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Piperidinylpyrroles: Design, Synthesis and Binding Properties of Novel and Selective Dopamine D4 Receptor Ligands

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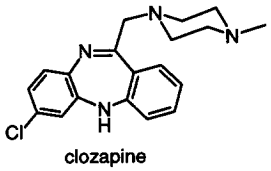
Abstract: Piperidinylpyrroles of type **3** were synthesized through a modified *Paal-Knorr* reaction. For the introduction of pyrrole-substituents high yielding transformations including *Sonogashira* cross-coupling reactions were utilized. Employment of the reagent TosMIC gave access to the regioisomeric oxazolyl derivatives **7** and **11** which showed the highest dopamine D4 receptor binding of the series investigated.

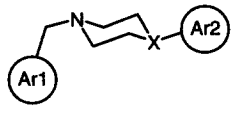
Recent investigations using molecular cloning technology have indicated the existence of a number of dopamine receptor subtypes which can be classified into two classes, D1-like (D1 and D5) and D2-like (D2, D3 and D4).[1] Classical neuroleptics that are used to treat schizophrenia are generally potent dopamine D2 receptor antagonists.[2] However, their use is associated with the lack of clinical efficiency in the negative symptoms of schizophrenia as well as mechanism-induced side effects including major movement disorders and increases in serum prolactin levels.[3] In contrast, the atypical antipsychotic agent clozapine shows preferential binding to the D4 subtype.[4] Further findings have prompted speculation that dysfunction of the D4 receptor system might be involved in the ethiology of schizophrenia [5] and have driven intensive structure activity relationship studies.[6]

Recent literature reports described selective D4 receptor antagonists including piperazines of the general structure **1** [7] and piperidine analogs of type **2** [8] when the aromatic features Ar1 and Ar2 are represented by either substituted phenyl rings or by heterocyclic moieties. Whereas heterocyclic π-systems play an important role for the Ar1 substructure of **1**, phenyl substituted pyrazoles and isoxazoles proved to be suitable as Ar2 surrogates within the lead compounds of type **2**.

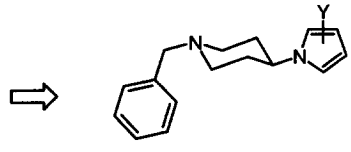
As a complement to our previous studies on the incorporation of pyrrole derived Ar1 surrogates into D4 ligands of type **1**,[9] this communication describes synthesis and receptor binding of novel piperidinylpyrroles (**3**) when pyrrole based π-systems represent the Ar2 subunit of **2**.



clozapine



1: X = N
2: X = CH



3: Y = CHO, CH=C(CN)$_2$, oxazol-5-yl, alkynyl

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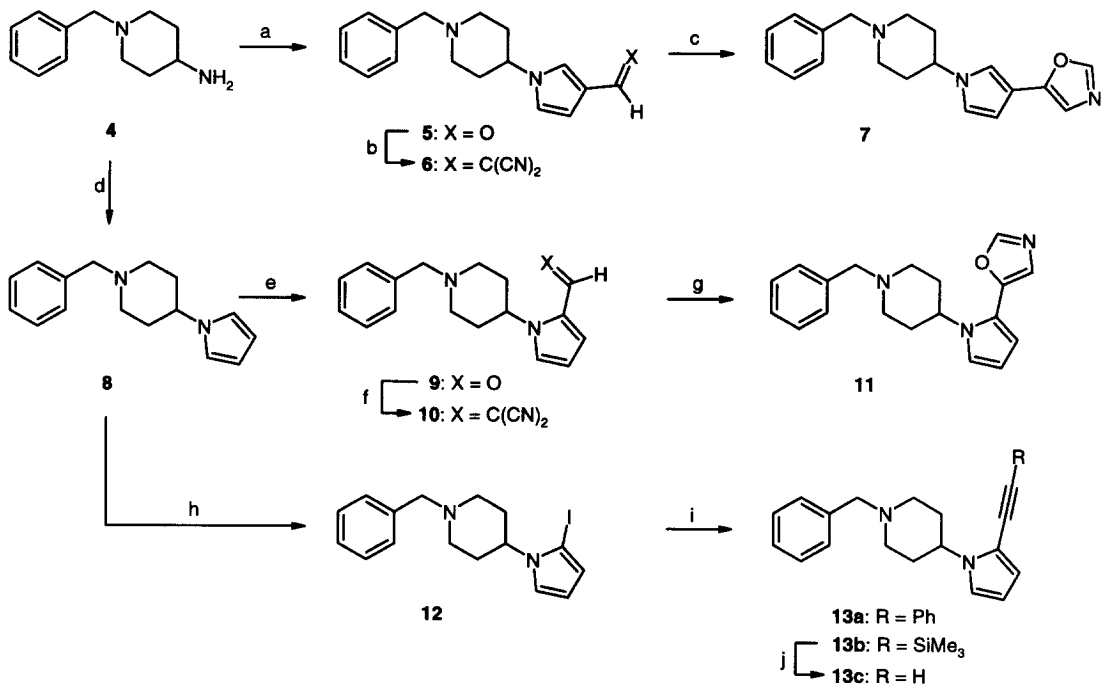
The target compounds were synthesized straightforwardly using commercially available 4-amino-*N*-benzylpiperidine (**4**) as a common starting material (*Scheme 1*). Incorporation of the pyrrole system was done by subjecting the primary amine **4** to modified *Paal-Knorr* reaction conditions. Employing 2,5-dimethoxytetrahydrofuran and the respective 3-carbaldehyde as 1,4-dicarbonyl equivalents gave access to the *N*-substituted pyrroles **8** and **5**, respectively. Since we intended SAR investigations on the extension of the pyrrole based π-system by aromatic or nonaromatic phenyl bioisosteres, the 3-positioned carbaldehyde group of **5** should be further modified. Thus, the 2,2-dicyanovinyl derivative **6** could be readily prepared by *Knoevenagel* condensation of **5** with malononitrile. Furthermore, construction of an oxazole ring as a conjugated heterocyclic substituent was achieved by cyclocondensation reaction of the carbaldehyde **5** with tosylmethyl isocyanide (TosMIC) [10] to give the target compound **7**.[11] Regioisomers of **5-7** bearing conjugated substituents in position 2 of the pyrrole ring could be synthesized starting from the *Paal-Knorr* product **8**. Thus, introduction of a formyl group under *Vilsmeier* conditions [9] afforded regioselectively the pyrrole-2-carbaldehyde **9** which could be transformed to the methylenemalononitrile **10** and the oxazole **11** [11] using the above mentioned reaction conditions. As a further test compound and flexible synthetic intermediate, we prepared the 2-iodopyrrole **12** by iodination of **8** with NIS.

Scheme 1

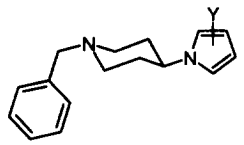


a: 2,5-dimethoxytetrahydrofuran-3-carbaldehyde (1.2 eq), NaOAc, AcOH, 75°C, 2 h (95%). b: $CH_2(CN)_2$ (1.2 eq), piperidine, MeOH 70%, RT, 1 h (75%). c: **5**, TosMIC (1.2 eq), NaOMe (3.1 eq), MeOH, reflux, 5 h (35%). d: 2,5-dimethoxytetrahydrofuran (1.3 eq), NaOAc, AcOH, 75°C, 3 h (91%). e: $POCl_3$ (2.0 eq), DMF, 0°C, 30 min (63%). f: $CH_2(CN)_2$ (1.2 eq), piperidine, MeOH 70%, RT, 1 h (87%). g: **9**, TosMIC (1.3 eq), NaOMe (2.0 eq), MeOH, reflux, 3 h (82%). h: NIS (1.1 eq), AcOH/CH_2Cl_2, -60°C, 1 h (79%). i: RCCH (R=Ph, $SiMe_3$), $Pd(PPh_3)_4$ (0.06 eq), CuI (0.14 eq), $EtMe_2N$, THF, RT, 3-4.5 h (84%, 81%). j: Bu_4NF (1.1 eq), THF, -15°C, 15 min (71%).

Palladium-catalyzed coupling under *Sonogashira* conditions allowed the introduction of alkyne residues as representatives for conjugated sp-hybridized π-systems.[12] Employing $Pd(PPh_3)_4$ and CuI as an effective catalyst combination as well as THF as a solvent and $EtMe_2N$ as a base, the phenylacetylene derivative **13a** and the alkynyl silane **13b** could be prepared in high yield. Fluoride induced desilylation of **13b** gave the terminal alkyne **13c**.[11]

Receptor binding profiles of the test compounds **5-13** were determined *in vitro* by measuring their ability to displace [^{3}H]spiperone from the cloned human dopamine receptor subtypes $D2_{long}$, $D2_{short}$,[13] D3 [14] and D4.4 [15] stably expressed in CHO cells.[16] D1 affinities were assessed *via* competition experiments using bovine striatal membrane preparations and the D1 selective radioligand [^{3}H]SCH 23390.[17] The Ki values of the test compounds were compared to those of the atypical antipsychotic drug clozapine which is known for its D4 preference. The binding data depicted in *Table 1* indicate the influence of the π-systems localized in position 2 or 3 of the pyrrole ring. It was found, that the attachment of a formyl, dicyanovinyl or oxazolyl function resulted in an enhancement of D4 binding when compared to the synthetic intermediates **8** and **12**. The strongest D4 recognition was exhibited by the oxazolylpyrroles **7** and **11** when the 2-substituted regioisomer (**11**) indicated higher affinity (Ki = 63 nM) but reduced selectivity over the D2 and D3 subtypes. Compared to clozapine, the oxazolyl substituted piperidinylpyrrole **11** showed a 4-fold lower affinity for the human D4.4 receptor and comparable D3 binding. However, the selectivity for D4.4 over $D2_{long}$, $D2_{short}$ and D1 was significantly higher. Strong reduction of the D4 binding was observed for the alkynyl substituted pyrroles **13a-c**. In conclusion, it was found that pyrrole derived structures can serve as representatives for the Ar2 moiety of D4 ligands when a suitable extension of the π-system is provided.

Table 1: Binding data (Ki values [nM]) of substituted piperidinylpyrroles employing human dopamine $D2_{long}$, $D2_{short}$, D3 and D4.4 as well as bovine D1 receptors.[18]



Compound	Y	Pos.	D1	$D2_{long}$	$D2_{short}$	D3	D4.4
5	CHO	3	61 000	49 000	65 000	31 000	960
6	$CH=C(CN)_2$	3	14 000	13 000	18 000	7 000	230
7	oxazol-5-yl	3	39 000	3 400	3 200	6 800	130
8	H	-	34 000	8 500	9 800	15 000	1100
9	CHO	2	5 800	1 400	1 500	2 500	200
10	$CH=C(CN)_2$	2	15 000	11 000	7 800	5 100	280
11	oxazol-5-yl	2	10 000	610	320	770	63
12	I	2	11 000	8 500	5 300	2 600	1 500
13a	C≡CPh	2	16 000	10 000	8 300	8 700	3 300
13b	$C\equiv CSiMe_3$	2	14 000	6 200	4 900	7 700	2 700
13c	C≡CH	2	14 000	6 600	6 300	7 900	940
clozapine			420	41	28	960	16

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11. NMR data of selected final products: ^{1}H NMR ($CDCl_3$, 360 MHz): **7** δ (ppm) = 1.93-2.07 (m, 4H, 3-H_2, 5-H_2), 2.12 (ddd, J=11.3, 11.3, 3.2 Hz, 2H, 2-H_{ax}, 6-H_{ax}), 2.97-3.05 (m, 2H, 2-H_{eq}, 6-H_{eq}), 3.55 (s, 2H, Ph$\underline{CH_2}$N), 3.82 (tt, J=10.6, 5.2 Hz, 1H, 4-H), 6.34 (dd, J=2.8, 1.7 Hz, 1H, 4-H, pyrrole), 6.74 (dd, J=2.8, 2.3 Hz, 1H, 5-H, pyrrole), 6.97 (s, 1H, 4-H, oxazole), 7.03 (dd, J=2.3, 1.7 Hz, 1H, 2-H, pyrrole), 7.26-7.37 (m, 5H, Ph), 7.74 (s, 1H, 2-H, oxazole). **11** δ (ppm) = 1.92-2.16 (m, 6H, 3-H_2, 5-H_2, 2-H_{ax}, 6-H_{ax}), 2.98-3.06 (m, 2H, 2-H_{eq}, 6-H_{eq}), 3.54 (s, 2H, Ph$\underline{CH_2}$N), 3.99-4.10 (m, 1H, 4-H), 6.23 (dd, J=3.7, 2.7 Hz, 1H, 4-H, pyrrole), 6.42 (dd, J=3.7, 1.7 Hz, 1H, 3-H, pyrrole), 6.93 (dd, J=2.7, 1.7 Hz, 1H, 5-H, pyrrole), 7.03 (s, 1H, 4-H, oxazole), 7.26-7.36 (m, 5H, Ph), 7.89 (s, 1H, 2-H, oxazole). **13c** δ (ppm) = 1.88-2.05 (m, 4H, 3-H_2, 5-H_2), 2.15 (ddd, J=11.7, 11.7, 2.7 Hz, 2H, 2-H_{ax}, 6-H_{ax}), 2.98-3.05 (m, 2H, 2-H_{eq}, 6-H_{eq}), 3.37 (s, 1H, C$\underline{CH}$), 3.55 (s, 2H, Ph$\underline{CH_2}$N), 4.19 (tt, J=11.5, 4.6 Hz, 1H, 4-H), 6.09 (dd, J=3.7, 2.7 Hz, 1H, 4-H, pyrrole), 6.46 (dd, J=3.7, 1.7 Hz, 1H, 3-H, pyrrole), 6.77 (dd, J=2.7, 1.7 Hz, 1H, 5-H, pyrrole), 7.24-7.36 (m, 5H, Ph).
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18. Binding data are the means of two to three experiments performed in triplicate at eight concentrations.