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**Design of Novel Phenylephrine and Paracetamol
Prodrugs by Computational Methods**

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Prodrugs by Computational Methods**

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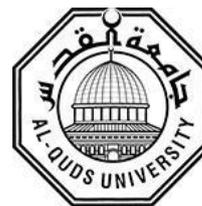
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Thesis Approval

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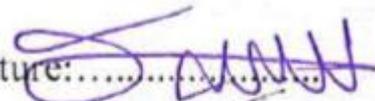
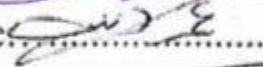
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Dedication

At first I want to thank my husband and my Supervisor Professor Rafik Karaman who helped through my whole career, encouraged me to pursue a study for a master degree and gave me the opportunity to be a researcher. Thank you very much my dear husband.

I would like to thank my family, my mother, father, sisters and brothers who stood solid to help me through the long years I spent with them. I am very grateful for their support, love and prayers that were the driving force for my success.

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:

Donia Ibrahim Karaman

Date: 5/1/2016

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Special thanks to my husband and my family for their help ;they were always with me and in a close proximity to help and without their assistance and support I could not achieve what I actually achieved.

Donia Karaman

Abstract

Using density functional theory (DFT) molecular orbital at B3LYP 6-31G (d, p) and B3LYP/311+G (d, p) levels and molecular mechanics (MM2) calculations intramolecular proton transfer in a number of Kirby's enzyme models, **1-10**, and of Bruice's di-carboxylic semi- esters, **11-15**, a number of Phenylephrine and Paracetamol prodrugs were designed aiming to provide medicines lacking bitter sensation and with higher bioavailability than their parent drugs.

It was found that the inter conversion rate of the designed paracetamol prodrugs is largely determined on the strain energies of the reaction's tetrahedral intermediates and reactants, and no correlation was found between the cyclization rate and distance between the nucleophile and the electrophile (r_{GM}). While in the case of phenylephrine prodrugs it was found that the driving force for the proton transfer efficiency is the distance between the two reactive centers (r_{GM}) and the attack angle (α) and the rate of the reaction is linearly correlated with r_{GM}^2 and $\sin(180^\circ - \alpha)$.

Using the experimental $t_{1/2}$ (the time needed for the conversion of 50% of the reactants to products) and EM (effective molarity) values for these processes the $t_{1/2}$ values for the conversion of the phenylephrine and paracetamol prodrugs to their parent drugs were calculated. The calculated $t_{1/2}$ values for phenylephrine ProD1 and ProD2 were very high (145 days and several years, respectively) whereas that of phenylephrine ProD3 was about 35 hours. On the other hand, the calculated $t_{1/2}$ values for paracetamol ProD1-ProD3 were 3 minutes, 1 hour and 8.4 hours, respectively.

Therefore, the intra-conversion rates of the phenylephrine prodrugs to phenylephrine and paracetamol prodrugs to paracetamol can be programmed according to the nature of the prodrug linker.

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List of Abbreviations

Abbreviations	Definition
DFT	Density Functional theory
EM	Effective Molarities
GP	Gas Phase
GM	Global Minimum
HLB	Hydrophilic Lipophilic Balance
HF	Hartree -fock method
H ₂ O	Water
MM	Molecular Mechanics
P	Product
PCM	Polarizable Continuum model
ProD	Prodrug
QM	Quantum Mechanics
r _{GM}	Distance in the Global minimum
t _{1/2}	Half Life
UFF	Universal Force Field
A	Angle of Attack
ΔG^{++}	Activation Energy

Chapter one
Introduction

Chapter one

Introduction

1.1 Background

The past five decades have witnessed an increasing number of chemists, biochemists, biologists and other researchers in various fields who use computational methods for better understanding the mechanism of organic reactions and biochemical processes as well as for predicting active biological molecules[1].

The term computational chemistry is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer.

Computational chemistry is the application of chemical, mathematical and computing skills to the solution of interesting chemical problems. It uses computers to generate information such as properties of molecules or simulated experimental results. In chemistry almost every aspect has been described in a qualitative or approximate quantitative computational scheme.

Computational chemistry has become a useful way to investigate materials that are too difficult to find or too expensive to purchase. It also helps chemists make predictions before running the actual experiments so that they can be better prepared for making observations[1].

HOW COMPUTATIONAL CHEMISTRY IS USED??!!

Computational chemistry is used in a number of different ways. One particularly important way is to model a molecular system prior to synthesizing that molecule in the laboratory. It uses the theoretical chemistry results, incorporated into efficient computer programs, to calculate the structures and physical and chemical properties of molecules. [2] This is very useful information because synthesizing a single compound could require months of labor and raw materials, and generate toxic waste.

A second use of computational chemistry is in understanding physical or chemical problems more completely. There are some properties of a molecule that can be obtained computationally and more easily than by experimental means. There are also insights into molecular bonding, which can be obtained from the results of computations that cannot be obtained from any experimental method. Thus, many experimental chemists are now using computational modeling to gain additional understanding of the compounds being examined in the laboratory [1].

Today the quantum mechanics (QM) such as ab initio, semi-empirical and density functional theory (DFT), and molecular mechanics (MM) are commonly and increasingly being used and broadly accepted as precise tool for predicting structure – energy calculations for drugs and prodrugs [3].

► *Quantum mechanics (QM)*

QM is the correct mathematical description of the behavior of electrons and thus of chemistry. In theory, QM can predict the property of an individual atom or molecule in an exact manner. In practice, the QM equations have only been solved exactly for one

electron systems. A myriad collection of methods has been developed for approximating the solution for multiple electron systems.

The quantum mechanics includes: (1) *ab-initio*, (2) semi-empirical and (3) DFT methods.

1- *Ab initio* Methods:

The term *ab initio* is Latin for "from the beginning". This name is given to computations that are derived directly from theoretical principles with no inclusion of experimental data. This is an approximate quantum mechanical calculation. The approximations made are usually mathematical approximations[1]. *Ab initio* methods typically are adequate only for small systems and are based entirely on theory from first principles. The *ab initio* molecular orbital methods (QM) such as HF, G1, G2, G2MP2, MP2 and MP3 are based on rigorous use of the Schrodinger equation with a number of approximations. *Ab initio* electronic structure methods have the advantage 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. The disadvantage of *ab-initio* methods is their enormous computational cost. They take a significant amount of computer time, memory, and disk space [4-8].

Schrodinger equation: Schrodinger equation a simple, rigorous fundamental equation of physics for describing quantum mechanical behavior developed to describe the behavior of an ensemble of two quantum level, non interacting systems which are under the influence of a perturbation. In this case the Schrödinger equation may be written, after a suitable transformation, in the form of the real three dimensional vector equation $d \mathbf{r}/dt = \boldsymbol{\omega} \times \mathbf{r}$, where the components of the vector \mathbf{r} uniquely determine ψ of a given system and the components of $\boldsymbol{\omega}$ represent the

perturbation. When magnetic interaction with a spin $\frac{1}{2}$ system is under consideration, \mathbf{r} & apos; space reduces to physical space. By analogy the techniques developed for analyzing the magnetic resonance precession model can be adapted for use in any two-level problems. The quantum-mechanical behavior of the state of a system under various different conditions is easily visualized by simply observing how \mathbf{r} varies under the action of different types of $\boldsymbol{\omega}$. Such a picture can be used to advantage in analyzing various MASER-type devices such as amplifiers and oscillators. In the two illustrative examples given (the beam-type MASER and radiation damping) the application of the picture in determining the effect of the perturbing field on the molecules is shown and its interpretation for use in the complex Maxwell & apos;s equations to determine the reaction of the molecules back on the field[9] .

The time-dependent one-dimensional Schrödinger equation is given by

$$i\hbar \frac{\partial \Psi}{\partial t} = -\frac{\hbar^2}{2m} \frac{\partial^2 \Psi}{\partial x^2} + V(x)\Psi(x,t) \equiv \tilde{H}\Psi(x,t),$$

Where i is the imaginary unit, Ψ is the time-dependent wave function, \hbar is h-bar, $V(x)$ is the potential, and \tilde{H} is the Hamiltonian operator[9].

2- Semi-empirical Methods:

Semi-empirical calculations are set up with the same general structure as a Hartree-Fock (HF) calculation in that they have a Hamiltonian and a wave function. Within this framework, certain pieces of information are approximated or completely omitted. Usually, the core electrons are not included in the calculation and only a minimal basis set is used. Also, some of the two-electron integrals are omitted .In order to correct for the errors introduced by omitting part of the calculation, the method is parameterized. Parameters to

estimate the omitted values are obtained by setting the results to experimental data or *ab initio* calculations. Often, these parameters replace some of the integrals that are excluded. The advantage of the semi empirical calculations is that they are much faster than *ab initio* calculations and their disadvantage is that the results can be erratic and fewer properties can be predicted reliably. If the molecule being computed is similar to molecules in the database used to parameterize the method, then the results may be very good. If the molecule being computed is significantly different from anything in the parameterization set, the answers (solutions) may be very poor[1].

The commonly used semi-empirical methods are MINDO, MNDO, MINDO/3, AM1, PM3 and SAM1. Calculations of molecules containing up to 100 atoms (this number can be increased if super computers are utilized) can be handled using semi-empirical methods[10, 11].

3- Density functional theory (DFT):

DFT has become very popular in recent years. This is justified based on the pragmatic observation that it is less computationally intensive than other methods with similar accuracy. This theory has been developed more recently than other *ab initio* methods to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules, and molecules in the condensed phases (solid phase) [12].

With this method the energy of a molecule can be determined from the electron density using functions that is functions of another function. This theory originated with a theorem by Hohenberg and Kohn. The original theorem was applied for the ground-state electronic energy of a molecule. A practical application of this theory was developed by Kohn and Sham who formulated a method similar in structure to the Hartree-Fock method[13].

The DFT method is adequate 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[12].

Although the use of DFT method is significantly increasing some difficulties still encountered when describing intermolecular interactions, especially van der 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[12].

► *Molecular Mechanics*

The most severe limitation of *ab initio* methods is the limited size of the molecule that can be modeled on even the largest computers. Semi-empirical calculations can be used for large organic molecules, but are also too computation-intensive for most bimolecular systems. 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[1].

Molecular mechanics is a mathematical approach used for the computation of structures, energy, dipole moment, and other physical properties. It is widely used in calculating many diverse biological and chemical systems such as proteins, large crystal structures, and relatively large solvated systems. However, this method is limited by the determination of parameters such as the large number of unique torsion angles present in structurally diverse molecules [14].

Molecular mechanics simulations, for example, use a single classical expression for the energy of a compound, for instance the harmonic oscillator. The database of compounds

used for parameterization, i.e., the resulting set of parameters and functions is called the force field, is crucial to the success of molecular mechanics calculations. A force field 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. These methods can be applied to proteins and other large biological molecules, and allow studies of the approach and docking of potential drug molecules. Since the size of the system which *ab initio* calculations can handle is relatively small despite the large sizes of biomacromolecules surrounding solvent water molecules such as in the cases of enzymes and receptors, isolated models of areas of proteins such as active sites have been investigated using *ab initio* calculations. However, 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 discrepancies, quantum mechanics/molecular mechanics (QM/MM) calculations are used, in which 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[15], and since then, there has been a significant progress on the development of a QM/MM algorithm and applications to biological systems [16, 17]

1.2 Phenylephrine:

Phenylephrine is (*R*)-3-[-1-hydroxy-2-(methyl amino) ethyl] phenol (Figure 2) with a molecular weight of 167.205 g/mol and molecular formula of $C_9H_{13}NO_2$. Its bioavailability is 38% through GI tract.

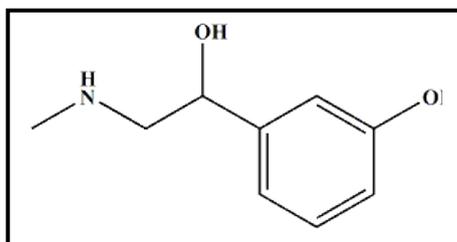


Figure 1: Chemical structure of phenylephrine

Phenylephrine is a powerful vasoconstrictor used as a nasal decongestant and cardio tonic agent, produces its local and systemic actions by acting on α_1 -adrenergic receptors peripheral vascular smooth muscle. Stimulation of the α_1 -adrenergic receptors results in contraction arteriolar smooth muscle in the periphery. Phenylephrine decreases nasal congestion by acting on α_1 -adrenergic receptors in the arterioles of the nasal mucosa to produce constriction; this leads to decreased edema and increased drainage of the sinus cavities[18, 19]

1.3 Paracetamol:

Paracetamol-acetyl-*p*-aminophenol, acetaminophen, is a white crystalline powder with a bitter taste having a molecular formula of $C_8H_9NO_2$ and molecular weight of 151.5 g/mol. Paracetamol consists of benzene ring with a hydroxyl and amide groups on the para positions.

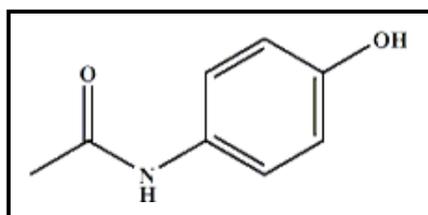


Figure 2: Chemical structure of Paracetamol

Paracetamol is an over the counter analgesic and anti-pyretic drug. It is used to relief minor aches. Paracetamol is used as pain killer by decreasing the synthesis of prostaglandin due to inhibiting cyclooxygenases (COX-1 and COX-2)[20].It is favored over aspirin as pain killer in patients who have excessive gastric secretion or prolonged bleeding[21].It was approved to be used as fever reducer in all ages.

1.4Research problem

1.4.1Phenylephrine:

Phenylephrine is completely absorbed after oral administration. It has a reduced bioavailability (compared to pseudoephedrine) following oral administration due to significant first-pass metabolism in the intestinal wall. Compared to IV administration; its bioavailability is approximately 38%. Peak serum concentrations are achieved approximately 0.75-2 hours following oral administration. Phenylephrine should be administered parenterally to achieve cardiovascular effects. Occasionally, systemic effects are observed following oral inhalation[19].

Phenylephrine from an oral dosage form undergoes pre-systemic conjugation in the small intestine to produce phenylephrine-glucuronide and phenylephrine-sulfate and it undergoes extensive pre-systemic metabolism, with a majority of the metabolism taking place within the enterocytes of the gastrointestinal tract. The metabolic pathway of phenylephrine is illustrated in Figure 4. Phenylephrine is metabolized by Phase I and Phase II enzyme systems, mainly monoamine oxidase and sulfotransferase, respectively. The ratios of the metabolites differ depending on the route of administration. Schering-Plough Research Institute (SPRI) conducted studies to determine the affinity and functional activity of *m*-hydroxymandelic acid, phenylephrine sulfate conjugate and phenylephrine glucuronide conjugate (Figure 4) at the human recombinant α -adrenoreceptors (α 1a and α 1b subtypes)

and α 2-adrenoreceptors (α 2a, α 2b and α 2c subtypes) [22]. The affinity of the above mentioned metabolites was determined by receptor binding assays. None of the conjugates tested demonstrated any activity in these test systems [23-26].

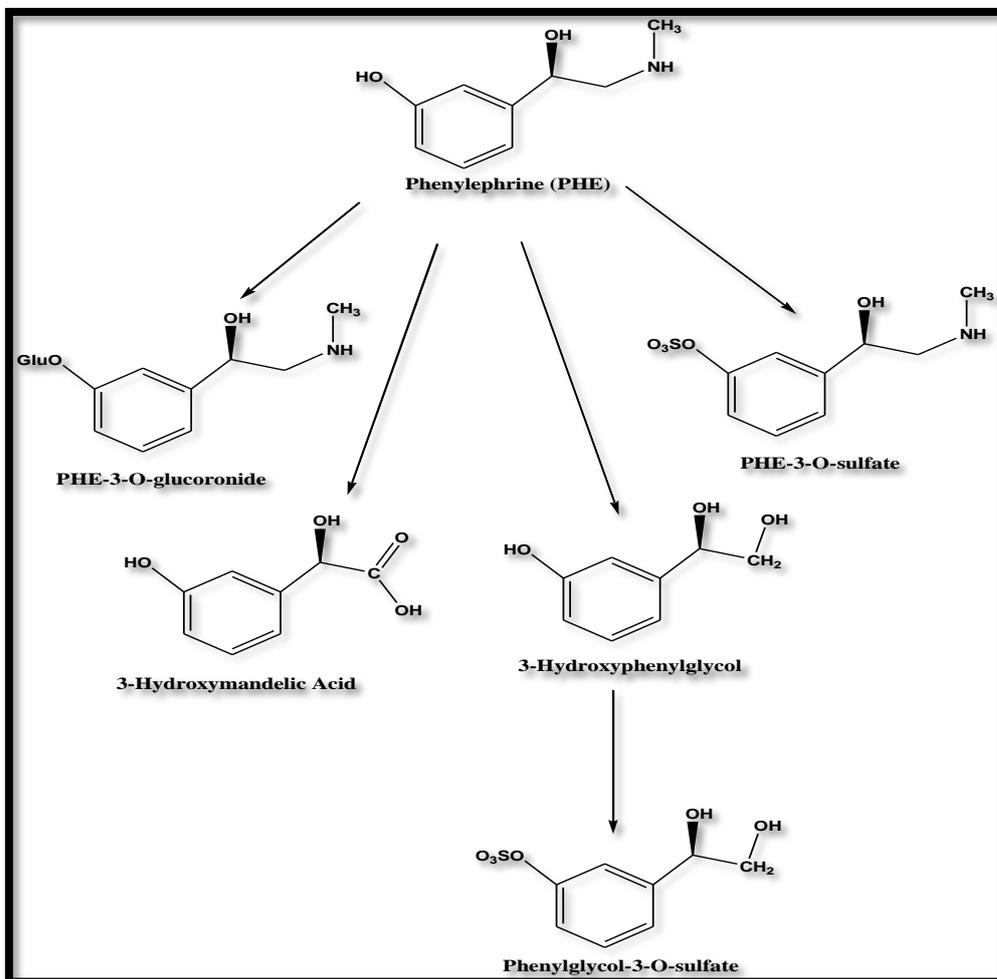


Figure 3: Metabolic pathways for phenylephrine in humans.

1.4.2 Paracetamol:

Paracetamol is the most used antipyretic agent over the world to reduce fever and pain in geriatrics and pediatrics. This pain killer has an extremely unpleasant and bitter taste which is difficult to mask. The bitter and unpleasant taste of a drug might reduce the patient compliance especially in geriatric and pediatric patients who administer the drug three to four times daily via a solution or suspension dosage form.

Paracetamol was found in the urine of patients who had taken phenacetin and later on, it was demonstrated that paracetamol was a urinary metabolite of acetanilide (Figure 3c). Phenacetin (Figure 3b), on the other hand, lacks or has a very slight bitter taste. Examination of the structures of paracetamol and phenacetin reveals that the only difference in the structural features between these three entities is the nature of the group in the *para* position of the benzene ring. While in the case of paracetamol the group is hydroxyl, in phenacetin it is ethoxy. Acetanilide has a chemical structure similar to that of paracetamol and phenacetin but lacks the group in the *para* position of the benzene ring, making it lack the bitter taste characteristic of paracetamol. These combined facts suggest that the presence of a hydroxyl group on the *para* position is the major contributor for the bitter taste of paracetamol. Therefore, it is expected that blocking the hydroxyl group in paracetamol with a suitable linker could inhibit the interaction of paracetamol with its bitter taste receptors and hence masks its bitter taste[27].

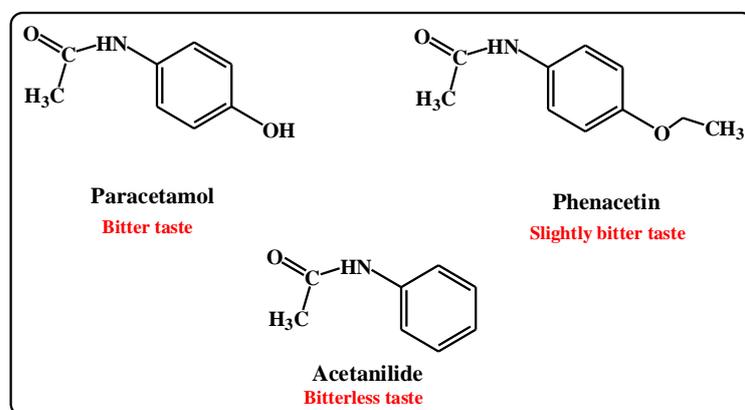


Figure4: Chemical structures of Paracetamol, Phenacetin and Acetanilide.

1.5 Thesis Objectives

1.5.1 General objective

The main goal of this research was to design prodrugs, with better bioavailability, lacking any bitter or unpleasant sensation 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.

1.5.2 Specific objectives

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

- 1- Converted to phenylephrine in a controlled manner.
- 2- The linker attached to the drug moiety and the whole phenylephrine prodrug moiety should have no toxicity and safe.
- 3- To be tasteless and provide systems with enhanced bioavailability compared to the naked phenylephrine.

► Calculations of Bruice's enzyme model for the design of paracetamol prodrugs with the following properties:

- 1- Be bitterless and converted to paracetamol in programmable manner.
- 2- The linker attached to the drug moiety and the whole paracetamol prodrug moiety should have no toxicity and safe.

1.6 Research questions

► Would the DFT and ab initio methods be capable of producing reaction rates similar to that obtained by Kirby and Bruice?

► Would the DFT calculations be good methods for the design of phenylephrine and paracetamol prodrugs that have the potential to mask the bitterness of the active drugs and be cleaved in physiological environments to furnish the active drugs and a non-toxic moiety and have a better bioavailability than their parent drug (applicable for phenylephrine)?

Chapter Two
Literature Review

Chapter two

Literature Review

2.1 Introduction

2.1.1 Enzymes

Enzymes are biological catalysts. Most of them are proteins; there are about 40,000 different enzymes in human cells, each controlling a different chemical reaction. They increase the rate of reactions by a factor of 10^{10} to 10^{18} fold than the non-enzymatic ones.

Enzymes are imposed for the interconversion of many of prodrugs to their active parent drugs. Among the most important enzymes in the bioconversion of prodrugs are those for amides, such as, trypsin, chymotrypsin, elastase, carboxy-peptidase, and amino-peptidase and for esters, such as paraoxnase, carboxyl esterase, acetylcholine-esterase and choline-esterase. Most of these enzymes are hydrolytic enzymes, however, non-hydrolytic ones, including all cytochrome P450 enzymes, are also capable of catalyzing the bioconversion of ester and amide-based prodrugs[28].

2.1.2 Intramolecular and intermolecular reactions

Intermolecular forces: The forces holding molecules together and play important roles in determining the properties of substances. Intermolecular forces are particularly important in terms of how molecules interact and form biological organisms or even life[29].

In general, intermolecular forces can be divided into several categories:

1. Strong ionic attraction; recall lattice energy and its relations to properties of solid. The more ionic, the higher the lattice energy.
2. Intermediate dipole-dipole forces; substances whose molecules have dipole moment, have higher melting point or boiling point than those of similar molecular mass, but their molecules have no dipole moment.
3. Weak London dispersion forces or van der Waal's force. These forces always operate in any substance. The force arises in from induced dipole and the interaction is weaker than the dipole-dipole interaction. In general, the heavier the molecule, the stronger the van der Waal's force of interaction. For example, the boiling points of inert gases increase as their atomic masses increase due to stronger London dispersion interactions.
4. Hydrogen bonding; certain substances such as H_2O , HF , NH_3 form hydrogen bonds, and the formation of which affects properties of substance. Other compounds containing OH and NH_2 groups also form hydrogen bonds. Molecules of many organic compounds such as alcohols, acids, amines, and amino acids contain these groups, and thus hydrogen bonding plays an important role in biological science.
5. Covalent bonding; covalent is really intramolecular force rather than intermolecular force. It is mentioned here, because some solids are formed due to covalent bonding. For example, in diamond, silicon, quartz etc., all atoms in the entire crystal are linked together by covalent bonding. These solids are hard, brittle, and have high melting points. Covalent bonding holds atoms tighter than ionic attraction.
6. Metallic bonding; forces between atoms in metallic solids belong to another category. Valence electrons in metals are rampant. They are not restricted to certain

atoms or bonds. Rather they run freely in the entire solid, providing good conductivity for heat and electric energy. This behavior of electrons gives special properties such as ductility and mechanical strength to metals.

Intramolecular forces: is any force that holds the atoms together making up a molecule or compound, they contain all types of chemical bond and are stronger than intermolecular forces[30].

Intramolecular reactions: In these reactions the functional groups bring together on the same molecule to model what goes on when an enzyme brings together the same functional groups in its active site[31]. The nature of the reaction (intermolecular or Intramolecular) is largely dependent on the distance between the two reacting centers. *ab initio* calculations done by Karaman and Menger demonstrated that when the distance between the two reacting centers is about 2.4Å, the reaction is intramolecular, whereas when the distance is 3Å and more, the reaction prefers the intermolecular process[32].

2.1.3 Prodrugs

Many therapeutic drugs have undesirable properties that may become pharmacological, pharmaceutical, or pharmacokinetic barriers in clinical drug application. Among the various approaches to minimize the undesirable drug properties while retaining the desirable therapeutic activity, is the chemical approach using prodrug.

The term "prodrug" was first introduced by Albert[33], to signify pharmacologically inactive chemical moiety that can be used to temporarily alter the physicochemical properties of a drug in order to increase its usefulness, by overcoming pharmaceutical, pharmacokinetic, or pharmacological barriers, such as low absorption, lack of site specificity, insufficient chemical stability, poor solubility, toxicity, and unacceptable

taste/odor. The use of the term usually implies a covalent link between a drug and a chemical entity. Generally, prodrugs can be enzymatically or chemically degraded *in vivo* to furnish the parent active drug which exerts a therapeutic effect. Ideally, the prodrug should be converted to the parent drug and non-toxic moiety as soon as its goal is achieved, followed by the subsequent rapid elimination of the released linker group [34, 35].

There are two major prodrug design approaches that are considered as widely used among all other approaches to minimize or eliminate the undesirable drug physicochemical properties while maintaining the desirable pharmacological activity:

- 1- The first approach is the targeted drug design approach by which prodrugs can be designed to target specific enzymes or carriers by considering enzyme-substrate specificity or carrier-substrate specificity in order to overcome various undesirable drug properties. This type of "targeted-prodrug" design requires considerable knowledge of particular enzymes or carriers, including their molecular and functional characteristics[36-38].
- 2- The second approach is the chemical design approach by which the drug is linked to inactive organic moiety which upon exposure to physiological environment releases the parent drug and a non-toxic linker which should be eliminated without affecting the clinical profile.

The prodrug chemical approach can be classified into two sub-classes:

(I)carrier-linked prodrugs; contain a group that can be easily removed enzymatically, such as an ester or labile amide, to provide the parent drug. Ideally, the group removed is pharmacologically inactive and nontoxic, and (II) bio-precursors; chemical entities that are metabolized into new compounds that may be active or further are metabolized to active metabolites, such as amine to aldehyde to carboxylic acid [34, 39-42].

However, there are major challenges facing the prodrug approach strategy including:

1. hydrolysis of prodrugs by esterase's; the most common approaches for prodrug design are aimed at prodrugs undergoing *in vivo* cleavage to the active drug by catalysis of hydrolyses such as peptidases, phosphates, and carboxyl-esterases [43]. The less than complete absorption observed with several hydrolyses-activated prodrugs of penicillins, cephalosporins, and angiotensin-converting enzyme inhibitors highlights yet another challenge with prodrugs susceptible to esterase hydrolysis. These prodrugs typically have bioavailability around 50% because of their premature hydrolysis during the absorption process in the enterocytes of the gastrointestinal tract [43]. Hydrolysis inside the enterocytes releases the active drug, which in most cases is more polar and less permeable than the prodrug and is more likely to be effluxes by passive and carrier-mediated processes back into the lumen than to proceed into blood, therefore limiting oral bioavailability.
2. Bioactivation of the prodrug by cytochrome P450 enzymes. The P450 enzymes are super family enzymes that account for up to 75% of enzymatic metabolism of drugs, including several prodrugs. There is accumulating evidence that genetic polymorphisms of prodrug-activating P450s contribute substantially to the variability in prodrug activation and thus to the efficacy and safety of drugs using this bioactivation pathway [44, 45].

To overcome these problems the novel prodrug approach for drugs that contain hydroxyl, phenol, or amine groups can be designed based on intramolecular processes (enzyme models), that were advocated to assign the factors playing dominant role in enzyme catalysis. The design of prodrugs is based on computational calculations using different molecular orbital and molecular mechanics methods, and correlations between

experimental and calculated rate values for some intramolecular processes. This approach does not require enzyme catalysis for the intraconversion of a prodrug to its active parent drug. The release rate of the active drug is determined only by the factors playing dominant role in the rate limiting step of the intra-conversion process.

Using this approach might have a potential to eliminate all disadvantages associated with prodrug interconversion by enzymes [28].

In the past five decades proposals have been made from attempts to interpret changes in reactivity versus structural variations in intramolecular systems. Many organic chemists and biochemists, such as Bender, Jencks, Bruice, Menger, Kirby and Walesh have extensively studied a variety of intramolecular systems (enzyme models) for understanding how enzymes catalyze biochemical reactions [46-50].

Among the proposals and hypothesis advocated by the above mentioned scientists and others to explain enzyme catalysis are:

- (I) Koshland “orbital steering” which suggests a rapid intramolecularity arises from a severe angular dependence of organic reactions, such as in the lactonization of rigid hydroxy acids [51].
- (II) “Proximity orientation” in intramolecular processes (near attack conformation) as proposed by Bruice and demonstrated in the lactonization of di-carboxylic acids semi-esters [52-54].
- (III) “Stereopopulation control” based on the concept of freezing a molecule into a productive rotamer as advocated by Cohen [55-57]
- (IV) Manger’s “spatiotemporal hypothesis” which postulates that the rate of reaction between two reactive centers is proportional to the time that the two centers reside within a critical distance [58-62]

(V) Kirby's proton transfer models on the acid-catalyzed hydrolysis of acetals and N-alkylmaleamic acids which demonstrated the importance of hydrogen bonding formation in the products and transition states leading to them [31, 63-70].

Recently Karaman's group has been researching the mechanistic pathways of some intramolecular processes that mentioned above which used as enzyme models for their utilization as prodrug linkers to commonly used drugs suffer from poor bioavailability or/and have bitter sensation [10-27]. Utilizing DFT and ab initio molecular orbital calculation methods, Karaman's group studied the following intramolecular processes (enzyme models):

(a) Acid-catalyzed lactonization of hydroxy-acids and proton transfer between two oxygens in rigid systems as investigated by Menger [58-61] and Cohen [55-57], (b) S_N2 -based cyclization reactions of di-carboxylic semi-esters to yield anhydrides as studied by Bruice [53, 71], (c) intramolecular S_N2 -based ring-closing reactions as researched by Brown's [72] and Mandolini's groups [73], (d) proton transfer between two oxygen's in Kirby's acetals and proton transfer between nitrogen and oxygen in Kirby's N-alkylmaleamic acids [31, 74-77].

The conclusions emerged from these studies are:

(1) The driving forces for enhancements in rate for intramolecular processes are both entropy and enthalpy effects. In the cases by which enthalpy effects were predominant such as ring-closing and proton transfer reactions proximity or/and steric effects were the driving force for the rate accelerations.

- (2) The nature of the reaction being intermolecular or intramolecular is determined on the distance between the two reactive centers.
- (3) In S_N2 -based ring-closing reactions leading to three-, four- and five-membered rings the *gem*-dialkyl effect is more dominant in processes involving the formation of an unstrained five-membered ring, and the need for directional flexibility decreases as the size of the ring being formed increases.
- (4) Accelerations in the rate for intramolecular reactions are a result of both entropy and enthalpy effects.
- (5) An efficient proton transfer between two oxygens and between nitrogen and oxygen in Kirby's acetal systems were affordable when a strong hydrogen bonding was developed in the products and the corresponding transition states leading to them.

Chapter three
Computational (Design) section

Chapter three

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 Gaussian2009

3.1.3 Molden

3.1.1 Arguslab:

Arguslab, a free downloaded program, is a molecular modeling, graphics, and drug design program that offers quite good on-screen molecule-building facilities, with a moderate library of useful molecules. This program can do geometry optimizations using the universal force field (UFF). This 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 are distinctly different from those obtained using some of the more conventional force fields, and wherever possible one needs to re-optimize at a higher level. For this, Arguslab offers geometry optimization using the MNDO, AM1 or PM3 semi-empirical methods, as well as single point calculations. There are also single point semi-empirical calculations using Extended Huckel (for a bigger element coverage) or ZINDO (for excited states for UV/visible absorption

prediction). Version 3.1 of Arguslab has good facilities for calculating electron density or orbital surfaces at the semi-empirical levels, and displaying them[78] .

Argus lab 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, we press the 'New' button (top left) to get a new molecule screen, *or* press the 'Open' button to read in a molecule which have saved previously in the your Argus directory.

In Arguslab, we need to save our molecule with whatever name we want before doing a geometry optimization as well as afterwards. This is so that all the ancillary files will have the right names. If we forget to change the file name before modifying a molecule, files will be saved automatically with the name used previously, possibly destroying data which we 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. We need to do it repeatedly to close all the windows (if we have several open) and then stop the program.

3.1.2 Gaussian 2009

Gaussian 09 is the latest version in the Gaussian series of computer program for computational chemistry designed to model a broad range of molecular systems under a variety of conditions, performing its computations starting from the basic laws of quantum mechanics. Theoretical chemists can use Gaussian 09 to perform basic research in established and emerging areas of chemical interest. Experimental chemists can use it to

study molecules and reactions of definite or potential interest, including both stable species and those compounds which are difficult or impossible to observe experimentally (short-lived intermediates, transition structures and so on)[79].

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

AM1, PM3, MINDO/3, MNDO, HF, DFT, MP2 and MP3 in all possible different levels can be run using Gaussian 09 installed on PC, a computer station or computer server.

► Creating the first input file: input files can be created in two ways:

- By hand: using local editor (VI, emacs and nedit)

- Using Molden:

► Viewing output files from files run in Gaussian 09. Further, input files for use in Gaussian 09 can be generated using Molden program.

► Dissecting the output file: 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 made for displaying molecular densities from the ab-initio packages, Games-US, Games-UK and Gaussian, as well as Mopac/Ampac. The benefit of using this programs format is simple. Molden can interpret

and convert information from all these programs into its own format, thereby providing a standardizing tool. The Molden program 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[80].

►Molden format:

1-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.

2-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 hp2392.

3-Also 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.

4- Molden 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.

5- Molden has a powerful Z-matrix editor which gives full control over the geometry and allows building molecules from scratch, including polypeptides.

3.2 Calculation methods:

3.2.1 Phenylephrine prodrugs

The Becke three-parameter, hybrid functional combined with the Lee, Yang, and Parr correlation functional, denoted B3LYP, were employed in the calculations using density functional theory (DFT). All calculations were carried out using the quantum chemical package Gaussian-2009 [81]. Calculations were carried out based on the restricted Hartree-Fock method [81]. The starting geometries of all calculated molecules were obtained using the Argus Lab program [82] 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-C3 in increments of 10° (i.e. variation of the dihedral angle O5C4C3C2, 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 [83]. Transition states were located first by the normal reaction coordinate method [84] where the enthalpy changes was 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 [81]. The “reaction coordinate method” [84] was used to calculate the activation energy in systems **1-10**, phenylephrine **ProD1- ProD3**, paracetamol **ProD1- ProD3** and **Inter**(Figures 5 - 7). 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” [84]. The transition state structures were verified by their only one negative frequency. Full optimization of the transition states was accomplished after removing any constraints 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 with and without the inclusion of solvent (water). The calculations with the incorporation of a solvent were performed using the integral equation formalism model of the Polarizable Continuum Model (PCM) [85-88]. 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.

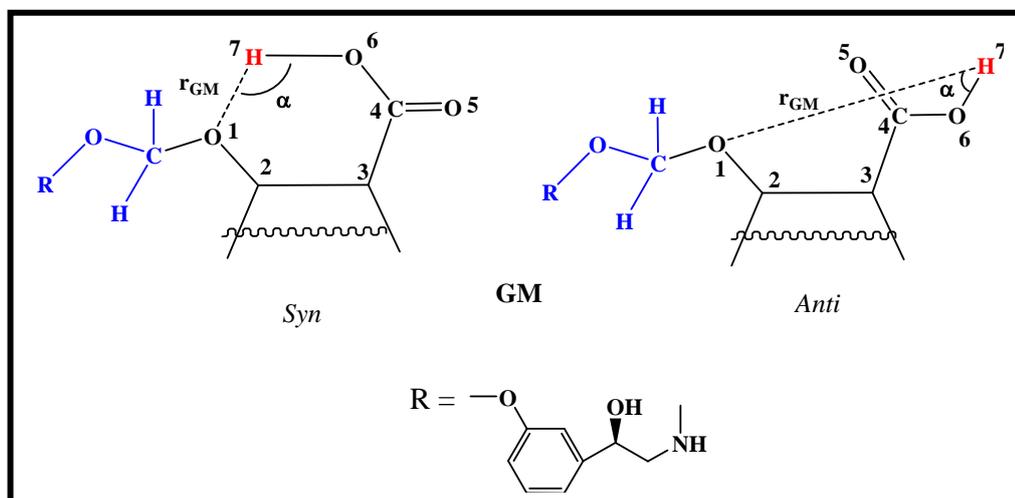


Chart 1: Schematic representation of the reactants in the proton transfers of phenylephrine **ProD1-ProD 3**. GM is the global minimum structure, r_{GM} is the O—H distance in the GM. α , is the angle of attack (hydrogen bonding) O1-H7-O6 in the GM.

3.2.2 Paracetamol prodrugs

The MM2 molecular mechanics strain energy calculations were carried out using Allinger's MM2 program [89]. The Becke three-parameter, hybrid functional combined with the Lee, Yang, and Parr correlation functional, denoted B3LYP, were employed in the calculations using density functional theory (DFT) at B3LYP/6-311 + G (d,p) level. All calculations were carried out using the quantum chemical package Gaussian-2009 [81]. The starting geometries of all studied molecules were obtained using the Argus Lab program [82] and were initially optimized at the HF/6-31G level of theory, followed by optimization at the B3LYP/6-311 + G (d,p) level. 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 C3-C4 in increments of 10° (i.e. variation of the dihedral angle C2C3C4C5, see Chart 2) and calculation of the energies of the resulting conformers.

Transition states were located first by the normal reaction coordinate method [84]. The "reaction coordinate method" [84] was used to calculate the activation energy in all systems studied. The transition state structures for all systems studied were obtained from the increase in the distance between the phenolic oxygen (O) and the carbonyl carbon (C) in increments of 0.1 Å (see Chart 2). The activation energy values for the cyclization reactions of all di-carboxylic semi-esters were calculated from the difference in energies of the global minimum structures (GM) and the derived transition states (TS). The transition state structures were verified by their only one negative frequency. Full optimization of the transition states was accomplished after removing any constraints imposed while executing the energy profile. The activation energies obtained from the DFT at B3LYP/6-311 + G (d,p) level of theory for all molecules were calculated with and without the inclusion of solvent (dielectric constant of 78.39, water). The calculations with solvent were performed using the integral equation formalism model of the Polarizable Continuum Model (PCM)

[85-88, 90]. 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.

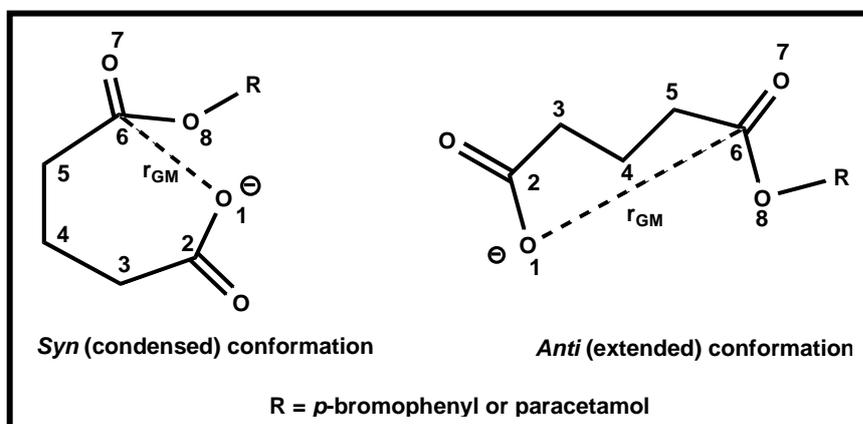


Chart 2: Schematic representation of the reactants in the cyclization reactions of di-carboxylic semi-esters and paracetamol prodrugs. (r_{GM}) is the distance between the nucleophile (O1) and the electrophile (C6).

Chapter4

Results and Discussion

Chapter4

Results and Discussion

4.1 Phenylephrine

It was revealed from Karaman's studies on intramolecularity that there is a need to further investigate the reaction mechanism for assigning the factors determining the reaction rate. This would allow for better design of an efficient chemical device that can be used as a prodrug linker and that will have the potential to chemically and not enzymatically liberate the active drug in a programmable and controlled manner. For example, the mechanism for proton transfer in Kirby's acetals was explored and directed the synthesis of novel prodrugs of aza-nucleosides for the treatment of myelodysplastic syndromes where the prodrug linker is attached to the hydroxyl group of the nucleoside[91]. The prodrugs were designed such that they undergo cleavage reactions in physiological environments such as stomach, intestine, and/or blood circulation, with rates that are solely dependent on the structural features of the pharmacologically inactive linker. Different linkers were also investigated for the design of a large number of prodrugs such as anti-Parkinson (dopamine), [92]anti-viral (acyclovir),[93] and anti-malarial (atovaquone) with enhanced dissolution, membrane penetration, and bioavailability[94]. In addition, prodrugs for masking the bitter taste of atenolol were also designed and synthesized [27, 95]. The role of the linkers in these prodrugs is to block the free phenol group, which is responsible for the bitter taste of the drug, in the corresponding parent drug and to enable the release of the drug in a programmable manner [27, 95].

Since phenylephrine is extensively metabolized by monoamine oxidase in the gastrointestinal tract and in the liver it has a reduced and variable bioavailability (only up to 38%) [96-99]. Therefore, development of more lipophilic prodrug that is stable in aqueous medium and has the capability to release the parental drug in physiological environments such as intestine is a significant challenge. In addition, masking the bitterness of phenylephrine which is considered as a challenge to health providers might assist in broad use of the drugs among children and geriatrics.

Two approaches could be considered to fulfill the requirements mentioned above:

Blocking the free amino group or/and blocking the phenolic hydroxyl group.

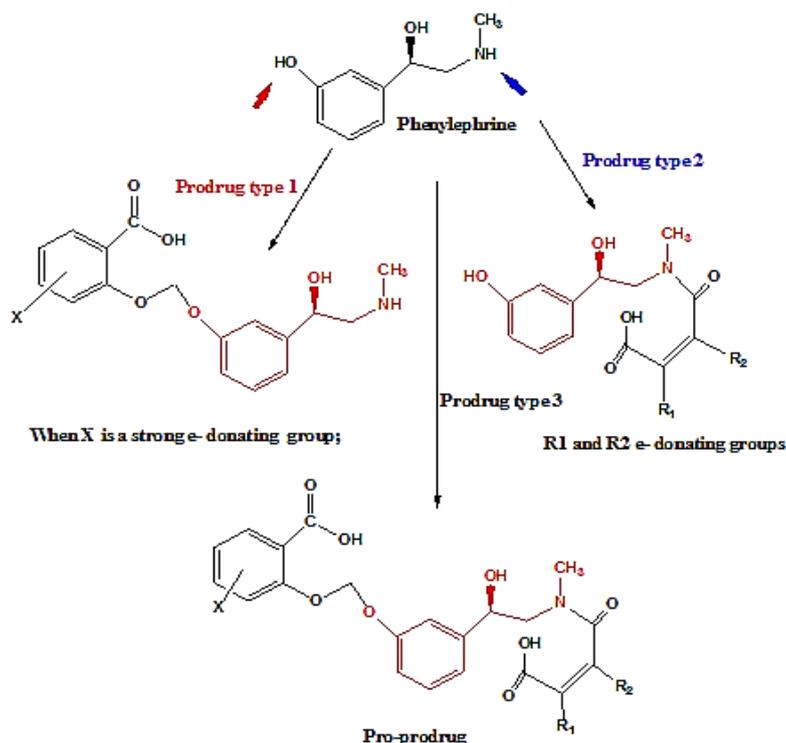
In this thesis, based on proton transfers in Kirby's enzyme models **1-10** reactions (Figure 5) [31, 74-77] I propose three phenylephrine prodrug systems (Figure 6). Figure 7 illustrates the intermolecular hydrolysis of acetal for a comparison with the intramolecular ones.

As shown in Figure 6, the phenylephrine prodrugs, **ProD1- ProD3**, have a carboxylic acid group (hydrophilic moiety) and a lipophilic moiety (the rest of the molecule), where the combination of both groups ensures a moderate HLB. It should be noted that the HLB value will be determined upon the physiologic environment by which the prodrug is dissolved. For example, for prodrugs intended to be given as solutions or syrups to children or pediatrics (for masking the bitterness of the parent drug) the prodrug will reach the stomach and it will primarily exist in the carboxylic acid form whereas in the blood circulation (in the cases of IV injection dosage form) the carboxylate anion form will be predominant. It is planned that **ProD1- ProD3** will be obtained as sodium or potassium salts and will be given to adults in the form of enteric coated tablets in order to assure release of the parent drug in the intestine (pH 6-8) and not in the stomach (pH 1). This is because the linker (Kirby's enzyme model) undergoes fast hydrolysis at low pH such as the

stomach. On the other hand, the prodrugs when dissolved in the intestine they can exist in both the carboxylate and free carboxylic acid forms (the ratio between the two forms will be determined on the pK_a value of the prodrug).

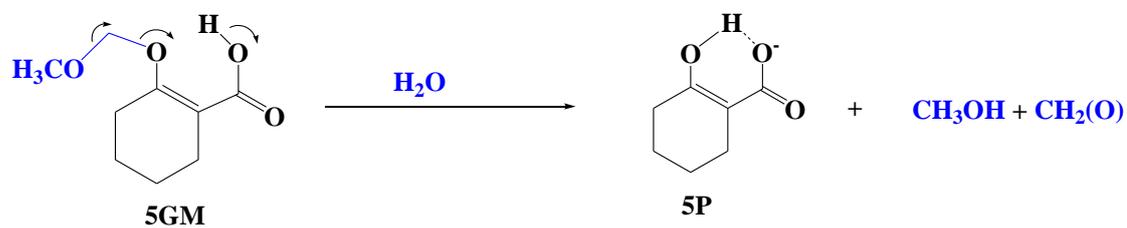
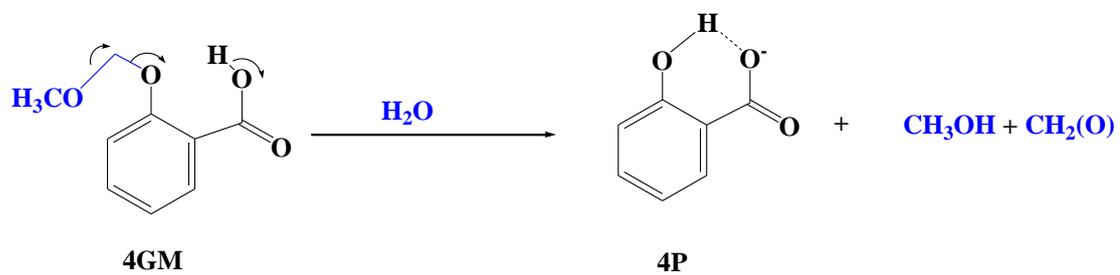
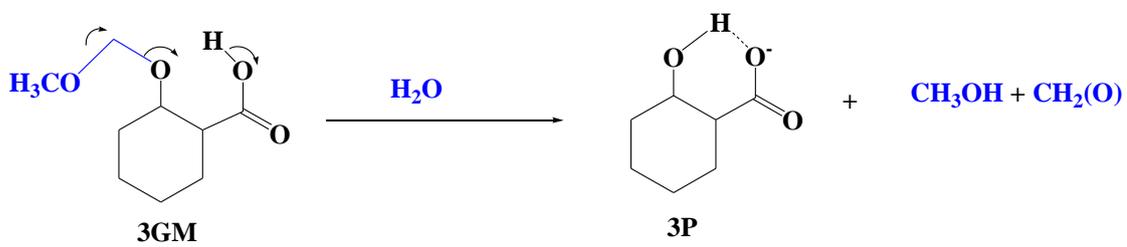
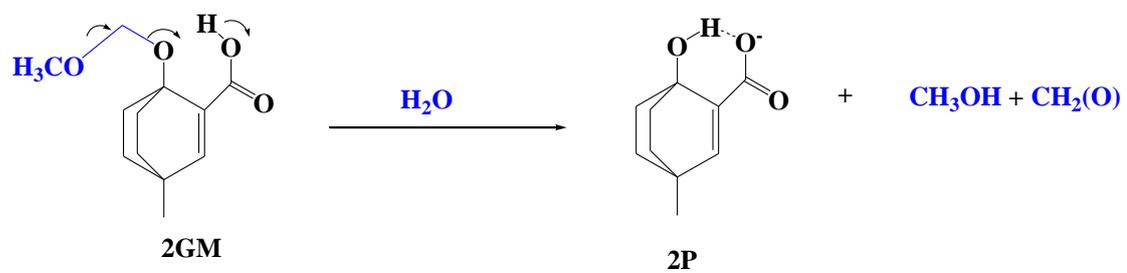
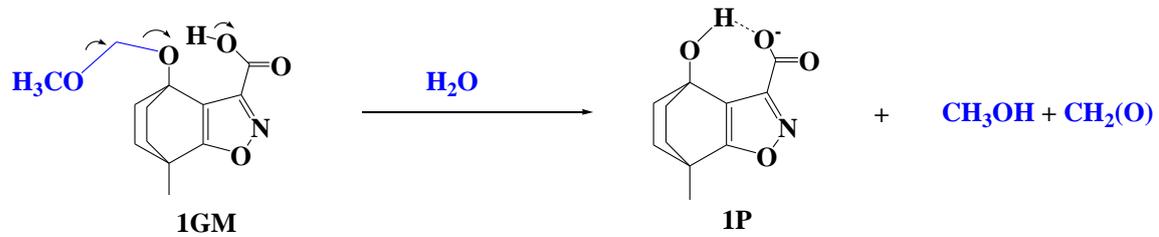
The aim of this work was to design various phenylephrine prodrugs with the potential to be tissue permeable, lack the bitterness of their parent drug and have the capability to chemically and not enzymatically undergo hydrolysis in the intestine to give phenylephrine in a sustain release manner. Scheme 1 illustrates possible approaches for the design of phenylephrine prodrugs based on proton transfers in Kirby's acetals and N-alkyl maleamic acids.

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 phenylephrine prodrugs **ProD1- ProD3** (prodrug type 1 in Scheme 1).



Scheme 1: Proposed approaches for phenylephrine prodrugs design

The DFT calculations study on processes **1-10** (Figure 5) is expected to draw the basis for the prediction of the pharmacokinetic profiles for phenylephrine prodrugs **ProD1- ProD3**.



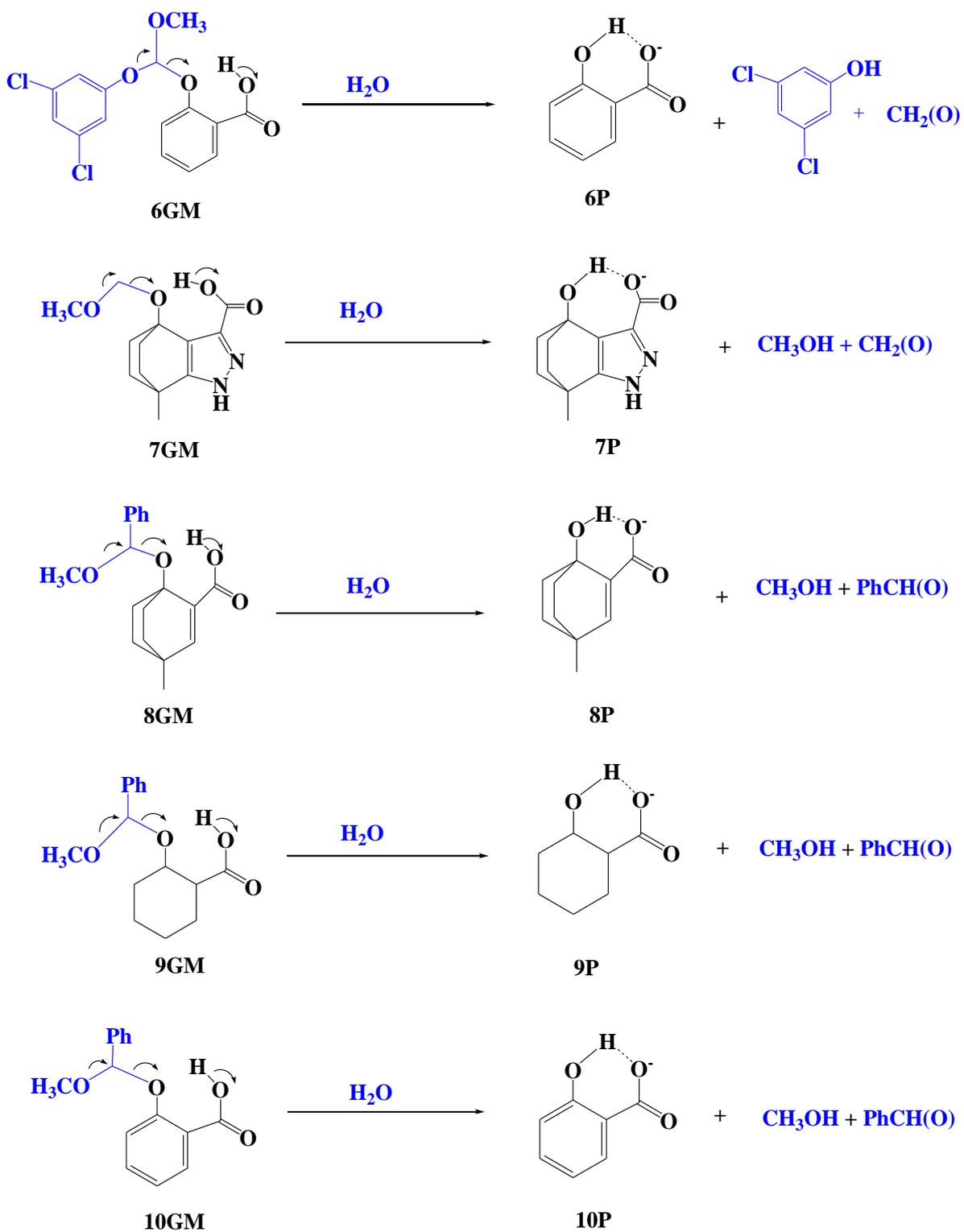


Figure 5: Proton transfer reactions in 1-10, where GM and P refer to the reactants and products, respectively.

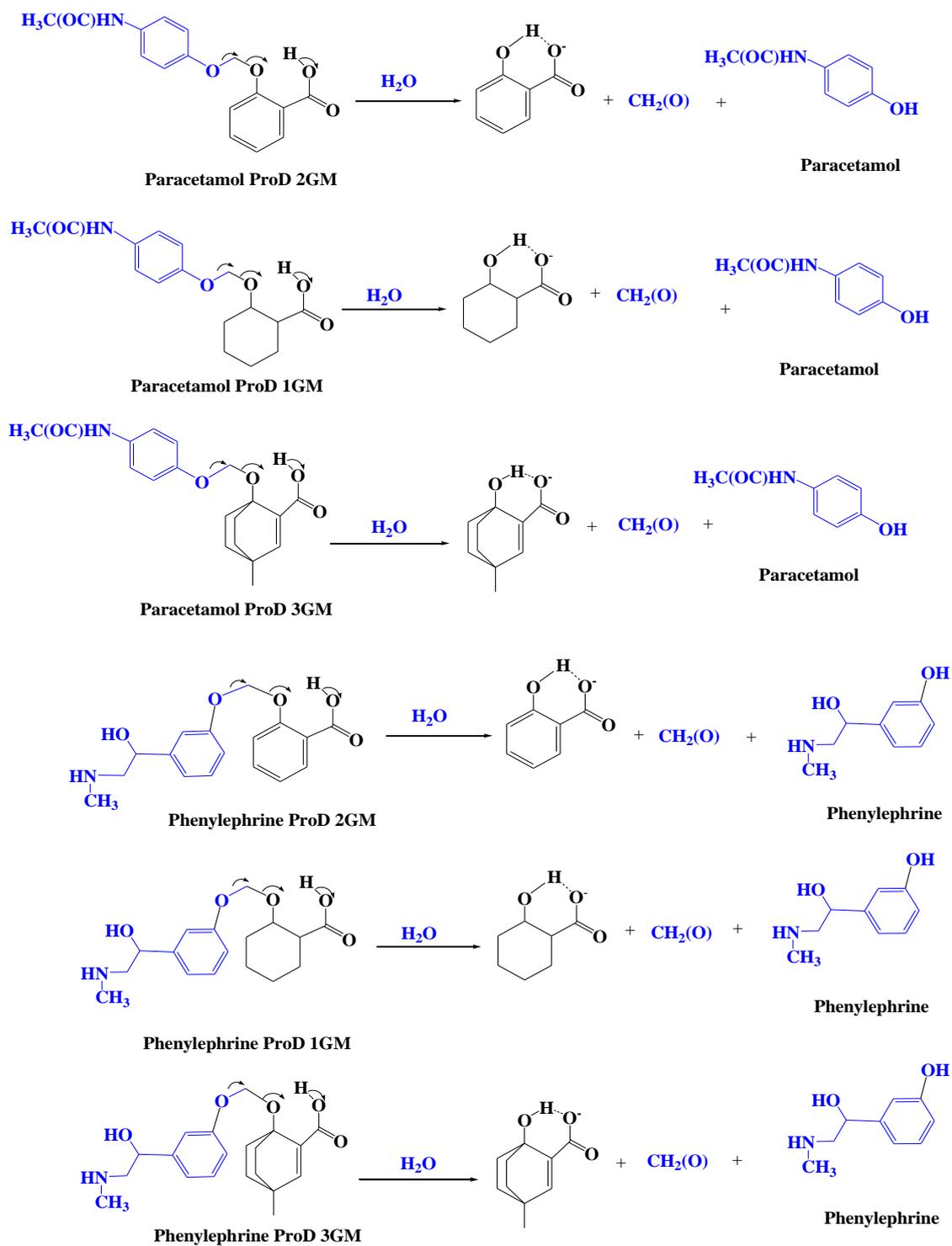


Figure 6: Proton transfer reactions in paracetamol ProD1- ProD3 and phenylephrine ProD1- ProD3.

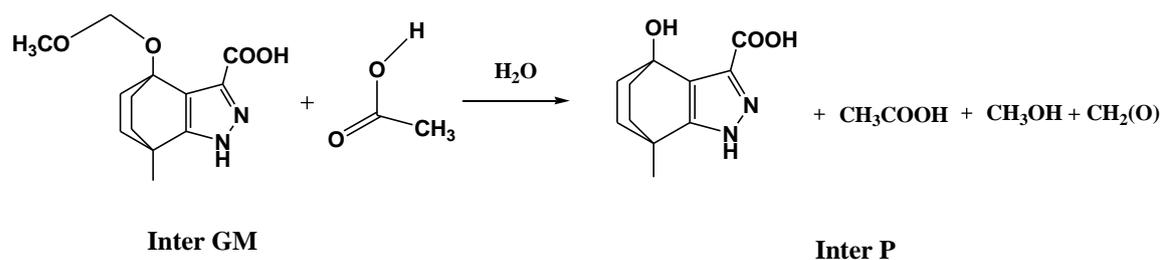


Figure 7: Intermolecular Proton transfer in Inter, where GM and Prefer to the reactants and products, respectively.

The kinetic studies done by Kirby's group on a proton transfer in some acetals used as enzyme models [31, 74-77] have inspired us to utilize these models as linkers to be covalently linked to phenylephrine and paracetamol [27] to provide prodrugs. Kirby's study on processes **1-10** (Figure 5) revealed that a proton transfer from the carboxylic hydroxyl group into the neighboring acetal oxygen is the rate-limiting step in the hydrolysis of these acetals.

In order to exploit systems **1-10** as prodrug linkers for phenylephrine and paracetamol Karaman has recently unraveled the mechanism for the hydrolysis of **1-10** using DFT calculation methods. In accordance with the report by Kirby [31, 74-77] Karaman found that the proton transfer is the rate-limiting step in the hydrolysis. In addition, his study showed that the driving force for the proton transfer efficiency is the proximity of the two reactive centers (r_{GM}) and the attack angle (α); and the rate of the reaction is linearly correlated with r_{GM}^2 and $\sin(180^\circ - \alpha)$. Acetals with short r_{GM} values and with α values close to 180° (forming a linear H-bond) are more reactive due to the development of a strong hydrogen bonds in their transition state and product structures[31, 64, 66-69, 74-77].

In similar to that done for processes **1-10** and paracetamol **ProD1- ProD3**, the DFT calculations for the hydrolysis of phenylephrine prodrugs **ProD1- ProD3** were directed

toward elucidation of the transition and ground state structures (reactants, intermediates and products). Calculations for all entities were conducted in the presence of one molecule of water in the gas phase and in a dielectric constant of 79.38 (water). It is expected that the stability of the ground and transition states will be different in solvent having low dielectric constant, such as the gas phase and solvent with high dielectric constant, such as water.

4.1.1 General Consideration:

The carboxylic acid moiety could be engaged in inter- or intramolecular hydrogen bonding. Therefore the free energy of the reactant is strongly dependent on its conformation. We were concerned with the identification of the most stable conformation (Global Minimum, GM) for each of phenylephrine **ProD1- ProD3** calculated in this study. The search for the global minimum structures for all prodrugs studied was accomplished by 36 rotations of the carboxyl group about the bond C3-C4 in increments of 10° (i.e. variation of the dihedral angle O5C4C3C2, see Chart 1) and calculation of the energies of the resulting conformers.

In the DFT calculations of the starting geometries in phenylephrine **ProD1- ProD3**, two different types of conformations were considered: one in which the carboxylic hydroxyl proton is *syn* to the alkoxy group in the β position of the carboxylic acid moiety (dihedral angle O5C4C3C2 = 0, Chart 1) and another in which it is *anti* (dihedral angle O5C4C3C2 = 180, Chart 1). The global minimum search for phenylephrine **ProD1- ProD3** revealed that all of them exist in the *syn* orientation (Figure 8a).

4.1.2 Optimized geometries of the entities involved in the proton transfers of phenylephrine ProD1- ProD3.

4.1.2.1 Global minimum geometries (GM):

Generally, reactions taking place in aqueous medium involve interactions between the hydrophilic moiety of the reactant and water. The strength of the interactions is dependent on the structural features of the reactants. Since the hydrolysis reactions of **1-10** were conducted in aqueous medium, we have calculated the geometries of the entities involved in these processes and phenylephrine **ProD1- ProD3** in the presence of one molecule of water followed by optimization in a dielectric constant of 78.39 (clusters of water). Figure 8a and Table 1 illustrate the DFT calculated properties for the global minimum structures of phenylephrine **ProD1- ProD3 (ProD1GM- ProD3GM)**. Figure S1a and Table S1 show that for processes **1-10(1GM-10GM)** and paracetamol **ProD1GM- ProD3GM**. Inspection of the optimized structures for **1GM-10GM**, paracetamol **ProD1GM –ProD3GM** and phenylephrine **ProD1GM- ProD3GM** indicates that **3GM, 6GM, 9GM**, paracetamol **ProD2GM** and phenylephrine **ProD2GM** exist in conformation by which the carboxylic hydroxyl group hydrogen bond with a molecule of water rather than intramolecularly. The preference of the carboxyl group in **3GM, 6GM, 9GM**, paracetamol **ProD2GM** and phenylephrine **ProD2GM** to be engaged intermolecularly with the solvent and not intramolecularly is due to the fact that the latter is energetically expensive due to a high energy barrier for the rotation of the carboxyl group around the C3-C4 bond [64, 66-69]. It is worth noting that Fife reported that acetal **9GM** shows no intramolecular general acid catalysis by the neighboring carboxyl group [70].

On the other hand, the optimized geometries **1GM-2GM**, **4GM-6GM**, **8GM-10GM**, paracetamol **ProD1GM**, paracetamol **ProD3GM** and phenylephrine **ProD1GM** phenylephrine **ProD3GM** exist in conformation by which the carboxylic hydroxyl proton is engaged intramolecularly via hydrogen bonding with the neighboring alkoxy oxygen. The intramolecular engagement results in the formation of a seven-membered ring for **1GM** and **7GM** and a six-membered ring for **2GM**, **4GM**, **5GM**, **8GM**, **9GM**, phenylephrine **ProD1GM**, phenylephrine **ProD3GM**, paracetamol **ProD1GM**, and paracetamol **ProD3GM** (see Figures 8a and S1a). Examination of the optimized global minimum structures in **Figures 8a and S1a** indicates that the DFT calculated hydrogen bonding length (r_{GM}) in the reactants engaged intermolecularly with a water molecule (**3GM**, **6GM**, **9GM**, paracetamol **ProD2GM** and phenylephrine **ProD2GM**) was in the range of 3.60 Å-3.76 Å and the attack angle α (the hydrogen bond angle, O1H7O6) in the range of 48°-58°. On the other hand, the r_{GM} and α values for **1GM**, **2GM**, **4GM**, **5GM**, **7G**, **8GM**, **10GM**, paracetamol **ProD1GM**, paracetamol **ProD3GM**, phenylephrine **ProD1GM** and phenylephrine **ProD3GM** were 1.69Å-1.79 Å and 143°-170.7°, respectively.

It should be indicated that the hydrogen bonding length, r_{GM} (O1-H7), varies according to the structural features of the reactant geometry.

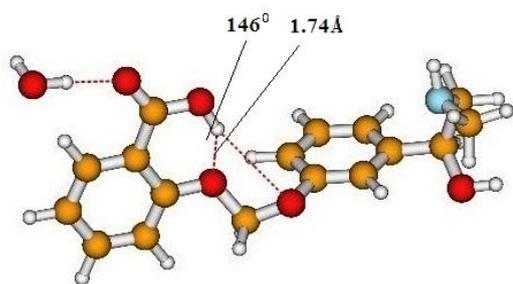
4.1.2.2 Transition state geometries (TS):

The optimized DFT calculated transition state geometries for **1-10 (1TS-10TS)**, paracetamol **ProD1- ProD3** (paracetamol **ProD1TS-3TS**) and phenylephrine **ProD1- ProD3** (phenylephrine **ProD1TS-3TS**) are illustrated in **Figures S1b** and 8b and Table 1. Inspection of the optimized structures in the figures revealed that all the TS geometries involve strong hydrogen bonding between the carboxylic hydroxyl proton (H7) and the

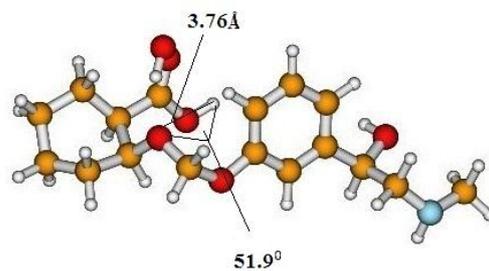
acetal oxygen (O1). The DFT calculated hydrogen bonding length (O1-H7) and angle (O1H7O6) in the optimized transition state structures was found in the range of 130°-170 °.

4.1.2.3 Product geometries (P):

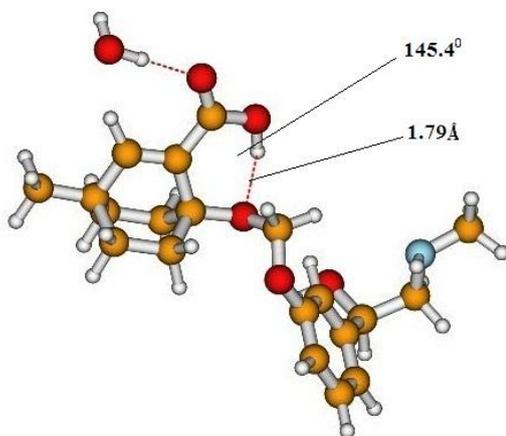
The DFT calculated geometries for the products in phenylephrine **ProD1- ProD3** (the same product anions as for paracetamol **ProD1- ProD3**) and **1-10 (1P-6P)** are illustrated in Figures 8c and **S1c**. Inspection of the calculated geometries indicates the presence of a strong hydrogen bonding between O1 and H7 where the bond length O1-H7 was found in the range 1.45 Å to 1.66 Å and the angle O1H7O6 was in the range of 154 ° - 170 °. These values are similar to that found for the corresponding transition state structures.



Phenylephrine ProD 1GM



Phenylephrine ProD 2GM



Phenylephrine ProD 3GM

Figure 8a: DFT optimized structures for the global minimum (GM) structures in the intramolecular proton transfer reaction of phenylephrine **ProD1-ProD 3**.

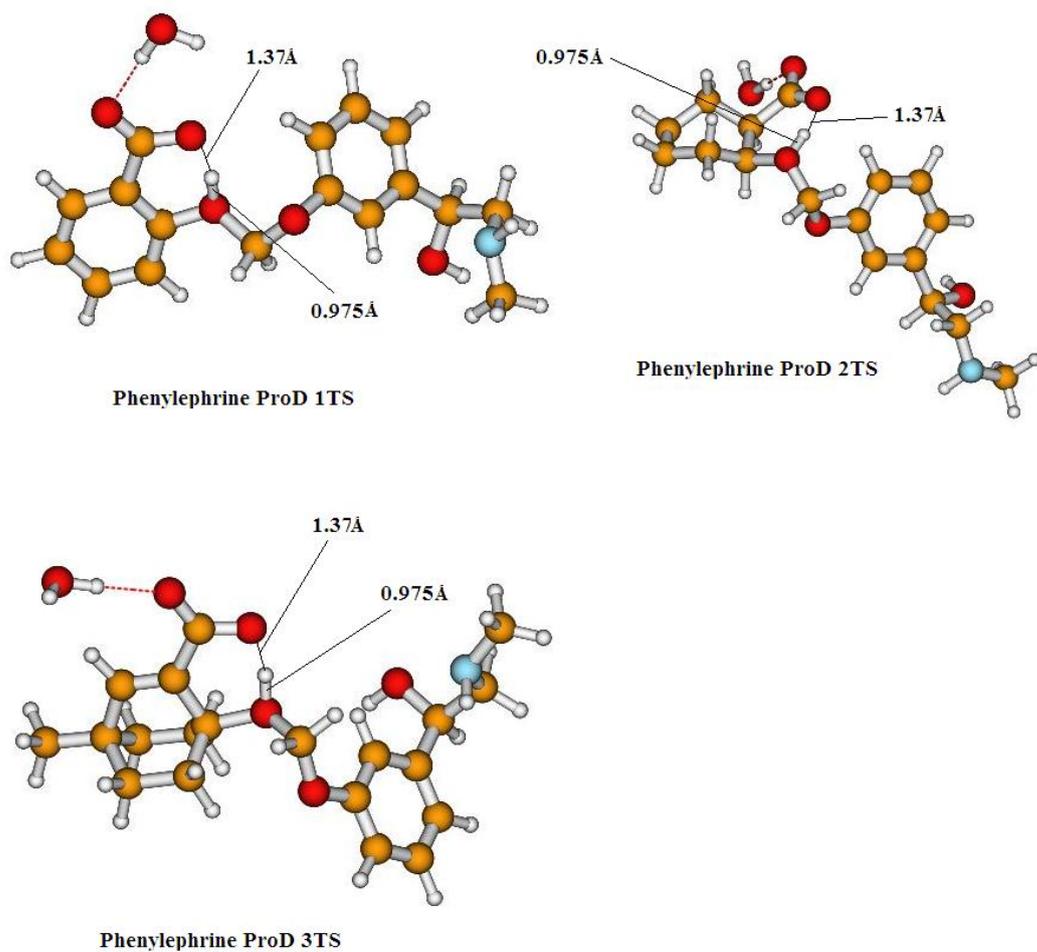


Figure 8b: DFT optimized structures for the transition state (TS) structures in the intramolecular proton transfer reaction of phenylephrine **ProD1-ProD 3**.

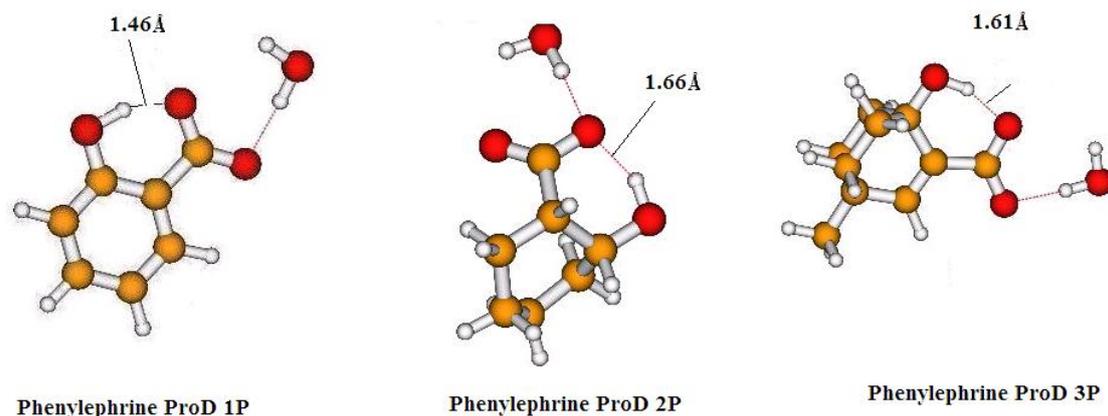


Figure 8c: DFT optimized structures for the linker product (P) structures in the intramolecular proton transfer reaction of phenylephrine **ProD1-ProD 3**.

4.1.3 DFT calculations of the kinetic and thermodynamic energies for the proton transfer reaction in 1-10, paracetamol **ProD1- ProD3** and phenylephrine **ProD1 - ProD3**.

The DFT at B3LYP/6-31G (d,p) level of theory kinetic and thermodynamic properties for phenylephrine **ProD1- ProD3** (Figure 6) were calculated using the quantum chemical package Gaussian-2009 [81]. The enthalpy and entropy energy values for all entities involved in the hydrolysis (global minimum structures (GM), transition states (TS) and products (P) were calculated in the gas phase and water. Table 1 lists the energy values for phenylephrine **ProD1GM - ProD3GM**, phenylephrine **ProD1TS - ProD3TS** and phenylephrine **ProD1P - ProD3P**, and Figures 8a - 8c show their DFT optimized structures, respectively. The calculated kinetic and thermodynamic properties for processes **1-10** and paracetamol **ProD1- ProD3**, and the optimized geometries of their GM, TS and P are depicted in **Table S1 and Figures S1a-S1c**, respectively.

The B3LYP/6-31G (d,p) activation energies were calculated in the presence of one molecule of water and with the inclusion of a cluster of water as a solvent. The calculation

results show that the energies with and without a cluster of water are completely different (Table 2). This indicates that the presence of water as a solvent has a vast effect on the proton transfer rate values. This is in accordance with the reports by Kirby and Fife that show the importance of water in the mechanistic pathway for the proton transfer in such systems [31, 70, 74-77].

Using the calculated DFT enthalpy and entropic energies for the global minimum structures of phenylephrine **ProD1-ProD 3** and their corresponding transition states (Table 1) we have calculated the enthalpy (ΔH^\ddagger), the entropic ($T\Delta S^\ddagger$), and the free activation energies (ΔG^\ddagger), in the gas phase and in the presence of cluster of water, for the proton transfer reaction in these processes. The calculated energies are listed in Table 2. Table 2 also includes the previously calculated energies for **1-10** and paracetamol **Pro D1- ProD3** [27].

Table 1: DFT (B3LYP) calculated properties for the proton transfer reactions of in phenylephrine ProD1- ProD3.

Compound	B3LYP, Enthalpy, H	B3LYP (gas phase)	B3LYP
	(gas phase) in Hartree	Entropy, S, Cal/Mol-Kelvin	Frequency Cm ⁻¹
Phenylephrine ProD1GM	-1166.5602839	179.16	-----
Phenylephrine ProD1TS	-1166.5047767	171.06	328.02i
Phenylephrine ProD2GM	-1093.7587484	167.34	-----
Phenylephrine ProD2TS	-1093.6797511	151.32	322.99i
Phenylephrine ProD3GM	-1285.7008951	190.67	-----
Phenylephrine ProD3TS	-1285.6515084	172.98	215.38i

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

4.1.3.1 The role of the distance O1-H7 (r_{GM}) and the angle O1H7O6 (α) on the rate of the proton transfer in processes phenylephrine ProD1- ProD3, 1-10 and paracetamol ProD1- ProD3

Careful inspection of 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 $r = 0.985$ (Figure 9a). In addition, examination of the activation energy values (ΔG^\ddagger) listed in Table 2 reveals that the energy needed to execute proton transfer in systems phenylephrine **ProD1- ProD3, 1-10** and paracetamol **ProD1- ProD3** is largely affected by both the distance between the two reactive centers r_{GM} (O1-H7), and the attack angle α (O1H7O6). Systems with low r_{GM} and high α values in their global minimum structures, such as **1**, paracetamol **ProD3**, phenylephrine **ProD3** and **7**, exhibit much higher rates (lower ΔG^\ddagger) than these with high r_{GM} and low α values, such as **9**, paracetamol **ProD2** and phenylephrine **ProD2**.

When r_{GM} and α values were examined for correlation with the water calculated DFT enthalpy energies (ΔH^\ddagger) a linear correlation was found between ΔH^\ddagger and $r_{GM}^2 \times \sin(180-\alpha)$ with a correlation coefficient of $R = 0.93$ (Figure 9b). On the other hand, a correlation of the activation free energies (ΔG^\ddagger) with $r_{GM}^2 \times \sin(180-\alpha)$ gave an R value of 0.87.

4.1.3.2 The effective molarities (EM) for processes phenylephrine ProD1-ProD3, 1-10 and paracetamol ProD1 - ProD3

The effective molarity (EM) value is commonly used as a measure for intramolecular efficiency. It is defined as a rate ratio of the intramolecular reaction and its corresponding intermolecular where both reactions are driven by the same mechanism. Values in the order of 10^9 - 10^{13} M have been measured for the EM in intramolecular processes occurring through nucleophilic addition. Whereas for proton transfer processes EM values of less than 10 M were reported [100] until recently where values of 10^{10} was reported by Kirby on the hydrolysis of some enzyme models [31, 64, 66-69, 74-77].

For obtaining the EM values for processes phenylephrine **ProD1- ProD3** we have calculated the kinetic and thermodynamic parameters for their corresponding intermolecular process, **Inter** (Figure 7).

Equation 5, which describes the EM term as a function of the difference in the activation energies of the intra- and the corresponding intermolecular processes, was derived from

Table 2: DFT (B3LYP/6-31G (d,p) calculated kinetic and thermodynamic properties for the proton transfers in phenylephrine **ProD1-ProD 3, 1-10** and paracetamol **ProD1-ProD3**.

System	log EM ^a (exp.)	log EM (calc.)	ΔH^\ddagger (GP)	$T\Delta S^\ddagger$ (GP)	ΔG^\ddagger (GP)	ΔH^\ddagger (H ₂ O)	ΔG^\ddagger (H ₂ O)
PEProD1	-----	6.91	34.83	-2.41	37.24	26.70	29.11
PEProD2	-----	-4.11	49.57	-4.77	54.54	39.82	44.59
PEProD3	-----	8.92	30.99	-5.27	36.26	21.08	26.35
1	12.600	12.72	29.30	0.03	29.27	21.22	21.19
2	-----	9.22	33.09	-1.25	34.34	24.71	25.96
3	-----	2.31	44.29	-2.23	46.52	34.76	36.99
4	4.0000	5.14	34.32	-3.42	37.74	27.53	31.52
5	4.3010	5.30	35.69	-3.83	39.52	27.49	31.32
6	1.5798	1.52	38.43	0.67	37.76	37.66	36.99
7	10.000	10.58	27.78	-2.68	30.46	21.47	24.15
8	3.4771	6.04	31.38	-3.71	35.09	26.64	30.35
9	-----	0.41	41.09	1.04	40.05	40.15	39.11
10	3.9777	5.30	29.04	-5.12	34.16	26.22	31.34
PProD1	-----	6.55	34.89	-1.56	36.45	28.09	29.65
PProD2	-----	-1.39	49.80	-3.20	53.00	39.65	42.85
PProD3	-----	11.75	31.56	0.79	29.77	23.30	22.51

ΔH^\ddagger is the activation enthalpy energy (kcal/mol). $T\Delta S^\ddagger$ is the activation entropy energy in kcal/mol. ΔG^\ddagger is the activation free energy (kcal/mol). log EM (exp.) and log EM (calc.) are the experimental and calculated effective molarities ($EM = k_{intra}/k_{inter}$). PE and P refer to phenylephrine and paracetamol, respectively. GP and H₂O calculated in the gas phase and water, respectively. a, see references 40-44 and 70-75.

equations 1- 4. Using equation 5 we have calculated the EM values for processes phenylephrine **ProD1- ProD3**. The calculated EM values for phenylephrine **ProD1-ProD3** along with that for **1-10** and paracetamol **ProD1- ProD3** are listed in Table 2.

$$EM = k_{intra}/k_{inter} \quad (1)$$

$$\Delta G_{inter}^{\ddagger} = -RT \ln k_{inter} \quad (2)$$

$$\Delta G_{intra}^{\ddagger} = -RT \ln k_{intra} \quad (3)$$

$$\Delta G_{intra}^{\ddagger} - \Delta G_{inter}^{\ddagger} = -RT(\ln k_{intra}/k_{inter}) \quad (4)$$

$$EM = e^{-(\Delta G_{inter}^{\ddagger} - \Delta G_{intra}^{\ddagger}) / RT} \quad (5)$$

Where T is 298° K and R is the gas constant

Examination of Table 2 demonstrates that **1**, **7** and paracetamol **ProD3** are the most efficient processes among all systems studied ($\log EM > 10$) and the least efficient are processes **9**, paracetamol **ProD2** and phenylephrine **ProD2** with $\log EM < 1$.

It is worth noting, that a good correlation was obtained when the calculated EM values were plotted against the experimental EM values with a correlation coefficient of $R = 0.97$ (Figure 9c).

Inspection of the calculated EM values for phenylephrine **ProD1- ProD3** listed in Table 2 indicates that phenylephrine **ProD3** is the most efficient process whereas phenylephrine **ProD2** is the least efficient process. Using the experimental $t_{1/2}$ (the time needed for the conversion of 50% of the reactants to products) values for processes **1** and **7** and the EM values for **1**, **7**, and phenylephrine **ProD1- ProD3** we have calculated the $t_{1/2}$ values for the degradation of phenylephrine **ProD1- ProD3** to their parental drug, phenylephrine. The calculated $t_{1/2}$ values for **ProD1** and **ProD2** were very high (145 days and several years, respectively) whereas that of **ProD3** was found to be about 35 hours.

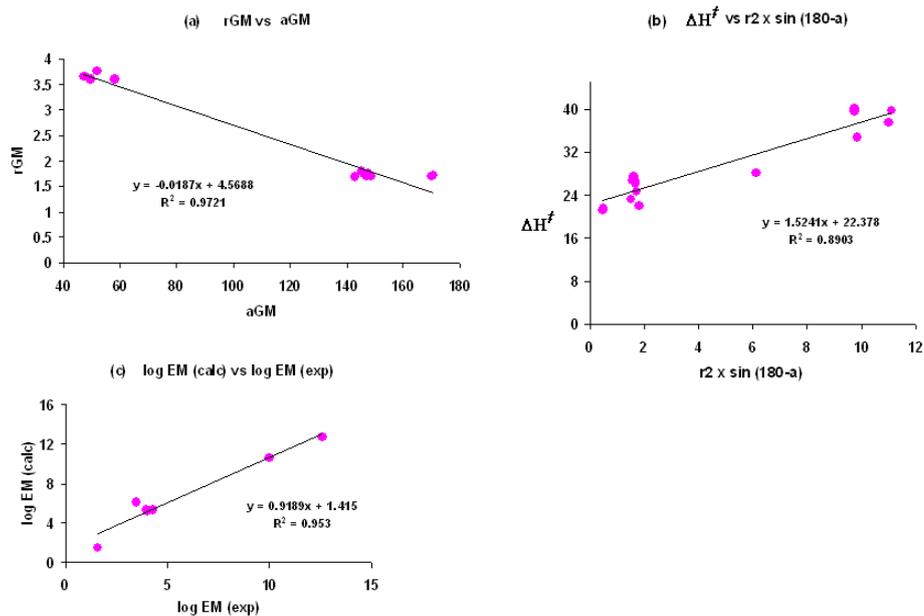


Figure 9: (a) Plot of the DFT calculated r_{GM} (\AA) vs. angle α ($^\circ$) in phenylephrine **ProD1-ProD 3, 1-10**, andparacetamol **ProD1- ProD3**, where (r_{GM}) and (α)are the distance between the two reactive centers and the attack (hydrogen bond) angle in the GM structure, respectively. (b) Plot of the DFT calculated ΔH^\ddagger vs. $r_{GM}^2 \times \sin(180-\alpha)$ in phenylephrine **ProD1-ProD 3, 1-10**, andparacetamol **ProD1- ProD3** (c) Plot of the experimental EM values vs. the calculated EM values in **1-10**.

4.2 Paracetamol

Bitter or unpleasant taste is a major problem in the food and medicine industries. As several oral pharmaceuticals and bulking agents have unpleasant, bitter-tasting components, Pediatric patients resist taking medicine due to their bitterness or unpleasant taste. The bitterness of these preparations leads to lack of patient compliance. The problem of bitterness of drugs in pediatric and geriatric formulations is creating a serious challenge to pharmacists [101].

The desire of improved palatability in bitter taste products has prompted the development of numerous formulations with improved performance and acceptability [102]. In order to satisfy the patient compliance for taking medicines bitterness masking becomes essential. Different approaches are commonly utilized to overcome bitter and unpleasant taste of drugs. This includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. But these approaches were found to be limited and could not overcome the problem of bitterness [103]. Thus, different strategies should be developed in order to overcome this serious problem.

Drugs or molecules interact with taste receptors on the tongue to give bitter, sweet or other taste sensations. Altering the ability of the drug to interact with taste receptors could reduce or eliminate their bitterness. This could be achieved by an appropriate modification of the structure and the size of a bitter compound.

During the last ten years, tremendous progress in the elucidation of bitter taste reception and transduction on the cellular level was made and many new molecules and compounds to reduce off-taste were reported. But none of those were found to eliminate the bitterness fully [104].

Since the discovery and identification of the receptor proteins responsible for bitter taste reception, the mechanism of bitter reception by taste receptor cells seems to be generally known nowadays. Bitter molecules bind to G-protein coupled receptor-type T2R on the apical membrane of the taste receptor cells located in the taste buds. In humans, about 25 different T2R are described. Additionally, several alleles are known and about 1000 different bitter phenotypes exist in human beings [104, 105].

Due to the wide variation of the structure basis of bitter tasting molecules, it is difficult to generalize the molecular requirements for bitterness. Nevertheless, it was noted that a bitter molecule needs a polar group and a hydrophobic moiety (mono polar-hydrophobic concept). A quantitative structure activity relationship (QSAR) model was developed and could be established for the prediction of bitterness of several analogues. For example, it was reported that an addition of pyridinium moiety to an amino acid chain of a variety of bitter amino acids compounds decreases the bitterness such as in the case of glycine (e.g. pyridinium glycyl betain). Other structural modifications, such as the increase in the number of amino groups/residues to more than 3 and reduction in the polyhydroxyl group/ COOH have been proven to decrease the bitterness in a significant manner. Furthermore, changing the configuration of bitter compounds by preparing isomer analogues was found to be important for binding affinity to enhance bitterness agonist activity (e.g. L-tryptophan is bitter while D-tryptophan is sweet, and there are many other examples) [104, 106].

Paracetamol is an odorless crystalline compound with a bitter taste widely used as pain killer and to reduce the temperature of patients with fever.

As mentioned before, the presence of hydroxyl group on the *para* position of paracetamol is the major contributor for its bitter taste. Hence, it is expected that blocking

the hydroxy group in paracetamol with a suitable linker could inhibit the interaction of paracetamol with its bitter taste receptor/s and hence masking its bitterness.

It seems reasonable to assume that the phenolic hydroxyl group in paracetamol is crucial for obtaining the bitter taste characteristic for paracetamol. This might be due to the ability of paracetamol to be engaged in a hydrogen bonding net with the active site of its bitter taste receptor *via* its phenolic hydroxyl group.

Continuing Karaman's research for utilizing enzyme models as potential linkers for drugs containing hydroxyl groups, I sought to study the mechanism and driving forces affecting the rate in the cyclization reactions of di-carboxylic semi-esters **11-15** (Figure 10) experimentally explored by Bruice and Pandit for their utilization as prodrugs linkers. It is expected that such linkers will have a potential to be good carriers to paracetamol. It is worth noting that linking the paracetamol with such linkers *via* its phenolic hydroxyl group will hinder its bitter taste. It should be emphasized that prodrugs shown in Figure 11 could be used in different dosage forms (tablets, syrups, suppositories, and etc.) because of their potential solubility in organic and aqueous media due to the ability of their carboxyl groups to be converted to the corresponding carboxylate salt.

Our proposed paracetamol prodrug systems based on the cyclization reaction of Bruice's di-carboxylic semi-esters are illustrated in Figure 11.

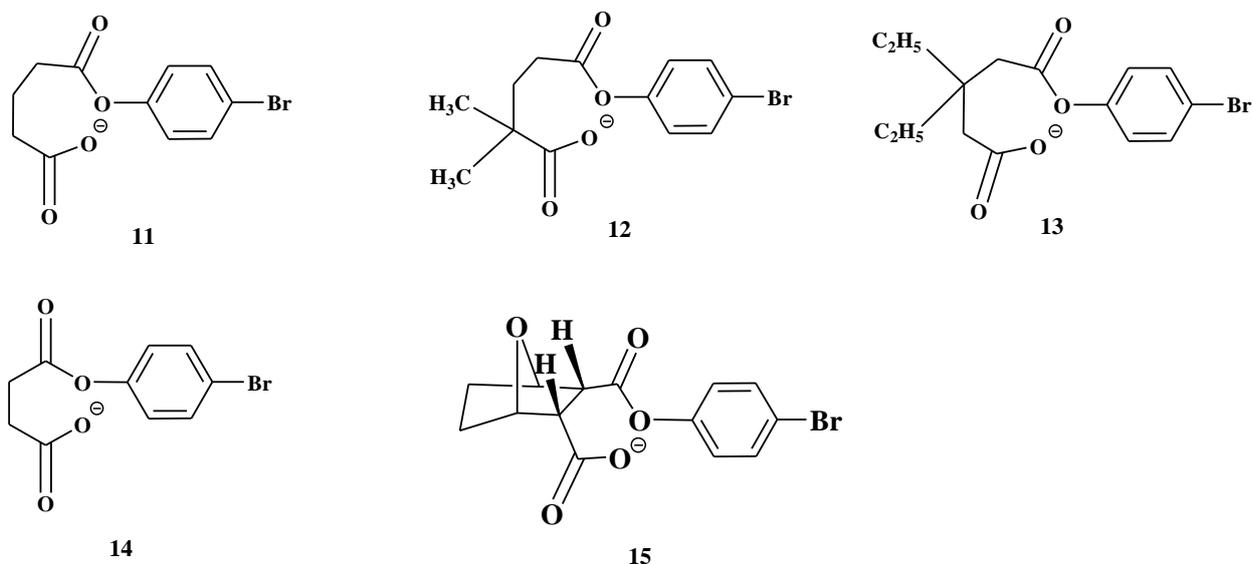


Figure 10: Chemical structures for di-carboxylic semi-esters 11-15.

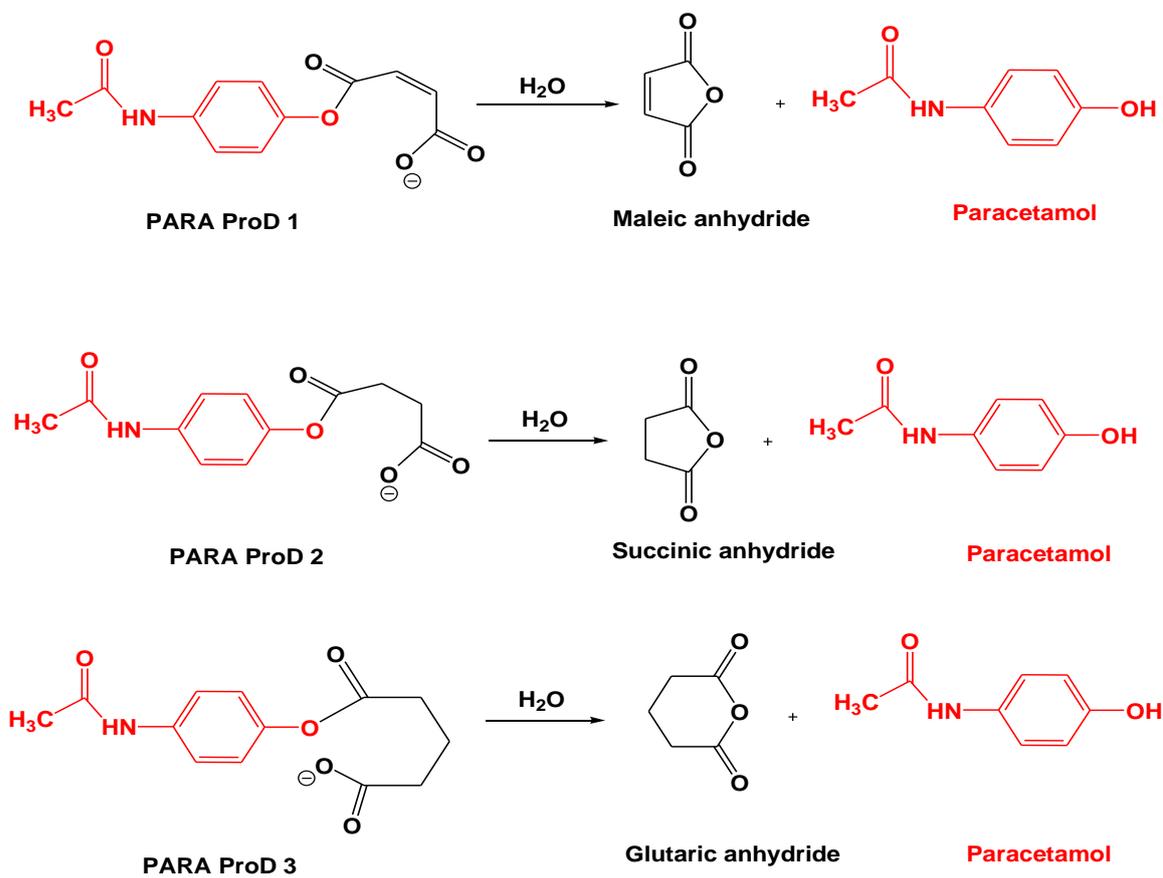


Figure 11: Chemical structures and cyclization reactions of Paracetamol prodrugs (PARA ProD1-3).

Bruice and Bandit have studied the hydrolysis of di-carboxylic semi-esters **11-15**(Figure 10) and found that the relative rate (k_{rel}) in this series is:**15>14>13>12>11**.

They attributed the acceleration in rate to proximity orientation. Using the observation that alkyl substitution on succinic acid influences rotamer distributions, the ratio between the reactive gauche and the unreactive anti-conformations, they proposed that gem-dialkyl substitution increased the probability of the resultant rotamer adopting the more reactive conformation. Therefore, for cyclization to occur, the two reacting centers must be in the gauche conformation. In the unsubstituted reactant, the reactive centers are almost completely in the anti-conformation in order to minimize steric interaction[52-54].

Menger and Bruice described the phenomenon of rate accelerations in some intramolecular processes to the importance of the proximity of the nucleophile to the electrophile of the ground state molecules.

Menger was developed an equation relating activation energy to distance in his “spatiotemporal” hypothesis and based on this equation, he concluded that enormous rate enhancements in reactions catalyzed by enzymes are achieved by imposing short distances between the reactive centers of the substrate and enzyme[58-62]. On the other hand, Bruice attributed the catalysis by enzymes to favorable ‘near attack conformations’. According to Bruice’s hypothesis, systems that have a high quota of near attack conformers will have a higher intramolecular reaction rate and *vice versa*. Bruice’s idea invokes a combination of distance between the two reacting moieties and angle of attack by which the nucleophile approaches the electrophile[52-54].

But others In contrast to the proximity proposal believe that high rate acceleration in intramolecular processes is due to steric effects (relief of the reactants strain energy[107, 108]).

Computational study was done by Karamanto test whether the discrepancy in the cyclization reaction rates of di-carboxylic semi-esters **11–15** is due to proximity orientation (difference in the distance between the nucleophile and the electrophile) or to strain effects, by using ab initio molecular orbital methods at B3LYP/6-31G (d,p) and HF/6-31G (d,p) levels, the ground state, intermediate and transition state structures as well as the activation energy values for the cyclization reactions of **11–15**. In accordance with the results by Bruice and Pandit, Karaman found that the cyclization reaction proceeds by one mechanism, by which the rate-limiting step is the tetrahedral intermediate collapse and not its formation (Figure 12). However, contrarily to Bruice’s et al. conclusion, Karaman found that the acceleration in rate is due to steric effects rather than to proximity orientation stemming from the “rotamer effect”[32].

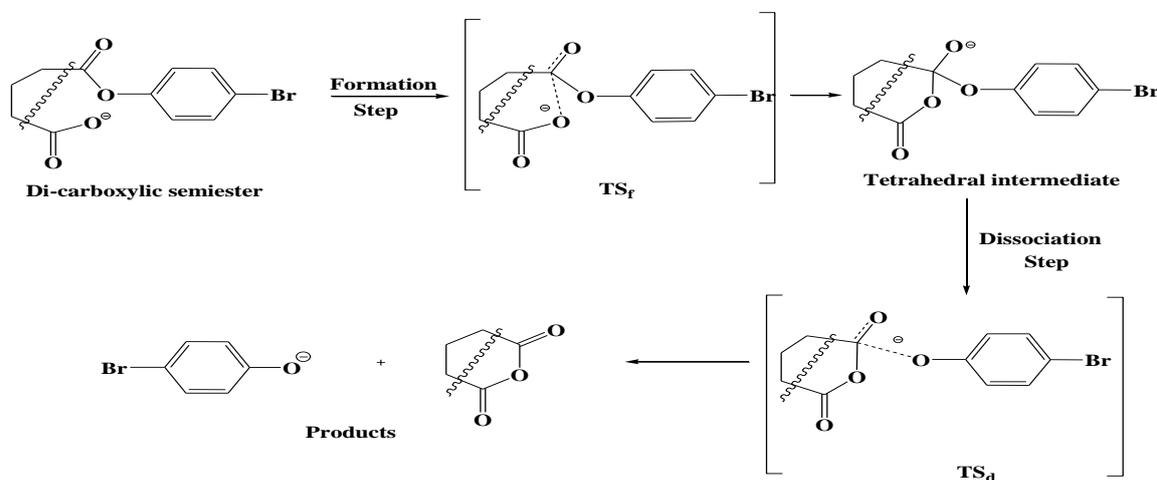


Figure 12: Proposed mechanism for the cyclization of di- carboxylic semi-esters **11–15**.

The conclusion emerged from the computational study by Karaman on the di-carboxylic semi-esters cyclization (Bruice’s enzyme model) are:

- (1) The activation energy in **11–15** is dependent on the difference in the strain energies of the transition states and the reactants, and there is no relationship between the

- cyclization rate and the distance between the nucleophile (O1) and the electrophile (C2).
- (2) The observation of opening the cyclic ring during the reaction rate limiting step supports the notion that the difference in the strain energies of the reactant and the transition states plays a crucial role in the discrepancy in the rates of cyclization of the di-carboxylic semi-esters **11–15**.
 - (3) Strained reactants such as **15** are more reactive than the less strained reactants, and the reactivity extent is linearly correlated with the strain energy difference between the transition state and the reactant (ΔE_s).
 - (4) The energy needed to provide a stable transition state for a strained system is less than that for the unstrained system, since the conformational change from the reactant to the transition state in the former is smaller[32].

4.2.1 General consideration

Continuing the strategy for exploring enzyme models in the design of novel prodrugs, Bruice's enzyme model (hydrolysis of di-carboxylic semi-esters) was employed in the design of paracetamol prodrugs (Figure 11) with the potential to be more bioavailable than their active parent drug and without better sensation. Furthermore, it is planned that the intraconversion rate of paracetamol prodrugs to paracetamol can be programmed according to the nature of the prodrug linker.

The calculations at B3LYP/6-311 + G (d,p) levels for the ring-closing reactions of di-carboxylic semi-esters **11-15** (Figure 10) and prodrugs paracetamol prodrugs **ProD1-ProD3** (Figure 11) were directed toward elucidation of the transition and ground state structures (reactants, intermediates and products). Calculations for all ground states, intermediates, transition states and products were run in water (dielectric constant of 78.39) and in the gas phase. It is expected that the stability of the ground and transition states will

be different in solvent having low dielectric constant, such as the gas phase and solvent with high dielectric constant, such as water.

The orientation of the carboxylate anion to the ester carboxyl moiety is very important and affecting the mode and rate of the ring-closing reaction. When the di-carboxylic semi-ester exists in the *syn* (condensed) conformation the cyclization will be more efficient than when the di-carboxylic semi-ester exhibits the *anti* (extended) conformation (Chart 2). This is because the distance (r_{GM}) between the nucleophile (C (O) O-) and the electrophile (-C (O)-OR) is shorter in the former case. In addition, the free energy of the reactant is strongly dependent on its conformation whether it is strained or not. In the cases where the ground state is strained the free energy of the reactant is high and consequently it is expected that the activation energy for the strained reactants to be less than that of the less-strained.

Therefore, it is a must to identify the most stable conformation (Global Minimum, GM) for each of di-carboxylic semi-esters **11-15**(Figure 10) and paracetamol**ProD1-ProD 3(PARA ProD1-3** in Figure 11). The search for the global minimum structures for all semi-esters was accomplished by 36 rotations of the carboxyl group about the bond C3-C4 in increments of 10° (i.e. variation of the dihedral angle C2/C3/C5/C6, see Chart 2) and calculation of the conformational energies.

In the calculations of the starting geometries in **11-15** and **PARA ProD1-3**, two different types of conformations were considered: one is *syn* and another is *anti*(Chart 2). It was found that the global minimum structures for **11-15** and **PARA ProD1-3** all exist in *syn*(condensed) conformation(see Figures 13a, 13b and S2a).

4.2.2 Optimized geometries for the entities involved in the ring – closing reactions of 11-15 and PARA ProD1-3.

(A) Reactants (GM):

The global minimum structures for **11-15 (11GM-15GM)** and paracetamol **ProD1-ProD 3 (PARA ProD1GM-ProD 5GM)** are illustrated in Figures 13a and 13b, respectively. Inspection of the calculated structures in Figures 13a, 13b and S2a demonstrates that all of them exhibit a *syn* (condensed) conformation where the r_{GM} distance (see Chart 2) varies according to the nature of the reactant. The r_{GM} values for **11-15** were in the range of 2.37Å – 4.34Å where the global minimum for **15** having the shortest distance (2.37Å) and for **12** the longest distance (4.34Å). For **PARA ProD1GM-ProD 3GM** the r_{GM} values range were 2.59Å, 4.14 Å and 4.12 Å, respectively, where **PARA ProD1GM** was with the shortest distance and **PARA ProD2-3GM** with the longest distances.

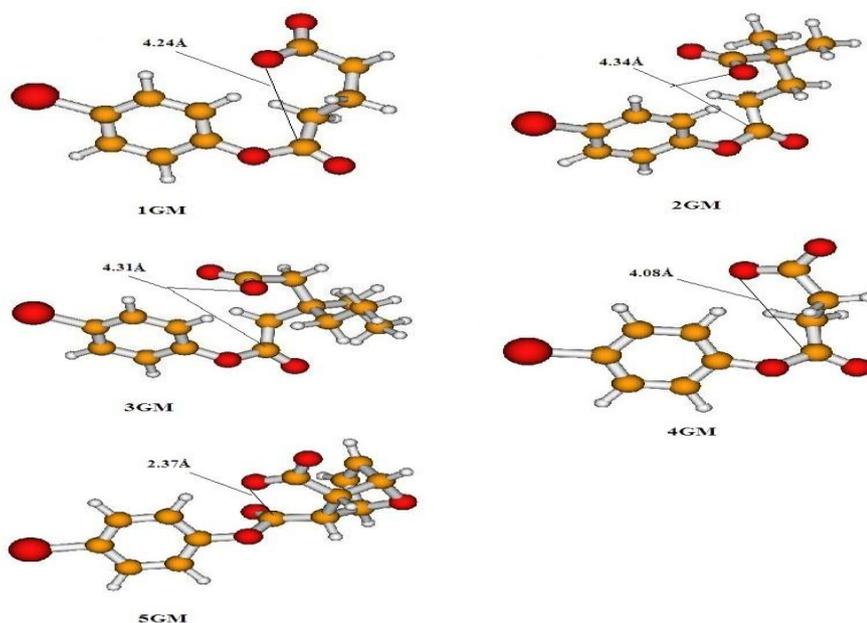


Figure 13a: DFT at B3LYP/6-311 + G (d,p) level optimized structures for the global minimum (GM) in di-carboxylic semi-esters 11-15.

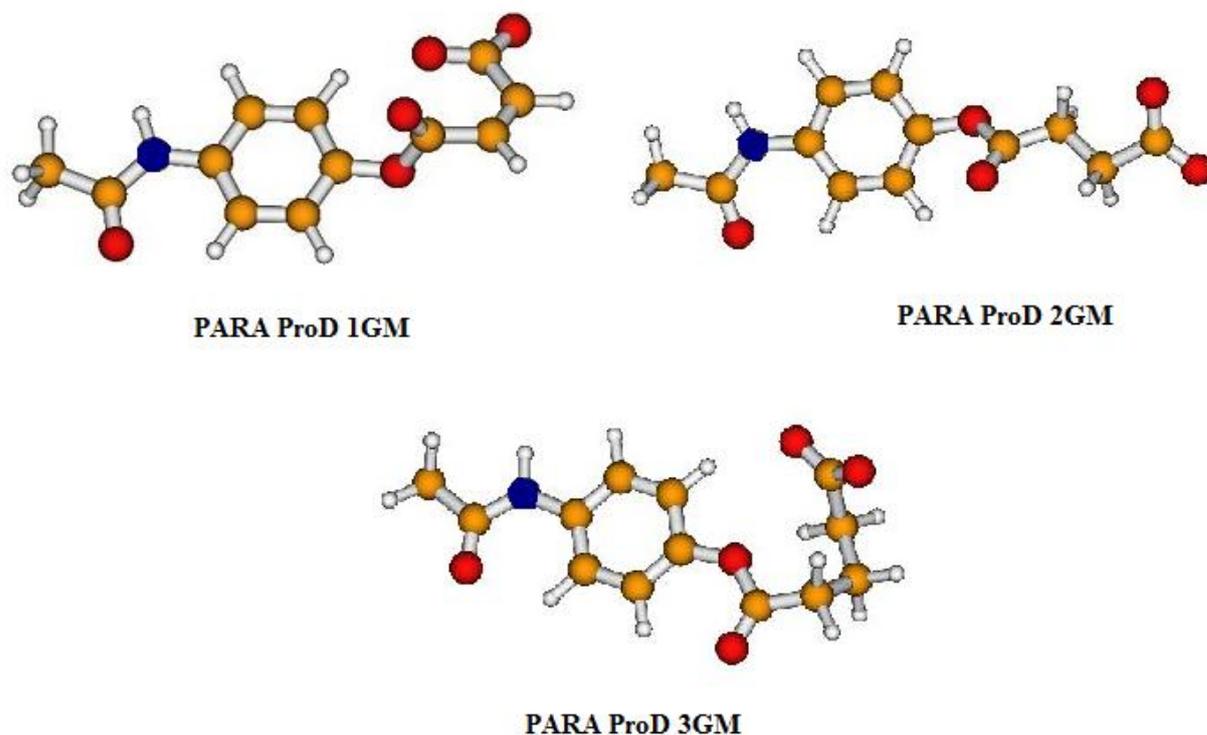


Figure13b: DFT at B3LYP/6-311 + G (d,p) level optimized structures for the global minimum (GM) in **PARA ProD1-ProD3**.

(B) Transition state geometries (TS):

From Figures (14a,14band S2b) we can see the calculated DFT optimized structures for the cyclization reactions of **11-15** and **PARA ProD1-ProD3** (**11TS-15TS** and **PARA 1TS-3TS**). Examination of the optimized TS structures indicates that all of them resemble that of the corresponding tetrahedral intermediates. Furthermore, the calculated O-C distances, O1-C6, O8-C6 and O1-C2 are significantly different. The distance range for O1-C6 in **1TS-5TS** was 1.602 Å - 2.282 Å, for O8-C6 was 1.759 Å - 1.903 Å and for O1-C2 was 1.282 Å – 1.329 Å. Similar O-C distance ranges were found for the prodrugs **PARAProD1TS- ProD3TS**.

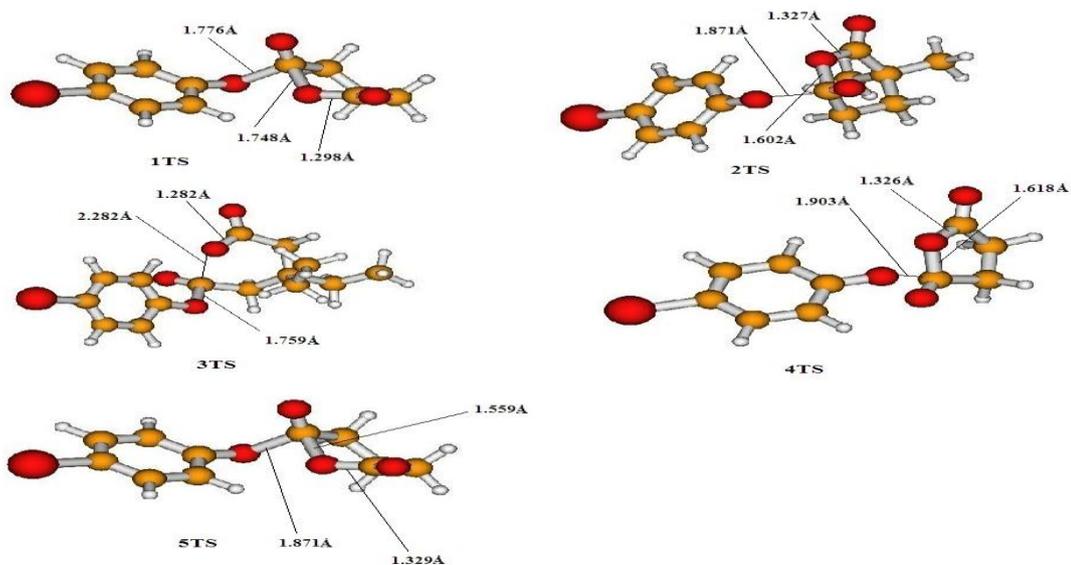


Figure 14a: DFT at B3LYP/6-311 + G (d,p) level optimized structures for the transition state (TS) in di-carboxylic semi-esters **11-15**.

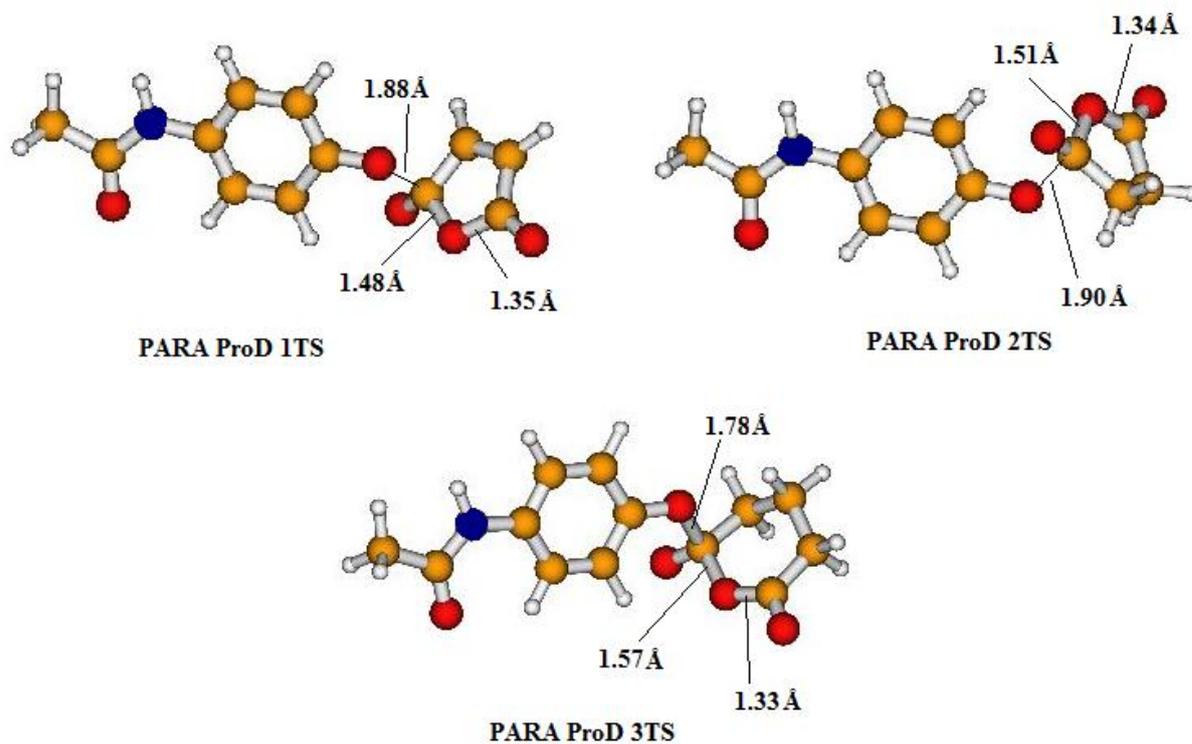


Figure 14b: DFT at B3LYP/6-311 + G (d,p) level optimized structures for the transition state (TS) in **PARA ProD1-ProD3**.

4.2.3 DFT calculations of the kinetic and thermodynamic energies for the cyclization reaction in 11-15 and PARA ProD1-ProD3

DFT calculations at B3LYP/311+G (d,p) level were performed for calculating the kinetic parameters for all entities involved in the reaction shown in Figure 12. As illustrated in Figure 12 the mechanism involves two steps:

- (1) The approach of the anionic carboxylate oxygen (O1) toward the carboxylic carbon (C6) to give a tetrahedral intermediate (for numbering, see Chart 2)
- (2) The dissociation of the tetrahedral intermediate to yield a cyclic anhydride and p-bromophenolate anion (paracetamol moiety).

The 'reaction coordinate' calculations for both steps revealed the following: (a) no transition state structures were found for the approach processes in **11-15** and **PARA ProD1- ProD3**. (b) The 'reaction coordinates' and frequency calculations for the intermediate dissociation route in systems **11-15** and **PARA ProD1- ProD3** demonstrated the presence of a transition state. Further, monitoring the dissociation processes revealed that upon increasing the distance between O8 and C6 (departure of the leaving group, for the numbering see Chart 2), opening of the cyclic ring was observed in systems **11-15** and **PARA ProD1- ProD3**. However, the cycle opening magnitude (the distances O1-C6, O8-C6 and O1-C2) was found to be dependent on the transition state nature (see Figures 14a, 14b and S2b).

Using the calculated B3LYP/311+G (d, p) values for the enthalpy and entropy of the global minimum (GM) and the transition state structures for the ring-closing reactions of di-carboxylic semi-esters **11-15** and **PARA ProD1- ProD3** (Table 3) the activation energy values for the rate-limiting step (ΔG^\ddagger) were calculated in the gas phase as well as in a dielectric constant of 78.39 (water). The calculated activation energy values in both media, ΔG^\ddagger_{GP} and $\Delta G^\ddagger_{H_2O}$, respectively, are summarized in (Table 4). Inspection of the

ΔG^\ddagger values shown in Table 4 demonstrated that the cyclization rate is largely affected by the nature (structural features) of the reactant.

We calculated, using Allinger's MM2 method [89], the strain energy values for the reactants and intermediates in systems **11–15** to examine whether the discrepancy in the rates for the reactions **11–15** stems from proximity orientation or due to steric effects (strain energy). The difference in values between the MM2 strain energies of the intermediates and reactants ($\Delta E_s = E_{\text{INT-GM}}$) are listed in (Table 4). The calculated MM2 (ΔE_s) values for the reactions of **11–15** were examined for correlation with the experimental ($\log k_{\text{rel}}$) values [53, 54] and the correlation results are depicted in equation (1) and illustrated graphically in Figure 15a. Eq. (1) and Figure 15a demonstrate a good correlation between the experimental $\log k_{\text{rel}}$ and the MM2-calculated strain energy values (ΔE_s) with a high correlation coefficient ($r = 0.90$).

Examination of Figure 15a and Table 4 reveals that for di-carboxylic semi-esters having narrow differences in the strain energy of their reactants and intermediates, such as in the case of system **14** the corresponding ring-closing reaction rates are high and vice versa.

It should be noted, that attempts to correlate the distance between O1–C6 (r_{GM}) with $\log k_{\text{rel}}$ gave random correlation. For example, the calculated O1–C6 distances for **11GM–14GM** are similar (4.08 Å- 4.34 Å), whereas the calculated ΔE_s and $\log k_{\text{rel}}$ experimental values differ significantly (see Table 4). These results suggest that the driving force for the enhancement in the ring-closing reaction is driven by strain effects in contrast to that suggested by Bruice *et al.*[53, 54]. In order to further support this conclusion, the B3LYP 6-31G (d,p) and B3LYP/311+G (d,p) activation energy values for **11-15** calculated in water ($\Delta G^\ddagger_{\text{H}_2\text{O}}$, see Table 4) were examined for correlations with $\log k_{\text{rel}}$ and the results are shown in equations (2-3) and represented graphically in Figure 15b. Again the correlation

results of $\Delta G_{\text{H}_2\text{O}}^\ddagger$ calculated by the two different methods with the experimental relative rates ($\log k_{\text{rel}}$) revealed to the same conclusions; the driving force for acceleration is due to strain effects and not to proximity orientation.

Comparison of the correlation of $\log k_{\text{rel}}$ values of **11-14** on the one hand with $\Delta G_{\text{H}_2\text{O}}^\ddagger$ as calculated by B3LYP/6-31G(d,p) (eq. 2') and B3LYP/6-311+G(d,p) (eq. 3) on the other hand revealed that B3LYP/6-311+G(d,p) is better in predicting cyclization reaction rates.

Table 3: DFT calculated properties for the cyclization reactions of 11–14 and PARA ProD1-ProD3.

Structure	B3L (gas phase)		B3L	B3L311, Enthalpy (gas phase) Hartree	B3L311 (gas phase)	
	B3L, Enthalpy (gas phase) Hartree	Entropy, Cal/Mol-Kelvin	Frequency Cm^{-1}		Entropy, Cal/Mol-Kelvin	Frequency Cm^{-1}
11GM	-3297.8759694	129.59	-----	-3300.5301241	131.03	-----
11TS	-3297.8525774	114.78	275.79i	-3300.5184233	124.60	265.95i
12GM	-3376.5109323	142.45	-----	-3379.1780952	143.55	-----
12TS	-3376.4967234	130.73	172.28i	-3379.1592899	139.10	174.97i
13GM	-3455.1311833	150.83	-----	-3457.8108932	155.49	-----
13TS	-3455.1111721	149.93	204.79i	-3457.7962563	151.83	208.06i
14GM	-3258.5576358	123.48	-----	-3261.2033556	124.61	-----
14TS	-3258.5603273	118.69	192.20i	-3261.2012838	119.71	204.88i
PARA ProD1GM	-----	-----	-----	-894.5135881	137.7	-----
PARA ProD1TS	-----	-----	-----	-894.5000652	134.42	122.3i
PARA ProD2GM	-----	-----	-----	-895.7415845	145.63	-----
PARA ProD2TS	-----	-----	-----	-895.7362310	136.14	137.9i
PARA ProD3GM	-----	-----	-----	-935.0653699	141.83	-----
PARA ProD3TS	-----	-----	-----	-935.0508694	141.13	179.0i

B3L and B3L311 refer to values calculated by B3LYP/6-31G(d,p) and B3LYP/6-311+G(d,p), respectively. GM and TS are global minimum and transition state structures, respectively.

Table 4: DFT calculated kinetic and thermodynamic properties for the cyclization reactions of **11–15** and **PARA ProD1- ProD3**.

System	log k_{rel} (exp.)	$E_{S_{INT-GM}}$ (MM2 calc.)	ΔG^\ddagger	ΔG^\ddagger	r_{GM} B3L	ΔG^\ddagger	ΔG^\ddagger
			(GP) B3L	(H ₂ O) B3L		(GP) B3L311	(H ₂ O) B3L311
11	3.00	8.70	19.09	29.37	4.24	9.26	20.33
12	3.30	9.30	12.22	21.10	4.34	13.13	22.03
13	5.26	8.07	12.83	16.13	4.31	10.27	13.98
14	5.36	4.24	1.43	9.03	4.08	2.76	12.54
15	7.90	2.31	10.48	16.51	2.37	-----	-----
PARA ProD1	-----	-----	-----	-----	-----	9.32	15.42
PARA ProD2	-----	-----	-----	-----	-----	6.15	18.83
PARA ProD3	-----	-----	-----	-----	-----	9.31	22.98

log k_{rel} is the experimental relative rate [53, 54]. ΔG^\ddagger is the activation free energy (kcal/mol). r_{GM} is the distance between the nucleophile (O1) and the electrophile (C6) in the reactant. B3L and B3L311 refer to calculated by B3LYP/6-31G (d,p) and B3LYP/6-311 + G(d,p), respectively. GP and H₂O calculated in the gas phase and water, respectively.

$$\Delta E_{S_{(INT-GM)}} = -1.4016 \log k_{rel} + 13.482 \quad (R = 0.9) \quad (1)$$

(For systems **11-15**)

$$\Delta G^\ddagger_{H_2O} (B3LYP/6-31G) = -6.135 \log k_{rel} + 44.859 \quad (R = 0.9) \quad (2)$$

(For systems **11-15**)

$$\Delta G^\ddagger_{H_2O} (B3LYP/6-311+G) = -3.589 \log k_{rel} + 32.491 \quad (R = 0.9) \quad (3)$$

(For systems **11-15**)

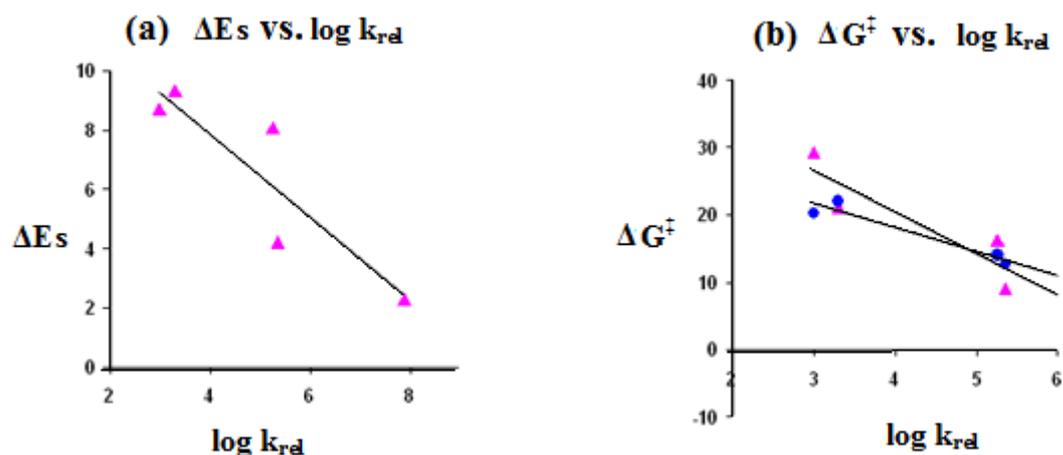


Figure 15: (a) Plot of the MM2 calculated difference in strain energies between intermediates and reactants ($ES_{(INT-GM)}$) vs. relative rate ($\log k_{rel}$) in di-carboxylic semi-esters **11-15**. (b) Plot of the DFT calculated ΔG^\ddagger vs. relative rate ($\log k_{rel}$) in di-carboxylic semi-esters **11-14**. Pink points for the values calculated by B3LYP/6-31 G(d,p) and blue points for that calculated by B3LYP/6-311 + G(d,p).

The relative rate, $\log k_{rel}$, (effective molarity (EM)) for processes **PARA ProD1-ProD3**

The experimental relative rates for the intramolecular ring-closing reactions of **11-15** were obtained from the division of the intramolecular rate and the corresponding intermolecular reaction [53, 54]. For obtaining the relative rates (effective molarity, EM) for processes **PARA ProD1-ProD3** we assume that their corresponding intermolecular process is similar to that for systems **11-15**.

Using equation (3) we have calculated the relative rate ($\log k_{rel}$) values for **PARA ProD1-ProD3**. The calculated $\log k_{rel}$ for **PARA ProD1-ProD3** obtained were 4.87, 3.80 and 2.65, respectively.

Examination of the calculated $\log k_{rel}$ values demonstrates that **PARAProD1** is the most efficient processes among all the systems investigated and the least efficient is **PARAProD3**.

Using the experimental $t_{1/2}$ (the time needed for the conversion of 50% of the reactants to products) value for process **11**, 3.75 hours [53, 54] and the calculated $\log k_{rel}$ values for **PARAProD1-ProD3** we have calculated the $t_{1/2}$ values for the conversion of **PARAProD1- ProD3** to their parent drug, paracetamol. The $t_{1/2}$ values for **PARAProD1-ProD3** were 3 minutes, 1 hour and 8.4 hours, respectively.

Chapter Five
Conclusions and future directions

Chapter 5

Conclusions and future directions

5.1 Conclusions

5.1.1 Phenylephrine conclusion

The DFT calculation results revealed that the rate of a proton transfer in processes phenylephrine **ProD1- ProD3** and **1-10** 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 reactants with short r_{GM} and α values close to 180° strong intramolecular hydrogen bonding provide stable transition states that lead to acceleration in rate.

Using the experimental $t_{1/2}$ (the time needed for the conversion of 50% of the reactants to products) and EM (effective molarity) values for these processes the $t_{1/2}$ values for the conversion of the three prodrugs to the parent drug, phenylephrine were calculated. The calculated $t_{1/2}$ values for **ProD1** and **ProD2** were very high (145 days and several years, respectively) whereas that of **ProD3** was found to be about 35 hours. Therefore, the best candidate to fulfill the requirements needed to reach better bioavailability than the naked phenylephrine is phenylephrine **ProD3**.

5.1.2 Paracetamol conclusion

From DFT calculation results on Bruice's di-carboxylic semi-esters (1-5) and paracetamol ProD1-ProD3 we can conclude the following:-

- 1- Ring – closing reaction rates of the studied systems were found to be dependent on the difference in the strain energies of the intermediates and reactants, and there was no relationship between the rate and the distance between the nucleophile and electrophile (r_{GM}).
- 2- The reactions of strained di-carboxylic semi-esters such as **4** are more efficient than the less strained semi-esters and the reactivity extent was linearly correlated with the strain energy difference between the intermediate and reactant (ΔE_s).
- 3- The activation energy required to give a stable transition state for a strained di-carboxylic semi-ester is less than that for the unstrained semi-ester, since the conformational change from the reactant to transition state in the former is smaller.
- 4- Based on the linearity obtained between the relative rate, activation energy and difference in strain energies of the intermediates and reactants for di-carboxylic semi-esters 1-4 we have calculated the relative rates for paracetamol ProD1-ProD3 to their parent drug, Paracetamol.

Using the experimental $t_{1/2}$ and the calculated relative rate values ($\log k_{rel}$) for PARA ProD1-ProD3 we have calculated the $t_{1/2}$ values for the conversion of PARA ProD1-ProD3 to their parent drug paracetamol, the $t_{1/2}$ values for PARA ProD1-PARA ProD3 were 3 minutes, 1 hour and 8.4 hours respectively.

5.2 Future directions

According to the DFT calculations done for systems **1-10** and the designed phenylephrine prodrugs, it is recommended to synthesize phenylephrine **ProD3** using Kirby's synthetic procedure. *In vitro* kinetic studies at different pH values should be made in order to be utilized for their *in vivo* pharmacokinetic studies which should be followed to determine the $t_{1/2}$ values for the conversion of the phenylephrine **ProD3** to its parent drug, phenylephrine.

Based on the DFT results of **11-15** and the designed paracetamol prodrugs, it is recommended to synthesize the two paracetamol prodrugs, **PARAProD2-ProD3** using Bruice's synthetic procedure. *In vitro* kinetic studies at different pH values and *in vivo* pharmacokinetic studies should be conducted for the determination of $t_{1/2}$ values for the conversion of the two paracetamol prodrugs to their parent drug, paracetamol.

In the *in vivo* studies, the prodrug should be administered to animals by I.V. injection and per-os, blood and urine samples should be collected at different times. The concentration of phenylephrine should be determined using a reliable bio-analytical method. Further, pharmacokinetic parameter values should be calculated including oral bioavailability, terminal elimination half-life and other pharmacokinetic parameters as deemed necessary.

In addition, bitter sensation studies should be conducted for phenylephrine and paracetamol prodrugs to determine if the designed prodrugs have or lack any bitter taste.

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Supplementary Material

Supplementary Material

Content:

- 1- Figures S1a-c
- 2- DFT calculated energies for the proton transfers in **1-10** and paracetamol **ProD1 – ProD 3**.
- 3- Xyz Cartesian coordinates for the DFT optimized GM, TS and P in processes phenylephrine **ProD 1- ProD 3** and **1-10**.
- 4- Figures S2a-b
- 5- Xyz Cartesian coordinates for the DFT optimized GM and TS in processes phenylephrine **11-14** and **PARA ProD1-ProD3**.

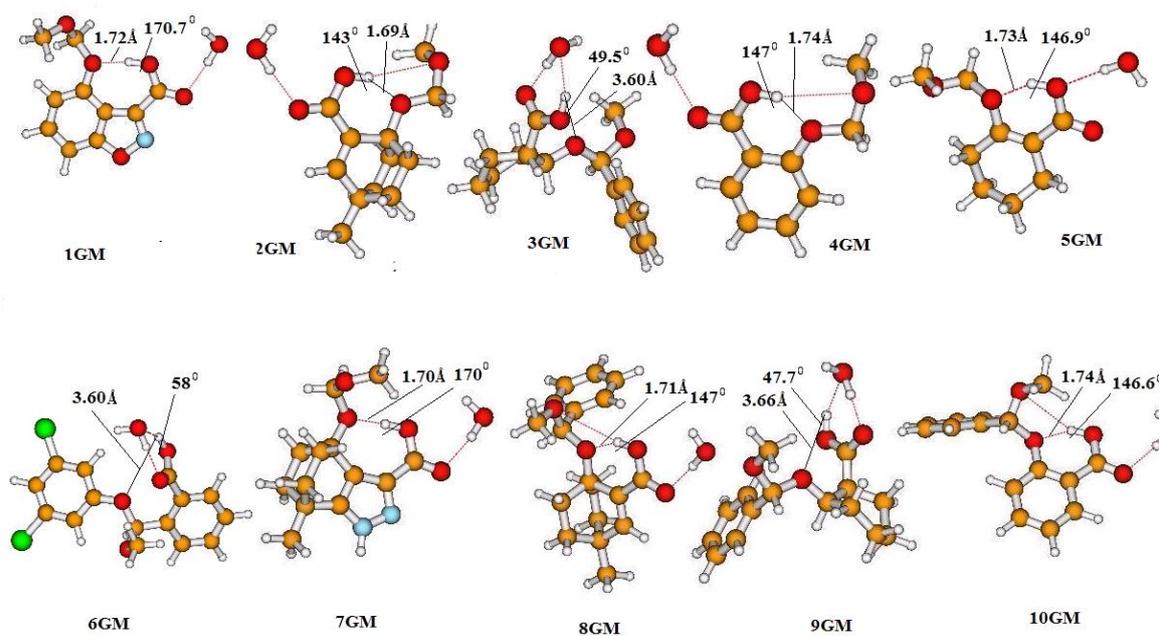


Figure S1a: DFT optimized structures for the global minimum (GM) structures in the intramolecular proton transfer reaction of **1-10**.

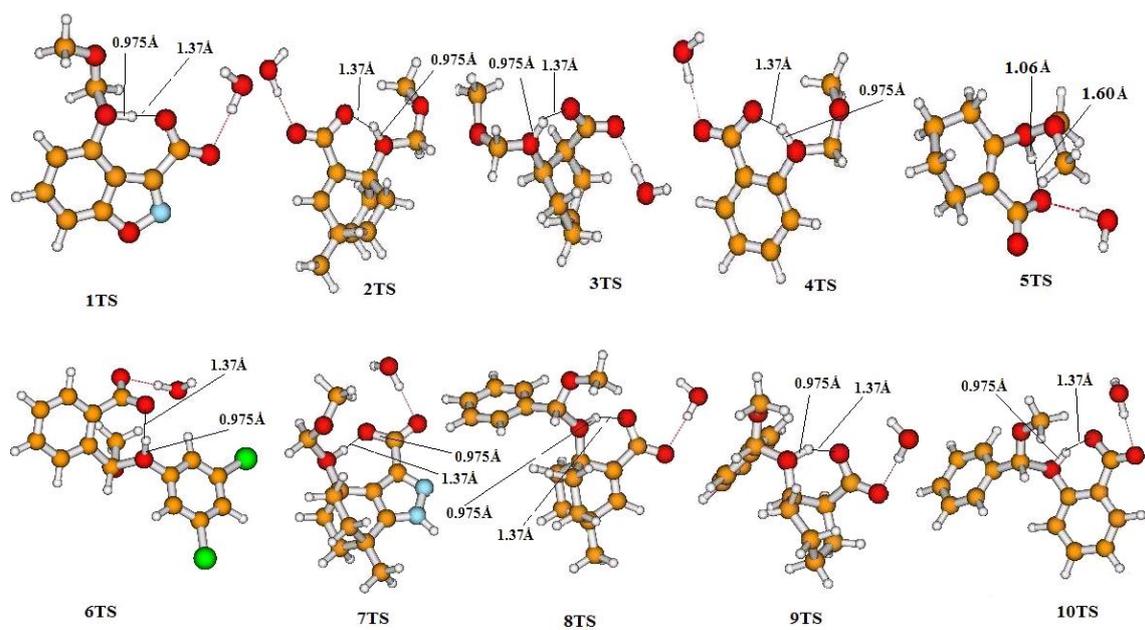


Figure S1b: DFT optimized structures for the transition state (TS) structures in the intramolecular proton transfer reaction of **1-10**.

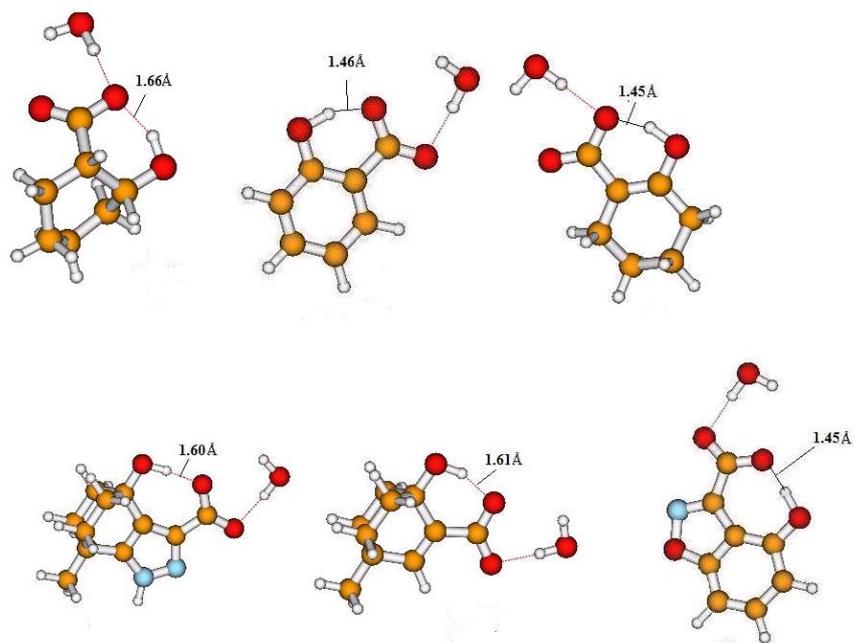


Figure 1Sc: DFT optimized structures for the product (P) structures in the intramolecular proton transfer reaction of **1-10**

Table S1. DFT (B3LYP) calculated properties for the proton transfer reactions of **1-10** and **paracetamol ProD 1- ProD3**.

Struct.	Enthalpy, H In Hartree	Entropy, S, Cal/Mol- Kelvin	Frequency Cm ⁻¹	Struct.	Enthalpy, H In Hartree	Entropy, S, Cal/Mol- Kelvin	Frequency Cm ⁻¹
1GM	-893.73201	135.57	-----	7TS	-993.00826	144.17	181.03i
2TS	-893.68532	135.66	165.49i	8GM	-1076.50693	172.52	-----
2GM	-845.44633	147.15	-----	8TS	-1076.45691	160.07	611.61i
2TS	-845.39359	142.97	558.92i	9GM	-957.37381	159.64	-----
3GM	-729.94298	129.27	-----	9TS	-957.32753	142.46	184.58i
3TS	-729.87241	121.80	390.28i	10GM	-961.00056	152.14	-----
4GM	-726.31205	132.92	-----	10TS	-960.93507	155.62	578.23i
4TS	-726.26559	119.33	132.40i	ProD 1GM	-1129.71308	171.26	-----
5GM	-728.72138	133.20	-----	ProD 1TS	-1129.63371	160.51	612.59i
5TS	-728.66450	120.34	522.39i	ProD 2GM	-1126.07858	165.90	-----
6GM	-1876.55809	152.33	-----	ProD 2TS	-1126.02298	160.67	215.70i
6TS	-1876.49684	154.58	719.08i	ProD 3GM	-1245.20203	173.32	-----
7GM	-993.05253	153.17	-----	ProD 3TS	-1245.15174	175.96	256.26i

B3LYP refers to values calculated by B3LYP/6-31G (d, p) in the gas phase. GM and TS are global minimum and transition state structures, respectively. P refers to paracetamol.

Phenylephrine ProD 1GM

C	-2.117941	-1.102334	2.329747
C	-1.142765	-1.132309	1.330078
C	-1.538090	-0.915967	0.008759
C	-2.867830	-0.650729	-0.315647
C	-3.833581	-0.613255	0.689405
C	-3.451025	-0.850667	2.016207
O	-0.658651	-0.927723	-1.069879
C	0.554163	-1.569335	-0.933688
O	1.475704	-0.666483	-0.288333
C	2.828919	-0.920310	-0.331505
C	3.700631	0.153049	-0.034300
C	5.081419	-0.095484	-0.045550
C	5.587882	-1.355074	-0.353749
C	4.712481	-2.398136	-0.648018
C	3.333665	-2.187674	-0.634449
C	3.254450	1.555722	0.290928
O	1.951144	1.848050	0.215352
C	-5.277044	-0.286322	0.368055
O	-5.585936	-0.826658	-0.917483
O	4.040769	2.427258	0.620215
C	-5.570025	1.231241	0.440120
N	-4.773280	2.034896	-0.473782
C	-5.329893	2.199535	-1.812460
O	6.845393	2.753823	0.233223
H	5.760856	0.723359	0.169327
H	6.660479	-1.516914	-0.365829
H	2.663607	-3.012349	-0.846051
H	5.094702	-3.386177	-0.886785
H	1.440085	1.055809	-0.042229
H	0.924363	-1.791641	-1.938919
H	0.468799	-2.482985	-0.331771
H	-3.141348	-0.488176	-1.349890
H	-0.102251	-1.293534	1.585972
H	-4.198664	-0.838136	2.804964
H	-1.826132	-1.275257	3.361282
H	-5.910902	-0.761872	1.135880
H	-5.360905	1.553488	1.466480
H	-6.660796	1.368403	0.284933
H	-6.503753	-0.597723	-1.116156
H	-4.601138	2.944972	-0.061900
H	-4.713725	2.906565	-2.375421
H	-6.372346	2.571480	-1.821023
H	-5.309942	1.243389	-2.339903
H	5.874233	2.735534	0.304675
H	7.127864	2.859649	1.150481

Phenylephrine ProD 1TS

O	-2.617666	1.440983	0.296984
O	-1.571318	-0.598029	0.002354
C	-0.434249	-1.143428	0.847965
O	0.312908	-0.093580	1.265102
C	1.192628	0.477070	0.315412
C	0.819620	1.672666	-0.291556
C	1.710479	2.248042	-1.197834
C	2.930414	1.630506	-1.478742
C	3.292834	0.434631	-0.849631
C	2.409008	-0.145301	0.066049
C	4.644305	-0.190854	-1.122342
O	4.497311	-1.611217	-1.055689
N	5.455645	0.049445	1.248410
C	5.946157	-1.230281	1.749731
C	5.737851	0.319438	-0.154240
C	-3.829558	1.024110	0.138055
O	-4.863669	1.694585	0.143469
C	-3.947665	-0.487032	-0.067796
C	-2.811910	-1.298805	-0.110334
C	-2.843309	-2.674279	-0.280461
C	-4.097679	-3.278250	-0.409044
C	-5.261100	-2.505913	-0.379649
C	-5.183588	-1.120308	-0.209347
O	-3.992219	4.412701	0.615037
H	-1.837564	0.319031	0.199174
H	6.705526	-0.112756	-0.481988
H	5.818793	1.402737	-0.298039
H	7.026721	-1.394665	1.578728
H	5.760486	-1.292567	2.825967
H	5.363396	-2.001977	-1.233272
H	5.822274	0.802465	1.819436
H	3.607281	2.083860	-2.198508
H	2.677441	-1.063221	0.574170
H	1.443305	3.174573	-1.696025
H	-6.067369	-0.491816	-0.176062
H	-6.228992	-2.985571	-0.485520
H	-4.157098	-4.353327	-0.545611
H	-1.933479	-3.263208	-0.324190
H	-0.897887	-1.633859	1.705014
H	-0.142669	2.121834	-0.067213
H	4.958005	0.106655	-2.136986
H	0.086706	-1.835359	0.181969
H	5.401714	-2.045611	1.267975
H	-4.309262	3.507740	0.434240
H	-3.055033	4.253305	0.782406

Phenylephrine ProD 2GM

C	1.438231	1.522745	1.445555
C	0.408264	0.584462	1.328142
C	0.625634	-0.562173	0.553960
C	1.849700	-0.748698	-0.096668
C	2.873343	0.192323	0.024637
C	2.661884	1.338050	0.805211
O	-0.300601	-1.561353	0.357432
C	-1.435284	-1.620309	1.204548
O	-2.398796	-0.641938	0.940111
C	-3.105560	-0.788427	-0.310104
C	-3.653182	0.616177	-0.673787
C	-4.982078	0.880943	0.040154
C	-6.076048	-0.075394	-0.491547
C	-5.492790	-1.424953	-0.974248
C	-4.250599	-1.820099	-0.162888
C	-2.599924	1.667294	-0.375211
O	-1.510682	1.504709	-1.166032
C	4.219550	-0.052227	-0.637904
O	4.843302	1.165811	-1.044176
O	-2.684773	2.547038	0.451595
C	5.194790	-0.772030	0.325187
N	6.444417	-1.275278	-0.219504
C	7.449390	-0.289915	-0.613966
H	-4.826937	0.736163	1.114079
H	-6.813165	-0.251927	0.299920
H	-4.512317	-1.869829	0.900871
H	-6.250638	-2.212567	-0.907379
H	-0.841831	2.134247	-0.847420
H	-1.141386	-1.477876	2.249817
H	-1.828675	-2.631980	1.053974
H	-3.807135	0.628058	-1.760724
H	-5.279780	1.925429	-0.083539
H	-6.620129	0.397844	-1.317067
H	-2.388428	-1.095570	-1.077907
H	-3.904099	-2.817757	-0.453524
H	-5.221588	-1.359588	-2.035909
H	1.981958	-1.644223	-0.697474
H	-0.550059	0.767416	1.797480
H	3.453548	2.074585	0.890890
H	1.269654	2.414062	2.043521
H	4.066357	-0.711109	-1.510474
H	4.648896	-1.616579	0.763392
H	5.423853	-0.080145	1.145194
H	4.225467	1.632319	-1.623326
H	6.259681	-1.916680	-0.986047

H	7.666455	0.356423	0.243443
H	7.164640	0.361222	-1.451250
H	8.375220	-0.815747	-0.871882

Phenylephrine **ProD 2TS**

O	2.867289	2.131705	-0.317291
O	2.219834	0.193506	-0.924681
C	3.008421	-0.429133	0.232046
C	3.259218	-1.900390	-0.084338
C	4.344959	-2.430251	0.870048
C	5.703460	-1.703573	0.657358
C	5.531861	-0.365928	-0.090690
C	4.293546	0.384697	0.404432
C	4.111294	1.806227	-0.202731
O	5.098625	2.463670	-0.500004
C	1.059111	-0.554455	-1.423103
O	0.199949	-0.974237	-0.421332
C	-0.823596	-0.106854	-0.018208
C	-2.102474	-0.657878	0.039364
C	-3.185035	0.124736	0.450518
C	-2.959414	1.460966	0.809422
C	-1.675110	1.997460	0.755336
C	-0.588008	1.220358	0.345270
C	-4.593747	-0.447596	0.459080
O	-5.381825	0.103159	1.512115
C	-5.323939	-0.139372	-0.872620
N	-6.593104	-0.795981	-1.123150
C	-7.741058	-0.383361	-0.318307
H	2.040416	1.140198	-0.775654
H	0.581973	0.143876	-2.121298
H	1.441958	-1.435914	-1.932514
H	2.338136	-0.317562	1.085677
H	2.338457	-2.482411	0.015068
H	3.613518	-1.999394	-1.117415
H	3.998789	-2.296900	1.902513
H	4.450191	-3.509972	0.725365
H	6.394405	-2.348264	0.102872
H	6.168655	-1.521706	1.632725
H	6.397405	0.286178	0.042265
H	4.404562	0.542855	1.486736
H	-2.235837	-1.698165	-0.243137
H	-3.797009	2.062481	1.145860
H	-1.504537	3.030044	1.043788
H	0.409158	1.648868	0.350289
H	-4.982581	-0.157613	2.352955
H	-4.528569	-1.544547	0.558535

H	-4.637300	-0.401908	-1.687035
H	-5.476326	0.946188	-0.922485
H	-6.483251	-1.805760	-1.096516
H	-8.642351	-0.854559	-0.724983
H	-7.866318	0.700748	-0.410897
H	-7.671560	-0.614210	0.752976
H	5.451842	-0.537018	-1.171355

Phenylephrine ProD 2GM

C	3.296172	-2.178864	-0.297354
C	4.004272	-1.312677	0.783789
C	4.027755	0.106299	0.271541
C	2.832201	0.650990	-0.026323
C	1.665973	-0.312430	0.198130
C	1.908439	-1.584369	-0.654319
C	3.076104	-1.312999	2.040543
C	1.682033	-0.734800	1.686680
O	0.366849	0.296208	-0.025216
C	-0.154236	0.347578	-1.346511
O	-0.772245	-0.844444	-1.754709
C	-2.024489	-1.152849	-1.261909
C	-2.612984	-0.517538	-0.165806
C	-3.900144	-0.893727	0.245566
C	-4.572967	-1.916982	-0.428472
C	-3.966520	-2.556709	-1.511926
C	-2.695146	-2.180333	-1.934121
C	-4.554504	-0.169673	1.415196
C	-5.361168	1.065688	0.977084
N	-4.594959	1.997953	0.164979
C	-5.311498	3.237929	-0.105290
C	2.726263	2.096505	-0.390692
O	3.660345	2.764812	-0.799056
C	5.398210	-1.849085	1.113377
O	1.526018	2.677653	-0.213101
O	-3.604708	0.268422	2.380693
O	6.415590	2.064675	-0.987069
H	4.960569	0.656850	0.171332
H	1.860939	-1.342517	-1.718034
H	3.931166	-2.233957	-1.186513
H	0.893364	2.001111	0.108583
H	-0.872174	1.173906	-1.341034
H	0.633970	0.535941	-2.079706
H	1.101997	-2.294175	-0.452838
H	5.880957	-1.242466	1.886841
H	6.043286	-1.835959	0.229005
H	5.344816	-2.880131	1.479031

H	3.192497	-3.201086	0.084347
H	1.440758	0.136519	2.302633
H	0.886079	-1.470301	1.840638
H	2.988946	-2.341335	2.409394
H	3.548403	-0.728832	2.836170
H	-2.093500	0.247657	0.396182
H	-5.563631	-2.221054	-0.101175
H	-4.487097	-3.356396	-2.030648
H	-2.209367	-2.661107	-2.776507
H	-5.277708	-0.859974	1.880491
H	-5.670126	1.583353	1.893055
H	-6.285963	0.709937	0.482299
H	-3.081681	-0.501165	2.642811
H	-4.351346	1.549557	-0.714231
H	-4.715200	3.866420	-0.773484
H	-5.452690	3.790670	0.830289
H	-6.309136	3.101646	-0.563291
H	5.472942	2.313080	-0.955132
H	6.836252	2.707803	-0.402793

Phenylephrine ProD 2TS

C	-2.858698	-2.576873	-1.350178
C	-2.135969	-1.433870	-1.001878
C	-2.617167	-0.532333	-0.055867
C	-3.865442	-0.765797	0.542019
C	-4.594328	-1.907178	0.198012
C	-4.089634	-2.807622	-0.743267
O	-0.914242	-1.290286	-1.659111
C	-0.305060	-0.061927	-1.704347
O	0.415336	0.239112	-0.453469
C	1.740683	-0.411051	-0.080957
C	2.815522	0.658818	-0.070380
C	3.995464	0.169613	0.341115
C	4.016723	-1.301985	0.699772
C	3.518245	-2.087947	-0.551494
C	2.147432	-1.538922	-1.046297
C	1.559158	-0.988501	1.332685
C	2.943920	-1.511152	1.814202
C	2.539600	2.112007	-0.435823
O	3.480578	2.908106	-0.484675
C	5.393747	-1.789699	1.151215
C	-4.401868	0.237525	1.552972
C	-5.163242	1.404249	0.895149
N	-4.420715	2.042579	-0.181933
C	-4.958534	3.344755	-0.561535
O	1.294793	2.378262	-0.648738
O	-3.362507	0.811419	2.337510

O	6.245001	2.658714	-0.084710
H	0.640657	1.187535	-0.472147
H	5.275287	2.726565	-0.197439
H	6.565564	2.459769	-0.971777
H	-4.391068	3.739156	-1.409492
H	-4.837183	4.045098	0.271554
H	-6.028520	3.336614	-0.839052
H	-5.327602	2.147070	1.683709
H	-6.160373	1.037474	0.586906
H	-5.126594	-0.282535	2.200718
H	-2.879541	0.088368	2.759981
H	-2.057150	0.341154	0.252828
H	-5.552892	-2.098874	0.672609
H	-4.656695	-3.696066	-1.003954
H	-2.447951	-3.259380	-2.086268
H	-1.004463	0.774218	-1.787735
H	0.409744	-0.070761	-2.524918
H	0.810652	-1.787647	1.302802
H	1.178433	-0.201682	1.989087
H	2.251181	-1.148614	-2.061877
H	1.382871	-2.319802	-1.061451
H	3.429346	-3.149791	-0.295327
H	4.263372	-2.010153	-1.347912
H	2.887510	-2.577291	2.062145
H	4.880749	0.797036	0.418028
H	5.732685	-1.237427	2.033446
H	6.138933	-1.643667	0.362595
H	5.373210	-2.855242	1.405086
H	-4.418531	1.430707	-0.993496
H	3.258386	-0.985165	2.719699

1GM

O	-1.880370	-1.209324	0.078365
H	-0.913044	-1.314117	-0.042036
O	0.788793	-1.221505	-0.294902
C	1.226641	0.078996	-0.221335
C	0.229510	1.060389	-0.041819
C	-1.210209	1.126186	0.078114
C	-2.279271	0.065939	0.092415
O	-3.454932	0.351844	0.132987
H	-4.615533	-1.278718	-0.050697
O	-5.133517	-2.093576	-0.144202
H	-4.514117	-2.768131	0.156603
N	-1.612326	2.365697	0.223332
O	-0.483165	3.176177	0.207210
C	0.616914	2.400368	0.048999

C	1.935254	2.847550	-0.026638
C	2.889713	1.857608	-0.197687
C	2.552706	0.490761	-0.289416
C	1.596001	-2.302410	-0.836163
O	1.997992	-3.190976	0.132486
C	3.071444	-2.757887	0.965575
H	3.960127	-2.513916	0.368872
H	2.788624	-1.890935	1.571113
H	3.305818	-3.592996	1.624699
H	2.427419	-1.863405	-1.398910
H	0.924796	-2.843832	-1.501679
H	3.349728	-0.230482	-0.404897
H	3.936770	2.132840	-0.258986
H	2.185062	3.897687	0.044780

1TS

O	-1.739320	-0.503634	-0.371521
H	-0.936692	0.590886	-0.557836
O	-0.334437	1.338724	-0.388568
C	-0.953206	2.105419	0.817524
O	-1.793107	3.041296	0.355738
C	-1.183004	4.205127	-0.221571
C	-1.274527	-1.683629	-0.121428
O	-1.913512	-2.716785	0.043983
C	0.246518	-1.720502	-0.017062
N	0.942058	-2.816516	0.136484
O	2.309129	-2.446133	0.190073
C	2.399606	-1.103760	0.067428
C	1.114414	-0.573227	-0.062841
C	0.977819	0.806245	-0.212569
C	2.088030	1.628942	-0.231617
C	3.368875	1.053453	-0.082441
C	3.553832	-0.317245	0.069264
H	4.538592	-0.755074	0.178094
H	4.234460	1.706966	-0.097007
H	1.979165	2.698352	-0.374430
H	-0.068703	2.470385	1.348696
H	-1.510430	1.332691	1.345667
H	-0.699603	3.953084	-1.169966
H	-1.989779	4.914633	-0.398997
H	-0.452035	4.641707	0.469596
H	-3.778163	-2.172196	0.018566
O	-4.698030	-1.850747	0.000041
H	-4.587137	-0.972517	-0.383875

1P

O	5.062547	0.513757	-0.001538
H	4.277273	-0.077442	-0.002733
O	2.746450	-1.109107	-0.000949
C	1.817280	-0.285661	0.000952
O	1.918318	0.989328	0.002799
C	0.383205	-0.811877	0.000361
N	0.123827	-2.096166	0.000410
O	-1.295085	-2.229044	0.000178
C	-1.845696	-0.987690	0.000040
C	-0.827852	-0.031135	0.000383
C	-1.141255	1.353010	-0.000218
O	-0.207796	2.295770	0.000008
C	-2.508651	1.682000	-0.000701
C	-3.500007	0.689466	-0.000670
C	-3.206497	-0.675624	-0.000463
H	-3.973538	-1.441007	-0.000624
H	-4.542487	1.000887	-0.001077
H	-2.779867	2.732908	-0.001070
H	4.612903	1.369165	-0.000318
H	0.720290	1.808080	0.000867

2GM

O	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.437879
C	1.443039	0.000000	1.932871
C	2.694185	-0.047871	1.107438
O	3.797090	0.020118	1.622302
H	5.271532	-0.033664	0.307483
O	5.962196	-0.062548	-0.376524
H	5.449521	-0.206269	-1.181356
O	2.569017	-0.182739	-0.218770
H	1.612240	-0.204424	-0.450488
C	-0.685984	1.272605	2.003378
C	-0.559777	1.285488	3.548972
C	1.537690	0.026681	3.273734
C	0.240203	0.041098	4.040995
C	0.436788	0.062620	5.557575
C	-0.556101	-1.220495	3.584993
C	-0.700276	-1.247414	2.039983
H	-1.548329	1.274787	4.022224
H	-0.208052	2.147642	1.554721
H	-1.739101	1.286252	1.703170
H	-0.247525	-2.147420	1.613600
H	-1.758044	-1.246004	1.755024
H	-0.040983	-2.118326	3.939045
H	-1.540479	-1.207161	4.066599
H	-0.526956	0.073316	6.077637

H	0.991137	-0.818970	5.896302
H	0.996132	0.950900	5.869487
H	2.506727	0.027442	3.763974
C	-1.212584	-0.264586	-0.716933
O	-1.027845	0.090633	-2.037615
C	-0.937868	1.496431	-2.262335
H	-0.875034	1.634010	-3.342554
H	-0.048061	1.923614	-1.788434
H	-1.831280	2.013371	-1.883793
H	-2.037835	0.296389	-0.250096
H	-0.055270	2.195496	3.887043
H	-1.432481	-1.337140	-0.707460

2TS

O	0.000000	0.000000	0.000000
H	0.000000	0.000000	0.975000
O	0.832865	0.000000	2.062767
C	1.801051	0.833738	1.874226
O	2.734969	1.080600	2.641776
H	2.423541	-0.009497	4.179169
O	2.214152	-0.562177	4.956489
H	1.358108	-0.924411	4.695817
C	-1.131163	-0.644655	-0.714932
O	-1.609905	-1.638894	0.078919
C	-0.699809	-2.731391	0.307881
H	0.119457	-2.416164	0.960149
H	-1.284158	-3.510814	0.795579
H	-0.302724	-3.108291	-0.643196
H	-0.705587	-0.988989	-1.665418
C	0.737399	1.180951	-0.521199
C	1.734254	1.564544	0.548192
C	2.489806	2.608365	0.185289
H	3.254311	3.003805	0.847447
C	3.091526	4.379780	-1.536379
C	2.200739	3.188257	-1.183135
H	4.148618	4.094631	-1.526205
H	2.958600	5.195232	-0.817873
H	2.857100	4.768044	-2.533453
H	3.424272	1.737429	-2.257965
H	0.529395	4.415571	-0.505572
C	2.371037	2.027039	-2.211333
C	0.690261	3.584500	-1.197547
C	1.494375	0.806149	-1.808798
C	-0.201176	2.371845	-0.798385
H	0.788617	0.559325	-2.610372
H	-0.902811	2.127677	-1.604400
H	2.091144	2.387187	-3.207692
H	0.423134	3.941931	-2.198340
H	-1.923417	0.090622	-0.864896

H	-0.785313	2.588037	0.100537
H	2.106135	-0.078714	-1.615549

3GM

C	0.000000	0.000000	0.000000
O	0.000000	0.000000	1.400529
C	1.306573	0.000000	1.970216
H	0.649453	-0.789701	-0.400449
O	0.489725	1.196214	-0.560689
C	-0.398290	2.317167	-0.467905
C	-1.209708	2.482090	-1.752657
C	-2.251575	3.616036	-1.609319
H	-2.466225	4.027502	-2.601214
C	-0.235525	4.871053	-0.700008
C	-1.763053	4.742231	-0.666752
H	-2.224005	5.695297	-0.945539
H	-2.086042	4.539189	0.362281
H	-3.197903	3.212650	-1.232234
H	-1.071935	2.166495	0.384379
H	0.598047	3.649662	0.912198
H	-1.704859	1.536247	-1.996362
H	-0.509859	2.689607	-2.568352
C	0.455913	3.588139	-0.169733
H	0.093371	5.045284	-1.729358
H	0.095993	5.732263	-0.110755
C	1.830890	3.426217	-0.792032
O	2.064428	3.579854	-1.985633
H	3.802119	3.199767	-2.101983
O	4.752793	2.976551	-2.116859
H	5.204166	3.828715	-2.152517
O	2.776886	3.108328	0.104244
H	3.628388	2.945497	-0.356104
H	1.879438	0.882365	1.667062
H	1.176889	0.001404	3.053759
H	-1.040600	-0.182175	-0.294026
H	1.863150	-0.902073	1.677641

3TS

C	0.000000	0.000000	0.000000
O	0.000000	0.000000	1.277458
H	1.168192	0.000000	1.993159
O	2.082806	0.216922	1.734217
C	2.423058	0.417395	0.273209
C	1.415659	-0.344736	-0.583400
O	-0.944741	0.279732	-0.749211
H	-0.696495	2.083307	-1.061526
O	-0.519104	3.032202	-1.205155

H	-1.054020	3.473166	-0.536566
C	2.439532	1.911107	-0.011604
C	2.810381	2.176974	-1.501935
C	2.830068	0.891813	-2.351350
C	1.597409	0.007469	-2.083361
H	0.689212	0.519471	-2.408987
H	1.661979	-0.912853	-2.670009
H	1.569310	-1.417345	-0.420120
H	3.417266	-0.023158	0.199007
H	1.443271	2.316345	0.180770
H	3.139397	2.409029	0.666757
H	3.749126	0.324145	-2.152719
H	2.866561	1.156556	-3.412378
H	2.056416	2.858881	-1.901332
H	3.780300	2.678222	-1.571383
C	3.164049	-0.246197	2.606935
H	2.756886	-0.121580	3.616378
H	4.017723	0.408222	2.441583
O	3.545561	-1.534041	2.324186
C	2.583939	-2.532195	2.695541
H	2.420314	-2.524799	3.779428
H	1.630697	-2.376020	2.181201
H	3.006045	-3.490184	2.398637

4GM

C	0.000000	0.000000	0.000000
O	0.000000	0.000000	1.371663
C	1.299920	0.000000	1.969697
H	1.901237	-0.840664	1.598054
H	1.830760	0.938100	1.777295
H	1.144713	-0.112929	3.042930
O	0.396539	1.314977	-0.472761
C	1.082376	1.450447	-1.656903
C	1.994702	2.522352	-1.765892
C	2.313469	3.493265	-0.665085
O	3.181803	4.336935	-0.791227
H	3.522671	5.368162	0.876857
O	3.654504	5.842650	1.714763
H	2.844627	5.641400	2.199285
O	1.616166	3.413290	0.481471
H	0.949414	2.699409	0.414228
C	2.680723	2.691905	-2.976295
C	2.480136	1.830952	-4.049898
C	1.573505	0.777790	-3.924383
C	0.870354	0.586902	-2.735528
H	0.144472	-0.214714	-2.658347
H	1.400081	0.102573	-4.756934
H	3.023438	1.980264	-4.976940

H	3.381552	3.516972	-3.037910
H	0.698204	-0.733518	-0.431310
H	-1.025745	-0.194369	-0.324751

4TS

O	-0.104851	1.194326	-0.628544
H	0.752284	0.731936	-0.674810
O	1.495422	-0.408091	-0.516745
C	0.745926	-1.379453	-0.111625
O	1.099205	-2.530363	0.149822
H	2.999263	-2.394212	0.022075
O	3.964354	-2.275339	-0.055199
H	4.000224	-1.470172	-0.586388
C	1.752670	2.638049	1.124766
H	1.956737	1.564553	1.076975
H	2.688448	3.187944	1.207036
H	1.108957	2.869039	1.981458
O	1.142822	3.082134	-0.104474
C	-0.132036	2.677115	-0.319198
H	-0.528688	3.174305	-1.202562
H	-0.798559	2.749423	0.549070
C	-1.135602	0.284045	-0.280942
C	-2.463242	0.684399	-0.268160
H	-2.759217	1.692295	-0.537185
C	-3.420008	-0.268613	0.094643
H	-4.466846	0.015358	0.118706
C	-3.037284	-1.574584	0.406431
H	-3.789854	-2.305640	0.682343
C	-1.692923	-1.943031	0.352695
H	-1.360704	-2.950876	0.576689
C	-0.713779	-1.012143	0.006008

5GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.534172
C	1.391885	0.000000	2.113358
C	2.513240	-0.254044	1.401453
C	2.443554	-0.589042	-0.076910
C	1.038820	-0.985910	-0.538134
O	1.493749	0.179590	3.490745
C	0.696796	1.194783	4.139680
O	-0.589691	0.784118	4.431320
C	-0.668457	-0.220765	5.443024
C	3.905991	-0.211305	1.947478
O	4.876661	-0.365671	1.232560
O	4.080963	0.013391	3.269586
H	-0.567682	0.853907	1.916896

H	-0.523694	-0.885402	1.922203
H	3.164402	-1.385829	-0.282029
H	2.802232	0.275773	-0.651493
H	1.004696	-1.026696	-1.631872
H	0.802525	-1.995488	-0.176347
H	-1.004800	-0.241602	-0.361986
H	0.233668	1.008595	-0.364529
H	0.622134	2.074698	3.495608
H	1.268519	1.427306	5.047264
H	-0.199265	-1.154517	5.115457
H	-1.729283	-0.391221	5.629981
H	-0.186527	0.117594	6.370520
H	6.141677	-0.165442	3.522273
O	7.103597	-0.252411	3.589335
H	7.349811	-0.366687	2.662634
H	3.204935	0.085766	3.700097

5TS

O	-3.992515	0.582469	-0.141609
H	-3.078323	0.612643	-0.498921
O	-1.445299	0.758259	-1.150192
H	-0.695239	-0.503338	-1.787202
O	-0.147090	-1.189521	-1.193666
C	0.941315	-0.472283	-0.585595
C	2.184554	-1.288605	-0.423877
C	3.389090	-0.372578	-0.136955
C	3.018783	0.738986	0.856528
C	1.886697	1.621154	0.310707
C	0.758918	0.814448	-0.279566
C	-0.627415	1.427525	-0.395917
O	-0.892465	2.420815	0.279170
C	-1.164121	-2.005634	-0.275225
O	-0.903062	-1.863461	1.024809
C	-1.614381	-0.835952	1.771663
H	-1.805471	-1.270178	2.753717
H	-2.552997	-0.563623	1.279032
H	-0.984573	0.048654	1.870273
H	-2.124673	-1.615805	-0.615341
H	-0.944672	-3.020996	-0.600868
H	2.351997	-1.884178	-1.329667
H	2.040581	-2.006291	0.396949
H	3.722836	0.082122	-1.078176
H	4.224541	-0.971801	0.239431
H	2.700387	0.285015	1.804178
H	3.897402	1.352733	1.081675

H	1.458605	2.264562	1.084958
H	2.270055	2.303968	-0.461160
H	-4.077658	1.455667	0.262452

5P

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.534468
C	1.393400	0.000000	2.120314
C	2.512868	-0.265071	1.392347
C	2.452746	-0.580324	-0.084066
C	1.045165	-0.983754	-0.541320
O	1.423221	0.264289	3.434446
C	3.858200	-0.250783	2.056794
O	4.877957	-0.496098	1.381344
O	3.857698	0.021819	3.331794
H	-0.540389	0.869997	1.930604
H	-0.538493	-0.881087	1.916971
H	3.179992	-1.370369	-0.302852
H	2.791369	0.285593	-0.677550
H	0.993508	-1.033977	-1.637879
H	0.811733	-1.991161	-0.167087
H	-1.003270	-0.237385	-0.380018
H	0.242437	1.008506	-0.363499
H	5.636714	-0.069637	3.736647
O	6.605000	-0.130768	3.905574
H	6.877616	-0.350558	3.003640
H	2.457584	0.206750	3.634129

6GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.388794
C	1.182705	0.000000	2.130042
C	2.382191	0.019349	1.423318
C	2.436038	0.036669	0.029576
C	1.227435	0.013035	-0.674069
Cl	3.890892	0.040831	2.323134
Cl	-1.535512	-0.014786	2.240919
O	1.136931	0.012383	-2.039151
C	2.267785	-0.348445	-2.826431
O	3.264067	0.633703	-2.843870
C	2.917050	1.886674	-3.447801
C	1.766418	-0.760187	-4.207441
C	2.648531	-1.527419	-4.977266
C	2.282868	-2.014716	-6.229486

C	1.004669	-1.757800	-6.724924
C	0.113195	-1.000427	-5.969877
C	0.490417	-0.479037	-4.724923
C	-0.495636	0.421929	-4.042601
O	-0.330240	1.628705	-3.913151
O	-1.608742	-0.222902	-3.668881
H	2.986834	-2.605727	-6.807022
H	0.700197	-2.147655	-7.691083
H	-0.883816	-0.796969	-6.347430
H	-2.233766	0.414777	-3.251152
H	3.634883	-1.747657	-4.578485
H	2.756601	-1.211221	-2.357925
H	2.083892	2.365350	-2.927090
H	2.647388	1.761461	-4.501632
H	3.811530	2.506114	-3.370253
H	1.167763	-0.006295	3.211801
H	3.383437	0.104301	-0.486882
H	-0.921221	-0.023512	-0.568765
H	-1.779360	2.062614	-3.010175
O	-2.597457	2.254126	-2.508726
H	-2.310972	2.305961	-1.587719

6TS

O	0.000000	0.000000	0.000000
H	0.000000	0.000000	1.060000
O	1.150614	0.000000	2.171795
C	1.983878	0.929506	1.910667
O	3.220961	0.862594	2.036545
H	3.425670	-0.862196	1.436646
O	3.484106	-1.786845	1.109805
H	3.091307	-2.277951	1.843215
C	-0.268040	-1.198551	-0.693840
C	0.647274	-2.236992	-0.567167
C	0.347965	-3.421419	-1.241808
C	-0.802772	-3.561439	-2.019488
C	-1.680605	-2.482270	-2.111343
C	-1.435585	-1.283600	-1.444058
Cl	-3.133950	-2.639948	-3.076310
H	-1.010227	-4.488344	-2.539029
Cl	1.449046	-4.775080	-1.119385
H	1.554466	-2.117907	0.029451
H	-2.131645	-0.456216	-1.503595
C	0.431003	1.324610	-0.779962
O	1.391805	0.990236	-1.659979
C	0.669022	2.394118	0.254443
C	0.167721	3.658969	-0.092511
C	0.405635	4.768947	0.712092

C	1.164135	4.621834	1.874588
C	1.673090	3.373141	2.221539
C	2.767538	0.824219	-1.233652
H	3.346169	0.840128	-2.156627
H	3.081813	1.634592	-0.574750
H	2.279717	3.254500	3.113196
H	1.361886	5.481132	2.508483
H	0.004440	5.737787	0.432492
H	-0.403195	3.775231	-1.010376
H	-0.467499	1.528890	-1.362433
H	2.897038	-0.134244	-0.728606
C	1.422447	2.240006	1.437202

7GM

O	-5.599904	-1.537723	0.271168
H	-4.727083	-1.918449	0.073593
O	-2.822698	-2.383538	-0.244055
C	-2.077582	-1.462111	0.019393
O	-2.570067	-0.273552	0.412353
H	-1.858562	0.375862	0.620851
O	-0.570490	1.480666	0.690997
C	-0.679428	2.901562	0.655377
O	-0.892078	3.411473	-0.619807
C	-2.181814	3.108577	-1.153827
C	-0.592908	-1.571994	-0.078065
N	-0.073047	-2.770420	-0.390299
N	1.255650	-2.576501	-0.426950
C	1.611862	-1.297054	-0.147677
C	0.442721	-0.608210	0.089019
C	2.906840	-0.541703	-0.092038
C	4.151666	-1.380225	-0.378876
C	2.737229	0.630914	-1.109783
C	2.948024	0.111208	1.325307
C	1.644408	0.915859	1.608788
C	0.686172	0.848051	0.386471
C	1.431204	1.440961	-0.843791
H	-5.363435	-0.656610	0.585808
H	-2.344343	2.028437	-1.233204
H	-2.222116	3.556468	-2.147562
H	-2.975787	3.542870	-0.530211
H	-1.519107	3.125886	1.326885
H	0.236445	3.365733	1.030670
H	1.881203	1.963769	1.823214
H	1.116137	0.517099	2.478565
H	1.666432	2.493248	-0.661843
H	0.765770	1.410391	-1.708676
H	2.730860	0.226051	-2.126469
H	3.614544	1.283285	-1.032845
H	3.825476	0.765405	1.378275

H	5.052826	-0.761412	-0.327840
H	4.111977	-1.823104	-1.380314
H	1.850777	-3.361198	-0.645980
H	4.264924	-2.189641	0.350946
H	3.086376	-0.669253	2.079830

7TS

O	0.718134	-1.357540	0.947740
H	1.250027	-0.548573	1.063008
O	2.107593	0.519140	1.024656
C	1.725689	1.596868	0.412634
O	2.463915	2.503851	0.020771
H	4.060871	1.576586	-0.152393
O	4.881402	1.051585	-0.273371
H	5.021398	0.711793	0.619615
C	0.240369	1.642718	0.157314
N	-0.416080	2.738552	-0.239454
N	-1.697720	2.337951	-0.427960
C	-1.875392	1.014449	-0.180889
C	-0.644396	0.534713	0.195319
C	-0.651940	-0.935805	0.463523
C	-1.675659	-1.221424	1.583877
C	-1.117440	-1.665652	-0.818929
C	-2.505111	-1.083222	-1.245045
C	-3.003559	0.023981	-0.255591
C	-4.351841	0.607529	-0.674936
O	1.965258	-2.191626	-0.931819
C	1.531957	-2.459810	0.319484
C	3.292111	-1.602395	-1.051730
H	-2.378020	3.022546	-0.719630
H	-4.295070	1.060643	-1.670663
H	-4.688593	1.374108	0.031374
H	-5.119144	-0.172278	-0.709287
H	-2.440227	-0.663128	-2.252669
H	-3.419679	0.079538	1.888935
H	-3.252633	-1.883579	-1.276946
H	-3.812454	-1.454431	1.119177
H	-1.207948	-2.740200	-0.625318
H	-1.728542	-2.301108	1.762855
H	-0.374781	-1.530054	-1.605321
H	-1.329589	-0.749767	2.506671
H	0.852229	-3.311158	0.310736
H	2.328808	-2.581767	1.059123
H	4.040894	-2.356866	-0.784837
H	3.411368	-0.705193	-0.441000
H	3.400720	-1.344452	-2.104159
C	-3.067033	-0.655527	1.153102

7P

O	-5.693040	-0.327560	0.202649
H	-4.910071	0.256666	0.106942
O	-3.373310	1.283402	-0.088765
C	-2.463548	0.432361	-0.067817
O	-2.606600	-0.838284	-0.026627
C	-1.022919	0.901354	-0.089565
N	-0.682083	2.198669	-0.089425
N	0.675636	2.209167	-0.041763
H	1.152411	3.094820	-0.030678
C	1.202697	0.954739	-0.019634
C	0.140887	0.084237	-0.047175
C	0.552736	-1.367326	-0.057323
C	1.543798	-1.556037	-1.247290
C	2.728862	-0.549668	-1.173442
C	2.586254	0.379104	0.064541
C	3.707947	1.414702	0.137600
C	2.575353	-0.558992	1.316334
C	1.399318	-1.572471	1.244580
H	0.974225	-1.427634	-2.170948
H	1.767700	-2.604092	1.255183
H	1.901047	-2.591589	-1.231457
H	3.687719	-1.079386	-1.100570
H	2.778227	0.067286	-2.077493
H	2.504735	0.057645	2.219100
H	0.732349	-1.458945	2.102742
H	4.685902	0.925104	0.199179
H	3.715109	2.057689	-0.750265
H	3.601626	2.055364	1.020623
H	3.540588	-1.080080	1.363847
O	-0.478162	-2.306101	-0.150155
H	-5.246324	-1.183514	0.181952
H	-1.339520	-1.807873	-0.031509

8GM

O	0.918098	2.439728	0.190998
H	0.193057	1.854629	0.508149
O	-0.388432	0.299274	0.811303
C	0.635318	-0.611777	0.364502
C	1.820308	0.201034	-0.148708
C	1.945320	1.691724	-0.231638
O	2.952438	2.221862	-0.668400
H	2.824514	4.192539	-0.726090
O	2.711738	5.158100	-0.744951
H	1.868829	5.277844	-0.291134
H	-1.906932	1.709711	-0.785154
C	-2.661000	0.935164	-0.874656
C	-4.574228	-0.008080	-2.014863

C	-4.596670	-1.063899	-1.103154
H	-5.346984	-1.843957	-1.189497
O	-2.163138	0.697159	2.181479
C	-1.472969	0.620463	3.425868
H	-1.536895	-0.390569	3.853035
H	-1.970161	1.322617	4.096338
H	-0.419791	0.901065	3.322077
H	-1.598772	-1.191781	1.585383
C	1.151846	-1.502420	1.527244
H	0.339736	-2.141845	1.888592
H	1.448775	-0.853120	2.355349
H	-0.658812	-2.161140	-0.449976
H	-0.221207	-0.909690	-1.602656
C	0.168137	-1.531845	-0.793597
C	2.342779	-2.364536	1.032289
H	2.120201	-3.432849	1.133304
H	1.141220	-3.467925	-1.140547
H	1.548504	-2.244706	-2.336827
C	2.650985	-2.058571	-0.465207
C	1.360662	-2.402067	-1.270648
C	3.856674	-2.855191	-0.966051
H	3.679109	-3.932056	-0.877369
H	4.064440	-2.634897	-2.018325
H	4.755704	-2.614647	-0.388972
C	2.840299	-0.567427	-0.569851
H	3.747683	-0.120297	-0.964536
H	-3.673456	-1.939103	0.635378
H	-5.307210	0.035738	-2.814729
H	-3.584214	1.814582	-2.605720
C	-3.651651	-1.118535	-0.077761
C	-2.679506	-0.121754	0.041512
C	-3.605030	0.991087	-1.898460
C	-1.696117	-0.165287	1.192862
H	3.236092	-2.167617	1.632406

8TS

O	1.358101	2.053886	-0.566779
H	0.179924	1.399864	-0.319684
O	-0.228789	0.684023	0.201038
C	-1.530906	0.956281	0.942274
O	-1.640059	2.313736	0.991011
C	-0.677438	2.998365	1.820159
C	-2.700131	0.355015	0.216744
C	-3.423290	-0.684830	0.807110
C	-4.517672	-1.243335	0.143823
C	-4.890136	-0.760167	-1.110136
C	-4.172079	0.285065	-1.699153
C	-3.080992	0.844129	-1.039401

C	0.554907	-0.570542	0.161348
C	-0.006174	-1.549617	-0.890212
C	0.956436	-2.768411	-0.965789
C	2.151626	-2.591222	0.024199
C	1.535716	-2.477586	1.452855
C	0.572296	-1.258553	1.540779
C	1.970818	-0.191167	-0.213998
C	2.360093	1.240387	-0.498730
O	3.554049	1.522724	-0.633258
C	2.785126	-1.251659	-0.281445
C	3.132939	-3.759987	-0.068602
H	3.556548	-3.836031	-1.075427
H	3.962733	-3.632096	0.634378
H	2.640016	-4.710731	0.161444
H	2.340594	-2.376759	2.186071
H	0.999917	-3.404250	1.687507
H	0.908995	-0.544330	2.297573
H	-0.436288	-1.589956	1.811040
H	-1.017830	-1.858221	-0.611277
H	-0.072993	-1.033946	-1.851680
H	1.344715	-2.885668	-1.981456
H	0.423391	-3.693445	-0.717367
H	3.833497	-1.137564	-0.540927
H	0.307546	2.990329	1.346089
H	-1.042061	4.020878	1.912970
H	-0.632074	2.534263	2.813195
H	-1.366313	0.498485	1.923922
H	-3.138602	-1.054634	1.788941
H	-5.077481	-2.049421	0.607700
H	-5.740406	-1.193220	-1.628116
H	-4.465887	0.665413	-2.672502
H	-2.527364	1.662792	-1.487647
H	3.581368	3.429623	-0.757201
O	3.544628	4.403890	-0.813932
H	2.607776	4.539563	-1.003124

8P

O	-5.052880	-0.867782	0.023300
H	-4.091662	-1.086825	0.002993
O	-2.298246	-1.398017	-0.027985
C	-1.816096	-0.239949	-0.014871
O	-2.467169	0.855992	-0.007012
C	-0.296734	-0.115660	-0.006980
C	0.437970	1.223655	-0.000266
O	-0.389084	2.358925	-0.002146
C	1.371075	1.239716	-1.246912
H	0.738078	1.263930	-2.138923
H	1.940325	2.177316	-1.232562
C	2.304964	0.003221	-1.243383

H	2.165549	-0.597967	-2.149414
H	3.362624	0.302957	-1.223385
C	2.006851	-0.885885	0.003392
C	0.522256	-1.178578	-0.005228
H	0.127536	-2.191213	-0.009854
C	2.869061	-2.149312	0.004858
H	2.670836	-2.762564	-0.882186
H	3.938255	-1.902368	0.010120
C	2.292096	-0.002385	1.257129
H	3.349926	0.297320	1.249547
C	1.358563	1.234514	1.255835
H	0.716654	1.255466	2.141569
H	1.928070	2.172051	1.250828
H	2.662845	-2.765880	0.887777
H	2.143041	-0.607232	2.159189
H	-4.973337	0.095966	0.026188
H	-1.319752	1.980061	-0.002580

9GM

C	2.248524	-0.819922	-1.004038
C	3.271974	-0.686831	-1.941031
C	4.368698	0.137420	-1.674803
C	4.441359	0.828613	-0.465316
C	3.418711	0.692180	0.475298
C	2.320630	-0.130778	0.212958
C	1.229455	-0.303114	1.251602
O	1.413723	-1.537574	1.874528
C	0.543931	-1.764576	2.978590
O	-0.071333	-0.306348	0.666036
C	-0.584357	0.971033	0.280757
C	-1.356741	1.655482	1.411191
C	-1.779764	3.084399	0.993662
C	-2.059859	3.188939	-0.525296
C	-2.568307	1.854477	-1.083525
C	-1.489954	0.746214	-0.962842
C	-2.137152	-0.624452	-0.871685
O	-1.602044	-1.515067	-1.716609
O	-3.065903	-0.889973	-0.114496
H	-0.741010	1.693104	2.316236
H	-2.229020	1.037141	1.647169
H	-1.000050	3.803490	1.270376
H	-2.674860	3.369327	1.557406
H	-2.048709	-2.385279	-1.598752
H	1.285692	0.512889	1.996953
H	0.661009	-0.982563	3.744105
H	0.832372	-2.726032	3.407848
H	-0.504351	-1.798378	2.664983
H	-3.457476	1.540962	-0.526419

H	0.250598	1.613646	-0.031831
H	-1.146126	3.479987	-1.059458
H	-2.790587	3.980713	-0.721290
H	-0.848262	0.743946	-1.847899
H	-2.870174	1.956644	-2.131241
H	5.289591	1.473575	-0.254670
H	5.161739	0.241691	-2.409838
H	3.212966	-1.222971	-2.884031
H	3.475521	1.227680	1.420155
H	1.383293	-1.441922	-1.209571
H	-3.327249	-2.610205	-0.426549
O	-3.441843	-3.559175	-0.640676
H	-2.978596	-4.016856	0.072923

9TS

O	-0.040625	0.658126	0.582760
H	0.306810	1.136396	-0.192593
O	1.584140	1.265628	-0.670743
C	2.102411	0.130621	-0.992926
O	3.231659	-0.071828	-1.445950
C	1.136261	-1.051966	-0.690214
C	0.502913	-0.737472	0.665593
C	1.490899	-0.795097	1.845069
C	2.646891	-1.790167	1.584491
C	2.181794	-2.955723	0.704153
C	1.793619	-2.450803	-0.701747
H	2.690967	-2.353612	-1.319685
H	1.131744	-3.175302	-1.187869
H	2.970524	-3.710199	0.619034
H	1.328433	-3.457726	1.182879
H	3.464549	-1.271731	1.073553
H	3.040589	-2.146993	2.541625
H	0.945356	-1.071511	2.755221
H	1.893537	0.209480	1.997877
H	-0.373401	-1.366709	0.837437
C	-1.451369	0.947353	1.049526
O	-1.584750	2.307090	0.980787
C	-0.729946	3.060659	1.855844
H	-1.092386	4.087627	1.817569
H	0.309244	3.019226	1.518126
H	-0.800827	2.684549	2.884165
H	-1.455655	0.560025	2.077446
C	-3.176394	-0.837330	0.667202
C	-4.106608	-1.489735	-0.144182
C	-4.332543	-1.037383	-1.443618
H	-5.055285	-1.543168	-2.076524
H	-4.653736	-2.344716	0.240354
H	-3.007717	-1.182974	1.684092
C	-2.703060	0.722109	-1.124904

C	-2.469051	0.265975	0.179767
H	-3.812268	0.425454	-2.941125
H	-2.166871	1.589795	-1.495668
C	-3.632041	0.070008	-1.931419
H	0.346939	-1.009225	-1.451475
H	4.041827	1.669024	-1.528299
O	4.408905	2.573033	-1.554434
H	3.630344	3.089593	-1.311319

9P

O	4.217100	-0.290763	0.739855
H	3.408303	0.080832	0.315968
O	1.863798	0.691604	-0.438011
C	1.108223	-0.342817	-0.375790
C	-0.338479	-0.121218	-0.946458
C	-0.999051	1.147187	-0.333119
C	-1.451155	0.858463	1.111307
C	-2.488440	-0.299608	1.184708
C	-2.613568	-1.060859	-0.149313
C	-1.234440	-1.373876	-0.751788
O	1.430417	-1.462979	0.063463
O	-0.176931	2.290447	-0.409089
H	-0.196216	0.090076	-2.014573
H	-0.681951	-2.054716	-0.095375
H	-1.364745	-1.903988	-1.704394
H	-3.176359	-1.991890	0.006297
H	-2.185162	-1.008678	1.965441
H	-3.476112	0.076918	1.483476
H	-1.859706	1.783981	1.532933
H	-0.559362	0.615173	1.700673
H	-1.905009	1.371349	-0.921634
H	3.883030	-1.183455	0.904371
H	-3.208335	-0.465295	-0.855715
H	0.748013	1.919586	-0.404488

10GM

O	-2.295307	-1.362638	-0.419840
H	-1.322574	-1.292351	-0.333796
O	0.028024	-0.280705	0.080911
C	-0.550736	0.966783	0.111536
C	-1.941801	1.046518	-0.115359
C	-2.841632	-0.130605	-0.353339
O	-4.043959	0.001343	-0.492565
H	-5.025275	-1.700347	-0.762674
O	-5.462231	-2.559038	-0.888462
H	-4.717273	-3.171521	-0.904067
C	0.040053	-2.202951	2.236117

C	1.194224	-0.611275	0.901798
C	2.473882	-0.447850	0.119688
C	3.556520	0.226974	0.689442
C	4.756340	0.352641	-0.013158
C	4.876021	-0.199431	-1.287927
C	3.795419	-0.876922	-1.859351
O	1.055990	-1.937508	1.268507
C	2.597848	-1.002145	-1.159509
H	0.182329	-1.585166	3.132315
H	0.140580	-3.254943	2.502970
H	-0.960098	-2.026035	1.828781
H	1.755410	-1.523335	-1.601120
H	1.165108	0.058105	1.774564
H	3.465154	0.651761	1.685948
H	5.592742	0.879624	0.434997
H	5.807217	-0.101710	-1.837235
C	0.200009	2.124864	0.331891
H	1.273002	2.056294	0.461382
H	0.161898	4.260756	0.512331
C	-0.431614	3.367618	0.342100
C	-1.805628	3.467743	0.121127
C	-2.545220	2.313597	-0.109950
H	-3.614006	2.354735	-0.285624
H	-2.293853	4.436130	0.123914
H	3.887396	-1.306968	-2.851730

10TS

O	-2.002854	-1.080235	-0.985299
H	-0.706141	-0.648131	-0.891905
O	-0.016567	-0.049388	-0.550410
C	0.918088	-0.784963	0.600543
O	0.645833	-2.089187	0.555116
C	-0.535166	-2.590614	1.239684
C	2.329029	-0.480983	0.224606
C	3.055886	0.451125	0.972255
C	4.384023	0.727433	0.643601
C	4.983951	0.073521	-0.432200
C	4.258657	-0.860954	-1.177999
C	2.935185	-1.141793	-0.851972
H	4.727787	-1.371403	-2.013176
H	6.016638	0.288070	-0.689618
H	4.947083	1.447217	1.229219
H	2.588442	0.953942	1.814549
H	-0.296615	-3.618780	1.509678
H	2.368623	-1.871102	-1.420863
H	-1.399987	-2.551161	0.575986
H	-0.717606	-2.002663	2.145390
H	0.557019	-0.258406	1.490357
C	0.065818	2.327081	-0.040179

C	-0.633692	3.506723	0.226608
C	-2.031025	3.511560	0.258940
C	-2.741892	2.334402	0.026708
C	-2.067784	1.141064	-0.236600
C	-2.780024	-0.169303	-0.506680
O	-3.978162	-0.282183	-0.232195
H	-3.826077	2.303045	0.054558
H	-2.562923	4.434922	0.465886
H	-0.081199	4.425263	0.398380
H	1.148307	2.309338	-0.088589
C	-0.673748	1.169448	-0.261238
H	-3.907508	-2.213753	0.034395
O	-3.910828	-3.173987	0.200592
H	-3.559053	-3.509047	-0.633138

10P

O	0.000000	0.000000	0.000000
H	0.000000	0.000000	0.985490
O	0.095320	0.000000	2.804304
C	1.324465	-0.045204	3.035823
O	2.254808	-0.080048	2.148324
C	1.793386	-0.061837	4.478143
C	3.182076	-0.113606	4.771684
O	4.089291	-0.147753	3.788849
C	3.600318	-0.128828	6.116531
C	2.662722	-0.093522	7.144544
C	1.292191	-0.042465	6.861658
C	0.876131	-0.027373	5.530340
H	-0.175495	0.011703	5.261491
H	0.564176	-0.015079	7.668732
H	3.004111	-0.105933	8.178470
H	4.666441	-0.168511	6.322914
H	0.955610	-0.036245	-0.142297
H	3.486979	-0.125604	2.931963

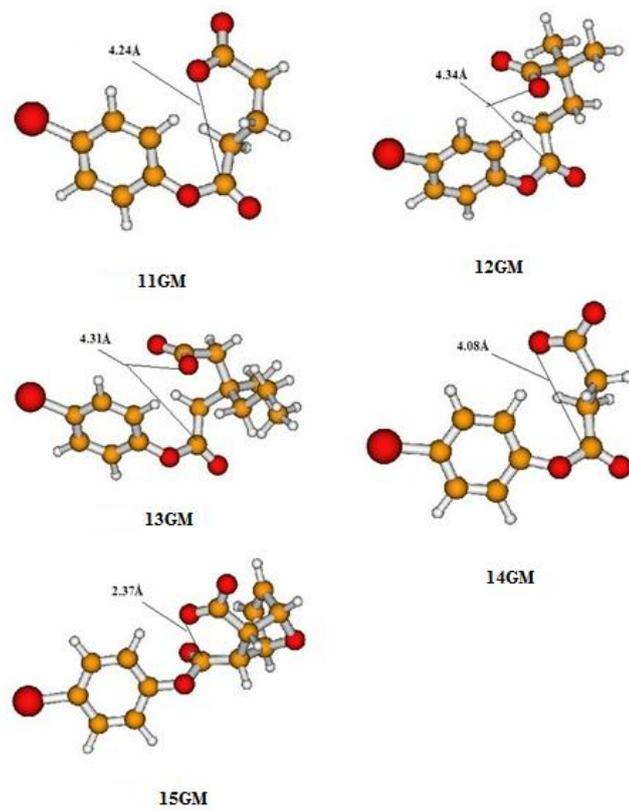


Figure S2a: DFT at B3LYP 6-31G (d,p) level optimized structures for the global minimum (GM) in di-carboxylic semi-esters **11-15**.

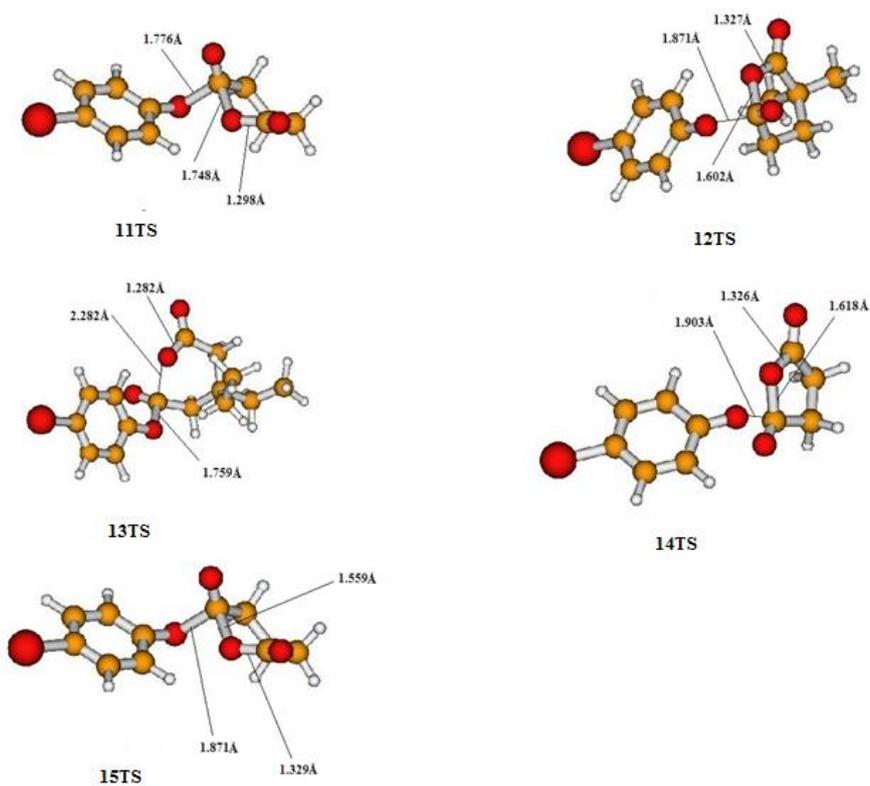


Figure S2b: DFT at B3LYP 6-31G (d,p) level optimized structures for the transition state (TS) in di-carboxylic semi-esters **11-15**.

11GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.395796
C	1.202587	0.000000	2.095632
C	2.394514	0.006605	1.377256
C	2.403045	0.013104	-0.011323
C	1.195647	-0.006736	-0.713388
Br	4.064847	0.010081	2.342953
O	-1.256680	-0.096739	-0.589579
C	-1.804427	0.742145	-1.545699
O	-2.973133	0.578174	-1.782823
C	-0.940591	1.750773	-2.259926
C	-0.726026	1.322982	-3.733610
C	0.278804	2.218863	-4.458185
C	1.773545	2.025555	-4.027919
O	2.550036	2.942641	-4.358868
O	2.037783	0.952395	-3.415090
H	-1.487395	2.698347	-2.238252

H	0.021668	1.899998	-1.775500
H	-1.700848	1.328068	-4.233084
H	-0.345369	0.298354	-3.757194
H	0.021690	3.278245	-4.347208
H	0.238308	2.007085	-5.533827
H	1.208201	-0.002932	3.178011
H	3.328207	0.043609	-0.571748
H	1.245061	0.037863	-1.801080
H	-0.947494	-0.008756	1.921335

11TS

O	-1.291406	-0.936869	-0.419327
C	-2.346563	-0.567778	0.960742
O	-2.761401	1.046521	0.434004
C	-3.814729	1.366086	-0.270968
C	-4.772743	0.246465	-0.693962
C	-4.154336	-1.147135	-0.754146
C	-3.486169	-1.487886	0.590346
O	-4.071338	2.522799	-0.587105
O	-1.773637	-0.498670	2.006239
C	-0.008410	-0.637925	-0.280212
C	0.968209	-1.584431	-0.659229
C	2.328461	-1.295712	-0.593810
C	2.733353	-0.053438	-0.119175
C	1.801277	0.899613	0.281382
C	0.442547	0.612772	0.198765
Br	4.626593	0.354560	-0.015068
H	3.060761	-2.033830	-0.898879
H	2.129487	1.864808	0.648478
H	-0.294407	1.347224	0.496234
H	0.632391	-2.551628	-1.017383
H	-3.069844	-2.497762	0.601151
H	-4.929160	-1.890813	-0.975594
H	-3.406015	-1.202819	-1.546907
H	-5.594825	0.257126	0.035183
H	-5.206577	0.543633	-1.651155
H	-4.215703	-1.419581	1.407371

12GM

C	-1.766626	2.205050	0.319065
C	-2.906556	1.414470	0.431227
C	-2.864906	0.107362	-0.044254
C	-1.714950	-0.418141	-0.618981

C	-0.576856	0.380797	-0.745865
C	-0.609260	1.685911	-0.262249
O	0.441935	2.585175	-0.408680
C	1.735037	2.439687	0.067613
C	2.186436	1.123691	0.650117
C	3.255876	0.480648	-0.269131
C	3.616931	-0.973026	0.095504
C	4.151511	-1.078006	1.530930
O	2.448878	3.402222	-0.042164
C	2.363792	-1.924712	-0.129692
O	1.636064	-1.623000	-1.116740
C	4.710488	-1.446211	-0.884382
O	2.238774	-2.882692	0.657488
H	2.626556	1.356636	1.623380
H	1.361377	0.432645	0.808005
H	4.150615	1.114081	-0.245930
H	2.880456	0.474378	-1.294671
H	-3.807794	1.811397	0.880486
H	-1.671680	-1.443269	-0.962638
H	0.318437	-0.075243	-1.166145
H	-1.764441	3.228807	0.673918
H	5.618754	-0.835513	-0.791932
H	4.353928	-1.383739	-1.916045
H	4.977301	-2.487458	-0.680454
H	5.029770	-0.432193	1.670275
H	4.430089	-2.109720	1.749645
H	3.395661	-0.796877	2.269182
Br	-4.443136	-0.991220	0.109265

12TS

O	-0.632786	2.236850	0.352792
C	-2.375603	1.580287	0.173471
O	-2.238295	0.324256	1.158324
C	-2.819043	-0.840642	0.923495
C	-3.283453	-1.195688	-0.516197
C	-3.447743	0.044711	-1.419173
C	-2.309611	1.059541	-1.241351
O	-3.110293	2.431721	0.583654
H	-1.340976	0.602042	-1.442268
H	-2.428154	1.916761	-1.906800
H	-4.397465	0.539516	-1.187988
H	-3.505969	-0.281479	-2.464757
C	-4.617916	-1.956213	-0.438210
H	-5.403244	-1.327305	-0.008661
H	-4.935020	-2.257450	-1.443178
H	-4.519838	-2.846094	0.184619

C	-2.198114	-2.138120	-1.088945
H	-2.485163	-2.467149	-2.093979
H	-2.087796	-3.018087	-0.451877
H	-1.223467	-1.648852	-1.154217
O	-2.923292	-1.672740	1.808614
C	0.473210	1.537969	0.259000
C	1.454291	1.888815	-0.707646
C	2.665435	1.212276	-0.812619
C	0.785175	0.442711	1.109308
H	0.058759	0.151935	1.856647
C	1.990519	-0.243349	0.999810
C	2.923875	0.145706	0.042449
Br	4.606300	-0.808984	-0.101697
H	2.203275	-1.072937	1.664174
H	3.397096	1.509944	-1.555030
H	1.238649	2.724865	-1.364721

13GM

C	-1.708834	2.157099	-0.012262
C	-2.974747	1.638279	0.244255
C	-3.231515	0.311054	-0.087630
C	-2.258545	-0.499231	-0.657516
C	-0.996508	0.029373	-0.931881
C	-0.730484	1.351643	-0.594465
O	0.477890	1.970995	-0.909875
C	1.672995	1.806413	-0.230088
C	1.821392	0.642649	0.726018
C	3.021530	-0.363741	0.461125
C	4.176739	-0.070635	1.461534
C	4.955682	1.239051	1.289342
O	2.522384	2.629756	-0.451608
C	2.484091	-1.783326	0.808642
C	1.184437	-2.224827	0.067355
O	1.222112	-2.196802	-1.194659
C	3.514625	-0.273151	-1.007819
C	4.594427	-1.284514	-1.411237
O	0.212253	-2.531750	0.794316
H	1.964885	1.100538	1.711024
H	0.894133	0.077647	0.785421
H	-3.742525	2.255674	0.692607
H	-2.446245	-1.542986	-0.869191
H	-0.232163	-0.622423	-1.352022
H	-1.473981	3.188071	0.225324
H	3.885993	0.737538	-1.192029
H	2.654686	-0.441671	-1.658509
H	5.479295	-1.241464	-0.766926

H	4.927204	-1.078430	-2.434128
H	4.203384	-2.303564	-1.397476
H	4.881483	-0.908872	1.417937
H	3.752040	-0.102466	2.472786
H	5.510211	1.260501	0.347393
H	5.681814	1.354997	2.101921
H	4.298252	2.110739	1.289329
H	2.283856	-1.828454	1.883775
H	3.270567	-2.515876	0.597184
Br	-4.983478	-0.415255	0.271084

13TS

O	0.252143	-1.214612	-0.331162
C	1.276580	-0.252302	-1.388786
O	1.533193	1.465487	0.091375
C	2.654138	2.028123	-0.119639
O	2.884512	3.240985	-0.224476
C	3.879196	1.077831	-0.209428
C	3.612209	-0.435731	-0.095196
C	2.633056	-0.873526	-1.240786
C	3.011857	-0.842043	1.287554
C	3.457183	-0.033833	2.513752
C	4.914469	-1.240382	-0.387867
C	6.078006	-1.078915	0.592780
H	6.945183	-1.644859	0.235551
H	6.384123	-0.034783	0.695137
H	5.826468	-1.457120	1.585603
H	5.269652	-0.975330	-1.391968
H	4.650688	-2.305953	-0.429460
H	4.539317	-0.032158	2.669961
H	2.995704	-0.456193	3.412761
H	3.124499	1.002551	2.439292
H	3.126664	-0.682207	-2.199533
H	2.447947	-1.949309	-1.167075
H	1.929014	-0.767810	1.225506
H	3.240161	-1.904962	1.453087
H	4.578236	1.402255	0.564608
H	4.377721	1.290213	-1.163635
C	-1.031602	-0.836727	-0.234277
C	-1.431130	0.501146	-0.063155
C	-2.778673	0.816057	0.090613
C	-3.731750	-0.197465	0.085296
C	-3.364286	-1.527627	-0.077250
C	-2.018184	-1.838811	-0.247926
Br	-5.603441	0.246112	0.318952
H	-4.111953	-2.310989	-0.079431

H	-3.076617	1.848405	0.225895
H	-0.670852	1.273270	-0.032055
H	-1.707648	-2.868658	-0.383087
O	0.740868	0.303758	-2.268059

14GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.390784
C	1.220763	0.000000	2.057995
C	2.421140	0.001380	1.361109
C	2.422211	-0.009495	-0.036062
C	1.202499	0.000249	-0.713593
O	1.041842	-0.083801	-2.088986
C	1.654185	0.674904	-3.090202
C	2.961024	1.350999	-2.803351
C	4.144605	0.399187	-3.130940
C	5.430444	0.714258	-2.286949
O	6.506039	0.732424	-2.912855
O	1.103512	0.656750	-4.159740
O	5.217218	0.872714	-1.054091
H	3.011686	2.233773	-3.443233
H	3.047343	1.668143	-1.765555
H	-0.932750	-0.000101	1.940098
H	3.369696	0.014067	1.882198
H	3.391151	0.033317	-0.533859
H	-0.931484	-0.005153	-0.553295
H	4.369775	0.433891	-4.197641
H	3.866839	-0.634695	-2.891272
Br	1.236896	0.004189	3.987854

14TS

O	1.574657	0.229319	0.918329
C	2.740291	1.031847	-0.353935
O	3.078643	-0.347818	-1.128511
C	3.961138	-1.040757	-0.430462
C	4.393680	-0.283362	0.826357
C	3.903464	1.144834	0.616626
O	4.385708	-2.133356	-0.754398
O	2.202351	1.872034	-1.011802
H	3.567381	1.645808	1.522826

H	4.662788	1.763613	0.125879
H	5.473150	-0.380218	0.958047
H	3.894507	-0.752339	1.676334
C	0.296377	0.156465	0.628737
C	-0.477440	1.290179	0.269556
C	-1.842450	1.188959	0.018034
C	-2.471377	-0.047451	0.124224
Br	-4.379234	-0.184273	-0.203659
C	-1.752315	-1.188279	0.467935
C	-0.385545	-1.084500	0.703584
H	0.192810	-1.966313	0.956524
H	-2.248998	-2.148755	0.541278
H	-2.412398	2.070285	-0.252981
H	0.018161	2.248426	0.187277

PARA ProD1 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.388444
C	1.199717	0.000000	2.099793
C	2.392915	0.004372	1.393552
C	2.408479	0.002271	-0.009284
C	1.201094	-0.003117	-0.711508
O	-1.205613	-0.087377	2.065198
C	-1.549437	0.943551	2.926602
C	-2.692142	0.554145	3.805353
C	-2.553450	-0.101724	4.957247
C	-1.203169	-0.569439	5.503184
O	-0.204541	-0.205761	4.824081
N	3.684482	0.002540	-0.635617
C	4.012890	0.002220	-1.962392
C	5.511212	0.009853	-2.242979
O	3.205127	-0.002122	-2.880066
O	-1.104118	2.055351	2.809266
O	-1.247862	-1.248804	6.549577
H	3.331789	0.001148	1.941774
H	1.157439	-0.021703	3.184316
H	1.206212	-0.005133	-1.790627
H	-0.946310	-0.001024	-0.528225
H	4.458459	0.005551	0.010326
H	5.753135	-0.860054	-2.857402
H	6.135368	-0.003896	-1.346410
H	5.749652	0.901736	-2.826837
H	-3.661937	0.905405	3.459768
H	-3.428242	-0.318791	5.565300

PARA ProD1 TS

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.417680
C	1.270693	0.000000	2.049370
C	2.445302	0.024934	1.313872
C	2.418879	0.024232	-0.087590
C	1.179822	0.007723	-0.738238
O	-1.094402	0.031973	2.141614
N	3.677969	0.035744	-0.757465
C	3.975117	0.108217	-2.084819
O	3.151671	0.179923	-2.988956
C	5.469089	0.088783	-2.400312
C	-2.450735	-1.206956	1.741847
O	-3.574051	-0.243262	1.761537
C	-4.109392	-0.209678	2.998566
C	-3.393145	-1.186555	3.859189
C	-2.425577	-1.750481	3.138434
O	-2.230985	-1.815032	0.715959
O	-5.040674	0.502610	3.307724
H	3.402458	0.040695	1.833462
H	1.299622	-0.001405	3.133854
H	1.148190	0.012868	-1.818222
H	-0.952731	-0.006977	-0.511527
H	4.469487	-0.010200	-0.135172
H	5.680529	-0.777844	-3.031540
H	6.114273	0.048744	-1.518634
H	5.713834	0.983056	-2.978129
H	-1.698233	-2.495513	3.427549
H	-3.657268	-1.339270	4.895916

PARA ProD2 GM

C	-0.914029	-0.674922	-0.411976
C	-0.248145	0.547081	-0.353335
C	-0.970919	1.718482	-0.140115
C	-2.350248	1.664139	0.012102
C	-3.026221	0.439090	-0.039932
C	-2.296887	-0.735721	-0.254795
O	1.107825	0.671689	-0.583320
C	2.027984	-0.052738	0.197056
C	3.425852	0.311409	-0.192196

C	4.472909	-0.783993	0.003974
C	5.934180	-0.202603	0.047622
O	6.832951	-1.004710	-0.287102
N	-4.433243	0.469945	0.140057
C	-5.349487	-0.546931	0.056777
C	-6.787639	-0.124738	0.327472
O	-5.072731	-1.705959	-0.204908
O	1.655483	-0.806073	1.054825
O	6.031296	0.986446	0.441630
H	-2.905949	2.583445	0.175052
H	-0.442260	2.662999	-0.099409
H	-2.811775	-1.682916	-0.301163
H	-0.351170	-1.584435	-0.571908
H	-4.805852	1.381452	0.355323
H	-6.914461	0.944990	0.509303
H	-7.152490	-0.676765	1.196550
H	-7.400538	-0.415794	-0.527944
H	3.742505	1.158239	0.435349
H	3.419817	0.691461	-1.216207
H	4.412239	-1.544471	-0.779460
H	4.299929	-1.290305	0.959192

PARA ProD2 TS

O	-3.215989	-1.090829	0.015907
C	-2.864214	-0.030095	1.032116
C	-3.910587	1.059736	0.812764
C	-4.354160	0.863531	-0.633344
C	-4.020409	-0.595534	-0.928646
O	-1.568246	0.870203	-0.026153
C	-0.310557	0.503278	0.018323
C	0.117683	-0.817539	0.315765
C	1.464892	-1.145024	0.318042
C	2.455060	-0.198181	0.025014
C	2.061527	1.111342	-0.272125
C	0.711702	1.444946	-0.263988
N	3.810332	-0.643798	0.051492
C	4.968375	0.029692	-0.181819
C	6.231707	-0.818377	-0.053773
O	-2.403922	-0.415872	2.076943
O	-4.428890	-1.244269	-1.866062
O	5.047699	1.218589	-0.475059
H	1.756743	-2.168433	0.550501
H	-0.623833	-1.569732	0.545874
H	2.811704	1.854812	-0.500300
H	0.408031	2.461890	-0.489843

H	3.910625	-1.619361	0.284520
H	6.766360	-0.793628	-1.006530
H	6.046681	-1.860368	0.220377
H	6.881067	-0.364704	0.698851
H	-3.478022	2.033879	1.028003
H	-4.726319	0.862495	1.516718
H	-3.763199	1.476547	-1.316836
H	-5.413494	1.043957	-0.826361

PARA ProD3 GM

C	-2.221237	1.031353	0.002006
C	-0.871139	1.395421	-0.024273
C	0.106963	0.406527	-0.118164
C	-0.251628	-0.945518	-0.159747
C	-1.589661	-1.295921	-0.128888
C	-2.588973	-0.313842	-0.051861
O	1.475357	0.582529	-0.134926
C	2.188202	1.738473	-0.223425
O	1.693719	2.843021	-0.229120
N	-3.934381	-0.768176	-0.029090
C	-5.102356	-0.058456	0.050287
O	-5.172216	1.160405	0.088569
C	3.652464	1.409437	-0.343772
C	4.299751	0.638775	0.831768
C	3.714964	-0.747603	1.141122
C	3.574156	-1.716237	-0.083667
O	2.604838	-2.511132	-0.021399
O	4.447088	-1.612387	-0.981633
C	-6.350253	-0.929750	0.141869
H	-1.862233	-2.347404	-0.160293
H	0.540801	-1.687793	-0.198575
H	-2.984623	1.791649	0.065166
H	-0.591225	2.435774	0.011752
H	-4.030047	-1.771786	-0.059597
H	-6.531815	-1.190535	1.189544
H	-6.272507	-1.856698	-0.432309
H	-7.200529	-0.351149	-0.215802
H	4.171486	2.356645	-0.504909
H	3.774181	0.765839	-1.223455
H	2.746476	-0.678011	1.634711
H	4.390034	-1.245083	1.851999
H	4.286571	1.267673	1.733467
H	5.346303	0.512672	0.540474

PARA ProD3 TS

C	-0.520426	0.400778	0.308947
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C	0.113786	-0.769658	-0.166326
C	-0.724580	-1.794755	-0.662997
C	-2.102887	-1.644415	-0.704548
C	-2.713338	-0.476259	-0.232116
C	-1.904512	0.545068	0.279108
O	1.423596	-0.949913	-0.200365
C	2.425867	-0.245512	1.085499
O	1.840872	-0.131550	2.139706
N	-4.136757	-0.414457	-0.307340
C	-5.001764	0.575305	0.049214
O	-4.679958	1.654594	0.530605
C	3.638211	-1.146402	0.894318
C	4.227520	-1.103543	-0.511958
C	4.586794	0.331771	-0.895007
C	3.523439	1.382543	-0.578820
O	3.520013	2.448083	-1.169148
O	2.675006	1.146917	0.412627
C	-6.472652	0.251250	-0.204224
H	-2.716638	-2.450581	-1.103783
H	-0.259255	-2.705770	-1.023575
H	-2.363535	1.451749	0.645561
H	0.092948	1.199842	0.700397
H	-4.558942	-1.244684	-0.692371
H	-7.021091	0.372707	0.732612
H	-6.651708	-0.755107	-0.591990
H	-6.871896	0.979234	-0.914943
H	3.319464	-2.154388	1.165283
H	4.378355	-0.819890	1.636236
H	4.827969	0.430477	-1.955201
H	5.479001	0.654620	-0.340869
H	3.491733	-1.503497	-1.211237
H	5.121928	-1.735579	-0.568673

تصميم أدوية مساعدة مبتكرة من الفينيلفرين والباراسيتامول بالطرق الحسابية

إعداد: دنيا إبراهيم خالد قرمان

إشراف: أ.د. رفيق قرمان

الملخص:

باستعمال الطرق الحسابية DFT molecular orbital على مستويات مختلفة من B3LYP 6-31G (d, p) و B3LYP/311+G (d, p) وحسابات MM2 لعملية نقل البروتون ضمن جزئي في عدد من نماذج الإنزيم لكل من العلماء كاري وبروس واستغلال هذه النماذج لتصميم باراسيتامول و فينيلفرين prodrug من دون طعم مر و ذو فعالية عالية للوصول إلى الدورة الدموية في الجسم مقارنة مع الدواء الأم.

لقد وجد أن معدل التحويل الداخلي لباراسيتامول prodrug يتأثر بشكل كبير بقوة strain لكل من المتفاعلات و رباعية الاسطوح المتوسطة ولا يوجد أي علاقة بين معدل cyclization و المسافة بين الذرة الساحبة للكروونات و الذرة المعطية للكروونات. بينما في حالة الفينيلفرين لقد وجد أن القوة الدافعة لنقل البروتون هو المسافة بين المركزين المتفاعلين و الزاوية بينهم و معدل حصول التفاعل يتناسب بشكل خطي مع كل منهما.

باستعمال قيمة $t_{1/2}$ التجريبية وهي عبارة عن الوقت الأزم لتحويل 50% من المتفاعلات إلى منتجات و قياس المعدل النسبي لهذا العمليات يتم حساب $t_{1/2}$ لعملية تحويل كل من الباراسيتامول و الفينيلفرين prodrug إلى الدواء الأم وكانت قيمة $t_{1/2}$ لفينيلفرين ProD1-3 كتالي : ProD1 و ProD2 عالية جدا 145 يوم و عدة سنوات لكل منهما على التوالي ول ProD3 كانت تقريبا 35 ساعة بينما في حالة الباراسيتامول ProD1-ProD3 كانت النتيجة 3 دقائق و 1 ساعة و 8.4 ساعات لكل منهم على التوالي.

وبالتالي فان معدل التحويل الداخلي لكل من الباراسيتامول prodrug و الفينيلفرين prodrug إلى الدواء الأم يمكن أن يحدد بالاعتماد على طبيعة الرابط الذي يتم ربطه بالدواء لعمل prodrug.