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]
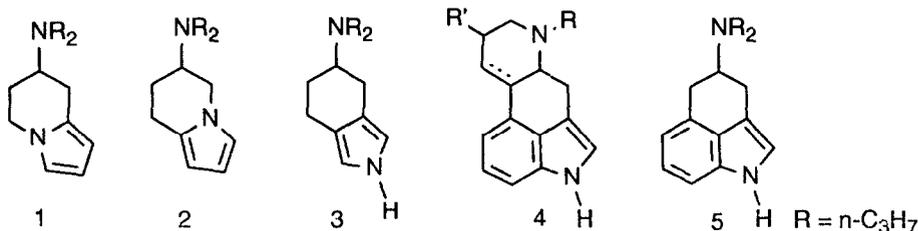
Computational Studies:

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
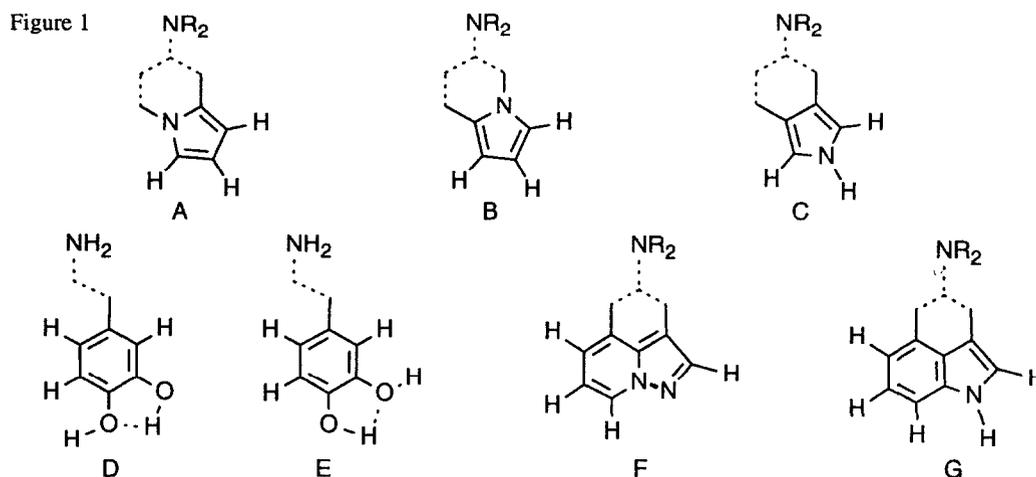
We first examined the MEP map of 1,2-dimethylpyrrole (A, B), included in the DA autoreceptor selective 7-aminoindolizine 1 (A) and its inactive regioisomer 2 (B), and compared that with the distribution of charge of C and G representative for the ergoline partial structures 3 and 5 (according to ref. 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).
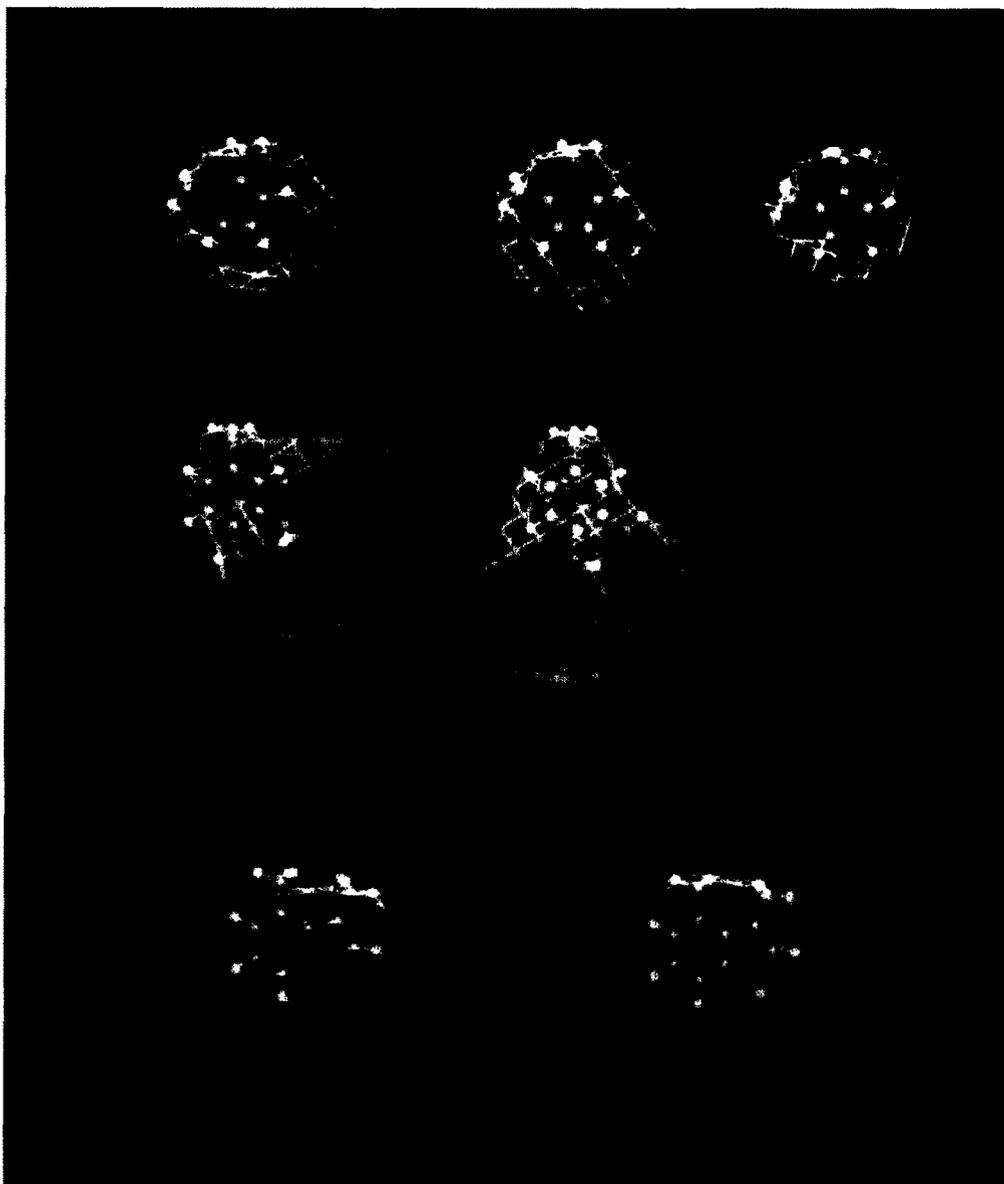

A very similar distribution of charge was obtained by calculation of G, the 3,4-dimethylindol fragment of the postsynaptically active derivative 5. The shapes of the isopotential curves of 1,2-dimethylpyrrole (A,B) differ from the former mentioned in a way that the negative potential is more extended to the region about the positions 3 and 4. The positive lopes are located in the vicinity of the N-CH₃ 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.
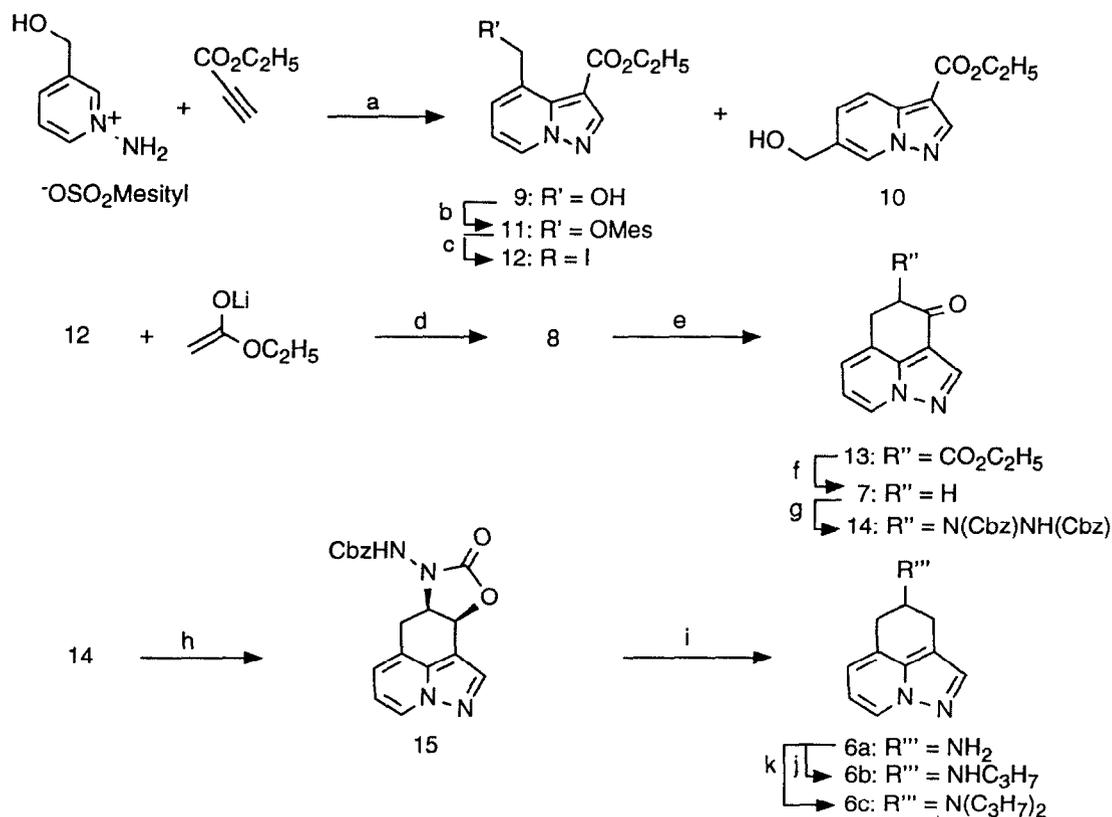
Scheme 1
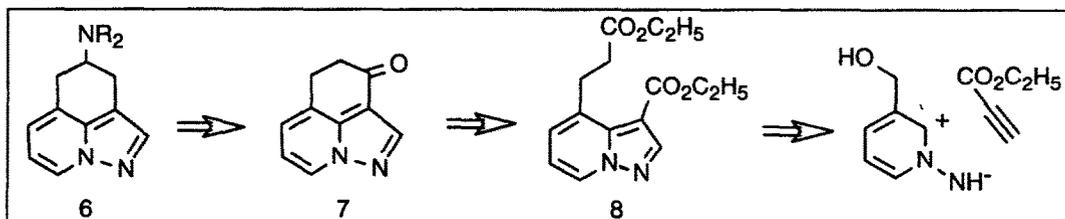
For the synthesis of the 3,4 disubstituted pyrazolopyridine 9 N-aminopyridinium mesitylenesulfonate [17] was reacted with ethyl propiolate. The reaction, which was promoted by air oxygen and K_2CO_3, resulted in an easily separable mixture of the regioisomeric heterocycles 9 and 10 in a 6:4 ratio. Subsequently, 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

References and Notes:

1 Carlsson, A., in *Pre- and Postsynaptic Receptors*, Usdin, E.; Bunney, W.E. Jr., Eds.; Marcel Dekker: New York 1975.
2 Seyfried, C.A.; Boettcher, H. *Drugs Fut.* 1990, *15*, 819. Abou-Gharbia, M.; Moyer, J.A., in *Annual Reports in Medicinal Chemistry*, Mc Call, J., Ed. 1990, Vol. *25*, Section 1. Tricklebank, M.D.; Bristow, L.J.; Hutson, P.H., in *Progress in Drug Research*, Jucker, E., Ed.; Birkhäuser Verlag: Basel 1992. Anderson, P.H.; Nielson, E.B. *Drug News & Perspectives* 1991, *4*, 150.
3 Hjorth, S.; Carlsson, A.; Wickström, H. *Life Sci.* 1981, *28*, 1225.
4 Seyfried, C.A.; Greiner, H.E.; Haase, A.F. *Eur. J. Pharmacol.* 1989, *160*, 31.
5 Andén, N.E.; Golembiowska-Nikitin, K.; Thornström, U. *Naunyn-Schmiedeb. Arch. Pharmacol.* 1982, *312*, 100.
6 Mierau, J.; Schingnitz, G. *Eur. J. Pharmacol.* 1992, *215*, 161.
7 Horn, A.S., in *Comprehensive Medicinal Chemistry*, Vol.3, Hantsch, C.; Sammes, P.G.; Taylor J.B., Eds.; Pergamon Press: Oxford 1990.
8 Gmeiner, P.; Mierau, J.; Höfner, G. *Arch. Pharm. (Weinheim)* 1992, *325*, 57.
9 Bach, N.J.; Kornfeld, E.C.; Jones, N.D.; Chaney, M.O.; Dorman, D.E.; Paschal, J.W.; Clemens, J.A.; Smalstig, E.B. *J. Med. Chem.* 1980, *23*, 481.
10 DISCOVER 3.0, BIOSYM Tech. Inc., San Diego.
11 MOPAC 6.0, Stewart, J.J.P., U.S. Air Force Academy. Stewart, J.J.P. *J. Comput. Chem.* 1989, *10*, 209.
12 GAUSSIAN 92, Gaussian, Inc., Pittsburgh.
13 INSIGHT 2.1.2, BIOSYM Tech. Inc., San Diego.
14 Kocjan, D.; Hodoscek, M.; Hadzi, D. *J. Med. Chem.* 1986, *29*, 1418.
15 Gmeiner, P., manuscript in preparation.
16 Gmeiner, P.; Sommer, J. *Arch. Pharm. (Weinheim)* 1990, *323*, 991. Gmeiner, P. Sommer, J. *Liebigs Ann. Chem.* 1991, 921.
17 Miki, Y.; Uragi, M.; Takemura, S.; Ikeda M. *J. Chem. Soc. Perkin Trans. 1*, 1985, 379.
18 Baldwin, J.E.; Lusch, M.J. *Tetrahedron* 1982, *38*, 2939.
19 Gmeiner, P.; Bollinger, B. *Tetrahedron Lett.* 1991, *32*, 5927. Gmeiner, P.; Bollinger, B. *Liebigs Ann. Chem.* 1992, 273.
20 Schneider, C.S; Mierau, J. *J. Med. Chem.* 1987, *30*, 494 and references cited therein.
21 Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L..; Barnett, A. *Life Sci.* 1984, *35*, 1885.
22 Creese, I.; Burt, D.R.; Snyder, S.H. *Life Sci.* 1975, *17*, 993.
23 The experiments were performed as described in ref. 8. Publication of further details is envisioned.
24 The studies were performed, according to: Gmeiner, P.; Sommer, J.; Höfner, G.; Mierau, J. *Arch. Pharm. (Weinheim)* 1992, *325*, 649 and ref. cited therein.