ABSTRACT

The present work is a Quantum Pharmacological study of Ca\textsuperscript{2+} channel blockers. Ab initio Hartree Fock 6-31G calculations have been performed to study the conformational aspects of various subclasses of these drugs that is, conformational aspects of 1,4 dihydropyridines, diltiazem and verapamil have been studied in detail. Conformational mapping has been performed to understand the differences between protonated and unprotonated form of drugs and to understand important pharmacophoric features as compared to a highly potent drug. Charge environment on the drugs has been studied utilizing complete molecular electrostatic potential maps in the form of contours.

Supermolecule type intermolecular interaction calculations have been employed to study the Ca\textsuperscript{2+} ion holding capacity of these drugs. Anchoring of dihydropyridines to receptor has also been studied. Ca\textsuperscript{2+} ion holding capacity has been investigated with the only restriction that the ion should not be covalently bound. (Covalent binding will lead to complete stop of ion flow leading to grossly disturbed ion gradient and death of patient). All the drugs are shown to be capable of holding Ca\textsuperscript{2+} ion in the unprotonated form.
Present study has suggested a unique ‘pH-Controlled self regulatory mechanism for dihydropyridines’, which explains their antiarrhythmic behaviour and may also be considered as an alternative to ‘use dependent blockade’.

Pharmacophoric features and ion holding capacity of diltiazem and verapamil have also been reported. Our study indicates the requirement of huge conformational change prior to verapamil’s capacity to hold Ca$^{2+}$ ion. This may be partially responsible for the fact that verapamil shows exclusively use dependent blockade as opposed to tonic block.
PROCLAMATION

I hereby declare that the subject manifested in this thesis, “A Quantum Pharmacological Study of Antiarrhythmic Drugs”, is the result of research carried out by me in the Department of Chemistry, University Institute of Engineering & Technology, C.S.J.M. University Kanpur, India under the supervision of Dr. Arpita Yadav.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

CSJMU/ Kanpur
Apr. 2005

(Anamika Awasthi)