Chapter 8

CONCLUDING REMARKS

In this study Ca\(^{2+}\) channel blockers have been studied utilizing a quantum pharmacological procedure. Three classes of Ca\(^{2+}\) channel blockers were studied, that is, Dihydropyridines, Benzothiazepines and Phenylalkylamines using quantum mechanical Hartree Fock techniques coupled with supermolecule type intermolecular interaction calculations on drug-receptor models. Drug's Ca\(^{2+}\) ion holding capacity was also investigated in each case. The study has come up with some important mechanistic aspects. Main findings arising from the entire study are summarised below:

8.1 1,4-Dihydropyridines:

1. Conformational study of this subgroup reiterates that bioactive conformation is the energetically less favoured syn-anti conformation, in which the ester in the 3 position of the DHP ring assumes the synperiplanar conformation, while the ester in the 5 position adopts the antiperiplanar conformation.
2. More active compounds exhibit smaller degree of ring distortion from planarity.

3. Bulky ester substituent at 5-position in pyridyl ring shows a minor difference in conformational features.

4. DHP’s are found in unprotonated form at physiological pH. When it gets protonated, there is a decrease in the coplanarity of C4.

5. DHP’s show overall negative charge environment hence a slightly positive/neutral charge environment would be complementary on the receptor.

6. Thr (III S5.14) is shown to be important in anchoring the drug to the active site, via H-bond at the stern.

7. Ca$^{2+}$ approaches from the essential side (syn-side) of the drug and this depends on conformational as well as electrostatic aspects.

8. Most favorable position is predicted when Ca$^{2+}$ can interact with the phenyl and pyridyl substituents both.

9. Interaction energy is reduced on moving the substituent from ortho to meta or para position in the aryl ring as non-coplanarity of C4 increases. This indicates that o-nitro nifedipine is most active as it shows least ring distortion from planarity, which is in conformity with experimental results.
10. A pH-controlled self-regulatory mechanism has been proposed based on our studies. According to this mechanism DHP's function as follows:

a) At physiological pH the drug enters the body in unprotonated form.

b) It gets H-bonded to receptor via one of the DHP sensing residues like Thr (III S5.14)

c) Essential side is still free to hold the Ca^{2+} ion. Unprotonated form holds the Ca^{2+} ion.

d) Physiological pH change triggers the protonation of drug and this form can no longer hold Ca^{2+} ion, but is still tightly held to receptor, so that Ca^{2+} is not a competitor for receptor site.

8.2 Benzothiazepines:

We have also studied the pharmacological features and Ca^{2+} holding capacity of this class of drugs by using same procedure. Main findings are as follows:

1. The most stable conformation of Diltiazem is predicted to be (2R, 3R) conformation, which is also referred to as the ordered form in the crystal.
2. The pharmacophoric triangle predicts that the two aryl rings should be \(~6.5\) Å distance apart making an angle of \(~50.4\) degrees.

3. This drug exists in protonated form at physiological pH. It may be anchored to the receptor via H-bonding to some proton acceptor group.

4. Unprotonated form is capable of trapping \(Ca^{2+}\) ion utilizing strong electrostatic interactions via carbonyl at \(C_4\) and ester substituent at 3 position.

**8.3 Phenylalkylamines:**

Phenylalkylamines are in general large compounds with lot of conformational freedom. Due to large size of the molecule very little computational work has been done in the past. Main findings of our study are as follows:

1. At physiological pH drug exists in protonated form, which has a half-folded conformation (open structure).

2. Unprotonated form of drug is found in "sandwich" or folded conformation (closed structure).
3. Pharmacophoric features extracted indicate that Verapamil is 'R' enantiomer with respect to chiral center. The two aryl rings should be 5.7 Å apart at an angle of 80.85°.

4. Unprotonated form holds the Ca$^{2+}$ ion and Ca$^{2+}$ is trapped somewhere near aryl ring, held by electrostatic interactions in the neighbourhood of chiral carbon and shows involvement of chiral carbon also.

5. A huge conformational change is required for holding the Ca$^{2+}$ ion (Drug has to become unprotonated). This could be one of the reasons why the drug shows exclusively use dependent blockade (in other words, only when absolutely essential). Phenylalkylamines also show negatively charged environment as drugs of other subgroups of this class.

To conclude, we state the most remarkable achievements of the entire study. For the first time in the history of Ca$^{2+}$ ion channel blockers a self-regulatory pH-controlled mechanism has been proposed for the functioning of DHP's as antiarrhythmic drugs. This mechanistic aspect also holds the importance in comparing with the neutral rhythmic action controlled by acetylcholine.

The study also highlights important pharmacophoric features of other two subclasses of Ca$^{2+}$ channel blockers i.e. Benzothiazepines
and Phenylalkylamines. For the first time, through computational
techniques we have probed the \( \text{Ca}^{2+} \) holding capacity of these
subclasses of drugs. Our results also throw light on the interestingly
huge conformational change required by Verapamil before being
capable of obstructing \( \text{Ca}^{2+} \) flow. This indicates in indirect way why
Verapamil probably shows exclusively use dependent blockade.

Further computational studies on interaction of
Benzothiazepines and Phenylalkylamines with the receptor will
clarify the differences in the mechanistic aspects of DHP’s and these
drugs.