CONTENTS

Topic                                      Page No.

1. Introduction                             
1.1 Cancer scenario and statistics         1
1.2 Pathophysiology of cancer              2
1.3 Possible treatments                     3
1.4. Important biological targets of lung cancer targeted therapy 7
1.5 Discovery of small molecule drugs in targeted cancer therapy 14
1.6 Important targets of anticancer drug discovery 18
1.7 Computer-aided drug design in drug discovery 23

2. Present work                             
2.1. Hypothesis of the present work         29
2.2. Literature search: Biological target identification 31

3. Materials and Methods                    
3.1 Computational chemistry                34
3.2 Synthetic chemistry                    44
3.3 Biological assays                      46

4. Results and Discussions                  
4.1 Structural requirements of matrix metalloproteainse-2 inhibitors 50
4.1.1 Molecular modeling                   50
4.1.2 Rational design of MMP-2 inhibitors  60
4.1.3 Syntheses of the designed compounds  61
4.1.4 Cellular and enzymatic assays        92
4.1.5 Summary                              99
4.2 Identification of other possible targets 100
4.2.1 Concept of dual MMP-2/HDAC-8 inhibitors 100
4.2.2 Development of pharmacophore models for HDAC-8 inhibitors 101
4.2.3 Design of Dual MMP-2/HDAC-8 inhibitors 106
4.2.4 Cellular assays                      108
4.2.5 Molecular dynamics (MD) simulation analyses 112
4.2.6 Summary                              115
4.3 Structural requirement of aminopeptidase N inhibitors 117