CHAPTER 7

SUMMARY AND CONCLUSION

The World Health Organization estimates that 60 per cent of the world's cardiac patients will be Indian by 2020. Nearly 50 per cent of CVD related deaths in India occur below the age of 70, compared with just 22 per cent in the West. In addition, researchers have determined that compared to people in other developed countries, the average age of patients with heart disease is lower among Indian people and Indians are more likely to have types of heart disease that lead to worse outcomes.

Despite significant advances in prevention and treatment, cardiovascular disease remains the leading cause of death in economically advanced countries. The developing world has also begun to experience a disconcerting growth in prevalence, where the insurgence of CVD has exacerbated the risk factors associated with indigenous communicable diseases. The overriding challenge for industrial players is to keep pace with epidemiological change in both the developed and developing world. This involves successfully integrating into localized healthcare systems and reimbursement structures, in addition to remaining aligned with product demand. In the field of novel drug research area, this challenge is being met with a focus on new molecules that reduce adverse effects, improve patient outcomes and extend the range of formulations for existing indications.

The high cost of tertiary level management of IHD is unaffordable for a large section of the population as well as for the state health care system. Therefore, there is a global approach for primary prevention by altering life style and diet on the one hand and research to identify newer and cheaper agents which can prevent or delay the occurrence of and/or complications of IHD on the other hand.

The various drugs, which have so far been tried out are calcium antagonists, beta blockers and free radical scavenger. Although these drugs provide significant benefit in acute conditions and in secondary prevention, they are not advisable or acceptable for chronic use as primary preventive measures in large number of patients, who possess a high level of risk of having acute ischemic episodes, later in life. Moreover, chronic use of various drugs in the treatment of IHD showed major limitations due to various side effects. Under such circumstances, other options need to be explored which will help in circumventing this problem. After an extensive literature survey, pyrazolone basic moiety was undertaken for

the novel drug development since it has been proved as cardiovascular agents by Mitsubishi-Tokyo Pharmaceuticals, Japan. In chapter 1, the physiology, pathology of myocardial ischemic reperfusion injury and its prevention by pyrazolone derivatives have been dealt as well.

Chapter 2 dealt the extensive literature survey on pyrazolone and its role in various cardio vascular diseases. **A review article regarding various pharmacological actions of pyrazolone has been published in Journal of Pharmacy Research.** In chapter 3, the aims and objective of the present work has been furnished.

In Chapter 4, the synthesis and structural characterization of novel analogues of the pyrazolone derivatives by UV, IR, NMR, Mass and CHN analysis have been presented. By maintaining the basic 3-methyl pyrazolone as substitution pattern, the derivatives were synthesized with a variety of different atoms and functional groups as substituent. This was achieved with the aim of emulating or surpassing the biological potency of the parent compound 3-methyl pyrazolone. Edaravone (pyrazolone derivative) has preventive effects on myocardial injury following ischemia and reperfusion in patients with acute myocardial infarction. Bearing this in mind, ten contrasting series of pyrazolone analogues were synthesized. **A research paper regarding synthesis and bioactivity evaluation has been published in Indian Journal of Chemistry Section B.**

Acute toxicity and gross behavior studies revealed that the entire series of compounds in present investigation were found to be nontoxic even up to 5000 mg/kg b.w. Amongst all, PYZ2 was studied for its acute and sub acute toxicity profile. **A research paper regarding analgesic, anti-inflammatory, antipyretic and toxicological evaluation of pyrazolone derivatives has been published in Saudi Pharmaceutical Journal.**

In chapter 4, the cardioprotective effect of pyrazolone derivatives on plasma lipid profile, serum marker enzymes, endogenous enzymatic and non-enzymatic antioxidants in cardiac tissues against isoproterenol (ISO) induced myocardial ischemic injury in rats has been described systematically. The result of the study has been published in **Pharmacology online 2, 986-994(2010), Italy.** The present study explored the cardioprotective effect of pyrazolone derivatives against ISO induced myocardial

ischemic injury in rats. The existing experimental evidence suggests that ISO induced the generation of free radicals in heart tissue. The generated reactive oxygen species such as superoxide radicals are potential to cause damage to various intracellular components. Heart tissue is particularly susceptible to free radical injury, because it contains low levels of detoxifying enzymes/molecules like SOD, GSH and CAT. Further ISO has high affinity towards cardiac myocyte leading to accumulation of ISO in heart. The ISO induce myocardial injury is critical to the heart because it would presumably have extremely adverse effect on heart. Hence the experimental protocol was designed in such a method that it would initiate ISO induced myocardial damage followed by pyrazolone derivatives intervention was used to explore the extent of control of progressive myocardial tissue damage.

Pretreatment of pyrazolone derivatives was able to reduce the ISO induced cardio toxic manifestations in multiple ways: Increase in the level of plasma triglycerides, total cholesterol and low density lipoproteins in ISO treated groups indicate that ISO may be interfering the metabolism or bio synthesis of lipids. Pretreatment of pyrazolone derivatives showed reduction of blood lipid profile with concomitant increase in HDL cholesterol was observed. The lipid lowering effect of pyrazolone derivatives may be due to inhibition of hepatic cholesterol biosynthesis, increased fecal bile acid secretion and stimulation of receptor mediated catabolism of LDL cholesterol and increase in the uptake of LDL from the blood by liver. Myocardial injury induced by ISO in rats was indicated by elevated level of the marker enzymes such as serum LDH and CPK.

Pyrazolone derivatives were found to inhibit ISO induced LDH and CPK in the serum of rat. It is widely reported that ISO induced free radical generation triggers the membrane peroxidation and disruption of cardiac myocyte which can lead to increased release of LDH and CPK in the serum. Pyrazolone derivatives pretreatment led to inhibition of LDH and CPK release which resulted in either complete reversal or considerable recovery of the serum enzyme activities. The cardio protective activity was further supported by increased level of myocardial anti oxidant enzymes like SOD, GSH and CAT in pyrazolone pretreated groups.

The anti oxidant potential of pyrazolone derivatives further supported by decreased lipid peroxidation because it is known to cause cellular damage and primarily responsible for reactive oxygen species induced heart damage. The increased levels of MDA and 4-HNE were observed in ischemic heart tissue. Pretreatment of pyrazolone derivatives efficiently counter acted reperfusion induced myocardial ischemic injury by significant decrease level of MDA and 4-HNE. The evaluation of anti oxidant potential of pyrazolone derivatives has been furnished by a publication in **Journal of Advanced Pharmaceutical Technology and Research.**

In chapter 5, the results of all the studies viz synthesis, characterization and cardioprotective studies have been described adequately. In chapter 6, the results were discussed with relevant references to draw the possible mechanism of pyrazolone derivatives. The results obtained for the synthesized pyrazolone derivatives were in conformity with reported literature.

Comprehensively, it is summarized that reperfusion of coronary flow is necessary to resuscitate the ischemic or hypoxic myocardium. The reperfusion injury induced ischemic myocardium may be protected by administration of exogenous cardioprotective agents or by classical ischemic preconditioning. Although protection provided by ischemic preconditioning appears to be robust, a drawback of the majority of preconditioning studies is that protection is not absolute when ischemia is severe and prolonged, even those preconditioned areas of myocardium will go further to develop complete infarction. Therefore, possibility of preconditioning the heart with an exogenous agent (e.g pyrazolone derivatives) was used in the present study to provide new avenues to induce preconditioning for cardio-protection and by an external pharmacological intervention. Administration of pyrazolone derivatives to preconditioned heart before the insult of ischemia produced a significant improvement to ischemic heart by reducing the elevated levels of lipid profiles, cardiac injury markers to near normal level in rat heart model.

Finally it can be concluded that, the pyrazolone derivatives were found to possess significant cardio protective property in animal models. Further structural modification and clinical studies will unveil the therapeutic efficacy of the pyrazolone pharmacophore in the field of new drug discovery on cardio vascular disease.