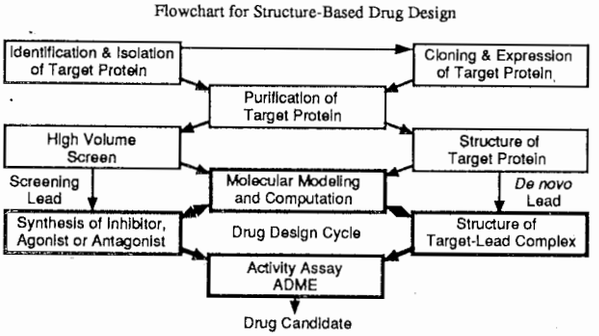
05-Molecular Modelling and Design for Proteins and Drugs



PS–05.03.19 INHIBITOR DESIGN FOR HUMAN RHEUMATOID ARTHITIC SYNOVIAL FLUID PHOSPHOLIPASE A_2. By Qiaolin Deng*, Luhua Lai, Yu Luo and Xiaojie Xu , Department of Chemistry, Peking University, Beijing, China

It is known that the phospholipases A_2 (PLA_2) associates with localized and systemic inflammatory process and tissue injury. In synovial fluids of patients with rheumatoid arthritic, high level of soluble PLA_2 (s–PLA_2) was detected . We used structure–based method to design the inhibitors of s–PLA_2.

The crystal structure data of bovine pancreatic PLA_2 (1BP2, 2.5A) and Crotalus atrox PLA2 (1PP2, 1.7A) were used as the basis to construct the 3–D structure of s–PLA_2 by applying homology protein structure prediction program developed in this laboratory. The sequence of s–PLA_2 has about 37% homology with that of 1BP2 and 44% homology with that of 1PP2. After energy minimization with CHARMM, DOCK program developed by I. D. Kuntz was used to search the CSD for molecules which have structural complementarity to this enzyme. According to their spatial complementarity and chemical properties, several molecules were chosen as the inhibitor templates . The synthesis and activity tests are under development.

PS–05.03.20 STRUCTURAL STUDIES OF DEXMEDETOMIDINE HYDROCHLORIDE, A NEW DRUG SUBSTANCE. By R. Rajala and E. Laine*, Department of Physics, University of Turku, Finland.

Dexmedetomidine hydrochloride (Recommended International Non-proprietary Name, Rec.INN), (+)-(S)-4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole hydrochloride is a novel, selective α2-adrenoceptor agonist synthesized by Orion Corporation Farmos, Oulu, Finland. Dexmedetomidine hydrochloride appears as a white or almost white crystalline powder. The molecular weight, true density, melting range of dexmedetomidine hydrochloride are 236.7, 1.17 grams per cubic centimetre and 156.5 - 157.5 °C, respectively.

The preliminary crystal structure determination of dexmedetomidine hydrochloride has been carried out. The crystal belongs to the monoclinic space group $P2_1$ with cell dimensions a = 7.851(2) Å, b = 7.463(2) Å, c = 11.596(2) Å and β = 98.29(2) °. The diffraction data has been collected on Rigaku AFC5S diffractometer with graphite monochromated MoKα radiation at 23°C. The molecular structure and packing in the unit cell have been solved by using matrix least-squares refinement to an R-value of 6.8 % with 870 observed reflections. All the calculations have been performed by using the TEXSAN crystallographic software package by Molecular Structure Corporation.

Dexmedetomidine hydrochloride appears in two different forms which represent the anhydrous (dry) and the hydrous (humid) form. The dry-humid structure transition of dexmedetomidine hydrochloride proved to be thermally reversible. The effect of moisture on the crystal structure of dexmedetomidine hydrochloride has been studied by using Philips PW1820, APD1700 automated powder diffractometer system with heating and humidity chamber and Perkin-Elmer DSC-7 differential scanning calorimeter.

