

Synthesis and D₂-like Binding Affinity of New Derivatives of N3-[(1-ethyltetrahydro-1H-2-pyrrolyl)methyl]-4,5-dihydrobenzo[g]indole-3-carboxamide and Related Compounds.

G.A. Pinna^a, M.A. Pirisi^a, G. Chelucci^b, J.M. Mussinu^a, G. Murineddu^a, E. Maciocco^c

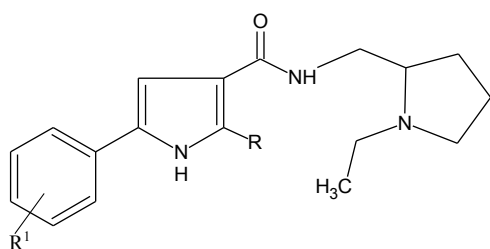
^aDipartimento Farmaco-Chimico-Tossicologico, Università di Sassari, Via Muroni 23, 07100 Sassari, Italy

^bDipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

^cDipartimento di Biologia Sperimentale, Università di Cagliari, Via Palabanda 12, 09123 Cagliari, Italy

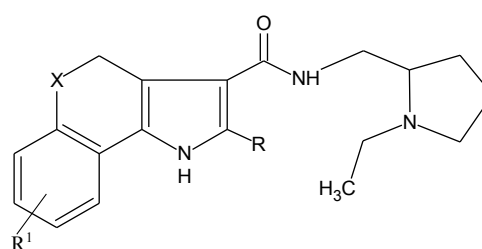
Dopamine receptors can be divided into two major families: the D₁-like and D₂-like receptors based on their pharmacological profiles and coupling with the enzyme adenylate cyclase.¹ Molecular cloning techniques have shown that the D₁-like family is further divided into D₁ and D₅ receptors, both of which activate adenylate cyclase, while the D₂-like family is divided into D₂, D₃ and D₄ 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 D₂-like receptors.³ From a pharmacological point of view D₂ 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 D₂ 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 IC₅₀ = 1030 μM

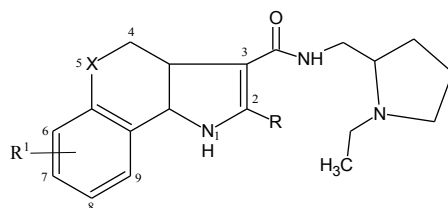
R = R¹ = H (**a**)



2 IC₅₀ = 160 nM

X = CH₂, R = R¹ = 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 CH₂/S in the ethylenic bridge with a view to determining those physicochemical parameters which contribute to D₂-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 ₂ CH ₂	CH ₂ CH 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 D₂-like receptors are reported.

1. Kebabian, J.W.; Calne, D.B. *Nature*, **1979**, 277, 93-96.

2. Civelli, O.; Bunzow, J.R.; Grandy, D.K. *Ann. Rev. Pharmacol. Toxicol.* **1993**, 32, 281-307.

3. Jaber, M.; Robinson, S.W.; Missale, C.; Caron, M.G. *Neuropharmacology* **1996**, 35, 1503-1519.

4a. Pinna, G.A.; Curzu, M.M.; Sechi, M.; Chelucci, G.; Maciocco, E. *Il Farmaco*, **1999**, 54, 542-550.

b. Pinna, G.A.; Curzu, M.M.; Sechi, M.; Chelucci, G.; Vianello, P.; Maciocco, E. *Il Farmaco*, **1998**, 53, 684-869.