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# SYNTHESIS AND EVALUATION OF SEVERAL CATECHOL BIOISOSTERES AS POTENTIAL DOPAMINE RECEPTOR LIGANDS

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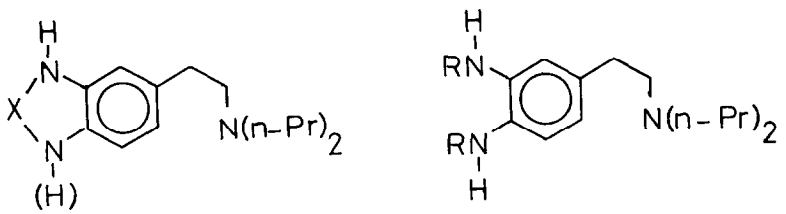
ABSTRACT: Derivatives of benzimidazole (I), benzimidazolone (II), benzimidazolethione (III), 2,3-dihydroxyquinoxaline (IV) and the noncyclic acetamide (V) and trifluoroacetamide (VI) of the corresponding 1,2-phenylenediamine were synthesized and tested for DA-ergic activity. III and IV had a moderate affinity for the $D_2$ receptors of the bovine caudate nucleus.

During the past years significant efforts have been dedicated to the design and synthesis of new ligands selective for the two main dopamine (DA) receptor subtypes[1]. Many of these compounds have been found to be suitable agents in the therapy of some diseases connected to the disturbance of the DA-ergic system[2], as well as useful tools for research. In this work our attention has been focused on the synthesis of several nitrogen-containing catechol bioisosteres to examine the consequences of the isosteric relationship between these compounds and the catechol moiety of the DA. For this purpose, compounds I-VI were synthesized, chemically characterized[3] and evaluated for their DA-ergic activity, i.e., their affinity for both $D_1$ and $D_2$ DA receptors of the bovine caudate nucleus. The structures of these compounds are depicted in Scheme 1.

SCHEME 1.

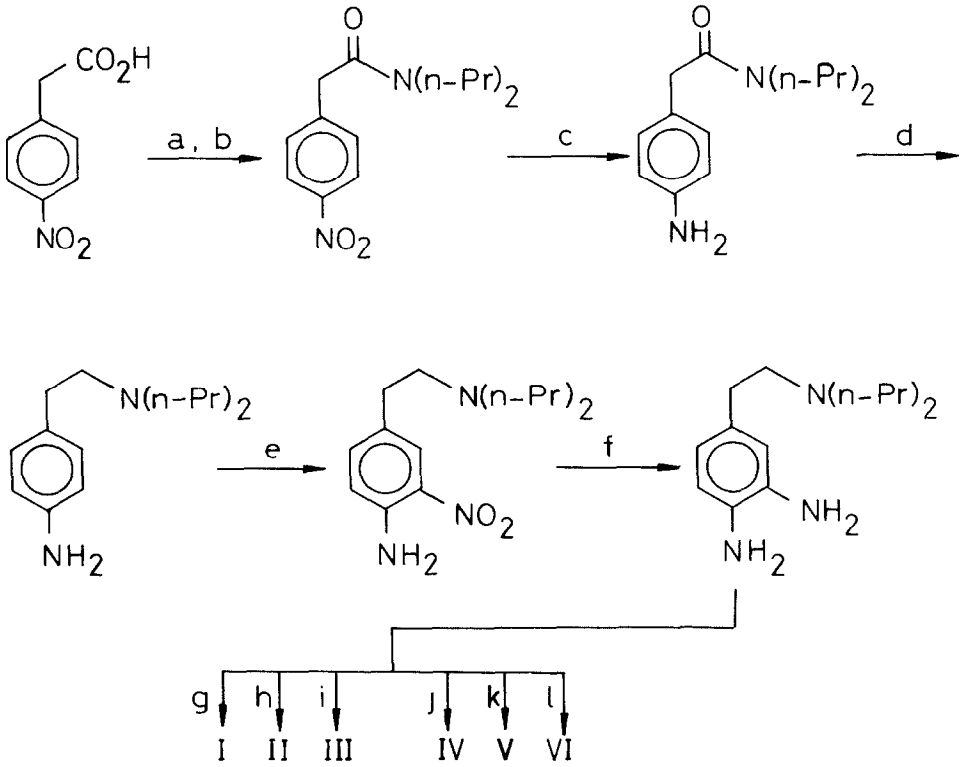



X: =N- (I); -CO- (II); -CS- (III); -CO-CO- (IV)
R: $CH_3$-CO- (V); $CF_3$-CO- (VI)

All these compounds are characterized by similar topology, but different acidity of the N-H proton in the heterocyclic part of the molecule, which was presumed to exert a similar function to one of the phenolic hydroxyl groups of DA, acting as H-bond donor and eliciting the receptor response[4].

Scheme 2 illustrates the synthetic pathways of all six compounds tested in this work. There was a good overall yield of the target compounds by each of these synthetic pathways.

SCHEME 2.




a. $PCl_5$, RT; b. di-(n-propyl)amine, $CH_2Cl_2$, RT; c. Raney Ni, $N_2H_4$, EtOH, 50°C; d. $LiAlH_4$, THF, reflux; e. $Ac_2O$, $HNO_3$; f. Raney Ni, $N_2H_4$, EtOH, 50°C; g. Formic acid; h. 1,1'-carbonyldiimidazole; i. $CsCl_2$ ; j. oxalic acid ; k. $Ac_2O$, Py; l. $(CF_3CO)_2O$, Py.

The affinity of each compound for binding to the two main DA-ergic receptor subtypes was determined by in vitro competitive displacement of the specific radioligands from synaptosomal membranes prepared from fresh bovine caudate nuclei[5]./$^3$H/SCH 23390 (spec.act. 80 Ci $mmol^{-1}$) and /$^3$H/spipe-

rone (spec.act. 70.5 $mmol^{-1}$) were used to label the $D_1$ and $D_2$ receptors, respectively[6]. The $IC_{50}$ values for the individual compounds, calculated from the competitive displacement curves, are listed in Table 1. Dopamine was evaluated in the same test system as a reference. Each value represents the mean$\pm$s.e.m. from at least three independent experiments done in triplicates.

TABLE 1.

| COMPOUND | $IC_{50}\pm$s.e.m.(μM) | |
|---|---|---|
| | DOPAMINE RECEPTOR SUBTYPE | |
| | $D_1$ | $D_2$ |
| I | > 100 | $50\pm9$ |
| II | > 100 | > 100 |
| III | > 100 | $1\pm0.2$ |
| IV | > 100 | $3\pm0.1$ |
| V | > 100 | > 100 |
| VI | > 100 | > 100 |
| DOPAMINE | $0.2\pm0.05$ | $8\pm2$ |

As seen from Table 1, none of the compounds synthesized in this work expressed affinity for $D_1$ DA-receptors. This could be related to previously published data which suggested there are more severe structural requirements for activation of the $D_1$ receptor comparing to those for the $D_2$ receptor[7]. However, compounds III and IV competed for /$^3$H/spiperone binding to $D_2$ receptors even more efficiently than DA itself. Compounds III and IV are weak acids with pKa values of 9.8[8] and 9.5[9], respectively, close to that of the catechol moiety of the DA[10]. The other compounds synthesized and examined for the DA-ergic activity are at least ten times weaker acids compared to the catechol. This suggests that the acidity of the proton bound to the heterocyclic nitrogen is one of the crucial prerequisites for the DA-ergic activity, i.e., for effective interaction with the DA receptors.

Further development of the compounds deriving from I, II, V and VI, as well as the improvement of the DA-ergic properties of the compounds III and IV could serve to obtain a series of novel nitrogen-containing bioisosteres of the catechol moiety of the DA. These new derivatives might be useful as strongly specific ligands of dopamine receptors in fundamental studies related to the examinations of dopaminergic structure-activity relationship. They may also find application in the treatment of pathologi-

cal conditions related to disturbances of the DA-ergic system.Further studies along this line are in progress.

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3. All compounds gave satisfactory $^{1}$H-NMR and IR spectra, as well as chemical microanalyses data (C, H, N, S). I. 5-/2-(N,N-di-n-propylamino)-ethyl/benzimidazole; II. 5-/2-(N,N.di-n-propylamino)ethyl/-1,3-dihydro--2H-benzimidazol-2-one; III. 5-/2-(N,N-di-n-propylamino)ethyl/-1,3-di - hydro-2H-benzimidazolol-2-thione; IV. 5-/2-(N,N-di-n-propylamino)ethyl/--1,4-dihydro-quinoxalin-2,3-dione; V. 4-/2-(N,N-di-n-propylamino)ethyl/--1,2-benzene diacetamide; VI. 4-/2-(N,N-di-n-propylamino)ethyl/-1,2-benzene ditrifluoroacetamide.

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