Preface

“Imagination is the beginning of creation. You imagine what you desire, you will what you imagine and at last you create what you will.”

-George Bernard Shaw
(1865-1950)

Imagination is the building block of a beginner’s work by which anyone gives concretism to the ideas into reality. Imagination provides continuity to ideas for constructing thinking and theorizing the hypothesis. It strengthens the will, the desire and the confidence, that motivates researcher to create the things. From Vedic period, there is a strong relation between humanity and diseases. Whenever man tried to become the master of nature and exploit it; such exploitation leads to the disturbance in natural equilibrium. Nature in turn fulfills this loss in the form of natural disasters and fatal diseases such as AIDS, Polio, Cancer, Diabetes, Anthrax etc. Some of these diseases are curable and under control but many of these are kept under investigation of scientists to prepare remedy that controls them. Our vadic literature like Upnishad, Charak-Sanhit, Shushrut-Sanhit thrown a searchlight on human efforts and remedies used for them from ancient times. “Chhandogya-Upnishad (vii, xii, 1)” says that: There is no need of medicines to cure ailments, however medicines will be required for extending the life span a bit more. But in fact it is true that man is always in search of remedy to get-rid of any sort of ailments from ancient times.

Diabetes has been described in the history of medicines ever since records were kept. Today it remains a major health problem world wide. In 2003, there were 189 million diabetics in the world and the projected figure for 2025 is 324 million (A WHO Reports). According to ‘Diabetes Atlas’ published by ‘International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. Indeed its global burden continues to increase in the way that India become the DIABETIC CAPITOL of world up to 2030 and every fifth person with diabetes will be an Indian. Due to these sheer numbers the economic burden due to diabetes in India is amongst the highest in the world. The real burden of this disease is however due to its associated complications which lead to increased morbidity and mortality. WHO estimates the mortality from diabetes, heart disease and stroke costs about 210 billion US dollars in India in the year 2005 and the cost increases up to 334 billion US dollars over the next 10 years and much of this estimate goes to diabetes alone.

Diabetes is a group of disease marked by high level of blood glucose resulting from defects in insulin production, insulin action or both. It can
lead to serious complications and premature death. The risk factors for increasing prevalence among Asian Indians included high racial susceptibility, central obesity and insulin resistance even with a low Body Mass Index (BMI). There are number of peoples dying of diabetes either due to insulin being unavailable or unaffordable. The development of more effective drugs for the treatment of patients those suffering from diabetes has been a major endeavour over the past 50 years and the 21st century now promises some dramatic new directions with dramatic advancement in various tools and techniques. However, the drug discovery and development process is still slow. As the processes are time consuming and expensive, there is an urgent need to follow a well refined and short path leading to the drug discovery for the treatment of diabetes, which is feasible and reduces the cost as well as time.

Amongst various advanced techniques, computational medicinal chemistry has made a more rational approach in the field of drug designing. The rational drug design of an agent with specific activity towards a selected target requires that this target be so precisely defined that it can be hit selectively in the presence of other identical or similar targets.

During past decades, definite and continuous improvements in this field correspond to the use of quantitative description of structural characteristics. The ease and success of finding the better drugs for any disease depends upon, how best we can rationalize the design of drug. QSAR is the process by which chemical structure is quantitatively correlated with a well defined process such as biological activity. It gives valuable information about the influences of electronic, steric as well as hydrophilic/hydrophobic features and quantifies these influences upon biological activity of drug agent. The use of QSAR allows identifying chemical structures that could have good inhibitory effects on specific targets and have low toxicity (non-specific activity), while many QSARs involve the interactions of a family of molecules with an enzyme or receptor binding site. QSAR can also be used to study the interaction between the structural domains of proteins. Protein-protein interactions can be quantitatively analyzed for structural variations resulted from site directed mutagenesis.

This work encompasses the use of Quantitative Structure Activity Relationship techniques for gaining insight into the essential physico-chemical and structural requirements in the molecules particularly Peroxisome-proliferative activated receptor (PPAR) agonists for their antidiabetic activity. The correlation equation between biological activities and physicochemical parameters of the series of drugs is established and in this way the effects of structural parameters of drug on their biological activity is being highlighted during interaction with receptor site. The best
fit equation has been developed and predictions will be made. The work incorporated in this thesis has been divided into following chapters:

1) **CHAPTER - I** : *Introduction*
2) **CHAPTER - II** : *QSAR: An Overview (with review of literature surveyed)*
3) **CHAPTER - III** : *Methodology of QSAR*
4) **CHAPTER - IV** : *QSAR- Physicochemical Parameters*
5) **CHAPTER - V** : *Diabetes and its treatment*
6) **CHAPTER - VI** : *New frontiers in Antidiabetic drugs targeting PPARs*
7) **CHAPTER - VII** : *Results and discussion*

I hope, this work will stimulate the original thoughts and further encourage those from technical and research background for the use of such advanced techniques to gain interest and important thoughts for the design of potent and effective molecules for the various targets to treat diabetes and other disease.