Theoretical study of the physicochemical properties of heterocyclic

In this work a fundamental and original research was made on the molecule of Hydantoin heterocyclic, the aim is to predict the reactivity and biological activity studied of the compound. The structural parameters, electronics and vibrational frequencies of Hydantoin at the ground state have been calculated by using, PM3, ab initio/HF and DFT/B3LYP methods. The optimized geometrical parameters are in good agreement with experimental values. Comparison of the obtained fundamental vibrational frequencies of Hydantoin result by DFT/B3LYP (6-311G++ (d, p)) method, are in a close agreement with the experimental data. The nature of substituent affects the electronic and energy parameters of basic core of Hydantoin. Also indeed, this qualitative and quantitative study allows us to predict the chemical reactivity of derivatives of Hydantoin.

Acquired PhD in computational and pharmaceutical chemistry, university of Biskra; MsC in physical chemistry, university of Batna. Studied DESS engineering chemistry, polytechnic of Montreal, Canada; Engineer electrochemistry, university of Setif, Algeria. Internship IRB, Montreal, Canada. Third level of English in high school of Montreal, Canada.

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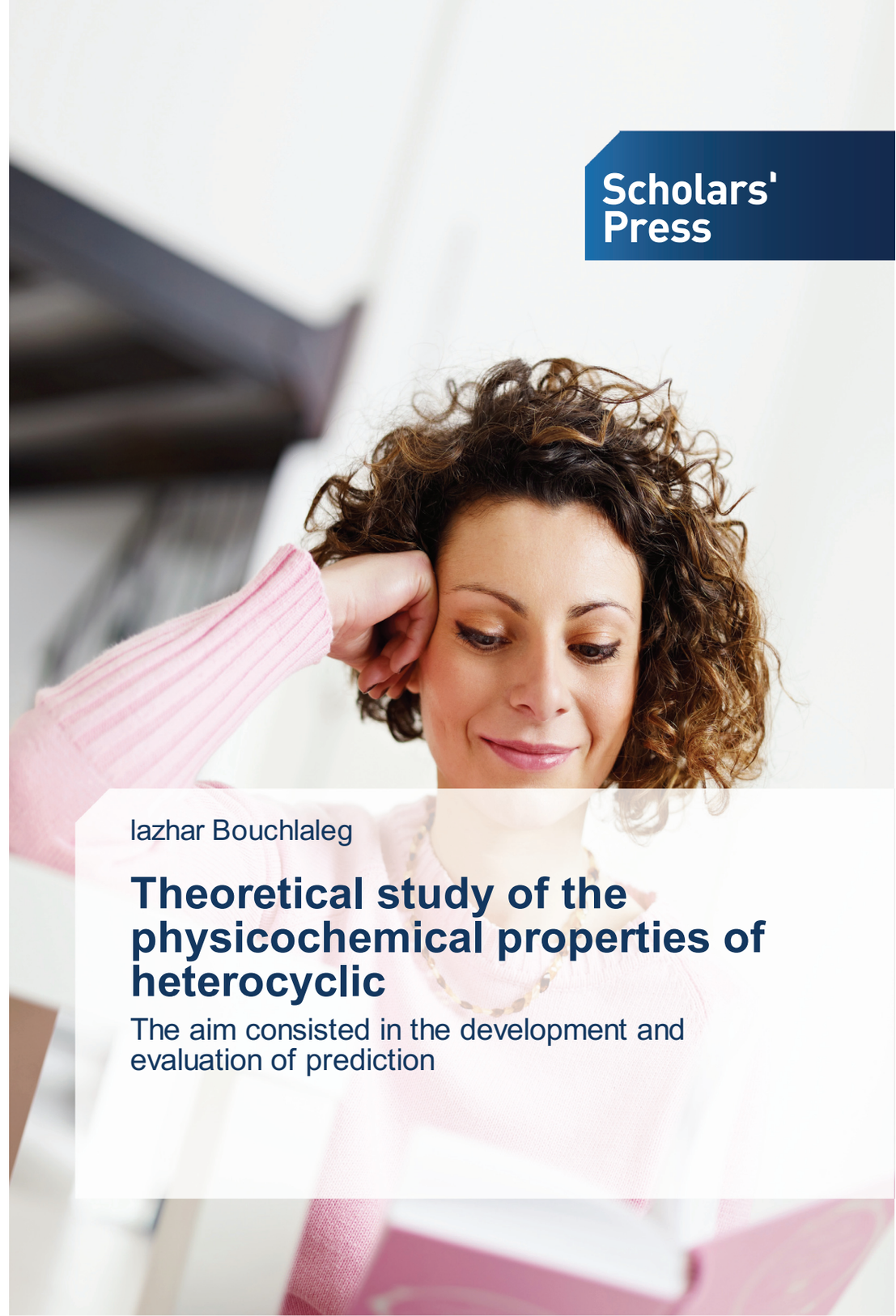
physicochemical of heterocyclic

Bouchlaleg



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List of Abbreviations

ADME :Absorption, Distribution, Metabolism and Excretion.
AM1 :Austin Model
B3LYP: Hybrid Functional, also called Becke3LYP
BLYP : Functional developed by Becke, Lee, Yang, and Parr
CCDC: Cambridge Crystallographic Data Centre
CCSD CC: Including Single and Double Excitation

CD : Cyclodextrin
CHA : Chemical Hamiltonian Approach
CIS CI : including Single Excitation

CNDO: Complete Neglect of Differential Overlap
CNDO: Complete Neglect of Differential Overlep.
CP: Counterpoise
CPU: Central Processing Unit
DNA: Desoxyribonucleic acid
E: Energy
GROMOS : Groningen Molecular Simulation
GUI: Graphical User Interface
HBD: Hydrogen Bond Donor
HF: Hartree-Fock.
HOMO: Higher Occupied Molecular Orbital .

IR: Infrared

Log P: Sharing Coefficient.
LUMO: Lowest Unoccupied Molecular Orbital.
MD: Molecular Dynamics
MEP: Molecular Electrostatic Potential
MINDO: Modified Neglect of Diatomic Overlap.
MM:Molecular Mechanics
MMFF: Merck Molecular Force Field
MNDO: Modified Neglect of Diatomic Overlap
MO : Molecular orbital's.
NDDO: Neglect of Diatomic Differential Overlap.

NMR: Nuclear Magnetic Resonance
OMF: Molecular orbital's frontier.
ONIOM: Our Own N-Layered integrated
PCM: Polarized Continuum Model
PES: Potential Energy Surface

RAHB: Resonance-Assisted Hydrogen Bonding
ROHF: Restricted open shell Hartree-Fock
SAR: Structure Property Relationship.

AMBER: Assisted Model Building with Energy Refinement
AO: Atomic Orbital
CBS :Complete Basis Set
BSSE : Basis Set Superposition Error

CC : Coupled Cluster
CCSD(T): CC Including Single, Double and Triple Excitation
CCL: Computational Chemistry List
CI :Configuration Interaction
CISD CI: including Single and Double Excitation
COX-2: Cyclooxigenase-2
DFT: Density Functional Theory.
CPK: Corey-Pauling-Koltun
CSD: Cambridge Structural Database
GGA Generalized Gradient Approximation
Gp: protecting group
GTO : Gaussian-Type Orbital
LDA : Local Density Approximation
HBA: Hydrogen Bond acceptor.
ΔH_f: Enthalpy of formation
INDO: Intermediate Neglect of Differential Overlapping.
IUPAC: International Union of Pure and Applied Chemistry.
LCAO: Linear Combination of Atomic Orbital.
MC: Monte Carlo
QM: Quantum mechanics.
MLP: Molecular Lipophilicity Pattern
MP3: Parametric Method 3.
min: minute.
MM: Molecular Mechanics
MPn: M**ø**ller-Plesset nth Order
SAM: Semi-ab initio Model.
QSAR: Quantitative Structure-Activity Relationships.
NSAID No steroidal Anti-inflammatory Drug
OF : Orbital frontier.
PC :Personal Computer
PDB: Brookhaven Protein Data Bank
QCISD(T) :Quadratic CI Including Single, Double and Triple Excitation
RHF: Restricted Hartree Fock
SCF Self: consistent field
SPASIBA: Spectroscopic Potentiel Algorithm for Simulating Biomolecular conformational

Adaptability
SCI-PCM: Self-Consistent Isodensity Polarized Continuum Model
SCRF: Self-Consistent Reaction Field
SP: Spironolactone
STO: Slater-Type Orbital
UFF: Universal Force Field.
ΔE: Energy Gap.
UFF: United Force Field
UHF: Unrestricted Hartree-Fock
VSEPR: Valence-Shell Electron Pair Repulsion
3D : three dimensions
μ: Dipole moment.
ν: Frequency
νth: Predict frequency
νexp**:** Experimental frequency

Table of contents

General Introduction

The subject of medicinal chemistry explains the design and production of compounds that can be used for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of already existing drugs, of their biological properties and their structure-activity relationships. Medicinal chemistry was defined by IUPAC specified commission as

"It concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level".

Medicinal chemistry covers the following stages:

(1) In the first stage new active substances or drugs are identified and prepared from natural sources, organic chemical reactions or biotechnological processes. They are known as lead molecules.

(2) The second stage is optimization of lead structure to improve potency, selectivity and to reduce toxicity.

(3) Third stage is development stage, which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it clinically useful.

Medicinal Chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants.[1,2] Today, scientists in this field are also equally concerned with the creation of new synthetic compounds as drugs. Medicinal chemistry is almost always geared toward drug discovery and development.

Medicinal Chemists apply their chemistry training to the process of synthesizing new pharmaceuticals. They also work on improving the process by which other pharmaceuticals are made. Most chemists work with a team of scientists from different disciplines, including biologists, toxicologists, pharmacologists, theoretical chemists, microbiologists, and biopharmacists.

Together this team uses sophisticated analytical techniques to synthesize and test new drug products and to develop the most cost-effective and eco-friendly means for production[3,4,5].

The chemical structure indices have a significant role in providing direction to the design of chemotherapeutic agents. These indices come from the experimental domain as well as through the computations. While the experimental properties of compounds have practical value, the indices from computational domain offer fast and economic inputs to simulations[5,6].

This thesis discusses various methods and issues involved in the generation of physicochemical, quantum chemical, graph theoretical, descriptors, molecular fingerprint and chemical space descriptors etc, for in silico molecular design approaches. A futuristic perspective of structural indices in drug design is outlined. All chemists use models, models are very useful because they often represent a simple way of describing and predicting scientific results without the work of performing the complex mathematical manipulations dictated by a rigorous theory.

The main purpose of this thesis was to perform computational investigations on Hydantoin using ab initio and Density Functional Theory (DFT) methods at an appropriate high level of theory, in order to get better insight into the structures and energetic of these compounds. Systematic investigations on the dependence of several geometric parameters of Hydantoin on the level of theory used led to the outcome that optimizations with best method DFT B3LYP/6-31G+(d,p), 6-31G++(d,p), 6-311G++(d,p) than ab initio /HF /6-31G+(d,p), 6-31G++(d,p) , 6-311G++(d,p) model chemistries yield a resulting geometry which is in excellent agreement with the experimental findings. We are interested in this work a computational study of the Hydantoin and Hydantoins.

In this thesis, molecular modeling approach was used to study the structural, vibrational and electronic nucleus of Hydantoin to present the most stable molecular conformation and also define the best method as the basis for study the chemical reactivity of this last. The study of the reactivity of the Hydantoin directly related to the study of their substitution. A qualitative study on the relationship structure-properties of a bioactive series of Hydantoin was carried out.

The manuscript of this work is presented in four chapters after general introduction

The first chapter of this manuscript will be devoted to an update on the Hydantoin .This work forms part of general program on the chemistry and biological activity of Hydantoin we discuss a few general synthesis methods of the Hydantoin. We will also present some biological activities of Hydantoin molecules.

In the second chapter, we present a theoretical overview on the various methods of molecular modeling used in our work (Quantum Mechanics (QM): DFT and ab-initio and molecular mechanics (MM).We will also present their field of application, these limits and used programs.

The third chapter includes a study of structural, vibrational and electronic of the Hydantoin molecule. In this chapter a comparative study with the different methods and experimental data. This investigation will lead to define the best method and the basis for these systems.

(This work was published in. **Journal of Pharmaceutical Research, Biological and Chemical Sciences Volume 6 Issue 2, Page No. 861, 2015**).

We will present a study of the effect of substitution on the ring Hydantoin in order to provide, the most reactive molecule. The reactivity of the Hydantoin is part of the qualitative theory of molecular orbitals borders (OMF) followed by a simple regression linear with a relationship between experimental and Predict frequencies.

Fourth Chapter study a quantitative study of the relationship structure activity derivatives of Hydantoin. An important objective of this study was to assess the relationships between structures and physicochemical properties associated with a selected series of Hydantoin derivatives reported in the literature and have a biological activity that is followed by a better determined by multiple linear regression MLR, SPSS, by a correlation of a biological activity relationship based QSAR descriptors.

(This work was published in: **Journal of Computational and Theoretical Nanoscience Vol. 12, 3949–3955(2015**).).

Finaly at the end general conclusion and future directions and perspectives falowed by two annex, publications and abstract.

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CHAPTER I

BIOLOGY AND APPLIED PHARMACEUTICAL BY USES CHEMISTRY SYNTHESIS OF HYDANTOIN

CHAPTER I: BIOLOGY AND APPLIED PHARMACEUTICAL BY USES CHEMISTRY SYNTHESIS OF HYDANTOIN

I .Introduction

The history of Hydantoins can be dated back to the year 1861 when Adolph von Baeyer,[1] former Munich professor of organic chemistry and Nobel prize winner in 1905, discovered Hydantoin itself. He found that the 2, 4-imidazolidinedione is a product of the hydrogenolysis of alluntoin. Inversion of the biological degradation of uric acid via allantoin was accomplished in the laboratories of Grimaux by reacting different mass with glyoxylic acid.[2]

The first classical synthetic pathway to Hydantoins was found in 1873 when Friedrich Urech published his work on the formation of 5-monosubstituted Hydantoins from amino acids and potassium cyanate followed by cyclization of the intermediate Hydantoic acid (ureido acid) with hydrochloric acid.[3] Prepared 5,5-disubstituted Hydantoins from amino nitriles(which were already available from the Strecker and Tiemann syntheses) and potassium cyanate and cyclization of the formed ureido acid with hydrochloric acid.[4]

Similar to this approach is the acid-catalyzed cyclization of thioureido acids obtained from reaction of alkyl or aryl isothiocyanates with amino acids[5] or amino nitriles, respectively. Another general access to 5-mono and 5, 5-disubstituted Hydantoins was provided by the Bucherer-Bergs method,[6] comprising the condensation of carbonyl compounds with potassium cyanide and ammonium carbonate.The condensation of a-dicarbonyl compounds with ureas represented a further classical methodology that involved a step similar to the benzilic acid rearrangement, first applied in the synthesis of phenytoin by Biltz.[7]

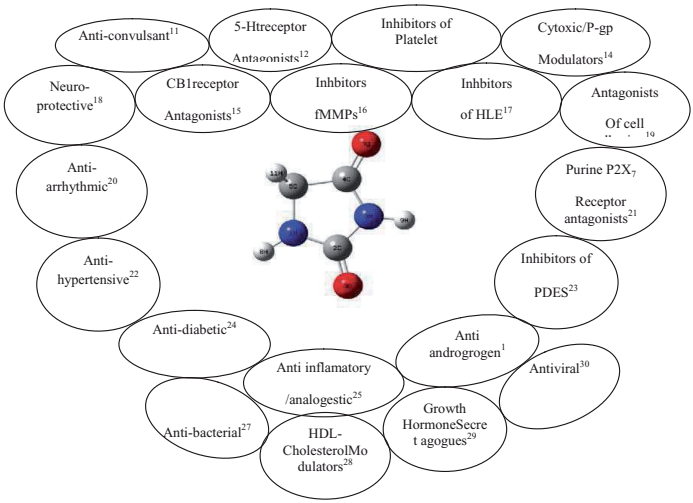
Nearly twenty years after the last review on the chemistry of Hydantoins published by L'opez and Trigo' in 1985. Therefore, this review will reflect allnew issues concerning the synthesis and reactions of Hydantoins, utilizing publications appearing since 1985and up to May 2004**.**

The Hydantoin, also known2, 4-imidazolidinedione is a saturated heterocyclic imidazole derivative compound. It has two functions lactams (cyclic amide). The Hydantoin can be obtained from urea or glycine. It can be seen as the product of the condensation of urea twice and glycolic acid. Hydantoin properties are relatively similar to those of the imidazolidine (completely saturated derivative of imidazole),

although having carbonyl functions on carbons 2 and 4 of the cycle. Cases of inflammatory syndromes induced by Hydantoin (lymphadenopathy, self-anticorps) are reported[8].We called Hydantoins substituted Hydantoin derivatives. Hydrogenation product of all Antoin and its derivatives are important intermediates in the synthesis of several amino acids [9] and are also used as anticonvulsants or antibacterial[10].The rapid development of organic medicinal and pharmaceutical chemistry has led to an enhanced interest in Hydantoins once again**.** New synthetic methods have been developed or older ones applied to new technologies or performed under improved conditions. Further, knowledge about the reactivity of Hydantoin has knowledge about the reactivity of Hydantoins has increased.

I.1.Biological Effects and Therapeutic Applications of Hydantoins

The discovery of biological activities of Hydantoins has made amazing progress during the last two decades,and Hydantoin derivatives have been therapeutically applied(**FigI.1**)[86]



FigI.1

I.2.Hydantoin derivatives and their pharmacological use

I.2.1 Physiological and biochemical role of Hydantoins

Hydantoins participate in the urine pool in the cell to provide precursors for nucleic acid synthesis, Hydantoinnases, Hydantoin transporters33[31].Hydantoin is a heterocyclic organic compound, the product of glycolic and urea, also known as glycolyurea. In a more general sense, Hydantoin refer to chemical compounds that have substituent groups bonded to Hydantoinring.

Hydantoin derivatives are famous for their physiological activity as anticonvulsants, which explain the continuous research interest on this class of compounds[32]. Epilepsy is widely recognized as one of the most known neurological diseases in man. Its most known characteristic is the uncontrolled convulsions, commonly known as phenytoin, is used since 1938, being the treatment of choice for generalized tonic-clonic seizure, instead of a high number of side effects related [33].They are also widely used in numerous pharmacological applications.Thus many derivatives have been identified as anticarcinologics, antimuscarins, antiulcers, antiarrythmics, antivirals, antidiabetics, serotoninand fibrinogen receptor antagonists, Inhibitors of the glycine binding site of the receptor and antagonists of leukocyte cell adhesion[93] and other activities including fungicidal and anti-HIV activity[35].

In general, all these activities are possible because of the interaction between the Hydantoin ring and the different substituent groups attached to it[35].It is well established that the type of substituent at 5- position in the Hydantoin ring is of crucial importance for pharmacological action of the corresponding compounds[36].

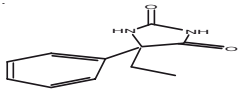
1.2.2 Uses of Hydantoins

1.2.2.a Pharmaceutical/Biological Properties: The medicinal uses of Hydantoin-containing compounds has become an active area of research in recent years, with novel derivatives being synthesised and tested for activity against various disorders[37].

The Hydantoin ring itself possesses no biological activity, but 5- and 5,5-substituted derivatives have a wide range of therapeutic applications.[39] Traditionally Hydantoin derivatives have been used as hypnotics, anticonvulsants, antiarrhythmics or as antibacterial agents.

The first application of a Hydantoin-containing compound as a medicine was the hypnotic nirvanol 10 (FigureI. 2), synthesised by Wernecke (1916).[38]

This compound was initially reported to possess similar activity to phenylbarbital 11, with less toxic side effects. However, it was later found that continued use of nirvanol did result in toxic side effects and the drug is now considered a narcotic agent.[40]



1O 11

FigureI. 2 - Example of the structures of nirvanol 10 and phenylbarbital 11.

The most well known medicinal use of a hydantoin is as the drug phenytoin, which is the sodium salt of 5, 5-diphenyl imidazolidine-2, 4-dione 12 (FigureI. 3).

This compound has a regulatory effect on the central nervous system (CNS) and has been applied successfully to epilepsy sufferers for more than 60 years as an anticonvulsant for the control of grand mal and psychomotor epilepsy.

Merrit and Putnam first identified that phenytoin was effective against induced seizures in cats and since becoming available for clinical use it has been applied as the drug of choice for treatment of tonic-clonic seizures.[39]

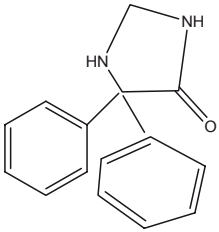


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Figure I.3 - The structure of phenytoin.

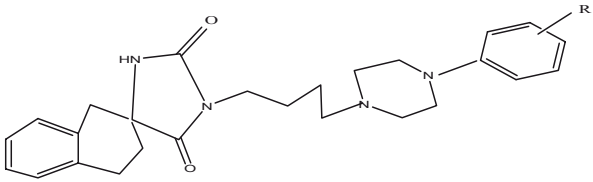
As with nirvanol, phenytoin also suffers from some serious side-effects which include hallucinations, fever, slurred speech and loss of balance; in addition, this drug cannot be administered to patients who are diabetic or have liver disease.

Even though this drug has been used for many years, work continues on the synthesis and determination of the structure activity relationships (SAR) of phenytoin derivatives in order to alleviate these problems.[49] However, despite these side effects the drug has recently found a host of new applications due to its antiviral, neuro-protective and cardio-protective properties.[38,50,51]

The neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) regulates the activity of the CNS through a number of receptor sub-types and plays an important role in a wide range of physiological systems.

The ability of drugs to act selectively at certain 5-HT receptor subtypes is believed to be effective in the treatment of epilepsy and mood disorders.

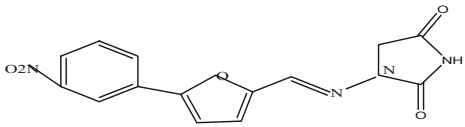
Pawlowski and co-workers have recently synthesised a range of βtetralonoHydantoins (FigureI. 4), which demonstrated high affinity for the 5-HT1A receptor and moderate-to-high affinity for the 5-HT2A receptor."[16]



R = H, 2-OMe, 3-Cl, 2-F, 4-F or 3-CF3

Figure I.4 - The structure of a range of high affinity 5-HT active compounds.[51]

Dantrolene 13 (FigureI. 5) is used clinically in the treatment of malignant hyperthermia and inhibits abnormal Ca2+ release from the sarcoplasmic reticulum (SR) and physiological Ca^{2+} release (PCR) from skeletal muscle. PCR is controlled by the ryanodine receptor (RyR1)[52] and once malignant hypothermia is triggered, it results in massive intracellular release of Ca^{2+}.[53]Both muscle contraction and relaxation are controlled by the cytoplasmic concentration of Ca^{2+} and derivatives of dantrolene have been synthesised to probe the intracellular release of Ca^{2+} with the aim of determining the Ca^{2+} regulatory systems of muscle cells[54].

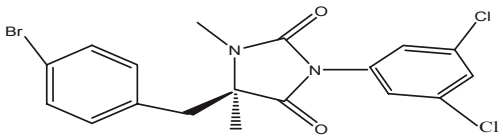


13

FigureI.5 - The structure of the dantrolene 13."[19]

An important anti-inflammatory agent is BIRT377 14 (FigureI. 6), which is a potent antagonist of lymphocyte function-associated antigen-1 (LFA-1).

The interaction between this enzyme and its ligands (cellular adhesion molecules) play a critical role in leukocyte adhesion. A leukocyte adhesion deficiency can result in poor inflammatory reponses, however, in the case of overactive immune or inflammatory reponses, anti-inflammatory agents like the Hydantoin 14 may have great potential applications towards the treatment of autoimmune diseases[55].

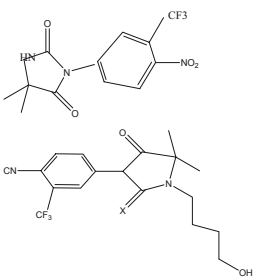


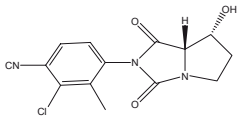
14

Figure I.6 - The structure of the anti-inflammatory agent, BIRT377.

The androgen receptor (NR3C4) Nuclear Receptor subfamily3,groupC,member 4 is a ligand-binding transcription factor in the nuclear hormone receptor super-family. This receptor is a key molecular target in the growth and progression of prostate cancer as androgen receptor expression is frequently observed in primary and metastatic prostate cancers.[56,57]

The receptor is activated by the binding of the androgens, testosterone and dihydrotestosterone; this signals the growth of prostate cancer cells. Androgen receptor agonists and antagonists have been shown to have a variety of biological applications[58] and recent work has shown that a range of Hydantoin-based antagonists have promising activity for the treatment of advanced prostate cancer, these compounds include nilutamide 15, BMS-564929 16 Bristol-Myers Squibb and RU 5906317:4-[4,4-dimethyl-3-(4-hydroxybutyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2iodobenzonitrile(Figure I.7).



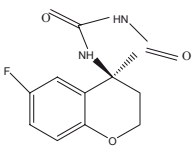


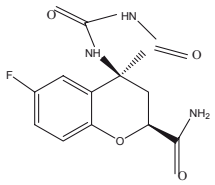
15 16 17

X = O or S

FigureI.7 - The structures of promising anti-androgen Hydantoin-containing analogues."[22, 23]

Hydantoin-containing compounds have been used to treat the onset of degenerative complications of diabetes, such as neuropathy, nephropathy, retinopathy, cataract formation and cardiovascular disease.[59]Sorbinil 18 (Figure 10) is an orally active aldose reductase (ALR) inhibitor that contains a spirohydantoin skeleton.1 Aldose reductase (ALR) belongs to the keto-reductase (AKR) superfamily of enzymes that are responsible for regulation of pro-inflammatory response; the synthesis of metabolically important compounds (like prostaglandins); and the modification of steroids in vivo.[6]Aldose reductase is the first enzyme in the polyol pathway, which catalyses the reduction of the aldehyde of glucose to sorbinil, and it is accepted that the polyol pathway plays an important role in the development of degenerative disorders associated with diabetes.[61] The closely related analogue fidarestat 19 has been used to probe binding to ALR1 and ALR2 by these types of compounds.[62]





18 19

FigureI. 8 - The structure of aldose reductase inhibitors sorbinil 18 and fidarestat 19.[63]

There are many more biological targets that Hydantoin containing compounds show activity for, this includes a range of N-3 alkyl substituted 5,5-diphenyl hydantoins and thioHydantoins which have a high affinity for the CB1 cannabinoid receptors.[64] This work is useful for understanding the endocannabinoid system of G-protein coupled receptors (GPCRs). Hydantoin containing compounds have also been found to be inhibitors of matrix metalloproteinases (MMPs),[65] human leukocyteelastase (HLE),[66]platelet aggregation[67] and of phosphodiesterase type 5 (PDE 5) induced muscle dysfunction.[68]

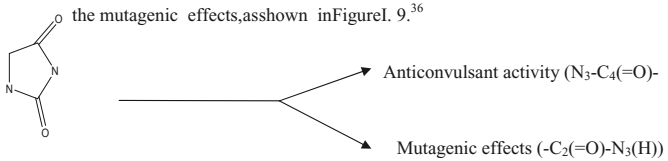
1.2.2. b Other Applications

Hydantoins, thiohydantoins and their substitution products also have a number of non-medical uses. In synthesis, Hydantoins are important precursors to natural and unnatural α-amino acids, which are vital for the production of pharmaceuticals, agrochemicals and fine chemicals. Hydantoins have also been shown to be effective chiral auxiliaries that promote the synthesis of optically active compounds at the βposition of an acyl group with excellent diastereoselectivity.[69]

In industry, Hydantoins, thiohydantoins and their substitution products are used as catalysts and stabilizer agents in polymer chemistry. Other polymers such as epoxy resins, moulds and lacquers have all been developed containing Hydantoin moieties while chlorinated Hydantoins have been used as bleaching agents, antiseptics and germicides.[38,39]

I.2.3 Structure of Hydantoin derivatives

As summarized by Roszak and Weaver[34] the Hydantoin ring can be split in to structural fragments responsible for the anticonvulsant activity and for the mutagenic effects,asshown inFigureI. 9.[36]



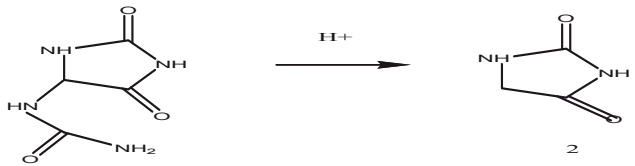
FigureI. 9. Structure of the Hydantoin ring and double activity (Ahmedova et al, 2009)[36]

In this chapter the Hydantoin nucleus and reactivity methods of synthesis of the core which hare well known,are under developed we are interested in some molecules with biological activity.

I.2.3.3Methods of Synthesis

1.2.3.3.a Hydantoin Chemistry and Natural Occurrence

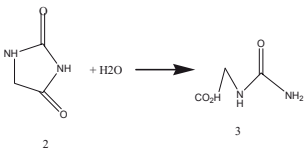
1.1.1 Discovery the compound Hydantoin, or imidazolidine-2,4-dione 2, was first isolated by Nobel laureate, Adolph von Baeyer, in 1861from the hydrogenolysis of allantoin 1(SchemeI. 1).1



SchemeI.1 - Example of Baeyer's synthesis of Hydantoin 2 from allantoin 1.

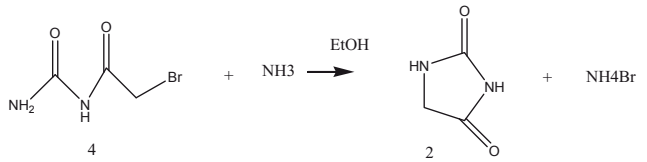
Several early acyclic structures for Hydantoin were proposed, however, Strecker surmised, in 1870, that since ureido (or Hydantoic) acid 3 (product of base-catalysed hydrolysis of Hydantoin) contains two hydrogen atoms and one oxygen atom more than Hydantoin, the ureido acid must result from the cleavage of the cyclic species 2 with the simultaneous addition of water

(SchemeI. 2).[37,38]



SchemeI. 2 - Strecker's proposed structures of Hydantoin 2 and Hydantoic acid 3.[38]

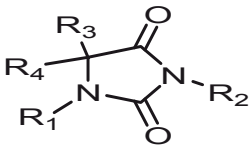
Further studies by Baeyer also demonstrated that Hydantoin could be obtained from bromoacetylurea 4 and Strecker noted that this transformation was best explained through the cyclic ureide representation of Hydantoin (SchemeI. 3).[38]



2 Scheme I. 3 - Baeyer's synthesis of Hydantoin 2 from bromoacetylurea 4.[38]

1.2.3.3. b Hydantoins

Over the last 150 years Hydantoin-containing compounds have become increasingly important in the chemical and pharmaceutical industries. Current methodology allows the synthesis of chiral compounds with up to four different points of diversity, through solution- or solid-phase methodologies.1,3 This technology makes Hydantoins highly desirable and interesting scaffolds for further synthetic elaborations. The general compound showed details the possible structures and substitution patterns of Hydantoins (Figure).



R1 = R2 = H, alkyl or aryl
R3 = R4 = H, alkyl or aryl

Figure I.10 - General structure showing the various points of diversity of the hydantoin scaffold.

Hydantoins are rigid, 5-membered heterocycles that are stable in dilute acid but will form ureido acid salts in basic solution.

Generally, Hydantoins with substitutents in the N-1 and/or the N-3 positions are less reactive to hydrolysing or oxidising agents,2 indicating the increased stability of such derivatives.

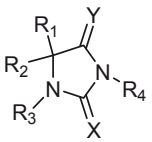
Hydantoins bearing no N-3 substitutents are weakly acidic; hydantoin 2 (Scheme 1) has a dissociation constant comparable to that of phenol or hydrocyanic acid (pKa~9 or 10).

This acidic character is a result of the dissociation of the N-3 proton and delocalisation of the negative charge over the two neighbouring carbonyl groups"[2,3]

1.2.3.3.c ThioHydantoins

Closely related analogues of Hydantoins are the ThioHydantoins, which may have one or both of the carbonyl oxygen atoms exchanged for a sulfur atom. These

compounds undergo analogous reactions in the presence of similar reagents.[38]The exchange of oxygen for sulfur gives rise to 2-thio, 4-thio or 2,4-dithio derivatives (Figure) and methodology exists for the mutual interconversion of Thiohydantoins and Hydantoins with relative ease.[40,41]Of the Thiohydantoins,2-thioHydantoins are the most notable with a large number of medicinal and industrial applications.[42]



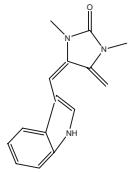
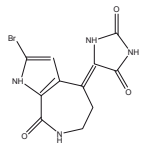
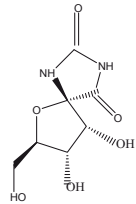
R1 = R2 = H, alkyl or aryl
R3 = R4 = H or alkyl
X = O or S Y = O or S

FigureI.11 General formulae of 2thio, 4-thio, or 2,4dithioHydantoins.

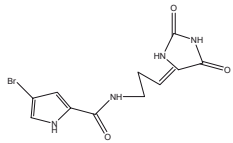
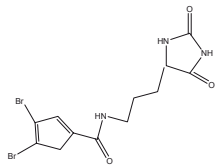
1.2.4 Natural Occurrence of Hydantoins

The Hydantoin moiety can be found widely in alkaloids isolated from marine organisms (and to lesser extent bacteria) and many Hydantoin containing alkaloids have been shown to have interesting biological profiles for the treatment of various disorders."[1] Figure 3 shows some of these alkaloids, where examples include the cytotoxic aplysinopsins[43] 5 (Thorecta sp.); this range of compounds have also been shown to inhibit neurotransmission.[44] (E)-Axinohydantoin 6 (from Axinella sp.) and related compounds have been shown to inhibit protein kinase C.[45]The closely related alkaloids mukanadin B 8 (from Agelas sp.) and midpacamide 9 (from Agelasmauritiana) are members of the oroidin family of alkaloids, which have many therapeutic applications, such as kinase inhibition or antiviral and antifungal activity.[46]

The first naturally occurring spironucleoside, (+)-Hydantocidin 7 (from Streptomyces hygroscopicus) was isolated by fermentation from soil samples collected from Japan in 1990.11 This compound is a potent non-selective herbicidal natural product which is active in plant growth regulation and shows low toxicity towards mammals.[47,48]

5 aplysinopsin (Thorecta sp.) 6 (E)-anxiohydantoin (Axinella sp.) 7hydantocidin (Streptomyces hygroscopicus)

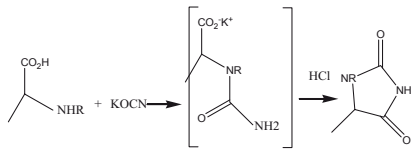
8 (Agelasmauritiana) mukanadin B (Agelas sp.) 9 midpacamid

FigureI.12 -Hydantoin-containing natural products.[45-52]

1.3 Methods of Preparation

1.3.1 Classical Methods of Synthesis

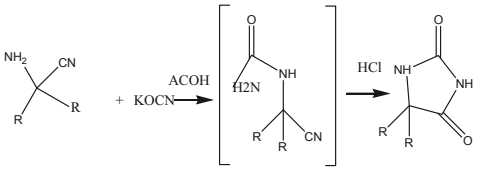
There are many different methods of synthesising Hydantoins, depending on the choice of starting materials; however, there are a few classical methods that are still commonly employed. Urech reported the first general method for the synthesis of 5monosubstituted Hydantoins in 1873, where α-amino acids are reacted with potassium cyanate to give α-ureido acids (Scheme 4). These intermediates are cyclised, under acidic conditions, to yield the desired hydantoins."[1]



R=H or alkyl

SchemeI. 4- The Urech method of synthesising 5-monosubstituted Hydantoins.[38]

Small alkyl groups are tolerated on the nitrogen atom of the starting material, which means that a limited range of N-1 substituted Hydantoins can also be prepared using this method.2 This methodology was optimised further by Read, in 1922, for the preparation of 5,5-disubstituted Hydantoins from α-aminonitriles. The intermediate α-ureido nitrile cyclises under acidic conditions to provide the corresponding Hydantoin (Scheme 5).[68]



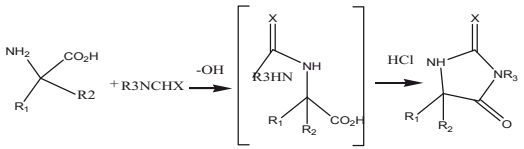
R=H, alkyloraryl

SchemeI. 5 - The Read method of synthesising 5,5-disubstituted Hydantoins.[37,38]

A similar reaction may be performed with α-amino acids and alkyl or aryl isocyanates (or isothiocyanates). The resultant α-ureido(or α-thioureido) acid is cyclised under acidic conditions to furnish the desired N-3 substituted Hydantoin, or 2-thiohydantoin(Scheme 6).[38]

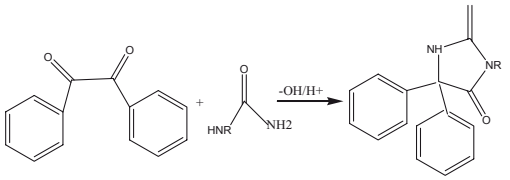
R1 = H, alkyl or aryl R2 = alkyl or aryl

R3 = alkyl or aryl X = O or S



Scheme I.6 - General method for the synthesis of N-3 substituted Hydantoins or 2-thioHydantoins.[38]

Other classical methods based on the reaction of α-amino acids (or cyanohydrins) with urea are well known.[38,39] However, the condensation of urea with α-dicarbonyl compounds and the Bucherer-Bergs reaction probably represent the most important classical methods employed for the synthesis of Hydantoins.[37]



20

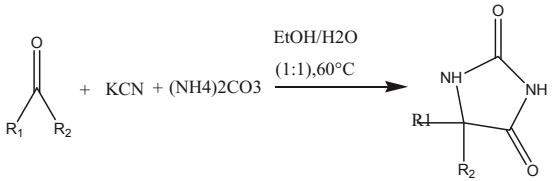
Scheme I. 7 - Example of the Biltz synthesis of phenytoin.[61]

The condensation of benzil 20 and urea(s) is thought to take place through a benzil/benzilic acid type rearrangement, 33 and not a pinacol rearrangement as had been suggested in the early literature.[62] This method is suitable for the synthesis of a range of N-3 and/or 5, 5-diaryl substituted Hydantoins and 2-thioHydantoins, with the medicinally important derivative phenytoin used as an example (Scheme 7). This method has been used to produce isotopically labeled derivatives of phenytoin, which are important for metabolic studies.[63]

1.3.2 The Bucherer-Bergs Reaction

1.3.2.1 Development

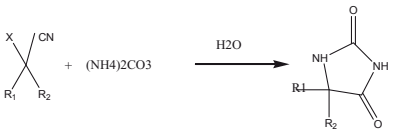
The Bucherer-Bergs[6,27,28] reaction produces 5- or 5,5-substituted Hydantoins via a multicomponent reaction (MCR) involving carbonyl groups, potassium cyanide and ammonium carbonate (Scheme 8). The Bucherer-Bergs reaction and other MCRs are convergent reactions, in which three or more starting materials react to form a product, with the product exhibiting functionality from each of the starting materials.



Scheme I.8 - Example of the Bucherer-Bergs synthesis of hydantoins.[37-39]

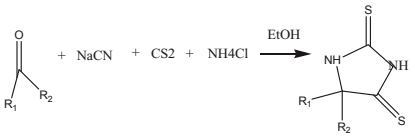
The Bucherer-Bergs reaction has been known since 1934 and is considered to be a general method for the synthesis of 5-substituted Hydantoins.1-3 Reactions of this

type were first reported by Ciamician and Silber (1905),[9] but it was work carried out by Bergs that led to a more desirable and shorter route. The Bergs reaction (1929) involved the condensation of carbonyl compounds with the salts, KCN and $(NH4)_2CO_3$ under a high pressure of CO_2 at 80 °C. This procedure was further modified by Bucherer (1934),[39,9,66] who found that the use of high pressure CO2 was unnecessary and that the optimum solvent was a water/ethanol (1:1) system (Scheme 8).[39]Henze found that these modifications increased the substrate range of the reaction where carbonyl derivatives such as ketones, aldehydes, semicarbazones, thiosemicarbazones, oximes, azines, phenylhydrazones, imidazolidines and azomethines were all readily converted into Hydantoins using this methodology.[9,64] Bucherer also noted that α-aminonitriles and cyanohydrins were transformed, in excellent yield, to Hydantoins in aqueous solution using only ammonium carbonate (SchemeI. 9).[9]



R1 = alkyl or aryl R2 = H, alkyl or aryl, X = NH2 or OH

SchemeI. 9 **-** Example of the Bucherer synthesis of Hydantoins from α-aminonitriles And cyanohydrins.[74]Carrington modified the conditions to allow the synthesis of 4-thio and 2,4dithiohydantoins.40,41 It was found that substitution of ammonium carbonate for ammonium thiocarbonate gave 4-thiohydantoins and that using carbon disulfide (CS2), ammonium chloride (NH4Cl) and sodium cyanide (NaCN) affords 2,4dithiohydantoins (Scheme I.10).



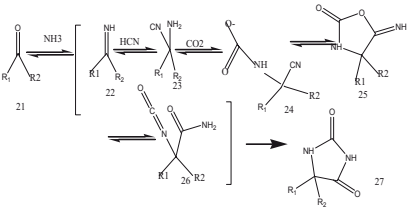
R1 = alkyl or aryl R2 = H, alkyl or aryl

Scheme I.10 **-** Example of the Carrington modification of the Bucherer-Bergs reaction.[81]

1.3.2.2 Mechanism of the Bucherer-Bergs Reaction

Bucherer proposed that the reaction mechanism proceeded initially through the formation of a cyanohydrin and not an imine, however, later thermodynamic and kinetic studies by Commeryas and Co-workers[72,73]revealed that the process begins

with the formation of the imine 22, through condensation of a ketone 21 (or aldehyde) and ammonia. The imine 22 undergoes hydrocyantion to furnish the α-iminonitrile 23, which further reacts with CO2 to give the intermediate, α-carboxyaminonitrile 24. This step is followed by intramolecular cyclisation to give 5imino-2-oxazolidinone 25, which rearranges to the isocyanatamide intermediate 26. This intermediate then undergoes cyclisation to give either 5- or 5,5-substitued Hydantoins 27 (SchemeI. 11).[72,73]



R1 = alkyl or aryl, R2 = H, alkyl or aryl

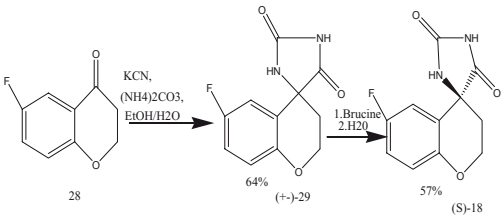
SchemeI. 11 - The intermediates of the Bucherer-Bergs reaction as proposed by Commeyras and Coworkers.[72,73]

Commeyras states that the key intermediate is the α-aminonitrile 23, which is in equilibrium with the α-carboxyaminonitrile 24. The stability of the carbamate is dependent on the pH and the concentration of CO2 in solution. The synthesis of the α-aminonitrile 23 is considered to be the fast step, which is followed by slow formation of the Hydantoin 27. The cyclisation of the carbamate 24 was shown to be the rate-determining step at pH < 9. However, at higher pH the reaction is controlled by fast partitioning of the cyclic intermediate 25 between the α-carboxyaminonitrile 24 and the isocyantamide 26 intermediates.[72, 73]

1.3.2.3 Uses of the Bucherer-Bergs Reaction

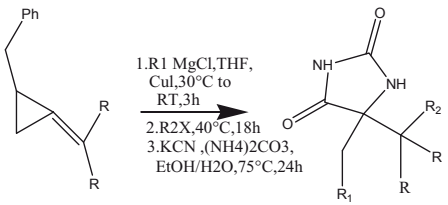
The Bucherer-Bergs reaction is routinely used for the synthesis of medicinal and industrially important compounds. The reaction has been employed for the industrial production of methionine[73] and the work of Koóš and Mičová has shown that the reaction can be used in carbohydrate chemistry to synthesise novel spironucleosides which may have important biological activity [77-79]Sarges and Co-workers employed the Bucherer-Bergs reaction to synthesise the aldose reductase inhibitor sorbinil 18 from benzopyranone 28 (SchemeI. 12).[79] The racemic hydantoin product is then optically resolved using brucine. The chiral resolution occurs as the free base of

brucine forms a crystalline complex with sorbinil, whereas the enantiomer of sorbinil only forms the complex with brucine hydrochloride.[79]



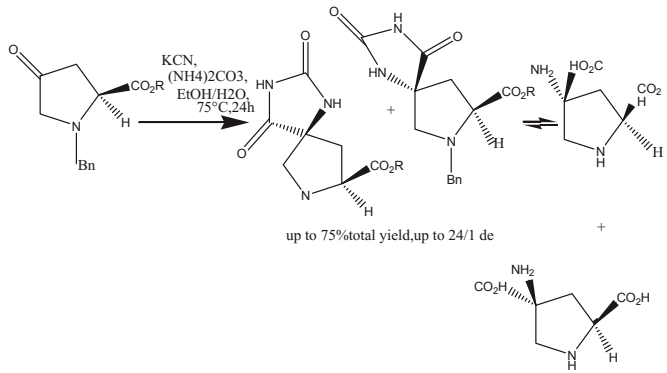
Scheme I.12 - Conditions employed by Sarges and co-workers for the synthesis of sorbinil.[79]

A recent variation of the Bucherer-Bergs reaction which involves the use of organometallic reagents has been reported by Shipman and Co-workers (Scheme 13).[80-82]The process involves generating imine derivatives from methyleneaziridines. In situ reaction with the Bucherer-Bergs reagents (KCN, $(NH4)_2CO_3$ and EtOH) generates three new C-C bonds in the highly branched 5,5disubstituted hydantoins.



R = H or Me R1 = alkyl or aryl,
R2 = alkyl or aryl,
X = halogen

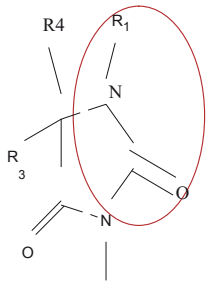
Scheme I.13 - Conditions employed by Shipman and Co-workers for the synthesis of 5,5-disubstituted hydantoins.[82-84]Tanaka also used the Bucherer-Bergs reaction to synthesis all four diastereoisomers of 4-amino-4-carboxyproline. Scheme 14 demonstrates the synthesis of two of the diastereoisomers; by using the other enantiomer of the ketone, all four diastereoisomers are produced. The diacid products are conformationally restricted analogues of L-glutamic acid, which is one of the major excitatory neurotransmitters in the mammalian CNS. These analogues can be used to probe the requirements for receptor binding of the excitatory amino acid at the active site of the N-methyl-D-aspartate (NMDA) receptor.[85]



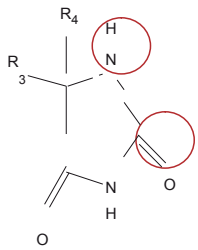
R = Me,Et, i-Pr or t-Bu.

SchemeI.14 - Example of the synthesis of diastereoisomers of 4-amino-4-carboxyproline by Tanaka and Co-workers.[85]

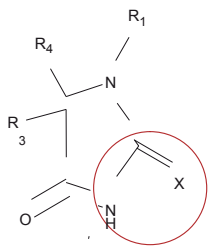
Figure I. 13Synthetic Strategies and Building Blocks in Hydantoin Formation [86]



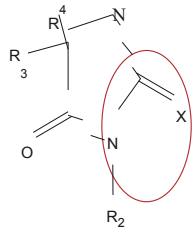
a



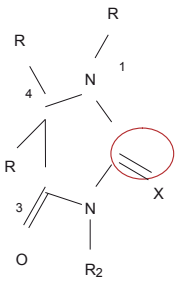
b



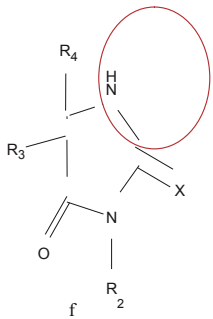
c



d



e

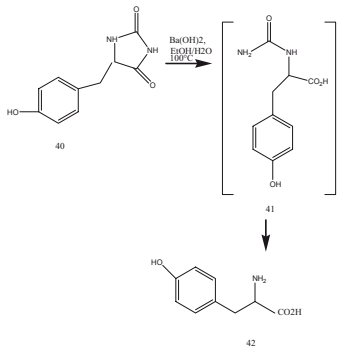


f

I.4 Reactivity of Hydantoins

I.4.1Hydrolysis of Hydantoins

The production of α-amino acids is possible from the hydrolysis of Hydantoins (or ThioHydantoins) in either acidic or basic media, or by enzymes. Hydantoins readily hydrolyse in base, however, acidic conditions need to be more extreme. For base catalysed hydrolysis of Hydantoin 40, the initial product is the ureido acid 41 (or thioureido acid), which is further hydrolysed to an α-amino acid, like tyrosine 42 (SchemeI. 14).[37-39] The reaction can also be applied to N-1 substituted Hydantoins, for the synthesis of corresponding N-substituted α-amino acids. This is an extremely important reaction as it can be used to produce unnatural α-amino acids that cannot be synthesised by any other means.

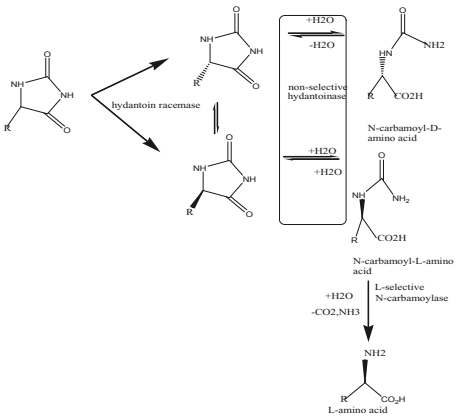


40 41 42

Scheme I.14 - Example of the hydrolysis of a Hydantoin in basic media to give (±)-tyrosine 42.[38]

The production of enantiomerically pure α-amino acids by enzymatic biocatalytic conversion of racemic 5-mono substituted Hydantoins, in certain bacteria, has been known for some time and has great potential applications in the production of natural and unnatural α-amino acids.[86,34,94] The biocatalytic pathway involves two consecutive hydrolysis steps: a non-selective Hydantoinase, and a selective N-carbamoylamino acid amidohydrolyase that furnishes the desired α-amino acid enantiomer. Depending on the desired enantiomer, this process may be fine tuned to produce either D- or L-α-amino acids. This pathway may also contain a Hydantoinracemase enzyme, which means that theoretically a 100 % conversion of

racemic Hydantoins to enantiopure α-amino acids may be achieved (Scheme I.15).[86,97,94]

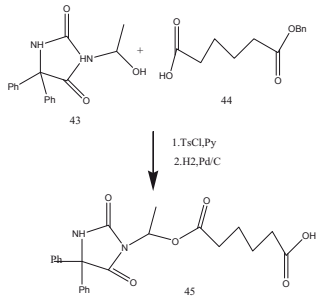


Scheme I.15 - Example of the biocatalytic conversion of racemic Hydantoins to enantiomerically pure α-amino acids.[26,62,97] The hydrolysis of Hydantoins is an extremely important transformation, which may be performed reliably with the use of enzymes or solution-based reagents to produce the industrially important products, α-amino acids.

I.4.2 N-Alkylation of Hydantoins

The introduction of substitutents at the N-3 position of the Hydantoin ring may be accomplished with ease using alkyl halides in alkaline solution. However, the synthesis of N-1 monosubstituted Hydantoins cannot be achieved through direct alkylation unless the C-5 position is an alkene.[38]The favorable position of the N-3 nitrogen between the two activating carbonyl groups explains this pattern of reactivity. Alkylation reactions at the N-3 position have also been carried out via a Mitsunobu coupling and Hydantoins containing only an N-1 substituent can be prepared through a suitable protecting group strategy.[37,38,88] The alkylation of Hydantoin derivatives is important as the pharmaceutical properties of Hydantoins can be varied significantly due to the introduction of substituent's at either nitrogen position. An example of this is the synthesis of potential water-soluble N-3substituted

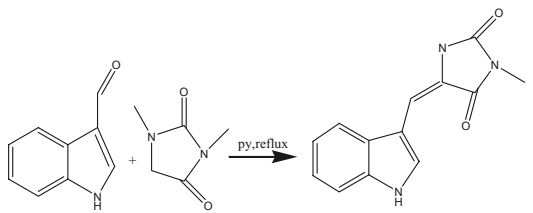
derivatives of phenytoin (45) from Hydantoin 43 and mono-protected acid 44 by Bosch and Co-workers (SchemeI.16).[99,97,98]



SchemeI.16 - Example of the synthesis of potential water-soluble derivatives of phenytoin by Bosch and Co-workers.[89]

I.4.3 Aldol-Type Reactions

The synthesis of C-5 unsaturated Hydantoin (or 2-thiohydantoin) derivatives can be achieved by reacting aromatic aldehydes with hydantoins bearing no substituents at the C-5 position. This reaction can be performed under either very acidic conditions[38] or by refluxing in pyridine.[1] This type of reaction was used by Pietra and co-workers to synthesis aplysinospsin 5 by reacting the indole 46 with N,N-dimethyl imidazolidine-2,4-dione 47 (SchemeI. 17).[90,99]

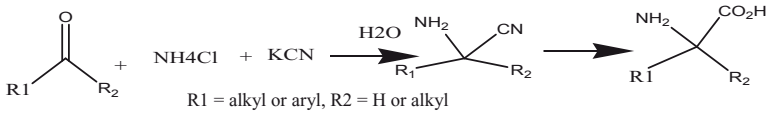


SchemeI.17 - Example of the synthesis ofaplysinospsin 5 by Pietra and Co-workers.[90]

1.5 The Strecker Reaction

The Strecker reaction (1850) involves the condensation of an aldehyde (or ketone) with ammonia and a cyanide source to give an α-aminonitrile, and is closely related to the Bucherer-Bergs reaction. This reaction is one of the classical methods of

preparing α-amino acids as α-aminonitriles can be readily hydrolysed in a separate step to provide the corresponding α-amino acids (Scheme I.18). The product of the Strecker reaction is also one of the intermediates in the Bucherer-Bergs synthesis, and the recent successful development of various asymmetric Strecker conditions,71 has increased the need to attempt an asymmetric modification to the Bucherer-Bergs reaction.



R1 = alkyl or aryl, R2 = H or alkyl

Scheme I.18 - Example of the Strecker synthesis of α-aminonitriles and α-amino acids.

Due to the importance of natural and unnatural α-amino acids (see Section 1.2.3), recent research on the Strecker reaction by many leading scientists, has resulted in the development of a catalytic asymmetric Strecker reaction, where the use of both organic and metal-based Chiral Lewis acid catalysts has led to a high-yielding process with outstanding enantioselectivity.[91]

I.6 Summary

Hydantoin-containing alkaloids have been isolated from many marine bio-organisms, and these derivatives have demonstrated novel biological activity. An important application of a Hydantoin is as the drug phenytoin, which has been the first choice treatment for certain convulsive disorders for over 60 years. Hydantoin-containing compounds have been developed to treat a vast assortment of medical conditions including viruses, heart problems, cancer, inflammatory response, diabetes, Ca^{2+} cellular control as well as possessing inhibitory action towards a host of CNS processes. Synthetically Hydantoins can be hydrolysed to α-amino acids, which have many key medical and industrial applications. Other derivatives have been used as antibacterial agents, herbicides and bleaching agents. There are many classical methods of synthesizing Hydantoins, with the Bucherer-Bergs reaction considered to be a general MCR the (MultiComponent Reactions) for the synthesis of 5- or 5,5substituted Hydantoins from aldehydes or ketones. This reaction is still frequently applied to the synthesis of novel hydantoin compounds, and new variations of the reaction continue to be developed.

1. Hydantoins are cyclic monoacylureas. They possess imidazoline-2, 4-dione heterocyclic system. Hydantoins are structurally related to barbiturates, differing in lacking the 6-oxo moiety.
2. Hydantoins are weakly acidic than barbiturates. Thus aqueous solution of sodium salts provide strongly alkaline solutions.

3. A clinically useful Hydantoin possess an aryl substituent at the 5-position

4. Hydantoin derivatives possessing of lower alkyl substituents have antiabsence activity.

5. Hydantoins activate Na+-K+-dependent and Ca^{++}-dependent ATP and increase Na^{+} transport.

Chemistry.Phenytoin occurs as phenytoin sodium, chemically phenytoin is 5, 5′diphenyl Hydantoin Mechanism of action. Phenytoin probably works by maintaining the deactivation of voltage-sensitive sodium channels, there by blocking the repetitive firing of neurons[24,31,32,33].

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CHAPTER II

THEORETICAL ASPECTS OF MODELING MOLECULAR

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II.1 Introduction

Molecular modeling is centered on applying the fundamental laws of physics and chemistry to the study of molecules.Its ultimate aim is to create models and simulations, which can help by predicting, rationalizing, and estimating the properties of molecules and their interactions.

The diverse applications of Hydantoins, during the past several decades' considerable efforts have been devoted to Hydantoins chemistry. Many experimental methods such as X-ray crystallography, NMR spectroscopy and IR have been developed to study the behaviors of functionalized Hydantoins.[1]

In order to get a better understanding of the binding events, a lot of theoretical methods including Molecular Mechanics (MM), Molecular Dynamics (MD), and more recently, Quantum Mechanical (QM) methods such as ab initio and Density Functional Theory (DFT), have also been used to study Hydantoins[1-2-3].

All these theoretical methods, when properly utilized in combination with each other, have proven to be extremely powerful in solving the structural, energetic, and dynamic problems associated with Hydantoin and Hydantoins .However, because the treatment of molecular systems as large as Hydantoins and Hydantoin by ab initio and DFT methods is extremely expensive computationally, comparatively few molecular calculations have been performed thus far based on more accurate ab initio and DFT methods on such systems.

Therefore, it was motivation and primary goal of this thesis to perform computational investigations on Hydantoins and Hydantoin using ab initio and DFT methods at an appropriate high level of theory, in order to get better insight into the structures and energetic of hydantoin and their derivatives.

This thesis describes the determination of the geometries and energetic of Hydantoins and Hydantoin inclusion mainly by DFT calculations at the B3LYP/6-31 G (d, p) level of theory. This level of theory was chosen because it has at present been proven the best approach for investigations on such systems.[1]

II.2 Geometry Optimization (Energy Minimization)

Geometry optimization is a technique used for locating a stable conformation of a model. As a general rule, this should be performed before performing additional computations or analyses of a model. Locating global and local energy minima is often accomplished through energy

minimization; locating a saddle point is referred to as optimizing to a transition state. The ability of a geometry optimization to converge to a minimum will depend on the starting geometry, the potential energy function used, and the settings for a minimum acceptable gradient between steps (convergence criteria).Geometry optimizations are iterative and begin at some starting geometry. First, the single point energy calculation is performed on the starting geometry. Then the coordinates for some subset of atoms are changed and another single point energy calculation is performed to determine the energy of that new conformation. The first or second derivative of the energy (depending on the method) with respect to the atomic coordinates then determines how large and in what direction the next increment of geometry change should be. Then the change is made.Following the incremental change, the energy and energy derivatives are again determined and the process continues until convergence is achieved, at which point the minimization process terminates. The starting geometry of the model will determine which minimum is reached.

II.2.1 Molecular Modeling and Computational Chemistry

Even though a theory may give a rigorous mathematical description of chemical phenomena, the mathematical difficulties might be so great that it is just not feasible to solve a problem exactly.[38] If a satisfactory result is desired, the best technique is often to do only part of the work, for example to completely leave out part of the calculation. Another approximation is to use an average rather than an exact mathematical description, to use perturbations, simplified functions, or to fit parameters to reproduce experimental results.QM gives a mathematical description of the behavior of electrons that has never been found to be wrong. However, the quantum mechanical equations have never been solved exactly for any chemical system other than the hydrogen atom. Thus, the entire field of computational chemistry is built around approximate solutions. Some of these solutions are very crude and others are expected to be more accurate than any experiment that has been conducted. If an approximation is used, one must ask how accurate an answer should be Computations of the energetic of molecules and reactions, for example, often attempt to attain what is called chemical accuracy, meaning an error of less than about one kcal/mol. This is sufficient to describe Vander Waals interactions, the weakest interaction considered to affect most chemistry. Chemists are therefore advised to develop an understanding of the nature of computational chemistry approximations and what results can be trusted with any given degree of accuracy. Molecular modeling is focused on applying the fundamental laws of physics and chemistry to the study of molecules. The ultimate aim is to create models and simulations, which can help by predicting, rationalizing, and estimating the properties of molecules and their interactions. Today, computational techniques performed by powerful computers have revolutionized molecular modeling to the extent that most calculations

could not be performed without the use of a computer.[2-3]It allows chemists to study chemical phenomena by running calculations on computers rather than by examining reactions and compounds experimentally. Some methods can be used to model not only stable molecules, but also short-lived, unstable intermediates and even transition states. In this way, they can provide information about molecules and reactions, which is impossible to obtain through observations. Molecular modeling and computational chemistry is therefore both an independent research area and a vital adjunct to experimental studies.

Molecular modeling has undergone a dramatic change over the last decades mainly due to two factors: 1. Today's high level of computer technology has allowed an increase in the size of systems that can be studied, the degree of accuracy of the models and the number of interactions feasible to calculate on a reasonable time scale.[3-4]

2. There has been tremendous progress in the experimental techniques that the different modeling tools rely on. X-ray crystallography and nuclear magnetic resonance (NMR) have been developed to a level where they are now applied routinely, which have an enormous impact on the number of experimentally determined molecular structures available. Among the various properties most typically studied by computational chemists, the determination of the "best" structure of isolated molecules - as they are the fundamental units from which pure substances are constructed - is a very common undertaking. In this case, "best" is defined as having the lowest possible energy.[5-6] This sounds relatively simple because it is about modeling of an isolated, single molecule. In the laboratory, however, one is much more typically dealing with an equilibrium mixture of a very large number of molecules at some non-zero temperature. In that case, measured properties reflect thermal averaging, possibly over multiple discrete stereo isomers, tautomers, etc., that are structurally quite different from the idealized model system, and great care must be taken in making comparisons between theory and experiment in such instances. To make a theory more closely mimic the experiment one has to consider not just one structure for a given chemical formula, but also all possible structures. That is, one characterizes the potential energy surface (PES) for a given chemical formula. Besides structural and energetic properties, several others that can be estimated by computational methods include spectral quantities, acidity, basicity (e.g., pKa values), and hydrogen bond strengths.[7-8]

II.2.2Overview of Computational Chemistry Methods all molecular calculation techniques can be classified under three general categories: ab initio and density functional electronic structure calculations, semi-empirical methods, and Molecular Mechanics.

TableII. 1 Summarizes some general characteristics for each of this methods.[9]

TabII. 1 General characteristic for computational methods

Method	Method description	Advantages	Disadvantages	Best for
Ab initio and DFT	Uses quantum physics; mathematically rigorous: no empirical parameters	Useful for abroad range of systems; does not depend on experimental data; calculates transition states and excited states	Computationally Expensive	Small systems (tens of atoms); electronic transitions; systems without experimental data; systems requiring high accuracy
Semi-empirical	Uses quantum physics, experimental parameters and extensive approximations	Less demanding computationallyabinitio methods; calculates transition states and excited states	Requires ab initio or experimental data for parameters; less rigorous than ab initio and DFT methods	Medium sized systems (hundreds of atoms)
Molecular Mechanics	Uses classical physics; relies on force fields with embedded empirical parameters	Computationally "cheap": fast and useful with limited computer resources	Does not calculate electronic properties; requires ab initio or experiment data for parameters	Large systems (thousands of atoms); systems or processes that do not involve bond breaking

II.2.3 Molecular Mechanics (MM) The term MM was coined in the 1970s to describe the application of classical mechanics to calculate the static properties of a molecule or a group of molecules, such as structure, energy, or electrostatics. If one is interested in dynamic properties like the time evolution of a molecular system, resulting in a trajectory of snapshots, one has to use molecular dynamics. Finally, if one needs to know thermodynamic properties like enthalpies, or include entropy or free energy, an alternative to sampling the conformational space by molecular dynamics is to apply Monte Carlo simulations the latter method does not concern time evolution at all, but is generally considered to generate statistically meaningful thermodynamic ensembles much more effectively. MM is often the only feasible means with which to model very large and non symmetric chemical systems such as proteins or polymers. MM is a purely empirical method that neglects explicit treatment of electrons, relying instead upon the laws of

classical physics to predict the chemical properties of molecules. As a result, MM calculations cannot deal with problems such as bond breaking or formation, where electronic or quantum effects dominate. Furthermore, MM models are wholly system-dependent; MM energy predictions tend to be meaningless as absolute quantities, and are generally useful only for comparative studies.[10-11]Despite these shortcomings, MM bridges the gap betweenquantum and continuum mechanics. There are many different MM methods.Each one is characterized by its particular force field. Generally, a standard modern MM force field can be written as

$E = E_{STRETCH} + E_{BEND} + E_{TORSION} + E_{NON\ BONDED}$ (1) TableII.2 gives the mathematical forms of energy terms often used in popular force fields.[12]TabII. 2 Common force field terms (l-bond length, θ-bond angle, k, α, A, B-constants particular to the elements in a certain hybridization state, n-an integer, r-nonbonding distance, q charge, D_e dissociation energy.

Name	Use	Energy term
Harmonic	Bond Stetch	$k(l-l_0)$
Harmonic	Angle Bend	$k(\Theta-\Theta_0)^2$
Cosine	Torsion	$K(1-COSn\Theta)$
Lennard Jonnes6-12	Vander-Waals	$4k(A/r)^{12}-(B/r)^6$
Lennard Jonnes10-12	Vander-Waals	$4k(A/r)^{12}-(B/r)^{10}$
Coulomb	Electrostatic	$q_1\ q_2/4\pi\varepsilon_0 r$
Taylor	Stretch bend	$k(\Theta-\Theta_0)\ [(l-l_0)(l-l)]$
Morce	Bond Stertch	$D_e[1-e^{-\alpha(l-l0)}]^2$

The constants may vary from one force field to another according to the designer's choice of unit system, zero of energy, and fitting procedure. All the constants in these equations must be obtained from experimental data or ab initio calculations.However, the database of compounds used to parameterize the method is crucial to its success.A MM method may be parameterized against a specific class of molecules, such as, for example, proteins.Such a force field would only be expected to have any relevance in describing other proteins.Other force fields are parameterized to give a reasonable description of a wide variety of organic compounds. A few

force fields have even been parameterized for all the elements. Many good forces fields have already been developed. A comprehensive comparison of several force fields focusing on the calculation of conformational energies of organic molecules has been published by Pettersson and Liljefors (1996).[13-14]Table II.3 lists some commonly used MM force fields that have been designed for organic molecules and are implemented in more than one software package. [15]There tend to be minor differences in the implementation leading to small differences In result from one software package to another.TableII.3. Commonly used MM force field.

Name	Description
MM2/MM3/MM4	The parameterizations provided by Norman Allinger and co workers are probably the best-known implementations of the MM concept and are widely used as a synonym for force field calculations in general. MM2 is designed primarily for hydrocarbons. It was extended by many functional groups to cover almost all kinds of small organic molecules. The MM3 method with significant improvements in the functional form is probably one of the most accurate ways of modeling hydrocarbons. It was also extended to handle amides, polypeptides, and proteins.
MM+	Extension of the MM2 force field; developed by Allinger and Coworkers.
AMBER (Assisted model building with energy refinement)	One of the most popular force fields for modeling proteins and nucleic acids.
GROMOS (Groningen molecular simulation)	It is a molecular dynamics computer simulation package for the study of bimolecular systems with the purpose of energy minimization and the simulation of molecules in solution or solid state by molecular dynamics, stochastic dynamics, or path-integral methods.
UFF (Universal Force Field)	It is a set of simple functional forms and parameters used to model the structure, movement, and interaction of molecules containing any combination of elements in the periodic table.
MMFF (Merck Molecular Force Field)	It is based primarily on quantum mechanical calculations of the energy surface and is able to handle all functional groups of interest in pharmaceutical design.

II.2.4 Ab Initio Electronic Structure Methods

The term ab initio is Latin for "from the beginning". This name is given to computations that are derived from theoretical principles with no inclusion of experimental data. Over the past three decades, ab initio electronic structure methods have become an indispensable tool in the study of both atoms and molecules and in modeling complex systems, consisting of two or more components.[16] The underlying main technology is the computational solution of the electronic Schrodinger equation. In its exact form, the Schrodinger equation is a many-body problem, whose computational complexity grows exponentially with the number of electrons. Two highly efficient approaches to solution of the electronic Schrodinger equation have arisen to date.

II.2.5 Wave function-based approaches expand the electronic wave function as a sum of Slater determinants, the orbital's and coefficients of which are optimized by certain numerical procedures. Hartree-Fock theory is the simplest method of this type, involving the optimization of a single determinant only. However, its usefulness is limited because of complete neglect of electron correlation. The second class of theoretical approaches is based on **density functional theory**. The premise behind this theory is that the energy of a molecule can be determined from the electron density instead of a wave function. Kohn and Sham who formulated a method similar in structure to the **Hartree-Fock** method developed a practical application of this theory. The advantage of using electron density is that it depends on three coordinates instead of 3N coordinates of N electrons only, thus scaling as N^3. Furthermore, at least some electron correlation can be included in the calculation. This results in faster calculations than HF calculations (which scale as N^4) and computations are a bit more accurate as well. The better DFT functional give results with accuracy similar to that of an MP2 calculation.[16-17]

II.2.6 Basic Quantum Mechanics (QM)

QM is the correct mathematical description of the behavior of electrons and thus of chemistry. In theory, QM can predict any property of an individual atom or molecule exactly. In practice, the QM equations have only been solved exactly for one-electron systems. A huge collection of methods has been developed for approximating the solution for multiple electron systems. These approximations can be very useful, but this requires an amount of sophistication on the part of the researcher to know when each approximation is valid and how accurate the results are likely to be. Schrodinger and Heisenberg devised two equivalent formulations of QM. Here, only the Schrodinger form is presented since it is the basis for nearly all computational chemistry methods. The Schrodinger equation is

$$H\Psi = E\Psi \qquad (2.2)$$

Where H is the Hamiltonian operator, a wave function and E the energy. In mathematics, an equation of this form is called an Eigen equation. Is then called the Eigenfunction and E an Eigen value. The operator and Eigenfunction can be a matrix and vector, respectively, but this is not always the case. The wave function is a function of the electron and nuclear positions. As the name implies, this is the description of an electron as a wave. As such, it can describe the probability of electrons being in certain locations, but it cannot predict exactly where electrons are located. The wave function is also called probability amplitude because it is the square of the wave function that yields probabilities. This is the only rigorously correct meaning of a wave function. In order to obtain a physically relevant solution of the Schrodinger equation, the wave function must be continuous, single-valued, normalizable, and anti-symmetric with respect to the interchange of electrons.The Hamilton operator H is, in general:

$$H = -\frac{\sum_i^{particles} \nabla_i^2}{2m_i} + \sum_{i<j} \sum qiqj/rij \qquad (2, 3)$$

Where

$$\nabla_i^2 = \partial^2/\partial x_i^2 + \partial^2/\partial y_i^2 + \partial^2/\partial z_i^2$$

The Laplacian operator acting on particle i. Particles are both electrons and nuclei. The symbols i m and q_i are the mass and charge of particle i, and r_{ij} is the distance between particles. The first term gives the kinetic energy of the particle within a wave formulation. The second term is the energy due to Coulomb attraction or repulsion of particles. This formulation is the time-independent, non-relativistic Schrodinger equation.

Additional terms can appear in the Hamiltonian when relativity or interactions with electromagnetic radiation or fields are taken into account. In currently available software, the Hamiltonian above is nearly never used. The problem, however, can be simplified by separating the nuclear and electron motions. This is called **the Born-Oppenheimer approximation**. Using atomic units, the Hamiltonian for a molecule with stationary nuclei is

$$H = \frac{-\sum_i^{electron} \nabla_i^2}{2} - \sum_i^{nucleon} \sum_j^{electrons} \frac{zi}{rij} + \sum_{i<j}^{e} \sum 1/rij \qquad (2, 4)$$

Here, the first term is the kinetic energy of the electrons only. The second term is the attraction of electrons to nuclei. The third term is the repulsion between electrons. The repulsion between nuclei is added onto the energy at the end of the calculate.

The motions of nuclei can then be described by considering this entire formulation to Ψ be a potential energy surface on which nuclei move. Once a wave function has been determined, any property of the individual molecule can be determined.

This is done by taking the expectation value of the respective quantum mechanical operator for that property, denoted with angled brackets <>.

For example, the energy is the expectation value of the Hamiltonian operator:

$$< E > = \int \Psi' H \Psi \mathrm{d}V \qquad (2.5)$$

Where Ψ' represents the complex conjugate wave function.For an exact solution, this is the same as the energy predicted by the Schrodinger equation. For any approximate wave function, this gives an approximation of the energy, which is the basis for some of the techniques described below. It is called **variational energy** because it is always greater than or equal to the exact energy. By substituting different operators, it is possible to obtain different observable properties, such as the dipole moment or electron density. Properties other than the energy are not variational, because only the Hamiltonian is used to obtain the wave function in the widely used computational chemistry methods.[18-19]

II.2.7 The Hartree-Fock (HF) Self-Consistent Field Approximation

The most common type of ab initio calculation is called a HF calculation, in which the primary approximation is **the central field approximation**. This means that the Coulomb electron-electron repulsion is taken into account by integrating the repulsion term. This gives the average effect of the repulsion, but not the explicit repulsion interaction. Instead, this is a variation calculation, meaning that the approximate energies calculated are all equal to or greater than the exact energy and tend to a limiting value called the **HF limit** as the basis set (see below) is improved. One of the advantages of this method is that it breaks the many-electron Schrodinger equation into many simpler one-electron equations. Each one-electron equation is solved to yield a single-electron wave function, called an orbital, and energy, called an orbital energy. The orbital describes the behavior of an electron in the net field of all the other electrons. The second approximation in HF calculations is because the wave function must be described by some mathematical function, which is known exactly for only a few one-electron systems. [5-6]

The functions used most often are linear combinations of Gaussian-type orbital (GTO). The wave function is formed from linear combinations of atomic orbital or, stated more correctly, from linear combinations.of "basis functions". Because of this approximation, most HF calculations give a computed energy greater than the HF-limit. The exact set of basic functions used is often specified by an abbreviation, such as STO-3G or 6-31G(d,p). The Gaussian functions are multiplied by an angular function in order to give the orbital the symmetry of a s, p, d, and so on. A constant angular term e.g. yields symmetry.

Angular terms of x, y and z give p symmetry. This pattern can be continued for the other orbitals. These orbitals are then combined into a determinant, the so-called **Slater Determinant**.

This is done to satisfy two requirements of QM. One is that the electrons must be indistinguishable. By having a linear combination of orbital in which each electron appears in each orbital, it is only possible to say that an electron was put in a particular orbital but not which electron it is.[6-7] The second requirement is that the wave function for fermions (an electron is a fermion) must be anti symmetric with respect to interchanging two particles. Thus, if electron 1 and electron 2 are switched, the sign of the total wave function must change and only the sign can change. This is satisfied by a determinant because switching two electrons is equivalent to interchanging two columns of the determinant, which in turn changes its sign. The functions put into the determinant do not need to be individual GTO functions, called Gaussian primitives.[8-9]They can also be a weighted sum of basic functions on the same atom or on different atoms. The steps in a Hartree-Fock calculation start with an initial guess for the orbital coefficients, usually using a semi-empirical method. This function is used to calculate energy and a new set of orbital coefficients, which can then be used to obtain a new set, and so on. This procedure continues iteratively until energies and orbital coefficients remain constant from iteration to the next one. This is called having the calculation converge.[10-11]The iterative procedure itself is called a **self consistent field procedure (SCF)**. A variation on the HF procedure is the way that orbital is constructed to reflect paired or unpaired electrons. If the molecule has a single spin, then the same orbital spatial function can be used for both theα and β spin electrons in each pair. This is called the **Restricted Hartree-Fock method (RHF).** If otherwise two completely separate sets of orbital's for theα and β electrons are used, this method is called the **Unrestricted Hartree-Fock method (UHF).**

However, the latter introduces an error into the calculation, called **spin contamination**, which could be large enough to make the results unusable depending on the chemical system involved. The RHF scheme results in forcing electrons to remain paired. This means that the calculation

will fail to reflect cases where the electrons should uncouple. Therefore, this limitation must be considered whenever processes involving pairing and impairing of electrons are modeled. [12-13]

II.2.7 .a Electron Correlation

The HF method yields, even in favorable cases and if large basis sets are employed, only an approximation to the exact solution of the electronic Schrodinger equation. It does not consider the instantaneous Coulomb interaction between electrons, nor does it take into account the quantum mechanical effects on electron distributions.

The effect of the N-1 electrons on the electron of interest is treated only in an average way. Therefore, in cases where accurate results are to be obtained, one has to go beyond the HF method. These methods are generally called post-SCF techniques. However, there are too many different methods for considering electron correlation to be described in detail here, so the discussion will be limited to the general principles of the most common techniques.[14-15]

II.2.7.b Configuration interaction(CI)

Solves the problem of electron correlation by considering more than a single occupation scheme for the MOs and by mixing the microstates obtained by permuting the electron occupancies over the available MOs. In its simplest form, a CI calculation consists of a preliminary SCF calculation, which gives the MOs that are used unchanged throughout the rest of the calculation.

Microstates are then constructed by moving electrons from occupied orbital's to vacant ones according to preset schemes. However, the problem is that if you want to consider every possible arrangement of all the electrons in all the MOs (a full CI), the calculations would become far too large even for moderate-sized molecules with a large basis set. Thus, two types of restriction are usually used: only a limited number of MOs are included in the CI, and only certain types of rearrangement (excitation) of the electrons are used.

The most economical form is that in which only one electron is promoted from the ground state to a virtual orbital (single excitations). This is abbreviated as CIS and has traditionally been used for calculating spectra. Adding all double excitations (in which two electrons are promoted) gives CISD, and soon.A more practical way of considering electron correlation is to use perturbation theory to apply a correction to the SCF energy.

Such an approach was first proposed by Moller and Plesset (1934) for atoms and was extended by Pople et al. (1976) to molecules.[16-17]Because it is a perturbation treatment, **Moller-Plesset**

(MP) theory can be applied considering the perturbation series to include different numbers of terms (i.e., to different orders). Second-order MP theory (MP2) is often used for geometry optimizations and fourth-order (MP4) for refining calculated energies. The reason, for instance, that MP3 theory is used less often is that the MP series tends to oscillate, so that using only the even-numbered orders gives results that are more consistent. MP techniques are size-consistent and computationally efficient, so that their use is very common.[18-19]

II.2.7.c The coupled cluster (CC) methods and quadratic CI form a further group of related techniques for considering electron correlation. These techniques represent the corrected wave function Ψ as the result of applying a so-called cluster operator to the HF wave function. The cluster operator can be built up from a series of operators that consider excitations of one, two, three, n electrons, where n is the total number of electrons in the molecule.

Thus, CC techniques can be truncated like MP methods, but are more accurate. However, they are also computationally more expensive. CC calculations using single and double excitations (CCSD) are common, but very often an additional perturbation term to take some triple excitations into account are used to give CCSD (T). CCSD(T) calculations (or the closely related QCISD(T) technique) represent about the best that is currently possible using an HF wave function as the starting point (reference wave function).[20-21] To sum up: ab initio calculations, in general, give very good qualitative results and can yield increasingly accurate quantitative results as the molecules in question become smaller.

The advantage of ab initio methods is that they eventually converge to the exact solution once all the approximations are made sufficiently small in magnitude.In general, the relative accuracy of results is HF<<MP<CISD≅MP4 ≅ CCSD <CCSD (T) <CCSDT< FULLCI

However, this convergence is not monotonic. Sometimes, the smallest calculation can give a very accurate result for a property under consideration. In ab initio calculations, there are four sources of error:

- The Born-Oppenheimer approximation
- The use of an incomplete basis set
- Incomplete correlation
- The omission of relativistic effects

The disadvantage of ab initio methods is that they are computational expensive.

These methods often take enormous amounts of computer CPU time, memory, and disk space. The HF method scales as N^4, where N is the number of basic functions. This means that a calculation twice as big takes 16 times as long (2^4) to complete. Correlated calculations often scale much worse than this.

In practice, extremely accurate solutions are only obtainable when the molecule contains a dozen electrons or less. However, results with an accuracy rivaling that of many experimental techniques can be obtained for moderate sized organic molecules. The minimally correlated methods, such as MP2, are often used when correlation is important to the description of large molecules.[22-23]

II.2.8 Density Functional Theory (DFT)

DFT has become very popular in recent years, because it is less computationally intensive than other methods with similar accuracy. The premise behind DFT is that the energy of a molecule can be determined from the electron density instead of a wave function.

This theory originated with a theorem by Hohenberg and Kohn that stated this was possible (Hohenberg and Kohn 1964). Kohn and Sham who formulated a method similar in structure to the Hartree-Fock method (Kohn and Sham 1965) developed a practical application of this theory. They suggested calculating the kinetic energy of the non-interacting electron density that corresponds to the real one exactly, and treating the correction from this energy to that of the real, interacting system approximately.

The correction to the non-interacting kinetic energy is known as **the exchange correlation (XC) energy** and is calculated as a function of the electron density. As the electron density itself is a function, the XC energy is a function of a function, which is known as a **functional**; hence the name “density functional theory”.

Its basic principles are described more fully by Koch and Holthausen (2001). The advantage of using electron density is that the integrals for Coulomb repulsion need be done only over the electron density, which is a three-dimensional function, thus scaling as N^3.

Furthermore, at least some electron correlation can be included in the calculation. These results in faster calculations than HF calculations (which scale as N^4) and computations those are a bit more accurate as well.

The better DFT functionals give results with accuracy similar to that of an MP2 calculation. The problem is that one does not know the functional(s) that translate the electron density into the

XC energy. There are now many alternative functionals available, but there is no way to say that functional A is better than functional B.

Thus, the major advantage of ab-initio theory, the ability to improve it systematically, is lost in DFT. There are, however, three basic types of functional.[24-25]

II.2.8.a The local density approximation (LDA)

is the oldest and simplest of the functional types still in use. It is based on the idea of a uniform electron gas, a homogeneous arrangement of electrons moving against a positive background charge distribution that makes the total system neutral.

This construct is abstract and not very realistic, but one does know the exact form of the exchange part of the XC functional for it and has accurate results to simulate for the correlation part. Importantly, the XC energy depends only on the electron density itself at a given position and so is easy to calculate. LDA calculations are thus very fast and often give good geometries. They tend, however, to give systematic errors in the energy and generally make bonds too strong. LDA calculations are therefore used less often for molecular applications than more sophisticated functionals.[26-27]

II.2.8.b The generalized gradient approximation (GGA)

Gives better results. GGA functionals are usually divided into exchange and correlation functionals, which are often derived separately and may be combined in different ways. The most important practical feature of GGA functionals is that they depend not only on the value of the electron density itself, but also on its derivative (gradient) with respect to the position in space. The inclusion of the first derivative of the density allows GGA functionals to treat the inhomogeneities in the electron density better than LDA functionals. Koch and Holthausen (2001) give an up-to-date list of GGA exchange and correlation functionals.[28-29]

The third class of density functional methods considered here, **the hybrid functionals**, are simply a combination of a GGA correlation functional with an exchange contribution that comes partly from an exchange functional and partly from HF theory, where the exchange energy is calculated exactly (Becke 1993a).[30-31]

The relative proportions of the HF exchange energy and those of the two GGA functionals vary between hybrid methods and are usually parameterized to fit a set of experimental data. Hybrid methods are generally the most accurate but suffer the disadvantage that calculating the HF exchange energy requires four-centre integrals.

Hybrid DFT calculations are thus more expensive computationally than GGA.Most DFT calculations today are being done with HF-optimized GTO basis sets. The accuracy of results tends to degrade significantly with the use of very small basis sets. For accuracy considerations, the smallest basis set used is generally 6-31G(d) or the equivalent.[32-33] Interestingly, there is only a small increase in accuracy obtained by using very large basis sets. This is probably because the density functional is limiting accuracy more than the basis set limitations.The accuracy of results from DFT calculations can be poor to good, depending on the choice of basis set and density functional.[34-35]

A variety of exchange-correlation functionals has been developed for use in DFT calculations; the names designate a particular pairing of an exchange functional and a correlation functional. For example, the popular BLYP functional is a combination of the gradient-corrected exchange functional developed by Becke (Becke 1986) and the gradient-corrected correlation functional developed by Lee, Yang, and Parr (Lee et al. 1988).

To date, the B3LYP hybrid functional (also called Becke3LYP) is the most widely used for molecular calculations with basis sets of 6-31G (d) or larger (Becke, 1993b).

This is due to the often optimal accuracy versus CPU time, and therefore the B3LYP method is the method of choice for many organic molecule calculations.[36-37] Due to the newness of DFT, its performance is not completely known and continues to change with the development of new functionals.

Cramer (2004) gives a broad overview of the applications and performance of DFT depending on the level of theory used. In addition, a detailed discussion on the advantages and disadvantages of DFT compared to MO theory is given.

In a recent publication (Lynch and Truhlar 2003), a variety of DFT-based calculations were performed to compute barrier heights for six small-molecule reactions and atomization (complete dissociation) energies for six different molecules.

The results for a variety of DFT functionals and basis sets were compared with each other and with results of HFbased techniques.[38-39]Unfortunately, as mentioned above, there is no systematic way to improve DFT calculations, thus making them unusable for very-high-accuracy work. It is therefore prudent to look for relevant literature and run test calculations before using this methods.[40-41]

II.2.9 Semi-empirical Methods Semi-empirical calculations are set up with the same general structure as a HF calculation in that they have a Hamiltonian and a wave function.

Within this framework, certain pieces of information are approximated or completely omitted.

Usually, the core electrons are not included in the calculation and only a minimal basis set is used. In addition, some of the two-electron integrals are omitted.[43-43] In order to correct for the errors introduced by omitting part of the calculation, the method is parameterized.

Parameters to estimate the omitted values are obtained by fitting the results to experimental data or ab initio calculations. Often, these parameters replace some of the integrals that are excluded. The advantage of semi-empirical calculations is that they are much faster than ab initio calculations.[45-46]The disadvantage of semi-empirical calculations is that the results can be erratic and fewer properties can be predicted reliably.

If the molecule being computed is similar to molecules in the database used to parameterize the method, then the results may be good.If the molecule being computed is significantly different from anything in the parameterization set, the answers may be very poor.

Semi-empirical calculations have been very successful in the description of organic chemistry, where there are only a few elements used extensively and the molecules are of moderate size. Some semi-empirical methods have been devised specifically for the description of inorganic chemistry as well. Table 4 presents an overview of some of the most commonly used semi-empirical methods.TabII. 4 Overview of some commonly used semi-empirical methods[47-48]

TabII. 4 Overview of some commonly used semi-empirical methods[47-48]

Name	Description
HUCKEL	The Huckel method is one of the earliest and simplest semi-empirical methods. A Huckel calculation models only the nvalence electrons in a planar conjugated hydrocarbon. A parameter is used to describe the interaction between bonded atoms. Huckel calculations do reflect orbital symmetry and qualitatively predict orbital coefficients. Huckel calculations can give crude quantitative information or qualitative insight into conjugated compounds, but are seldom used today.
CNDO(Complete Neglect of Differential Overlap)	It is the simplest method of this type and models valence orbitals only by using a minimal basis set of Slater type orbitals. It is still sometimes used to generate the initial guess for ab initio calculations on hydrocarbons.
MNDO (Modified Neglect of Diatomic Overlap)	This method has been found to give reasonable qualitative results for many organic systems and has been incorporated into several popular semi-empirical programs. It is still used, but the more accurate AM1 and PM3 methods have surpassed it in popularity.
AM1 (Austin Model 1)	The Austin Model 1 method is still popular for modeling organic compounds. Hydrogen bonds are predicted to have the correct strength, but often the wrong orientation. Depending on the nature of the system and information desired, either AM1 or PM3 will often give the most accurate results obtainable for organic molecules with semi-empirical methods. On average, AM1 predicts energies and geometries better than MNDO, but not as well as PM3. Computed bond enthalpies are consistently low.
PM3	set of parameters. The PM3 method is also currently extremely popular for organic systems. It is more accurate than AM1 for hydrogen bond angles, but PM3 uses nearly the same equations as the AM1 method along with an improved M1 is more accurate for hydrogen bond energies. The PM3 and AM1 methods Aare also more popular than other semi-empirical methods due to the availability of algorithms for including salvation effects in these calculations. There are also some known strengths and limitations of PM3. Overall heats of formation are more accurate than with MNDO or AM1. Hypervalent molecules are also treated more accurately. PM3 tends to predict that the barrier to rotation around the C-N bond in peptides is too low. Moreover, it tends to predict 3 sp nitrogen as always being pyramidal. Some spurious minima are predicted. Proton affinities are not accurate. Some polycyclic rings are not flat. The predicted charge on nitrogen is incorrect. No bonded distances are too short. Hydrogen bonds are too short by about 0.1, but the orientation is usually correct. On average, PM3 predicts energies and bond lengths more accurately than AM1 or MNDO.

Semi-empirical methods Huckel calculation models only the n valence electrons in a planar conjugated hydrocarbon. A parameter is used to describe the interaction between bonded atoms. Huckel calculations do reflect orbital symmetry and qualitatively predict orbital coefficients. [49-50]Huckel calculations can give crude quantitative information or qualitative insight into conjugated compounds, but are seldom used today CNDO (Complete Neglect of Differential Overlap) It is the simplest method of this type and models valence orbital only by using a minimal basis set of Slater type orbital.

It is still sometimes used to generate the initial guess for ab initio calculations on hydrocarbons MNDO (Modified Neglect of Diatomic Overlap) This method has been found to give reasonable qualitative results for many organic systems and has been incorporated into several popular semi-empirical programs.

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Depending on the nature of the system and information desired, either AM1 or PM3 will often give the most accurate results obtainable for organic molecules with semi-empirical methods. On average, AM1 predicts energies and geometries better than MNDO, but not as well as PM3. Computed bond enthalpies are consistently low.PM3 uses nearly the same equations as the AM1 method along with an improved set of parameters.[52-53]The PM3 method is also currently extremely popular for organic systems.

It is more accurate than AM1 for hydrogen bond angles, but AM1 is more accurate for hydrogen bond energies. The PM3 and AM1 methods are also more popular than other semi-empirical methods due to the availability of algorithms for including solvation effects in these calculations.[54-55] There are also some known strengths and limitations of PM3. Overall heats of formation are more accurate than with MNDO or AM1. Hypervalent molecules are also treated more accurately. PM3 tends to predict that the barrier to rotation around the C-N bond in peptides is too low.

Moreover, it tends to predict 3 sp nitrogen as always being pyramidal.[56-57]Some spurious minima are predicted. Proton affinities are not accurate. Some polycyclic rings are not flat. The predicted charge on nitrogen is incorrect. No bonded distances are too short. Hydrogen bonds are too short by about 0.1, but the orientation is usually correct. On average, PM3 predicts energies and bond lengths more accurately than AM1 or MNDO to sum up: Semi-empirical methods can provide

results accurate enough to be useful, particular for organic molecules with computation requirements low enough to make them convenient on PCs.[58-59] These methods are generally good for predicting molecular geometry and energetic and can be used for predicting vibrational modes and transition structures but do so less reliably than ab initio methods. They generally give poor results for van der Waals and dispersion intermolecular forces, due to the lack of diffuse basis functions.[60-61]

II.2.10 Basis Sets

A basis set is a set of mathematical functions from which a wave function can be constructed. As considered, each MO in HF theory is expressed as a linear combination of basic functions, the coefficients for which are determined from the iterative solution of the HF SCF procedure. The full HF wave function is expressed as a Slater determinant formed from the individual occupied MOs. In the abstract, the HF limit is achieved by use of an infinite basis set, which necessarily permits an optimal description of the electron probability density. In practice, however, one cannot make use of an infinite basis set. Thus, much work has gone into identifying mathematical functions that allow wave functions to approach the HF limit arbitrarily closely in as efficient a manner as possible.[61-62]

Efficiency in this case involves three considerations:

- Because the number of two-electron integrals increases as N^4 where N is the number of basic functions, so keeping the total number of basic functions to a minimum is computationally attractive.

- In addition, however, it can be useful to choose basis set functional forms that permit the various integrals appearing in the HF equations to be evaluated in a computationally efficient fashion. Thus, a larger basis set can still represent a computational improvement over a smaller basis set if evaluation of the greater number of integrals for the former can be carried out faster than for the latter.

- Finally, the basic functions must be chosen to have a form that is useful in a chemical sense. That is, the functions should have large amplitude in regions of space where the electron probability density (the wave function) is also large, and small amplitudes where the probability density is small.

The simultaneous optimization of these three considerations is at the heart of basis set development. Most semi-empirical methods use a predefined basis set. When ab initio or DFT

calculations are done, a basis set must be specified. Although it is possible to create a basis set from scratch, most calculations are done using existing basis sets.[63-64]

The type of calculation performed and basis set chosen mainly determine the accuracy of results. What follows below is a discussion of standard basis sets and considerations on how to choose an appropriate one. The orbital used in ab initio calculations usually have the following functional form:

$$\varphi = Y_{lm} \sum \quad i \sum_j C\,ij\, e^{-\zeta_{ij}\, r2} \qquad 2.6$$

The Ylm -function gives the orbital the correct symmetry (s, p. d, etc.) is called a Gaussian primitive function. The contraction coefficients Cij and exponentsζ_{ij} are read from a database of standard functions and do not change over the course of the calculation. This predefined set of coefficients and exponents is called a basis set. By using such a predefined basis set, the program must only optimize the molecular orbital coefficients C_i . Each C_i may weigh a sum of typically one to nine primitive Gaussian functions, called a contraction. Basis sets of contracted functions are called segmented basis sets.

As mentioned above, the choice of basis set has a large effect on the amount of CPU time required to perform a calculation. In general, the amount of CPU time for HF calculations scales as N^4 . This means that making the calculation twice as large will make the calculation take 16 times (4^2) as long to run.[65-66] Making the calculation twice as large can occur by switching to a molecule with twice as many electrons or by switching to a basis set with twice as many functions. Disk use for conventional calculations scales as N^4 and the amount of RAM use scales as N^2 for most algorithms. Some of the largest CI calculations scales N^8 or worse.[67-68]

The orbital in Equation 2.6 are referred to as Gaussian type orbital (GTOs), since they incorporate Gaussian functions,$e^{-\zeta_{ij}\, r2}$ The exact solution to the Schrodinger equation for the hydrogen atom is a Slater type orbital (STO) of the form $e^{-\zeta_{ij}\, r2}$. GTO basis sets require more primitives to describe the wave function than are needed for STO calculations.

However, the integrals over GTO primitives can be computed analytically, which is so much faster than the numeric integrals over STO functions that any given accuracy can be obtained most quickly using GTO functions. As such, STO basis sets are sometimes used for high-accuracy work, but most calculations are now done with GTO basis sets.

Choosing a standard GTO basis set means that the wave function is being described by a finite number of functions.[70-71]

This introduces an approximation into the calculation since an infinite number of GTO functions would be needed to describe the wave function exactly.

Differences in results due to the quality of one basis set versus another are referred to as basis set effects. In order to avoid the problem of basis set effects, some high-accuracy work is done with numeric basis sets. These basis sets describe the electron distribution without using functions

With a predefined shape. A typical example of such a basis set might be a cubic spleen set in which a large number of third-order polynomials are used. Each polynomial would describe the wave function for just a small range of distances from the nucleus.[72-73]

The coefficients of these polynomials are then chosen so that the wave function and its derivatives will be continuous as well as describing the shape of the wave function. Basis sets are identified by one of a number of notation schemes.

These abbreviations are often used as the designator for the basis set in the input to ab initio computational chemistry programs. The following is a look at the notation for identifying some commonly available contracted GTO basis sets. The smallest basis sets are called minimal basis sets. The most popular minimal basis set is the STO-3G set.[74-75]

This notation indicates that the basis set approximates the shape of a STO orbital by using a single contraction of three GTO orbitals. One such contraction would then be used for each orbital, which is the definition of a minimal basis. Minimal basis sets are used for very large molecules, qualitative results, and in certain cases quantitative results.

There are STO-nG basis sets for n=2-6. Another family of basis sets, commonly referred to as the Pople basis sets, are indicated by the notation 6-31G. This notation means that each core orbital is described by a single contraction of six GTO primitives and each valence shell orbital is described by two contractions, one with three primitives, and the other with one primitive.[76-76]

These basis sets are very popular, particularly for organic molecules. Other Pople basis sets in this set are 3-21G, 4-31G, 4-22G, 6-21G, 6-311G, and 741G.

The Pople basis set notation can be modified by adding one or two asterisks, such as 6-31G* or 6-31G**.[78-79]A single asterisk means that a set of d-primitives has been added to atoms other than hydrogen. Two asterisks mean that a set of p-primitives has been added to hydrogen as well. These are called polarization functions because they give the wave function more flexibility to change shape.

Adding polarization functions usually decreases the variational total energy by about the same amount as adding another contraction.[80]Polarization functions are used because they often result in more accurate computed geometries and vibrational frequencies. The Born-Oppenheimer separation of the electronic and nuclear motions is cornerstone in computational chemistry.

Once the electronic Schrodinger equation has been solved for a large number or nuclear geometries (and possibly also for several electronic state, the potential energy surface (PES) is known. The motion of nuclei on the PES can then be solved either classically (Newton) or by Quantum (Schrodinger) methods. If there are N nuclei,the dimensionality of PES is 3N,i.e.

There are 3N nuclear coordinates, three describe the overall translation of the molecule,and three describe the overall rotation of the molecule with respect to three axes.

For a linear molecule, Only two coordinates are necessary for describing the rotation this leaves 3N-6(5) coordinates to describe the internal movement of the nuclei, which for small displacements may be chosen as "Vibrational normal coordinates" It should be stressed that nuclei are heavy enough that Quantum effects are almost negligible, i.e. they behave to a good approximation as classical particles.[81]

The 3-21G* basis is an exception to the notation above. In this particular case, the d-functions are added only to 2nd row atoms, Al through Ar. One or two plus signs can also be added, such as 6-31+G*or 6-31++G*. [82-83]

A single plus sign indicates that diffuse functions have been added to atoms other than hydrogen. The second plus sign indicates that diffuse functions are being used for all atoms. These diffuse functions are primitives with small exponents, thus describing the shape of the wave function far from the nucleus. Diffuse functions are used for anions, which have larger electron density distributions. They are also used for describing interactions at long distances, such as van der Waals interactions. The effect of adding diffuse functions is usually to change the relative energies of the various geometries associated with these systems. Basis sets with diffuse functions are also called augmented basis sets.[83-84]As the Pople basis sets have further expanded to include several sets of polarization functions, f functions and so on, there has been a need for a new notation. In recent years, the types of functions being added have been indicated in parentheses. An example of this notation is 6-31G(dp,p) which means that extra sets of p and d functions have been added to no hydrogen atoms and an extra set of p functions has been added to hydrogen.Thus, this example is synonymous with 6-31+G**.

II.3 SOFTWARES USED

II.3.1ChemDraw ChemDrawUltra is among the most popular commercial chemical drawing software. It is available as a separate program or integrated into the commercial software suite ChemOffice from CambridgeSoft Inc. with Chem3D (3D molecule viewer, modeling software), ChemFinder (database manager), ChemInfo (chemical databases and catalogs), and E-Lab Notebook (organizer). The drawing software comprises a comprehensive collection of standard tools to sketch 2D chemical structures, but there are also some other features that are very useful for chemists. IUPAC standard names can be generated from chemical structures and on the other hand, for the most substances a structure can be created by typing in a systematic chemical name. Stereocenters can be identified using Cahn-Ingold-Prelog rules. Additional physical properties such as boiling point, melting point, etc., of chemical compounds can also be computed.

II.3.2 GaussView

GaussView is a graphic interface for use with the Gaussian ab initio program. It can be used to build molecules, set up the options in the input file, run a calculation, and display results. The program has several building modes. Compounds can be built one atom at a time by selecting the element and hybridization. There are also libraries of ring systems, amino acids, nucleosides, and common organic functional groups. The user can manually set bond lengths, angles, and dihedral angles. But does not go as far as giving the user the ability to enforce symmetry constraints. GaussView can also be used to set up ONIOM QM/MM calculations. The graphic molecule-building functions are very easy to use. The molecular structures are rendered with good-quality shading on a blue background. Isosurfaces produced from cube files or checkpoint files can also be displayed. Molecular vibrations can be animated on screen and vibrational displacement vectors displayed. The vibrational line spectrum may be displayed too, but the user has no control over the axes. There is no way to set the background color. The display can be saved using several image file formats.

II.3.3 HyperChem HyperChem is an integrated graphic interface, computational, and visualization package. HyperChem incorporates ab initio, semi empirical, and MM programs. These can be used for computing vibrational frequencies, transition states, electronic excited states, and QM/MM, simulations. The program has a drawing mode in which the backbone can be sketched out and then hydrogen atoms added automatically.

This sketcher does not set the bond lengths or angles, so the use of a MM optimization before doing more time-consuming calculations is highly advised. Building biomolecules is made easier

with a sugar builder and amino-acid sequence editor. Periodic systems can be constructed with a crystal builder and a polymer builder, which are very easy to use. The graphic interface incorporates a variety of rendering modes. It is possible to visualize molecular surfaces and animations of vibrational modes.

Both electronic and vibrational spectra can be displayed with intensities. The program can produce good-quality graphics, including ray-traced renderings, suitable for publication. A number of common-structure file formats can be read and written. The user can specify that all results for a given session be written to a log file. While a calculation is running, no actions can be taken other than changing the molecular orientation on screen.

The program has a scripting ability that can be used to automate tasks. The built-in scripting allows the automation of menu selections and execution of jobs. The MM force fields available include MM+and AMBER. Parameters missing from the force field will be automatically estimated. The user has some control over cut-off distances for various terms in the energy expression. Solvent molecules can be included along with periodic boundary conditions. Biomolecule computational abilities are aided by functions for superimposing molecules, conformation searching, and QSAR descriptor calculation. The semi-empirical techniques available include, among others, CNDO, INDO, MINDO/3, ZINDO, MNDO, AM1, and PM3.

The ab initio module can run HF, MP2 (single point), and CIS calculations. A number of common basis sets are included. Some results, such as population analysis, are only written to the log file.

II.3.4 **Programs and materials used**

This work was done in the IT and pharmaceutical chemistry team of the Laboratory of Molecular Chemistry and Environment (LMCE) at the University of Biskra. The first calculations were optimized using a 8.03 HyperChem software[86].

The geometry of the Hydantoin and its derivatives; were first fully optimized by molecular mechanics with the force field MM + (rms = 0.001 Kcal / A). In the next step, a parallel study was conducted using the Gaussian 09 software[87]. We based on the type of method ab initio Hartree-Fock (HF)[87] and the theory of density functional (in English: DFT Density Functional Theory) with functional B3LYP[88] using the bases follows: 6-31G+, 6-31G ++ (d, p), 6-311G ++ (d, p).All calculations are do nein a Station (HP Micro-processor Intel Xeon X3430CPU, 4GB of RAM). Anda PC(High TECH-PC Dell Micro-processor Intel(R) Core (TM)i5-2450M CPU@2.50GHz 2;50 GHz 6Go ofRAM) Type of system 64 bit.

II .References

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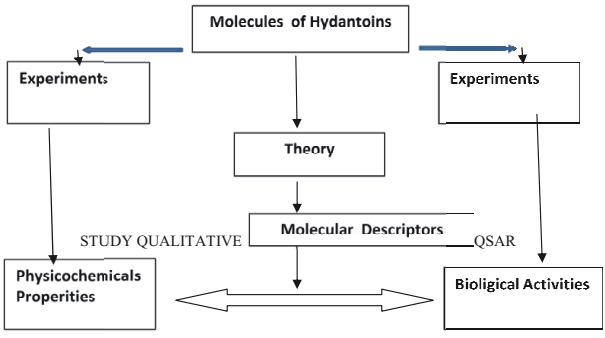
2nd Part: Results and Discussion

Figure organizational work



Chapter III

In silico evaluation of Molecular Structure, Vibrational Spectra and Substitution Effect of Hydantoin

Chapter III

In silico evaluation of Molecular Structure, Vibrational Spectra and Substitution Effect of Hydantoin

III.1 Introduction

Hydantoin (2, 4-imidazolidinedione, glycol urea) was first discovered by Bayer in 1861 as a hydrogenation product of all Antoin and its derivatives are important intermediates in the synthesis of several amino acids[1] and are also used as anticonvulsants or antibacterial[2].

The hydantoin, also known2, 4-imidazolidinedione is a saturated heterocyclic imidazole derivative compound. It has two functions lactams. The Hydantoin can be obtained from urea or glycine. It can be seen as the product of the condensation of urea twice and glycolic acid. Hydantoin properties are relatively similar to those of the imidazolidine, although having carbonyl functions on carbons 2 and 4 of the cycle. Cases of inflammatory syndromes induced by Hydantoin are reported[3]. We called Hydantoins substituted Hydantoin derivatives.They are used in pharmacy as antiepileptic these include among pharmaceutical compounds Hydantoin category ethotoin, phenytoin, mephenytoin and fosphenytoin.

Hydrations are biologically active molecules widely used in medicine as antiepileptic, antischisto_somal, antiarythmic, antibacterial and tuberculostatic drugs [4, 5]. It is also an effective medication for the treatment of metastatic prostate cancer. It is the parent compound of antiepileptic drug biphenyl hydantoin[6]. A Hydantoin derivative shows biological activity against human parasites like trematodeos[7]. Beside its medical usage it's also used as herbicides and fungicides [8, 9].

In recent years, the theoretical study of geometry and electronic structures has proved to be very efficient to predict the physical-chemistry properties of large systems [10-11]. The theoretical calculation of vibrational properties is used to understand the spectra's of large number of donor-acceptor systems [12-13].

Consequently, these calculations can be performed at different accuracy levels depending on the aim of the theoretical study. The substituents attached to the molecular framework can enhance or diminish the reactivity. The mechanistic conclusions based on the linear relationships with free energy have been extremely fruitful. The substituent's were variable donating and with drawing to study the effect of such change on the geometric, electronic and vibrational properties of the studied molecules. Correspondingly, changes in reactivity in one reaction series caused by changes in substitution are related to changes in equilibrium or reactivity in another series caused by the same changes in substitution [14-15].

Accordingly, objective of the present research is to study the geometric, electronic and vibrational spectra will characterize and predict the molecular and spectroscopic properties of hydantoin. Thus, in this work we have studied of the substituent groups effects at different positions in the hydantoin ring and compared between experimental and predict frequencies by linear regression, Also, we have calculated the structure of hydantoin and derivatives by using ab initio/HF and DFT/B3LYP methods [16-17].

III.2 Computational details

Initial calculations were optimized using HyperChem 8.03 software[18]. The geometries of hydantoin and its derivatives; were first fully optimized by molecular mechanics, with MM+ force-field (rms = 0.001 Kcal/Å). Further, geometries were fully re-optimized by using PM3 method [19]. In the next step, a parallel study has been made using Gaussian 09 program package[20,21], at various computational levels,HF/6-31G+(d,p),6-31G++(d,p),6-311G++ (d,p),and DFT(B3LYP)/6-31G+(d,p), 6-31G++ (d,p), 6-311G++ (d,p). The calculated results have been reported in the present work.

III.3 Results and discussion

III.3.a Molecular geometry of Hydantoin

The molecular structure of hydantoin is shown in (Figure 1). With this structural model, hydantoin belongs to Cs point group symmetry. The optimized geometrical parameters of hydantoin by ab initio/HF and DFT method have been depicted and compared with experimental parameters [22] obtained from the crystal structure analyses of hydantoin in (TableIII. 1).

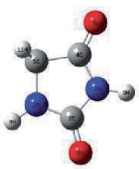


Figure III.1: Conformation 3D of molecular structure and atom numbering adopted in this study for hydantoin (GaussView 09)

Table III. 1: Comparison of the experimental and calculated values of bond lengths and bond angles of Hydantoin

Parameters	Exp.	ab initio/HF			DFT(B3LYP)		
Bond Length (A°)	[22]	6-31G+(d,p)	6-31G++(d,p)	6-311G++(d,p)	6-31G+(d,p)	6-31G++(d,p)	6-311G++(d,p)
C2-O6	1,222	1,19183	1,19188	1,18516	1,21581	1,21583	1,20705
C2-N1	1,371	1,3556	1,35556	1,35568	1,36382	1,36379	1,36137
C2-N3	1,393	1,3899	1,38991	1,39025	1,40388	1,40390	1,40267
N3-C4	1,367	1,3662	1,3662	1,36635	1,36987	1,36987	1,36775
C4-O7	1,225	1,18847	1,18850	1,18216	1,21483	1,21482	1,20641
C4-C5	1,460	1,5218	1,52188	1,52148	1,51962	1,51967	1,51714
C5-N1	1,457	1,4433	1,44329	1,44259	1,43253	1,43253	1,43006
Bond angle(°)							
O6-C2-N1	128,2	128,3769	128,373	128,438	128,646	128,649	128,752
O6-C2-N3	124,4	125,744	125,745	125,761	126,085	126,083	126,115
N3-C2-N1	107,4	105,879	105,883	105,801	105,269	105,268	105,133
C4-N3-C2	111,67	113,309	113,310	113,406	113,430	113,432	113,578
O7-C4-C5	125,3	127,070	127,075	127,089	127,121	127,120	127,125
C5-C4-N3	106,8	105,770	105,768	105,655	105,259	105,257	105,117
N1-C5-C4	104,7	101,820	101,823	101,919	102,843	102,842	102,926
C2-N1-C5	109,4	113,221	113,217	113,219	113,199	113,202	113,246
Dihedral angles(°)							
C5-N1-C2-N2	4,1	4,5	4,6	5,4	4,0	4,0	3,0
N1-C2-N2-C4	6,7	3,6	3,7	4,3	1,9	1,9	3,0
O2-C2-N1-C5	176,1	179,985	179,984	176,984	179,978	179,978	176,979
O4-C4-C5-N1	176,0	179,989	179,991	179,985	176,0	179,987	179,987

Thus, in this work was revealed good between the experimentally obtained values data are in good agreement with the theoretical calculations for bond lengths, bond angles but dihedral angles N1-C2-N2-C4 made exception the predicts values are not consistent with the values experimentals this may be due to probably steric of connections to terminals end of the link chain and closing the cycle of a rotary manner or disrotatory in synthese reaction of Hydantoin this means that the cycle closes from of C5-N1-C2-N2.

The nearly of the calculated geometries from the experimental parameters are 1,364A° (C2–N1) at B3LYP/DFT, 1,39A°(C2–N3) and 1,517A°(C4-C5) at ab initio/HF ,and 1,367A°(N3-C4)at B3LYP/DFT or ab initio/HF for the bond lengths and 128,373°(O6-C2-N1),105,77°(C5-C4-N3) at ab initio/HF basis sets for the bond angles.

On the other hand dihedral angles 4° (C5-N1-C2-N2) and 176,978° (O4-C4-C5-N1) which is close to the currently accepted experimental values .which confirms that the structure of the hydantoin is planar geometry between 0 ° and 180°.

III.3.b Vibration frequencies of Hydantoin

IR spectroscopy can give a great deal of information on small ring heterocyclic, because of the effects of ring strain on the frequencies of vibration of substituent's attached to the ring, and because the ring vibrations fall into a readily accessible region of the IR spectrum [23, 33 and34].

Experimental and theoretical (DFT_B3LYP/6–31G++ (d, p)) vibrational wave numbers of Hydantoin were given in Table III.2.

Hydantoin consists of 11 atoms, which has 27 normal modes. These normal modes of the title molecule have been assigned according to the detailed motion of the individual atoms.

All normal modes assigned to one of 21 types of motion

(C–H, C=O, C–H, and N–H stretching's; HCH, CCN, CCH, NC=O, CC=O, NCN, CNC, CNH, and NCH bindings, and HNC=O, OCCH, HCNH, NCNH, CNC=O, NCCN, CNCC, and NCNC twisting)

The asymmetric C-H stretching frequency decreases with increasing ring size, predicted by a calculation analysis.

The results obtained from the calculations show that, while the harmonic corrections of wave numbers are closer to the experimental ones rather than wave numbers of forms gave the best fit to the experimental ones.

The vibrational wave numbers of the forms of hydantoin obtained from the DFT calculations are almost the same except one value 429,743$Cm^{-1}$of mode 4 at ab-initio.

Table III. 2: Comparison of the experimental and calculated vibrational spectra of hydantoin.

Mode N^0	Symmetry	EXP. IR [24]	ab- initio/HF			DFT(B3LYP)			Assignment
			6-31G+(d,p)	6-31G++ (d,p)	6-311G++ (d,p)	6-31G+ (d,p)	6-31G++ (d,p)	6-311G++ (d,p)	
1	A		-10.2319	-15.0455	-97.6155	122.4518	123.4995	128.5824	ν N1_H8
2	A		150.6568	151.1778	138.5342	148.0355	148.3966	144.7564	νN3_H9
3	A		386.5634	387.9254	378.1519	380.9977	380.9031	385.3754	νasC5_H10 andνasC5_H11
4	A	428	429.7797	429.743	433.4412	382.4965	385.0823	389.9752	νsymC5_H10 and C5_H11
5	A	554	598.0108	598.9993	588.1646	534.4869	534.4075	540.4346	νN1_H8,νC2=o6 and νC4=o7
6	A		602.3857	602.405	606.8822	542.3242	542.2391	545.114	ωC5_H10,ωC5_H11and νN1_H8,N3_H9andτ C2=O6,C4=O7
7	A	580	650.0336	649.6981	646.1346	596.9489	597.2729	601.288	δC5_H10,δC5_H11 and ν N1_H8
8	A	632	687.2993	687.323	686.8045	622.5079	622.4737	624.1676	δC5_H10,δC5_H11 and ν N1_H8
9	A	670	766.4352	766.4259	766.2077	766.4014	698.4869	701.9823	δC5_H10,δC5_H11 and νN1_H8

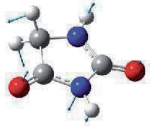
10	A	719	842.3027	842.9322	852.636	728.4884	728.9946	746.5964	τ N3_H7 and νC5_H10
11	A	785	956.7526	956.6458	953.9418	884.0849	883.9607	882.9414	ωC5_H10,ωC5_H11and νN1_H8,N3_H9andτC2 =O6,C4=O7
12	A	899	1063.4758	1063.4445	1059.8529	969.6732	969.365	968.2432	ωC5_H10,ωC5_H11and νN1_H8,N3_H9and νC4=O7
13	A		1122.0938	1121.9287	1119.2377	971.2799	971.2526	968.2617	τC5_H10, τ C 5_H11
14	A	990	1165.4106	1165.3967	1162.911	1073.971	1074.1322	1072.2072	ωC5_H10,ωC5_H11 and ν N1_H8
15	A	1075	1304.8551	1304.5813	1301.5487	1144.4085	1143.4119	1147.0616	ωC5_H10,ωC5_H11,ω N1_H8and ωN3_H9
16	A		1313.5705	1313.393	1303.747	1182.4483	1182.6149	1175.6719	τ C 5_H10,TC5_H11and νC4=O7
17	A	1197	1455.1549	1455.3184	1450.1199	1269.5502	1269.5006	1265.0279	ωC5_H10,ωC5_H11,νN 1_H8andνN3_H9
18	A	1287	1455.1532	1506.7196	1502.0856	1313.136	1312.9686	1307.5245	νC2=O7
19	A	1377	1529.991	1581.9712	1522.1306	1363.731	1363.6334	1361.2266	ωC5_H10,ωC5_H11and νN1_H8,νN3_H9
20	A	1429	1582.1884	1581.9712	1575.1308	1400.1721	1399.7912	1392.09	ω C5_H10,ω C5_H11andνC2=O6,νN 3_H9,νC4=O7
21	A		1632.6486	1633.0206	1627.3155	1434.5981	1434.5353	1426.929	τC5_H10,TC5_H11and νN3_H9
22	A	1696	1994.0682	1993.8253	1986.6061	1826.3929	1826.2343	1822.838	ρC5_H10,ρC5_H11 and νN3_H9
23	A	1774	2038.8534	2038.7555	2031.0495	1865.0979	1864.9699	1863.2827	ωC5_H10,ωC5_H11and νN1_H8,νN3_H9
24	A	2944	3225.3185	3225.3719	3207.6462	2979.6648	2979.4272	2966.5839	νN1_H8,νC5_H10and νC5_H11
25	A		3271.4889	3271.475	3249.9602	3023.3671	3023.2278	3006.1303	ωN1_H8,

									ωC5_H10,ωC5_H11and νC2=O6,νC4=O7
26	A	3130	3892.6359	3892.586	3875.3775	3570.2473	3570.2409	3554.3144	νC5_H10,νC5_H11andν N3_H9
27	A	3257	3925.6805	3925.4852	3907.0397	3600.002	3599.8007	3584.495	τ N 1_H8,ρC5_H10,ρC5_H 11and ωN3_H9

IR_{exp}: Experimental Infrared; asym: asymmetric; sym: symmetric; ν: bond stretching δS: scissoring; τ: twisting; ω: wagging; ρ: rocking;

Figure III.2 DIFFERENTS FIGURES OF 27MODES WITH BOND OF HYDANTOIN RING

MODE N°1(NH,CH,CN)



MODE N° 2(NH,CH,CO,CN)

MODE N° 3(CN,NH,CH)

MODE N° 4(CO,NH,CH,CN)

MODE N°5(NH,CN,CH)

MODE N°6(CH,NH,CO,CN)

MODE N°7(CH,NH,CN)

MODE N°8(NH,CO,CH)

MODE N°9(CO,CN,CH)

MODE N°10(CO,NH,CN,CH)

MODE N°11(NH, CN,NH)

MODE N°12(CN, NH, CH)

MODE 13(CN,CH)

MODE14(CH,CN,NH)

MODE 15(CN,CH)

MODE 16(CH,CN,NH)

MODE 17(CH,CN,NH)

MODE 18(NH,CN)

MODE 19(NH,CH,CO)

MODE 20(CN,CH,NH)

MODE 21(CH,CN)

MODE 22(NH,CO,CN)

MODE 23(NH,CN,CO)

MODE 24(CN,CH)

MODE 25(CH,CN)

MODE 26(NH,CN)

MODE 27(NH,CN)

The diatomic molecules have only one link, which can be stretched. The more complex molecules have many connections, and vibration maybe combined, leading to the infrared absorption at the characteristic frequencies which can be linked to chemical groups.

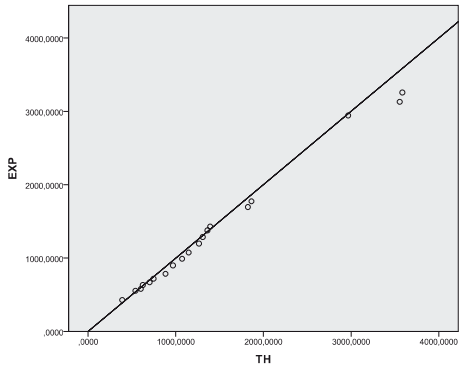
For example, atoms of CH2, which is commonly found in organic compounds, can vibrate in six different ways: stretching and skew symmetric, scissoring, and rocking, agitation outside plane wagging and twisting ν_1 (NH) stretching mode for monomer was observed at (moderate intensity) (3599,8–3570,24 cm–1), ν_2 CH_2 group (C5-H10,C5-H11) wave numbers symmetric and asymmetric stretching mode was observed at (2979,43 and 3023,23Cm^{-1}) with twisting ,waging and scissoring the absorption in the large 428Cm^{-1}, 429,743428Cm^{-1} ,429,7797428$Cm^{-1}$and 433,4412428Cm^{-1} the experimental values in good agreement with that obtained from ab-initio/HF theory using basis 6-31G+(d,p) set and 6-311G++(d,p) .ν_3 C2=O6 and ν C4=O7 stretching modes were observed with I-R intensity at 200Cm^{-1}, 371623Cm^{-1} and frequency 1864,9723Cm^{-1}These considerations thus provide additional support.

Cyclic imides represent an important class of compounds in medicinal chemistry due to its large spectrum of biological activities [23, 35]; are in a good agreement with the observed IR spectral data. In conclusion, the 6-311G++base (d, p) lead to prediction soft he theoretical molecular conformation similar to that given by the experiment in the case of the Hydantoin molecule studied.

This conclusion is based on the comparative study between the frequencies calculated internal modes, using the molecular conformation calculated by DFT/B3LYPand ab initio/HF, and experimental frequencies.

III.3.c Linear regression between experimental frequencies (vexp) and Predict frequency (vth) :Use linear regression or correlation by IBM - SPSS Statistics V19.0. When you want to know whether one measurement variable is associated with another measurement variable; you want to measure the strength of the association (r^2); or you want an equation that describes the relationship and can be used to predict unknown values. in fact our comparison between experimental frequencies and Predict frequencies amounts to a linear regression method we found[36].Following the linear regression models, When you are testing a cause-and-effect relationship, the variable that causes the relationship is called the independent variable and you plot it on the THaxis, while the effect is called the dependent variable and you plot it on the EXP axis. (FigureIII.2).

$\nu_{Experimental} = 0{,}904\ \nu_{Predict} + 62{,}776$ with a good agreement Predicted values



R = 0,997

Figure III.2 linear regression between frequencies (experimental (vexp) and Predict (vth))

III.3.d Electronic properties of Hydantoin

HOMO and LUMO refer to Highest Occupied Molecular Orbital and Lowest Unoccupied Molecular Orbital. According to the Frontier Orbital Theory, nucleophilic attack occurs by electron flow from a (HOMO of) nucleophile into the LUMO of the electrophile. In stable molecules, occupied electrons always reside on orbitals with negative energies and unoccupied orbitals have positive energies. The energies of HOMO and LUMO are related to the reactivity of the molecule: molecules with electrons at accessible (near-zero) HOMO levels tend to be good nucleophiles because it does not cost much to donate these electrons toward making a new bond. Similarly, molecules with low LUMO energies tend to be good electrophiles because it does not cost much to place an electron into such an orbital.Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important parameters for quantum chemistry. We can determine the way the molecule interacts with other species; hence, they are called the frontier orbitals [25]. Energies of the HOMO and the LUMO are very popular quantum chemical descriptors. The HOMO represents the ability to donate an electron; their energy is directly related to the ionization potential and characterizes the susceptibility of the molecule to attack by electrophiles. On the other hand, the LUMO as an electron acceptor; their energy is directly related to the electron affinity and characterizes the susceptibility of the molecule to attack by nucleophiles [26].HOMO and LUMO energies, energy gap ΔE=EHOMO-ELUMO) and dipole moments of Hydantoin calculated at ab initio/HF and B3LYP/DFT in 6-31G basis set is given in (Figure 2).The value of energy gap (|ΔE|) between HOMO and LUMO

energies is -0, 1662 a.u. obtained at DFT/B3LYP (6-311G) whereas the (ΔE) is -0,36899a.u. Obtained at HF/ab initio (6-31G) .Atomic charges of hydantoin, which have been calculated by Mullikan method at the ab initio/HF (6–31G), and DFT/ B3LYP (6–31G) levels of calculation are shown in below (Fig III. 3).

(1) (2)

(1)LUMO and (2) HOMO of the Hydantoin (HF/(6-31G+(d,p))

(3) (4)

(3) LUMO and (4) HOMO of the Hydantoin (DFT/B3LYP (6-31G+ (d,p))

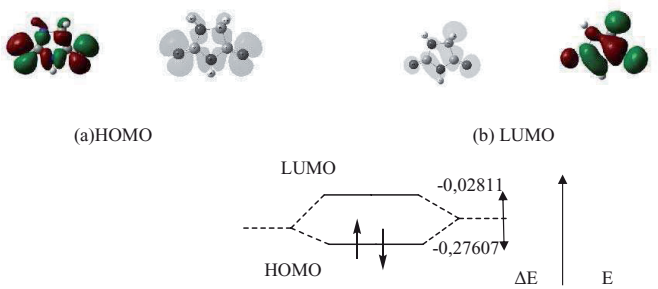
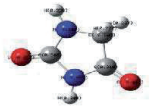


Fig III. 2 3D plot (a,b) of The Hydantoin (DFT/B3LYP (6-311G (d,p))

Atomic charges of Hydantoin, which have been calculated by Mullikan method at the ab initio/HF (6–31G) and DFT/ B3LYP (6–31G) levels of calculation are shown in below (FigureIII. 3).

ab initio/HF (6-31G(d,p))



DFT/B3LYP(6-31G(d,p))

Fig III.3: The Mulliken charges (Q_M) of hydantoin

Shows that the atoms N1, N2, C5 and O6,O7 have negative Mullikan charges which leads to electrophilic substitution, whereas at the atom C2,C3 have positive Mullikan charge which lead to preferential site nucleophilic attack.

III.3.e Substituent effects on the electronic structure in hydantoin and derivatives:

Substituent effects play a fundamental role in a variety of observed physical and chemical phenomena. For example, substituent effects influence the rates of nucleophilic substitutions and the molecule's reactivity, [27] vibrational specters, [28] acid-base properties, [29] the conformations of molecules, and so forth. The calculated values of (methyl, chloride) substituted hydantoin are given in (TableIII.4), (TableIII.5), (TableIII.6), (TableIII.7), (TableIII.8) and (TableIII.9). The chemical structures of the compounds studied of hydantoin and derivatives are shown in

(Figure 4)/ (Table III.3). In (TableIII.4), (TableIII.6) and (TableIII. 8), HOMO and LUMO energies, energy gaps ΔE, heat of formation and dipole moments are reported for hydantoin and its derivatives. In TableIII.5, TableIII.7 and TableIII. 9 net atomic charges are also reported.

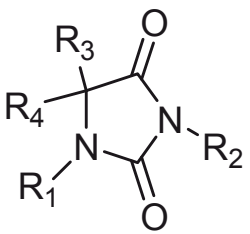


Fig III.4: Structure of hydantoin derivatives

Table III.3: Series of hydantoin and group's substituted hydantoin

Compound	R_1	R_2	R_3	R_4
Hydantoin	H	H	H	H
Series 1				
A1	CH3	H	H	H
A2	H	CH3	H	H
A3	H	H	CH3	H
A4	H	H	H	CH3
A5	CH3	CH3	H	H
A6	CH3	H	CH3	H
A7	H	CH3	CH3	H
A8	H	CH3	H	CH3
A9	H	H	CH3	CH3
A10	CH3	H	H	CH3
A11	CH3	CH3	CH3	H
A12	CH3	H	CH3	CH3
A13	H	CH3	CH3	CH3
A14	CH3	CH3	H	CH3
Series 2				
B1	Cl	H	H	H
B2	H	Cl	H	H
B3	H	H	Cl	H
B4	H	H	H	Cl
B5	Cl	Cl	H	H
B6	Cl	H	Cl	H
B7	Cl	H	H	Cl

B8	H	Cl	Cl	H
B9	H	H	Cl	Cl
B10	H	Cl	H	Cl
B11	Cl	Cl	Cl	H
B12	H	Cl	Cl	Cl
B13	Cl	H	Cl	Cl
B14	Cl	Cl	H	Cl
Series 3				
C1	CH3	Cl	H	H
C2	Cl	CH3	H	H
C3	CH3	H	Cl	H
C4	CH3	H	H	Cl
C5	Cl	Cl	CH3	CH3
C6	Cl	Cl	Cl	CH3
C7	CH3	CH3	CH3	Cl
C8	CH3	CH3	Cl	Cl
C9	CH3	Cl	Cl	Cl
C10	Cl	CH3	CH3	CH3
C11	CH3	CH3	CH3	Cl
C12	Cl	Cl	Cl	CH3
C13	CH3	Cl	CH3	CH3
C14	Cl	CH3	Cl	Cl

TableIII. 4: Energies of hydantoin and derivatives (series1):

Compound	System	Heat of formation Kcal/mol	HOMO(a.u)	LUMO(a.u)	ΔE(a.u)	μ(D)
Hyd	Hydantoin	-78,79776133	-0,42345	0,05446	0,36899	3,2857
A1	1-methyl hydantoin	-78,7978101	-0,39690	0,05901	0,33789	3,6195
A2	2-methyl hydantoin	-77,6590342	-0,40865	0,0552	0,35345	2,4968
A3	3-methyl hydantoin	-86,3483048	-0,42878	0,05919	0,36959	3,3385
A4	4-methyl hydantoin	-86,3483048	-0,4287	0,05920	0,36959	3,3380
A5	1-2 dimethylhydantoin	-79,4127366	-0,38677	0,06152	0,32525	2,8278
A6	1-3 dimethylhydantoin	-79,4127357	-0,38676	0,06153	0,32523	2,8271
A7	2-3 dimethylhydantoin	-87,1501982	-0,41630	0,05935	0,35695	2,6060
A8	2-4 dimethylhydantoin	-87,1596230	-0,41630	0,05937	0,35693	2,6038
A9	3-4 dimethylhydantoin	-92,6008067	-0,42509	0,06196	0,36313	3,4735
A10	1-4 dimethylhydantoin	-87,2730850	-0,40393	0,06122	0,34271	3,5864
A11	1-2-3 trimethylhydantoin	-88,0193806	-0,39734	0,06158	0,33576	2,8173
A12	1-3-4 trimethylhydantoin	-88,0220162	-0,39031	0,06157	0,32874	3,9191
A13	2-3-4 trimethylhydantoin	-93,3863432	-0,41430	0,06244	0,35186	2,7222
A14	1-2-4 trimethylhydantoin	-88,0325819	-0,39748	0,06157	0,33591	2,8123

Heat of formation by PM3/HOMO, LUMO, ΔE and μ by ab initio/HF (6-31G+ (d,p)

TableIII. 5: Mullikan charges of hydantoin and derivatives (series1):

Comp.	Hydantoin	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14
1N	-0,662	-0,436	-0,658	-0,565	-0,565	-0,437	-0,437	-0.560	-0.560	-0.506	-0.356	-0.354	-0.300	-0.510	-0.354
2C	0,869	0,845	0,826	0,774	0,774	0,709	0,709	0.722	0.722	0.790	0.766	0.654	0.871	0.727	0.653
3N	-0,639	-0,657	-0,441	-0,603	-0,603	-0,482	-0,482	-0.405	-0.405	-0.614	-0.606	-0.420	-0.660	-0.396	-0.420
4C	0,447	0,447	0,378	0,462	0,462	0,337	0,337	0.397	0.398	0.498	0.448	0.350	0.545	0.442	0.350
5C	0,116	0,062	0,098	0,250	0,250	0,088	0,088	0.256	0.256	0.297	0.146	0.223	-0.176	0.312	0.225
6O	-0,663	-0,660	-0,661	-0,470	-0,635	-0,646	-0,646	-0.634	-0.634	-0.638	-0.643	-0.638	-0.655	-0.632	-0.638
7O	-0,581	-0,585	-0,583	0,339	-0,582	-0,584	-0,584	-0.577	-0.577	-0.577	-0.582	-0.576	-0.585	-0.571	-0.576
8C	0,366	0,177	0,176	0,186	0,470	-0,122	-0,122	-0.170	-0.170	-0.387	-0.425	-0.165	-0.406	-0.171	-0.166
9C						-0.093	-0,093	-0.476	-0.476	-0.481	-0.206	-0.445	0.090	-0.411	-0.152
10C										0.375	0.181	0.173	0.163	0.168	-0.446

Net charge calculated by ab initio/HF (6-31G+ (d, p))

We note that the heat of formation decrease approximately to 8, 55 kcal/mole at addition of methyl group, to 13, 8 Kcal/mole at addition dimethyl/mole group and to 14, 59 Kcal/mole at addition trimethyl. In the mono-substituted alkyl group category, the hydantoin showing maximum positive charge on 2th position carbon (0, 8669996) which leads to nucleophile substitution (Table 5).

The compound A1 is further supported by the smaller HOMO-LUMO energy gap (0.33789a.u) (Table 5) which depicts the chemical reactivity of the compound; higher is the HOMO-LUMO energy gap, lesser is the flow of electrons to the higher energy state, making the molecule hard and less reactive. On the other hand in smaller HOMO-LUMO gap, there is easy flow of electrons to the higher energy state making it softer and more reactive (HSAB principle: hard and soft acids and bases). Hard bases have highest-occupied molecular orbitals (HOMO) of low energy, and hard acids have lowest-unoccupied molecular orbitals (LUMO) of high energy [30, 31, and 32]. In the case of dimethyl substituted of hydantoin the C-2 position compound (A5) shows, smaller HOMO-LUMO energy gap (0,32525a.u) (Table 5). We also note that the methyl substituent (donor effect) has the effect of increasing the energy of the HOMO, with little change in the LUMO (Table 5). The presence of a donor groups in the C2 and C4 positions causes the decrease in dipole moment (compound A1), the compound (A12) shows maximum dipole moment value (3,9191D) (Table 5) . In the present work, we have studied chloride of substituted hydantoin long the same line of methyl substituted hydantoin for a comparative study.

Table III.6: Energies of hydantoin and derivatives (series2):

Compound	System	Heat of formation (Kcal/mol)	HOMO (a.u)	LUMO (a.u)	ΔE (a.u)	M (D)
B1	1Chloro hydantoin	-74,1649614	-0,42345	0,05446	0,37004	2,4138
B2	2-Chloro hydantoin	-72,8548642	-0,41660	0,04702	0,36958	4,3353
B3	3-Chloro hydantoin	-82,9777505	-0,44696	0,05759	0,389201	1,8814
B4	4-Chloro hydantoin	-82,9777505	-0,44696	0,05759	0,389201	1,8817
B5	1-2-Dichloro hydantoin	-70,0553113	-0,41043	0,05824	0,35219	3,3234
B6	1-3-Dichloro hydantoin	-79,8009974	-0,43018	0,05451	0,37567	1,2144
B7	1-4-Dichloro hydantoin	-79,8009974	-0,43019	0,05450	0,37569	1,2151
B8	2-3 Dichlorohydantoin	-79,0124588	-0,43441	0,05017	0,38424	2,8990
B9	3-4 Dichlorohydantoin	-85,7464978	-0,44976	0,05919	0,27219	1,1926
B10	2-4 Dichlorohydantoin	-79,0124587	-0,43441	0,05017	0,38424	2,8998
B11	1-2-3 Trichlorohydantoin	-75,9042986	-0,43540	0,04971	0,38569	3,2857
B12	2-3-4 Trichlorohydantoin	-81,4208831	-0,43682	0,05758	0,37924	2,0732
B13	1-3-4 Trichlorohydantoin	-81,1562699	-0,43097	0,05710	0,37387	0,3099
B14	1-2-4 Trichlorohydantoin	-74,9048532	-0,43547	0,04970	0,38577	2,1185

Heat of formation by PM3/HOMO, LUMO, ΔE and μ by ab initio /HF (6-31G+ (d, p)

TableIII .7: Mullikan charges of hydantoin and derivatives (series 2)

Comp.	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14
1N	-0.475	-0.659	-0.526	-0.526	-0.502	-0.331	-0.331	-0.515	-0.501	-0.515	-0.322	-0.514	-0.252	-0.322
2C	0.870	0.857	0.771	0.770	0.781	0.796	0.796	0.744	0.860	0.744	0.727	0.848	0.918	0.726
3N	-0.652	-0.494	-0.590	-0.589	-0.568	-0.606	-0.607	-0.419	-0.614	-0.420	-0.429	-0.507	-0.642	-0.428
4C	0.438	0.408	0.418	0.418	0.362	0.396	0.396	0.363	-0.640	0.363	0.319	0.431	0.532	0.319
5C	0.093	0.112	0.143	0.143	0.129	0.076	0.076	0.161	0.482	0.161	0.155	0.009	-0.349	0.155
6C									0.002	-0.643	-0.638	-0.656		
6O	-0.628	-0.631	-0.616	-0.616	-0.589	-0.587	-0.587	-0.586	-0.629	-0.586	-0.576	-0.598	-0.596	-0.554
7O	-0.569	-0.549	-0.544	-0.544	-0.537	-0.531	-0.532	-0.508	-0.508	-0.508	-0.493	-0.473	-0.496	-0.493
8Cl	0.153	0.217	-0.015	-0.015	0.240	0.122	0.122	-0.007	0.079	0.184	0.199	0.239	0.222	0.199
9Cl					0.293	0.039	0.039	0.184	0.079	-0.007	0.029	0.088	0.135	0.131
10Cl									0.375	0.182	0.132	0.088	0.136	0.029

Net charge calculated by ab initio/HF(6-31G+(d,p)

The heat of formation is increased approximately 4, 18 Kcal/mol for each addition of chloride group. In mono-substituted chloride derivatives, 2chloro hydantoin (compound B2) is predicted to be more chemically reactive on the basis of least HOMO-LUMO energy gap (0.36958a.u) (Table 6) and shows maximum positive charge (0,87) in carbon C-2 leading to favored site for nucleophilic attack (Table 7).

In di-substituted chloride derivatives, the carbon C-2 in 3-4-dichloro-Hydantoin (compound B9) shows maximum positive charge (0,861) leading to favored site for nucleophilic attack (Table 7). The compound3-4 -dichloro-hydantoin (B9) is more reactive than2-chloro Hydantoin (B2), this is due to smaller HOMO-LUMO energy gap (0.27219) which reflects a chemical stability (Table 6).

The tri-substituted Hydantoin (compound B13) is predicted to be the most reactive with smaller HOMO-LUMO energy gap (0.37387a.u) (Table 6) and these considerations thus Provide additional support maximum positive charge (0.91795) in carbon C-2 leading to favored site for nucleophilic attack (Table 6) of all Hydantoin systems.

We note also that the chloride substituent (attractor effect) lowers the energies of HOMO and LUMO, his influence on the energy of the LUMO is more important. The compound B2 shows

the maximum dipole moment value (4,3353D), it would be originate from an attractor effect in position C2.

Table III.8: Energies of Hydantoin and derivatives (series3):

Comp.	System	Heat of formation (Kcal/mol)	HOMO (a.u)	LUMO (a.u)	ΔE (a.u)	M (D)
C1	2Chloro1methyl Hydantoin	-74,7661312	-0,39908	0,05525	0,34383	4,7539
C2	1Chloro2methyl Hydantoin	-78,6613821	-0,41525	0,06578	0,34978	1,5690
C3	3Chloro1methyl Hydantoin	-84,2207686	-0,42377	0,05962	0,36415	2,3295
C4	4Chloro1methyl Hydantoin	-84,2198834	-0,42374	0,05966	0,36408	2,3270
C5	1-2-Dichloro3-4dimethyl hydantoin	-85,8826626	-0,41802	0,05947	0,35855	3,8543
C6	1-2-3Trichloro 4methyl hydantoin	-83,9253767	-0,43186	0,05459	0,37727	3,0007
C7	4Chloro1-2-3trimethyl hydantoin	-93,0151461	-0,41105	0,06193	0,34501	2,6604
C8	3-4 Dichloro1-2 dimethylhydantoin	-87,4553305	-0,41403	0,06446	0,34957	1,3357
C9	1Methyl 2-3-4Trichloro hydantoin	-82,3525281	-0,42287	0,05874	0,36413	2,8458
C10	1Chloro 2-3-4 Trimethylhydantoin	-90,5357157	-0,40556	0,06515	0,34041	2,2414
C11	2Chloro 1-3-4 Trimethylhydantoin	-89,7065127	-0,40760	0,05819	0,34941	5,0247
C12	2Methyl1-3-4 Trichlorohydantoin	-82,1378200	-0,42148	0,06047	0,36101	0,7206

Heat formation by PM3/HOMO, LUMO, ΔE and μ by ab initio/HF (6-31G+ (d, p))

Table III. 9: Mullikan charges of hydantoin and derivatives (series3)

Comp.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
1N	-0.432	-0.351	-0.335	-0.335	-0.224	-0.173	-0.195	-0.226	-0.223	-0.235	-0.238	-0.627
2C	0.749	0.707	0.775	0.776	0.757	0.755	0.683	0.738	0.790	0.723	0.722	0.785
3N	-0.563	-0.413	-0.601	-0.602	-0.434	-0.439	-0.422	-0.466	-0.563	-0.411	-0.434	-0.464
4C	0.373	0.348	0.392	0.393	0.441	0.429	0.412	0.386	0.449	0.404	0.446	0.381
5C	0.097	0.067	0.102	0.102	0.001	-0.138	0.008	-0.215	-0.254	0.071	0.115	-0.243
6C									0.002			
6O	-0.618	-0.592	-0.627	-0.627	-0.565	-0.555	-0.621	-0.602	-0.579	-0.592	-0.606	-0.580
7O	-0.550	-0.562	-0.544	-0.544	-0.525	-0.483	-0.528	-0.507	-0.474	-0.560	-0.537	-0.494
8C	-0.121	-0.162	-0.227	-0.227			-0.169	-0.127	-0.132		-0.173	
8Cl	0.153	0.081	-0.009	-0.009	0.124	0.152				0.111		0.259
9C							-0.154			-0.155	-0.441	-0.108
9Cl	0.270				0.193	0.201			0.294		0.173	
10Cl						0.115		0.090	0.109			0.122
11Cl							0.018	0.089	0.109			0.121
10C					-0.335		-0.448			-0.343	-0.371	
11C					-0.388					-0.414	-0.371	

Net charge calculated by ab- initio/HF (6-31G+(d,p))

The heat of formation is decreased for each addition of methyl group and increased for each addition of chloride group.

In the mono-substituted methyl group, the (compound C3 and C4) showing positive charge on 2th position carbon (0,776) and in the mono-substituted chloride group, the (compound C2) showing positive charge on 2th position carbon (0,79) which leads to nucleophilic substitution (Table 9). In mono-substituted chloride derivatives the compound (C1) are predicted to be more chemically reactive on the basis of least HOMO-LUMO energy gap (0,34383a.u) and maximum dipole moment value (4,753D)(Table 8).

The di-substituted hydantoin (compound C8) is predicted to be the most reactive with smaller HOMO-LUMO energy gap (0,34957a.u) (Table 8) and positive charge (0, 4428) in carbon C-2 leading to favored site for nucleophilic attack (Table 9).

In tri-substituted chloride derivatives, the compound (C10) is more reactive due to smaller HOMO-LUMO energy gap (0,34041a.u) which reflects a chemical stability of all tri-substituted Hydantoin systems (Table 8),the compound (C11) with the maximum dipole moment value (5,024D) and more lest smaller HOMO-LUMO energy gap (0,34941a.u) table (8).

The different substitutions shown the best small energy(0,27219a.u) compared with all compounds is 3-4 dichloroHydantoin is predicted to be most reactive and the maximum dipole moment value(5,024D) is 2Chloro1-3-4 trimethylHydantoin involve asymmetric compound and positive charge to best favored site for nucleophilic attack is compound 1chloro Hydantoin.

III.4 CONCLUSION

The present study has confirmed previous conclusions that the aim of this work was qualitative, we are trying to clarify the characterization of Hydantoin, throw computational methods. Bond lengths and angles have been calculated by using HF/6-31(G+), 6-31G++(d,p) and 6-311G++(d,p) and DFT/B3LYP/6-31(G+), 6-31G++(d,p) and 6-311G++(d,p)methods and compared with experimental values. All compared data have been shown to have a good agreement with each other.

We have carried out ab initio and density functional theory calculation on the vibrational spectrum of hydantoin. The vibrational frequencies of infrared intensities with the stretching wave numbers calculated by DFT/B3LYP (6-311++G (d, p)) method agree satisfactorily with experimental results.

On the basis of agreement between the calculated and experimental results, assignments of all the fundamental vibrational modes of hydantoin were examined and proposed in this investigation.

This study demonstrates that scaled DFT/B3LYP calculations are powerful approach for understanding the vibrational spectra of medium sized organic compounds.

In the substituted chloride group, 3-4 dichlorohydantoin is predicted to be the most reactive with least HOMO-LUMO energy gap of all methyl-hydantoin derivatives.

The tri-chloroo-hydantoin is predicted to be the most reactive with all chloro and methyl derivatives. The presence of acceptor in B9(3-4dichloro hydantoin) group position causes the decrease in energy gaps, which reflects a chemical stability and show the maximum dipole moment value in B2(2-Chloro hydantoin) derivatives.

Hydantoins constitute an important class of heterocyclic in medicinal chemistry because many derivatives thus can identify activities that offer interesting against a wide range of biological targets.

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CHAPTER IV

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP STUDY FOR DEVELOPMENT OF PLASMIN INHIBITORS CONTROLLED BY THE SPACER HYDANTOIN

CHAPTER IV: Quantitative Structure Activity Relationship Study for Development of Plasmin Inhibitors Controlled by the Spacer Hydantoin

IV.1. Introduction

Cardiovascular (CVS) diseases and cancer are major health problems which concerns the medical community all over the world. The former is the principal leading cause of death followed by cancer. Plasmin and the plasminogen activator system play important role in normal physiological function and human disease. The interplay between all the components of plasminogen activator system is highly regulated, and disturbance in any of these pathways may result in serious diseases such as thrombosis, bleeding, neurological disorders, and cancer [1-3].

Plasmin is a proteolytic enzyme that is formed from plasminogen in blood plasma and dissolves the fibrin in blood clots, also called fibrinolysin. Plasmin has been found to be involved in a whole range of pathological conditions, such as thrombosis, cancer and Alzheimer's disease [4]. Thus, antiproteolysis which is performed by plasmin inhibitors, has become a key target in therapeutic strategies aimed at inhibiting angiogenesis, tumor growth, metastasis and invasion. Additionally, plasmin inhibitors, which have a different mode of action from prior anti-cancer drugs, have become regarded as a potential therapy for the treatment of cancer [5].

However, the necessary proof of concept validation of therapeutic use fullness of plasmin inhibitors has not been provided. This would be due to the lack of bioavailable and low molecular weight plasmin inhibitors [6].Hydantoins are a class of antiepileptic drugs universally used in the treatment of epilepsy [7–10]. Two most common Hydantoins are phenytoin and mephenytoin. Mephenytoin (marketed as Mesantoin by Novartis) was introduced approximately10 years after phenytoin, in the late 1940s.

The significant metabolite of mephenytoin is nirvanol (5-ethyl-5-phenylhydantoin), which was the first Hydantoin briefly, used as a hypnotic. However, nirvanol is quite toxic and Mephenytoin was only considered after other less toxic anticonvulsants had failed. Mephenytoin is no longer available in the US or the UK but it and its metabolite are still studied largely. Besides anticonvulsant, various other activities of Hydantoin derivatives were reported in literature, such as antimicrobial, antifungal or antitumor activities [9, 11–13].

Nowadays, because of different range of activities and toxicity of its metabolites synthesis, the modeling of new Hydantoin derivatives becomes significant.

Quantitative structure-activity relationship (QSAR) is a tool to rationalize the interaction of chemical compounds with living subject.

The fundamental idea of QSAR consists of the possibility of a relationship between a set of descriptors [14-18], which are derived from molecular structure and a molecular response [19-21]. QSAR can be regarded as a computer-derived rule that quantitatively describes biological

activity in terms of chemical descriptors. Once a QSAR is known, prediction or generation of new compounds with better activity is promising [22].

The general purpose of multiple linear regressions MLR is to quantify the relationship between more than one independent variables and a dependent variable [23, 24].

A set of coefficients defines the single linear combination of independent variables that best describes the inhibition activity.

The pIC50 value for each molecule would then be calculated as a composite of each molecular descriptor weighted by its respective coefficients [25, 26].

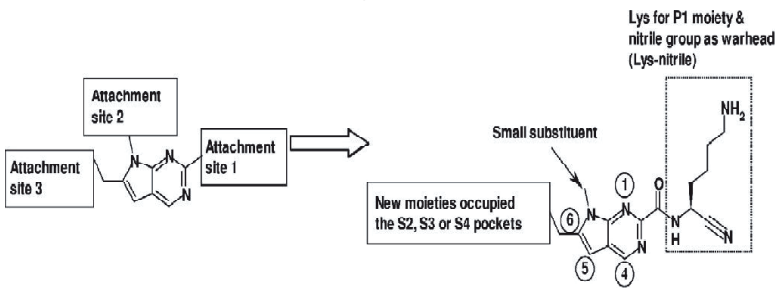
Following our interest in this field, our present research aimed to describe the structure-property relationship studies on Hydantoins and developing QSAR models with respect to their specific activity of Plasmin inhibition.

IV.2. Materials and methods

IV.2.1. Experimental details

The structural features of the core structure gave us a clue to the discovery of the novel chemotype for plasmin inhibitors unlike previously published plasmin inhibitors. Since the heterocyclic structure of pyrrolopyrimidine has three potential attachment sites, we considered it as the prime scaffold for plasmin inhibitors in order to exploit the SAR toward P4/S4 interaction (Figure 1)

FigIV.1



As a simple entry onto the pyrrolopyrimidine scaffold, Hydantoin derivatives were designed as potent inhibitors of Plasmin which could, explain its role in inhibiting tumor growth. The structures and inhibitory activities expressed as values of IC_{50} were adopted as reported by Naoki Teno et al [27].

IV.2.2. Descriptors generation

First, the eighteen investigated molecules were preoptimized by means of the Molecular Mechanics Force Field (MM+) included in HyperChem version 8.03package[28].After that, the resulted minimized structures were further refined using the semi empirical PM3Hamiltonian implemented also in HyperChem. We chose gradient norm limit of0.01kcal/Å for the geometry optimization. PM3 optimized geometry was used to calculate a number of physicochemical descriptors: Surface area grid (SAG), molar volume (MV), molar weight (MW), partition coefficient octanol/water (logP), hydration energy (HE), the molar refractivity (RF) and molar polarizability (Pol).

Calculation of logP is carried out using atomic parameters derived by Viswanadhan and Coworkers [29].Computation of molar refractivity was made via the same method as logP.

Atomic contributions to the refractivity presented by Ghose and Crippen have been used in our study [30]. Solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bordet al [31] using the atomic radii of Gavezotti[32]Polarizability was estimated from additively scheme given by Miller with a 3% in precision for the calculation [33], where different increments are associated with different atom types.

IV.2.3. Regression analysis

Multiple linear regressions (MLR) is a method based on the principle of polylinearity (Eq.1):

$$Y_0 = a_0 + a_1D_1 + a_2D_2 + a_3D_3 + \ldots\ldots + a_nD_n \qquad (1)$$

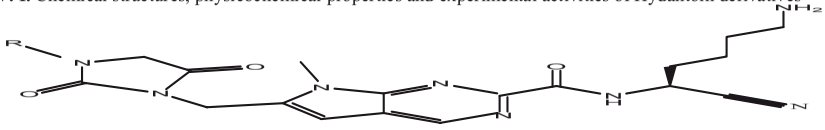
Where D_1, D_2, D_3 and D_n are descriptors, n is the number of descriptors.

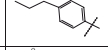
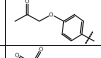
The intercept (a_0) and regression coefficient of the descriptors are determined using the least squares method. The quality criteria of the fit in regression analysis are coefficient of determination (R^2), standard error (SE), and Fisher test (F) for significance of the equation. The acceptance level for the individual independent variable was set to 95% significance level. For testing the validity of the predictive power of selected MLR models the leave-one out (LOO) technique were carried out using SPSS version 19 for windows. The developed models were validated by the calculation of following statistical parameters: predictive residual error sum of squares (PRESS), sum of squares of deviation of the dependent variable values from their mean (SSY). For that, we can say LOO is a good method to validate the prediction of a regression model without selecting another sample or data splitting [34].

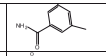
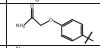
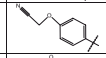
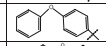
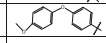
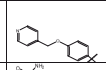
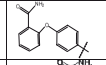
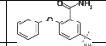
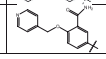
IV.3. Results and discussion

IV.3.1. Structure-Physicochemical Property Relationships:- In the first step of our study, we have studied seven physical chemical proprieties of series of eighteen Hydantoins which act as plasmin inhibitors (TableIV.I).

TableIV. I. Chemical structures, physicochemical properties and experimental activities of Hydantoin derivatives



Comp.	R	Plasmin pIC_{50}exp.[27]	pIC_{50} pred.	pIC_{50} resd.	SAG $Å^2$	MV $Å^3$	MW (a.m.u)	LogP	HE (Kcal/mol)	RF $Å^3$	Pol $Å^3$
1		3.880	3.825	0.060	816.39	1380.00	492.51	-2.11	-15.16	134.36	49.57
2		3.745	3.650	0.094	840.86	1438.22	504.44	-2.50	-17.18	140.61	52.13
3		3.481	3.356	0.125	890.12	1522.15	516.60	-0.56	-13.40	147.72	55.16
4		3.796	3.907	-0.111	860.97	1456.40	517.55	-2.99	-20.00	142.05	52.93
5		3.678	3.801	-0.123	845.88	1428.68	499.53	-1.78	-19.61	139.21	51.51
6		3.602	3.692	-0.089	905.55	1519.71	532.56	-2.66	-17.95	145.35	54.05
7		3.585	3.600	-0.015	859.82	1455.11	539.57	-3.61	-24.56	142.59	50.31
8		3.603	3.509	0.093	881.13	1498.23	553.60	-3.36	-22.19	147.49	52.15
9		3.658	3.761	-0.104	810.85	1377.26	485.51	-1.69	-19.23	134.83	49.67

10		4.000	3.928	0.072	847.36	1431.54	502.53	-3.09	-18.35	139.52	51.81
11		3.398	3.542	-0.144	904.35	1522.69	535.56	-3.65	-23.22	143.58	53.76
12		3.886	3.784	0.101	871.06	1463.28	515.53	-2.62	-23.91	140.92	52.15
13		4.292	4.302	-0.009	921.33	1560.45	552.59	-2.26	-20.53	160.30	58.12
14		4.194	4.066	0.127	996.76	1689.94	596.65	-2.85	-22.08	171.27	62.43
15		4.060	3.9363	0.124	950.20	1613.59	567.61	-3.21	-21.83	160.89	59.24
16		4.004	4.0632	-0.058	964.04	1649.34	595.62	-3.74	-24.98	168.12	61.39
17		3.292	3.6261	-0.333	994.68	1714.24	609.64	-3.34	-24.01	172.72	63.23
18		3.770	3.5765	0.193	991.00	1705.22	612.65	-4.72	-25.04	167.90	62.71

The molecular volume and the molecular surface are defined by determining the volume or the area occupied by the Van der Waals envelope of the molecule considered. Called polarizability, the ease with which an electron cloud is deformed under the influence of an electric field. The molecule undergoes some distortion and acquires an electric dipole moment proportional to the electric field induced. The refractive index does not vary much for most organic compounds; the molar refraction essentially depends on the volume. Molecular polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities.

The attractive part of the Van der Waals interaction is a good measure of the polarizability. Highly polarizable molecules can be expected to have strong attractions with other molecules. The polarizability of a molecule can also enhance aqueous solubility [35]. The molar refractivity (RF) is important criterion to measure the steric factor.

It is usually designated as a simple measure of the volume occupied either by an individual atom or group of atoms [36]. Molar refractivity is specifically significant in a situation when the substituent possesses either electron or lone pairs of electrons.

Polarizability and molar refractivity relatively increase with the size and the molecular weight of the studied Hydantoins (TableIV. I). This result is in agreement with the formula of Lorentz-Lorenz which gives a relationship between polarizability, the molar refractivity and the molecular size [37, 38]. As seen, the compound 17 substituted by bulky radical has great values ofpolarizability (63, 23 $Å^3$) and molar refractivity (172, 72$Å^3$).

In contrast, the (compound 1) is a small molecule in the series studied above; it has small values of polarizability (49, 57$Å^3$) and molar refractivity (134, 36$Å^3$). The presence of the hydrophobic groups in the structure induces a decrease of the hydratation energy [39]; whereas, the lower energy (13, 40 kcal/mol) was checked on the compound 3 (TableIV. I).

Indeed in the biological environment the polar molecules are surrounded by water molecules where hydrogen bonds can be established between the water molecule and the molecules understudy. The donor sites of proton interact with the oxygen atom of water and the acceptor sites of proton interact with the hydrogen atoms of water molecule. These interactions of weak energy are generally reversible in particular between messengers and receivers [40].

Compound 18 does possess five donor sites of proton (HBD) and fifteen acceptor sites of proton (HBA). On the other hand, compounds 1 and 3 possess three donor sites and eleven acceptor sites of proton. The first having higher value, it has two more donor and four acceptor sites of protons.

This property supports the first compound, not only by fixing on the receiver, but in more activates it. It is thus about an agonist. It has as a consequence a better distribution in fabrics. But generally the studied series has more than 10 hydrogen bond acceptors which explain that Hydantoin derivatives are probably more polar and hardly absorbed [41].

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity Hansch and Leo reasoned that highly lipophilic molecules will be distributed into the lipid interior of membranes and will be retained there [30]. For good oral bioavailability, the log P should be greater than 0.5 and less than5($0.5<\log P<5$). For logP too high, the drug has low solubility and a logP too low; the drug has difficulty to penetrate the lipid membranes [42].

Conversely to energy of Hydratation, the lipophilicity increases proportionally with the substituent's group. As seen in table I, compound 3 has high value of log P (-0.56), this compound generally has good intestinal absorption owing to a good balance between solubility and passive diffusion permeability. In fact, the metabolism is minimized because of the lower binding with metabolic enzymes. Compound 18 presents the low coefficient of division (-4.72).

This compound provides a good solubility but a low absorption and penetration in cellular membranes. Moreover; the studied series tend to be released highly by the kidney, due to their polarity. These compounds may have also, Para cellular permeation when their molecular weights lower than 500ua (Da)[26, 43-44].

IV.3.2. Quantitative Structure-Activity Relationships Studies

QSAR (Quantitative Structure Activity Relationships) have been applied for decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable mathematical and statistical model for prediction of the activities of new chemical entities. (QSAR) have helped the scientists in the development of mathematical relationships linking chemical structures and pharmacological activity in quantitative manner of series of compound.

The fundamental principle underlying the QSAR is that the difference in structural properties is responsible for the variations in biological activities of the compounds. In the classical QSAR studies, affinities of ligands to their binding sites, inhibition constants, rate constants, and other biological end points, with atomic, group or molecular properties such as lipophilicity, polarizability, electronic and steric properties (Hansch analysis) or with certain structural features (Free-Wilson analysis) have been correlated. QSAR certainly decreases the number of compounds to be synthesized by facilitating the selection of the most promising candidates.

In This seeks to provide a view of the different QSAR approaches employed within the current drug discovery process to construct predictive structure– activity relationships and also discusses the limitations that are fundamental to these approaches, as well as those that might be overcome with the improved strategies.Quantitative Structure Activity Relationships are often used in the ligand structure-based drug design. The QSAR relates potency or toxicity of a set of similar drugs with a variety of molecular descriptors. Many descriptors can be calculated rapidly using empirical formulas based on the structure and the connectivity of atoms in the molecule.

For example, descriptors such as the molecular weight and the number of H-bond acceptors are easy to determine. Some descriptors, such as logP and molecular polarizability can be approximated from atomic or group contributions.

Descriptors that relate to electronic structure, such as the HOMO and LUMO energies, must be obtained from quantum chemical calculation. Oftentimes, descriptors of different nature and origin are mixed together. For example, the reactivity of a molecule can be described both in terms of its HOMO energy (a quantum-mechanical descriptor) and the bulk of the substituent (constitutional descriptor).Since chemical structure was elucidated, the relationship between

chemical structure and biological activity has intrigued scientists. It has been recognized that the investigate of QSARs may provide useful tools for obtaining information regarding the effects of chemicals on man and the environment. Initially developed to assess the value of drugs, QSARs are now proposed as a method to assess general toxicity. QSARs are based on the assumption that the structure of a molecule (its geometric, steric and electronic properties) contains the features responsible for its biological activity.[44-45]For example,biological activity can be expressed quantitatively as in the concentration of a substance required to give a certain biological response.When the information encoded in the molecular structure is expressed by molecular descriptors in the form of numbers, one can form a quantitative structure-activity relationship between the two.By QSAR models, the biological activity of a new or untested chemical can be inferred from the molecular structure of similar compounds whose activities[45].

QSAR's most general mathematical form is:

Activity = f (physiochemical properties and/or structural properties)

It is therefore evident that the three key components required for the development of a QSAR model are:

•Some measure of the activity for a group of chemicals in a biological or environmental system

– Toxicological endpoint

•A description of the physicochemical properties and/or structure for this group of chemicals

– Molecular descriptors

•A form of statistical relationship to link activity and descriptors

In the second step of our study, Hydantoin derivatives were evaluated for their inhibitory activity. In order to determine the role of structural features, QSAR study was undertaken. A set of 18 derivatives of Hydantoins were used for multi-linear regression model generation.

The different physicochemical descriptors calculated in the first step of our study were used as independent variables and were correlated with the biological activity. Developing a QSAR model requires a diverse set of data, and thereby, a large number of descriptors have to be considered. Descriptors are numerical values that encode different structural features of the molecules.Selection of a set of appropriate descriptors from a large number of them requires a method, which is able to

discriminate between the parameters. Pearson's correlation matrix has been performed on all descriptors by using SPSS statistics19 Software. The analysis of the matrix revealed five descriptors for the development of MLR models. The values of descriptors used in MLR analysis are presented in (TableV. I).The correlation between the biological activities and descriptors expressed by the following relation:

$$pIC_{50} = 5.023 + 0.024\ S - 0.025\ V + 0.46\ RF + 0.147\ Pol - 0.080\ logP \quad \text{eq. (1)}$$

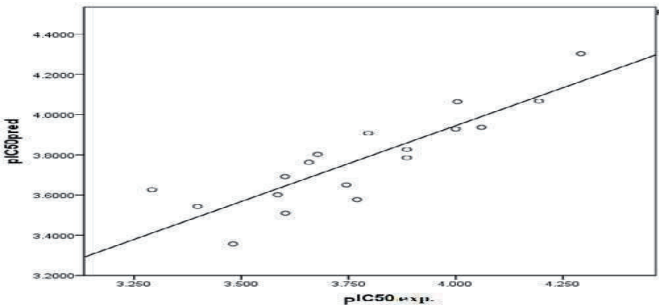
$$n = 18,\ r = 0.868,\ F = 7.351,\ SE = 0.159.$$

Where n is the number of compounds, r is the correlation coefficient, F is the Fischer statistics and SE is the standard error of estimation.These statistical parameters indicate that our QSAR model allowed us to determine firmly the correlation between independent variables with plasmin inhibition from r value and suggests its high predictive power from F value which found to be statistically significant at 95% level, since it is higher as compared to tabulated value.The negative coefficient of V and log P explain that any increase in the volume and Lipophilicity of the molecules cause a decrease in the biological activity. In other hand the increasing of the surface, refractivity and polarizability result increasing of the plasmin inhibitory.In order to test the validity of the predictive power of selected MLR model (Eq. 1), the leave-one out technique (LOO) was used. The developed model was validated by calculation of the following statistical parameters: predicted residual sum of squares (PRESS), total sum of squares deviation (SSY) and cross validated correlation coefficient (r^2_{adj} and r^2_{cv}) and are represented in table II. PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. Its value being less than SSY points out that model predicts better than chance and can be considered statically significant. The smaller PRESS value means the better of the model predictability. Also, the value $r^2_{adj} = 0.651$ and $r^2_{cv} = 0.754$ allowed us to indicate firmly the correlation between different parameters; independent variables and specific activity of Hydantoins.

Table IV . II. Cross-validation parameters

Model	PRESS	SSY	PRESS/SSY	S_{PRESS}	r^2_{cv}	r^2_{adj}
1	0.304	1.234	0.246	0.129	0.754	0.651

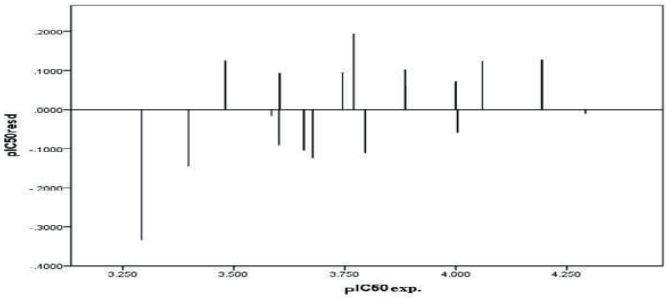
However, the only way to estimate the true predictive power of developed model is to predict the by calculation of values of the investigated Hydantoins activities as predicted pIC_{50} using the QSAR model (eq.1). Figure.2 shows the plot of linear regression predicted versus experimental values of the biological activity of Hydantoins outlined above. The plot show a good deal of correspondence with experimentally reported data having $R^2 = 0,754$.



FigV.2. Predicted plots versus experimental observed specific Plasmin activity of Hydantoins.

To investigate the presence of a systematic error in developing the QSAR models, the residuals of predicted values of the biological activity were plotted against the experimental values, as shown in figure 3.

The propagation of the residuals on both sides of zero indicates that no systemic error exists [46], which mean that this model can be successfully applied to predict the specific activity of plasmin inhibition by Hydantoins compounds.



FigV.3. Plots of the residual values against the experimentally observed.

IV.4 QSAR Theoretical and Multi-Parameter Optimization (MPO)

Allow these complex data that involve significant uncertainties levels be better used to quickly target the choice of compounds with a good balance of properties, but they all have their strengths and weaknesses. In research on the needs for an MPO method is ideal in drug discovery; there are factors that must be considered. The factors to be considered ideal for DFO Interpretability (interpretability): The criteria of the property and their impact on the priority of the compound should be easy to understand.

Flexibility (flexibility): Each project will have a series of ownership criteria as: therapeutic goals expected of the project, the route of administration, and the conditions of competition on the market. The project team must be able to define appropriate criteria based on their experience or historical evidence.

Weighting (weight):The project team should be able to assign different weights to each criterion of the property, as different criteria have different degrees of importance to the outcome of the project. Uncertainty (uncertainty): It is important to avoid rejection of potentially valuable compounds based on a property value that does not meet one criteria, this value has a high level of uncertainty.

Methods DFO

Rules of Thumb (Lipinski rules and Veber rules)

Calculated Metrics (Ligand Efficiency and Ligand lipophilicity Efficiency)

Pareto optimization(Desirability functions and Probabilistic scoring)

Rules of Thumb The most common approach used to study the quality of the compound compared with criteria for their power, these rules providing instructions regarding the characteristics of desirable compound (Lipinski, Veber, Lu, Johnson and other rules involving parameters such as proportion of SP3 carbon, the number of aromatic rings, etc.).Lu Propose the four basic characteristics that Lipinski has identified as being met by the majority of compounds taken orally according to a 2245 analysis of compounds based on World Drug Index data (WDI) .

Lipinski's ruleThe characteristics of Lipinski: are

1- **Molecular Weight (MW) <500uma(Da)**
2- **Logarithm of the octanol / water partition coefficient (log P) <5**
3- **Number of Hydrogen Bond Donors (HBD) <5**
4- **Number of Hydrogen Bond Acceptors (HBA) <10**

Molecular Weight (MW) Compounds which have molecular **weights <500 Da (u.m.a)** easily pass through cell membranes.

Note: The calculation of this parameter may be performed by several programs, such as:

HyperChem, ChemAxon, Sybyl-X, etc.

Logarithm of the octanol / water partition coefficient (log P)

The compounds which have log P <5 values are better solubilized in aqueous and lipid solutions.

Note: The calculation of this parameter is made by several software containing different

Approximations such as: HyperChem (Log P comes by Ghose, Pritchett and Crippen). Discovery Studio (Log P comes by Ghose and Crippen).

Number of Hydrogen Bond Donors (HBD) and Acceptors (HBA)

The decrease of the hydrogen bonds promotes the passage of the aqueous phase to the lipid bilayer membrane for penetration by passive diffusion.

Note: The calculation of these 2 parameters is performed as follows:

The number of HBD is the sum of the atoms N and O.

The number of HBA is the sum of OH and NH groups to make our result table n°IV. I in norm of Lipinski after the switching Lipinski rules of the standards are respected for (logP<5, HBA<10 and MW<500(u.m.a) for compounds(**1,5,9**).

After the rule of Lipinski candidates for the administration is orally and Compounds which have log P<5 values are better solubilizedin aqueous and lipid solutions, as shown in (TableIV.III).

TableIV. III: Lipinski rules of validation

Compounds	Log P<5	MW<5000Da(u.m.a)	HBD<5	HBA<10
1	/	/	x	/
2	/	X	x	/
3	/	X	x	/
4	/	X	x	/
5	/	/	x	/
6	/	X	x	/
7	/	X	x	/
8	/	X	x	/
9	/	/	x	/
10	/	X	x	/
11	/	X	x	/
12	/	X	x	/
13	/	X	x	/
14	/	X	x	/
15	/	X	x	/
16	/	X	x	/
17	/	X	x	/
18	/	X	x	/

(/) valid, (x) not valid

Our results show the rules of Lipinski candidates 1, 5 and 9 for the administration is orally and compounds wich have Log P<5 values are better solubilizedin aqueous and lipid solutions

V.5. Conclusion

From the present investigation it can be concluded that the model was found to be more efficient to predict the specific activity of our studied Hydantoin derivatives. In the present work, and by using this model, we have successfully determined quantitatively the necessary parameters needed to predict the studied activity.

MLR regression analysis was used to develop the models and to predict biological activity from derived molecular descriptors belonging to Hydantoin series.

The developed QSAR model shows that hydrophilic and polar derivatives of Hydantoin are a potential alternative to give a good plasmin inhibition activity.

It involves the mathematical and statistical analysis of data which helps to reduce the number of educated guesses in molecular modification QSAR is thus a scientific achievement and an economic necessity to reduce an empiricism in drug design to ensure that every drug synthezed and pharmacologically tested should be as meaningful.

through the rules of Lipinski shows candidate for the administration is orally and our Compounds with Number of Hydrogen Bond Acceptors the decrease of the hydrogen bonds promotes the passage of the aqueous phase to the lipid bilayer membrane for penetration by passive diffusion the calculation of these parameter HBA is performed as follow this is a proof better solubilizedin aqueous and lipid solutions.

The rules of Lipinski are respected for **1, 5, 9** compounds are consistent, suggesting that these compounds theoretically will not have problems with oral bioavailability.

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General Conclusion

The present study has confirmed previous conclusions that the aim of this work was qualitative, we are trying to clarify the characterization of Hydantoin, throw computational methods. Bond lengths and angles have been calculated by using HF/6-31(G+), 6-31G++(d,p) and 6-311G++(d,p) and DFT(B3LYP)/6-31(G+), 6-31G++(d,p) and 6-311G++(d,p) methods and compared with experimental values. All compared data have been shown to have a good agreement with each other. We have carried out ab initio and density functional theory calculation on the vibrational spectrum of Hydantoin.

The vibrational frequencies of infrared intensities with the stretching wave numbers calculated by DFT/B3LYP (6-311++G (d, p)) method agree satisfactorily with experimental results. On the basis of agreement between the calculated and experimental results, assignments of all the fundamental vibrational modes of Hydantoin were examined and proposed in this investigation.

This study demonstrates that scaled DFT/B3LYP calculations are powerful approach for understanding the vibrational spectra of medium sized organic compounds. In the substituted chloride group, 3-4 dichloroHydantoin is predicted to be the most reactive with least HOMO-LUMO energy gap of all methyl-Hydantoin derivatives.

The tri-chloro-hydantoin is predicted to be the most reactive with all chloro and methyl derivatives. The presence of acceptor in B9(3-4dichloro hydantoin) group position causes the decrease in energy gaps, which reflects a chemical stability and show the maximum dipole moment value in B2(2-Chloro hydantoin) derivatives.

Hydantoins constitute an important class of heterocyclic in medicinal chemistry because many derivatives thus can identify activities that offer interesting against a wide range of biological targets.

One of the aim of these work present in this study consisted in the development and evaluation of the quantitative structure activity relationships (QSAR) for the prediction of the Plasmin inhibition by Hydantoin derivatives, whereas Plasmin is a proteolytic enzyme that is formed from plasminogen in blood plasma and dissolves the fibrin in blood clots.

The compounds used are potent inhibitors of the Plasmin which could, explain its role in inhibiting tumor growth.Various physicochemical descriptors were used in multiple linear regressions method (MLR) to develop the theoretical models, than using a cross-validation with leave-one-out method to optimize the model as well as possible to fit with the biological data .From the present investigation it can be concluded that the model was found to be more efficient to predict the specific activity of our studied Hydantoin derivatives. In the present work, and by using this model, we have successfully determined quantitatively the necessary parameters needed to predict the studied activity. MLR regression analysis was used to develop the models and to predict biological activity from derived molecular descriptors belonging to Hydantoin series.

The developed QSAR model shows that hydrophilic and polar derivatives of Hydantoin are a potential alternative to give a good plasmin inhibition activity. QSARstudies were carried out on eighteen Hydantoin derivatives (Hydantoins).

The compounds usedare blood plasmain hibitors, which could at least partially explain their anticancer activity. (That studies can may decrease the suffering of the sick, who can use humanity).A procedure of multilinear regression (MLR), was used to develop the relationship between molecular descriptors and biological activities of Hydantoins.Our results suggesta QSAR model with the following descriptors: SAG, V, D, log Pand W for each IC50 biological activity.The predictive model was estimated by cross-validation method by leave-one-out. A strong correlation between the values of the predicted and experimental activity was observed, indicating the validation and quality of QSAR models derived with the rules of Lipinski are respected.

Conclusion and Future Directions, it was the aim of this thesis to perform computational investigations on Hydantoins; As to the further development of molecular modeling and computational chemistry, Optimization of the accuracy of methods and perspectives to solve the current problems.Hence, it is hoped that a large number of important new applications of docking and biopolymer are with our advances in future theory study, software and computational hardware, larger data sets and systems of increasing size should be amenable to study.

ANNEX I

THE MOLECULAR VIBRATIONS BY INFRARED

III.1.a Theory of infrared absorption spectrometry

IR radiation does not have enough energy to induce electronic transitions as seen with UV. Absorption of IR is restricted to compounds with small energy differences in the possible vibrational and rotational states. For a molecule to absorb IR, the vibrations or rotations within a molecule must cause a net change in the dipole moment of the molecule. The alternating electrical field of the radiation interacts with fluctuations in the dipole moment of the molecule. If the frequency of the radiation matches the vibrational frequency of the molecule then radiation will be absorbed, causing a change in the amplitude of molecular vibration.[1]

--Molecular rotations Rotational transitions are of little use to the spectroscopic. Rotational levels are quantized, and absorption of IR by gases yields line spectra. However, in liquids or solids, these lines broaden into a continuum due to molecular collisions and other interactions.

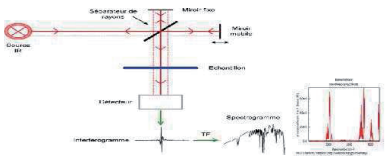


Figure -Schematic diagram of the analysis by infrared absorption spectroscopy.[7]

-Molecular vibrations The positions of atoms in a molecules are not fixed; they are subject to a number of different vibrations. The simple two-atomic oscillator illustrates well some of the fundamental principles that govern the relationship between the vibrational spectrum of a molecule and its structure and environment.

The frequency, n, of a two-atomic oscillator is given by $\nu = (k/m_t)^{0,5}/2\pi$, where k is the force constant between the two atoms, and m_r the reduced mass ($1/m_r = 1/m_1+1/m_2$).

The frequency rises when the force constant increases, that is when the electron density in the bond between the two atoms increases. Any inter- or intramolecular factor that alters the electron density in the bonds will affect the vibrational spectrum.

The second important influence on the frequency is the mass of vibrating atoms, the larger the mass, the slower the vibration. This effect is often used as a tool for the interpretation of spectra, when the sample is isotopically labelled in order to shift the frequency of vibrations that involve the labelled atoms.[8]

III.I.b Information that can be derived from the vibrational spectrum[45,46]

Chemical structure. The chemical structure of a molecule is the dominating effect that determines the vibrational frequencies via the strengths of the vibrating bonds and the masses of the vibrating atoms. This effect may seem to be of minor relevance to biophysicists since the chemical structure of a protein cannot be deduced from the vibrational spectrum and will often be inert in biophysical investigations.

-Stretching: Change in inter-atomic distance along bond axis

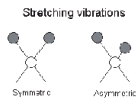
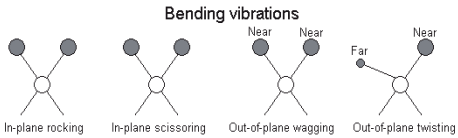


Figure III a Vibrations fall into the two main categories of stretching and bending.

-Bending: Change in angle between two bonds. There are four types of bend:



Rocking, Scissoring, Wagging, And Twisting

Figure (IIIb)

-Vibrational coupling

In addition to the vibrations mentioned above, interaction between vibrations can occur (coupling) if the vibrating bonds are joined to a single, central atom.

Vibrational coupling is influenced by a number of factors;

- Strong coupling of stretching vibrations occurs when there is a common atom between the two vibrating bonds

- Coupling of bending vibrations occurs when there is a common bond between vibrating groups
- Coupling between a stretching vibration and a bending vibration occurs if the stretching bond is one side of an angle varied by bending vibration
- Coupling is greatest when the coupled groups have approximately equal energies
- No coupling is seen between groups separated by two or more bonds

- Table IIIA The Infrared spectral regions are as follows:

Region	Wavelength Range, nm	Wavenumber Range, cm^{-1}	Frequency Range, Hz
Near	0.78-2.5	12800-4000	$3.8x10^{14}$-$1.2x10^{14}$
Middle	2.5-50	4000-200	$1.2x10^{14}$-$6.0x10^{12}$
Far	50-1000	200-10	$6.0x10^{12}$-$3.0x10^{11}$
Most used	2.5-15	4000-610	$1.2x10^{14}$-$2.0x10^{13}$

This energy is absorbed in the transitions caused by vibration, and rotation

Like in all spectrometry's, IR excites the analyze to be studied and gets a measurement of the changes. These changes can be related to the type of analyze being observed. The source of this excitation is of course infrared radiation. [1-2]

III.1.c Quantum Treatment of Vibrations

Transitions in vibrational energy levels can be brought about by absorption of radiation, provided the energy of the radiation exactly matches the difference in energy levels between the vibrational quantum states and provided also that the vibration causes a fluctuation in dipole. Infrared measurements permit the evaluation of the force constants for various types of chemical bonds.

INFRARED INSTRUMENT Three main types

1. Dispersive grating spectrophotometers, qualitative.
2. Multiplex instruments, like Fourier transform, for both quantitative and qualitative work.
3. No dispersive spectrophotometers, quantitative.

The infrared part of the electromagnetic spectrum is divided into three regions: the near, medium and far infrared, appointed in relation to the visible spectrum. The far infrared, from approximately 400-10 cm^{-1}, adjoining the microwave region, has low energy and can be used for rotational spectroscopy. The average infrared radiation, ranging approximately from 4000 to 400 cm^{-1} can be used to study the fundamental vibrations and associated Rovibrational structure. The near infrared, more energy, from approximately 14,000 to 4 000 cm^{-1} may excite the harmonic vibrations. The names and classifications of these sub regions are essentially conventions.They are not based on strict divisions or exact molecular or electromagnetic properties.Infrared spectroscopy exploits the fact that the molecules have specific frequencies at which they rotate or vibrate in correspondence with discrete energy levels (vibrational modes).

These resonant frequencies are determined by the shape of the potential energy surfaces, and the atomic masses by the associated vibronic coupling. To a mode vibrational in a molecule is active in the infrared, it must be associated with changes in the permanent dipole.

In particular, in the Born-Oppenheimer approximation and harmonic when the molecular Hamiltonian corresponding to the electronic ground state can be approximated by a harmonic oscillator in the vicinity of the molecular equilibrium geometry, the resonance frequencies are determined by the methods normal corresponding to the potential energy surface of the fundamental molecular electronic state.

Nevertheless, the resonance frequencies can be in a first approach related to the strength of the bond, and atomic masses of termination. Therefore, the frequency of vibration may be associated with a particular link. Diatomic molecules have only one link, which can be stretched.[2-3]The most complex molecules have many bonds, and vibration may be combined, leading to infrared absorptions at characteristic frequencies which can be linked to chemical groups.

The infrared spectrum of a sample is established by passing a beam of infrared light through the sample. Examination of the transmitted light indicates the amount of energy absorbed at each wavelength. This can be done with a monochromatic beam, with a change in wavelength over time, or by using a Fourier transform instrument to measure all wave measurements simultaneously. We can then produce absorbance spectra or transmittance and indicate the absorption wavelengths.

The analysis of these characteristics indicates details of the molecular structure of the sample. This technique works almost exclusively on the samples having covalent bonds. Simple spectra were obtained from samples with few active connections in the infrared and with high degrees of purity. The more complex molecular structures lead to more absorption bands and thus to more complex spectra. [3]

-Vibrational modes

1. A normal mode is a molecular vibration where some or all atoms vibrate together with the same frequency in a defined manner.
2. Normal modes are basic vibrations in terms of which any other vibration is derived by superposing suitable modes in the required proportion.
3. On the other hand, no normal mode is expressible in terms of any other normal mode. Each one is pure and has no component of any other normal mode (i.e. they are orthogonal to each other). Mathematically, the integralis

$$\int \psi A \psi B dR = 0 \qquad \text{(integration is done over the entire space)}$$

4. The required number of "normal modes" is equal to the vibrational degree of freedom available so the number of modes for a nonlinear molecule is $3N-6$ and that for a linear molecule is $3N-5$.
5. Each mode has a definite frequency of vibration. Sometimes 2 or 3 modes may have the same frequency but that does not change the fact that they are distinct modes; these modes are called degenerate.
6. Sometimes some modes are not IR active but they exist all the same.[4]

The number of vibrational normal modes can be determined for any molecule from the formula given above. For a diatomic linear molecule, N = 2 so the number of modes is $3\times2-5=1$. For a triatomic linear molecule (CO_2), it is $3\times3-5=4$

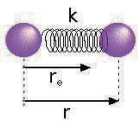
And triatomic nonlinear molecule (H_2O), it is $3\times3-6=3$

-Energetics [5,10]For studying the energetics of molecular vibration we take the simplest example, a diatomic heteronuclear molecule AB. Homonuclear molecules are not IR active so they are not a good example to select. Let the respective masses of atoms A and B is mA and mB. So the reduced mass μAB is given by:

μAB=mAmB/ (mA+mB*)* The equilibrium internuclear distance is denoted by req.

However as a result of molecular vibrations, the internuclear distance is continuously changing; let this distance be called r (t).

Let x (t) =r (t) −req.According to the following figure



When *x* is non-zero, a restoring force F exists which tries to bring the molecule back to *x*=0, that is equilibrium. For small displacements this force can be taken to be proportional to *x*. F=−kx where k is the force constant.

The negative sign arises from the fact that the force acts in the direction opposite to *x*.

This is indeed a case of Simple Harmonic Motion where the following well known relations.

$$x(t)=A\sin(2\pi vt) \qquad \text{where } v=12\pi k\mu AB$$

The potential energy is given by $V=12kx^2$.

The total energy E (Kinetic+Potential) is obtained by solving the Schrödinger equation:

$$-h^2 8\pi^2 \mu AB d^2\psi dx^2+12kx^2\psi=E\psi$$

A set of wave functions ψ_n) and the corresponding Eigenvalues E_n are obtained. $E_n=(n+(1/2))hv$ where n is an integer (-1,0,1,2 etc.). The energy is quantized, the levels are equally spaced, the lowest energy is (1/2) hv, and the spacing between adjacent levels is hv.[5,8]

-Interaction with Electromagnetic Radiation

As show above, the energy difference between adjacent vibrational energy levels is $h\nu_{vibration}$. On the other hand, the photon energy is $h\nu_{photon}$. Energy conservation requires that the first condition for photon absorption be,

$H\nu_{vibration} = h\nu_{photon}$ or $\nu_{vibration} = \nu_{photon}$.

Such photons are in IR region of the electromagnetic spectrum.

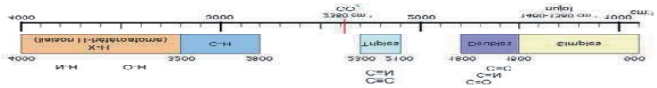
In addition, two more conditions must be met.

1. For absorption of electromagnetic radiation, the dipole moment of the molecule must change with increasing internuclear separation resulting from the vibration (i.e, $d\mu/dD \neq 0$).
2. The probability of a transition from one state to another is large if one of the state is add and another even.

This is possible if $n_{final} - n_{initial} = +1$ (for absorption).

At room temperature, modes are predominantly in energy state n = 0, so this transition is from n = 0 to n = 1, and $\Delta E = h\nu$.[5,6]

III.2 Applications



Spectroscopy in the IR region can determine the frequency and intensity of absorption. These frequencies are generally specific for specific bonds such as c-c, c (double bond) c, c (triple bond) c, c-o, c (double bond) o, etc. So the IR absorption data is very useful in structure determination. The intensity depends on the concentration of the responsible spectrum So it is useful for quantitative estimation and for identification.[6,7]

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ANNEX II

QSAR Theoretical and Multi-Parameter Optimization (MPO)

ANNEXII :QSAR Theoretical and Multi-Parameter Optimization (MPO)

II.1 Introduction of Q.S.A.R

It has been nearly 40 years since the quantitative structure-activity relationship (QSAR) paradigm first found its way into the practice of agrochemistry, pharmaceutical chemistry, toxicology, and eventually most facets of chemistry[1]. Crum-Brown and Fraser[2] (1868) expressed the idea that the physiological action of a substance in a certain biological system (Φ) was a function (f) of its chemical composition and constitution (C).

$\Phi = f\,C$ Equation [1]

Thus, an alteration in chemical constitution, ΔC, would be reflected by an alteration in biological activity ΔΦ. Richardson[3] (1868) expressed the chemical structure as a function of solubility. Mills[4] (1884) developed a QSPR model for the prediction of melting and boiling points in homologous series, results were accurate to better than one degree. Richet[5] (1893) Correlated toxicities of a set of alcohols, ethers and ketones with aqueous solubility and showed that their cytotoxicities are inversely related to their corresponding water solubilities.

Overton and Meyer[6,7] (1897, 1899) correlated partition coefficients of a group of organic compounds with their anesthetic potencies and concluded that narcotic (depressant) activity is dependent on the lipophilicity of the molecules. The seminal work of Hammett[8,9] (1935, 1937) gave rise to the σρ culture correlated the effect of the addition of a substituent on benzoic acid with the dissociation constant, postulated electronic sigma-rho constants and established the linear free energy relationship (LFER) principle. Hammett found that a linear relationship resulted when substitutions of different groups were made to aromatic compounds. $\log K = \rho \log K' = \rho\,\sigma\, K_0 K_{0'}$

K_0 and $K_{0'}$ are equilibrium constants for unsubstituted compounds and K and K' are the equilibrium constants for substituted compounds. Hammett used benzoic acid as reference compound yielding the σ.

To interpret this equation, if the linear relation defines $\rho > 1$, then the effect of the substitutions is greater than making the same substitutions on benzoic acid.

The σ describes the properties of the substitution groups. If σ is positive, the group is electron withdrawing. If σ is negative, the group is electron donating.

The magnitude of σ indicates the degree of these effects. In 1939, Ferguson[10] correlated depressant action with the relative saturation of volatile compounds in their vehicle and introduced a thermodynamic generalization to the toxicity. Bell and Roblin[11] (1942) Studied antibacterial activities of a series of sulfanilamides in terms of their ionizations. Albert[12] (1948) examined the effects of ionization/electron distribution and steric access on the potencies of a multitude of aminoacridines.

Taft[13] (1952) Postulated a method for separating polar, steric, and resonance effects and introduced the first steric parameter, ES. Hansch and Muir[14] (1962) Correlated thebiological activities of plant growth regulators with Hammett constants and hydrophobicity.

Using the octanol/water system,a whole series of partition coefficients were measured, and thus a new hydrophobic scale was introduced. The parameter π, which is the relative hydrophobicity of a substituent, was defined in a manner analogous to the definition of sigma[15]. $\Pi X = \log PX - \log PH$ Equation [2]

PX and PH represent the partition coefficients of a derivative and the parent molecule, respectively. The contributions of Hammett and Taft together laid the basis for the development of the QSAR paradigm by Hansch and Fujita[16] (1964), which combined the hydrophobic constants with Hammett's electronic constants to yield the linear Hansch equation and its many extended forms. $\text{Log } 1/C = a\sigma + b\pi + ck$

There is a consensus among current predictive toxicologists that Corwin Hansch is the founder of modern QSAR. In the classic article[17] it was illustrated that, in general, biological activity for a group of 'congeneric' chemicals can be described by a comprehensive model:

$\text{Log}1/C50 = a\pi + b\varepsilon + cS + d$ Equation [3]

In which C, the toxicant concentration at which an endpoint is manifested (e.g. 50% mortality or effect), is related to a hydrophobicity term, p,

(this is a substituent constant denoting the difference in hydrophobicity between a parent compound and a substituted analog, it has been replaced with the more general molecular term the log of the 1-octanol/water partition coefficient, log Kow), an electronic term, 1, (originally the Hammett substituent constant, s) and a steric term, S, (typically Taft's substituent constant, ES).

Due to the curvilinear, or bilinear, relationship between log1/C50 and hydrophobicity normally found in single dose tests the quadratic π^2 term was later introduced to the model. Hansch[18] (1969) Developed the parabolic Hansch equation for dealing with extended hydrophobicity ranges. $\text{Log } 1/C = -a(\log P)^2 + b.\log P + c\sigma + k$

Free and Wilson[19] (1964) formulated an additive model, where the activity is discretized as a simple sum of contributions from different substituents.

$BA = ai\ xi + u$ BA is the biological activity, u is the average contribution of the parent molecule, and ai is the contribution of each structural feature; xi denotes the presence Xi = 1 or absence Xi = 0 of a particular structural fragment. Fujita and Ban[20] (1971) simplified the Free-Wilson equation estimating the activity for the non-substituted

compound of the series and postulatedFujita-Ban equation that used the logarithm of activity, which brought the activity parameter in line with other free energy-related terms. Log BA = Gi Xi + u in this equation, u is defined as the calculated biological activity value of the unsubstituted parent compound of a particular series.

Gi represents the biological activity contribution of the substituents, whereas Xi is ascribed with a value of one when the substituent is present or zero when it is absent. Kubinyi[21] (1976) Investigated the transport of drugs via aqueous and lipoidal compartment systems and further refined the parabolic equation of Hansch to develop a superior bilinear (non-linear) QSAR model.

Log 1/C = a. log P- b.log (β. P + 1) + k

Hansch and Gao[22] (1997) Developed comparative QSAR (C-QSAR), incorporated in the CQSAR program.

Heritage and Lowis[23,24](1997) Developed Hologram QSAR (HQSAR), where the structures are converted into all possible fragments, which are assigned specific integers, and then hashed into a fingerprint to form the molecular hologram. The bin occupancies of these holograms are used as the QSAR descriptors, encoding the chemical and topological information of molecules. Cho and workers[25] (1998) Developed Inverse QSAR, which seeks to find values for the molecular descriptors that possess a desired activity/property value. In other words, it consists of finding the optimum sets of descriptor values best matching a target activity and then generating a focused library of candidate structures from the solution set of descriptor values.

Labute[26] (1999) Developed Binary QSAR to handle binary activity measurements from high throughput screening (e.g., pass/fail or active/inactive), and molecular descriptor vectors as input. A probability distribution for actives and in actives is then determined based on Bayes' Theorem.

II.2 QSAR Theory

The overall goals of QSAR retain their original essence and remain focused on the predictive ability of the approach and its receptiveness to mechanistic interpretation. Rigorous analysis and fine-tuning of independent variables has led to an expansion in development of molecular and atom-based descriptors, as well as descriptors derived from quantum chemical calculations and spectroscopy[27].

It is now possible not only to develop a model for a system but also to compare models from a biological database and to draw analogies with models from a physical organic database[28]. This process is dubbed model mining and it provides a sophisticated approach to the study of chemical-biological interactions. All QSAR analyses are based on the

assumption of linear additive contributions of the different structural properties or features of a compound to its biological activity, provided that there are no nonlinear dependences of transport or binding on certain physicochemical properties. This simple assumption is proven by some dedicated investigations, for example the scoring function of the de novo drug design program LUDI (eqn.1)[29,30,31] ; in addition, the results of many Free Wilson and Hansch analyses support this concept.

$$\Delta Gbinding = \Delta G_0 + \Delta G_{hb} + \Delta G_{ionic} + \Delta G_{lipo} + \Delta G_{rot} \quad (1)$$

Overall loss of translational and rotational entropy, $\Delta G_{binding}$ = + 5.4KJ mol-1 Ideal neutral hydrogen bond, ΔGhb= -4.7 KJ mol^{-1} Ideal ionic interaction, ΔG_{ionic} = -8.3 KJ mol^{-1} Lipophilic contact, ΔGlipo = -0.17 J mol-1 $Å^{-2}$ Entropy loss per rotatable bond of the ligand, ΔG_{rot} = +1.4 KJ mol^{-1} Eqn.1 correlates the free energy of binding, $\Delta G_{binding}$, with a constant term, ΔG_0, that describes the loss of overall translational and rotational degrees of freedom and ΔG_{hb}, $\Delta G_{ionic}$and ΔG_{lipo}, which are structure-derived energy terms for neutral and charged hydrogen bond interactions and hydrophobic interactions between the ligand and the protein; ΔG_{rot} describes the loss of internal rotational degrees of freedom of the ligand. Eqn1 1 holds for a wide range of energy values: the $\Delta G_{binding}$ of 45 different ligand-protein complexes ranges from -9 to -76 KJ mol^{-1}, which corresponds to binding constants between 2.5 × 10 -2 M and 4 × 10-14 M; its standard deviation of 7.9 KJ mol-1 corresponds to a mean error of about 1.4 log units in the prediction of ligand binding constants from the mathematical model[29,30,31].

Because of the extra thermodynamic relationship between free energies ΔG and equilibrium constants K (eqn.2) or rate constants k (k_{on} = association constant, k_{off} = dissociation constant of ligand-receptor complex formation), the logarithms of such values can be correlated with binding affinities.

$$\Delta G = -2.303\ RT \log K = -2.303\ RT \log k_{on} / k_{off} \quad (2)$$

Logarithms of molar concentrations C that produce a certain biological effect can be correlated with molecular features or with physiological properties that are also free-energy-related equilibrium constants; normally the logarithms of inverse concentrations, log1/C, are used to obtain larger values for the more active analogs.

Development of Receptor Theory The idea that drugs interacted with specific receptors began with Langley, who studied the mutually antagonistic action of the alkaloids, pilocarpine and atropine. He realized that both these chemicals interacted with some receptive substance in the nerve endings of the gland cells[32]. Paul Ehrlich defined the receptor as the binding group of the protoplasmic molecule to which a foreign newly introduced group binds[33]. In 1905 Langley's studies on the effects of curare on muscular

contraction led to the first delineation of critical characteristics of a receptor: recognition capacity for certain ligands and an amplification component that results in a pharmacological response[34]. Receptors are mostly integral proteins embedded in the phospholipid bilayer of cell membranes. Rigorous treatment with detergents is needed to dissociate the proteins from the membrane, which often results in loss of integrity and activity. Pure proteins such as enzymes also act as drug receptors.

Their relative ease of isolation and amplification have made enzymes desirable targets in structure based ligand design and QSAR studies. Nucleic acids comprise an important category of drug receptors. Nucleic acid receptors (aptamers), which interact with a diverse number of small organic molecules, have been isolated by in vitro selection techniques and studied[35].

Recent binary complexes provide insight into the molecular recognition process in these biopolymers and also establish the importance of the architecture of tertiary motifs in nucleic acid folding[36]. Groove-binding ligands such as lexitropsins hold promise as potential drugs and are thus suitable subjects for focused QSAR studies[37]. It is now possible to isolate membrane bound receptors, although it is still a challenge to delineate their chemistry, given that separation from the membrane usually ensures loss of reactivity. Nevertheless, great advances have been made in this arena, and the three-dimensional structures of some membrane- bound proteins have recently been elucidated. To gain an appreciation for mechanisms of ligand-receptor interactions, it is necessary to consider the intermolecular forces at play.

Considering the low concentration of drugs and receptors in the human body, the law of mass action cannot account for the ability of a minute amount of a drug to elicit a pronounced pharmacological effect. The driving force for such an interaction may be attributed to the low energy state of the drug receptor complex:

KD = [Drug] [Receptor] / [Drug Receptor Complex].

Thus, the biological activity of a drug is determined by its affinity for the receptor, which is measured by its KD, the dissociation constant at equilibrium. A smaller KD implies a large concentration of the drug-receptor complex and thus a greater affinity of the drug for the receptor. The latter property is promoted and stabilized by mostly non-covalent interactions sometimes augmented by a few covalent bonds.

The spontaneous formation of a bond between atoms results in a decrease in free energy; that is, ΔG is negative. The change in free energy ΔG is related to the equilibrium constant

Keq. $\Delta G^\circ = -RT \ln Keq$ Thus, small changes in ΔG_0 can have a profound effect on equilibrium constants.

Types of Intermolecular Forces Bond that formed between drug-receptor interactions include covalent, ionic, hydrogen, dipole-dipole, Vander Waals, and hydrophobic interactions. Most drug-receptor interactions constitute a combination of the most of these bonds which are reversible under physiological conditions.

Covalent bonds are not as important in drug-receptor binding as non-covalent interactions. Alkylating agents in chemotherapy tend to react and form an Ammonium ion, which then alkylates proteins, preventing their normal participation in cell divisions. Baker's concept of active site directed irreversible inhibitors was well established by covalent formation of Baker's antifolate and dihydrofolate reductase[38].

Ionic (electrostatic) interactions are formed between ions of opposite charge with energies that are nominal and that tend to fall off with distance. They are ubiquitous and because they act across long distances, they play a prominent role in the actions of ionizable drugs. The strength of an electrostatic force is directly dependent on the charge of each ion and inversely dependent on the dielectric constant of the solvent and the distance between the charges. Electrostatic interactions are generally restricted to polar molecules. Hydrogen bonds are ubiquitous in nature.

Their multiple presences contribute to the stability of the α-helix and base-pairing in DNA. Hydrogen bonding is based on an electrostatic interaction between the non-bonding electrons of a heteroatom (e.g., N, O, S) and the electron- deficient hydrogen atom of an -OH, SH, or NH group.

Hydrogen bonds are strongly directional, highly dependent on the net degree of salvation, and rather weak, having energies ranging from 1 to 10 kcal/mol[39,40]. Bonds with this type of strength are of critical importance because they are stable enough to provide significant binding energy but weak enough to allow for quick dissociation. The energy of dipole-dipole interactions can be described by Equation, $E = 2\mu 1\mu 2\cos\theta_1 \cos\theta_2/Dr_3$

where μ is the dipole moment, θ is the angle between the two poles of the dipole, D is the dielectric constant of the medium and r is the distance between the charges involved in the dipole. There are also strong interactions between non-polar molecules over small intermolecular distances. Dispersion or London/van der Waals forces are the universal

attractive forces between atoms that hold non-polar molecules together in the liquid phase.

They are based on polarizability and these fluctuating dipoles or shifts in electron clouds of the atoms tend to induce opposite dipoles in adjacent molecules, resulting in a net overall attraction. The energy of this interaction decreases very rapidly in proportion to $1/r_6$, where r is the distance separating the two molecules.

These Vander Waals forces operate at a distance of about 0.4-0.6 nm and exert an attraction force of less than 0.5 kcal/mol.

Hydrophobicity refers to the tendency of non-polar compounds to transfer from an aqueous phase to an organic phase[41,42]. When a non-polar molecule is placed in water, it gets solvated by a sweater of water molecules ordered in a ice-like manner. This increased order in the water molecules surrounding the solute results in a loss of entropy. Association of hydrocarbon molecules leads to a squeezing out of the structured water molecules. The displaced water becomes bulk water, less ordered, resulting in a gain in entropy, which provides the driving force referred to as a hydrophobic bond.

II.2.1 Objectives of QSAR

Mostly all the QSAR methods focus on the following goals:

1. Quantitative relationship between the structure and physiochemical properties of substances and their biological activity are being used as the foundation stone in search of new medicines. The mathematical and statistical analysis helps us to predict the drug activity.

2. QSAR makes it easy now to reach the conclusion for any of the congener that still not in process, in way that whether it will optimal and profitable or not.

3. To quantitatively correlate and recapitulate the relationships between trends in chemical structure alterations and respective changes in biological endpoint for comprehending which chemical properties are most likely determinants for their biological activities.

4. To optimize the existing leads so as to improve their biological activities.

5. To predict the biological activities of untested and sometimes yet unavailable compounds.

V.2.2 Techniques and tools of QSAR

1. Compound Selection: In setting up to run a QSAR analysis, compound selection is an important angle that needs to be addressed. One of the earliest manual methods was an approach devised by Craig, which involves two-dimensional plots of important physicochemical properties. Care is taken to select substituent's from all four quadrants of the plot[43]. The Topless operational scheme allows one to start with two compounds and

construct a potency tree that grows branches as the substituent set is expanded in a stepwise fashion[44]. Topless later proposed a batch wise scheme including certain substituents such as the 3,4-Cl_2, 4-Cl, 4-CH_3, 4-OCH_3, and 4-H analogs[45].

2. Biological Parameters: In QSAR analysis, it is vital important that the biological data be both accurate and precise to develop a meaningful model.

The equilibrium constants and rate constants that are used extensively in physical organic chemistry and medicinal chemistry are related to free energy values ΔG. Thus for use in QSAR, standard biological equilibrium constants such as Ki or Km should be used in QSAR studies. Percentage activities (e.g.,% inhibition of growth at certain concentrations) are not appropriate biological endpoints because of the nonlinear characteristic of dose-response relationships. These types of end points may be transformed to equieffective molar doses. Only equilibrium and rate constants pass muster in terms of the free-energy relationships or influence on QSAR studies. Biological data are usually expressed on a logarithmic scale because of the linear relationship between response and log dose in the midregion of the log dose-response curve. Inverse logarithms for activity (log 1/C) are used so that higher values are obtained for more effective analogs.

Various types of biological data have been used in QSAR analysis.

II.2.3 Statistical Methods: Linear Regression Analysis the most widely used mathematical technique in QSAR analysis is multiple regressions (MRA). Regression analysis is a powerful means for establishing a correlation between independent variables and a dependent variable such as biological activity[46].

$Yi = b + a Xi + Ei$ certain assumptions are made with regard to this procedure[47]:

1. The independent variables, which in this case usually include the physicochemical parameters, are measured without error. Unfortunately, this is not always the case, although the error in these variables is small compared to that in the dependent variable.
2. For any given value of X, the Y values are independent and follow a normal distribution. The error term Ei possesses a normal distribution with a mean of zero.
3. The expected mean value for the variable Y, for all values of X, lies on a straight line.
4. The variance around the regression line is constant. The best straight line for model $Yi = b + a Zi + E$ is drawn through the data points, such that the sum of the squares of the vertical distances from the points to the line is minimized. Y represents the value of the observed data point and Ycalc is the predicted value on the line.

The sum of squares $SS = (Yobs - Ycalc)^2$.

ANNEXII :QSAR Theoretical and Multi-Parameter Optimization (MPO)

Parameters used in QSAR

A.Hydrophobicity Parameters: More than a hundred years ago, Meyer and Overton made their discovery on the correlation between oil/water partition coefficients and the narcotic potencies of small organic molecules[48,49]. 1.1

B.Estimation of hydrophobicity:-

Hansch established a model to measure the Lipophilicity in term of partition coefficient. Drug travels to the site of action that means solubility in 1- Octanol that simulate the lipid membrane then it goes to via cytoplasm that is simulated by Aqueous buffer "water" Hansch proposed the Lipophilicity measurement in term of partition coefficient "P"

P = [C] Octanol / [C]water It is called "Distribution coefficient".

With help of the partition coefficient we can determined the hydrophobic (π) like the difference caused in the partition coefficient of substituted and unsubstantiated compounds is relevant to the attached new susbtituent in it Formula is

$\pi = \log Px - \log PH$

Px denotes for substituted compound by "x", PH denotes unsubstituted "x = H"

Eg. - Consider the log P values for benzene (logP = 2.13), chlorobenzene (logP = 2.84), and Benzamide (logP = 0.64), since benzene is the parent compound, the substituents constants for Cl and CONH2 are 0.71 and -1.49 respectively. Having obtained these values, it is now possible to calculate the theoretical log P value for media Chlorobenzamide. Π values of aromatic substituent

c. Partition coefficient: - It is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium.

P = Concentration of drug in organic phase Concentration of drug in aqueous phase

Hydrophobic compounds will have a high P value, whereas hydrophilic compounds will have a low P value. The hydrophobic character of a drug can be measured experimentally by testing the drug's relative distribution coefficient. Octanol is a suitable solvent for the measurement of partition coefficients for many reasons[50,51].

It is cheap, relatively nontoxic, and chemically unreactive. The hydroxyl group has both hydrogen bond acceptor and hydrogen bond donor features capable of interacting with a large variety of polar groups. Despite its hydrophobic attributes, it is able to dissolve many more organic compounds than can alkanes, cycloalkanes, or aromatic hydrocarbons. It is UV Transparent over a large range and has a vapor pressure low enough to allow for reproducible measurements. Varying substituents on the lead compound will produce a series of analogues having different hydrophobicities and therefore different P values. Various substituents make to hydrophobicity. This contribution is known as the

substituent hydrophobicity constant. These π values are characteristic for the substituents and can be used to calculate how the partition coefficient of a drug would be affected by adding these substituents. QSAR would allow us to predict the most promising and satisfying structures (closest to the optimum value log Po).

The substituent hydrophobicity constant is a measure of how hydrophobic a substituent is, relative to hydrogen. A positive value of π indicates that the substituent is more hydrophobic then hydrogen. A negative value indicates that the substituent is less hydrophobic. By plotting these P value against the biological activity of these drugs. It is possible to see if there is any relationship between the two properties.

The biological activity is normally expressed as 1/C so a graph is drawn by plotting log1/C versus log P values to correlate the activity and partition coefficient or hydrophobicity. In studies where the range of the log P values are ranges between 1 to 4 and a straight-line graph is obtained i.e. there is an existence of relation between hydrophobicity and biological activity. As per the equation is log (1/C) = K1 log P + K2.

II.3 Conclusion

(i) Serum albumin binding increases as log P increases that mean hydrophobic drugs bind more strongly to serum albumin than hydrophilic drug.

(ii) It helps us to know how strongly a drug binds to serum albumin that can be important in estimating effective dose levels for that drug and drugs of similar structure and predict Some time log P Values increases over the given ranges results in decreased activity But drugs which are independent of cell target action like Eg.- General Anaesthetics.

These are related to the log P factor alone to operate in cell membrane only no receptor interaction. These functions by entering the central nervous system (CNS) and'dissolving' into cell membranes where they affect membrane structure and nerve function.

(i) Anaesthetic activity increases with increasing hydrophobicity.

(ii) They depend upon lipophilicity only.

(iii) There is an optimum value for log P (log P_0), beyond which increasing hydrophobicity causes a decrease in anaesthetic activity.

Finally, hydrophobic drugs are often more susceptible to metabolism and subsequent elimination. Lipophilicity has a relationship with concentration and indirectly with biological activity.

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ملخص

في هذا العمل الاساسي، والبحث الأصلي علي حلقة غيرمتجانسة لجزيء ا لهيدانتوين، لهدف التنبؤ بالتفاعل والنشاط البيولوجي للمركب المدروس.

تم حساب الوسا نط البنيوية الهيكلية، الإلكترونية وترددات الذبذبات الاهتزازية للهيدانتوين بطرق PM3 ,ab initio / HF و DFT / B3LYP كما ان المعايير الهندسية الأمثل هي في اتفاق جيد مع القيم التجريبية كذلك المقارنة بين الترددات الاهتزازية التي تنتجها طريقة ((DFT/ B3LYP (6-311++G (d, p)) في اتفاق جيد مع المعطيات التجريبية .طبيعة المستبدل تؤثر على الوسا نط الإلكترونية والطاقوية لنواة الهيدانتوين الأساسية .فإن هذه الدراسة تتيح لنا في الواقع التنبؤا بالفاعلية الكيميانية للمشتقات الهيدانتوين.

كما تم في هذا العمل، إجراء الدراسة النوعية والكمية لكل علاقة بين البنية والخصائص / الأنشطة أ يضا لمجموعة متنوعة من المشتقات النشطة بيولوجيا من الهيدانتوين.

Abstract

In this work a fundamental and original research was made on the molecule of Hydantoin heterocyclic, the aim is to predict the reactivity and biological activity studied of the compound.

The structural parameters, electronics and vibrational frequencies of Hydantoin at the ground state have been calculated by using, PM3, ab initio/HF and DFT/B3LYP methods. The optimized geometrical parameters are in good agreement with experimental values. Comparison of the obtained fundamental vibrational frequencies of Hydantoin result by DFT/B3LYP (6-311G++ (d, p)) method, are in a close agreement with the experimental data. The nature of substituent affects the electronic and energy parameters of basic core of Hydantoin. Also indeed, this qualitative and quantitative study allows us to predict the chemical reactivity of derivatives of Hydantoin.

Résumé

Dans ce travail, une recherche fondamentale et originale à été faite sur une molécule Hétérocyclique de l'Hydantoin, dans le but est de prédire la réactivité et de l'activité biologique du composé étudié.

Les paramètres structuraux, électroniques et les fréquences de vibration de l' Hydantoin ont été calculés par les méthodes: PM3, ab initio / HF et DFT/B3LYP.

Les paramètres géométriques optimisés sont en bon accord avec les valeurs expérimentales. La comparaison des fréquences de vibration obtenus par la méthode DFT/B3LYP (6-311++G (d, p) sont en bon accord avec les données expérimentales. La nature de substituant influe sur les paramètres électroniques et énergétiques de noyau de base Hydantoin. En effet, cette étude nous permet de prédire la réactivité chimique des dérivés de l'Hydantoin. Également dans ce travail, une étude qualitative et quantitative de la relation structure-propriétés/activités a été effectuée pour une série bioactive de dérivés de l' Hydantoin.