Structural Requirements of Na^+-dependent Antidopaminergic Agents Compared with Na^+-independent Analogs

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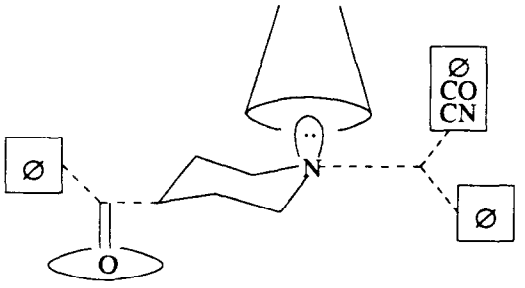
Various classes of compounds, including butyrophenones, diphenylbutylpiperidines, tricyclics, orthopramides, indolones and imidazolidinones, are used as antipsychotic drugs. Some of these share the feature that their binding to dopamine receptors is highly sodium-dependent. The present work is an attempt to define the three-dimensional (3D) and electronic requirements leading to this particular behavior.

Using an interactive flexible molecular fitting program, MGS, we are able to point out three pharmacophoric elements oriented exactly in the same way in all the Na^+-dependent antipsychotics: a nitrogen lone pair, a phneyl ring, and a carbonyl moiety.[1]

On the opposite, for the Na^+-independent analogs, the two last mentioned pharmacophoric elements are not always present. Moreover, two II regions are occupied on the other side of the molecule (on the right of our pharmacophoric model).[2] We attribute the extra-pyramidal effects of these compounds to the binding through these II sites.



Na^+-dependent neuroleptics

Na^+-independent neuroleptics

1 Collin, S., Evrard, G., Vercauteren, D. P., Durant, F., Carrupt, P. A., van de Waterbeemd, H., and Testa, B. *J. Med. Chem.* (accepted)
2 Collin, S., Norberg, B., Evrard, G., Durant, F., Tollanaere, J. P., and Moereels, H., *Eur. J. Med. Chem.* 1988, **23**, 69–76

Interactive Computer-Aided Molecular Design Using the PHIGS Standard on IBM Workstations

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The molecular modeling graphics system developed at the Scientific Computing Facility of the University of Namur is based on graPHIGS, the IBM implementation of the PHIGS (Programmers' Hierarchical Interactive Graphics Standard) standard. It is a workstation-independent software, highly interactive, using pop-up menus, status, rulers, programmed keys, mouse, and so on. It runs on all GDDM terminals and the 5080 workstation, for which real-time interactivity is fully achieved via the use of a 5085 graphic processor. The program was written in FORTRAN on a 4341–2 processor running under VM/CMS Rel.5.

In this actual version, the molecular structures are represented as wire frames and/or dot surfaces envelopes. Hierarchical graphic data allows easy and interactive three-dimensional (3D) manipulations of one or more structures, i.e., generation of various conformers, link of preexistent fragments, comparison (least-squares fitting) of molecular models and molecular models and molecular motions simulations (from MC or MD studies). Intra- or intermolecular geometric calculations are naturally included.

The progam is interfaced with the IBM Winchester Solid Modelling program, WINSOM, which allows the user to build high-quality raster pictures (stick-and-ball, space-filling, ribbon) of any structure, and with an in-house software for representation and manipulation of molecular properties (isocontour of electrostatic potential, isodensity surface, etc.).

In this contribution, we particularly stress the importance in molecular modeling of the interactive characteristics and hierarchy concepts offered by PHIGS.

GEMM: An Interative Geometry Manipulator for Molecular Modeling

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An interactive molecular graphics package called GEMM (Generate, Edit, Manipulate Macromolecules) is developed, which can be used as a geometry manipulator for molecular modeling. GEMM offers a strong geometry manipulation facility that can be used to construct a complex molecule system. GEMM can help users rearrange the prime structure to form a secondary, tertiary or higher-order structure. This software has been used for many molecular modeling projects at NIH. By using GEMM, the molecule model can be built easily and transferred to other molecular analysis software for further study. For example, the x,y,z coordinates of the molecular system can be sent to the CHARMM program for energy calculation and molecular dynamics.