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Dopamine Autoreceptor Agonists:

Computational Studies, Synthesis and Biological Investigations

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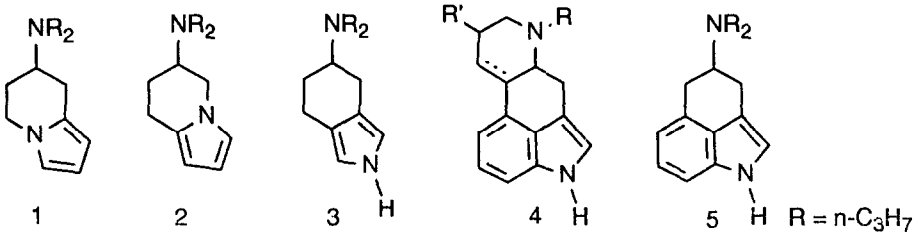
Abstract: Based on molecular modeling studies on the electronic properties of dopamine and dopamine agonists the pyrazolo[1,5-a]pyridine structure has been evaluated as a catechol surrogate. The azaergoline analogue **6**, including this moiety has been synthesized *via* 1,3-dipolar cycloaddition, anionic ring closure and electrophilic amination. The target compounds (**6**) exhibit DA autoreceptor agonistic activity.

Presynaptic dopamine receptors serve an inhibitory feed back function on dopaminergic neurotransmission.[1] Functionally, stimulation of the D-2 autoreceptor inhibits dopamine (DA) synthesis, release and DA neuronal firing. Since schizophrenia is associated with hyperactivity in the mesolimbic system (A 10 system) application of selective DA autoreceptor agonists is a very promising approach to a new class of neuroleptic drugs. [2] These atypical neuroleptics may offer a more subtle neurotransmitter regulation than the classical neuroleptics with D-2 antagonistic properties. As a consequence, considerable efforts have been dedicated to the design and synthesis of DA autoreceptor agonists without appreciable activity at the postsynaptic DA receptors resulting in compounds as (-)-3-PPP,[3] EMD 23448,[4] BHT 920 (talipexole) [5] and SND 919 (pramipexole).[6]

Since it is assumed that the binding sites of the postsynaptic D-2 receptor and its presynaptic analogues are very similar,[7] it seemed to be a valuable strategy to modify the structure of known D-2 receptor agonists. We have previously reported that the (S)-enantiomer of the aminotetrahydroindolizine **1** strongly reduces DA synthesis, causes sedation in mice and reveals strong and selective affinity to the D-2 receptor, labeled with the selective autoreceptor agonist SND 919.[8] On the other hand the regioisomer **2** exhibits only a low order of dopaminergic effects. Thus, structural manipulation of the aromatic moiety seems to be very promising but also very sensitive. **1** and **2** are structurally related to the DA agonistic isoindole derivative **3**, which is assumed to be the pharmacophoric core-structure of the ergolines (**4**).[9] Based on these observations, we here report on molecular design, synthesis and pharmacological investigations of analogues of the DA active tricyclic ergolines **5**.[9]



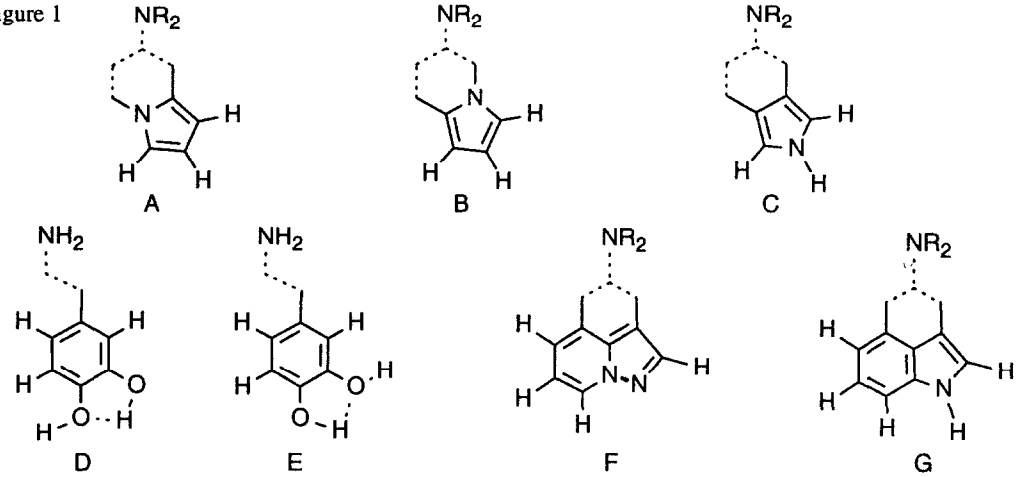
Computational Studies:

We planned to find suitable heterocyclic structures which should mimic the catechol framework of DA by comparing their molecular electrostatic potentials (MEPs) with those of DA and tri- or bicyclic ergoline analogues. Thus the charge distribution and the resultant electrostatic environment should be examined in detail.

This work was performed according to the following strategy: a) The structure of the molecules was first minimized employing the CVFF force field of the program DISCOVER.[10] b) Then, the geometry was further optimized by use of the MOPAC program system choosing the PM3 parameter set.[11] c) Based on the so obtained geometries ab initio calculations were performed using the GAUSSIAN 92 program system.[12] The single point calculations were performed at the RHF level of theory using the 6-31G* basis set. In consideration of the ab initio charge distributions an energy grid was calculated employing the DOCKING module of the program system INSIGHT II.[13] e) Finally, isopotential curves at -2.5 (white) or -7.5 (yellow) as well as 2.5 kcal/mol (pink) were contoured representing the interaction between a positive test charge (probe) and the calculated charge distribution.

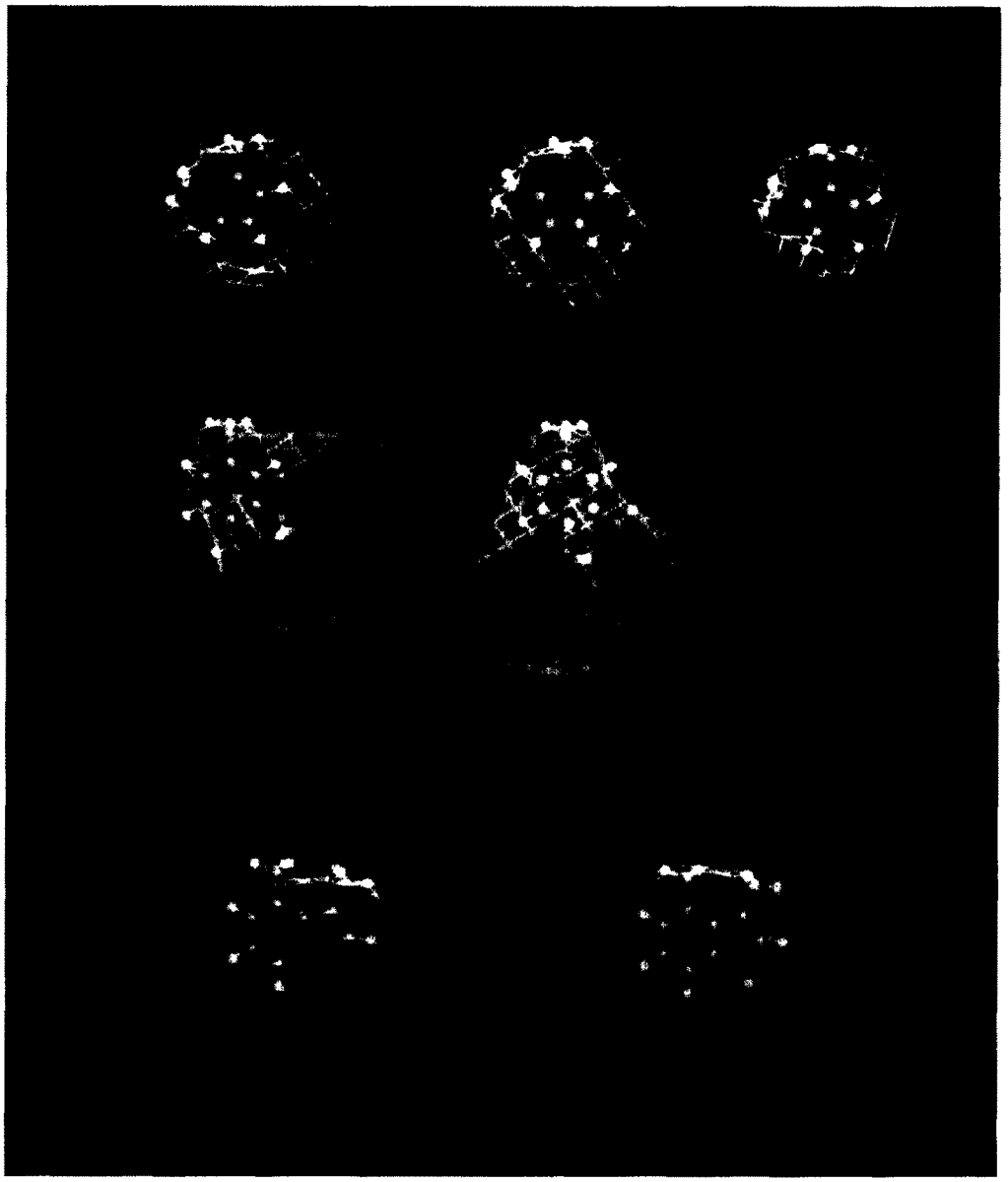
Before evaluating a new candidate the methyl- or dimethyl-substituted aromatic fragments of the aminoindolizidines **1** and **2** (**A**,**B**), as well as the substructures of the postsynaptically active bi-, and tricyclic ergoline analogues **3** and **5** (**C**, **G**) and of two dopamine low energy conformations (**D**, **E**) were subjected to the above described calculation procedure (Figures 1 and 2). The alkylamine containing residues of the molecules (dotted lines) should influence the electrostatic properties of the corresponding core fragments in a very similar manner, and thus have been neglected for this comparison.

Figure 1



We first examined the MEP map of 1,2-dimethylpyrrole (**A**, **B**), included in the DA autoreceptor selective 7-aminoindolizine **1** (**A**) and its inactive regioisomer **2** (**B**), and compared that with the distribution of charge of **C** and **G** representative for the ergoline partial structures **3** and **5** (according to ref. 9, **3** and **5** exhibit typical postsynaptic DA agonistic activity). Due to recent theoretical studies [14] and PM3 calculations [15] a positive electrostatic potential was supposed to be located adjacent to the N-H feature of **C** and a large region of negative potential above the heterocycle which we anticipated to be maximally displaced from the positive "N-H region". The three-dimensional MEP map of **C** confirms this assumption, however, the negative energy contours show only a low order of polarization.

Figure 2. Molecular electrostatic potential maps for the core fragments **A-G** based on ab initio calculations (6-31 G*). The displayed potential energies are -2.5 (white), -7.5 (yellow) and 2.5 kcal/mol (pink).



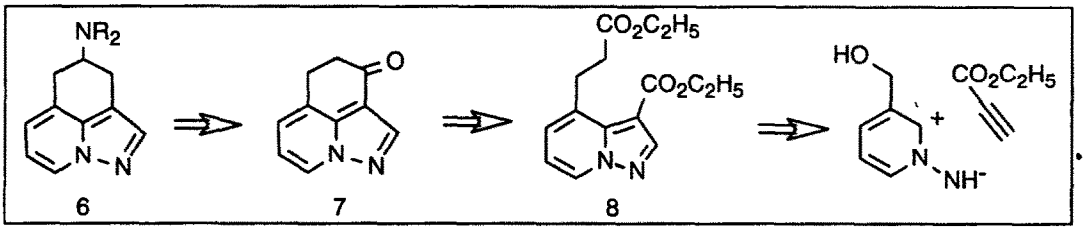
A very similar distribution of charge was obtained by calculation of **G**, the 3,4-dimethylindol fragment of the postsynaptically active derivative **5**. The shapes of the isopotential curves of 1,2-dimethylpyrrole (**A**,**B**) differ from the former mentioned in a way that the negative potential is more extended to the region about the positions 3 and 4. The positive lopes are located in the vicinity of the N-CH_3 substituent. When the structures are positioned as shown in the Figures 1 and 2, this results in a polarization from the "northwest" to the

"southeast" in **A** (representative for the core structure of the selective DA agonist **1**) and from the "north" to the "south" for **B** (representative for the inactive isomer **2**). Then, studies on the 4-methylcatechol fragment of extended forms of DA were performed. Especially, the conformational isomers **D** and **E** should be of interest since these are stabilized by intramolecular hydrogen bonding. Whereas the H-bond donor is provided by the meta-OH group in **D** the para-OH group serves as a H-bond donor in **E**. By comparing **A** and **B** with the two low energy conformers of 4-methylcatechol (**D** and **E**) an analogous location and shape of the molecular isopotential maps of **A** and **D** as well as **B** and **E**, respectively, can be seen although the region of the negative potentials is much larger for **D** and **E** (here, negative isopotentials are contoured at -7.5). Thus, it can be reasoned that **A**, incorporated in the potent autoreceptor agonist **1** mimics the DA conformer including the fragment **D** whereas **B** is a surrogate for **E**. As a consequence, we assume that the methylcatechol substructure of DA adopts conformation **D** when interacting with the DA autoreceptor. Therefore, for the design of DA autoreceptor selective tricyclic ergoline analogues we tried to find a heterocyclic system which is structurally related to dimethylindole **G** and, at the same time, exhibits electrostatic properties, which are comparable with the DA fragment **D**. A suitable candidate should be the pyrazolo[1,5-a]pyridine framework **F**. Since its MEP map is related to that of **D**, we hoped that the tricyclic azaergoline analogue **6** should selectively recognize the DA autoreceptor.

Synthesis

Our plan of synthesis for the target compound, the pyrazolo[4,3,2-i,j]quinoline **6**, is outlined in Scheme 1. It was envisioned to approach to **6** via the aromatic ketone **7** by electrophilic amination and reduction of the C=O group. According to previous investigations on the synthesis of peri-fused tetrahydropyrazolo[1,5-a]pyridines,[16] the central intermediate **7** should be obtained by anionic ring closure reaction of the diester **8**. The pyrazolopyridine system should be prepared by 1.3-dipolar cycloaddition under oxidative conditions.

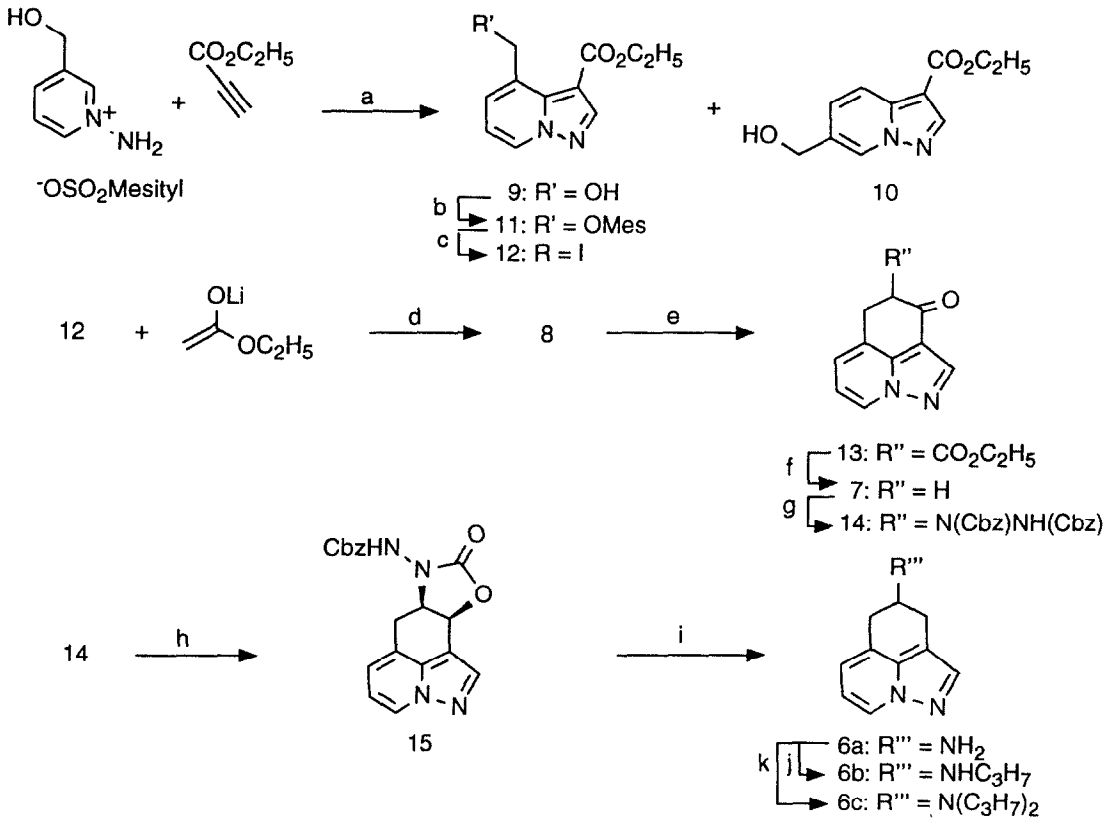
Scheme 1



For the synthesis of the 3,4 disubstituted pyrazolopyridine **9** N-aminopyridinium mesitylenesulfonate [17] was reacted with ethyl propiolate. The reaction, which was promoted by air oxygen and K_2CO_3, resulted in an easily separable mixture of the regioisomeric heterocycles **9** and **10** in a 6:4 ratio. Subsequently, the hydroxymethyl side chain of **9** was activated by converting into the sulfonic ester **11**. Heating of **11** with NaI in acetone gave nucleophilic displacement to accomplish **12** in 81 % yield over both steps. Upon treatment of **12** with an ester enolate, derived from ethyl acetate and LDA, the cyclization precursor **8** was formed. 6-(enol exo)-exo-trig ring closure [18] was achieved in 91 % yield by treating **8** with 1 equivalent of NaHMDS at 0° C. Subsequently, the ß-ketoester **13** was converted into the aromatic ketone **7** by use of aqueous HCl. Electrophilic amination and reductive degradation was achieved by following our previously described procedure employing dibenzyl azodicarboxylate as an electrophilic nitrogen source.[19] Thus, deprotonation of **7** by LiHMDS and subsequent addition of dibenzyl azodicarboxylate yielded the protected hydrazino ketone

14. Highly stereoselective cis-reduction with L-Selectride ^{R} at -78°, followed by transesterification at room temperature gave access to the oxazolidinone **15** which could be transformed into the primary amine **6a** by hydrogenolysis. Finally, **6a** was "reductively alkylated" to give **6b** and **6c**, respectively.

Scheme 2



a) DMF, K_2CO_3, RT (25 % of **9** and 17 % of **10**). b) MesCl, Et_3N, THF, RT. c) NaI, acetone, reflux (81 %, based on **9**). d) THF, 0° C (78 %). e) NaHMDS, THF 0° C (91 %). f) 6 N HCl, reflux (90 %). g) LiHMDS, dibenzyl azodicarboxylate, THF, -78° C (52 %). h) L-Selectride^{R}, THF, 1. -78°, 2. RT (90 %). i) Pd-C (10 %), Raney-Ni, 50 bar H_2, EtOH, 60° C (38 %). j) propionic aldehyde, $NaCNBH_3$, MeOH, RT, 1h (36 %). k) propionic aldehyde, $NaCNBH_3$, MeOH, RT, 3h (80 %).

Biological Investigations

The dopaminergic properties of the new azaergoline analogues **6** were investigated using receptor binding studies as well as behavioral activity tests. Agonistic activity on the prejunctional DA receptor was determined by measuring the inhibition of γ-butyrolacton (GBL) induced acceleration of DA synthesis.[20] Employing rat striatal membranes, the test compounds **6a-c** were evaluated for their binding affinity to the dopamine D-1 receptor labelled with [^{3}H]-SCH 23390 [21] and to the D-2 receptor sites labelled with [^{3}H]-spiroperidol [22] and [^{3}H]-SND 919,[23] a compound which in functional in vivo experiments pointed out to be a selective autoreceptor agonist.[6] It turned out, that the dipropylamine **6c** is a potent compound at displacing the DA autoreceptor agonist [^{3}H]-SND 919 (Table 1). Moreover, **6c** posseses a large separation of

affinity for the [^{3}H]-SND 919 site as compared to the [^{3}H]-spiroperidol site or to the D-1 receptor, labelled with [^{3}H]-SCH 23390. Using the γ-butyrolactone test for establishing selective action on DA autoreceptors a 57 % lower L-Dopa level was measured after injecting 10 mg / kg of **6c**. In comparison, for (-)-PPP a 50 % L-Dopa inhibition at 6.3 mg/kg is reported.[2] Treatment of mice with **6c** did not produce stereotyped behavior (due to postsynaptic DA receptor stimulation) nor catalepsy (a typical extrapyramidal effect of classical neuroleptics), up to 100 mg /kg.[24]

Table 1

compd	D-1 [a]	D-2 [b]	D-2 [c]	GBL - test [d]
6a	> 100	> 100	2.8 ± 0.38	---
6b	> 100	> 100	2.7 ± 0.67	---
6c	> 100	50.4 ± 15.5	0.26 ± 0.10	57 ± 3
(S)-1	14.5 ± 0.14	7.1 ± 4.0	0.03 ± 0.001	62 ± 1
(-)-PPP	---	7.8 ± 1.0	0.014 ± 0.003	---

[a] 3H-ligand: SCH 23390 (0.3 nM); IC_{50} values (μM), ±S.E.M..[b] 3H-ligand: spiroperidol (0.5 nM); IC_{50} values (μM), ± S.E.M..[c] 3H-ligand: SND 919 (0.5 nM), IC_{50} values (μM), ± S.E.M..
[d] % inhibition of GBL - induced L-Dopa accumulation, dose of test compound 10 mg / kg

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