

Contents

Abstract	i
Acknowledgement	ix
Table of Contents	xi
List of Tables	xv
List of Figures	xvii
Abbreviations used in the Thesis	xx
List of Symbols used in the Thesis	xxii

Chapter 1: General introduction and Methodology

1.1 An Overview of DNA	1-1
1.1.1 History of DNA	1-1
1.1.2 Structure of DNA	1-3
1.1.2.1 DNA is a double Helix	1-5
1.1.2.2 DNA can occur in different three dimensional forms	1-6
1.1.3 DNA Damage	1-8
1.1.3.1 Spontaneous Mutations	1-8
1.1.3.1.1 Tautomeric Shift	1-9
1.1.3.1.2 Replication Mutation	1-10
1.1.3.1.3 Spontaneous Lesions	1-11
1.1.3.1.4 Transposons	1-13
1.1.3.2 Induced Mutation	1-13
1.2 Cancer	1-14
1.2.1 Classification of the Disease	1-15
1.2.2 Causes of Cancer	1-17
1.2.3 Symptoms of Cancer	1-17
1.2.4 Treatment of Cancer	1-18

1.3 Discovery and Use of Platinum Based Compounds	1-18
1.3.1 Structure Activity Relationship (SAR) of Platinum Anticancer Agents	1-20
1.3.2 New Platinum Anticancer Agents/Trans-Platinum(II) Complexes	1-21
1.4 Mode of Action of Platinum Based Drugs	1-22
1.4.1 Hydrolysis Mechanism	1-22
1.4.2 DNA Binding	1-23
1.5 Gold anticancer agents	1-26
1.6 Camptothecin	1-27
1.7 Computational Chemistry Perspective	1-31
1.8 Molecular Mechanics (MM)	1-33
1.9 Quantum Mechanics (QM)	1-34
1.9.1 Hartee-Fock Method (HF)	1-36
1.9.1.1 The restricted and Unrestricted Hartee-Fock Methods	1-38
1.9.2 Density functional theory	1-39
1.9.2.1 Hohenberg Kohn Theorem	1-41
1.9.2.2 The Kohn-Sham Theory	1-42
1.9.2.3 Exchange-Correlation Energy Funtionals	1-45
1.9.2.3.1 Local Density Approximation (LDA)	1-45
1.9.2.3.2 Generalized Gradient Approximation (GGA)	1-46
1.9.3 Reactivity Descriptors	1-46
1.9.3.1 DFT-based Descripotrs	1-46
1.9.3.2 Physiochemical Descripotrs	1-49
1.9.4 Basis Sets	1-49
1.9.4.1 Stater Type Orbitals (STO)	1-50
1.9.4.2 Gaussain Type Orbitals (GTO)	1-50
1.9.4.3 Minimal Basis Set	1-51
1.9.4.4 Split valence, Double and Triple-Zeta Basis Set	1-51

1.9.4.5 Polarized Basis Sets	1-52
1.9.4.6 Numerical Basis Set	1-53
1.9.4.7 Effective Core Potential (ECP)	1-53
1.10 Regression Analysis	1-54
1.10.1 Development of a Regression Model	1-55
1.10.2 Common Molecular Descriptors	1-56
1.10.3 Applications of Regression	1-56
1.11 Molecular Docking Simulation	1-57
1.11.1 Docking Approaches	1-57
1.12 Quantum Mechanics/Molecular Mechanics (QM/MM) Methods	1-58
1.13 Objectives of the Present Investigation	1-60

Chapter 2: Application of physicochemical and DFT based descriptors for QSAR Study of camptothecin derivatives

2.1 Introduction	2-1
2.2 Theoretical Background	2-3
2.2.1 QSAR calculation	2-3
2.3 Results and Discussion	2-3
2.4 Conclusion	2-13

Chapter 3: A comparative QSAR analysis and molecular docking studies of camptothecin derivatives as DNA-topoisomerase I inhibitor: A impartial approach to anticancer drug design

3.1 Introduction	3-1
3.2 Methodology	3-3
3.2.1 Computational Details	3-3
3.2.2 Docking	3-3
3.3 Results and Discussion	3-4
3.3.1 QSAR analysis	3-8
3.3.2 Docking Study	3-15
3.4 Conclusion	3-17

Chapter 4: Kinetics and thermochemistry of hydrolysis mechanism of a novel anticancer agent *trans*-[PtCl₂(dimethylamine)(isopropylamine)]: A DFT study

4.1 Introduction	4-1
4.2 Computational Details	4-3
4.3 Results and Discussion	4-4
4.3.1 Structural Analysis	4-4
4.3.2 Energy Profiles	4-7
4.4 Conclusion	4-10

Chapter 5: Theoretical investigation on the interaction of transplatin with DNA: A QM/MM study

5.1 Introduction	5-1
5.2 Methodology	5-3
5.2.1 Hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) Method	5-3
5.3 Results and Discussion	5-4
5.3.1 Hybrid QM/MM Calculation	5-4
5.4 Conclusion	5-9

Chapter 6: Gold anticancer metallodrugs: Computational strategies to identify potential candidates

6.1 Introduction	6-1
6.2 Methodology	6-2
6.2.1 QSAR Modelling	6-2
6.2.2 Molecular Docking Simulation	6-2
6.2.3 Absorption Distribution Metabolism Excretion-Toxicity (ADME-TOX)	6-3
6.3 Results and Discussion	6-3
6.3.1 Structural Profile and Evaluation of Descriptors	6-3
6.3.2 Stability and Reactivity Index	6-12

6.3.3 DFT based QSAR Models	6-14
6.3.4 Docking Simulation	6-18
6.3.5 ADME Toxicity Study	6-23
6.3.5.1 Absorption	6-23
6.3.5.2 Distribution and Metabolism	6-25
6.3.5.3 Excretion and Toxicity	6-28
6.4 Conclusion	6-29

Chapter 7: General Conclusion and Future Challenges

7.1 Conclusion	7-1
7.1.1 General Introduction and methodology	7-1
7.1.2 Application of physicochemical and DFT based descriptors for QSAR Study of camptothecin derivatives	7-1
7.1.3 A comparative QSAR analysis and molecular docking studies of camptothecin derivatives as DNA-topoisomerase I inhibitor: A impartial approach to anticancer drug design	7-2
7.1.4 Kinetics and thermochemistry of hydrolysis mechanism of a novel anticancer agent <i>trans</i> -[PtCl ₂ (dimethylamine)(isopropylamine)]: A DFT study	7-2
7.1.5 Theoretical investigation on the interaction of transplatin with DNA: A QM/MM	7-3
7.1.6 Gold anticancer metallodrugs: computational strategies to identify potential candidates	7-3
7.2 Future prospects of the present investigation	7-3