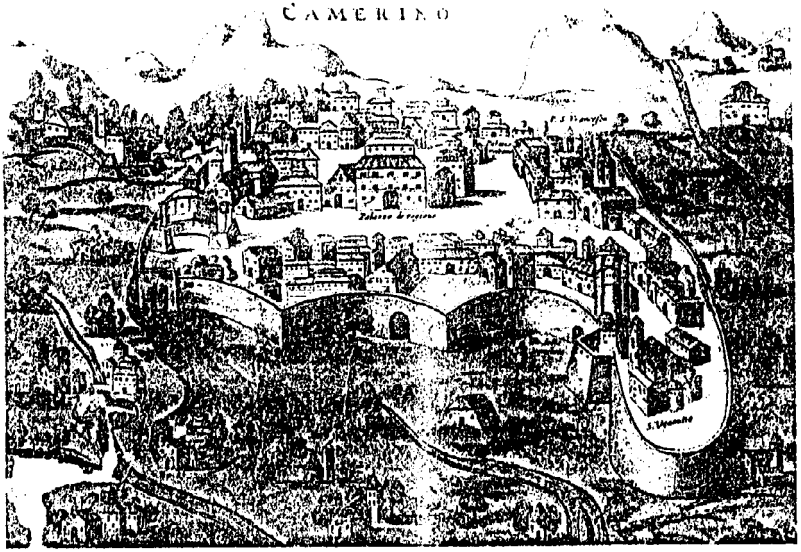
10th CAMERINO-NOORDWIJKERHOUT SYMPOSIUM

PERSPECTIVES IN RECEPTOR RESEARCH

PROGRAMME AND ABSTRACTS



September 10-14, 1995

UNIVERSITA' DEGLI STUDI DI CAMERINO

DOPAMINERGIC PROPERTIES OF 2-SUBSTITUTED BENZIMIDAZOLES: SYNTHESIS AND BIOCHEMICAL EVALUATION

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A neurotransmitter dopamine acts in both the central and peripheral nervous systems. Disturbances of the dopamine receptors have been implicated in numerous severe neurological and psychiatric disorders such as schizophrenia and Parkinson's disease, as well as in vascular regulation. Also, dopamine receptors represent sites of action of a number of psychotropic drugs, e.g. neuroleptics, cocaine and amphetamine. Thus, ligands selective for the dopamine receptors are of great significance not only as useful tools for fundamental research, but also as potential therapeutic agents.

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As a part of a systematic program aimed at the synthesis of a new generation of dopaminergic ligands, our efforts have been concentrated during the recent years on the improvement of several previously synthesized catechol bioisosteres (1-3). One of these bioisosteres 5-/2--(N,N-di-n-propylamino)ethyl/benzimidazole (compound A) expressed a moderate affinity for the binding to the D-2 and extremely weak affinity for the D-1 dopamine receptors of the synaptosomal membranes of the bovine caudate nucleus. In the present work this compound was used as a parent molecule and by introducing methyl-, isopropyl-, difluoromethyl-, dichloromethyl- or dibromomethyl-groups into position 2 of the molecule, five new compounds, herein referred to as 1-5 were produced. Upon thorough chemical analyses they were checked for the dopaminergic activity by in vitro binding assays using synaptosomal membranes prepared from the fresh bovine caudate nuclei and /^{3}H/SCH 23 390 (D-1 receptor selective) and /^{3}H/spiperone (D-2 receptor selective) as the radioligands. Values for inhibitory constants (IC_{50}) determined from competition binding curves and Hill coefficients (n_H) calculated from saturation binding data are listed in Table 1. For the purpose of comparison, parent compound A was simultaneously evaluated in the same in vitro binding assays.

None of the compounds synthesized and evaluated throughout this work expressed significant affinity for the binding to the D-1 receptors. As seen from Table 1, introduction of methyl- (compound 1) or isopropyl-group (compound 2) into position 2 of the compound A led to a significant loss of the affinity for the dopamine D-2 receptors in relation to the parent molecule. The same holds true for the difluoromethyl-substitute (compound 3). However, introduction of dichloromethyl (compound 4) or dibromomethyl- (compound 5) groups into position 2 of A produced dopaminergic ligands that acted as stronger competitors to /^{3}H/spiperone binding to D-2 receptors in comparison with compound A under conditions of prevented binding of the radioligand to $5HT_2$ receptors (50 nM ketanserin).

Hill coefficients close to unity suggest that compounds 3-5 acted as antagonists at the dopamine D-2 receptor. Based on the calculated electrostatic potential (MEP) values it was supposed that the compound 3 would express higher affinity for the dopamine D-2 receptors than the compounds 4 and 5. However, opposite to our expectations and theoretical considerations dibromomethyl substitute (compound 5) and dichloromethyl-substitute (compound 4) of benzimidazole were approximately 200-fold and 100-fold stronger competitors to /^{3}H/spiperone binding to D-2 dopamine receptors, than the parent molecule A, respectively.

Table 1. IC_{50} values and Hill coefficients of the compounds 1-5 for the dopamine D-2 receptors

COMPOUND	IC_{50}(nM/L)	n_H
1	>100 000	-
2	>100 000	-
3	10 000	0.95
4	598	1.03
5	231	1.09
A	50 000	1.05

These data demonstrate a high level of tolerance of the dopamine receptor molecule toward the introduction of relatively bulky groups such as dibromomethyl- and dichloromethyl- into the ligand molecule. The structural patterns of the compounds 3-5 will be further developed with an aim of improving their dopaminergic activity, while preserving their strict selectivity for the D-2 class of the dopamine receptors.

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