ 7.92 (1H, d, J = 7.6 Hz, ArH), 7.59 (1H, dd, J = 7.6 and 7.5 Hz, ArH), 7.50 (1H, dd, J = 7.6 and 7.5 Hz, ArH), 7.40 (1H, d, J = 7.6 Hz, ArH), 6.98 (1H, dd, J = 8.1 and 7.8 Hz, ArH), 6.91 (1H, dd, J = 8.2 and 1.47 Hz, ArH), 6.75 (1H, s, methine), 6.61 (1H, dd, J = 7.8 and 1.47 Hz, ArH), 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); CIMS m/z 271 (MH^+). Anal. ($C_{16}H_{14}O_4$) C, H.

2-((2,3-Dimethoxyphenyl)methyl)benzoic Acid (22). Via the hydrogenolysis procedure of deSilva and Snieckus,[31] a solution of 17.16 g (63.56 mmol) of lactone **21** in 250 mL of glacial acetic acid was placed in a 500 mL Parr hydrogenation bottle along with 3.5 g of 10% Pd on activated carbon. This mixture was shaken under 50 psi of H_2, while heating at 80 °C, for 8 h. The reaction was allowed to cool to ambient temperature before purging the H_2 and removing the catalyst by filtration. The clear colorless solution was then concentrated, and the product was recrystallized from methanol to give 16.64 g (96%) of pure **22** as white prisms. This compound has been reported once in the literature[45] but appears to be a misnaming of 2-((3,4-dimethoxyphenyl)methyl)benzoic acid, based on NMR data and subsequent products in the same reference: mp 134–135 °C; ^1H NMR ($CDCl_3$) δ 8.01 (1H, d, J = 7.7 Hz, ArH), 7.40 (1H, dd, J = 7.5 and 7.6 Hz, ArH), 7.27 (1H, dd, J = 7.5 and 7.8 Hz, ArH), 7.14 (1H, d, J = 7.8 Hz, ArH), 6.94 (1H, dd, J = 7.7 and 8.2 Hz, ArH), 6.79 (1H, d, J = 8.2 Hz, ArH), 6.60 (1H, d, J = 7.7 Hz, ArH), 4.43 (2H, s, CH_2), 3.84 (3H, s, OCH_3), 3.64 (3H, s, OCH_3); CIMS m/z (relative intensity) 273 (MH^+, 7), 272 (25), 255 (100); EIMS m/z (relative intensity) 272 (M^+, 100), 255 (36), 239 (78). Anal. ($C_{16}H_{16}O_4$) C, H.

2-((2,3-Dimethoxyphenyl)methyl)benzenemethanol (23). A solution of 9.97 g (36.65 mmol) of **22** in 200 mL of dry tetrahydrofuran under a nitrogen atmosphere was treated with 97 mL of 1.0 M borane–tetrahydrofuran complex, and the reaction mixture was heated at reflux overnight. The tetrahydrofuran was then removed by rotary evaporation, and the residual oil was redissolved in 200 mL of methanol (added slowly to avoid excess frothing). This solution was heated at reflux for 4 h to decompose the residual borane and borate esters. Removal of the methanol and methyl borate *via* rotary evaporation yielded 9.46 g (100%) of **23** as a clear oil which was used without further purification. An analytical sample was purified by Chromatotron (dichloromethane): ^1H NMR ($CDCl_3$) δ 7.37 (1H, ddd, J = 5.2, 4.5, and 3.1 Hz, ArH), 7.20 (2H, ddd, J = 5.7, 3.4, and 1.3 Hz, 2ArH), 7.11 (1H, ddd, J = 5.2, 4.4, and 3.2 Hz, ArH), 6.95 (1H, dd, J = 8.0 and 7.8 Hz, ArH), 6.79 (1H, dd, J = 8.2 and 1.4 Hz, ArH), 6.63 (1H, d, J = 7.7 Hz, ArH), 4.69 (2H, s, Ar_2CH_2), 4.06 (2H, s, CH_2O), 3.84 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 2.02 (1H, br s, OH); CIMS m/z (relative intensity) 259 (MH^+, 7), 241 (100). Anal. ($C_{16}H_{18}O_3$) C, H.

2-((2,3-Dimethoxyphenyl)methyl)benzaldehyde (24).[32] To a stirred suspension of 12 g of pyridinium chlorochromate and 1 g of sodium acetate in 200 mL of dichloromethane was added 9.46 g (36.65 mmol) of **23**, as a solution in 100 mL of dichloromethane. The resulting dark solution was stirred at ambient temperature under a nitrogen atmosphere for 2 h and then was poured into 600 mL of ethyl ether causing formation of a dark tarry precipitate. Filtration through Celite and solvent removal gave a dark oil which was again dissolved in ethyl ether with precipitation of more dark tar. The mixture was again filtered through Celite 545, and the solvent was removed by rotary evaporation to yield an amber oil which was further purified by flash chromatography (dichloromethane) to provide 8.90 g (95%) of pure aldehyde **24** as a clear colorless oil which solidified after 2 days under high vacuum: mp 34–37 °C; ^1H NMR ($CDCl_3$) δ 10.31 (1H, s, CHO), 7.84 (1H, d, J = 7.6 Hz, ArH), 7.46 (1H, dd, J = 7.4 and 7.6 Hz, ArH), 7.35 (1H, dd, J = 7.4 and 7.6 Hz, ArH), 7.20 (1H, d, J = 7.6 Hz, ArH), 6.93 (1H, dd, J = 7.8 and 8.1 Hz, ArH), 6.79 (1H, d, J = 8.1 Hz, ArH), 6.55 (1H, d, J = 7.7 Hz, ArH), 4.43 (2H, s, CH_2), 3.84 (3H, s, OCH_3), 3.75 (3H, s, OCH_3); CIMS m/z (relative intensity) 257 (MH^+), 239 (86); IR 1690 cm^{-1}. Anal. ($C_{16}H_{16}O_3$) C, H.

2-Amino-1-(2-(2,3-dimethoxyphenyl)methylphenyl)-ethan-1-ol (25). To a solution of 8.90 g (34.77 mmol) of aldehyde **24** in 200 mL of dichloromethane was added 5.0 mL (37.50 mmol) of trimethylsilyl cyanide, *via* syringe, and a catalytic amount (570 mg, 5 mol%) of zinc iodide.[46] This mixture was stirred under nitrogen at ambient temperature. After only a few minutes, the reaction mixture began spontaneous reflux so stirring was maintained until reflux ceased, approximately 4 h. TLC (dichloromethane) showed complete consumption of starting material, so the reaction mixture was washed with H_2O (1 × 100 mL), and the water was back extracted with dichloromethane (2 × 50 mL). The combined organic extracts were then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to yield the crude cyano silyl ether as an orange oil. This was not further characterized but was immediately dissolved in 200 mL of dry tetrahydrofuran under nitrogen. To this stirred solution was slowly added 100 mL of a 1.0 M solution of borane–tetrahydrofuran complex, in tetrahydrofuran (100 mmol). The resulting solution was heated at reflux overnight. The tetrahydrofuran was then removed *in vacuo*, and the residual sticky oil was redissolved in 400 mL of 5% HCl in methanol and again heated at reflux overnight under a nitrogen atmosphere to decompose the borane–amine complex. The solvent was again removed *in vacuo* to yield the crude amine hydrochloride salt of **25** which was redissolved in H_2O (150 mL). The aqueous solution was washed with ethyl ether (1 × 50 mL), basified with concentrated NH_4OH, and extracted with dichloromethane (3 × 100 mL). The combined dichloromethane fractions were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to yield 9.1 g (91%) of the free base **25** as a white amorphous solid of sufficient purity for further reaction. An analytical sample was purified by conversion to the hydrochloride salt and recrystallization from ethanol/ethyl acetate: mp (HCl salt) 148–152 °C; ^1H NMR (free base, $CDCl_3$) δ 7.50 (1H, dd, J = 7.7 and 1.4 Hz, ArH), 7.24 (1H, ddd, J = 7.7, 7.4, and 1.0 Hz, ArH), 7.18 (1H, ddd, J = 7.6, 7.4, and 1.4 Hz, ArH), 7.07 (1H, dd, J = 7.6 and 1.0 Hz, ArH), 6.92 (1H, t, J = 8.0 Hz, ArH), 6.78 (1H, dd, J = 8.2 and 1.3 Hz, ArH), 6.54 (1H, dddd, J = 7.8, 0.73, 0.92, and 0.55 Hz, ArH), 4.87 (1H, dd, J = 8.2 and 3.7 Hz, methine), 4.03 (2H, d, J = 1.8 Hz, Ar_2CH_2), 3.84 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.81 (1H, dd, J = 12.9 and 3.7 Hz, NCH-H), 2.67 (1H, dd, J = 12.9 and 8.2 Hz, H-CHN), 1.1–1.9 (3H, very br s, OH and NH_2); CIMS m/z (relative intensity) 288 (MH^+, 100), 270 (78). Anal. ($C_{17}H_{22}ClNO_3$) C, H, N.

10-(Aminomethyl)-9,10-dihydro-1,2-dimethoxyanthracene (19). Following a modification of the method of Pridgen *et al.*,[33] 1.11 g (3.88 mmol) of the free base **25** was dissolved in 20 mL of dichloromethane under a nitrogen atmosphere, and the solution was cooled for 20 min in an ice–salt bath. To the cold solution was added 2.0 mL each of trifluoroacetic acid and concentrated H_2SO_4, and the resulting two-phase mixture was stirred vigorously for 1 h while cooling was maintained. This cold mixture was diluted with an equal volume of H_2O and carefully basified with concentrated NH_4OH. An additional 50 mL of a saturated solution of NH_4Cl in 5% NH_4OH was added to the cold alkaline mixture, and then the organic layer was separated. The aqueous fraction was extracted repeatedly with chloroform, and the combined organic extract was washed with saturated 5% NH_4OH/NH_4Cl, dried ($MgSO_4$), and filtered. Solvent removal and purification by Chromatotron (dichloromethane/methanol, NH_3) provided 702 mg of the free base **19** as a light amber oil which was a single spot on TLC: ^1H NMR ($CDCl_3$) δ 7.32 (1H, m, ArH), 7.28 (1H, m, ArH), 7.21 (2H, m, 2ArH), 7.00 (1H, d, J = 8.3 Hz, ArH), 6.81 (1H, d, J = 8.2 Hz, ArH), 4.24 (1H, d, J = 19.3 Hz, Ar_2CH-*H*), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.84 (1H, m, methine), 3.79 (1H, d, J = 19.3 Hz, Ar_2CH-*H*), 2.80 (2H, ddd, J = 7.0, 3.2, and 3.0 Hz, CH_2N), 1.30 (2H, br s, NH_2); CIMS m/z 270 (MH^+); high-resolution EIMS 269.1408 (calcd 269.1416).

10-((2′-Chloroacetamido)methyl)-9,10-dihydro-1,2-dimethoxyanthracene (26). A solution of 907 mg (3.37 mmol) of amine **19** in 50 mL of dichloromethane was cooled for 20

min under nitrogen in an ice bath before the addition, *via* syringe, of 0.7 mL (5.06 mmol) of triethylamine followed by 0.3 mL (3.77 mmol) of α-chloroacetyl chloride. The reaction mixture was allowed to stir and gradually warm to ambient temperature for 2 h with TLC monitoring (3:1 hexane/ethyl acetate, NH_3). When TLC showed complete reaction, the mixture was washed with H_2O (1 × 30 mL), and the aqueous fraction was back-extracted with dichloromethane (2 × 25 mL). The combined organic fractions were then dried ($MgSO_4$) and filtered, and the solvent was removed to provide 991 mg (85%) of **26** as a yellow oil which began to darken quickly and so was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.34 (1H, m, ArH), 7.28 (1H, m, ArH), 7.23 (2H, m, ArH), 7.01 (1H, d, J = 8.3 Hz, ArH), 6.82 (1H, d, J = 8.3 Hz, ArH), 6.55 (1H, br s, CONH), 4.28 (1H, d, J = 19.4 Hz, Ar_2CH-*H*), 4.07 (1H, dd, J = 7.7 and 7.4 Hz, methine), 4.01 (2H, s, CH_2Cl), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.81 (1H, d, J = 19.4 Hz, Ar_2CH-*H*), 3.40 (2H, dd, J = 13.3 and 6.0 Hz, CH_2N); CIMS m/z (relative intensity) 348 (13), 347 (9), 346 (MH^+, 40), 239 (44); EIMS m/z (relative intensity) 345 (M^+, 1.2), 346 (1.6), 343 (1.8), 240 (18), 239 (100); high-resolution EIMS 345.1139 (calcd 345.1132).

6,7-Dimethoxy-1,2,3,4,8,12b-hexahydroanthr[4,4a,10-*de*]azepin-3-one (27). Via a modification of the procedure of Ladd *et al.*,[17] a solution of 1.72 g (4.98 mmol) of crude **26** in 350 mL of absolute methanol was placed under nitrogen in a quartz photoirradiation cell[44] and irradiated for 1 h with a 450-W medium-pressure mercury vapor lamp. The reaction mixture was then neutralized by addition of saturated aqueous $NaHCO_3$ to pH 7, and the solvent was removed *in vacuo*. The residue was redissolved in 75 mL of dichloromethane, washed with H_2O (1 × 50 mL) and saturated aqueous $NaHCO_3$ (1 × 50 mL), dried ($MgSO_4$), and filtered. Solvent removal provided an amber oil which was recrystallized from ethyl acetate to yield 506 mg (36% based on recovered **26**) of lactam **27** as off-white crystals: mp 234–237 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (1H, dd, J = 4.8 and 3.8 HZ, ArH), 7.25 (3H, m, 3ArH), 6.64 (1H, s, ArH), 6.17 (1H, br s, CONH), 4.20 (1H, d, J = 18.9 Hz, Ar_2-CH-*H*), 4.17 (1H, br d, J = 10.1 Hz, methine), 3.93 (1H, d, J = 15.0 Hz, ArCH-*H*), 3.92 (1H, m, NCH-*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.81 (1H, d, J = 14.7 Hz, ArCH-*H*), 3.79 (1H, d, J = 18.9 Hz, Ar_2CH-*H*), 3.76 (1H, m, *H*-CHN); CIMS m/z 310 (MH^+); high-resolution CIMS 310.1432 (calcd 310.1443). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

6,7-Dimethoxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine (28). The lactam **27** (128 mg, 0.414 mmol) was dissolved, under nitrogen, in 25 mL of dry tetrahydrofuran. To this stirred solution was added, *via* syringe, 1.3 mmol (1.3 mL of a 1 M solution) of borane–tetrahydrofuran complex, and the mixture was heated at reflux overnight. The reaction was then allowed to cool to ambient temperature, and the tetrahydrofuran was removed *via* rotary evaporation. The residue was carefully redissolved in 5% methanolic HCl and again heated overnight at reflux, under nitrogen. The methanol was removed, and the residue was redissolved in 100 mL of H_2O, washed with ether (1 × 30 mL), and basified to pH 11 with concentrated NH_4OH. The alkaline mixture was then extracted with dichloromethane (3 × 50 mL), the combined organic extract was dried ($MgSO_4$), and filtered, and the solvent was removed to yield 107 mg (88%) of **28** as the free base. An analytical sample of this was reconverted to the hydrochloride salt and recrystallized from ethanol/ethyl acetate to give white needles: mp (HCl salt) >213 °C dec; ^{1}H NMR (HCl salt, DMSO-d_6) δ 10.19 (1H, br s, HN-H^+), 9.16 (1H, br s, *H*-NH^+), 7.59 (1H, d, J = 7.4 Hz, ArH), 7.29 (3H, m, 3ArH), 6.93 (1H, s, ArH), 4.84 (1H, d, J = 9.7 Hz, methine), 4.12 (1H, d, J = 20.8 Hz, Ar_2CH-*H*), 3.91 (1H, d, J = 20.3 Hz, Ar_2CH-*H*), 3.81 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.57 (1H, ddd, J = 12.8, 4.9 and 4.4 Hz, *H*-CHN), 3.46 (1H, dd, J = 14.2 and 12.5 Hz, ArCH-*H*), 3.37 (1H, d, J = 12.5 Hz, ArCH-*H*), 3.00 (1H, br m, *H*-CHN), 2.91 (1H, ddd, J = 15.4, 5.3, and 5.0 Hz, NCH-*H*), 2.76 (1H, br m, NCH-*H*); CIMS m/z 296 (MH^+); high-resolution CIMS 296.1639 (calcd 296.1651). Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.85; H, 6.70; N, 4.23. Found: C, 69.37; H, 6.84; N, 4.28.

6,7-Dihydroxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4-*cd*]azepine Hydrobromide (5). A solution of 107 mg (0.363 mmol) of the free base **28** in 15 mL of dichloromethane was cooled for 20 min in a dry ice–acetone bath (−78 °C) followed by the dropwise addition of 0.12 mL (1.27 mmol) of neat boron tribromide (BBr_3). The reaction mixture was allowed to warm to ambient temperature, with stirring, over 2 h. The reaction was then quenched by the addition of 6 mL of methanol and stirring for another 15 min. The solution was then concentrated *in vacuo*, and ethyl acetate was added to induce crystallization. After several days in the freezer, 56 mg (45%) of **5**·HBr was collected as off-white needles: mp >200 °C dec; ^{1}H NMR (HBr salt, DMSO-d_6) δ 9.24 (1H, br s, OH), 9.14 (1H, br m, HN-H^+), 8.82 (1H br m, *H*-NH^+), 8.44 (1H, br s, OH), 7.48 (1H, d, J = 7.1 Hz, ArH), 7.28 (3H, m, 3ArH), 6.61 (1H, s, ArH), 4.59 (1H, d, J = 10.1 Hz, methine), 4.05 (1H, d, J = 20.8 Hz, Ar_2CH-*H*), 3.77 (1H, d, J = 20.7 Hz, Ar_2CH-*H*), 3.54 (1H, br d, J = 11.6 Hz, H-CHN), 3.37 (1H, m, ArCH-*H*), 3.27 (1H, m, ArCH-*H*), 2.96 (1H, m, NCH-*H*), 2.73 (2H, m, CH_2N); CIMS m/z 268 (MH^+); High Res. CIMS 268.1327 (calcd 268.1338). Anal. ($C_{17}H_{18}BrNO_2$) C, H, N.

10-(Aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene Hydrobromide (6). Via the same procedure described for **4**, 196 mg (0.729 mmol) of the free base **19** was treated with 0.2 mL (2.12 mmol) of neat BBr_3. Workup and crystallization from methanol/ethyl acetate yielded 119 mg (51%) of **6**·HBr as off-white needles: mp >210 °C dec; ^{1}H NMR (HBr salt, DMSO-d_6) δ 9.25 (1H, br s, OH), 8.55 (1H, br s, OH), 7.70 (3H, br s, NH_3), 7.37 (2H, m, 2ArH), 7.25 (2H, m, 2ArH), 6.69 (1H, dd, J = 8.1 Hz, ArH), 6.67 (1H, d, J = 8.1 Hz, ArH), 4.14 (1H, d, J = 19 Hz, Ar_2CH-*H*), 4.11 (1H, dd, J = 8.2 and 7.7 Hz, methine) 3.69 (1H, d, J = 19 Hz, Ar_2CH-*H*) 2.85 (2H, m, CH_2N); CIMS m/z 242 (MH^+). Anal. ($C_{15}H_{16}$-$BrNO_2$) C, H, N.

Molecular Modeling. All computations were performed for the free amines using a Tektronix CAChe worksystem running Tektronix proprietary software (CAChe Version 2.8, Tektronix, Inc., 1991). Energy minimization of all structures was performed with CAChe Molecular Mechanics Version 2.8 which uses Allinger's MM2 force field[47] as augmented by Tektronix. Minimized structures were refined further using MOPAC Version 2.8 software, by James J. P. Stewart, which evaluates the Schrödinger equation using the AM1 semiempirical Hamiltonian developed by M. J. S. Dewar.[48] Generation of the energy profiles associated with ring inversion for **2**–**6** was also performed using MOPAC Version 2.8. Superpositions were defined as three point overlaps using the two catechol oxygens and C1 of the phenyl ring in the dopamine pharmacophore.

Pharmacology. Tissue Preparation. Male Sprague–Dawly rats weighing 200–400 g were decapitated and the brains quickly removed and placed into ice-cold saline. Brains were then sliced into 1.5 mm coronal slices with the aid of a dissecting block according to the method of Heffner *et al.*[49] The striatum was dissected from two slides containing the majority of this region, and the tissue was either used immediately or stored at −70 °C until the day of the assay.

Radioligand Competition Assays. Radioligand competition assays at the D_1 receptor were done according to the method of Schultz *et al.*[50] with minor modifications. Rat striata were homogenized by seven manual strokes in a Wheaton Teflon–glass homogenizer in ice-cold 50 mM HEPES buffer with 4.0 mM $MgCl_2$, pH 7.4 (25 °C). Tissue was centrifuged at 27000*g* for 10 min, the supernatant was discarded, and the pellet was homogenized (5 strokes), resuspended in ice-cold buffer, and centrifuged again. The final pellet was suspended at a concentration of approximately 2.0 mg wet weight/mL.

Assay tubes containing tissue, 0.3 nM [^{3}H]SCH 23390, and increasing concentrations of test compound in a final volume of 1 mL (assay buffer: 50 mM HEPES buffer with 4.0 mM $MgCl_2$, pH 7.4) were incubated at 37 °C for 15 min. Nonspecific binding of [^{3}H]SCH 23390 was defined by adding unlabeled SCH 23390 (1 μM). Binding was terminated by filtering with 15 mL of ice-cold buffer on a Skatron filtration apparatus using glass fiber filter mats (Skatron no. 7034). Filters were allowed to dry and 2.0 mL of OPTIPHASE HI-SAF II scintillation fluid was added. After shaking for 30 min, radioactivity was determined on an LKB-1219 Betarack liquid scintillation

counter. Tissue protein levels were estimated using the BCA protein assay reagent.

The binding procedure and protein analysis was identical to that described for the D_1 receptor except that [^{3}H]spiperone was used as the radioligand. Nonspecific binding of [^{3}H]-spiperone was defined by adding unlabeled chlorpromazine (1 μM). Ketanserin tartrate (50 nM) was used to mask binding of [^{3}H]spiperone to serotonin receptors.

Data from both receptor systems were analyzed by nonlinear regression using the Prism software package (Graph Pad, Inc.). The IC_{50} values obtained were converted to $K_{0.5}$ *via* the use of Cheng-Prusoff relationship for single-site competition model. While these values do not represent true K_D's (because the Hill coefficients were often <1), the $K_{0.5}$'s permit interexperimental comparisons better than the IC_{50} value (which is radioligand concentration dependent) does.

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