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2,2-Dicyanovinyl as a Nonaromatic Aryl Bioisostere: Synthesis, Binding Experiments and SAR Studies of Highly Selective Dopamine D4 Receptor Ligands

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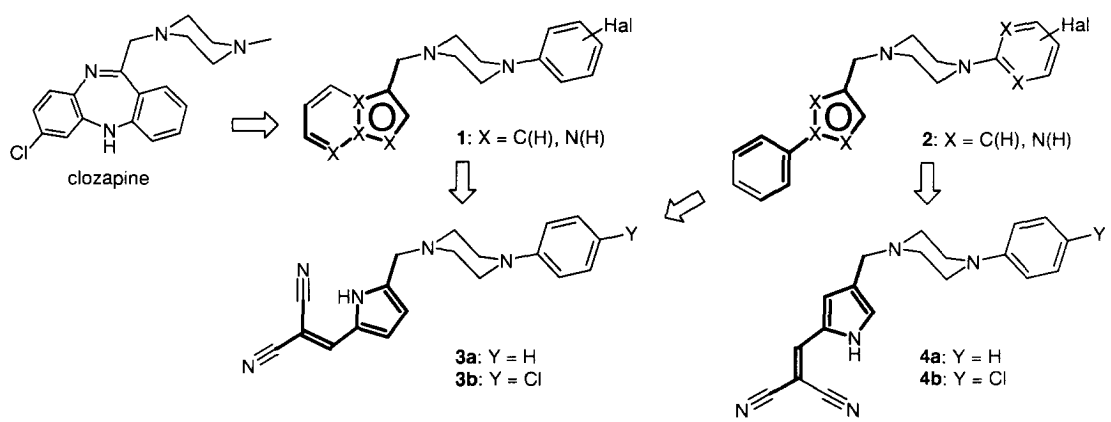
Abstract: The phenylpiperazinylmethyl substituted pyrrolylmethylenemalononitriles of type **3** and **4** were synthesized and evaluated as strong and selective dopamine D4 receptor ligands.

It is widely accepted that the activity of classical neuroleptics, which are mostly employed for the treatment of schizophrenia, is due to their blockade of dopamine D2-like receptors in limbic brain areas.[1] However, their use is often accompanied by extrapyramidal side effects resulting from attenuation of dopaminergic activity in the striatum.[2] Recent molecular cloning studies have led to the characterization of three subtypes in the D2-like family (D2, D3 and D4).[3] The localization and distribution of D4 receptors within the brain and the observation that the atypical antipsychotic agent clozapine preferentially binds to the D4 receptor caused great efforts in the development of selective D4 antagonists.[4] Very recently, piperazinylmethyl substituted 10π-heterocycles of type **1** including indole and azaindole substructures [5,6] as well as the phenylpyrrolyl and phenylimidazolyl derivatives of type **2** [7] were found to selectively recognize the D4 subtype. Within the scope of our SAR studies we were intrigued by the question whether a nonaromatic π-system could work as a bioisostere for the six-membered aromatic subunits of the lead structures **1** and **2**. As an interesting structural candidate for this kind of replacement, we chose the 2,2-dicyanovinyl group.[8]



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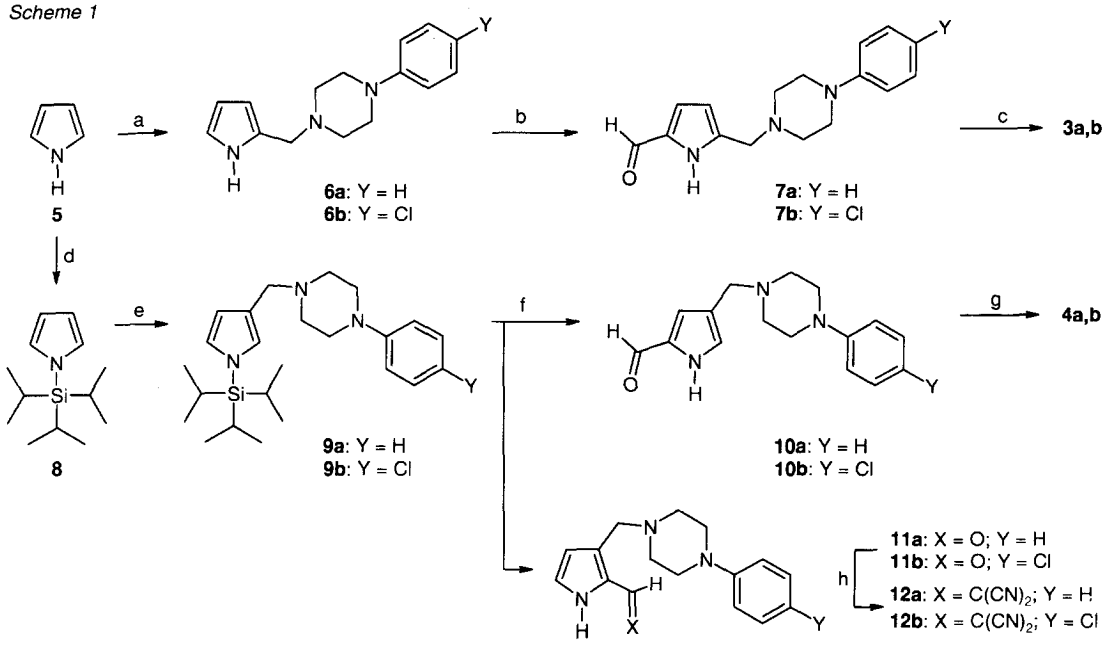
When attached to the 2-position of piperazinylmethyl substituted pyrroles essential parts of the diazaendiine system superimpose with the respective aromatic positions of the leads. Due to earlier observations on 2-formylpyrroles,[9] we expected a preferred *s-trans* disposition of the 2,2-dicyanovinyl functionality. Thus, the 2,5-substituted pyrroles of type **3** closely relate to both the lead structures **1** and **2** when parts of the aromatic six-membered rings can be matched with the vinyl sp^2 atoms and the *cis*- or *trans*-positioned sp carbon, respectively. On the other hand, the 2,4 disubstituted regioisomers of type **4** should be able to mimic the structural properties of the biaryls **2**. Here, we describe synthesis, dopamine receptor binding studies and computational investigations of the target compounds **3** and **4**. For comparison, 2,3-disubstituted regioisomers were also evaluated.

The synthesis of the test compounds could be done choosing common building blocks and classical organic reactions (*Scheme 1*). Thus, aminomethylation in position 2 was performed by subjecting pyrrole (**5**) to *Mannich* conditions. The reaction products **6a,b** were prepared when employing 1-phenylpiperazine and 1-(4-chlorophenyl)piperazine as the respective secondary amines. Subsequent *Vilsmeier* formylation afforded the 2,5-disubstituted carbaldehydes **7a,b** which could be readily transformed into the target compounds **3a,b** [10] by condensation with malononitrile under *Knoevenagel* conditions. For an alternative aminomethylation in position 3 the sterically demanding triisopropylsilyl moiety (TIPS) was applied as a directing group preventing from a concurrent electrophilic attack at the pyrrole 2-position.

Scheme 1

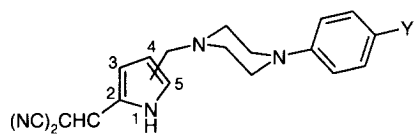


a: CH_2O/H_2O (1.0 eq), 1-phenylpiperazine or 1-(4-chlorophenyl)piperazine, AcOH, 0°C, 30 min (81%, 76%). b: $POCl_3$ (2.0 eq), DMF, 0°C, 30 min (37%, 40%). c: $CH_2(CN)_2$ (1.3 eq), piperidine, MeOH, RT, 45 min (49%, 86%). d: 1. NaH (1.1eq), 0°C, 60 min; 2. TIPS-Cl (1.0 eq), DMF, 0°C, 60 min (66%). e: CH_2O/H_2O (1.0 eq), 1-phenylpiperazine or 1-(4-chlorophenyl)piperazine, AcOH, 5°C, 20 h (62%, 65%). f: 1. Bu_4NF (1.0 eq), THF, RT, 15 min (74%, 76%); 2. $POCl_3$ (2.0 eq), DMF, 0°C, 90 min (**10a**,**11a** 42% and 18%, **10b**, **11b** 38% and 22%). g: $CH_2(CN)_2$ (1.1 eq), piperidine, MeOH, 0°C, 45-90 min (78%, 71%). h: $CH_2(CN)_2$ (1.1 eq), piperidine, MeOH, RT, 30 min (90%, 63%)

Unless the *Mannich* reactions with the TIPS-protected pyrrole **8** [11] proceeded much slower than for pyrrole (**5**), complete regioselectivity was observed. The aminomethylation products **9a,b** were isolated in 62 and 65% yield, respectively. On the other hand, formation of both possible regioisomers took place for the subsequent formylation reaction which was performed after fluoride induced *N*-deprotection. The 4- and 3-piperazinylmethyl substituted pyrrole-2-carbaldehydes **10a,b** and **11a,b**, which were formed in 2:1 ratios of isomers, could be easily separated by flash chromatography. Finally, the carbaldehydes **10a,b** and **11a,b** were coupled to malononitrile affording the dicyanomethyl derivatives **4a,b** [10] and **12a,b**,[10] respectively.

The affinities of the test compounds for the dopamine $D2_{long}$, $D2_{short}$,[12] D3 [13] and D4.4 [14] receptors were determined *in vitro* by measuring their ability to displace [^{3}H]spiperone from the cloned human dopamine receptor subtypes stably expressed in Chinese hamster ovary (CHO) cells.[15] D1 binding values were assessed *via* competition experiments employing bovine striatal membrane preparations and the D1 selective radioligand [^{3}H]SCH 23390.[16] Clozapine was utilized as a reference drug. The Ki values depicted in *Table 1* indicate strong and selective D4 receptor binding of the dicyanovinyl substituted target compounds **3a,b** and **4a,b**. Compared to clozapine the 2,4-disubstituted phenylpiperazine derivative **4a** (Ki = 3.9 nM) has a 4-fold greater affinity for the human D4.4 receptor and a 70-, 200-, 140-, and 10-fold higher selectivity over D1, $D2_{long}$, $D2_{short}$ and D3, respectively. The D4 selectivities for the *p*-chlorophenylpiperazine analog **4b** proved to be even higher. The 2,5-disubstituted regioisomers **3a,b** showed about 2-fold lower D4 affinities than **4a,b** but almost complete subreceptor selectivity. On the other hand, strong reduction of the D4 binding was observed for the 2,3-disubstituted regioisomers **12a,b** with Ki values of 165 nM and 125 nM, respectively.

Table 1: Binding data (Ki values [nM]) of piperazinylmethyl substituted pyrroles employing human dopamine $D2_{long}$, $D2_{short}$, D3 and D4.4 as well as bovine D1 receptors.[17]



Compound	Y	Subst. Pos.	D1	$D2_{long}$	$D2_{short}$	D3	D4.4
3a	H	5	58 000	>100 000	>100 000	5 250	9.3
3b	Cl	5	39 500	48 500	59 000	31 000	11
4a	H	4	7 200	1 850	975	2350	3.9
4b	Cl	4	5 300	7 350	10 300	6 950	5.7
12a	H	3	22 000	4 000	12 750	6 950	160
12b	Cl	3	13 500	8 950	15 000	7 600	125
clozapine			420	39	28	960	16

Conformational analysis of the final products **3** and **4** were performed using NMR spectroscopy and *ab initio* molecular orbital calculations. Thus, NOE experiments showed a strong dipolar exchange of magnetism between the vinyl-H and the 3-H of the pyrrole ring clearly indicating the coplanar *s-trans* orientation of the two π-systems. The antiperiplanar orientation of the dicyanovinyl group was confirmed as the most stable conformer by *ab initio* derived computational studies.[18] Employing the polarization basis set 6-31G* geometry optimization

processes predicted the minimum energy conformations of **3a** and **4a** which are shown in *figure 1*. Compared to the respective *s-cis* derivatives these structures were favored by 4 kcal/mol which might be due to their considerably lower dipole moments. It is worthy to note, that the calculated minimum energy conformations show a perpendicular disposition of the phenylpiperazine system related to the substituted pyrrole which might be of interest for an elucidation of the bioactive conformation and for receptor mapping studies.

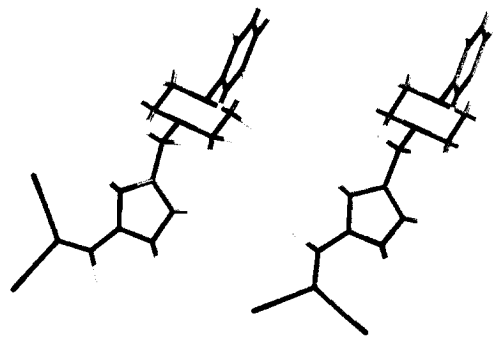


Figure 1: Conformational representation of **3a** (left) and **4a** (right)

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10. NMR data of selected final products: ^{1}H NMR ($CDCl_3$, 360 MHz): **3b** δ (ppm) = 2.65-2.69 (m, 4H, 2x $N\underline{CH_2}CH_2$), 3.19-3.24 (m, 4H, 2x $CH_2\underline{CH_2}N$), 3.68 (s, 2H, $Ar\underline{CH_2}N$), 6.28 (d, J=4.1 Hz, 1H, 4-H), 6.81-6.85 (m, 2H, Ph), 6.90 (br s, 1H, 3-H), 7.17-7.22 (m, 2H, Ph), 7.39 (s, 1H, $\underline{CH}$=$C(CN)_2$), 10.16 (br s, 1H, NH). **4b** δ (ppm) = 2.57-2.61 (m, 4H, 2x $N\underline{CH_2}CH_2$), 3.13-3.17 (m, 4H, 2x $CH_2\underline{CH_2}N$), 3.48 (s, 2H, $Ar\underline{CH_2}N$), 6.80-6.85 (m, 2H, Ph), 6.94 (br s, 1H, 3-H), 7.17-7.22 (m, 2H, Ph), 7.24-7.26 (m, 1H, 5-H), 7.44 (s, 1H, $\underline{CH}$=$C(CN)_2$), 9.66 (br s, 1H, NH). **12b** δ (ppm) = 2.56-2.60 (m, 4H, 2x $N\underline{CH_2}CH_2$), 3.13-3.17 (m, 4H, 2x $CH_2\underline{CH_2}N$), 3.60 (s, 2H, $Ar\underline{CH_2}N$), 6.40 (t, J=2.5 Hz, 1H, 4-H), 6.80-6.85 (m, 2H, Ph), 7.17-7.23 (m, 3H, Ph und 5-H), 8.08 (s, 1H, CH=$C(CN)_2$), 9.81 (br s, 1H, NH).
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17. Binding data are the means of two to three experiments performed in triplicate at eight concentrations.
18. *Ab initio* calculations and visualizations have been done using the programs *GAUSSIAN 94 Rev. E.2 (Gaussian Inc.)* and *PC SPARTAN PLUS (Wavefunction, Inc.)*.