Synthesis and Dopaminergic Activity of Some 3-(1,2,3,6-Tetrahydro-1-pyridylalkyl)indoles. A Novel Conformational Model To Explain Structure–Activity Relationships

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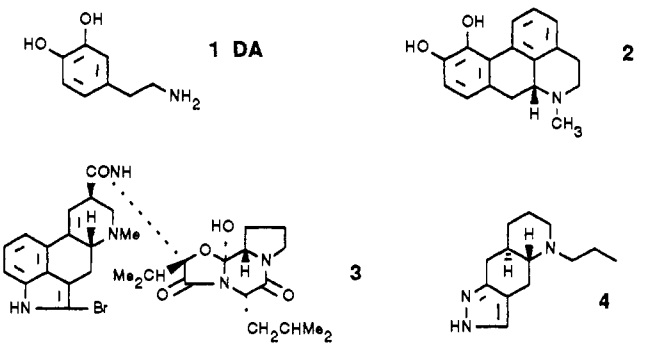
The synthesis and dopaminergic properties of a novel type of dopamine agonist is described. The number and kind of essential structural elements differ significantly from that of the rigid apomorphine-type dopamine agonists. Using standard molecular modeling techniques, a conformational model is developed proposing a U-shaped conformation which might be energetically preferred through aromatic π–π-interactions between both of the electron rich aromatic structural elements of this class of compounds. Superimposition of conformations of the lead compound **28** with apomorphine yields a novel model explaining the atypical structure–activity relationships found in this class of indolealkylamines.

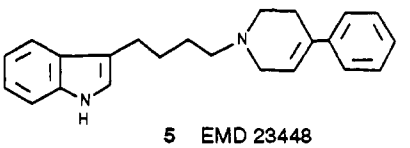
Dopamine (DA, 1) is an important neurotransmitter both in the central nervous system and in peripheral tissues. Malfunction of the dopaminergic system has been proposed to play a major role in diseases like schizophrenia and parkinsonism.[1] Although treatment is available with drugs influencing the dopaminergic system, the therapy of these diseases is far from being satisfactory. Particularly DA agonists with specific action on DA receptor subtypes have recently drawn much attention in this field.[2] Structural aspects of these agents have been extensively reviewed:[3] DA agonists (Chart I) structurally derive from either DA itself (rigid analogs with a hydroxyphenethylamine moiety like apomorphine (**2**) and partial structures thereof) or the ergot skeleton (bromocryptine (**3**), quinpirole (**4**)).

The molecular substructure responsible for the dopaminomimetic activity in the case of apomorphines and related structures is the rigid dopamine as has been established by the thorough work of Cannon[4] and other groups.[5] Kornfeld and co-workers in comparing the absolute configuration of apomorphine and ergot compounds came to the hypothesis that the rigid pyrroleethanamine moiety of the ergot structures is responsible for the DA-agonist activity of these compounds.[6]

We found a new class of compounds, 3-(1,2,3,6-tetrahydro-1-pyridylalkyl)indoles,[7] not sharing any of these structural features of DA agonists. The protagonist of this group of compounds, **5** (EMD 23448), discovered in a random screening program in rats with unilateral 6-hydroxydopamine lesions in the substantia nigra (Ungerstedt model),[8] has proved to be a potent DA autoreceptor agonist and agonist at supersensitive postsynaptic D_2-receptors with virturally no activity at the normosensitive postsynaptic D_2-receptor.[9,10]

Chart I





5 EMD 23448

† Preclinical Pharmaceutical Research.
‡ Central Analytical Laboratory.

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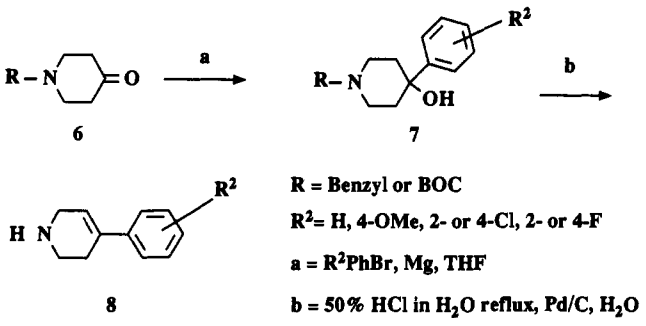
Scheme I



To understand the structure–activity relationship in this class of DA agonists we investigated the structural features necessary for the unique DA agonistic profile of this compound by modifying the structural elements: the indole, the four-carbon chain, and the 4-phenyl-1,2,3,6-tetrahydropyridine. Furthermore we applied molecular modeling techniques to find an explanation for the unique structure–activity relationships in this class of DA agonists in comparison to other DA agonists acting at D_2-receptors.

Chemistry

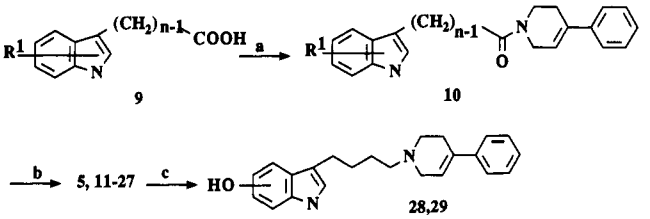
The 4-phenyl-1,2,3,6-tetrahydropyridines **6** were prepared as indicated in Scheme I via reaction of the corresponding phenyl Grignard reagent with either *N*-benzyl- or *N*-(*tert*-butoxycarbonyl)-4-piperidone. The *N*-benzyl group was removed by hydrogenolysis over Pd/C. Acidic dehydration of the 4-hydroxy-4-arylpiperidine **7** (refluxing HCl) yielded the desired N-unsubstituted 4-aryl-1,2,3,6-tetrahydropyridines **8**. The *N*-(*tert*-butoxycarbonyl) group was removed under acidic dehydration conditions.

Indole-3-alkanoic acids **9**, if not commercially available, were obtained following a Japp–Klingemann-type Fischer indole synthesis.[11] Suitably substituted anilines were diazotized, and the diazonium salts were condensed with ethyl 1-oxocyclohexane-2-carboxylate. The resulting substituted phenylhydrazones were converted under acidic conditions to the corresponding 2-(ethoxycarbonyl)indole-3-butanoic acids, which after saponification and decarboxylation yielded the desired compounds. The *N*-methylindole-3-butanoic acid was prepared by methylation of indolebutanoic acid.

As indicated in Scheme II, the indole-3-alkanoic acids **9** were condensed with the 1,2,3,6-tetrahydropyridines **8** by means of *N,N*-carbonyldiimidazole in tetrahydrofuran. The amides **10** obtained were reduced by LAH or by dihydrobis(methoxyethanolato-*O,O'*)aluminate sodium in THF to the tertiary amines **5** and **11–27**.

Cleavage of the methoxy compounds **26** and **27** to the corresponding phenols **28** and **29** was only possible with mild reagents due to the sensitivity of these indoles to strong acid. Superior to acidic conditions with pyridine hydrochloride was a reductive ether cleavage by diisobutylaluminum hydride in refluxing toluene.[12]

Scheme II



a = 8, N,N-Carbonyldiimidazole, THF
b = Red-Al, THF or LAH, THF
c = DIBAH, Toluene, THF 100°C

Biological Results

Dopaminergic activity of compounds **5**, **10–29** was evaluated by their ability to displace tritiated receptor ligands in rat striatal membranes; [^{3}H]ADTN, a dopamine agonist[13] and [^{3}H]spiperone, a DA antagonist[14] were used. Furthermore, dopaminergic activity was determined in vivo by the ability of the compounds to induce contralateral rotational behavior in rats with unilateral, 6-hydroxydopamine-induced lesions of the substantia nigra,[8] a measure for the action on supersensitive postsynaptic D_2-receptors. The biological data obtained for the various compounds tested are summarized in Table I.

Firstly we examined the role of the carbon chain length in these molecules (compounds **5**, **11–14**). In the ligand binding experiments no significant differences were found in the ability of the compounds to displace the tritiated ligands. In contrast, in the Ungerstedt rat model, the peak activity was clearly found in the compound with the four-carbon chain, whereas none of the other products reached a significant activity after oral administration in this test. The amides **10** did not show any binding affinity in the binding assays used up to a concentration of 100 nM (results not shown), pointing to the importance of a basic nitrogen for the dopaminergic activity.

Surprisingly, all variations in the basic part of the indole alkylamines **15–21** led to loss of activity in the Ungerstedt model. Not only substituents in the phenyl part, but also hydrogenation of the double bond in the tetrahydropyridine as well as omission of the phenyl substituent led to inactive compounds. The remaining binding capacity of some of these compounds may represent a weak dopamine antagonistic action.

The products with substituents in the indole **21–28** generally retained the DA agonist activity. One exception is the 1-methyl-substituted indole pointing out the importance of the free indole NH for dopaminergic activity, and another exception is the 5-chloro compound.

A remarkable increase in dopaminergic activity was obtained with the 5-hydroxyindole compound **28** which is approximately 1 order of magnitude more potent than **5**, as could be shown in dose–response studies in the Ungerstedt model presented in Table II. This result was also confirmed in tests for D_2-autoreceptor selectivity (reversal of GBL-induced striatal DOPA accumulation)

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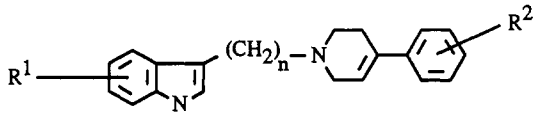
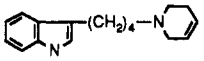
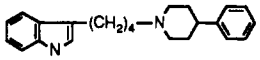
Table I. Physical Properties, Ligand Binding, and Pharmacological Evaluation of Target Compounds



compd	R^1	R^2	n	yield %	mp, °C	formula	receptor binding[a] [^{3}H]SPIP IC_{50} nM	receptor binding[a] [^{3}H]ADTN K_I, nM	contralateral turning, turns/first hour ± SEM, (n = 4 rats, 3 mg/kg po)
5	H	H	4	89	221	$C_{23}H_{26}N_2$·HCl	105 ± 35	6.39 ± 0.94	864 ± 108
11	H	H	2	54	262–263	$C_{21}H_{22}N_2$·HCl	100	81	<50
12	H	H	3	92	239–241	$C_{22}H_{24}N_2$·HCl	50	12	~250
13	H	H	5	38	258–260	$C_{24}H_{28}N_2$·HCl	60	13	<50
14	H	H	6	36	208	$C_{25}H_{30}N_2$·HCl	40	4.3	<100
15	H	4-F	4	28	254	$C_{23}H_{25}FN_2$·HCl	90	15	<100
16	H	2-F	4	39	110–112	$C_{23}H_{25}FN_2$	20	4.0	186 ± 64
17	H	4-Cl	4	48	260–262	$C_{23}H_{25}ClN_2$·HCl	100	46	100
18	H	2-Cl	4	44	168–170	$C_{23}H_{25}ClN_2$·HCl	100	21	<50
19	H	4-OMe	4	66	229	$C_{24}H_{28}N_2O$·HCl·0.5H_2O	700	41	<50
20				59	140–141	$C_{17}H_{22}N_2$·HCl	>1000	>1000	<100
21				72	213–215	$C_{23}H_{28}N_2$·HCl	>100	>100	<50
22	1-Me	H	4	71	171–173	$C_{24}H_{28}N_2$·HCl	100	15	121 ± 42
23	2-Me	H	4	62	218–220	$C_{24}H_{28}N_2$·HCl	50	5.4	318 ± 168
24	5-F	H	4	59	229	$C_{23}H_{25}FN_2$·HCl	10	1.6	552 ± 258
25	5-Cl	H	4	29	226–228	$C_{23}H_{25}ClN_2$·HCl	50	3.1	<50
26	5-OMe	H	4	63	181	$C_{24}H_{28}N_2O$·HCl	20	4.4	504 ± 96
27	6-OMe	H	4	53	208–210	$C_{24}H_{28}N_2O$·HCl	9.0	1.8	792 ± 120
28	5-OH	H	4	79	274	$C_{23}H_{28}N_2O$·HCl	5.95 ± 0.90	0.88 ± 0.22	948 ± 72
29	6-OH	H	4	44	189	$C_{23}H_{26}N_2O$	8.0	2.5	786 ± 240

[a] Means ± SD of 2–4 independent determinations where applicable. For single determinations the coefficient of variation for triplicates of one concentration was 2–4%.

Table II. Pharmacological Data of **5** and **28** in Rat Models of D_2-Receptor Activity

compound no., mg/kg	total contralateral turns, means ± SEM (n = 3–6 rats) t = 1 h	total contralateral turns, means ± SEM (n = 3–6 rats) t = 2 h	striatal DOPA accumulation, ED_{50}, mg/kg sc[a] reversal of GBL-induced	striatal DOPA accumulation, ED_{50}, mg/kg sc[a] inhibition of reserpine-induced	striatal AcCh concentration, ED_{50}, mg/kg sc[a] (increase, intact rat)
5			2.3	0.8	>3
0.3 po	99 ± 60	236 ± 156			
1 po	201 ± 68	412 ± 136			
3 po	825 ± 137	1731 ± 219			
0.1 sc	44 ± 12	68 ± 20			
0.3 sc	422 ± 87	936 ± 364			
28			0.12	0.074	>30
0.1 po	251 ± 40	287 ± 50			
0.3 po	397 ± 120	534 ± 192			
1 po	830 ± 234	1694 ± 520			
3 po	926 ± 175	2010 ± 328			
0.03 sc	399 ± 67	718 ± 217			
0.1 sc	1132 ± 162	2246 ± 296			
2 (apomorphine)			0.13	0.051	0.28
0.03 sc	1268 ± 201				
synaptic site		postsynaptic	presynaptic	post-/presynaptic	postsynaptic
receptor state		supersensitive	normosensitive	supersensitive	normosensitive

[a] Data from ref 27: ED_{50} values were of obtained from dose–response curves with 4–6 doses and 4–10 rats per dose with SEM values ≤10% of absolute values for individual doses.[15]

and for supersensitive post- and presynaptic D_2-receptors (inhibition of reserpine-induced DOPA accumulation). In the case of normosensitive rats, compounds **5** and **28** in contrast to apomorphine did not show activity in increasing striatal acetylcholine concentration, even in high doses,[15] indicating lack of activity at normosensitive, postsynaptic D_2-receptors. Compound **28** (EMD 38362) has been chosen for further development. Due to its superior solubility, the methanesulfonate salt (EMD 49 980) was selected for further clinical evaluations.

Molecular Modeling

The molecular geometry of **5** obtained by X-ray single crystal determination was minimized with the Tripos force field.[16] The free base of **5** was used for this calculation. Since the resulting conformation exhibits significant

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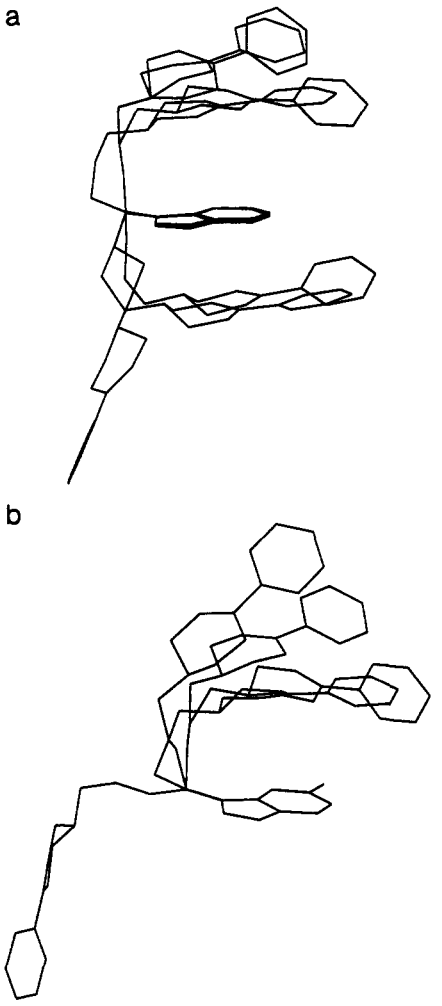

Figure 1. (a) Superposition of low-energy conformations of **5** found within 1 kcal/mol. The reference system for the fit is the indole ring system. (b) Superposition of low-energy conformations of **28** found within 1 kcal/mol. The reference system for the fit is the indole ring system.

distortions in the tetrahydropyridyl ring, the two ring systems were kept fixed as aggregates. A full conformational search was performed for the parent structure **5** and its most active derivative **28**, respectively. To determine the preferred conformation of **5** and **28** the five bonds of the aliphatic carbon chain were systematically rotated by 30°. The additional rotatable bond of the hydroxy group of **28** was treated in the same manner. The results were analyzed with the SEARCH routine of the SYBYL program. The energies of all conformations were calculated. Charges were generated with the Gasteiger–Marsilli algorithm. The computations reveal for **5** 888 conformations within 5 kcal/mol and 136 within 3 kcal/mol of the energy minimum and for **28** 7229 and 1047 conformations, respectively. As expected the conformational analysis of both compounds **5** and **28** yield, due to their molecular flexibility, various different conformations within a reasonable low-energy range. A superimposition of the lowest energy conformations of **5** and **28** within 1 kcal/mol is shown in Figure 1, parts a and b, respectively. It turns out that the most favored conformations for both molecules adopt a U-turn bringing the two aromatic systems of the opposite ends of the molecules in close spatial neighborhood.

There are remarkable differences of the low-energy conformations between **5** and **28** concerning the distance and orientation of the aromatic moieties. However, corresponding orientations of both molecules were found in the conformations calculated within 3 kcal/mol above the global minimum, respectively. Hydroxy substitution modifies the relative energetic preference of common conformations. The indole hydroxy substituent obviously has a profound influence on the interaction of the two aromatic ring systems in these indolealkylamines.

This type of calculation does not allow clear-cut conclusions to be drawn about the receptor-bound conformation of **5** or **28** but allows a description of the intrinsic conformational behavior of these flexible molecules. Various conformations are energetically favored. No direct evidence can be obtained on which conformations will be selected for the interaction with the DA receptor, but it is interesting to note that U-shaped conformations dominate as low-energy conformations of the dopaminergic molecules considered here.

Results and Discussion

Numerous contributions on the structural and conformational requirements of the dopaminergic pharmacophore have been published, and a number of rigid dopamine analogs have been synthesized and conformationally analyzed to understand the interaction of dopamine agonists with the dopamine receptor.[1,17-20] The spatial relationship between the phenolic hydroxyl group, the aromatic ring, and the basic nitrogen atom have been found to be similar in all molecules shown to be able to activate central pre- and postsynaptic D_2-receptors. Concerning the aromatic ring-to-side chain orientation, near coplanarity of the catechol ring and the ethylamine side chain of DA is required for activity. DA seems to interact with its receptors in a fully extended trans conformation.[1]

The current understanding of DA receptor structural requirements apparently does not agree with the structure–activity relationship for the dopaminergic activity in the indolebutylamine series. Essential structural elements for the dopaminergic activity are (1) the indole NH functionality, (2) the electron-rich aromatic indole, (3) an aliphatic chain of four carbons, (4) the basic nitrogen in the tetrahydropyridine moiety, (5) the double bond in the tetrahydropyridine moiety, and (6) the unsubstituted 4-phenyl substituent in the tetrahydropyridine moiety. Especially the two last requirements taken together with the required four-carbon-chain are in contrast with the previous conception of dopaminergic activity. Therefore it was necessary to analyze the conformational features of this class of molecules to reach an understanding of its DA activity in relation to the well-established description of known DA agonists.

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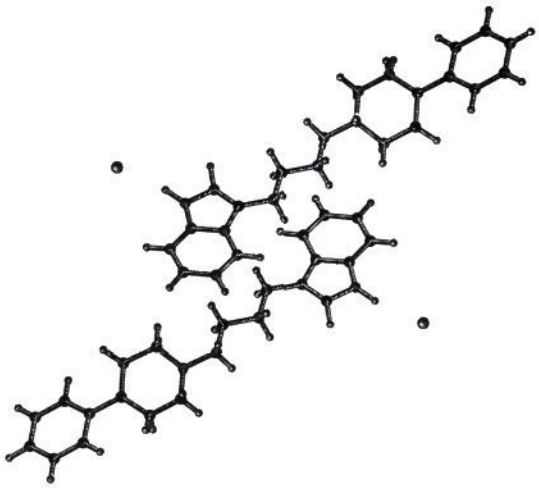

Figure 2. The two conformational isomers found in the X-ray crystal structure of compound **5** (EMD 23448).

In the crystal form compound **5** adopts an extended form represented by two different conformations as shown in Figure 2. This behavior reflects the remarkable flexibility of the molecule. Due to its hydrochloride form, ionic interactions dominate the molecular packing and therefore, the molecular conformation seems to be strongly determined by crystal forces. To understand structure–activity relationships in this new class of DA agonists, we tried superpositions with the prototype rigid DA agonist apomorphine.[21] Apomorphine, although not a selective DA agonist, seemed especially suitable to us for its molecular structure contains a rigid conformation of the dopaminergic pharmacophore, the *m*-hydroxyphenethylamine unit.[1] No reasonable fit can be obtained by superpositioning the hetero atoms N and O and the aromatic ring system of these two structures. Therefore the conformations in the crystalline state, especially the steric pattern of the essential structural elements, cannot be used to explain the DA agonistic activity of **5**.

From inspection of the topology of **5** and its more potent derivative **28**, it is obvious that, due to the aliphatic chain of five freely rotatable bonds, the molecule is extremely flexible. The theoretical analysis using molecular mechanics reflects this by yielding numerous conformations within a reasonable energy range. It is not possible to draw a clear conclusion for a specific preferred conformation from these computational results. As shown in Figure 3a,b the favored conformations span a wide range of foldings from more extended conformations as found in the crystal structure to more turn-like structures bringing the two aromatic systems of the individual molecules in close spatial contact. Within the SYBYL force field applied here the U-shape belongs to the most favored conformations in vacuum.

The main conclusion from the conformational analysis is that the molecular topology of **5** and its derivatives enables the two aromatic residues to get in close contact and presumably to interact with each other. This finding opens an approach to explain the DA agonistic properties of indolealkylamines. Assuming that the indolealkylamines and apomorphine bind to the same receptor site in the same mode, it is necessary that a similar volume

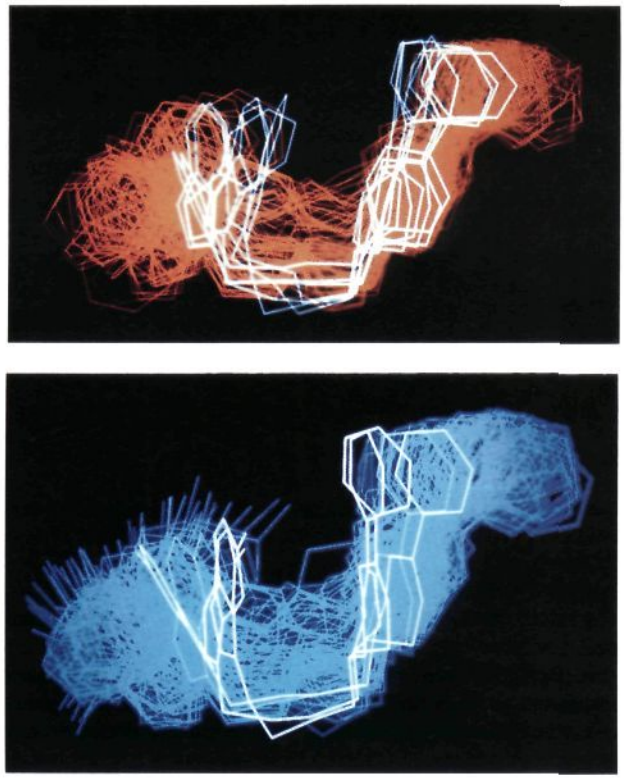

Figure 3. (top) Superposition of low-energy conformations of **5** found within 3 kcal/mol. The conformations within 1 kcal/mol are given in white. (bottom) Superposition of low-energy conformations of **28** found within 3 kcal/mol. The conformations within 1 kcal/mol are given in white.

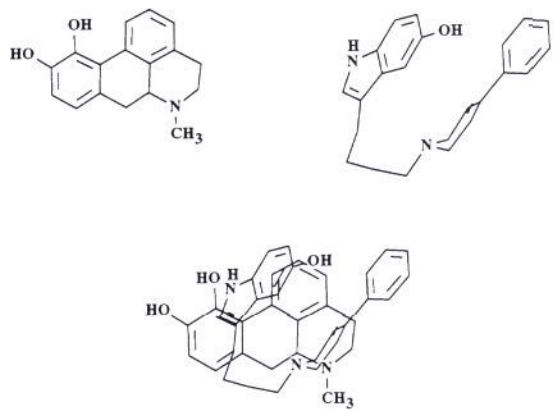

Figure 4. Superposition of the minimum-energy conformation of **28** with apomorphine. The indole NH function is mimicking the apomorphine hydroxy group.

and an appropriate orientation of the functional groups is present. Therefore a fit procedure was applied,[22] in which the overlapping volume of apomorphine[23] and **28** can be maximized. In Figure 4 additional constraints were imposed to minimize the distance between the corresponding functional groups (indole NH versus apomor-

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(22) In the fit procedure the overlapping volume is calculated by the volume of intersecting caps of the atomic spheres, where three translational and three rotational degrees of freedom were considered for the respective molecule. A random number generator is used to sample various orientations and a gradient minimization technique to find the optimum fit. The details of this procedure will be published elsewhere.

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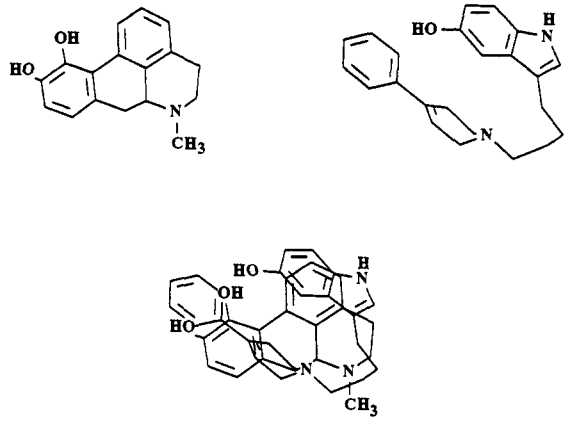

Figure 5. Superposition of the minimum-energy conformation of **28** with apomorphine for maximum volume overlap without consideration of additional distance constraints between the functional groups.

phine hydroxy group; basic nitrogens). In the model obtained for the superimposition of both molecules only the phenyl moiety of **28** protrudes significantly out of the common volume. Apomorphine appears sandwiched between both sides of the U-shaped **28**, so that the structural elements relevant for the interaction with a receptor are pointing in the same directions in space.

Another superimposition of both molecules is obtained when the same procedure for maximum volume overlap is performed without consideration of additional distance constraints between the functional groups. The result is shown in Figure 5. In this case the volume fit is further improved substantially; especially the aromatic moieties of **28** and apomorphine have similar positions in space. This model implicates that not the indole NH function but the 5-hydroxyindole substituent mimics the 11-hydroxy group of apomorphine, since both groups point into the same direction in space; however, both are bound to spatially different aromatic systems.

The following discussion of dopaminergic activity in the series of indolealkylamines refers primarily to the first model (Figure 4), since the second molecular fit is only applicable if a 5-hydroxyindole substituent is present. However, the improved biological activity of **28** versus **5** may be explained by the accessibility of the additional preferred orientation as shown in Figure 5. In general, the structure–activity relationship within this series may be explained by estimating the influence of substitutions on the interaction of both aromatic ring systems of the indolealkylamines. Strong interactions between π systems play an important role in various conformational phenomena.[24] The preferred geometries of π–π interactions depend on various parameters like separation, their relative orientation, and the polarization of the π systems.

The aliphatic carbon chain serves as a spacer between both aromatic ring systems. An energetically optimum distance of the aromatic systems can obviously not be achieved with a short carbon chain. However, increasing the length of the carbon chain spacer above the optimum of 4 carbons would result in a higher spatial demand of the molecule to reach the optimum distance between the aromatic systems.

The basic nitrogen in the tetrahydropyridine ring plays the same important role as the amine function in apomorphine and dopamine itself. Removal of the double bond influences the relative orientation of the 4-substituted phenyl ring. A tetrahedral carbon in a piperidine ring would result in a more perpendicular orientation of both rings compared to an almost planar orientation found in the crystal structure of **5**. The approach of the two aromatic systems to each other would be hindered by a nonplanar system. Additionally the double bond extends the aromatic system and thus favors π–π interaction. The space at the receptor site seems to be limited because even small substituents in the 4-phenyl ring result in a loss of dopaminergic activity.

Our model based on Figure 4 assumes that the indole NH function can mimic the aromatic OH group in apomorphine and dopamine, which is in accordance with the loss of dopaminergic activity by N-methylation of **5**. The aromaticity of the electron rich indole heterocycle seems to play an important role. Introduction of a chlorine atom significantly diminishes the dopaminergic activity, since the electron density of the aromatic rings is diminished.[24]

We tried to integrate our knowledge of structure–activity relationships in this class of dopamine agonists into the existing models of D_2-receptors derived from rigid analogs of DA. The fundamental of our model is the assumption of a strong intramolecular interaction between the π systems within the indolebutylamines. This type of attraction plays an important role in various conformational phenomena.[24] In recent D_2-receptor modeling studies phenylalanines seem to play an important role in the interaction with D_2-agonists.[25] The intrinsic potential of an intramolecular π–π interaction of the indolealkylamines may overlap with this receptor–ligand π–π interaction. The steric and electronic parameters that influence an optimum π–π interaction seem to play a crucial role to understand the structure–activity relationship in this group of DA agonists. The model of a U-shaped conformation of the indolealkylamines allowing a strong aromatic interaction may serve as novel explanatory tool in similar classes of atypical DA agonists[26] as well as in other catecholamine and serotonin receptor ligands characterized by a carbon chain spacer, whose length has been found to play a critical role in structure–activity relationships.

Experimental Section

Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. IR, ^{1}H-NMR, and mass spectra are in agreement with the structures and were recorded on a Brucker IFS 48 IR spectrophotometer, a Bruker AMX 300 MHz NMR spectrometer (TMS as an internal standard), and Vacuum Generators VG 70-70 or 70-250 at 70 eV, respectively. Crystal data were collected on an Enraf-Nonius CAD-4 diffractometer with monochromatic Mo K_α radiation. Elemental analyses (obtained with a Perkin-Elmer 240 B CHN analyzer) were within 0.4% of theoretical values. All reactions were followed by TLC carried out on E. Merck F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure. The obtained crystalline material was recrystallized from EtOH.

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General Methods. 1-[4-(3-Indolyl)butanoyl]-1,2,3,6-tetrahydro-4-phenylpyridine (10) (n = 4, R_1 = H). A solution of 4-(3-indolyl)butanoic acid (20.2 g, 0.1 mol) in 500 mL of THF is treated with *N,N'*-carbonyldiimidazole (16.2 g, 0.1 mol). After stirring for 1 h at room temperature, 1,2,3,6-tetrahydro-4-phenylpyridine hydrochloride (19.6 g, 0.1 mol) was added and stirring at room temperature was continued overnight. After evaporation the obtained residue was dissolved in ethyl acetate, washed with 1 N HCl and water, evaporated, and recrystallized from 1 L of EtOH to yield 22.1 g (67%), mp 156–157 °C. Anal. ($C_{22}H_{22}N_2O$) C, H, N.

3-[3-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-indole, Hydrochloride (5). A volume of 39.3 mL of a 70% solution of dihydrobis(methoxyethanato-*O,O'*)aluminate sodium in THF (40.4 g, 140 mmol) was added to a suspension of 1-[4-(3-indolyl)butanoyl]-1,2,3,6-tetra-4-phenylpyridine (9.6 g, 28 mmol) in THF. The obtained solution was stirred for 2 h at room temperature. After treatment with water and extraction with ethyl acetate, the organic layer was dried and concentrated in vacuo. The hydrochloride (6.1 g, 60%) was obtained from acetone by addition of 2-propanolic HCl as a pure crystalline product: mp 221 °C. Anal. ($C_{23}H_{26}N_2$·HCl) C, H, N, Cl.

5-Hydroxy-3-[4-(1,2,3,6-tetrahydro-4-phenyl-1-pyridyl)-butyl]indole, Hydrochloride (28). To 5-methoxy-3-[3-(1,2,3,6-tetrahydro-4-phenyl-1-pyridyl)butyl]indole (36 g, 0.1 mol) in 100 mL of toluene was added 200 mL of a 20% solution of diisobutylaluminum hydride (corresponding 34.1 g = 0.23 mol DIBAH) in toluene over a time course of 1 hour to yield a clear solution. The mixture was refluxed for 1.5 h. After cooling, excess hydride was decomposed by addition of 70 mL of ethanol and 50 mL of a 1:1 ethanol–water mixture. The resulting precipitate was collected and washed three times with 100 mL of acetone. The resulting acetone solutions were concentrated to yield the crystalline base of the desired product. The hydrochloride was obtained by treating a solution of the free amine in ethanol with HCl-saturated ethanol to yield 28.7 g (75%): mp 274 °C; ^{1}H-NMR (300.13 MHz, DMSO-d_6) δ 10.67 (br, 1 H, HN^+), 10.47 (d, 1 H, NH, J = 2.1 Hz), 8.56 (br, 1 H, OH), 7.50–7.28 (m, 5 H, phenyl), 7.12 (d, 1 H, indole-H7, $J_{6,7}$ = 8.6 Hz), 7.03 (d, 1 H, indole-H2, $J_{2,NH}$ = 2.2 Hz), 6.82 (d, 1 H, indole-4H, $J_{4,6}$ = 2.3 Hz), 6.59 (dd, 1 H, indole-H6, $J_{6,7}$ = 8.6 Hz); 6.16 (t br, 1 H, olef H), 3.95 (m br, CH), 3.72 (m, CH), 3.60 (m br, CH), 3.35–3.12 (m, CH, CH_2), 2.96–2.61 (m br, CH_2), 2.65 (t, CH_2, J = 7.1 Hz), 1.90–1.61 (m, $2CH_2$). Anal. ($C_{23}H_{26}N_2O$·HCl) C, H, N, Cl.

Crystal Data. **5**: $C_{23}H_{26}N_2$·HCl; M = 366.94; monoclinic; $P2_1/c$; a = 1572.6 (3) pm; b = 746.7 (1) pm, c = 1764.3 (2) pm and β = 105.67° (1); $V = 1994.7 \times 10^6$ pm^3; z = 4; ρ_x = 1.222 g cm^{-3}; μ(Mo K_α) = 1.974 cm^{-1}; F(000) = 784; no. of reflections with $I > 3\sigma(I)$ = 1811; no. of refinement parameters = 236; final R values, R = 0.054; R_w = 0.052. The crystal structure is disordered. The two enantiomer conformations present in the unit cell are indistinguishable due to the centrosymmetry of the crystal. For both carbon–carbon bonds, the 4,5-double bond and the 3,4-single bond, of the tetrahydropyridine moiety a mean length of 1.41 Å is obtained.

Pharmacological Methods. Receptor Binding Assays. The affinities of compounds for DA receptors were determined in a total volume of 2 mL containing 2–3 nmol/l [^{3}H]ADTN or 0.1 nmol/l [^{3}H]spiperone, respectively, and 0.3–1.0 mg of protein of rat striatal membranes per mL. Assay buffer was 50 mmol/L Tris/HCl, pH 7.1, 120 mmol/L NaCl, 5 mmol/L KCl, 1 mmol/L $CaCl_2$, 1 mmol/L $MgCl_2$, and 0.1% ascorbic acid in the case of ADTN and 50 mmol Tris/HCl, pH 7.7 and 0.1% ascrobic acid in the case of spiperone. Incubations were carried out at 37 °C for 15 min and terminated by rapid filtration (Whatman GF/B) and three washes with ice-cold buffer. Nonspecific binding was determined in the presence of 1 μmol/L (+)-butaclamol.[13,14]

Effects on Turning Behavior in 6-OH-DA-Lesioned Rats. Drugs were administered orally or subcutaneously to rats treated at least 1 month previously with unilateral injections of 6-hydroxydopamine into the substantia nigra (8 μg of 6-OH-DA per rat), and turns were recorded as previously described.[8]

DOPA Accumulation. Test compounds were administered to male Wistar rats. For the reversal of GBL-induced DOPA accumulation, 750 mg/kg GBL ip in saline and 100 mg/kg NSD 1015 ip in saline were administered 45 min prior to decapitation. For inhibition of reserpine-induced DOPA accumulation, reserpine (5 mg/kg sc) was given 19 h and NSD 1015 (100 mg/kg ip in saline) 45 min prior to decapitation. The striatum was dissected within 2 min and immediately processed for HPLC analysis.

Striatal Acetylcholine Concentration. Wistar rat striatum was dissected out on ice within 45 s and immediately sonicated in ice-cold 15% 1 N formic acid/acetone. Supernatants were lyophilized in a vacuum centrifuge. ACh was determined radioenzymatically.

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Registry No. **5**, 73966-53-7; **5**·HCl, 73966-59-3; **8** (R^2 = H), 10338-69-9; **8** (R^2 = 4-F), 1978-59-2; **8** (R^2 = 2-F), 143682-23-9; **8** (R^2 = 4-Cl), 30005-58-4; **8** (R^2 = 2-Cl), 97429-96-4; **8** (R^2 = 4-MeO), 59954-73-3; **9** (n=4, R^1 = H), 133-32-4; **9** (n=2, R^1 = H), 87-51-4; **9** (n=3, R^1 = H), 830-96-6; **9** (n = 5, R^1 = H), 1210-84-0; **9** (n=6, R^1 = H), 25177-65-5; **9** (n-4, R^1 = 1-Me), 16244-09-0; **9** (n=4, R^1 = 2-Me), 7394-83-4; **9** (n=4, R^1 = 5-F), 319-72-2; **9** (n=4, R^1 = 5-Cl), 105907-11-7; **9** (n=4, R^1 = 5-OMe), 83696-90-6; **9** (n-4, R^1 = 6-OMe), 36764-18-8; **10** (n=4, R^1 = R^2 = H), 73966-54-8; **10** (n=2, R^1 = R^2 = H), 143682-24-0; **10** (n=3, R^1 = R^2 = H), 143682-25-1; **10** (n=5, R^1 = R^2 = H), 143682-26-2; **10** (n=6, R^1 = R^2 = H), 143682-27-3; **10** (n=4, R^1 = 1-Me, R^2 = H), 143682-28-4; **10** (n=4, R^1 = 2-Me, R^2 = H), 143682-29-5; **10** (n=4, R^1 = 5-F, R^2 = H), 143682-30-8; **10** (n=4, R^1 = 5-Cl, R^2 = H), 143682-31-9; **10** (n=4, R^1 = 5-OMe, R^2 = H), 143682-32-0; **10** (n=4, R^1 = 6-OMe, R^2 = H), 143682-33-1; **11**, 15471-94-0; **11**·HCl, 143682-34-2; **12**, 143682-35-3; **12**·HCl, 143682-36-4; **13**, 143682-37-5; **13**·HCl, 143682-38-6; **14**, 143682-39-7; **14**·HCl, 143682-40-0; **15**, 143682-41-1; **15**·HCl, 143682-42-2; **16**, 143682-43-3; **17**, 143682-44-4; **17**·HCl, 143682-45-5; **18**, 143682-46-6; **18**·HCl, 143682-47-7; **19**, 143682-48-8; **19**·HCl, 143682-49-9; **20**, 143682-50-2; **20**·HCl, 143682-51-3; **21**, 143682-52-4; **21**·HCl, 143682-53-5; **22**, 73966-60-6; **22**·HCl, 143682-54-6; **23**, 143682-55-7; **23**·HCl, 143682-56-8; **24**, 143682-57-9; **24**·HCl, 143682-58-0; **25**, 143682-59-1; **25**·HCl, 143682-60-4; **26**, 143682-61-5; **26**·HCl, 143682-62-6; **27**, 143682-63-7; **27**·HCl, 143682-64-8; **28**, 112192-04-8; **28**·HCl, 108050-82-4; **29**, 143682-65-9.