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Synthesis and D_2-like Binding Affinity of New Derivatives of N3-[(1-ethyltetrahydro-1H-2-pyrrolyl)methyl]-4,5-dihydrobenzo[g]indole-3-carboxamide and Related Compounds.

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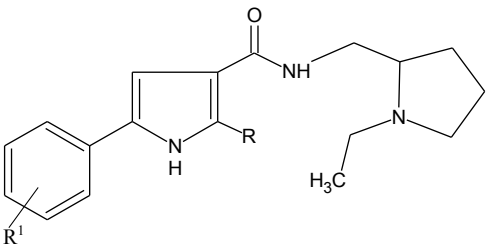
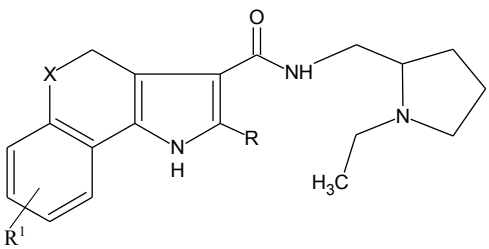
Dopamine receptors can be divided into two major families: the D_1-like and D_2-like receptors based on their pharmacological profiles and coupling with the enzyme adenylate cyclase.[1] Molecular cloning techniques have shown that the D_1-like family is further divided into D_1 and D_5 receptors, both of which activate adenylate cyclase, while the D_2-like family is divided into D_2, D_3 and D_4 receptors, which either inhibit cyclic adenosine monophosphate (cAMP) production or are not coupled to adenylate cyclase.[2] Psychotic disorders, such as schizophrenia, seem to be characterized by an overactivity of dopamine-secreting neurons in the 'limbic brain', rich in D_2-like receptors.[3] From a pharmacological point of view D_2 receptor antagonist have been shown to treat these diseases effectively; however, a long term treatment is associated with the induction of disabling side effects such as extrapyramidal syndrome (EPS) and irreversible tardive dyskinesia. The therapeutic benefit of D_2 antagonists in treating psychotics disorders has been fully accepted with the discovery of more effective antipsychotic drugs characterized by minimal induction of extrapyramidal effects (atypical antipsychotic).[3] Therefore the synthesis of novel antipsychotic with a better pharmacological profile remains a primary goal in the research for the therapy of psychoses.[3]

In previous papers[4a,b] we have reported the syntheses and structure-activity relationships of a series of 5-phenyl-3-pyrrole carboxamide and related 4,5-dihydrobenzo[g]indole-3-carboxamide analogues whose most representative terms were **1a** and **2a** respectively.



1 IC_{50}= 1030 μM

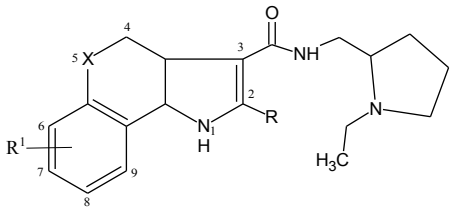
R = R^1 = H (**a**)



2 IC_{50}= 160 nM

X = CH_2, R = R^1 = H (**a**)

Encouraged by these results we carried out several modifications of **2a**. A first objective of this study was to seek correlations between the electronic and hydrophobic properties of the benzene and pyrrole substituents as well as to evaluate the bioisosteric replacement CH_2/S in the ethylenic bridge with a view to determining those physicochemical parameters which contribute to D_2-like binding affinity. Moreover, the spatial arrangement of the two aryl/heteroaryl rings of **2a** would be expected to influence bioactivity profoundly; thus the preparation of 1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[b]pyrrole analogues was also contemplated and their biological evaluation should permit some understanding of the importance of the relative positions of the aryl/heteroaryl rings.



2	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
X	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	S	CH_2CH_2	CH_2CH_2
R	H	H	H	H	H	H	H	Cl	H	H	Cl
R^1	H	6-Cl	7-Cl	8-Cl	7,8-Cl_2	8-CH_3	7-OCH_3	H	H	H	H

The synthesis of the new benzo[g]indole-3-carboxamide derivatives and related compounds, **2b-k** and their *in vitro* binding to the dopamine D_2-like receptors are reported.

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