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Design of Novel Dopamine Prodrugs - A Computational Approach

Esraa Tayseer Mohammad Qaattoush

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Prepared By

Esraa Tayseer Mohammad Qaattoush

B. Sc., Pharmacy, Al-Quds University, Palestine

Supervisor

Prof. Dr. Rafik Karaman

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Design of Novel Dopamine Prodrugs – A computational Approach

Prepared by: Esraa Tayseer Mohammad Qattoush

Registration No.: 21213197

Supervisor: Prof. Dr. Rafik Karaman

Master thesis Submitted and Accepted, Date: ……..

The names and signatures of the examining committee members are as follows:

1- Head of Committee: Prof. Dr. Rafik Karaman — Signature:……

2- Internal Examiner: Dr. Hatem Hejaz — Signature:……

3- External Examiner: Dr. Naser Shraim — Signature:……

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Dedication

This thesis is dedicated to my parents who sacrificed a lot for me to be what I am now. I am very grateful for their love, support and prayers, to my dear husband who stood solid to help and support me and to my lovely kids.

Esraa Qattoush

Declaration

I certify that the thesis submitted for the degree of master is the result of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same) has not be submitted for a higher degree to any other university or institution.

Signed: ……..

Esraa Tayseer Mohammad Qattoush

Date: 26/8/2017

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First and foremost, I am deeply thankful to Almighty Allah from whom I always receive help and protection.

I would like to express my special appreciation and thanks to my supervisor Professor Dr. Rafik Karaman, I would like to thank you for encouraging my research and for allowing me to grow as a researcher.

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Abstract

Parkinson patients have insufficient dopamine in specific regions of the brain, so attempts have been made to replenish the deficiency in the dopamine. Dopamine itself doesn't cross blood brain barrier, but its precursor, levodopa (LD) is actively transported into the CNS and is converted to dopamine in the brain. The bioavailability of LD is less than 10% with only 1% of administered oral levodopa penetrates the brain. Large doses of levodopa are required because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension. To minimize the conversion to dopamine (DA) outside the central nervous system (CNS), LD is usually co-administered with peripheral inhibitors of amino acid decarboxylase (carbidopa or benserazide). In spite of that, other central nervous side effects such as dyskinesia, on-off phenomenon and end-of-dose deterioration still remain.

In this project, a number of dopamine prodrugs were designed using DFT molecular orbital at B3LYP 6-31G (d, p) levels and molecular mechanics (MM2) calculations aiming to provide prodrugs that are expected to give better bioavailability than the parental drug owing to improved absorption. Furthermore, the proposed prodrugs are believed to be more effective than L-dopa because the latter undergoes decarboxylation in the periphery before reaching the blood–brain barrier.

The DFT calculation results revealed that the rate of a proton transfer in processes dopamine **ProD 1**-**ProD 5** is largely dependent on the geometric variations of the reactant (GM) mainly the distance between the two reactive centers, r_{GM}, and the angle of attack α. It was found that systems with low r_{GM} and high α values in their global minimum structures, such as **ProD 1** and **ProD 2**, exhibit much higher rates (lower $\Delta G^{\ddagger}$) than these with high r_{GM} and low α values, such as **ProD 3**-**ProD 5** and the rate of the reaction is linearly correlated with r_{GM} and $(1/\alpha)$.

Moreover, it was found that the intraconversion rate of the designed dopamine prodrugs is largely determined on the strain energies of the reaction's tetrahedral intermediates

(Es_{INT}). Systems having strained tetrahedral intermediates were found to be with low rates and vice versa.

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List of Abbreviations

Abbreviations	Definition
Å	Angstrom
BBB	Blood Brain Barrier
CDS	Chemical drug delivery system
CNS	Central Nervous System
DA	Dopamine
Da	Dalton
DDC	Dopa Decarboxylase
DFT	Density Functional Theory
DOPH	2-Amino-*N*-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide
GLUT-1	Glucose transporter
GP	Gas Phase
GM	Global Minimum
GSH	Glutathione
H	Enthalpy
HF	Hartree-Fock
HLB	Hydrophilic Lipophilic Balance
H-Bond	Hydrogen Bond
H_2O	Water
IV	Intravenous
L	Leucine
LD	Levodopa
MM	Molecular Mechanics
MO	Molecular Orbital
P	Product
PCM	Polarizable Continuum Model
PD	Parkinson's Disease
PDDP	*N*-3,4-bis(pivaloyloxy)-dopamine-3-(dimethylamino)propanamide
ProD	Prodrug

pH	Potential of Hydrogen
QM	Quantum Mechanics
r_{GM}	Distance in the Global Minimum
S	Entropy
$t_{1/2}$	Half Life
TS	Transition State
UV	Ultaviolet
α	Angel of Attack
$\Delta G^{\ddagger}$	Activation Energy
$\Delta H^{\ddagger}$	Enthalpy activation energy
$T\Delta S^{\ddagger}$	Entropy activation energy

Chapter one

Introduction

1. Introduction

1.1 Prodrug Approach

1.1.1 Prodrug Concept

Many therapeutic drugs possess adverse properties that may become pharmacological, pharmaceutical or pharmacokinetics barriers in the clinical drug application [1]. There are many approaches to eliminate or reduce the undesirable drug properties while retaining the desirable therapeutic action, but the prodrug approach offers possibly the highest flexibility and has been demonstrated as an important means of improving drug efficiency [2].

The term prodrug was first introduced in 1958 by Albert [3]. A prodrug is a pharmacologically inactive chemical derivative of a drug molecule that converted to its active form by enzymatic and/or chemical transformation within the mammalian system [4]. Prodrug design may be useful in solving many problems associated with solubility, absorption, site specificity, instability, prolonged release, toxicity, poor patient acceptability (unpleasant taste or odor, produce gastric irritation or pain, etc) and formulation problems [5-8].

Prodrugs can be categorized according to two major criteria, chemical classes (carrier-linked prodrugs, bioprecursors, sit-specific chemical delivery systems, etc.) and mechanism of activation (enzymatic versus nonenzymatic, activation by oxidation, reduction or hydrolysis, catabolic versus anabolic reaction) [9].

1.1.2 Prodrug Applications

1.1.2.1 Improving Solubility of Drugs

Prodrugs can be used to increase the aqueous solubility of the parent drug molecule by attaching ionizable or polar neutral groups, such as phosphates, amino acids, or sugar moieties [8, 10-11]. Enzymes such as phosphatases, esterases, glucosidase, amidases or peptidases in plasma or other tissues can then breakdown the molecules into its active

form. Fosphenytoin is a good example of a prodrug which by the addition of a phosphate group has enhanced the aqueous solubility of phenytoin by a factor of 7,000 fold [13].

1.1.2.2 Increasing Permeability & Absorption of Drugs

Prodrug can be utilized to promote membrane permeation and either oral or topical absorption by increasing drug lipophilicity via masking polar and ionizable groups within a drug molecule [14]. A hydrophilic hydroxyl, thiol, carboxyl, phosphate, or an amine group on the parent drug can be transformed to more lipophilic alkyl or aryl esters, and these prodrugs are readily converted to the parent drugs via hydrolysis catalyzed by esterase enzyme [15-16]. An example of this type of prodrug is oseltamivir which is an ethyl ester prodrug and undergoes rapid conversion by carboxylesterase to its parent drug. The bioavailability of the more lipophilic oseltamivir is almost 80%, whereas the corresponding value for free carboxylate is as low as 5%. [13].

Another method to increase the oral absorption is to design prodrugs, which have structural features similar to substrates that are absorbed by carrier-mediated transport [13]. Enalapril is an example of an ester prodrug which improves the bioavailability from 3% (active drug) to 40%. The ethyl ester moiety increases lipophilicity and is also a substrate of the PEPT1transporter [17].

1.1.2.3 Taste Masking

Bitterness of the drug is the major reason for patient incompliance. In order to eliminate the bitter taste of a drug and hence increasing its efficacy, the prodrug approach can be used either by decreasing the drug solubility in saliva or by masking the functional group that is responsible for the drug's binding to the taste receptors located on the tongue [18].

1.1.2.4 Modifying the Distribution Profile

The prodrug approach is one of the most promising site-selective drug delivery strategies which exploit target cell- or tissue- specific endogenous enzymes and transporters [19]. One example is the prodrug capecitabine which is metabolized initially in the liver and subsequently in tumor cells to form the anticancer agent 5-fluorouracil [17].

1.1.2.5 Preventing from Rapid Metabolism

Many oral drugs have low bioavailability due to the first pass metabolism in the gastrointestinal tract and liver [20]. The prodrug approach can also protect the rapid metabolic breakdown of the drug and thereby increase its oral bioavailability by masking the metabolically labile functions [21].

1.1.3 Prodrug approaches for the CNS delivery

Most therapeutic agents cannot distribute into the brain due to the presence of the blood brain barrier (BBB) that is formed by brain capillary endothelial cells. So drugs must cross the BBB to enter the brain from the bloodstream [22]. Therapeutic agents to be able to cross the BBB should have either physicochemical properties that allow passive diffusion through the BBB or have the structural features so that the drug can access one of the endogenous BBB transporters and enter the brain [23]. The endogenous BBB transport systems are classified as carrier mediated transport, receptor mediated transport and active efflux transport [24-27]. Whereas the drug to be able to cross the BBB by passive diffusion should be lipid soluble, have a molecular weight < 500 Da, neutral or uncharged at physiological pH and be able to form less than eight H-bonds with water [28-29].

The prodrug strategy is broadly used to optimize physicochemical properties that allow for passive diffusion via the transcellular route or to insert structural features necessary to serve as a substrate for one of the endogenous influx transport systems [23].

1.1.3.1 Lipidization Approach

Prodrug approaches are utilized to increase drug delivery to the brain and used passive drug uptake processes by chemically modifying a drug to become more lipophilic, enter through BBB more readily, and is then converted back to the parent drug within the brain.

There are two methods to make the drug more lipophilic. First, the polar functional group on the drug can be masked by conjugating it with a lipophilic moiety. Second, the drug can be conjugated to a lipophilic drug carrier. Both methods of reformulation of the drug

lead to the production of a prodrug that is more lipophilic and can cross the BBB, and then the drug is metabolized within the brain and release the parent drug.

Chemical drug delivery system (CDS) is an effective prodrug approach that uses improved lipophilicity and requires multiple steps bioactivation for conversion to active drugs. It captures the drug inside the brain by converted the prodrug into a more hydrophilic derivatives after crossing CNS. Thus decrease the efflux of drug from the CNS and provide a sustained release for it [30-31].

1.1.3.2 Carrier-Mediated Prodrugs

There are several endogenous influx transporters at the brain capillary endothelium that forms the BBB. These include carrier mediated transport systems from the bloodstream to the brain for essential nutrients such as amino acids, glucose and vitamins [32-33]. So these membrane transporters can take part in drug transport if the drug molecules have similar structural properties to endogenous substrates [33].

Carrier-mediated prodrug approach based on linking the parent drug to an endogenous transporter substrate so that can be recognized and transported through BBB by transporter systems and enters to the CNS [34].

1.1.4 The Problem with Classic Prodrug Approach

The key problem with the classic prodrug approach is the difficulty in predicting the bioconversion rate of the prodrug to the parent drug, and thus its pharmacological or toxicological effects. Moreover, it is difficult to predict always the rate of hydrolysis, and bioconversion can be affected by various factors such as age, health conditions and gender [35-37].

The classic prodrug approach was focused on altering various physiochemical parameters, whereas the modern computational approach, considers designing prodrugs through attaching appropriate linkers with drugs having poor bioavailability which upon exposure to physiological environments release the parent active drugs in a

programmable (controlled) manner resulting in an improvement of their bioavailability. With the possibility of designing prodrugs with different linkers, the release rate of the parent active drugs can be controlled [38].

1.2 Computational Approach

Computational methods have been used for calculating molecular properties of ground and transition states in the areas of organic, bioorganic and medicinal chemists. Computational chemistry uses principles of computer science to assist in solving chemical problems. It uses also the theoretical chemistry results, combined with efficient computer programs in order to calculate the structures, physical and chemical properties of molecules.

Currently, quantum mechanics (QM) such as *ab initio*, semi-empirical and density functional theory (DFT), and molecular mechanics (MM) are commonly being used and broadly known as reliable tools for predicting structure-energy calculations for drugs and prodrugs alike [45].

1.2.1 Quantum Mechanics (QM)

Quantum mechanics (QM) is defined as the science that describes the behavior of electrons and thus of chemistry. It includes *ab initio*, semi-empirical and density functional theory (DFT).

1.2.1.1 *Ab initio* Method

Ab initio is a Latin term which means “"from the beginning", this term is set to computations that are derived directly from theoretical principles with no inclusion of experimental data. This is considered as an approximate quantum mechanical calculations that are usually made from mathematical approximations [40]. *Ab initio* methods normally are sufficient only for small systems and are based entirely on theory from first principles.

Furthermore, the *ab initio* molecular orbital methods (QM) including HF, G1, G2, G2MP2, MP2 and MP3 are based on rigorous use of the Schrodinger equation with a number of approximations. The advantages that are accounted for the *ab initio* electronic structure methods that they can be made to converge to the exact solution, when all approximations are sufficiently small in magnitude and when the finite set of basic functions tends toward the limit of a complete set. The convergence is usually not monotonic, and sometimes the smallest calculation gives the best result for some properties. While the disadvantage of *ab- initio* methods is their enormous computational cost. They take a significant amount of computer time, memory, and disk space [41-45].

1.2.1.2 Semi-empirical Methods

Semi empirical calculations have the advantage in that they are much faster than *ab initio* calculations with a disadvantage that the results can be erratic and fewer properties can be predicted consistently. If the molecule being computed is similar to molecules in the database used to parameterize the method, then the results may be very good. If the molecule being computed is significantly different from anything in the parameterization set, the answers (solutions) may be very poor [40].

Semi-empirical calculations have a Hamiltonian and a wave function and are set up with the same general structure as a Hartree-Fock (HF) calculation. Within this framework, certain pieces of information are approximated or completely omitted. Typically, only a minimal basis set is used and the core electrons are not included in the calculation. Also, some of the two-electron integrals are omitted. The method is parameterized to correct for the errors introduced by omitting part of the calculation. Parameters to estimate the omitted values are obtained by setting the results to experimental data or *ab initio* calculations. Often, these parameters replace some of the integrals that are excluded.

Moreover, the most frequently used semi-empirical methods are MINDO, MNDO, MINDO/3, AM1, PM3 and SAM1. Calculations of molecules containing up to100 atoms (this number can be increased if super computers are utilized) can be handled using semi-empirical methods [46, 47].

1.2.1.3 Density Functional Theory (DFT)

Density Functional Theory (DFT) has been developed more recently than other ab initio methods in order to investigate the electronic structure of many-body systems, specifically atoms, molecules, and molecules in the condensed phases (solid phase) [48]. With this method, the electron density can determine the energy of a molecule by using functions that is functions of another function.

Still, this theory originated with a theorem by Hoe burg and Kohn and a practical application by Kohn and Sham. The original theorem was applied for the ground-state electronic energy of a molecule. However, the practical application of this theory was similar in structure to the Hartree-Fock method [49].

DFT has become very common in recent years because of the pragmatic observation that it is less computationally intensive than other methods with similar accuracy. Also, this method is sufficient for calculating structures and energies for medium-sized systems (30-60 atoms) of biological, pharmaceutical and medicinal interest and is not restricted to the second row of the periodic table. Although using the DFT method is significantly increasing some difficulties still encountered when describing intermolecular interactions, especially van deer Waals forces (dispersion); charge transfer excitations; transition states, global potential energy surfaces and some other strongly correlated systems. Incomplete treatment of dispersion can adversely affect the DFT degree of accuracy in the treatment of systems which are dominated by dispersion [48].

1.2.2 Molecular Mechanics

The limited size of the molecule that can be modeled on even the largest computers is considered as the most severe limitation of ab initio methods. To illustrate, semi-empirical calculations can be used for large organic molecules, a well they are too computation-intensive for most bimolecular systems. Besides, if a molecule is so big that a semi-empirical treatment cannot be used effectively, it is still possible to model its behavior avoiding quantum mechanics totally by using molecular mechanics [40].

Molecular mechanics is a mathematical approach which is widely used in calculating many diverse biological and chemical systems such as proteins, large crystal structures, and relatively large solvated systems, it also used for the computation of structures, energy, dipole moment, and other physical properties. Though, this method is limited by the determination of parameters such as the large number of unique torsion angles present in structurally diverse molecules [50].

Molecular mechanics simulations use a single classical expression for the energy of a compound, for example, the harmonic oscillator. The database of compounds used for parameterization is crucial to the success of molecular mechanics calculations; for instance, the resulting set of parameters and functions is called the force field that parameterized against a specific class of molecules, for instance proteins, would be expected to only have relevance when describing other molecules of the same class. The applicable way for this method could be done on proteins and other large biological molecules, and allow studies of the approach and docking of potential drug molecules. Subsequently, the size of the system which ab initio calculations can handle is relatively small despite the large sizes of bio-macromolecules surrounding solvent water molecules such as in the cases of enzymes and receptors, isolated models of areas of proteins including active sites have been investigated using ab initio calculations. Though, the disregarded proteins and solvent surrounding the catalytic centers have also been shown to contribute to the regulation of electronic structures and geometries of the regions of interest. To overcome these inconsistencies, quantum mechanics/molecular mechanics (QM/MM) calculations are used, in that the system is divided into QM and MM regions where QM regions correspond to active sites to be studied and are described quantum mechanically. MM regions correspond to the remainder of the system and are treated molecular mechanically. The pioneer work of the QM/MM method was accomplished by Warshel and Levitt [51], and since then, there has been a significant progress on the development of a QM/MM algorithm and applications to biological systems [52,53].

1.3 Dopamine

3,4-Dihydroxyphenethylamine is a neurotransmitter that is naturally produced in the body. In the brain, it activates the five types of dopamine receptors– D1, D2, D3, D4, and D5. Dopamine is produced in several areas of the brain, including the substantial nigra and the ventral tegmental area [39]. Dopamine has the following chemical structure (Figure 1).

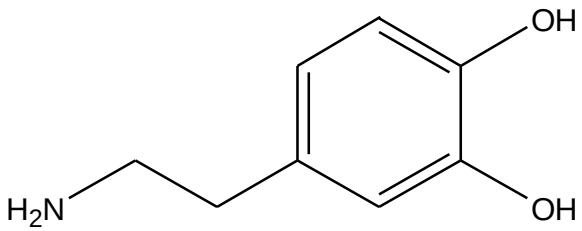


Figure 1: Structural formula of dopamine

Dopamine is also a neurohormone released by the hypothalamus, and its main task to act as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary. Dopamine has several functions in the brain. It exists in the regions of the brain that regulate movement, emotion, motivation, and the feeling of pleasure. Shortage of dopamine, particularly the death of dopamine neurons in the nigrostriatal pathway, causes Parkinson's disease, in which a person loses the ability to perform smooth, controlled movements [39].

Dopamine can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, because dopamine cannot cross the blood–brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and dopa-responsive dystonia, LD (levodopa), which is the precursor of dopamine, is given because it can cross the blood–brain barrier [39].

Levodopa is typically co-administered with an inhibitor of peripheral decarboxylation [dopa decarboxylase (DDC)], such as carbidopa or benserazide [54, 55].

1.4 Parkinson's disease

Parkinsonism is a progressive neurological disorder of muscle movement that is manifested clinically by bradykinesia, tremor, rigidity, flexed posture, postural instability, and freezing of gait. It is characterized pathologically by the loss of pigmented dopaminergic neurons in the substantial nigra [56].

Although the exact cause of PD remains unknown, most cases are hypothesized to be a result of multiple factors acting together, including ageing, genetic susceptibility, and environmental exposures [57].

1.5 Problem Statement

Patients with Parkinson's disease have insufficient dopamine in specific regions of the brain, so attempts have been made to replenish the deficiency in the dopamine [58]. Unfortunately, peripherally administered (outside of the central nervous system) dopamine is not effective because it cannot cross the blood brain barrier. The reason for its inability to cross the BBB has to do with at least two influencing factors. The first is that dopamine is a hydrophilic molecule which is expected to exist primary in the ionized forms (Figure 2) in a physiologic environment of pH 7.4 (blood circulation) resulting in a greater degree of difficulty in crossing cell membranes. The second is the absence of a transporter for dopamine to pass the blood brain barrier into the brain [59].

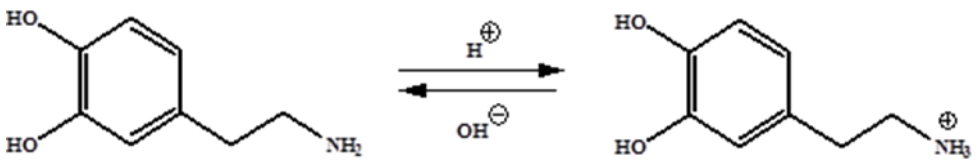


Figure 2**:** Ionized form of dopamine at physiological environment

However, the precursor to dopamine, LD (Figure 3), was and still the best choice of treatment for this disease. LD is able to get into the brain *via* a large neutral amino acid carrier or L (leucine) system [60]. Once LD gets inside the brain it can then be metabolized by dopa decarboxylase or amino acid decarboxylase to form dopamine within the dopaminergic neurons within the substantia nigra [61].

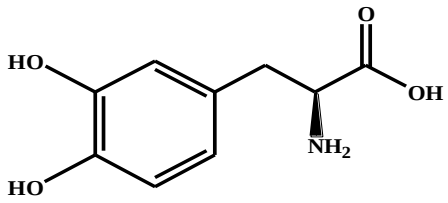


Figure 3**:** Chemical structure of Levodopa

Because much of the drug is decarboxylated to dopamine in the periphery, high doses of LD are required, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension [62]. These drawbacks of LD are the known reason of disability in PD patients [63, 64]. They can be explained according to this manner: In the normal brain the basal ganglia always maintained to satisfy the brain needs of dopamine for motor control and others, but LD oral administration have a low bioavailability of 10% with only 1% of LD reaching the brain. This is due to the erratic gastrointestinal metabolism the drug faces before it attaches to the l-amino acid carrier that transports it actively through the duodenum where it enters the blood stream intact [65-70]. With the co-administration of either carbidopa or benserazide, an increase of LD bioavailability by two-fold was observed with only 5% to 10% of administered LD enters the brain [71, 72]. As a result, lessened amounts of dopamine put the brain under fluctuations that are hard to accommodate [73, 74]. To minimize the conversion to DA outside the CNS, LD is usually given in combination with peripheral inhibitors of amino acid decarboxylase such as carbidopa or benserazide. In spite of that, other central nervous side effects such as dyskinesia, on-off phenomenon and end-of-dose deterioration still remain [75].

The main factors responsible for the poor bioavailability and the wide range of inter- and intra-patient variations of plasma levels are the LD physicochemical properties such as low lipid solubility which resulted to unfavorable partition, and the high susceptibility to chemical and enzymatic degradation [76]. Starting from these considerations the prodrug approach has been applied to dopamine in order to overcome its metabolism problems and to improve its bioavailability.

1.6 Thesis Objectives

1.6.1 General Objective

The main goal of this study was to design novel dopamine prodrugs for the treatment of Parkinson's disease that have the potential for higher bioavailability than the current medications when given in different dosage forms and having the potential to release their parent drugs in a controlled manner, using a variety of different molecular orbital and molecular mechanics methods and correlations between experimental and calculated reactions rates.

For achieving this goal, the dopamine prodrugs physicochemical properties must have the following:

(i) To be soluble and stable in physiological environment.

(ii) To have a moderate hydrophilic lipophilic balance (HLB) value.

(iii) To provide upon chemical cleavage the parent drug in a controlled manner.

(iv) To furnish upon cleavage a safe and non-toxic by-products.

1.6.2 Specific Objectives

Calculations of Kirby's enzyme model mechanism for the design of dopamine prodrugs which should have the following properties:

- A chemically driven sustained release system that releases the dopamine in a controlled manner.
- The linker attached to the drug moiety and the whole dopamine prodrug moiety should have no toxicity and safe.

- A drug with a high bioavailability and efficient pharmacokinetic properties.

1.7 Research Questions

Would the DFT calculations be good methods for a design of Dopamine prodrugs that have the potential for higher bioavailability than the current medications when given in different dosage forms and be cleaved in physiological environments to furnish the active drugs and a non-toxic moiety?

Chapter Two

Literature Review

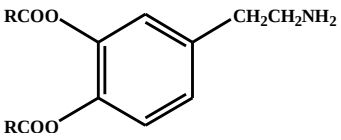
2 Literature Review

Literature reveals that many efforts have been made to synthesize prodrugs to improve bioavailability, decreased side effects, and potentially enhanced CNS delivery of the dopamine.

2.1 Previous Attempts to Make Prodrugs of Dopamine

2.1.1 Ester dopamine prodrugs

Dopamine has poor permeation across the BBB and other cell membranes due to its complete ionization at physiological pH. Therefore, it cannot be used for PD [77].In order to resolve these problems, Casagrande et al. and Borgman *et al*. have prepared a number of lipophilic 3,4-*O*-diesters prodrugs of DA (Figure 4) as a latent lipophilic derivatives of DA to be used in the therapy of parkinsonism, hypertension and renal failure [77,78]. But the results showed that *O*-acetylation was not enough to provide entry into CNS while preservation intrinsic dopaminergic activity and *N*-alkylation of the DA molecule are also required.



1. R = CH_3
2. R = $CH(CH_3)_2$
3. R = $C(CH3)_3$
4. R = C_6H_5
5. R = C_2H_5O

Figure 4**:** A series of lipophilic 3,4-*O* diesters dopamine pro-drugs.

2.1.2 Chemical delivery systems

To enhance the permeation of DA to central nervous system, chemical delivery systems (CDSs) have been established. These prodrug devices have been prepared by joining DA with a pyridinium/dihydropyridine redox carrier. A dihydropyridinium-type CDS is lipophilic enough to cross the membrane of CNS by passive transport and then undergoes an enzymatic oxidation to an ionic pyridinium precursor, this lead to locked compounds in the CNS [79]. CDS used also for brain-enhanced delivery of neurotransmitters, steroids, anticonvulsants, antibiotics, antiviral, anticancer, neuropeptides and their

analogs [79-81].This carrier enables the prodrug to cross BBB and then be oxidized to a quaternary precursor that is retained in the CNS, to provide a DA in a sustained release form (Figure 5).

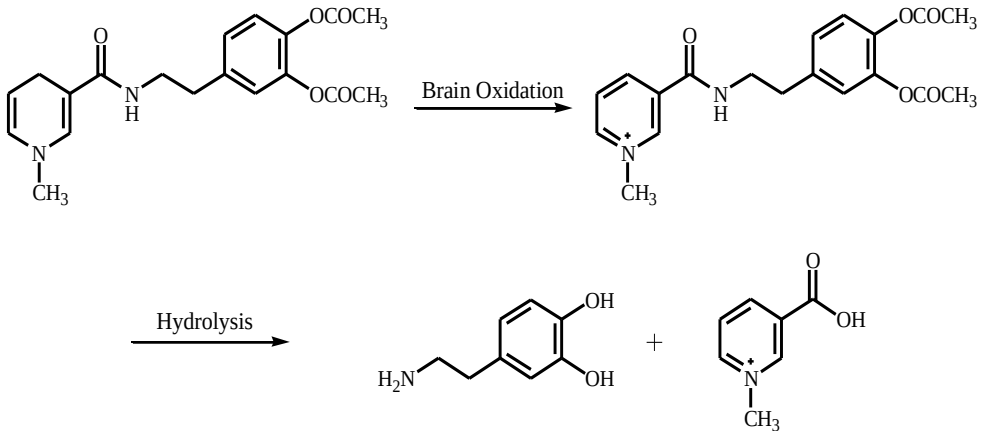


Figure 5: Dopamine delivery from pyridinium/dihydropyridine redox carrier system.

The use of the dihydropyridine is actually restricted due to instability of its 5,6-double bond, which undergoes air-oxidation and/or hydration. This oxidation/hydrolysis reaction yields 6-hydroxy-1,4,5,6-tetrahydropyridine, which does not undergo enzymatic oxidation in *vivo* to give the corresponding quaternary pyridinium salt [82]. In order to overcome this problem, Carelli *et al*. suggest an interconvertible tetrahydrobipyridine/pyridinium salt (Figure 6) by irreversible dimerization of two pyridinyl radicals accomplish by one-electron electro-chemical reduction of pyridinium salts as nicotin-amide coenzymes or their models. In contrast with monomeric dihydropyridines, the tetrahydrobipyridines are more stable and easily oxidized back to the compound pyridinium salts by chemical oxidants or by oxygenase and peroxidase enzymes [81].

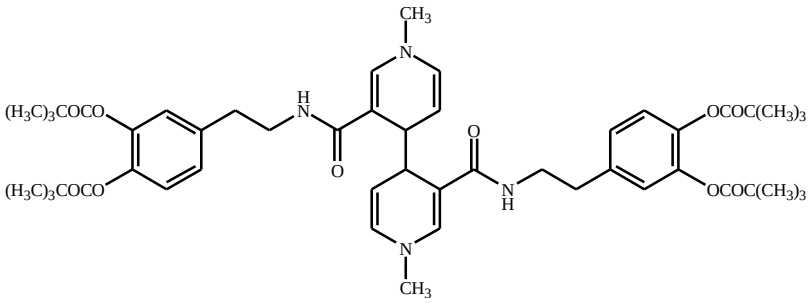


Figure 6**:** Chemical structure of tetrahydrobipyridine.

2.1.3 Peptide transport-mediated prodrugs

2-Amino-*N*-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide (DOPH), an amide prodrug of DA, has been earlier proposed by Giannola *et al*. (Figure 7) [83]. It is synthesized by condensation of dopamine with a neutral amino acid to be able to interact with the BBB endogenous transporters and easily enter the brain. (DOPH) has the capacity to be slowly cleaved by cerebral enzyme ($t_{½}$ 460 min) and produce free dopamine in the brain, but it undergoes a rapid hydrolysis in human plasma ($t_{½}$ 28 min). Chemical stability studies on DOPH showed that no DA release occurred in the gastrointestinal tract and the prodrug was able to pass through a simulated intestinal mucosal membrane.

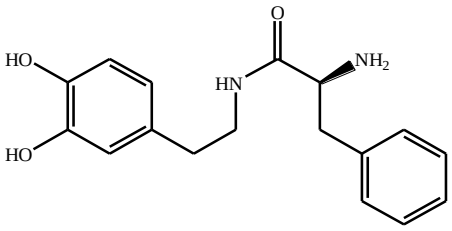


Figure 7: Chemical structure of 2-amino-*N*-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide (DA-PHEN)

In another study and in an attempt to enhance BBB permeability of dopamine, More and Vince focused on the glutathione uptake transporters that are located on the luminal side of the BBB. The broad substrate specificity displayed by these transporters provides vast

opportunity for rational prodrug design. The design of glutathione transporter targeted prodrug involved three components: the carrier, glutathione (GSH), the active drug, and a suitable linker for conjugation of the carrier with the drug molecule. The prodrug in (Figure 8) in which the dopamine is covalently linked via an amide bond to glutathione (GSH) showed high affinity for the GSH transporter at the BBB, released dopamine at the active site and possessed a good stability balance between the periphery and brain [84].

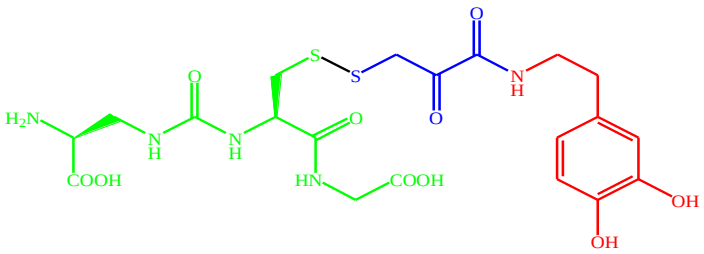


Figure 8: Chemical structure of the anti-Parkinson's prodrug of dopamine. Shown in green is the carrier, metabolically stable glutathione analogue; in blue is the linker, mercaptopyruvic acid, and in red is the active drug moiety.

N-3,4-bis(pivaloyloxy)-dopamine-3-(dimethylamino)propanamide (PDDP) (Figure 9), a brain specific derivative of dopamine, was designed and prepared, which consists of a brain targeted ligand, N,N-dimethyl amino group, and two dipivaloyloxy groups for lipophilic modification. Tissue distribution, brain bioavailability, and therapeutic efficacy of PDDP were evaluated and compared with L-DOPA and another brain dopamine prodrugs without N,N-dimethyl amino group which showed a more marked accumulation in rats brain microvascular endothelial cells than brain dopamine prodrugs through an active transport process. Following IV administration, the concentration of PDDP in the CNS was 269.28- and 6.41-folds higher than that of L-DOPA and brain dopamine prodrugs at 5 min, respectively. Therefore, PDDP would be a promising drug candidate that can be applied for targeted PD treatment [85].

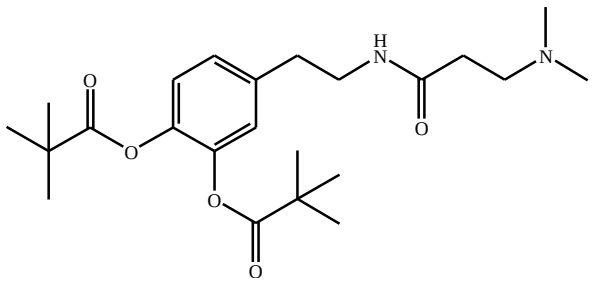


Figure 9: Chemical structure of N-3,4-bis(pivaloyloxy)-dopamine-3-(dimethylamino)propanamide (PDDP)

2.1.4 GLUT1 carrier-mediated prodrugs

With the aim of overcoming the problem of the low BBB permeability of dopamine, a novel glycosyl derivatives of dopamine were synthesized which have the ability to be transported by GLUT1. Fernandez and coworkers described the synthesis and biological activities of several glycosyl derivatives of dopamine by conjugating sugar with dopamine through a succinyl linker, carbamate bond, glycosidic and ester bonds. They linked the amino group of dopamine to the C-6, C-3 and C-1 of the sugar through a succinyl linker or a carbamate bond. In another series, the sugar was linked to the phenolic groups of dopamine through a glycosidic bond and ester bonds. The affinity of these prodrugs for glucose carrier GLUT-1 using human erythrocytes was also tested [86, 87]. When incubated with the brain extracts, the nature of the bond that links DA with glucose affected the rate in which the prodrug releases dopamine. The glycosyl conjugates substituted at the C-6 position of the sugar were more potent inhibitors of glucose transport in contrast to that of C-1 and C-3 substituted derivatives. From the studied compounds, the carbamate derivatives 9, 11 and 12 were the prodrugs of choice, in particular compound 9, which showed the best affinity for GLUT-1, even with higher affinity than glucose itself [88, 89].

In another study, Bonina et al. and Ruocco et al. have prepared dopamine glycoside prodrugs by attaching DA to C-3 position of glucose (19 in Figure 10) and to C-6 of galactose (20 in Figure 10) by a succinyl spacer. Pharmacological studies showed that

these two prodrugs were found to be more active than LD in reversing reserpine-induced hypo-locomotion in rats.

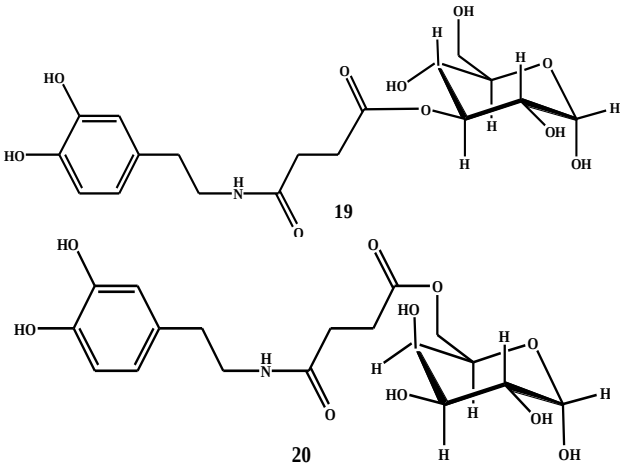


Figure 10: Chemical structures of glycosuccinyl-derivatives of dopamine.

2.2 Enzyme Model

Despite that some success has been obtained using the different strategies by which prodrugs of dopamine were used to supply dopamine in adequate concentrations and sustained release manner, the prodrugs chemical approach involving enzyme catalysis has many limitations related to many intrinsic and extrinsic factors that can affect the process. For example, the activity of many prodrug-activating enzymes may be varied due to genetic polymorphisms, age-related physiological changes, or drug interactions, causing variation in clinical effects [90-94].

Karaman's group has explored a number of intra-molecular processes to gain insight into enzyme catalysis, toward the development of prodrug linkers that can be covalently attached to commonly used drugs which could have the potential for higher bioavailability over existing medications and would be chemically, and not enzymatically, be converted to release the active drugs in a controlled manner [95-130], by using ab-initio and density functional theory (DFT) molecular orbital methods.

2.2.1 Computationally Designed Dopamine Prodrugs Based on proton transfer reaction in some of Kemp's acid amide derivatives

Karaman's group have been designed a number of dopamine prodrugs to be used in the treatment of Parkinson's disease with a higher bioavailability than the current medication. These designed prodrugs have the following physicochemical features: (i) owning moderate hydrophilic lipophilic balance (ii) soluble in physiological environment (iii) deliberate dopamine in a controlled manner, and (iv) undergo chemical cleavage to nontoxic by-products [59].

They explored the proton transfer reaction in some of Kemp's acid amide derivatives by using enzyme models as potential linkers to be linked to amine-drugs [117]. Based on the DFT calculations on proton transfer mechanism of these acid amides, two dopamine derivatives were proposed. As shown in (Figure 11), ProD 32 and ProD 33 have a carboxylic group as a hydrophilic moiety and the rest of the prodrug as a lipophilic moiety, where the combination of both moieties secures a moderate HLB. Furthermore, at physiological pH in the blood circulation the expected predominant form of dopamine is the ionized form while its prodrug 32 and prodrug 33 are predicted to exist in the ionic and free acid forms. So, ProD 32 and ProD 33 may have a higher bioavailability than dopamine due to improved absorption. Also, the designed prodrugs can be used in many dosage form (e.g. enteric coated tablets) because they are predicted to be soluble in organic and aqueous media due to the ability of the carboxylic group to be converted to the corresponding carboxylate anion in physiological environments of pH 5.0-7.4 (intestine and blood circulation).

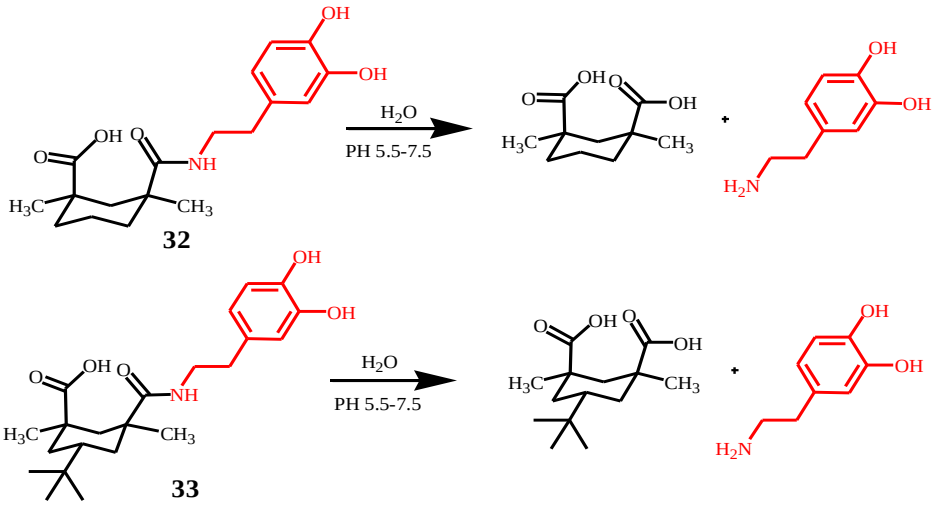


Figure 11: Dopamine prodrugs, ProD 32- ProD 33.

2.2.2 Computationally Designed Prodrugs Based on Intramolecular Amide Hydrolysis of Kirby's *N*-Alkylmaleamic Acids

Kirby *et al*. studied the efficiency of intramolecular catalysis of amide hydrolysis by the carboxyl group of a number of substituted *N*-methylmaleamic acids and found that the reaction is remarkably sensitive to the pattern of substitution on the carbon–carbon double bond [132] .

Karaman *et al*. utilized *N*-alkylmaleamic acids as prodrug linkers for amine drugs such as, atenolol, acyclovir, cefuroxime, and other drugs, having poor bioavailability or/and undesirable (bitter) taste, and have unraveled the mechanism for the acid-catalyzed hydrolysis using DFT and molecular mechanics methods [113-115, 131].

Based on the DFT calculation results on the acid-catalyzed hydrolysis of *N*-alkylmaleamic acids [132], acyclovir [113], atenolol [114] and cefuroxime [115] several prodrugs were designed and the reactions of the intraconversion of the designed prodrugs into the parent drugs were computationally studied. The prodrugs are composed of the carboxylic acid amide linker having a carboxylic acid group (hydrophilic moiety) and the

rest of the prodrug molecule (a lipophilic moiety). The combination of both groups secures a prodrug moiety with a potential to have high permeability (a moderate HLB).
So as I mentioned previously this approach was utilized by Karaman et al, to achieve desirable acyclovir, atenolol and cefuroxime prodrugs that are capable of being stable in aqueous solutions, more lipophilic, less bitter (cefuroxime and atenolol) and to have the potential to release the corresponding drugs in a slow release manner.

It is worth noting that all of the developed techniques for enhancing the bioavailability of active ingredients are based on design prodrugs so that they undergo cleavage in physiologic environments via enzyme catalysis and/or *via* in *vivo* chemical reactions. But Karaman's approach is a novel chemical approach involves a design of prodrugs for enhancing bioavailability of pharmaceuticals based on intramolecular processes using density functional theory (DFT) and *ab initio* methods and correlations of experimental and calculated reactions rates. No enzyme is needed to catalyze the interconversion of a prodrug to its corresponding drug.

Chapter Three

Methodology

Computational (Design) Section

3. Computational (Design) section

Calculation programs and methods used in the thesis

3.1 Calculation programs:

The following programs were exploited in the design calculations:

3.1.1 Arguslab

3.1.2 Gausian2009

3.1.3 Molden

3.1.1 Arguslab:

Arguslab is considered as a molecular modeling, drug and graphics design program that offers a moderate library of useful molecules, with quite good on-screen molecule-building facilities and it is a free downloaded program. Furthermore, it can do geometry optimizations using the UFF force field that covers all elements of the Periodic Table because it is not restricted to known atom types in its parameterization, though it does use some common ones. The resulting energies of this program are clearly disguisable from those obtained using some of the more conventional force fields, and wherever possible one needs to re-optimize at a higher level. Consequently, Arguslab offers single point calculations, as well as geometry optimization using the MNDO, AM1 or PM3 semi-empirical methods. There are also single point semi-empirical calculations using ZINDO (for excited states for UV/visible absorption prediction) or Extended Huckel (for a bigger element coverage). Version 3.1 of Arguslab has good facilities for calculating electron density or orbital surfaces at the semi-empirical levels, and displaying them also [133].

Arguslab writes its own format of molecule file, like .xml, but it can also write xyz files for input to other programs, e.g. Molden. It creates (and leaves behind) a lot of temporary files, which need to be managed.

To start work using Arguslab free program the users have two choices, they can press the 'New' button (top left) to get a new molecule screen, *or* press the 'Open' button to read in a molecule which has saved previously in the Argus directory.

Besides, using the Arguslab the users can save their molecule with whatever name they want before doing a geometry optimization as well as afterwards. Accordingly, all the additional files will have the right names and if they forget to change the file name before modifying a molecule, files will be saved automatically with the name used previously, possibly destroying data which they wanted to keep. It is best not to maximize the molecule window, because then its title bar will display the name by which we are currently saving the files. Just drag its bottom right corner so that it fills most of the Arguslab worktop. To stop using Argus lab, click File Exit, if we have molecule windows open, this will just close one of these. The users need to do it repeatedly to close all the windows (if they have several open) and then stop the program.

3.1.2 Gausian 2009

There are many versions of the Gaussian series of computer program for computational chemistry and Gaussian 09 is the latest version that is designed to model a broad range of molecular systems under a variety of conditions and perform its computations starting from the basic laws of quantum mechanics. Both theoretical chemists and experimental chemists can use Gaussian 09, to illuminate, theoretical chemists uses it to perform basic research in established and emerging areas of chemical interest whereas experimental

chemists can use it to study molecules and reactions of definite or potential interest, as well as stable species and those compounds which are difficult or impossible to observe experimentally such as short-lived intermediates, transition structures and so on) [134].

Another work for Gaussian 09 is that it can it can model both their ground state and excited states and it can also predict energies, molecular structures, vibration frequencies and numerous molecular properties for systems in the gas phase and in solution.

Moreover, there are different levels that can be run using Gaussian 09 installed on PC, a computer station or computer server; for example, AM1, PM3, MINDO/3, MNDO, HF, DFT, MP2 and MP3 .

Using the Gaussian 09 the input files can be created in two ways: by hand using a local editor (VI, emacs and nedit) or by using Molden. And to view output files from files run in Gaussian 09, input files for use in Gaussian 09 can be generated using Molden program. Finally, dissecting the output file in that the Z-matrix represents how the software knows the molecular geometry (structure). Notice that the molecule has no charge and a multiplicity of 1 (all paired electrons). The structure is also represented as a more standard xyz coordinate system. The distance matrix shows the distance of each atom from the other atoms, in units of angstroms.

3.1.3 Molden:

Molden is a computational program package that can interpret and convert information from the ab-initio packages, Games-US, Games-UK and Gaussian, as well as Mopac/Ampac programs into its own format, and it made for displaying molecular

densities from these programs. Furthermore, the benefit of using this programs format is simple. It can also be used as a visual Z-matrix molecule editor, thereby allowing users to create the molecule of their choice and being able to save the geometry in the Molden format [135]. Molden format incorporates numerous data stores in a text file; each piece of data is headed by a key term e.g. [MO] for molecular orbitals, [STO] for slater type orbital basis sets, plus many others like [GTO],[GEOMETRIES] etc. It also supports contour plots, 3-d grid plots with hidden lines and a combination of both. It can write a variety of graphics instructions; postscript, X-Windows, VRML, povray, OpenGL, tekronix4014 and hpgl, hp2392. Moreover, this format can animate reaction paths and molecular vibrations. It can calculate and display the true or multipole derived electrostatic potential and atomic charges can be fitted to the electrostatic potential calculated on a Connolly surface. Molden has a powerful Z-matrix editor which gives full control over the geometry and allows building molecules from scratch, including polypeptides. It also features a stand-alone force field program ambfor, which can optimize geometries with the combined Amber (protein) and GAFF (small molecules) force fields. Atoms type can be done automatically and interactively from within Molden, as well as firing optimization jobs.

3.2 Calculation methods:

In our calculations, the Becke three-parameter, hybrid functional combined with the Lee, Yang, and Parr correlation functional, denoted B3LYP, were employed using density functional theory (DFT). All calculations were carried out using the quantum chemical package Gaussian-2009 [136].

Calculations were carried out based on the restricted Hartree-Fock method [136]. The starting geometries of all calculated molecules were obtained using the Argus Lab program [137] and were initially optimized at the HF/6-31G level of theory, followed by optimization at the B3LYP/6-31G(d,p). Total geometry optimizations included all internal rotations. Second derivatives were estimated for all 3N-6 geometrical parameters during optimization. The search for the global minimum structure in each of the systems studied was accomplished by 36 rotations of the carboxyl group about the bond C4-C6 in increments of 10° (i.e. variation of the dihedral angle O5C4C6C7, see Chart 1) and calculation of the energies of the resulting conformers.

An energy minimum (a stable compound or a reactive intermediate) has no negative vibrational force constant. A transition state is a saddle point which has only one negative vibrational force constant [138]. Transition states were located first by the normal reaction coordinate method [139] where the enthalpy changes were monitored by stepwise changing the interatomic distance between two specific atoms. The geometry at the highest point on the energy profile was re-optimized by using the energy gradient method at the B3LYP/6-31G (d, p) level of theory [136]. The "reaction coordinate method" [139] was used to calculate the activation energy in dopamine **ProD 1- ProD 5** (Figures 15 - 17).

In this method, one bond length is constrained for the appropriate degree of freedom while all other variables are freely optimized. The activation energy values for the proton transfer processes (transfer of H7 from O6 into O1, Chart 1) were calculated from the difference in energies of the global minimum structures (GM) and the derived transition

states. Verification of the desired reactants and products was accomplished using the "intrinsic coordinate method" [83]. The transition state structures were verified by their only one negative frequency. Full optimization of the transition states was accomplished after removing any constrains imposed while executing the energy profile. The activation energies obtained from the DFT at B3LYP/6-31G (d,p) level of theory for all molecules were calculated in a gas phase and water phase. The calculations with the incorporation of a solvent were performed using the integral equation formalism model of the Polarizable Continuum Model (PCM) [140-143]. In this model, the cavity is created via a series of overlapping spheres. The radii type employed was the United Atom Topological Model on radii optimized for the PBE0/6-31G (d) level of theory.

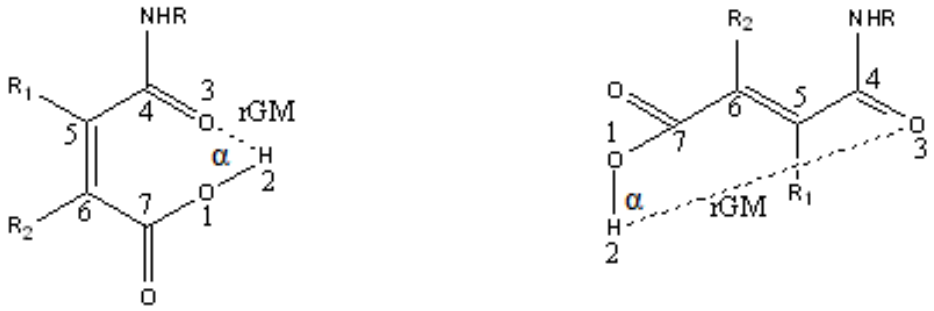


Chart 1: Schematic representation of the reactants in the proton transfers of dopamine **ProD 1-ProD 5**. GM is the global minimum structure, r_{GM} is the O—H distance in the GM. α, is the angle of attack (hydrogen bonding) O1-H2-O3 in the GM.

Chapter Four

Results and Discussion

4. Results and Discussion

Acid-catalyzed hydrolysis of *N*-alkylmaleamic acids 1-7 (Figure 12) was kinetically studied by Kirby's group; they concluded that the amide bond cleavage occurs due to intramolecular nucleophilic catalysis by the adjacent carboxylic acid group and the rate-limiting step is the tetrahedral intermediate breakdown [144].

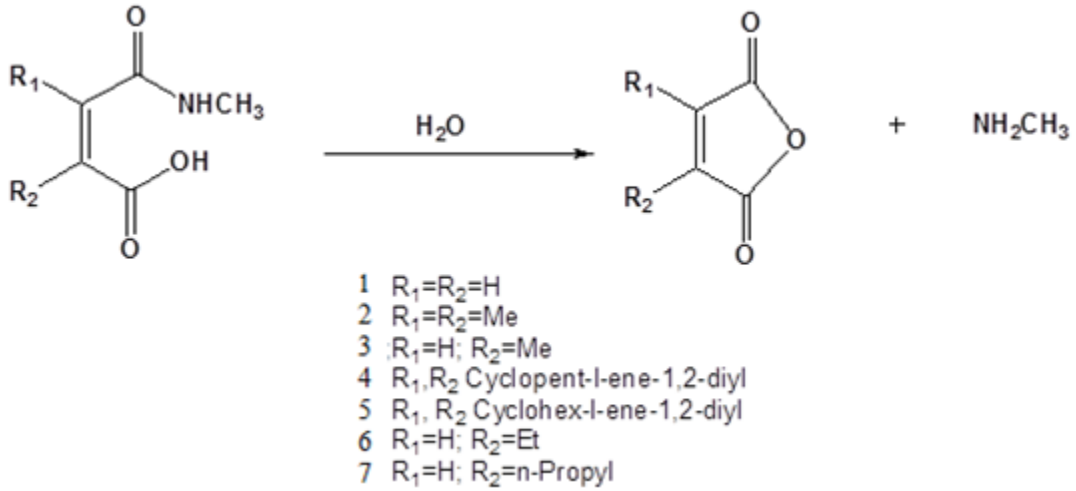


Figure 12: Acid-catalyzed hydrolysis of *N*-alkylmaleamic acids.

DFT calculations on the acid-catalyzed hydrolysis of Kirby`s *N*-alkylmaleamic acids that were done by Karaman's group showed that the rate limiting step in aqueous medium is the collapse of the tetrahedral intermediate whereas in the gas phase the rate limiting step is the formation of the tetrahedral intermediate. Furthermore, Karaman's calculations revealed a correlation between the acid-catalyzed hydrolysis efficiency and the following parameters:

1. The difference between the strain energies of intermediate and product and intermediate and reactant.

2. The distance between the hydroxyl oxygen of the carboxylic group and the amide carbonyl carbon.

3. The attack angle.

The calculations also demonstrated that the acid catalyzed reaction involves three steps: (1) proton transfer from the carboxylic group to the adjacent amide carbonyl oxygen, (2) nucleophilic attack of the carboxylate anion onto the protonated carbonyl carbon; and (3) dissociation of the tetrahedral intermediate to provide products (Figure 13).

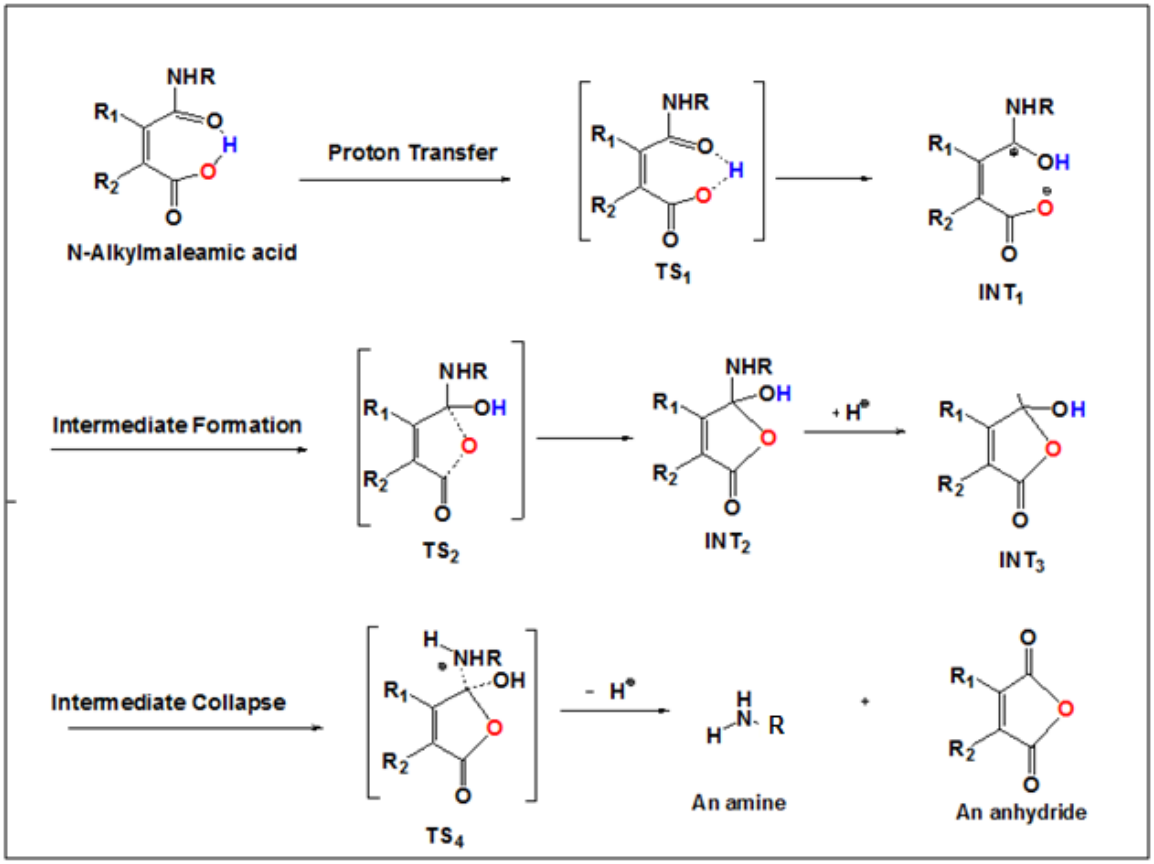


Figure 13: Proposed mechanism for the acid-catalyzed hydrolysis of *N*-alkylmaleamic acids.

Based on the calculation results of Kirby`s model (proton transfer in *N*-alkylmaleamic acids) we proposed some prodrugs of dopamine by linking this drug with anhydride linker such as maleic, succinic, dimethylmaleic, 1,2-cyclohexanedicarboxylic and hexahydro-4-methylphthalic (Figure 14) in order to: (1) improve the bioavailability of the parent drugs, (2) to make a chemical device that is capable of releasing the parent drug in a sustained release manner.

As shown in Figure 14, Dopamine **ProD 1- ProD 5** have a carboxylic group (hydrophilic moiety) and a lipophilic moiety (the rest of the prodrug), where the combination of both moieties secures a modified HLB.

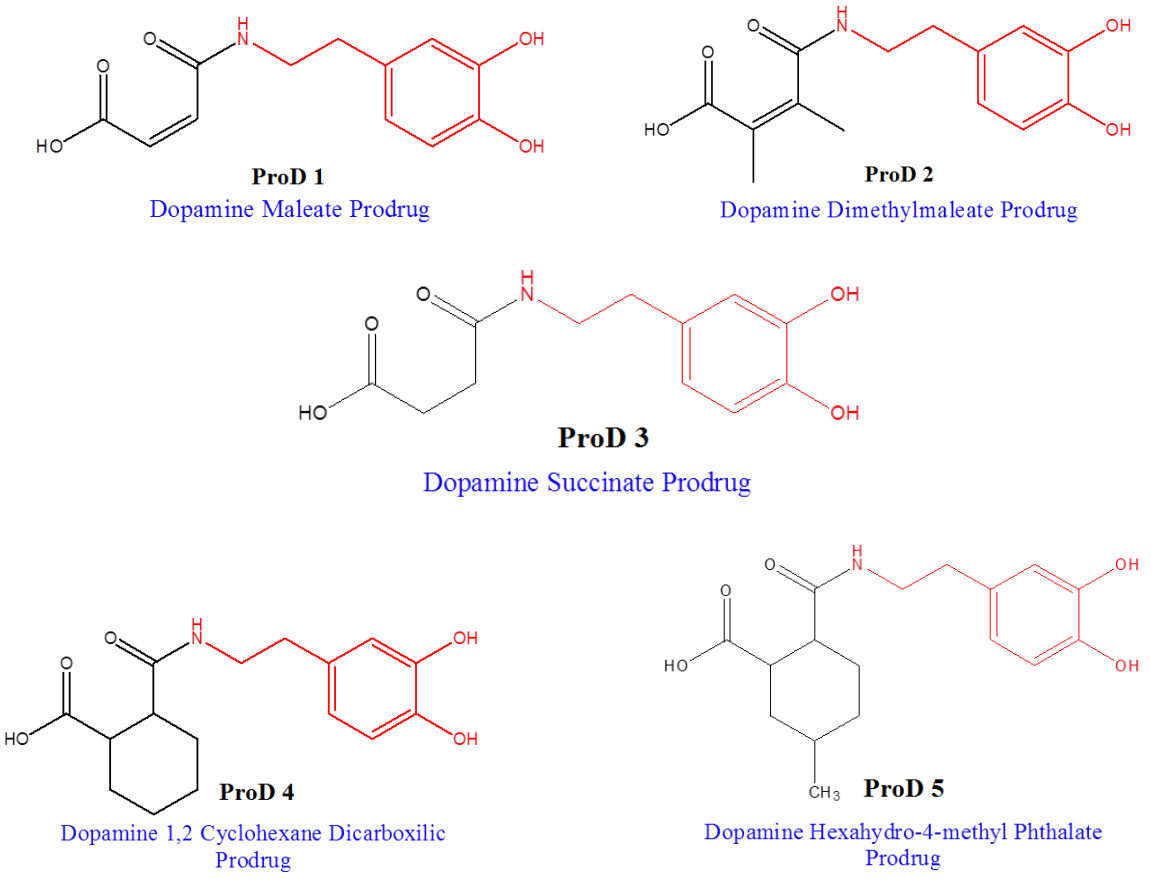


Figure 14: Structural formula of the proposed dopamine prodrugs.

The main advantage of Karaman's proposed prodrugs is their ability to release the drug *via* chemical cleavage in a controlled manner depending on nature of the linker.

So the aim of this work was to design various dopamine prodrugs by replacing the *N*-methyl amide group in 1–7 (Figure 12) with dopamine drug, as shown for **ProD 1-ProD 5** in Figure 14.

In this section, we report DFT at B3LYP 6-31G (d,p) level calculations of ground state and transition state structures, vibrational frequencies, and reaction trajectories for intramolecular proton transfer in dopamine prodrugs **ProD 1- ProD 5.**

Computations were directed toward elucidation of the transition and ground state structures (global minimum, intermediates and products) for the acid-catalyzed hydrolysis of dopamine **ProD 1– ProD 5** in the gas phase and in water phase (a dielectric constant of 79.38). It is expected that the stability of the chemical entities (GM, TS and P.) will be different in the gas phase compared to that in water (a relatively high dielectric constant).

4.1 General Consideration

Because the energy of a carboxylic acid amide molecule is strongly dependent on its conformation and the latter determines its ability to be engaged in intramolecular hydrogen bonding, we were concerned with the identification of the most stable conformation (global minimum) for each of prodrugs **ProD 1– ProD 5** calculated in this study. This was accomplished by 360° rotation of the carboxylic group about the bond C6-C7 (i.e., variation of the dihedral angle O1C7C6C5, Chart 1), and 360° rotation of the carbonyl amide group about the bond C4-C5 (i.e., variation of the dihedral angle O3C4C5C6) in increments of 10° and calculation of the conformational energies (see Chart 1).

In the DFT calculations for dopamine **ProD 1– ProD 5**, two types of conformations in particular were considered: one in which the amide carbonyl is *syn* to the carboxyl group and another in which it is *anti*. The global minimum search for dopamine **ProD 1- ProD 5** revealed that **ProD 1, ProD 2, ProD 4** and **ProD 5** exist in the *syn* orientation while ProD3 exists in the *anti* orientation (Figure 15).

4.2 Optimized geometries of the entities involved in the proton transfers of dopamine ProD 1- ProD 5.

4.2.1 Global minimum geometries (GM):

The calculated B3LYP/6-31 G (d,p) geometries along with selected bond distances and bond angles for the global minimum structures of **ProD 1GM-5GM** are illustrated in Figure 15.

Examination of the calculated geometries of **ProD 1GM-5GM** (Figure 15) indicates that **ProD 1** and **ProD 2** exhibit conformation by which the carboxyl group is engaged intramolecular in a hydrogen bond with the neighboring amide oxygen.

The calculated B3LYP/6-31 G (d,p) intramolecular hydrogen bonding length (r_{GM} in Chart 1) in **ProD 1GM** and **ProD 2GM** was found in the range of 2.90Å −3.03Å and that for the hydrogen bond angle α (the hydrogen bond angle, O1H2O3 in Chart 1) in the range of 137.4°-128.8°.

Inspection of the optimized structures for **ProD 3GM-5GM** indicates that the calculated DFT values for the intermolecular distance (r_{GM} in Chart 1) range between 4.11Å and 5.89Å, while the angle α was found in the range 23.1°- 61.3°.

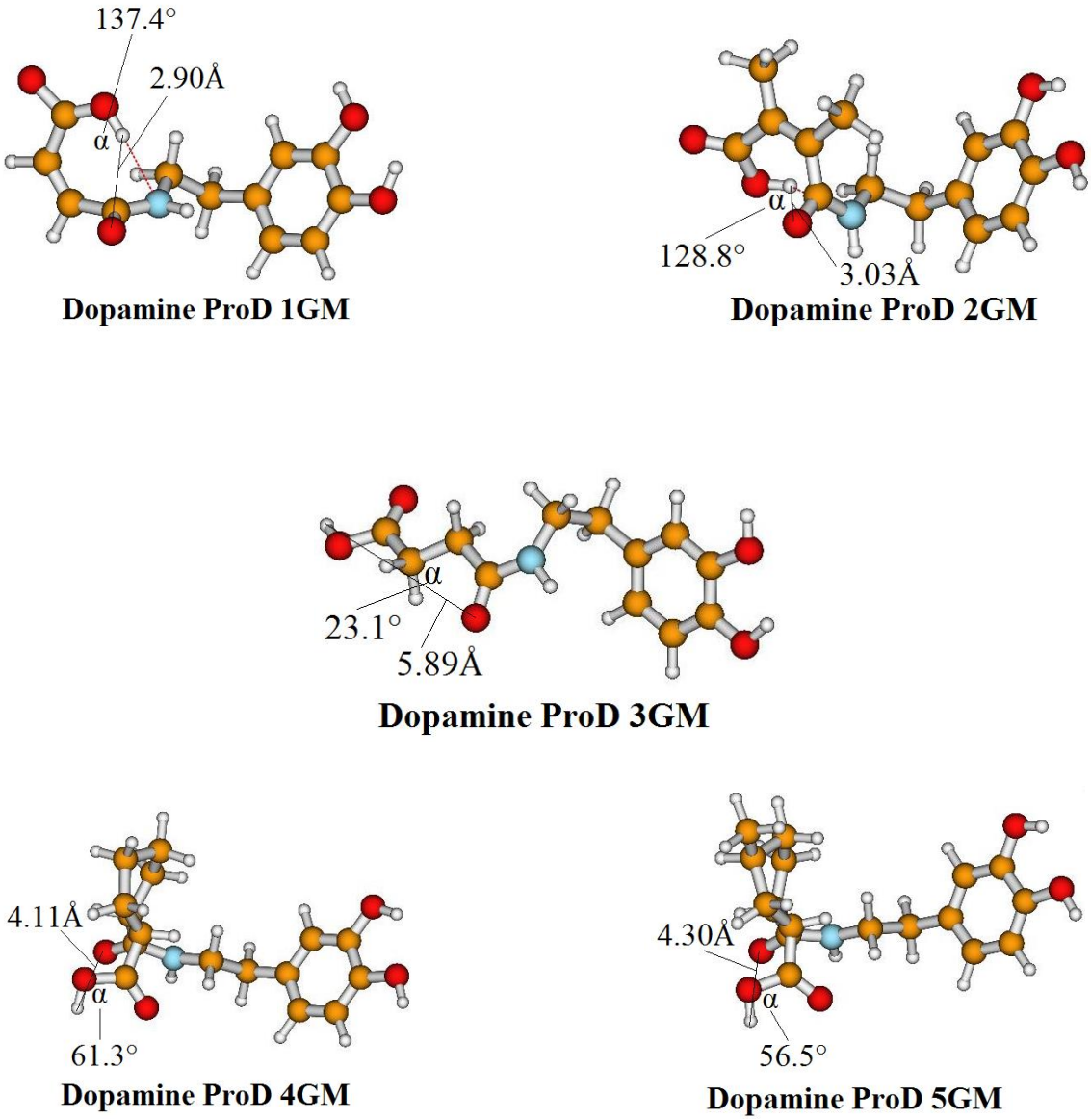


Figure 15: DFT optimized structures for the global minimum (**GM**) structures in the intramolecular proton transfer reaction of dopamine **ProD 1-ProD 5**.

4.2.2 Transition state geometries (TS):

The calculated properties for the transition state geometries of **Pro D1-Pro D5 (ProD 1TS-ProD 5TS**) are summarized in Table 1 and illustrated in Figure16.

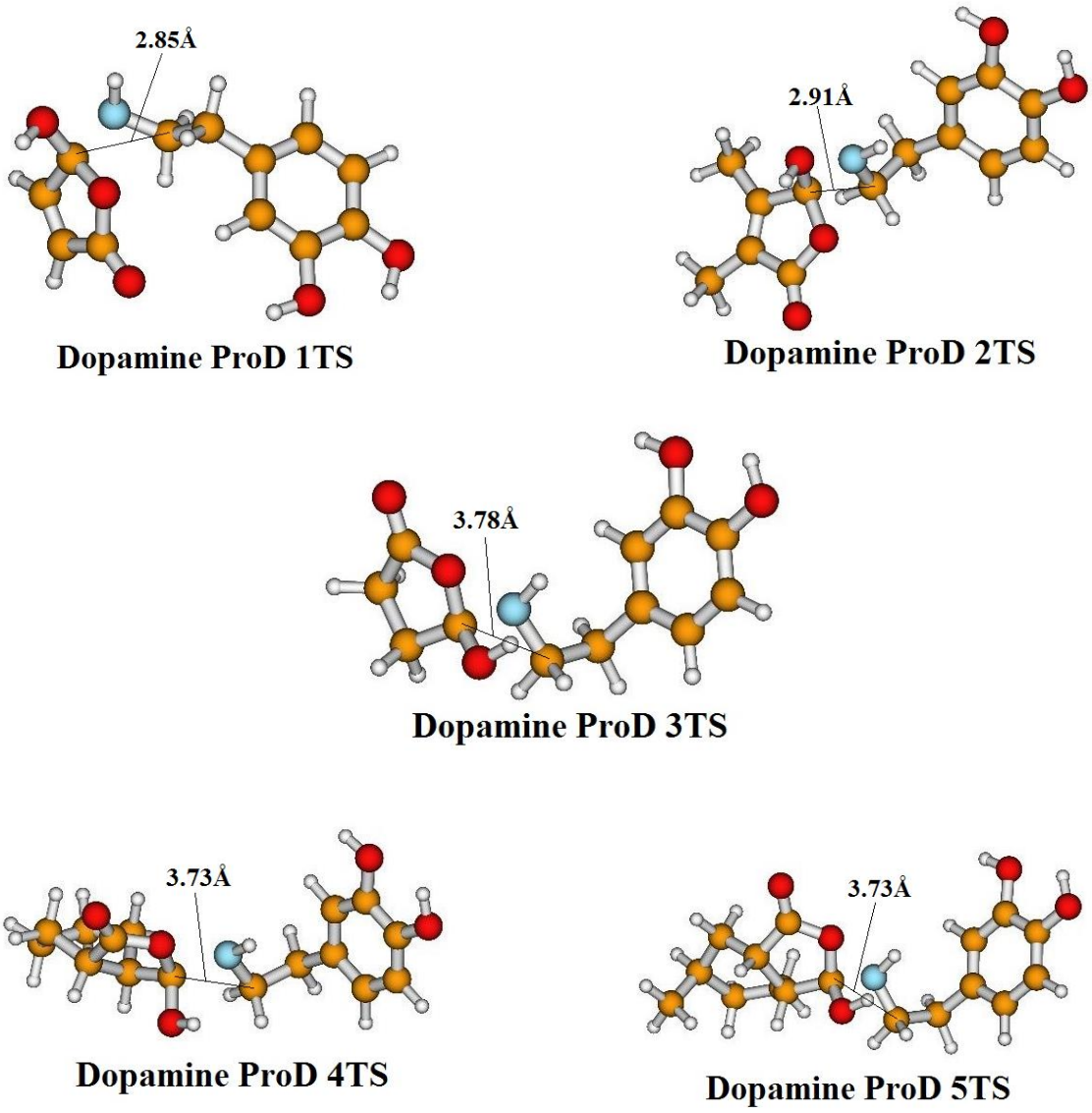


Figure 16: DFT optimized structures for the transition state (**TS**) structures in the intramolecular proton transfer reaction of dopamine **ProD 1-ProD 5**.

4.2.3 Product geometries (P):

The calculated properties for the product geometries of Pro D1-Pro D5 (ProD 1P-ProD 5P) are summarized in Table 1 and illustrated in Figure17.

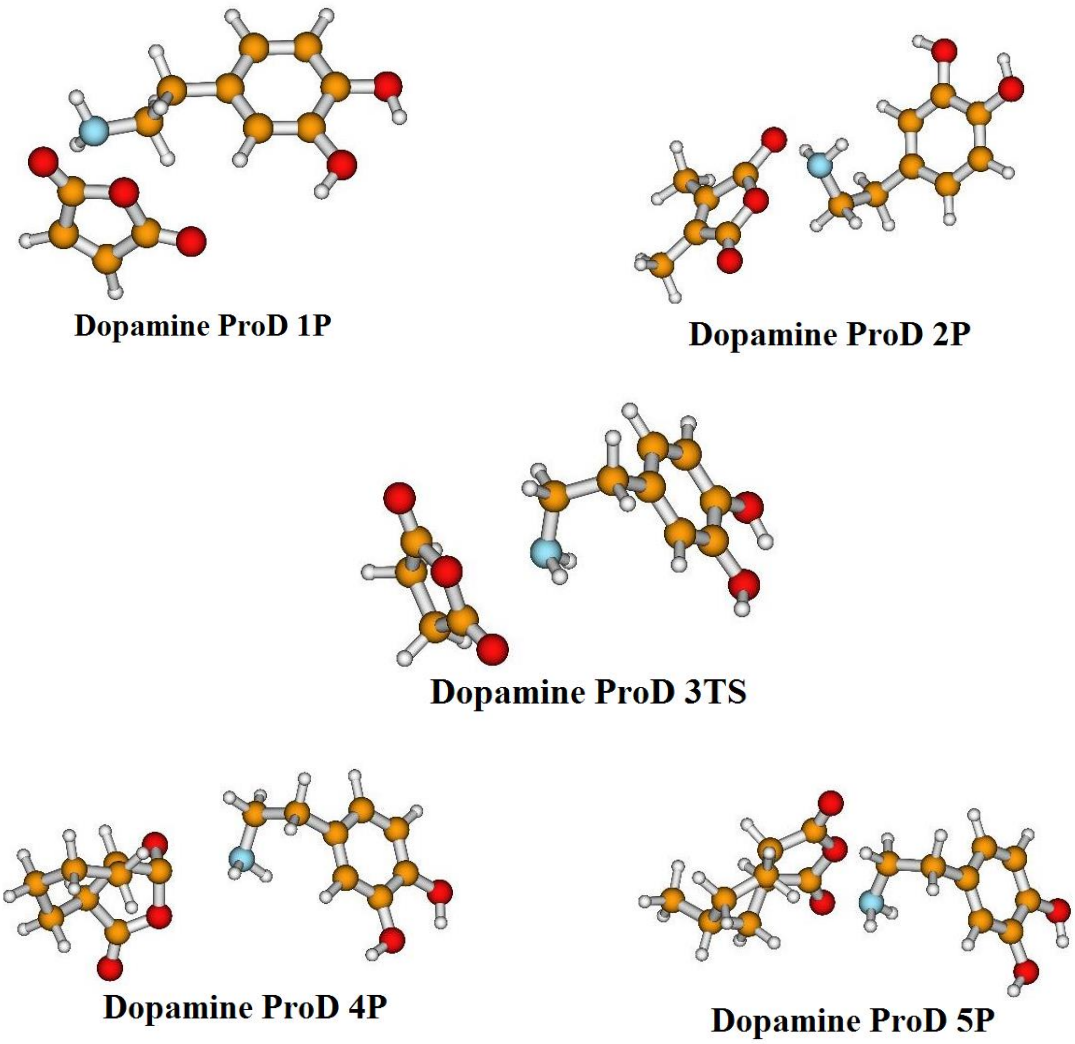


Figure 17: DFT optimized structures for the product (**P**) structures in the intramolecular proton transfer reaction of dopamine **ProD 1-ProD 5**.

4.3 DFT calculations of the kinetic and thermodynamic energies for the proton transfer reaction in dopamine ProD1- ProD5.

Using the quantum chemical package Gaussian-2009 [136] we calculated the DFT at B3LYP/6-31 G (d,p) level of theory kinetic and thermodynamic properties for all entities involved in the hydrolysis (global minimum structures (GM), transition states (TS) and products (P). The enthalpy and entropy energy values for all entities were calculated in the gas phase and cluster of water.

Table 1 lists the energy values for dopamine **ProD 1GM** – **ProD 5GM** dopamine **ProD 1TS** – **ProD 5TS** and dopamine **ProD 1P** – **ProD 5P**, and Figures 15 - 17 show their DFT optimized structures, respectively.

Using the calculated DFT values for the enthalpy and entropy of the global minimum structures of dopamine **ProD 1**-**ProD 5** and their corresponding transition states (Table 1) we have calculated the enthalpy activation energies ($\Delta H^{\ddagger}$), entropy activation energies ($T\Delta S^{\ddagger}$), and the free activation energies in the gas phase and water phase ($\Delta G^{\ddagger}$) for the proton transfer reaction in these processes. The calculated energies are listed in Table 2.

Table 1: DFT (B3LYP) calculated properties for the proton transfer reactions of in dopamine **ProD1- ProD5.**

Compound	B3LYP, Enthalpy, H (gas phase) in Hartree	B3LYP (gas phase) Entropy, S, Cal/Mol-Kelvin	B3LYP Frequency Cm^{-1}
Dopamine **ProD 1GM**	-895.9897836	138.243	-------
Dopamine **ProD 1TS**	-895.9363582	130.648	-196.447
Dopamine **ProD 2GM**	-974.6348381	156.577	-------
Dopamine **ProD 2TS**	-974.5908693	149.1	-114.636
Dopamine **ProD 3GM**	-897.2366718	147.57	-------
Dopamine **ProD 3TS**	-897.1765335	133.033	-64.076
Dopamine **ProD 4GM**	-1053.276895	161.519	-------
Dopamine **ProD 4TS**	-1053.228622	150.338	-46.434
Dopamine **ProD 5GM**	-1092.59478	168.32	-------
Dopamine **ProD 5TS**	-1092.544031	157.15	-44.925

B3LYP refer to values calculated by B3LYP/6-31G (d, p). (GM) and (TS) are global minimum and transition state structures, respectively.

Table 2: DFT (B3LYP/6-31G (d,p) calculated kinetic and thermodynamic properties for the proton transfers in dopamine **ProD 1**-**ProD 5**.

System	$\Delta H^{\ddagger}$ (GP)	$T\Delta S^{\ddagger}$ (GP)	$\Delta G^{\ddagger}$ (GP)	$\Delta H^{\ddagger}$ (H_2O)	$\Delta G^{\ddagger}$ (H_2O)
Dopamine**ProD1**	33.52459878	-2.255715	35.78031378	33.74416208	36.81662708
Dopamine**ProD2**	27.59055391	-2.220669	29.81122291	30.81535457	33.03602357
Dopamine**ProD3**	37.73696366	-4.317489	42.05445266	40.88658947	45.20407847
Dopamine**ProD4**	30.29145232	-3.320757	33.61220932	33.71209667	37.03285367
Dopamine**ProD5**	31.8449615	-3.31749	35.1624515	35.47287009	38.79036009

4.3.1 The role of the distance O3-H2 (r_{GM}) and the angle O1H2O3 (α) on the rate of the proton transfer in processes dopamine ProD 1- ProD 5.

Table 2 indicates that the distance between the two reactive centers r_{GM} (O1-H7) varies according to the conformation of the global minimum structure (GM). Short r_{GM} distance values were achieved when the values of the attack angle (α) in the GM conformations were high and close to 180°, whereas small values of α resulted in longer r_{GM} distances.

In fact when the r_{GM} values were plotted against the corresponding α values linear correlation was obtained with $R^2 = 0.9074$ (Figure 18). In addition, examination of the activation energy values ($\Delta G^{\ddagger}$) listed in Table 2 reveals that the energy needed to execute proton transfer in systems dopamine **ProD 1- ProD 5** is largely affected by both the distance between the two reactive centers r_{GM} (O3-H2), and the attack angle α (O1H2O3). Systems with low r_{GM} and high α values in their global minimum structures, such as **ProD 1 and ProD 2**, exhibit much higher rates (lower $\Delta G^{\ddagger}$) than these with high r_{GM} and low α values, such as **ProD 3-ProD 5**.

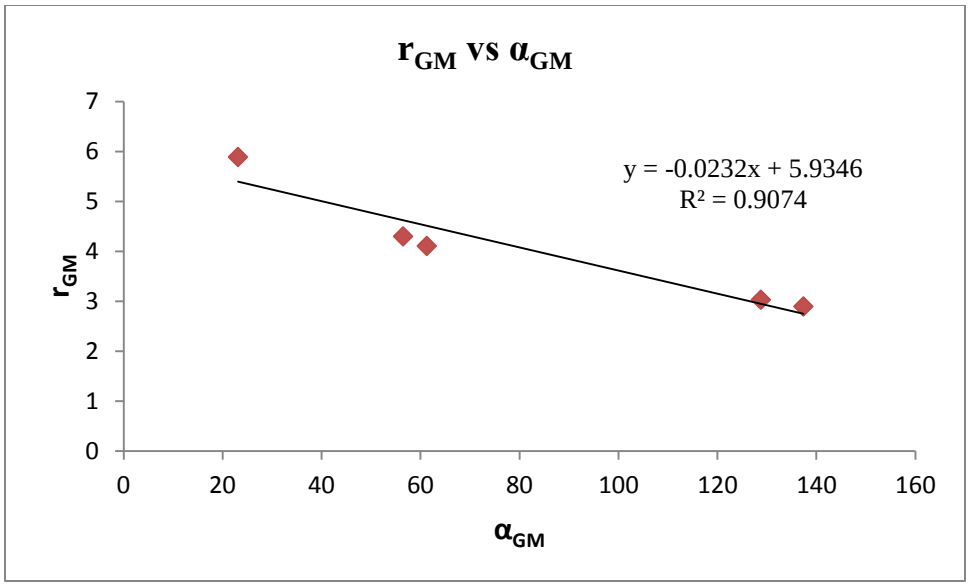


Figure 18: Plot of the DFT calculated r_{GM} (Å) vs. angle α (°) in dopamine **ProD 1-ProD 5**, where (r_{GM}) and (α) are the distance between the two reactive centers and the attack (hydrogen bond) angle in the GM structure, respectively.

When r_{GM} and α values were examined for correlation with the water calculated DFT activation free energies ($\Delta G^{\ddagger}$), a linear correlation was found between $\Delta G^{\ddagger}$ and r_{GM} x (1/α) with a correlation coefficient of R^2= 0.8835 (Figure 19). On the other hand, a correlation of the activation free energies ($\Delta G^{\ddagger}$) with r_{GM}^2 gave an R^2 value of 0.8832, and with r_{GM} gave an R^2 value of 0.8517.

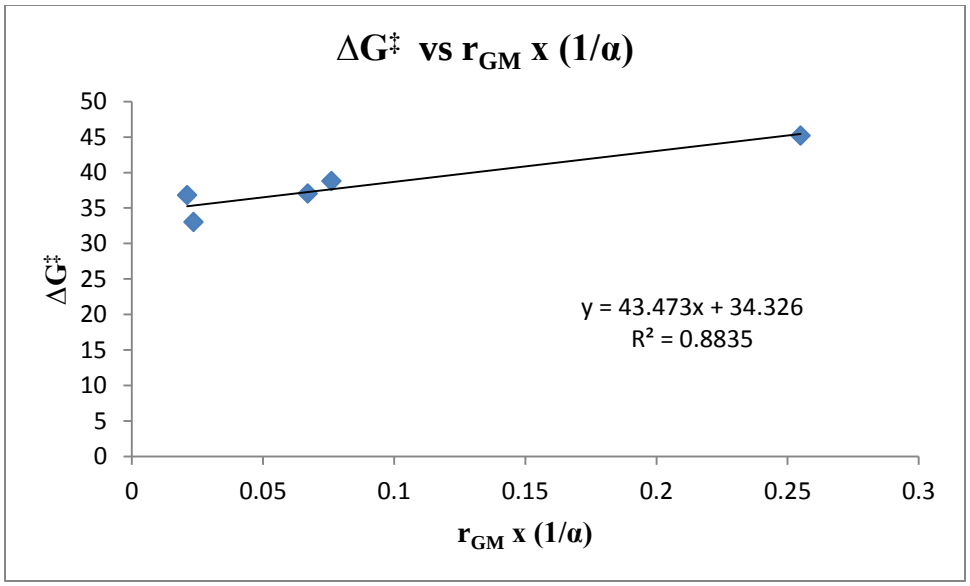


Figure 19: Plot of the DFT calculated $\Delta G^{\ddagger}$ vs. r_{GM} x (1/α) in dopamine **ProD 1-ProD 5**

4.3.2 The role of the strain energy of the intermediates (Es_{INT}) on the rate of the proton transfer in processes dopamine ProD 1- ProD 5.

We calculated, using Allinger's MM2 method [145], the strain energy values for the intermediates (Es_{INT}) in process dopamine **ProD 1-PoD 5** to examine the role of the (Es_{INT}) on the rate of the proton transfer in process dopamine **ProD 1-PoD 5.**

The MM2 strain energies of the intermediates are listed in (Table 3). The calculated MM2 (Es_{INT}) values for the process dopamine **ProD 1-PoD 5** were examined for correlation with the calculated DFT activation free energies ($\Delta G^{\ddagger}$), a linear correlation was found between $\Delta G^{\ddagger}$ and Es_{INT} with a correlation coefficient of R^2= 0.9414 (Figure 20).

Table 3: DFT (B3LYP) calculated kinetic and thermodynamic properties for the acid catalyzed hydrolysis of 1-7 N-alkylmaleamic acid and dopamine ProD 1- ProD 5

System	$\Delta G^{\ddagger}_{H2O}$ (kcal/mol)	Es_{INT}	log k_{rel} [146]
1	33.06	20.55	0
2	20.05	16.16	4.371
3	28.42	17.32	1.494
4	38.11	27.89	-4.377
5	23.12	19.25	2.732
6	27.28	17.59	1.516
7	27.55	18.55	1.648
ProD 1	36.82	9.24	------
ProD 2	33.04	4.85	------
ProD 3	45.20	-1.30	------
ProD 4	37.03	8.75	------
ProD 5	38.79	9.47	------

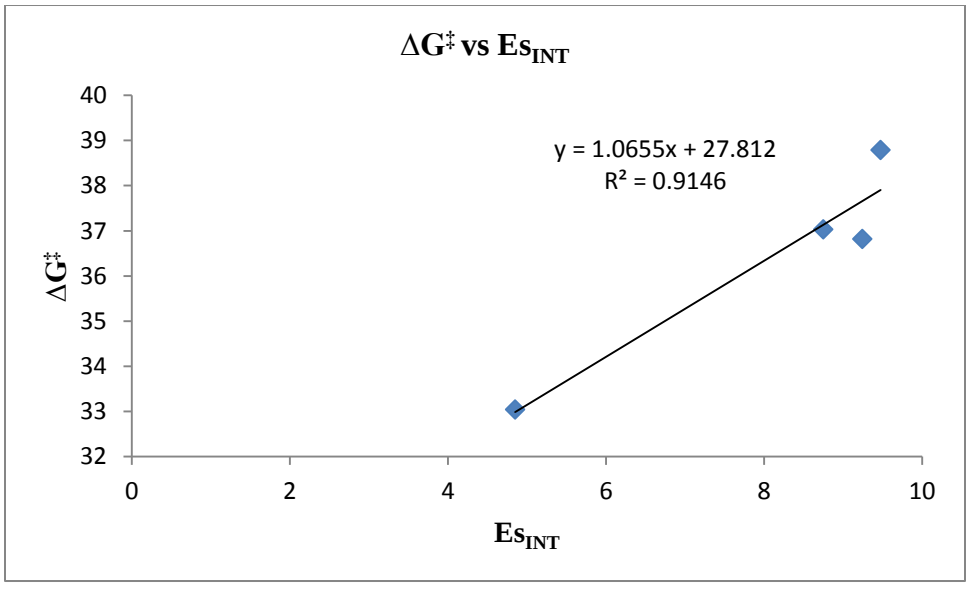


Figure 20: Plot of the DFT calculated $\Delta G^{\ddagger}$ vs. Es_{INT} in dopamine **ProD 1-ProD 5**

Examination of Figure 20 and Table 3 reveals that the rate of a proton transfer in processes dopamine **ProD 1**- **ProD 5** is largely dependent on the strain energy of the tetrahedral intermediate. Systems having strained tetrahedral intermediates were found to be with low rates and vice versa.

In order to further support this conclusion, the B3LYP 6-31G (d,p) activation energy values for **1-7** *N*-alkylmaleamic acid calculated in water ($\Delta G^{\ddagger}_{H2O}$, see Table 3) were examined for correlations with log k_{rel} (relative rate) and the results are shown in (Figure 21). A linear correlation was found between $\Delta G^{\ddagger}_{H2O}$ and log k_{rel} with a correlation coefficient of R^2= 0.9303.

Furthermore, a linear correlation was found between the strain energies for intermediates of 1-7 *N*-alkylmaleamic acid (Es_{INT}) and log k_{rel} (Figure 22) with a correlation coefficient of R^2= 0.885.

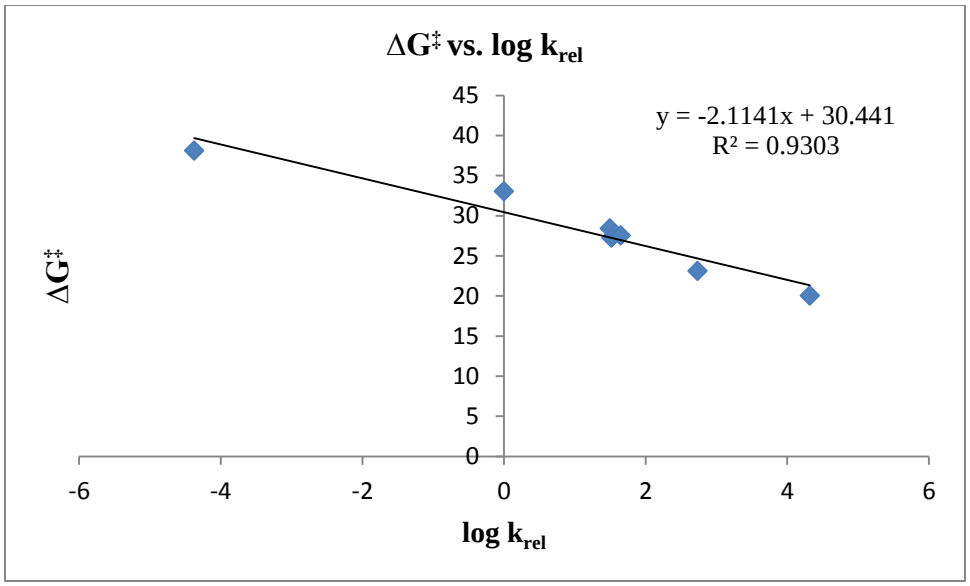


Figure 21: Plot of the DFT calculated $\Delta G^{\ddagger}$ vs. relative rate ($\log_{krel}$) in 1-7 *N*-alkylmaleamic acid.

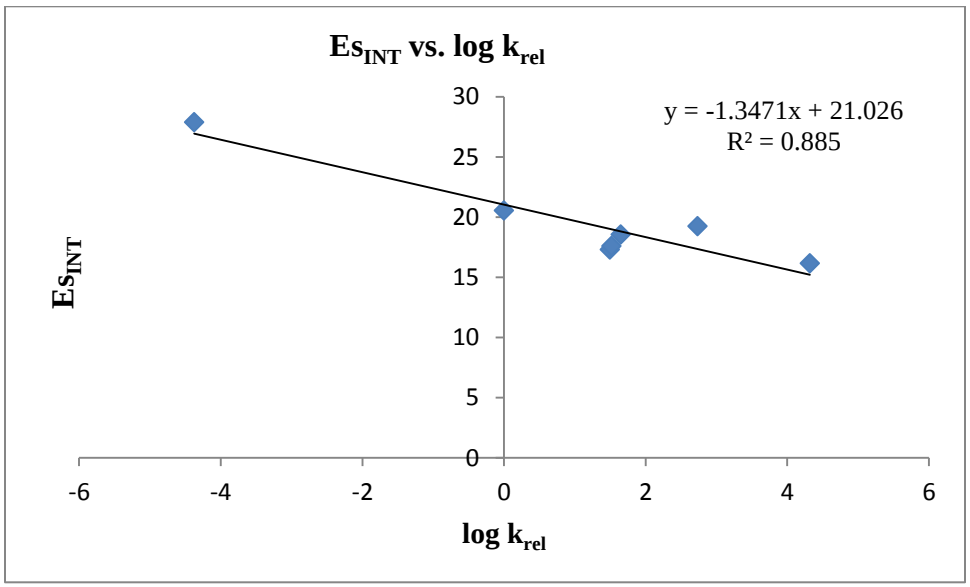


Figure 22: Plot of the Es_{INT} for intermediates of 1-7 *N*-alkylmaleamic acid vs. relative rate ($\log_{krel}$).

Chapter Five

Conclusions and Future Directions

5. Conclusions and future directions

5.1 Conclusions

Based on the DFT calculations results of Kirby`s enzyme model (proton transfer in *N*-alkylmaleamic acids), novel dopamine prodrugs for the treatment of Parkinson's disease that can improve the overall biopharmaceutical profile of the current medications to enhance effectiveness and to ease the use of the medications were designed.

The designed dopamine prodrugs have a carboxylic group as a hydrophilic moiety and a hydrocarbon skeleton as a lipophilic moiety, where the combination of both groups ensures a modified hydrophilic lipophilic balance value.

DFT calculations were made to find a candidate to be used as an efficient dopamine prodrug. The DFT calculation results revealed that the rate of a proton transfer in processes dopamine **ProD 1**- **ProD 5** is largely dependent on the geometric variations of the reactant (GM) mainly the distance between the two reactive centers, r_{GM}, and the angle of attack α. It was found that systems with low r_{GM} and high α values in their global minimum structures, such as **ProD 1** and **ProD 2**, exhibit much higher rates (lower $\Delta G^{\ddagger}$) than these with high r_{GM} and low α values, such as **ProD 3**-**ProD 5**.
Moreover, it was found that the rate of a proton transfer in processes dopamine **ProD 1**-**ProD 5** is largely dependent on the strain energy of the tetrahedral intermediate. Systems having strained tetrahedral intermediates were found to be with low rates and vice versa.

Therefore, I conclude that the best candidate to fulfill the requirements needed to reach better bioavailability than the parent dopamine is dopamine **ProD 1** and **ProD 2.**

5.2 Future directions

Our future directions are (i) to synthesize dopamine **ProD 1** and **ProD 2** using Kirby's synthetic procedure [12]. (ii) *In vitro* kinetic studies at different pH values should be made in order to be utilized for the *in vivo* pharmacokinetic studies which should be

followed to determine the $t_{1/2}$ values for the conversion of the dopamine **ProD 1** and **ProD 2** to their parent drug, dopamine.

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Supplementary Material

Supplementary Material

Xyz Cartesian coordinates for the DFT optimized GM, TS and P in processes Dopamine **ProD 1**- **ProD 5**.

Dopamine **ProD 1GM**

C	-4.019845	-0.164614	-0.476160	M H
C	-3.408892	1.013659	-0.008612	H
C	-2.252503	0.954040	0.757795	M H
C	-1.669030	-0.283294	1.081006	H
C	-2.283033	-1.447952	0.609111	H
C	-3.448392	-1.392342	-0.161736	H
C	-0.387223	-0.339305	1.886379	H
C	0.872835	-0.013776	1.061547	H
N	1.050167	-0.958617	-0.030427	H
C	2.214519	-1.416258	-0.559007	L H
O	2.270117	-2.065945	-1.597720	H
O	-4.050066	2.177811	-0.366748	H
O	-5.156891	-0.103582	-1.223539	H
C	3.498757	-1.264970	0.219664	H
C	4.317937	-0.205441	0.281923	M H
C	3.999309	1.113095	-0.305445	L H
O	2.943190	1.447701	-0.807465	H
O	5.059691	1.955022	-0.218507	H
H	-1.799982	1.878773	1.112912	H
H	-1.853060	-2.415547	0.851618	H
H	-3.926636	-2.295750	-0.525041	M H
H	-5.382782	0.832140	-1.335791	H
H	-0.273127	-1.334904	2.328378	M H
H	-0.434175	0.376808	2.716104	H
H	1.754727	-0.064356	1.704956	H
H	0.816944	1.009507	0.669699	H
H	0.251228	-1.107383	-0.637289	H
H	3.847079	-2.205174	0.642803	H
H	5.292025	-0.295177	0.752230	H
H	4.776545	2.786820	-0.633812	L H
H	-3.554936	2.939462	-0.040739	H

Dopamine **ProD 2GM**

C	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.397076	H
C	1.221221	0.000000	2.107387	M H
C	2.432548	0.000636	1.406504	H
C	2.427151	0.004447	0.006803	H
C	1.212736	0.002446	-0.687277	H
O	1.285078	0.002672	3.478320	H
O	-1.148052	-0.002072	2.159579	H
C	3.720618	0.006522	-0.730794	H
C	4.365052	1.399177	-0.769472	L H
N	3.690200	2.326865	-1.636223	H
C	3.774140	3.696183	-1.491526	H
O	3.350545	4.439520	-2.397126	H
C	4.294346	4.258660	-0.203421	H
C	3.265609	4.417224	0.853801	M H
C	5.567456	4.663536	-0.033553	L H
C	6.030485	5.298190	1.228212	H H
C	6.606524	4.544350	-1.072385	H
O	7.521173	5.328611	-1.335016	H
O	6.570693	3.397392	-1.811352	H
H	3.377036	-0.004007	1.968160	M H
H	1.210621	0.006894	-1.786687	H
H	-0.950742	-0.000465	-0.550417	M
H	0.379523	-0.021092	3.820346	H
H	-1.902842	-0.008418	1.556408	H
H	4.445910	-0.678745	-0.216783	H
H	3.573049	-0.382332	-1.771864	H
H	5.436651	1.284197	-1.109705	H
H	4.377069	1.820484	0.275929	H
H	3.376904	1.982388	-2.514247	L H
H	7.272632	3.424222	-2.480771	H
H	3.658505	4.055029	1.836233	H
H	2.337701	3.847347	0.606877	M H
H	2.998974	5.499416	0.959754	L H
H	7.019120	5.799418	1.085420	L H
H	6.130499	4.524880	2.029917	H
H	5.290495	6.063729	1.570262	M H

Dopamine **ProD 3GM**

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.400794
C	1.229891	0.000000	2.096180
C	2.438120	-0.000567	1.397145
C	2.430961	0.001682	-0.003300
C	1.211175	0.000573	-0.688406
O	1.150192	0.001206	3.472566
O	-1.215119	-0.000864	2.036259
C	3.719860	-0.011358	-0.746850
C	4.464163	1.329624	-0.648531
N	3.810507	2.446457	-1.271776
C	4.009958	2.826605	-2.588719
C	5.213639	2.313348	-3.359517
C	6.499800	2.961966	-2.878069
C	7.598488	1.954088	-2.744751
O	8.820530	2.406573	-3.131097
O	3.216295	3.630484	-3.114193
O	7.544782	0.797452	-2.317482
H	3.390499	-0.005793	1.945114
H	1.202541	-0.002249	-1.788339
H	-0.959096	-0.001071	-0.536438
H	2.050753	-0.029058	3.820872
H	-1.055013	-0.008321	2.991297
H	3.545486	-0.271989	-1.822978
H	4.391753	-0.800159	-0.315731
H	5.492219	1.196176	-1.092961
H	4.588079	1.582550	0.443858
H	2.944608	2.724417	-0.863753
H	5.047612	2.560924	-4.440994
H	5.268838	1.195943	-3.271488
H	6.816914	3.772334	-3.585577
H	6.367610	3.432563	-1.866511
H	9.485553	1.711953	-3.001399

Dopamine **ProD 4GM**

C	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.555752	H H
C	1.460311	0.000000	2.096633	M H
C	2.173514	1.314472	1.675909	H H
C	1.716534	1.851894	0.295267	H H
C	1.244575	0.692312	-0.593812	H H

C	-0.943652	-1.062917	2.141172	H
O	-1.953442	-0.711529	2.744691	H
C	1.479342	-0.228301	3.597092	H
O	1.786127	-1.270841	4.138666	L H
N	-0.700152	-2.398481	1.934056	H
C	0.525857	-3.086651	1.534586	H
C	0.212521	-4.547452	1.168644	H
C	1.447168	-5.304933	0.730285	H
C	2.279469	-5.924495	1.667821	M H
C	3.441064	-6.588264	1.262349	L H
C	3.777851	-6.635868	-0.084912	H
C	2.951893	-6.019162	-1.040392	H
C	1.798278	-5.360652	-0.626347	H
O	4.892386	-7.263179	-0.597402	H
O	3.273596	-6.066750	-2.364038	M H
O	1.073280	0.854826	4.299288	H
H	4.081962	-7.071457	1.996698	M
H	2.023893	-5.895056	2.723010	H
H	1.173327	-4.897820	-1.384479	H
H	5.397993	-7.667741	0.118189	H
H	4.096983	-6.571515	-2.444877	H
H	-0.543325	-4.558784	0.375295	H
H	-0.233803	-5.041749	2.041457	H
H	0.958155	-2.592558	0.660063	L H
H	1.275325	-3.056484	2.335459	H
H	-1.380292	-2.964143	2.428883	H
H	-0.457234	0.929442	1.904323	M H
H	2.001423	-0.850802	1.679073	L H
H	3.253800	1.123322	1.652970	L H
H	2.005981	2.081525	2.437077	H
H	0.851629	2.511393	0.456275	M H
H	2.066605	-0.028896	-0.703182	L H
H	1.019821	1.050890	-1.604871	L H
H	-0.908430	0.515693	-0.330122	H
H	-0.076443	-1.021309	-0.385448	H
H	1.056357	0.582764	5.232393	H
H	2.593915	2.317666	-0.151029	H

Dopamine **ProD 5GM**

C	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.527022	H
C	1.428386	0.000000	2.067591	M H
C	2.137866	1.301820	1.691722	H H

C	1.702631	1.819451	0.323773	H
C	1.233006	0.679270	-0.567784	H H
C	-0.899816	-1.113337	2.053652	H
O	-2.012106	-0.813512	2.536445	H
C	1.452870	-0.199772	3.559499	H
O	1.852235	-1.188158	4.181077	L H
C	2.830486	2.586707	-0.336122	H
N	-0.578093	-2.450217	1.977120	H H
C	0.692954	-3.002202	1.598562	H
C	0.633989	-4.513966	1.327004	H
C	1.995723	-5.015466	0.988397	M H
C	2.910428	-5.298823	2.009557	L H
C	4.185864	-5.772036	1.709935	H
C	4.553416	-5.962914	0.374953	H
C	3.637542	-5.679414	-0.661828	H
C	2.356972	-5.206475	-0.348928	H
O	5.792758	-6.422854	-0.014725	M H
O	3.942889	-5.840830	-1.989930	H
O	0.989880	0.840413	4.301158	M H
H	4.900270	-5.993262	2.514725	H
H	2.620964	-5.143741	3.059236	H
H	1.652000	-4.993190	-1.164435	H
H	6.302546	-6.609824	0.784396	H
H	4.843152	-6.192344	-2.049784	H
H	-0.076681	-4.723690	0.485993	H
H	0.251936	-5.050502	2.235131	L H
H	1.057148	-2.487945	0.664181	H
H	1.447169	-2.819769	2.421553	H
H	-1.235257	-3.082057	2.377721	M H
H	-0.483235	0.957859	1.884758	L H
H	2.001562	-0.858989	1.617365	L H
H	3.242808	1.116404	1.698118	H
H	1.923217	2.086712	2.462337	M H
H	0.834622	2.521237	0.473121	L H
H	2.061374	-0.067402	-0.677990	L H
H	1.002092	1.073514	-1.590263	H
H	-0.922684	0.533005	-0.348385	H
H	-0.056480	-1.045352	-0.397629	H
H	1.018154	0.607750	5.242997	H
H	2.473614	3.061122	-1.280593	H
H	3.679163	1.905601	-0.582074	H
H	3.204047	3.387087	0.345183	H

Dopamine **ProD 1TS**

O	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.492114
C	1.488364	0.000000	1.807878
C	2.210069	-0.033626	0.689812
C	1.279687	-0.089935	-0.472579
N	-0.912209	-1.420282	2.229431
C	-0.640648	-2.764083	1.707733
C	-1.514743	-3.181540	0.499616
C	-0.968843	-4.399045	-0.212215
C	-1.329033	-5.698424	0.156161
C	-0.775689	-6.810740	-0.484651
C	0.151457	-6.638963	-1.507553
C	0.519015	-5.335377	-1.884961
C	-0.032258	-4.232214	-1.246620
O	0.691623	-7.720220	-2.140035
O	1.436186	-5.262487	-2.909663
O	-0.656418	1.150645	1.922401
O	1.542649	-0.210254	-1.645106
H	-1.058052	-7.820583	-0.205666
H	-2.056983	-5.850243	0.948643
H	0.262754	-3.231091	-1.558075
H	1.295701	-7.384316	-2.819381
H	1.613819	-4.336920	-3.120667
H	-1.566363	-2.339075	-0.195008
H	-2.536264	-3.374516	0.851188
H	0.415655	-2.811352	1.428027
H	-0.771629	-3.487107	2.520949
H	-1.903237	-1.198795	2.259262
H	1.826779	0.027120	2.836300
H	3.285069	-0.039721	0.568125
H	-0.322526	1.891320	1.397583

Dopamine **ProD 2TS**

O	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.468718	H
C	1.485280	0.000000	1.826865	M H
C	2.220753	0.006016	0.705476	H
C	1.293231	-0.012538	-0.460088	H
N	-0.942122	-1.405339	2.196998	H
C	-0.579860	-2.755266	1.762781	H
C	-1.371598	-3.810308	2.555894	H

C	-2.870677	-3.729535	2.352963	H
C	-3.490619	-4.368347	1.273199	L H
C	-4.867818	-4.269205	1.066340	H
C	-5.655654	-3.524716	1.939717	H
C	-5.044483	-2.879296	3.027573	H
C	-3.672450	-2.980936	3.230856	H
O	-7.001058	-3.429500	1.743460	M H
O	-5.902424	-2.171899	3.840206	L H
O	-0.662386	1.160870	1.895588	H
C	1.890392	0.033677	3.260867	H H
C	3.698937	0.035853	0.490607	H
O	1.569740	-0.025422	-1.634670	H
H	-5.349587	-4.767708	0.231769	M H
H	-2.892309	-4.957159	0.583347	H
H	-3.218163	-2.478465	4.082952	M H
H	-7.359079	-2.870703	2.449627	H
H	-5.404097	-1.741334	4.545815	H
H	-1.131616	-3.697264	3.619017	H
H	-1.012648	-4.798918	2.247522	H
H	-0.744840	-2.901858	0.684801	H
H	0.490300	-2.901539	1.947695	H
H	-1.934516	-1.231837	2.055553	L H
H	-0.413233	1.866432	1.282588	H
H	3.987307	0.923698	-0.082363	H
H	4.016879	-0.830182	-0.099462	M H
H	4.248953	0.036361	1.434167	M H
H	1.515613	-0.852964	3.784150	M H
H	1.433998	0.899015	3.754465	H
H	2.974237	0.087031	3.382695	M H

Dopamine **ProD 3TS**

O	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.449036	H
C	1.484298	0.000000	1.845365	M H
C	2.141395	0.725541	0.670000	H
C	1.191485	0.465900	-0.491910	H
N	-0.869375	1.554767	1.917920	H
C	-1.290172	1.687327	3.314160	H
C	-1.972987	3.048157	3.542392	H
C	-3.249054	3.224420	2.744929	H
C	-4.473871	2.748778	3.226685	L H
C	-5.645473	2.874763	2.477387	H
C	-5.614151	3.480392	1.224366	H

C	-4.390413	3.963315	0.730245	H
C	-3.225857	3.837655	1.480530	H
O	-6.755716	3.606461	0.491696	M H
O	-4.458978	4.551914	-0.511500	L H
O	-0.589783	-1.184241	1.896931	H
O	1.379835	0.625096	-1.667999	H
H	-6.596539	2.511734	2.852767	H
H	-4.518582	2.278479	4.205289	H
H	-2.289406	4.226633	1.084732	M H
H	-6.521466	4.045872	-0.339834	H
H	-3.576884	4.816588	-0.800901	M
H	-1.259690	3.840590	3.290532	H
H	-2.192797	3.139196	4.612147	H
H	-1.966149	0.879129	3.634157	H
H	-0.401692	1.623796	3.952871	H
H	-1.661888	1.689498	1.293089	H
H	1.647263	0.480596	2.810977	H
H	1.819833	-1.037737	1.910639	L H
H	3.146329	0.382421	0.417883	H
H	2.183983	1.807864	0.830245	H
H	-1.511504	-1.191835	1.598609	M H

Dopamine **ProD 4TS**

O	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.441586	H
C	1.489776	0.000000	1.857147	M H
C	2.136664	-0.767552	0.677266	H
C	1.181162	-0.508143	-0.480376	H
C	3.586881	-0.346216	0.356684	H
C	4.310346	0.051153	1.649327	H H
C	3.635318	1.271932	2.323154	H
C	2.128487	1.386420	1.991583	H H
N	-0.984269	1.467962	1.916142	L H
C	-1.430759	1.525317	3.309273	H
C	-2.193805	2.834986	3.576203	H
C	-3.465767	2.968791	2.764091	H
C	-4.669869	2.411157	3.208809	H
C	-5.835526	2.500053	2.445066	M H
C	-5.818918	3.150449	1.214408	L H
C	-4.616187	3.715495	0.757672	H
C	-3.457517	3.626255	1.522034	H
O	-6.955114	3.241018	0.467671	H
O	-4.697895	4.343109	-0.464485	H

O	-0.519695	-1.241264	1.882866	M H
O	1.367337	-0.673916	-1.656824	H
H	-6.770785	2.073207	2.791978	M
H	-4.703027	1.904730	4.169664	H
H	-2.537202	4.077023	1.155042	H
H	-6.732736	3.722146	-0.343731	H
H	-3.828120	4.670851	-0.725039	H
H	-1.524260	3.676308	3.366207	H
H	-2.435037	2.872393	4.644636	H
H	-2.060362	0.667006	3.589103	L H
H	-0.546696	1.488944	3.956317	H
H	-1.775373	1.560507	1.282666	H
H	1.587563	-0.554072	2.795006	M
H	2.098594	-1.844699	0.879310	M H
H	1.616024	1.979851	2.753203	M H
H	1.987896	1.929579	1.049601	H
H	4.133921	2.195538	2.007932	M H
H	3.771225	1.207221	3.409080	M H
H	4.300660	-0.805820	2.335218	M H
H	5.364851	0.265592	1.445904	H
H	3.584516	0.496938	-0.343587	H
H	4.104826	-1.162580	-0.154333	H
H	-1.389624	-1.353504	1.470665	H

Dopamine **ProD 5TS**

O	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.413281	H
C	1.452091	0.000000	1.892137	M H
C	2.179566	-0.639275	0.677165	H
C	1.237543	-0.377543	-0.488611	H
C	3.603742	-0.102111	0.430646	H
C	4.292299	0.167885	1.774301	H H
C	3.543210	1.254718	2.588045	H
C	2.050589	1.376113	2.206106	H H
N	-0.861874	1.571693	1.781863	L H
C	-1.575563	1.459885	3.053494	H
C	-2.508091	2.674274	3.255847	H
C	-3.649425	2.735421	2.262645	H
C	-4.858483	2.075133	2.508740	H
C	-5.900342	2.097619	1.578706	M H
C	-5.751293	2.783961	0.377103	L H
C	-4.542470	3.451984	0.119131	H
C	-3.508280	3.428520	1.048455	H

O	-6.766319	2.810618	-0.532989	H
O	-4.488789	4.108113	-1.090466	H
O	-0.678514	-1.082605	1.913966	M H
O	1.451899	-0.454880	-1.666574	H
H	-6.840167	1.590947	1.772175	M
H	-4.994545	1.539299	3.444333	H
H	-2.581012	3.956328	0.833035	H
H	-6.462014	3.331817	-1.291247	H
H	-3.618035	4.507929	-1.207370	H
H	-1.904690	3.586667	3.193200	H
H	-2.911446	2.623745	4.274068	H
H	-2.168593	0.536825	3.157621	L H
H	-0.835868	1.449553	3.864149	H
H	-1.552745	1.550307	1.026998	H
H	1.513646	-0.642569	2.775221	M
H	2.218104	-1.728897	0.804907	M H
H	1.486517	1.861876	3.005161	M H
H	1.929459	2.021220	1.329569	H
H	4.019788	2.229704	2.436990	M H
H	3.634285	1.033537	3.657920	M H
H	5.334518	0.462802	1.613998	M H
H	3.557423	0.820731	-0.158580	H
H	4.168112	-0.819951	-0.171042	H
H	-1.519595	-1.158612	1.437892	H
C	4.799483	-0.847647	2.676497	H
H	5.236782	-0.369820	3.551924	H
H	4.016028	-1.135999	3.375763	H
H	5.350787	-1.595399	2.108297	H

Dopamine **ProD 1P**

O	2.535086	-0.767970	-0.945705
C	3.683824	-0.003575	-0.694514
C	4.185361	-0.397517	0.651714
C	3.394618	-1.361746	1.129660
C	2.307518	-1.594448	0.142123
N	2.118088	2.035683	0.821779
C	0.690960	1.714219	0.985049
C	-0.011325	1.622344	-0.379313
C	-1.408488	1.050704	-0.275831
C	-2.535618	1.869253	-0.162198
C	-3.815324	1.322830	-0.026055
C	-3.986549	-0.057450	0.000438
C	-2.857774	-0.887334	-0.114447

C	-1.588522	-0.342094	-0.252675
O	-5.232667	-0.598460	0.130960
O	-3.120456	-2.239237	-0.084454
O	4.146316	0.743673	-1.505630
O	1.360488	-2.334280	0.205071
H	-4.692779	1.955781	0.056945
H	-2.419587	2.949594	-0.184830
H	-0.730881	-1.005751	-0.346619
H	-5.129666	-1.562037	0.118074
H	-2.291169	-2.729006	-0.158400
H	0.602402	1.001238	-1.039769
H	-0.049233	2.623771	-0.827773
H	0.618534	0.743360	1.491556
H	0.146911	2.434646	1.617825
H	2.221804	2.852152	0.221915
H	5.066972	0.052538	1.087129
H	3.448185	-1.901093	2.065418
H	2.519657	2.294120	1.720414

Dopamine **ProD 2P**

O	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.468718	H H
C	1.485280	0.000000	1.826865	M H
C	2.220753	0.006016	0.705476	H
C	1.293231	-0.012538	-0.460088	H
N	-1.534401	-2.288826	2.654843	H
C	-1.172138	-3.638752	2.220625	H
C	-1.963877	-4.693794	3.013738	H
C	-3.462956	-4.613022	2.810807	H
C	-4.082897	-5.251834	1.731043	L H
C	-5.460097	-5.152691	1.524184	H
C	-6.247933	-4.408202	2.397561	H
C	-5.636761	-3.762783	3.485417	H
C	-4.264729	-3.864423	3.688700	H
O	-7.593337	-4.312986	2.201304	M H
O	-6.494703	-3.055386	4.298050	L H
C	1.890392	0.033677	3.260867	H H
C	3.698937	0.035853	0.490607	H
O	1.569740	-0.025422	-1.634670	H
H	-5.941865	-5.651194	0.689613	H
H	-3.484588	-5.840646	1.041191	M
H	-3.810442	-3.361952	4.540796	H
H	-7.951358	-3.754190	2.907471	M

H	-5.996375	-2.624821	5.003659	H
H	-1.723895	-4.580751	4.076861	H
H	-1.604926	-5.682405	2.705367	H
H	-1.337119	-3.785345	1.142645	H
H	-0.101979	-3.785025	2.405539	H
H	-2.526795	-2.115323	2.513397	H
H	3.987307	0.923698	-0.082363	L H
H	4.016879	-0.830182	-0.099462	H
H	4.248953	0.036361	1.434167	H
H	1.515613	-0.852964	3.784150	M H
H	1.433998	0.899015	3.754465	M H
H	2.974237	0.087031	3.382695	L H
H	-1.323862	-2.183296	3.634945	H
O	-1.319871	0.012797	1.935385	M H

Dopamine **ProD 3P**

O	0.000000	0.000000	0.000000	M H
C	0.000000	0.000000	1.409171	H
C	1.443559	0.000000	1.867178	M H
C	2.132814	0.728913	0.710010	H
C	1.208881	0.481756	-0.474241	H
N	-1.087614	2.723317	2.042134	H
C	-1.650768	2.734753	3.391077	H
C	-2.388960	4.064357	3.663316	H
C	-3.620944	4.260729	2.805373	H
C	-4.871725	3.786049	3.215540	L H
C	-6.003385	3.931761	2.409733	H
C	-5.904454	4.557676	1.170627	H
C	-4.653914	5.039519	0.748186	H
C	-3.530108	4.893690	1.553978	H
O	-7.006682	4.704483	0.381539	M H
O	-4.654049	5.648129	-0.487069	L H
O	-0.754589	-1.003987	1.925680	H
O	1.404728	0.649341	-1.644402	H
H	-6.974629	3.569608	2.730563	H
H	-4.968760	3.300180	4.182729	H
H	-2.570676	5.277225	1.211745	M H
H	-6.726136	5.160074	-0.426520	H
H	-3.758178	5.925434	-0.715759	M
H	-1.683622	4.887600	3.504179	H
H	-2.673369	4.082919	4.721990	H
H	-2.340349	1.898753	3.594883	H
H	-0.826210	2.644954	4.110245	H

H	-1.863588	2.752228	1.374956	H
H	1.560295	0.483667	2.836994	H
H	1.781552	-1.038909	1.947473	L H
H	3.142916	0.387068	0.478379	H
H	2.161390	1.808917	0.882603	H
H	-0.492985	3.527945	1.919440	L H

Dopamine **ProD 4P**

O	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.441586
C	1.489776	0.000000	1.857147
C	2.136664	-0.767552	0.677266
C	1.181162	-0.508143	-0.480376
C	3.586881	-0.346216	0.356684
C	4.310346	0.051153	1.649327
C	3.635318	1.271932	2.323154
C	2.128487	1.386420	1.991583
N	-1.613555	2.406495	2.219546
C	-2.060045	2.463850	3.612677
C	-2.823092	3.773519	3.879607
C	-4.095053	3.907324	3.067496
C	-5.299156	3.349690	3.512213
C	-6.464812	3.438586	2.748470
C	-6.448205	4.088982	1.517812
C	-5.245474	4.654028	1.061077
C	-4.086804	4.564788	1.825438
O	-7.584400	4.179551	0.771075
O	-5.327182	5.281642	-0.161081
O	-0.519695	-1.241264	1.882866
O	1.367337	-0.673916	-1.656824
H	-7.400071	3.011740	3.095383
H	-5.332314	2.843263	4.473068
H	-3.166488	5.015556	1.458446
H	-7.362022	4.660679	-0.040327
H	-4.457407	5.609384	-0.421635
H	-2.153547	4.614841	3.669611
H	-3.064324	3.810926	4.948041
H	-2.689648	1.605539	3.892507
H	-1.175983	2.427477	4.259721
H	-2.404659	2.499040	1.586071
H	1.587563	-0.554072	2.795006
H	2.098594	-1.844699	0.879310
H	1.616024	1.979851	2.753203

H	1.987896	1.929579	1.049601	
H	4.133921	2.195538	2.007932	
H	3.771225	1.207221	3.409080	
H	4.300660	-0.805820	2.335218	
H	5.364851	0.265592	1.445904	
H	3.584516	0.496938	-0.343587	
H	4.104826	-1.162580	-0.154333	
H	-0.964546	3.157407	2.043529	

Dopamine **ProD 5P**

O	-1.408551	1.245472	1.447692	M H
C	-1.908610	-0.028904	1.704266	H
C	-3.197463	-0.245142	0.917531	M H
C	-3.500236	1.135448	0.299326	H H
C	-2.244749	1.949078	0.559000	H
C	-3.874827	1.079176	-1.194204	H
C	-4.887732	-0.049777	-1.470570	H H
C	-4.295048	-1.435389	-1.056940	H H
C	-3.046369	-1.351339	-0.155893	H H
N	0.405296	-1.413191	-0.847466	L H
C	0.946563	-2.198347	0.267537	H
C	2.452960	-2.545936	0.185008	H
C	3.354466	-1.330927	0.164343	H
C	3.688625	-0.660839	1.347489	H
C	4.487045	0.483643	1.332399	M H
C	4.970763	0.985703	0.127111	L H
C	4.642263	0.323745	-1.066497	H
C	3.843474	-0.815437	-1.046904	H
O	5.757968	2.099062	0.110437	H
O	5.168208	0.887668	-2.209218	H
O	-1.332708	-0.783028	2.438625	M H
O	-1.940655	3.023086	0.123499	H
H	4.748777	0.999821	2.250101	M
H	3.321547	-1.038350	2.297768	H
H	3.611948	-1.319555	-1.984205	H
H	5.984560	2.280900	-0.813905	H
H	4.925878	0.355686	-2.976964	H
H	2.630209	-3.156010	-0.711080	H
H	2.704985	-3.178178	1.045900	H
H	0.750139	-1.645634	1.191436	L H
H	0.371733	-3.129695	0.334431	H
H	0.940355	-0.550851	-0.937895	H
H	-3.969714	-0.549153	1.632541	L H

H	-4.304567	1.632779	0.854960	L H
H	-2.866711	-2.308216	0.343174	M H
H	-2.144866	-1.159551	-0.746269	H
H	-4.030553	-2.016898	-1.946760	L H
H	-5.073194	-2.011789	-0.541514	L H
H	-5.067610	-0.060303	-2.552399	M H
H	-2.970841	0.912460	-1.790606	H
H	-4.274416	2.048447	-1.506769	H
C	-6.238764	0.218039	-0.786702	H
H	-6.974306	-0.541727	-1.070330	H
H	-6.156312	0.195921	0.306561	H
H	-6.643548	1.196051	-1.070318	H
H	0.541177	-1.918676	-1.721680	H

تصميم طلائع أدوية مبتكرة من الدوبامين – النهج الحسابي

إعداد: اسراء تيسير محمد قطوش

إشراف: البروفيسور رفيق قرمان

الملخص:

من المعروف أن مرضى الباركنسون (Parkinson) يعانون من نقص في مادة الدوبامين (dopamine) في مناطق معينه في الدماغ، لذلك كانت المحاولات لتعويض هذا النقص من الدوبامين. الدوبامين وحده لا يمر من الحاجز الدموي الدماغي لكن طليعه الليفودوبا (Levodopa) استطاع العبور إلى الجهاز العصبي المركزي (CNS) ليتم تحويله الى الدوبامين في الدماغ. عند اعطاء الليفودوبا (LD) عن طريق الفم كان التوافر الحيوي له أقل من 10% مع أقل من 1 % من الجرعة تخترق الدماغ. جرعات كبيرة من الليفودوبا مطلوبة، لأن الكثير منه يتم تحويله إلى الدوبامين خارج الدماغ مما يؤدي إلى الآثار الجانبية التي تشمل الغثيان، التقيؤ، عدم انتظام ضربات القلب وانخفاض ضغط الدم. للحد من التحويل إلى الدوبامين خارج الجهاز العصبي المركزي(CNS) عادة ما يعطى الليفودوبا مع مثبط الإنزيم المسئول عن نزع مجموعة الكربوكسيل (carboxyl group) من الدوبامين مثل (Carbidopa, benserazide) (كاربيدوبا و بنسيرازايد). على الرغم من ذلك، آثار عصبية مركزية جانبية أخرى كخلل في الحركة، وتدهور الحالة عند نهاية الجرعة لا تزال قائمة.

في هذا المشروع تم تصميم دوبامين prodrugs باستعمال الطرق الحسابية DFT molecular orbital على مستويات مختلفة من B3LYP 6-31G (d, p) وحسابات MM2 بهدف الحصول على prodrugs والتي من المتوقع أن يكون لها توافر حيوي أعلى من الدواء الأم بسبب تحسن امتصاص الدوبامين prodrug المحتمل. علاوة على ذلك، يعتقد بان هذه prodrugs لها فعالية أكثر من الليفودوبا، لأن هذا الأخير يخضع لنزع الكربوكسيل في المحيط الخارجي قبل الوصول إلى حاجز الدماغ الدموي.

كشفت نتائج حساب DFT أن معدل نقل البروتون في العمليات الدوبامين ProD 1- ProD 5 يعتمد بشكل كبير على الاختلافات الهندسية للمفاعل (GM) وبشكل أساسي على المسافة بين المركزين المتفاعلين، r_{GM}، وزاوية الهجوم α. حيث وجد ان الانظمة ذات المسافة المنخفضة (r_{GM}) وقيم الزاوية α المرتفعة مثل ProD1 و ProD2 في هياكلها تظهر معدلات اعلى بكثير (أقل $\Delta G^{\ddagger}$) من تلك التي لها مسافة مرتفعة (r_{GM}) و قيمة الزاوية α منخفضة مثل ProD3-ProD5 و يرتبط معدل التفاعل ارتباطا خطيا مع r_{GM} و(α /1).

علاوة على ذلك، لقد وجد أن معدل التحويل الداخلي لدوبامين prodrug يتأثر بشكل كبير بقوة strain لكل من رباعية الاسطوح المتوسطة ، حيث ان من تملك strain اعلى يكون معدل التحويل الداخلي أقل ، والعكس صحيح.

عمادة الدراسات العليا
جامعة القدس

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إعداد
اسراء تيسير محمد قطوش

بكالوريوس صيدلة-جامعة القدس، فلسطين

المشرف الرئيسي: بروفيسور رفيق قرمان

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