## CONTENTS

### CHAPTER 1. INTRODUCTION 1 - 53

1.1. Definition of Diabetes 1
1.2. History 1
1.3. Classification 2
1.3.1. Type 1 Diabetes 3
1.3.2. Type 2 Diabetes 4
1.3.3. Metabolic Syndrome 4
1.3.4. Prediabetes 6
1.4. Relation among Insulin Resistance, Prediabetes and T2DM 7
1.5. Causes 8
1.6. Diabetes Symptoms 11
1.7. Diagnosis 14
1.8. Complications of Diabetes 17
1.9. Diabetes Prognosis 18
1.10. Prevalence of T2DM 19
1.11. Economic Burden of Diabetes in India 23
1.12. Morbidity and Mortality associated with Diabetes 24
1.13. Treatment of Diabetes 25
1.13.1. Type 1 Diabetes 26
1.13.2. Type 2 Diabetes 27
1.14. Diabetic Medications 27

1.15. Peroxisome Proliferator Activated Receptors and T2DM 33
1.15.1. PPARα 36
1.15.2. PPARγ 37
1.15.2. PPARδ 38
1.16. Role of PPAR Agonists in the Therapy of Type 2 Diabetes 39
1.16.1. PPARα and PPARγ Agonists 39
1.16.2. The PPAR dual agonists 41
1.16.3. PPAR pan agonists 45
1.17. Partial Agonism to the Rescue 47
1.18. Computational methods in the design of multiple receptor activating ligands

2. REVIEW OF LITERATURE

2.1. General

2.1.1. Diabetes: The Disease
2.1.2. Types of Diabetes Mellitus
2.1.3. Insulin Dependent Diabetes Mellitus: Type1
2.1.3.1. Etiology of Type 1 Diabetes
2.1.3.2. Pathophysiology of Type 1 Diabetes
2.1.4. Non-Insulin Dependent Diabetes Mellitus: Type2
2.1.4.1. Etiology of Type 2 Diabetes
2.1.4.2. Pathophysiology of Type 2 Diabetes
2.1.5. Diabetes and the Metabolic Syndrome
2.1.6. Insulin and Diabetes Mellitus
2.1.6.1. Insulin Secretion
2.1.6.2. Insulin; Role in Regulation of Metabolism
2.1.6.3. Insulin Action under the Control of Nutrient Intake and Hormones
2.1.6.4. Wnt Signaling, GLP1, and Insulin Secretion
2.1.6.5. Mechanism of Insulin Resistance
2.1.6.6. Insulin Action and Endothelial Functions
2.1.7. Insulin Receptor
2.1.7.1. The Mechanics of Transmembrane Signaling
2.1.7.2. Molecular Mechanisms for Insulin-Stimulated Glucose Transport
2.1.7.3. Insulin Signaling and Glucose Transport
2.1.8. Therapeutic Intervention for Hyperglycemia
2.1.8.1. Sulfonylureas
2.1.8.2. Meglitinides: Repaglinide and Nateglinide
2.1.8.3. Biguanides
2.1.8.4. Thiazolidinediones: Pioglitazone and Rosiglitazone
2.1.8.5. α-Glucosidase Inhibitors
2.1.8.6. Dipeptidyl Peptidase IV Inhibitors
2.1.8.7. Emerging Approaches
2.1.9. Peroxisome Proliferator Activated Receptors
2.1.9.1. PPARs function at the Cellular Level
2.1.9.2. PPARs in Whole Body Physiology
2.1.9.3. Therapeutic Potential of PPARs Ligands
2.1.10. Functional and Structural Insight of PPARγ
2.1.11. Structural Insight of PPARα
2.1.12. Comparison of structures of LBDs and binding modes to Ligands among the three PPARs subtypes
2.1.13. Insight of Structure, Activity and Side Effects of PPARs Agonists (Synthetic Ligands)
   2.1.13.1. PPARα Agonists
   2.1.13.2. PPARγ Agonists
   2.1.13.3. Dual PPARs Agonists
      2.1.13.3.1. Dual PPAR α/γ Agonists
      2.1.13.3.2. Dual PPAR γ/δ Agonists
      2.1.13.3.3. Dual PPAR α/δ Agonists
   2.1.13.4. Pan Agonists
   2.1.14. Partial Agonists to keep away/reduce adverse effects

2.2. Computational
   2.2.1. Molecular Modeling Techniques
      2.2.1.1. Computational Methodology
      2.2.1.1.1. Quantum Mechanical Methods
      2.2.1.1.2. Quantitative Structure Activity Relationship
      2.2.1.1.3. Molecular Docking
      2.2.1.1.4. Pharmacophore Mapping
   2.2.1.2. Virtual Screening

3. EXPERIMENTAL
   3.1. Computational
      3.1.1. Data Set for Generating CoMSIA Models
      3.1.2. Generating Molecular Structures and Alignment of the Dataset Molecules
      3.1.3. CoMSIA 3D QSAR Modelling
      3.1.4. Generation of COMFA Models
3.1.5. Design, Building, Activity Prediction of NCEs with Standard Fragment 184
3.1.6. Design, Building and Activity Prediction of NCEs as PPARα/γ Partial Agonists 186
3.1.7. Design, Building and Activity Prediction of NCEs as PPAR agonists 186
3.1.8. Docking Studies of Designed NCEs (New PPARα/γ Partial Agonists) 187
3.1.8.1. Docking studies at PPARα (1K7L) 187
3.1.8.2. Docking Studies at PPARγ (1FM9) 188
3.1.8.3. Docking Studies of the Benzylidene/Benzyl Thiazolidinedione Based and Benzyldiene/Benzyl Diethyl Malonate Based NCEs 188
3.1.9. Final Selection of Designed NCEs (as Partial Agonsists) for Synthesis 188
   Tables: Computational 190
   Figures: Computational 233

3.2. Synthesis 302-356
3.2.1. Left Hand Side Moieties and Related Intermediates 303
3.2.2. Right Hand Side Moieties and Related Intermediates 310
3.2.3. Synthesis of the Targeted NCEs 316
3.2.3.1. Benzimidazolyl Based NCEs and Related Intermediates 316
3.2.3.2. Indolyl Based NCEs and Related Intermediates 329
3.2.3.3. Acridonyl Based NCEs and Related Intermediates 336
3.2.4. Synthesis of the Other NCEs 344
3.2.4.1. Heterocyclyl Linked Thiazolidinediones Based ONCEs and Related Intermediates 344
3.2.4.2. Heterocyclyl Linked Diethyl Malonate Based ONCEs 352
   Tables: Experimental - Synthesis 357

4. RESULTS AND DISCUSSION 364-575
4.1. Computational 364-391
4.1.1. Selection of Dataset 364
4.1.2. Generation of Significant CoMSIA Models 364
4.1.3. Validation of the Generated Models 365
4.1.4. Contour Analysis (CoMFA) 366
4.1.5. Generation of CoMFA Models 371
4.1.6. Failure of Dual Agonists and Preference of Partial Agonists 372
4.1.7. Design and Activity Prediction of NCEs with Standard Fragment 372
4.2. Synthesis 392-575

4.2.1. Chemistry and Spectral Interpretation 392-411

Synthetic Schemes: (1-7) 412
IR Plates: (IR1-IR42) 425
PMR Plates: (PMR1-PMR41) 467
MS Plates: (MS1-MS29) 525
Mass Fragmentation Charts: (1-22) 554

5. SUMMARY 576-590

6. REFERENCES 591-635