CONTENTS

1. **Introduction**.....1-42
1.1 Role of Computer Aided Drug Design in Drug Discovery..... 1
1.1.1 CADD and drug discovery 2
1.1.2 Ligand-based drug design..... 3
1.1.2.1 3D-QSAR 4
1.1.2.1.1 CoMFA..... 5
1.1.2.1.2 CoMSIA..... 7
1.1.2.1.3 Evaluation of the predictive ability of the model: Validation of 3D QSAR models..... 8
1.1.2.2 Pharmacophore modeling..... 10
1.1.3 Structure-based drug design..... 11
1.1.3.1 Homology modeling..... 12
1.1.3.2 Molecular dynamics 14
1.1.3.3 Molecular docking..... 15
1.1.3.4 Structure-based virtual screening..... 17
1.1.3.5 *de Novo* designing..... 18
1.2 Enzymes as Targets for Discovery of New Drugs..... 21
1.2.1 Tumor Necrosis Factor Alfa Converting Enzyme (TACE) as an attractive target for the treatment of RA..... 22
1.2.1.1 Cytokines and RA..... 23
1.2.1.2 Tumor necrosis factor-α..... 25
1.2.1.3 Structure of TACE 27
1.2.1.4 Functions of TACE..... 31
1.2.1.5 Regulation of TACE..... 32
1.2.2 Neuraminidase as a target for the swine flu..... 32
1.2.2.1 Mechanism of action of neuraminidase inhibitors..... 33
1.2.2.2 Development of neuraminidase inhibitors..... 34
1.2.3 Aromatase as a target for the treatment of breast cancer..... 35
1.2.3.1 Estrogens..... 35
1.2.3.2 Estrogen biosynthesis..... 36
1.2.3.3 Aromatase..... 37
1.2.3.4 Mechanism of aromatase..... 37
1.2.3.5 Structure of aromatase..... 39
1.2.3.6 Aromatase localization..... 40
1.2.3.7 Aromatase in breast cancer..... 41
1.2.3.8 Aromatase inhibitors in the treatment of breast cancer 41
1.2.3.9 Aromatase inhibitors 42
2 **Review of Literature**.....43-56
2.1 Molecular Modeling Studies of TACE and Its Inhibitors..... 43
2.2 Molecular Modeling Studies of Neuraminidase, Inhibitors and related studies 46
2.3 Molecular Modeling Studies of Aromatase Enzyme and its Inhibitors..... 50
3 **Aims and Objectives**.....57-59
3.1 Studies on TACE Inhibitors..... 59
3.2 Studies on Influenza Neuraminidase Type A Inhibitors..... 59
3.3 Studies on Aromatase Inhibitors..... 59
4 **Results and Discussion**..... 60-146
4.1 3D-Quantitative Structure Activity Relationship Studies on Benzothiadiazepine Hydroxamates as Inhibitors of TACE..... 60

4.2 Development of Predictive 3D-QSAR CoMFA and CoMSIA Models for β-Aminohydroxamic Acid-Derived TACE Inhibitors..... 76
4.3 Development f Predictive Pharmacophore Model For *In Silico* Screening, 3D-QSAR CoMFA and CoMSIA Models for Lead Optimization, and Designing of Newer Potent TACE Inhibitors..... 90
4.4 Molecular Modeling Studies of Novel 2-Imidazolidinones and Tetrahydropyrimidin-2(1*H*)-ones as Potential TACE Inhibitors 114
4.5 Molecular Modeling Studies of Some New Heterocyclic Inhibitors of TACE 121
4.6 Determining of Structural Requirements of Influenza Neuraminidase Type A Inhibitors and Binding Interaction Analysis with the Active Site of A/H1N1 by 3D-QSAR CoMFA and CoMSIA Modeling 126
4.7 Molecular Modeling Studies of Some Novel Androstanes as Potential Aromatase Inhibitors..... 141
5. Experimental.....147-156
5.1 Molecular Modeling Hardwares and Softwares.....147
5.1.1 Hardwares..... 147
5.1.2 Softwares..... 147
5.2 Calculation of Biological Activity in Terms of pIC_{50} (Negative Log of IC_{50} in Molar Concentration)..... 148
5.3 3D-QSAR Studies..... 148
5.3.1 Structure building, optimization, calculation of descriptors and partial charges..... 148
5.3.2 General alignment rules..... 149
5.3.3 Segregation of compounds into training and test data sets..... 149
5.3.4 CoMFA analysis..... 150
5.3.5 CoMSIA analysis..... 150
5.3.6 Partial least square (PLS) analysis..... 150
5.3.7 Evaluation of the predictive ability of CoMFA and CoMSIA models..... 151
5.4 Docking Studies..... 151
5.4.1 Selection of crystal structure of TACE..... 151
5.4.2 Protein preparation and grid generation 151
5.4.2.1 Preparation of TACE..... 151
5.4.2.2 Receptor grid generation..... 152
5.4.3 Docking/calculation of binding energies..... 153
5.5 Pharmacophore Generation..... 153
5.6 Virtual Screening 155
6. References.....157-181

Summary.....I-VII

List of Publications