DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL CONFORMATIONALLY RESTRICTED ANALOGUES OF DOPAMINE

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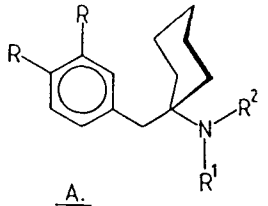
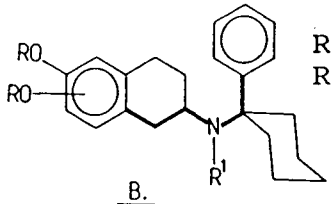
Dopamine (DA) occupies a unique position owing to the extensive dopaminergic innervation in the central nervous system (CNS) as well as the periphery. Disorders associated with these dopaminergic neurons have thus been implicated as the cause of several neuorological, endocrinological, and cardiovascular diseases. DA agonists are of clinical utility in Parkinsons disease (Ellefson et al 1980) while DA antagonists have clinical value in treatment of neurosychiatric diseases (Cross et al 1983). This, together with investigation of receptor imaging, led to certain delineations of the stereochemical aspects required for different types of dopaminergic binding (D_1 and D_2 receptors). Structures A and B were designed to include the dopamine skeleton in either α-rotamer, or B-rotamer dispositions of the possible dopamine conformers.

$R = OCH_3$, OH
$R^1 = H$
R^2 = cyclohexane
R^1, R^2 = cyclo(C_5H_{10})



A.



B.

$R = CH_3$, H
$R^1 = H$

Structure (A) incorporates the α-carbon into a quaternary assembly with the cyclohexyl moiety to provide an antiperiplaner conformation of DA framework. The cyclohexyl moiety in such a structure (A) might be considered as a parachute; thus directing the opposite side of the molecule towards the complementary binding sites on the receptor surface; whereas structure (B) incorporates an arylcycloalkyl moiety which might serve as haptophoric grouping upon binding interaction with the target receptor sites.

Seven compounds of type (A) [which are N,N-disubstituted-α-cycloalkyl-B-(3- or 4-methoxy (or hydroxy) or 3,4-dimethoxy (or dihydroxy) phenethylamines] and six compounds of type (B) [which are N-(1-arylcycloalkyl) 5,6- or 6,7-dimethoxy or dihydroxy-2-aminotetralines; were prepared via condensation of appropriate amines with cyclohexanone, potassium cyanide at a certain pH to afford the corresponding carbonitrile derivatives. These were alkylated with n appropriate organo lithium-compound (Klair et al 1969) and dealkylation to the catechols was achieved by the use of hydrobromic acid or boron tribromide (Kaiser et al 1982). An Interchem display program for computer modelling studies has also been manipulated in a trial to determine the probable overlap of the binding functions of the newly synthesized compounds with their corresponding ligands. The infra-red, ^1H NMR and mass spectra and the elemental analysis of all the compounds were entirely consistent with their proposed structures.

-Cross, A, et al. (1983) Eur.J.Pharmacol. 88: 223-227
-Ellefson, C.R. et al (1980) J Med.Chem. 23:977-980
-Kaiser, C. et al (1982) J.Med.Chem. 25: 697-702
-Kalir,A, et al (1969) J.Med.Chem. 12: 473-477