PREFACE

Cardio Vascular Disease (CVD) is the single largest cause for mortality and morbidity in the world as reported in WHO report 2007. The overall burden continues to grow in both developed and developing countries, but there are distinct differences in the pattern of growth between the two, as the expected rate of increase in CVD in developing countries in the next two decades is likely to be almost twice that in the developed countries. Ischemic heart disease is the leading cause of death in developed countries, but third to AIDS and lower respiratory infections in developing countries. The deaths due to CVD in India were 32% in 2007 and are expected to rise from 1.17 million in 1990 and 1.59 million in 2000 to 2.03 million in 2010. In addition, Indians tend to have premature coronary heart disease, at least a decade or so earlier than their counterparts in the developed countries and also have higher case fatality rate. It is most likely that the rapid demographic and health transitions currently occurring in India make a major contribution to gene–environmental interactions and early life influences of fetal malnutrition that may be a cause of increased CVD in India. Although a relatively new epidemic in India, it has quick become a major health issues with deaths due to CVD expected to be double during 1985-2015 (WHO 2004). In India almost 2.6 million individuals are predicted to die due to coronary heart disease (CHD)' constituting nearly 54% of all CVD deaths by 2020.

The work has been divided into the following two parts. Part I: Synthesis of pyrazolone derivatives and Part II: Cardio protective evaluation of those derivatives. Part I of the thesis represent the synthetic part which originates from the observations of cardioprotective activities of pyrazolone derivatives. It covers the synthesis of pyrazolone derivatives from 3-methyl pyrazol-5-one. The structures of the synthesized compounds have been elucidated by UV, IR, ^{1}H NMR, Mass spectral data and elemental analysis. A research paper regarding synthesis, characterization and biological evaluation has been published in **Indian Journal of Chemistry Section B.**

Acute toxicity and gross behavior studies revealed that pyrazolone compounds in present investigation were found to be nontoxic up to 5000 mg/kg body weight in albino mice. All

the animal experiments were performed by the approval of Institutional Animal Ethics Committee, Himalayan Pharmacy Institute, East Sikkim.

The main objective of the investigational work carried out and represented in this thesis, has been to synthesize a number of new organic compounds and to evaluate their cardioprotective effects to furnish a possible cardioprotective agent. The objective has also been to explore and evaluate the activities of those compounds in other areas to provide a suitable lead which may be utilized in the future to pursue a new line of investigations. The work is based upon the combined approaches of both exploitation and exploration, the main stay of investigations in the domain of medicinal chemistry, and more particularly, the synthetic drugs; the former being concerned with the assessment, improvement and extension of a lead and the latter with the search for a new lead.

Part II of the thesis represents the exploration of cardioprotective effect of pyrazolone derivative. This work is based on the reported literature by Yukihito Higash et al 2006 on cardioprotective properties of pyrazolone derivatives. The present study investigates the cardioprotective effect of pyrazolone derivatives (PYZ1-PYZ10) 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. Isoproterenol induced myocardial injury in rats is a widely used experimental model for evaluation of cardioprotective effect of various drugs. This is because of pathophysiological changes following ISO administration in rats are similar to those taking place during myocardial injury in humans. Therefore, it is a suitable model to study myocardial ischemic injury.

Lipid metabolism plays an important role in myocardial injury produced by ischemia. Hence the estimation of lipid profile can be directly correlated with the intensity of myocardial injury. In the present study also, isoproterenol administration caused a significant rise in the serum lipids thereby increases lipid biosynthesis and lipid peroxidation. Rats treated with pyrazolone derivatives showed decreased concentration of

total cholesterol, triglycerides, LDL cholesterol in serum indicates the beneficial effects of pyrazolone derivatives in reducing hyperlipidemia caused by isoproterenol.

Pretreatment with the pyrazolone derivatives at 10 mg/kg body weight for 5 days prevented the elevation of serum marker enzymes namely lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) in myocardial injured rats. ISO-induced animals exhibited decreased levels of superoxide dismutase (SOD) and glutathione (GSH) in the heart, which were restored to near normal levels following treatment with pyrazolone derivatives. These derivatives also attenuated lipid peroxidation (LPO) in the heart and improved the imbalance in lipid profile (TG, LDL, VLDL, HDL) caused by ISO. These findings revealed the cardioprotective effect of pyrazolone derivatives against isoproterenol induced myocardial injury. A communication describing the cardio protective properties and anti oxidant activities of pyrazolone derivatives has been published in (i) **Pharmacology Online and (ii) Journal of Advanced Pharmaceutical Technology & Research respectively.**

Since the cardio protective activities of pyrazolone derivatives have been encouraging, the biological evaluation of these derivatives had led to an important conclusion regarding the structure activity relationship and a possible mode of action in this class of compounds. On the other hand, the results obtained in this study have helped to reach a conclusion on structure activity relationship and Yukihito Higash observation on cardio protective properties of pyrazolone derivatives. Moreover the compounds have also been screened for analgesic, anti inflammatory and antipyretic activity since myocardial injury is associated with inflammatory response. Some of the drugs are available in the market as NSAID possess analgesic, anti-inflammatory and antipyretic activity. Hence these pyrazolone compounds also have screened for the same. All these activities have been furnished in concomitant publication in **Saudi Pharmaceutical Journal (Elsevier Publication).** Taking a lead from these activities, the original molecules may be suitably tailored to furnish useful therapeutic agents in future.