

CONTENTS

	Statement	v
	Certificate	vi
	Acknowledgement	vii
	Preface	ix
CHAPTER 1		
	STRONG AND WEAK HYDROGEN BONDS IN BIOLOGY	1-12
1.1	Introduction	1
1.2	Definition of a hydrogen bond	1
1.3	Defining strong and weak hydrogen bond	2
1.4	Classification of hydrogen bonds	2
1.4.1	Very strong hydrogen bond	3
1.4.2	Strong hydrogen bond	4
1.4.3	Weak hydrogen bonds	4
1.4.4	Other weak interactions in biology	4
1.5	Methods of studying hydrogen bonds	5
1.5.1	Crystallography	5
1.5.2	Crystallographic databases	6
1.5.3	Statistical analysis	6
1.6	Some technical glitches	7
1.7	Geometrical parameters	7
1.7.1	Distances and angles	7
1.7.2	Geometric criteria for other weak interaction	8
1.7.3	Furcation in hydrogen bond	9
1.8	The weak hydrogen bond in protein–ligand complexes	9
1.8.1	Evidence of weak hydrogen bonds in protein–ligand complexes	10

Chapter 2

HBAT: A COMPLETE PACKAGE FOR THE ANALYSIS OF STRONG AND WEAK		
HYDROGEN BONDS IN MACROMOLECULAR CRYSTAL STRUCTURES		13-20
2.1	Introduction	13
2.2	Program description	14
2.2.1	Hardware and software requirement	14
2.2.2	Program availability	14
2.2.3	Input details	15
2.3	Methodology	15
2.3.1	Identification and classification of interactions	15
2.3.2	Hydrogen bonds with single atom acceptors	16
2.3.3	Hydrogen bonds with multi-atom acceptors	16
2.3.4	Halogen bonds	17
2.3.5	Donor and acceptor furcation	17
2.3.6	Cooperativity	18
2.4	Example	18
2.5	Conclusions	20

CHAPTER 3

STRONG AND WEAK HYDROGEN BONDS IN THE PROTEIN-LIGAND INTERFACE		21-44
3.1	Introduction	21
3.2	Materials and methods	22
3.3	Results and discussion	25
3.3.1	Hydrogen bond geometry. Lengths and angles.	25
3.3.2	Hydrogen bond geometry. Furcation.	30
3.3.3	Hydrogen bond geometry. The resolution problem	33
3.3.4	Residue frequency	37
3.3.5	Interactions involving water	40
3.3.6	Lipinski's rule extended	41
3.3.7	Protein-ligand interactions in kinases	41
3.3.8	Other weak interactions	41
3.4	Conclusions	43

CHAPTER 4**STRONG AND WEAK HYDROGEN BONDS IN PROTEIN–LIGAND COMPLEXES OF****KINASES: A COMPARATIVE STUDY** 45-72

4.1	Introduction	45
4.2	Materials and Methods	46
4.2.1	Dataset	46
4.2.2	Geometry optimization	47
4.2.3	Hydrogen bond analysis	47
4.2.4	Water in the active sites of kinase	47
4.3	Results and discussion	48
4.3.1	Residue frequency	48
4.3.2	Hydrogen bond motif and Synthons	54
4.3.3	Role of conserved residue	66
4.3.4	Active site solvation	69
4.4	Conclusions	71

CHAPTER 5**STRONG AND WEAK HYDROGEN BONDS IN DRUG–DNA COMPLEXES: A****STATISTICAL ANALYSIS** 73-91

5.1	Introduction	73
5.2	Materials and methods	74
5.2.1	Drug–DNA complexes from PDB	74
5.2.2	Hydrogen bond analysis tool (HBAT)	76
5.2.3	Docking of HAT Inhibitors	76
5.3	Results and discussion	79
5.3.1	Overview of strong and weak hydrogen bond in drug–DNA complexes	79
5.3.2	Hydrogen bond analysis	79
5.3.3	Donor furcation	84
5.3.4	Hydrogen bond geometry	85
5.3.5	Human African Trypanosomiasis (Docking)	87
5.3.6	Hydrogen bonds in HAT inhibitors	89
5.4	Conclusions	90

CHAPTER 6**INTRODUCTION TO MOLECULAR MODELING AND PHARMACOPHORE**

MODELING	93-103
6.1 Introduction	93
6.2 Tools for molecular modeling	93
6.2.1 Quantum mechanics	94
6.2.1.1 <i>Ab initio</i>	94
6.2.1.2 Semiempirical methods	94
6.2.1.3 Density functional theory	95
6.2.2 Molecular mechanics	95
6.2.3 QM/MM	96
6.3 Simulation tools	96
6.4 Rational drug design another face of molecular modeling	97
6.4.1 Quantitative structure activity relationship	98
6.4.2 Docking and scoring functions	98
6.4.3 <i>De Novo</i> ligand design	98
6.4.4 Virtual screening	99
6.4.5 ADMET prediction	99
6.4.6 Chemoinformatics	99
6.5 Pharmacophore modeling	100
6.5.1 Historical perspectives	100
6.5.1.1 Pharmacophore models in the early years	101
6.5.1.2 Pharmacophore modeling after the use of computers	101
6.5.2 Pharmacophore modeling methods	102
6.5.3 Application of pharmacophore modeling in rational drug design	102
6.6 As we move on to following chapters	103

CHAPTER 7**PHARMACOPHORE MODELING ON EGFR KINASE INHIBITORS: A NOVEL**

STRATEGY FOR LIGAND BASED VIRTUAL SCREENING	105-126
7.1 Introduction	105
7.2 Materials and methods	106
7.2.1 Database profile	106
7.2.2 HipHop	107

7.2.3	HypoGen	108
7.2.4	LigandScout and GOLD	112
7.3	Results and discussion	113
7.3.1	HipHop	113
7.3.2	HypoGen	115
7.3.3	Model validation	117
7.3.4	Mining	120
7.3.5	Active site and structure based pharmacophore	120
7.3.6	Docking	122
7.3.7	Ligand based pharmacophore model versus structure based model	124
7.4	Conclusions	126

CHAPTER 8

PHARMACOPHORE MODELING, DOCKING AND VIRTUAL SCREENING OF

ACETYLCHOLINESTERASE INHIBITORS 127-149

8.1	Introduction	127
8.2	Materials and methods	128
8.2.1	Structure Building	128
8.2.2	HypoGen	129
8.2.3	Docking (GOLD)	131
8.2.4	Database screening	131
8.3	Results and discussion	133
8.3.1	HypoGen	133
8.3.2	Docking analysis	138
8.3.3	Comparative study of pharmacophore and docking	145
8.3.4	Database screening	146
8.4	Conclusions	149

CHAPTER 9

CONCLUSIONS AND FUTURE PROSPECTS 151-152

9.1	PART I	151
9.2	PART II	151

REFERENCES AND NOTES	153-180
APPENDIX I	181-197
APPENDIX II	199-208
APPENDIX III	209-223
ABOUT THE AUTHOR	225
LIST OF PUBLICATIONS	227