of molecules can be offered via an automatic computional method. Databases of molecules with known biological and pharmacological activity especially may serve as a fruitful basis. Another aspect is the usage of this technology for selection of test compounds in the experimental biological screening of molecules (mass screening).

From a molecule with a given biological activity, different pharmacophors are deducible, and these may serve as the starting point for the search of new molecular topologies carrying the same biological activity. For this dedicated purpose, the software package IDEA has been developed at E. Merck. IDEA allows one to retrieve pharmacophoric patterns defined by atomic distances. Additional molecular features, such as hydrogen donors and acceptors, ring systems, and flexible chains, are treated as dummy atoms and are therefore accessible for retrieval within this approach. Furthermore, a representation of the electrostatic or hydrophobic field is used to allow nontopological information to be treated. IDEA handles multiple conformations of molecules, as well as multimolecular arrangements. Various databases from different sources like the Cambridge Crystallographic Datasystem, the Chapman-Hall Dictionary, and the Drug Data Report, as well as in-house 3D data, were converted and merged together to be retrievable by the IDEA system.

The IDEA package consists of three main modules and various software tools. The main modules handle the generation of a searchable database for molecular systems, the search for a pharmacophoric pattern, and the preparation of data for interactive graphical display and analysis. The graphical representation, as well as the generation of input requests, are handled by the CPECM Program, which allows comparison, classification, and selection of specific entries out of the hits found. In addition, numerical and text information on the molecular systems considered can be retrieved with the CPECM program.

The approach of the IDEA system will be presented, and some examples of concrete applications will be discussed.

CAVEAT, ILIAD, AND TRIAD: 3D SEARCHING FOR MOLECULE DESIGN

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To mimic a peptide, constrain an acyclic inhibitor by macrocyclization, or design a ligand *de novo* to complement a receptor site, functional groups or molecular fragments must be positioned by a structural framework in a way that addresses the *orientation* of bonds, in contrast to simply the *location* of atoms. To devise a molecule that conforms to a structural model is most efficiently approached by engineering a framework to enforce specific vector relationships among the bonds that link the functional units to it. The program CAVEAT was developed for this purpose, to search three-dimensional databases for structures containing bonds with a specific orientation. A structural database is preprocessed to determine the relationships between all pairs of relevant bonds in each molecule. The resulting CAVEAT database can then be searched rapidly to identify potential templates or linking fragments.

To complement existing databases as a source of templates, two databases of computed, minimized structures have been generated. TRIAD contains 411,000 tricyclic hydrocarbons, and ILIAD has 110,000 structures built up from linear chains of 5 units.

A companion program to CAVEAT, called CLASS, carries out a post-search screening and clustering of structures to speed the evaluation of hits. CLASS allows flexible definition of structural or functional characteristics for inclusion or exclusion from the list of hits, including template tracing and avoidance of steric interactions, and it clusters hits that represent similar structural information. A benchmark 3-vector CAVEAT search through the TRIAD database yields 750 hits that are screened and clustered into 6 distinct groups by CLASS; all this takes less than 3 minutes on an SGI Indigo.

DENSITY FUNCTIONAL PSEUDOPOTENTIAL STUDIES OF MOLECULAR GEOMETRIES, VIBRATIONS, AND BINDING POTENTIALS. APPLICATION TO METALLOCARBOHEDRENES

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Density functional theory has been found to provide a very computationally cost-effective method for the study of molecular systems. We have recently enhanced the computational capabilities of the DGauss density functional theory program by implementing norm-conserving pseudopotentials which include scalar relativistic effects. A comprehensive study of molecular calculations comparing the use of the pseudopotentials relative to all electron basis sets, and experimental results was carried out. We find that, in general, pseudopotential bond distances are within 0.1 Å of experimental and all-electron results, and relative uncertainties of vibrational frequencies are, on the average, less than 12%. For binding energies, pseudopotential results agree well with corresponding all-electron results. We have also applied the pseudopotential density functional method to investigate the stability, bonding, and geometric structure of the recently discovered metallocarbohedrenes. It is found that the previously proposed T_h dodecahedron structure is dynamically unstable. Instead, a new structure of D2d symmetry is found to be more strongly bound.

DESIGN AND PRELIMINARY RESULTS OF LEAPFROG, A SECOND GENERATION *DE NOVO* DRUG DISCOVERY TOOL

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Interest in *de novo* drug discovery tools is rapidly increasing, with recent literature reports of new programs from a