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**Design of Novel Raloxifene Prodrugs by Computational
Methods**

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Design of Novel Raloxifene Prodrugs by Computational Methods

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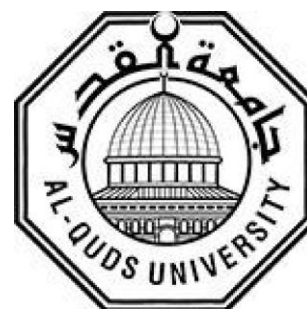
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Thesis Approval

Design of Novel Raloxifene Prodrugs by Computational Methods

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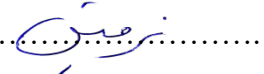
Dedication

I would like to thank my husband for his insistence on providing me with support and assistance in every step of my educational journey. Without him, I would not have reached this stage.

Also, I would like to thank my family, my mother, father, sisters, brothers, my mother and father-in-law who gave me support and help to get to this step of success. Also, Special thanks to my colleagues and friends in the Department of Pharmaceutical Sciences.

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:

Nermeen Nader Ibrahim Hajjaj

Date: 22/12/2021

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Abstract

A number of Kirby's enzyme models for six Raloxifene prodrugs on both sides (left and right sides) are designed based on molecular orbital of DFT at B3LYP 6-31G (d, p) level and molecular mechanics (MM2) calculations of the intramolecular proton transfer which run in the gas and water phase for right side and in the gas phase for left side to provide a medicine of controlled release for Raloxifene to enhance the bioavailability than its parent drug.

Results proves that Raloxifene **ProD1-ProD6** processes on two sides are major affected and depended on two factors of the global minimum (**GM**) which includes the distance between the two reactive centers r_{GM} and the angle of attack α that also affected on the rate of a proton transfer for Raloxifene where lower ΔG^\ddagger (higher rates) refer to system of low r_{GM} and high α values for example **ProD4** and **ProD6** at left side and **ProD5** and **ProD6** at right side also, the system of higher ΔG^\ddagger (lower rates) refer to high r_{GM} and low α values, for example (**ProD1, ProD2, ProD3, ProD5**) at left and (**ProD1, ProD2, ProD3, ProD4**) at right. Thus, it is recommended that Raloxifene **ProD4, ProD6** at the left side and **ProD5 and ProD6** at right side should be entered and tested *in vitro* and *in vivo* trials steps of synthesis.

Moreover, it was found that the internal conversion rate of Raloxifene prodrugs is significantly affected by the strain energy of each value which refers to the difference between the strain energy of tetrahedral intermediate and the reactant, since the higher the strain the lower the internal conversion rate, and vice versa.

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List of Abbreviations

Abbreviations	Definition
ΔG^\ddagger	Activation Energy
AF	Activation Factors
A	Angle of Attack
Å	Angstrom
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
CYP450	Cytochrome 450
DFT	Density Functional Theory
r_{GM}	Distance in the Global Minimum
DCIS	Ductal carcinoma in situ
H	Enthalpy
ΔH^\ddagger	Enthalpy of activation energy
S	Entropy
$T\Delta S^\ddagger$	Entropy of activation energy
E2	Estradiol
ER	Estrogen Receptor
ERE	Estrogen Responding Elements
FDA	Food and Drug Administration
GP	Gas Phase
GI	Gastrointestinal
GM	Global Minimum
HF	Hartree-Fock
HP	Helper Proteins
HRT	Hormone Replacement Therapy
HLB	Hydrophilic Lipophilic Balance
HPMC	HydroxyPropyl Methyl Cellulose
INT	Intermediate
MOA	Mechanism of Action
MM	Molecular Mechanics
MO	Molecular Orbital
ProD	Prodrug
QM	Quantum Mechanics
RLX	Raloxifene
RRE	Raloxifene Responding Elements
SERM	Selective Estrogen Receptor Modulator
EsINT	Strain energy of the intermediate
TS	Transition State
UFF	Universal Force Field

Chapter One

Introduction

Chapter One: Introduction

1.1 Background

Computational chemistry is a branch of chemistry that draws on chemical, mathematical, and computing skills to describe the behavior of atomic-scale matter, including molecular physical and chemical properties, molecule structures and simulated experimental results. These computations have the effect of decreasing the time and money spent on chemical synthesis. In addition, computational chemistry has over the past five decades put a major finger on the scale of drug and pro-drug design, allowing scientists to better understand the mechanistic details of biochemical processes, organic reactions and the biological activities of molecule [1-3]. Computational chemistry offers particular advantages for scientists whose research requires materials that are expensive or difficult to obtain, and helps in predicting reaction outcomes before proceeding with wet-lab synthesis.

Methods in computational chemistry are classified as either molecular mechanics (MM) or quantum mechanics (QM). The latter category comprises density functional theory (DFT), *ab initio*, and semi-empirical methods [1].

➤ Quantum Mechanics (QM)

Quantum mechanics consists of the physical laws that govern the behavior of very small and very light objects, namely those existing at the molecular to sub-atomic levels. QM methods can predict the properties of an individual molecule or atom and in correctly describing the behavior of electrons thus describe the behavior of chemistry as a whole. However, an exact solution to the Schrödinger equation, which describes particle wave functions and so the probabilistic values of their physical properties, has only been determined for the one-electron system [4, 5].

The Schrödinger equation is as follows:

$$\hat{H} \Psi = E \Psi$$

where \hat{H} is the Hamiltonian operator, whose value is a function of nuclear, electronic kinetic and potential energies in the atom/molecule being described, Ψ is the wave function describing electron locations in a probabilistic manner, and E is the energy of the system, in turn a function of the individual electron energies, which are significant in interpreting electronic spectroscopy.

The category of quantum mechanical methods is divided into three types:

(1) Ab Initio.

(2) Semi Empirical.

(3) DFT.

1. Ab Initio Methods

When applied to a molecular system containing tens to hundreds of atoms, *ab initio* methods resolve atom nucleus positions, total electrons, electron density, electronic energy and other properties besides. These methods are particularly important as tools for exploring the functionalities of biological macromolecules as products of three-dimensional and electronic structure [6], such as by constructing isolated models of a protein's functional regions (e.g. its active sites).

Molecular orbital methods in this category include the HF, G1, G2, G2MP2, MP2, and MP3 methods, which apply the Schrödinger equation rigorously but also with several approximations.

However, *ab initio* methods have some limitations; in particular, they include only small-sized molecules, and do not consider proteins or solvents that surround the catalytic center. By

implication, *ab initio* calculations referencing only catalytic centers face difficulties in elucidating the mechanisms of biological systems.

2. Semi-Empirical Methods

This category of methods, based on Hartree-Fock formalism, are substantially faster to complete than their *ab initio* counterparts and furthermore allow the consideration of electron correlation effects. However, applying full Hartree-Fock Formalism to large molecules are very expensive [7]; semi-empirical methods are reasonable for molecules comprising up to 60 atoms.

In addition to computational expense, the results obtained by these methods may be considerably in error if the molecule of interest is insufficiently similar to those in the database used to parametrize the method. Thus, another limitation of semi-empirical methods is that their accuracy depends on the investigated molecule being similar to known molecules [8].

Nonetheless, semi-empirical methods are commonly utilized and provide a great deal of information with relevance to practical applications. The most widely-used implementations are MINDO, MNDO, MINDO/3, AM1, PM3, and SAM1 [9].

3. Density Functional Theory (DFT)

The third category of quantum mechanical methods, DFT, is popularly employed in physics and chemistry to model the electronic structure of many-body systems. A key tenet of this theory is that the properties of many-electron systems can be determined with functions that observed as their input other functions, termed “functionals”. DFT specifically references electron density, which is spatially dependent and is primarily used to describe the ground state of medium-sized systems (30-60 atoms), particularly for molecules of biological and pharmaceutical interest [10, 11]. Indeed, DFT methods are held to be the standard in many chemistry applications, for example B3LYP/6-31G(d) [6].

DFT methods also suffer from several limitations; for example, their treatment of dispersion is incomplete, which can have adverse effects on predictions for systems in which dispersion dominates. In addition, it is critical in each application of DFT to determine the most appropriate method for the situation and especially so when describing the intermolecular interactions of pro-drugs in a design model.

➤ **Molecular Mechanics (MM)**

The mathematical approach of molecular mechanics is utilized to calculate the physical properties of a molecule of interest, including its energy, optimized geometry and dipole moment. Such methods are applied to a wide range of biological and chemical systems, including macromolecules like proteins, large crystal structures, and relatively large solvated systems [12, 13].

Pure molecular mechanics is limited in some circumstances, such as when calculating the values of many distinct torsion angles among structurally-diverse molecules. To get around these limitations, QM and MM methods are applied in tandem; that is, the system of interest is divided into QM and MM regions and the respective approaches applied, with the former regions comprising active sites and the latter everything else. This QM/MM joint approach was pioneered by Warshel and Levitt [14], and has since seen considerable development and application to biological systems [15, 16].

1.2 Osteoporosis

Osteoporosis is the most chronic metabolic-bone disease that classified as a systemic defect on mass and microstructure of bone caused fragility fractures affects all populations with different ages groups particularly postmenopausal osteoporosis [17].

In the last century, postmenopausal osteoporosis is the most an important public health issue widespread which lead to establish different measures including pharmacologic and non-pharmacologic to improve menopause-related symptoms. Taking into account the future

fracture is a very important point to maintain and decrease a poor quality of life, a dependent living situation, and an increased risk of death that specially associated with old age [18, 19].

One of the first treatments used is the hormone replacement therapy (**HRT**) [18, 20] that gave a clear decrease in vertebral and non-vertebral osteoporosis fractures risk in older women with maintaining bone mass [18]. It is not used as a first line of therapy because of the different side effects associated with this medicine like the potential risk of developing breast cancer [20]. According to that, a series of non-hormonal compounds were developed with a high affinity for estrogen receptors (ER), a selective one (estrogen agonist effect, not antagonist one that affects the breast and endometrium negatively) [21, 22]. These compounds were called Selective Estrogen Receptor Modulators or SERM [21].

1.3 Raloxifene

The benzothiophene Raloxifene—IUPAC name [6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]-[4(2-piperidin1-ylethoxy) phenyl]methanone (Figure 1), chemical formula C₂₈H₂₇NO₄S, molecular weight 473 g/mol, bioavailability 2% by way of the GI tract—is a second-generation selective modulator of estrogen receptors (SERM) that has received approval from the FDA[23] for long-term osteoporosis treatment in postmenopausal women, also approved for breast cancer risk reduction. It is the only drug of its class to have reached the market, and is predominantly sold under the brand Evista, with Optruma being next most prevalent. Raloxifene acts to inhibit bone resorption, slightly elevated spine mineral density, and reduces risk of vertebral fractures, though the drug has no impact on non-vertebral or hip fractures [24, 25]. It additionally exerts an anti-proliferative effect on estrogen-sensitive breast cancer [18, 23].

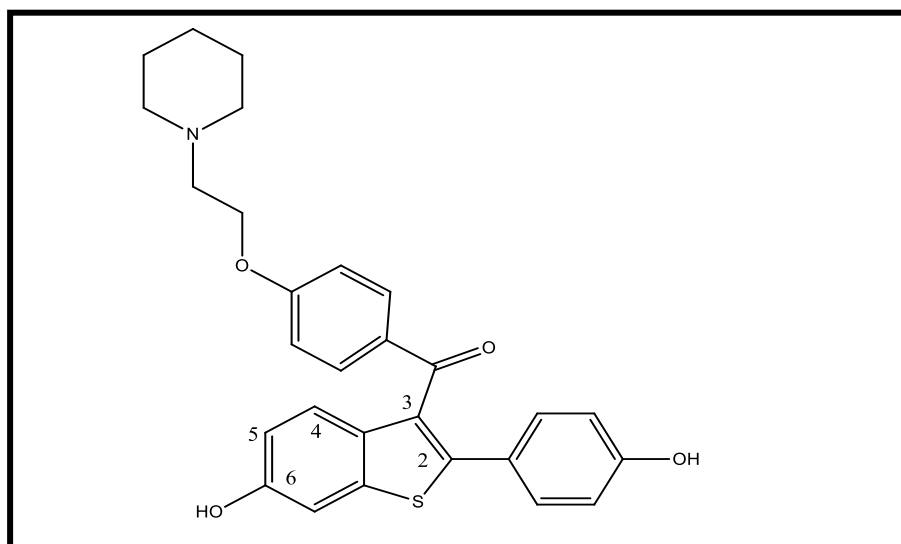


Figure 1: Chemical structure of Raloxifene drug.

1.3.1 Pharmacodynamic Properties

As a selective modulator of estrogen receptors, Raloxifene is able to partially mimic the effects of estrogens, specifically in the context of the cardiovascular system and bone. It also acts as an estrogen antagonist when present in breast and endometrial tissue [26].

1.3.2 Mechanism of Action (MOA)

Once the estradiol (E2) enters the nucleus of the target organ cells and binds on a series of unoccupied, inactive proteins (ER), ER conformational changes occurred to get the active form for enabling (E2-ER) complex to simultaneously dimerize and subsequently interact with the Estrogen Responding Element (ERE) (specific sequence of DNA) [27-29].

ER have two different isoforms, the first one is predominantly activating and the second inhibits the former. Also, it has two activation factors (AF), **AF-1/AF-2** where **AF-1 is located** at the exact site of interaction with the specific DNA sequence. Meanwhile **AF-2 is located** at the site where the ligand binds. The AF-2 region must interact with the E2 side-chain to activate this group of genes and synthesize the associated protein [23]. Therefore, agonist and antagonism effect related to the receptor location tissue where different structures should be generated depending on ligand nature that act at different way due to the presence of two

different domains inside ER the agonist estrogen-type ligands and the second one for antagonist estrogen type ligands and SERM (see figure2) [23].

Thus, ER action depends on whether the alpha or beta ER subtype is predominant in the tissue in question of:

- The nature of the ligand that binds to them (estrogen, antiestrogen, or SERM).
- The cell transcription machinery (ERE and AF).
- And on the presence or absence of “helper” or regulating proteins (HP).

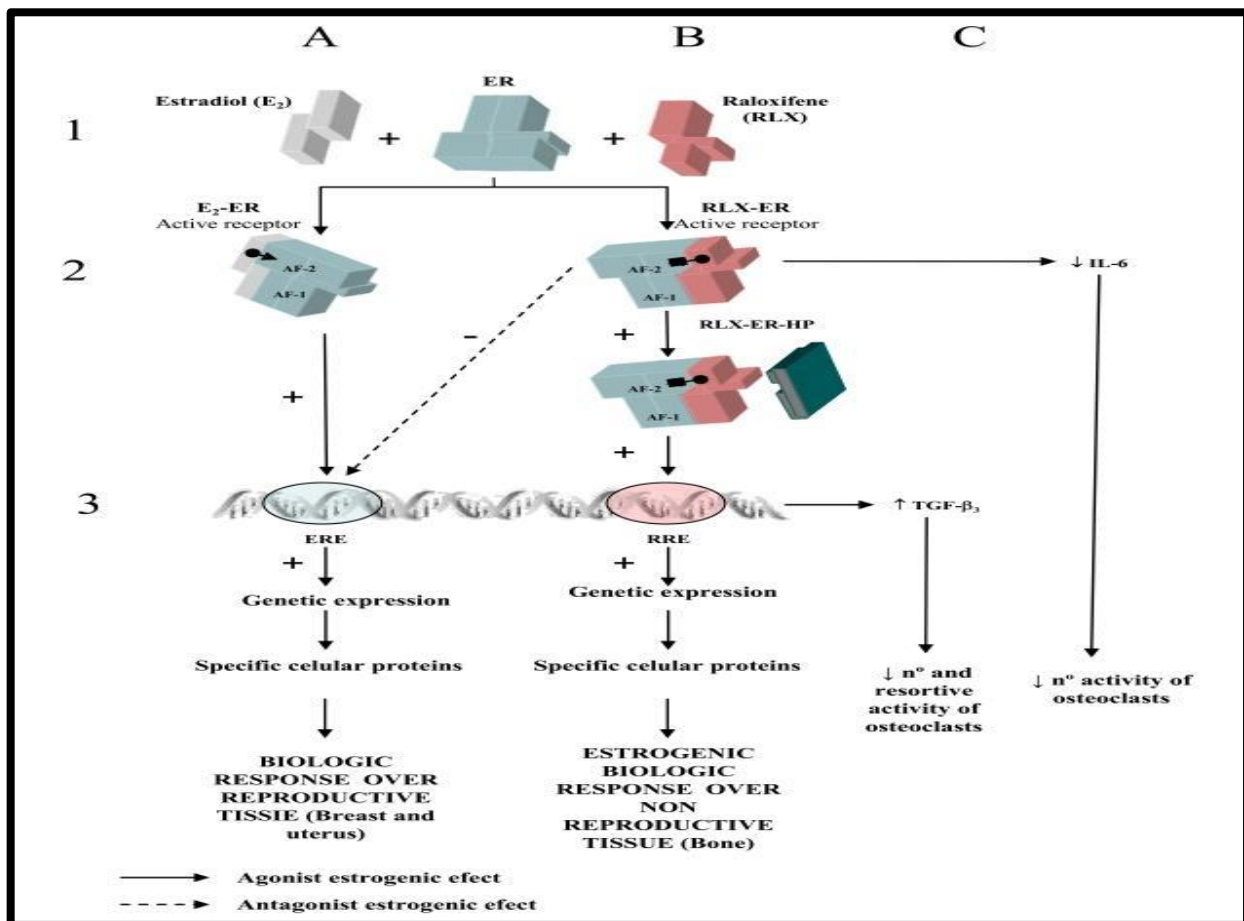


Figure 2: The mechanism of action for Raloxifene [18].

The exact mechanism of action (MOA) for Raloxifene is not fully cleared as yet. So, depending on the natural MOA to E2, Raloxifene must enter the nucleus and bind to the ER via its benzothiophene ring moiety where the conformational change for protein receptor is getting after the Raloxifene binding to the ERE [23].

Raloxifene basic side-chain does not completely bind so that allowing for a possibility of interaction with AF-2, that prevents the activation of genes and their transcription. which predict the estrogen antagonist effects of the drug on uterine and breast tissues. However, in bone and in other non-reproductive tissues ER (RLX-ER) and with the help of a series of HP (activating, helping, and/or adapting proteins) would activate a specific sequence of DNA known as the Raloxifene Responding Element (RRE) [30].

1.3.3 Effect on Breast Cancer

Breast cancer is both the most commonly diagnosed cancer and the second leading cause of death from cancer in women. A number of different studies and clinical trials have been undertaken in the effort to collect clinical data that allows for appropriate risk stratification, the better to reduce breast cancer incidence and implement prevention strategies [31].

In 2013, FDA approved raloxifene, along with tamoxifen, for the reduction of breast cancer risk. In particular, these drugs are recommended by the US Preventive Services Task Force for women who are at high risk of breast cancer [32].

For reducing breast cancer risk, raloxifene is taken in pill form once daily for five years. It is effective against both ductal carcinoma *in situ* (DCIS) and invasive breast cancer, and can achieve an overall risk reduction of about 40%. Relative to tamoxifen, raloxifene features less risk of thromboembolic events; however, both drugs are similar in terms of risks for other cancers, fractures, ischemic heart disease, and stroke [33].

1.4 Research Problem

Being an important drug, a number of studies have been made concerning Raloxifene's effectiveness and safety. Raloxifene absorption is approximately 60%, with peak plasma levels

from an oral dose being reached after six hours; it exhibits high binding to plasma proteins (>95%), including albumin and α 1 acid glycoprotein [34]. However, the utility of Raloxifene remains limited by its poor bioavailability, a mere 2%, which low figure is driven by the drug's lipophilic nature, poor solubility, and extensive hepatic first-pass metabolism [35]. A number of strategies are used to overcome these traits, stretching back many years; these include:

- Complexation with cyclodextrin and subsequent use of carbopol and HPMC to produce mucoadhesive microspheres [36].
- Packaging in pro-liposomes with or without surface charge to improve oral delivery [37].
- Formulation as a microemulsion to increase aqueous solubility and bioavailability [38].
- Packaging in nanostructured lipid carriers to improve oral bioavailability [39].

1.5 Thesis Objectives

1.5.1 General Objective

This research primarily aimed to design six Raloxifene-based prodrugs by adding a linker on both two-hydroxyl groups, 6-hydroxyl group (right side) and 2-(4-hydroxyphenyl) (left side) having enhanced bioavailability and the potential for controlled release of the parent drug (i.e. Raloxifene). The design process utilized diverse molecular orbital and mechanics methods, and furthermore investigated the correlation of experimental and calculated reaction rates.

1.5.2 Specific Objective

Kirby's enzyme model was utilized to design six Raloxifene prodrugs, with modifications being made on both sides. Prodrugs were intended to achieve the following properties:

- 1- Convert to Raloxifene by means of a controlled mechanism.
- 2- Enhance bioavailability relative to Raloxifene, the active/parent drug.
- 3- Utilize linkers that are safe and non-toxic.

1.6 Research Questions

1. Are DFT and *ab initio* methods capable of producing reaction rates similar to those obtained with Kirby's model?
2. Is the DFT approach a good method with which to design Raloxifene prodrugs that use non-toxic moieties, are capable of being cleaved to produce the active drug under physiological conditions, and exhibit superior bioavailability?

Chapter Two

Literature Review

Chapter Two: Literature Review

2.1 Enzymes

Enzymes are protein structures that act as biological catalysts in human cells. Many enzymes act to increase the rate of a reaction by 10^{10} to 10^{18} fold relative to its non-enzymatic execution; for example, orotidine monophosphate decarboxylase enhances the rate of reactions it catalyzes by 10^{17} , and cyclophilin by 10^5 [40]. Accordingly, many studies have been conducted to determine enzymes' mechanisms of action and the intramolecular processes involved (enzyme models). Karaman's group, which focuses on designing novel prodrug linkers, has recently employed the mechanisms of some enzyme models to better comprehend enzyme-mediated catalysis [41-47].

Overall, studies have demonstrated that in enzymatic reactions, acceleration of the rate constant relates to substrate binding to the active site, also termed the enzyme pocket. The binding energy (ΔG) of the resulting complex is considered the primary driver of catalysis and the preeminent contributor to the reaction mechanism, as that energy is utilized to overcome activation barriers imposed by physical and thermodynamic factors [48].

2.2 Intramolecular and Intermolecular Reactions

2.2.1 Intramolecular Forces

Intramolecular forces include all types of chemical bonds through which atoms are held together to comprise a molecule. They are considered stronger than intermolecular forces [49]. Enzyme-mediated intramolecular reactions involve bringing molecules together within the active site such that their functional groups are able to interact. Karaman and Menger's *ab initio* calculations demonstrated that intramolecular reactions are preferable when the reacting centers are positioned within about 2.4 Å of each other. At distances exceeding 3 Å, the intermolecular pathway typically predominates [50].

2.2.2 Intermolecular Forces

Intermolecular forces are those that hold multiple molecules together, thereby defining the properties of the substance they constitute; such forces are integral to molecular interactions and their collective organization into biological organisms and all manner of life [85].

Intermolecular forces can be classified in to the following types:

- Dipole-dipole interaction: Present in materials having a molecular dipole moment, such materials feature higher boiling and melting points than counterparts having similar molecular mass but no dipole moment.
- Weak London dispersion forces, a.k.a. van der Waal's force: A force that originates with an induced dipole, though generally greater in magnitude for heavier molecules, as reflected by the increase of boiling point for inert gases having greater atomic mass, this force is weaker than dipole-dipole interactions.
- Strong ionic attraction: Occurs between oppositely-charged ions on account of electrostatic attraction, and thus is a major type of bonding in ionic compounds.
- Hydrogen bonding: A distinct case of dipole-dipole interaction. Involves the bonding of a hydrogen atom that is connected to highly electronegative atoms such as N, O, or F.
- Metallic bonding: Interactions that occur between atoms in metallic solids on account of the rampancy of valence electrons associated with metals. These electrons are not constrained to remain with their source atoms or to a covalent bond instead, the electrons freely traverse the entire solid, enabling the ready conduction of heat and electric energy. This behavior provides metals with unique properties such as ductility and mechanical strength.

2.3 Prodrugs

Generally, the efficiency with which a drug is utilized by the body—its bioavailability—and performs its effective use for disease treatment depends on physicochemical properties of the drug, for example its solubility and polarity. It is well-documented that oral medicines feature detrimental pharmacokinetic profiles that stem directly from their adverse physiochemical properties. Such problems need to be taken into account quite early in the drug discovery process in order to ensure the developed drug is both cost-effective and therapeutically effective.

Prodrugs, introduced by Albert et al. in 1958, were designed to solve some of the problems associated with the undesirable pharmaceutical, pharmacodynamic, and pharmacokinetic properties of their parent drugs, for example low oral absorption, disagreeable taste and/or odor, insufficient solubility, poor stability, lack of site specificity, and toxicity [51]. As a solution to these issues, prodrug design has become a widely popular and very important field of scientific research and experimental synthesis. At present, prodrugs make up fully 10% of all drugs on the market; in the period of 2000-2008, prodrugs comprised 20% of the small-molecule drugs to receive approval [52].

Prodrugs usually consist of the corresponding parent drug and a non-toxic “linker,” a chemical moiety to which it is covalently bound. *In vivo*, that bond is degraded by enzymatic or chemical reaction to release the active drug with the desired therapeutic effect, while the released linker moiety is subject to rapid elimination [53, 54]. The preeminent challenge that must be overcome is the enzymatic conversion of the prodrug to its active parent with associated realization of the desired therapeutic effect. Consequently, a novel method of prodrug design was introduced that utilized knowledge of intramolecular processes (enzyme models) to identify the key factors contributing to enzyme-mediated catalysis of the prodrug [50, 55, 56].

In targeted prodrug design, intramolecular or chemical activation is respectively used to attach the drug moiety to a carrier/enzyme or an inactive organic moiety in such a way that an appropriate physiological environment is required to reverse the attachment. Effective prodrug design thus requires considerable familiarity with available enzymes and carriers along with their functional and molecular characteristics. As suggested by Stella and Himmelstein, key requirements for successfully targeting a prodrug include its rapid transport to the site of action, local and selective cleavage, and reliable retention at that site [57].

Prodrugs not activated by enzymes are majorly impacted by the rate-limiting step of the intramolecular reaction required for their activation. Design of such prodrugs relies upon informed molecular orbital (MO) and molecular mechanics (MM) calculations; for some processes, correlations of experimental and calculated rate values are also taken into account [1, 55].

2.3.1 Conventional Prodrug Classification

Prodrug designs are categorized into two sub-classes on the basis of chemical approach:

- (1) Bio-precursors are those prodrugs in which metabolic reactions are essential to induce the necessary functional groups; these do not require any carrier and can yield new products that may themselves be active or that undergo further metabolism, as in the case of transforming an amine to aldehyde to carboxylic acid [58-60].
- (2) Carrier-linked prodrugs are those in which the promoiety containing the active drug is covalently linked to an inactive, pharmacologically non-toxic, and easily eliminated carrier; the linkage is then cleaved either non-enzymatically or by an enzyme (as in the case of an ester or labile amide) to release the active parent drug [61, 62].

2.3.2 Disadvantages Associated with the Prodrug Approach

The prodrug strategy for drug design features several major challenges:

- Bioactivation by cytochrome P450 enzymes: This enzyme superfamily is highly consequential in drug metabolism, carrying out some 75% of all drug-associated metabolic reactions. Genetic polymorphisms in P450 enzymes that activate prodrugs thus contribute substantially to variability in bio-precursor activation, efficacy and safety [63, 64].
- Esterase hydrolysis: Ester-based prodrugs are the most common design when planning for *in vivo* cleavage. Such cleavage depends on the activity of hydrolyses (e.g. peptidases, phosphatases, and carboxyl-esterases); however, hydrolases may cleave prodrugs prematurely during their absorption by enterocytes in GI, leading to such prodrugs having bioavailability of only about 50% [65]. Once released, the active drug is unlikely to pass into the blood, but rather is prone to efflux back into the lumen on account of being more polar and less lipophilic.

The novel prodrug design approach using enzyme models overcomes some of these problems, especially in the context of molecules that contain hydroxyl, phenol or amine groups. This method avoids any need for enzymatic catalysis to convert a prodrug and release its parent drug, hence potentially eliminating all enzyme-associated disadvantages. The rate of the active drug's release is dictated only by those factors that govern the rate-limiting step [66].

Many proposals from organic chemists and biochemists over the last five decades have attempted to interpret the effects of structural variations on the reactivity of intramolecular systems (enzyme models), particularly in the context of biochemical enzyme catalysis. These hypotheses include:

- I. Proximity orientation, proposed by Bruice, which involves a near attack conformation such as that exhibited during the lactonization of di-carboxylic acids semi-esters [67-69].
- II. Orbital steering, proposed by Koshland, in which organic reactions feature severe angular dependence that results in rapid intramolecularity, such as occurs during the lactonization of rigid hydroxy acids [70].
- III. The spatiotemporal hypothesis of Manger, in which two reactive centers are proposed to have a reaction rate proportional to the period over which the intervening distance is below a critical threshold [71-75].
- IV. Stereopopulation control, postulated by Cohen, in which a molecule might be frozen in such a way as to become a productive rotamer [76-78].
- V. The proton transfer models of Kirby, which revealed the centrality of hydrogen bonding to producing the transition states and final products resulting from the acid-catalyzed hydrolysis of acetals and N-alkylmaleamic acids [56, 79-86].

Kirby's model has been used to design several prodrugs, such as the antihypertensive atenolol, the better to mask its unpleasant taste [87] tranexamic acid, which is used to treat heavy bleeding [88] aza-nucleoside, which is utilized in myelodysplastic syndromes [89] phenylephrine, a decongestant [3] atovaquone, an anti-malarial [90] acyclovir, an anti-viral [91] and cefuroxime, an antibacterial [92]. In these prodrug designs, a hydroxyl group on the active drug is bonded to an acetal moiety, and the rate of release of the active parent drug in a physiological environment is purely determined by the linker's structural features.

Recently, Karaman's group has employed DFT and *ab initio* molecular orbital calculations to explore the mechanistic pathways of intra-molecular processes [41] and identify those factors that define reaction rate and its most limiting step. Among these enzyme models are:

1. Intramolecular acid-catalyzed hydrolysis in maleamic acid amide derivatives using Kirby's models [33,31, 36].
2. Oxygen-oxygen and nitrogen-oxygen proton transfer in Kirby acetals and enzyme models, respectively [56].
3. Oxygen-oxygen proton transfer in rigid systems as described by Menger [71] and Cohen [76-78].
4. The production of anhydrides through S_N2 -based-cyclization of di-carboxylic semi-esters, as described by Bruice [68, 93].
5. Intramolecular S_N2 -based ring-closing reactions, defined by Brown and Mandolini [94].

The conclusions of Karaman's studies on intramolecularly are as follows:

- The rates of intramolecular processes enhanced by a driving force are influenced by both enthalpy and entropy. When enthalpic effects predominate, for example in ring-cyclization and proton transfer, the driving forces are steric effects and/or proximity.
- Whether a reaction is intermolecular or intramolecular is determined by the separation of the reactive centers; at distances of about 2.4 Å, the reaction is intramolecular. While, the intermolecular process is preferred when the reaction centers are 3 Å or more far.
- In the closing of three-, four and five-membered rings by means of S_N2 based reactions, greater ring size decreases need for directional flexibility. For formation of an unstrained five-membered ring in particular, the gem-dialkyl effect predominates.

- Finally, in Kirby's acetal systems, efficient oxygen-oxygen and oxygen-nitrogen proton transfer is achievable when the transition states and corresponding products feature strong hydrogen bonds [41, 43, 46].

2.4 Computational Design of Raloxifene Prodrugs that Undergo Intramolecular Acid Hydrolysis Using Kirby's Models

Intramolecularity is widely utilized in models of enzyme catalysis mechanisms, e.g., proton transfer, on account of the functional groups of the active site and substrate being held in close proximity to each other—noncovalently in the case of the enzyme residues, and covalently upon carrying out the intramolecular process. The tremendous efficiency achieved in enzyme-mediated catalysis is the culmination of numerous factors, most of which are recognized, but none of which are yet fully understood. Hence, there remains a great deal of research needed on the chemistry of enzyme catalysis [95, 96].

Here, Kirby's enzyme model was used to investigate the mechanism by which maleic acid (Figure 3) undergoes acid-catalyzed hydrolysis to produce Raloxifene. This investigation revealed that the carboxylic acid group adjacent to hydrogen bond of hydroxyl group performs an intramolecular nucleophilic catalysis resulting in the bond's cleavage, and hydrolysis of the bond mostly depends on the substitution of the carbon-carbon double bond [97].

Consequently, this reaction is rate-limited by the dissociation of the tetrahedral intermediate. In 1990, Katagi previously reported the rate-limiting step to be the intermediate's formation rather than its dissolution, determined by means of AM1 semi-empirical calculations [98]. Kluger and Chin subsequently reported the rate-limiting step of intramolecular hydrolysis to be a function of both solution acidity and the leaving group's basicity [99].

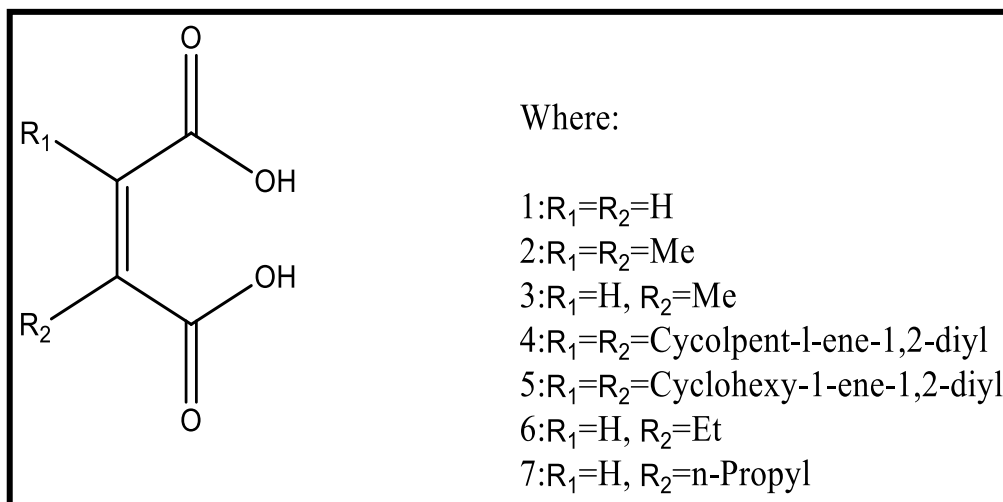


Figure 3: Chemical structures of maleic acids and their derivatives.

Chapter Three

Computational (Design) section

Chapter Three: Computational (Design) Section

The software used to perform calculations in the course of this thesis consisted of:

- 1) Argus Lab
- 2) Gaussian 09
- 3) Molden

3.1 Argus Lab

This free program is popularly utilized for molecular modeling, graphics and drug design. It is able to produce models with optimized 3D geometry using the UFF force field. It also allows drawing and editing molecular structures; the rotation, translation, and modification of atoms/molecules and critically, the execution of MM and semi-empirical QM calculations.

Geometry optimization in Argus Lab may use the MM methods of UFF/Amber force fields and the QM methods of semi-empirical MNDO, AM1, or PM3 for single point calculations. Also supported are Extended Huckel for greater element coverage and ZINDO for excited states and the prediction of UV/visible absorption. Version 3.1 has good ability to semi-empirically calculate and display electron density and orbital surfaces [100].

Argus Lab saves molecules in formats like “xml”, but can also export “xyz” files accepted as input by other software such as Molden. Notably, the program makes extensive use of temporary files, which require some managing.

Steps for using ArgusLab:

- Click the Argus Lab icon to open.
- After the software has initiated, click 'New' for a new molecule screen, or click 'Open' to load a molecule from a saved file.

- Run AM1 and UFF calculations. Be sure to save two separate files for your molecule, one prior to making any modification and the other following geometrical optimization.
- The molecule window should not be maximized, as its title bar will then display the name of the most recently saved file. Just drag the bottom right corner out until the window takes up most of the screen.
- When finished, click File > Exit to close the program.

3.2 Gaussian 2009

Gaussian comprises a line of electronic structure programs, of which 09 is the most recent version and also is freely downloadable. The software was introduced in 1970 by John Pople, a researcher in quantum computational chemistry who went on to receive the 1998 Nobel Prize.

Gaussian is useful for any researcher who applies the fundamentals of quantum mechanics in order to predict the energies, molecular structures, vibration frequencies, and other molecular properties of atomic or molecular systems.

As illustrated by Gaussian, the facilities are available for experimental chemists to investigate molecules and reactions for which it is difficult or even impossible to carry out experimental observations, such as reactions that feature toxicity, combustibility, radioactivity, short-lived intermediates and transition structures, and the like [101]. Gaussian 09 is able to run AM1, MNDO, MINDO/3, PM3, HF, DFT, MP2 and MP3 at all possible levels.

Steps for using Gaussian 09:

- The input is a .gjf file produced in one of two ways:
 - By hand in a local editor (e.g. VI, emacs, or nedit)
 - With the Molden software, which can also:
 - View files output by Gaussian 09.

- Dissect the output file. In that file, the Z-matrix represents the molecule's geometry (structure). Importantly, the molecule lacks any charge and has a multiplicity of 1 (all electrons are paired). A more standard xyz coordinate system is also used to represent molecular structure. The pairwise distances of all atoms (in angstroms) are contained in the distance matrix.

3.3 Molden

The computational package Molden is used to display molecular density as calculated by one of the *ab initio* packages GAMESS-UK, GAMESS-US, or Gaussian or by semi-empirical packages such as MOPAC. In computational workflows, Molden provides a means of standardization as it is capable of interpreting a number of file formats output by other programs.

Molden also can serve as a visual Z-matrix molecule editor offering full control over molecule geometry, with which users can create a given molecule from scratch [102]. It enables the visualization of molecular orbitals, electron density, and the difference between atomic and molecular density. For the last case, both spherically averaged and oriented ground state atomic density may be subtracted in the context of several standard basis sets.

For visualization, Molden has the ability to generate contour plots, 3-d grid plots with hidden lines, and the combination of the two. Additionally, it is able to compose graphics instructions in a variety of formats: *XWindows*, *postscript*, *OpenGL*, *VRML*, *povray*, *tekronix4014*, *hpgl*, *hp2392*, and *Figure*. Molden is also able to animate reaction paths and molecular vibrations, and to calculate multipole derived electrostatic potentials with fitting of atomic charges on a Connolly surface [92].

The file format to which Molden saves data incorporates multiple elements, each denoted with an identifier, e.g. [MO] for molecular orbitals, [STO] for slater type orbital basis sets, and more such as [GTO], [GEOMETRIES], etc. A stand-alone force field program (Ambfor) allows

geometry optimization by means of Amber (protein) and GAFF (small molecules) force fields. Atom typing and execution of optimization jobs can be carried out automatically and interactively from within Molden.

3.4 Calculation Methods

3.4.1 Raloxifene Prodrugs

DFT-based calculations for Raloxifene prodrugs utilized the Becke three-parameter, hybrid functional in combination with the Lee, Yang, and Parr correlation functional (B3LYP). All calculations employed the QM package Gaussian-2009 and the restricted Hartree-Fock method. Starting geometries were determined with Argus Lab and initially optimized per AM1 and HF/6-31G, with subsequent optimization per B3LYP/6-31G (d, p). All internal rotations were incorporated into total geometry optimizations (see chart 1).

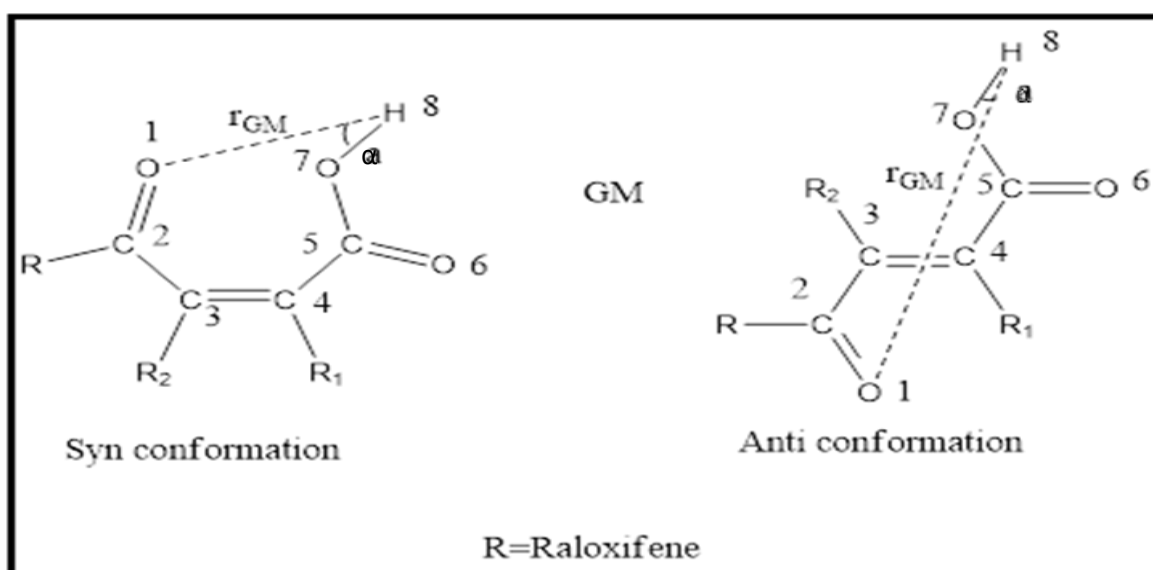


Chart 1: Schematic of reactant structures for Raloxifene proton transfers. GM, global minimum structure; r_{GM} , O—H distance; α , angle of attack (hydrogen bonding) for O1-H8-O7.

During optimization, all geometrical parameters had their second derivatives estimated. No negative vibrational force constant indicated an energy minimum, i.e., a stable compound or reactive intermediate, while solely one negative constant at a saddle point indicated a transition state.

When locating transition states, the normal reaction coordinate method was applied first, in which the inter-atomic distance between an atom pair was adjusted stepwise and the resulting enthalpy change monitored. For the highest point in the energy profile, the molecular geometry was re-optimized by means of the energy gradient method at the B3LYP/6-31G (d, p) level of theory.

For transition states, full optimization was realized after the removal of any constraints applied in the course of the energy profile. Activation energies were calculated for all molecules according to DFT both with and without water (dielectric constant 78.39).

For calculations incorporating a water molecule, the integral equation formalism model of the polarizable continuum model was employed, which constructs the cavity by means of a series of overlapping spheres. The United Atom Topological Model radius type was applied, with radii being optimized for the PBE0/6-31G (d) level of theory.

To facilitate our calculation of Raloxifene properties using the DFT (B3LYP/6-31G (d, p)) method that is the standard model for medium molecules (30-60 atoms in size) and to decrease cost of time, I simplified the drug's structure as shown in (Figure 4).

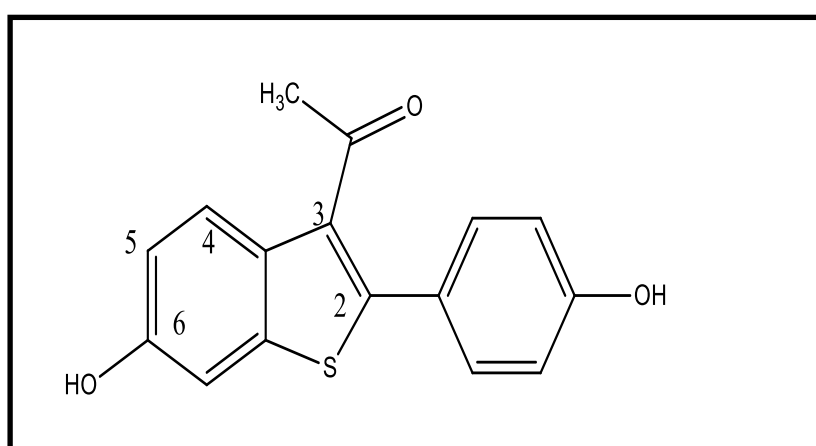


Figure 4: The Simplified chemical structure of Raloxifene drug.

Chapter Four

Results and Discussion

Chapter Four: Results and Discussion

4.1 Raloxifene

On side of intramolecularly Karman's studies proved the necessary to determine the factors that affect the reaction rate according to their mechanism for getting best design of an effective chemical innovation which used as a linker on prodrug and that liberate the active drug in programmable and controlled manner via chemically and not enzymatically.

Because of the presence of two phenolic hydroxyl groups at Raloxifene on two sides (left side or/and right side), there are two ways for linkers blockage to get Raloxifene prodrugs that expected to investigate and achieve the desired goals (figure 5).

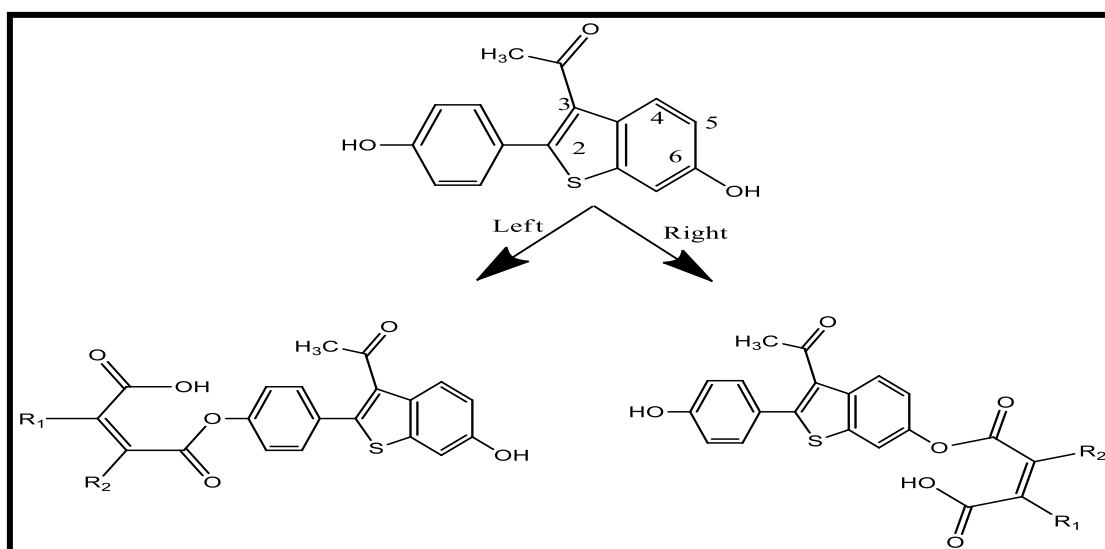


Figure 5: The proposed side for Raloxifene linkers binding on left and right sides

Our strategy in Raloxifene prodrug design depended on an ester bond formation (esterification) between maleic acid and Raloxifene entity (Figure 6). Six maleic linkers are proposed (Figure 7) were linked to hydroxyl groups on both left and right sides which depend on the proton transfer reactions of Kirby's enzyme model that undergo acid hydrolysis reaction pathway (figure 8 a and b).

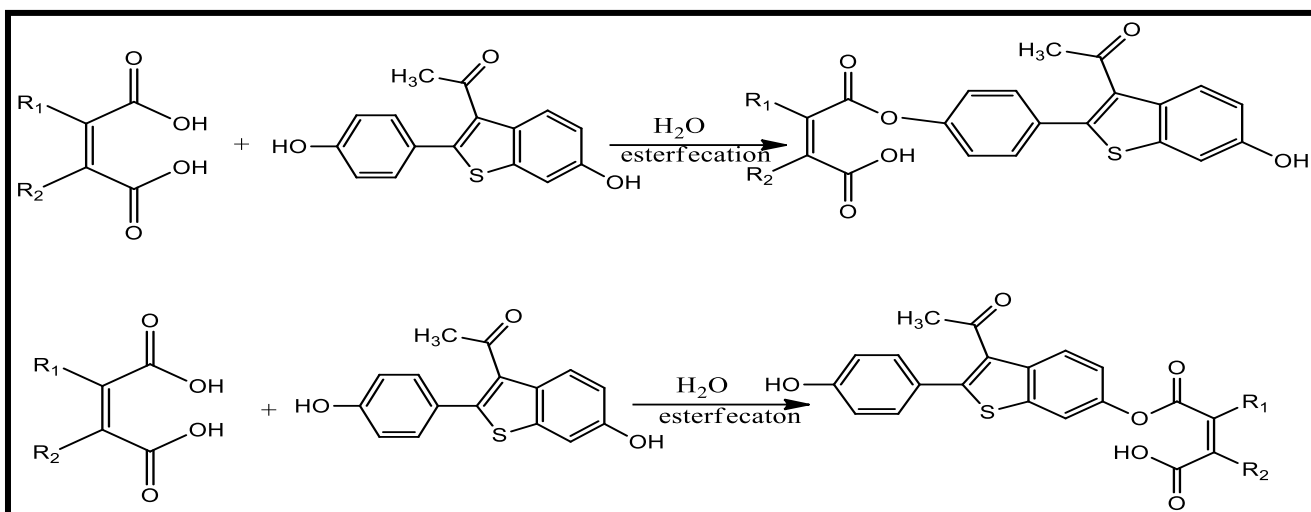


Figure 6: Esterification of maleic acid with Raloxifene, where R_1 and R_2 are maleic derivatives.

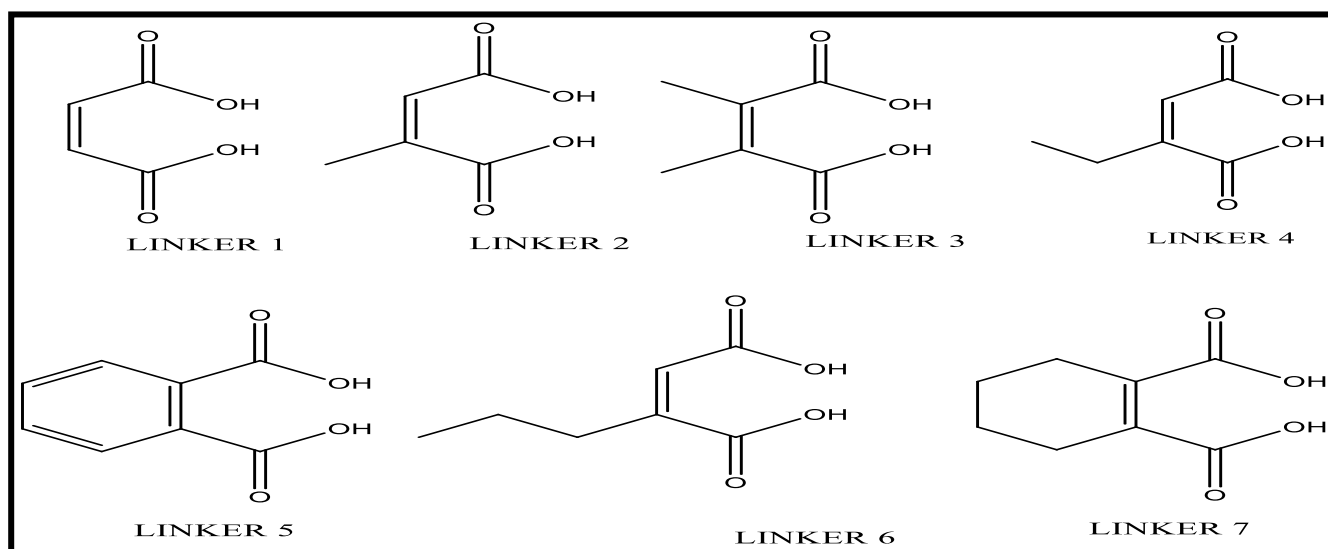


Figure 7: The proposed linkers used in the Raloxifene prodrugs for both sides.

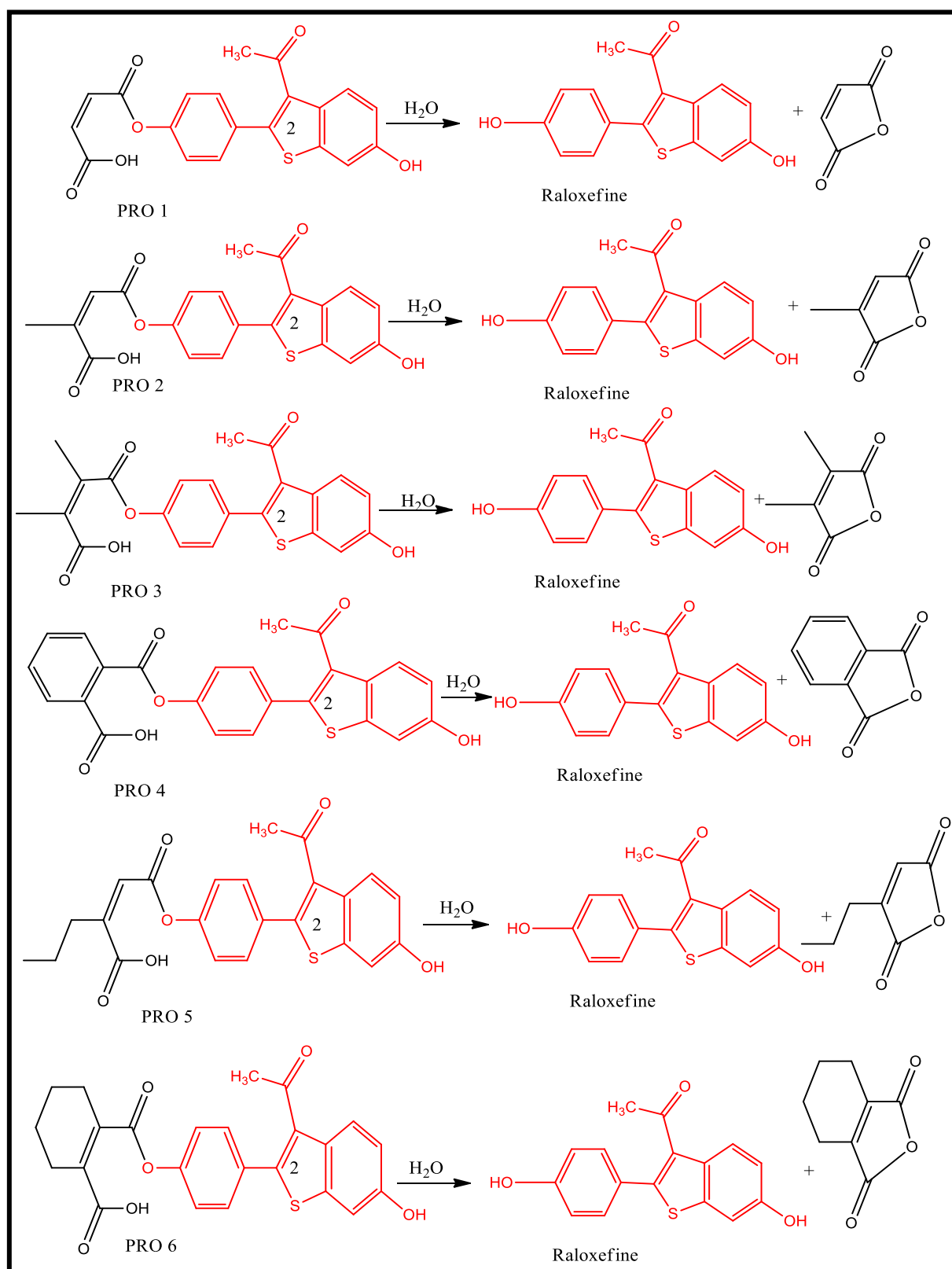


Figure 8a: Acid hydrolysis of the proposed Raloxifene Prodrugs Design on left side **ProD1-ProD6**.

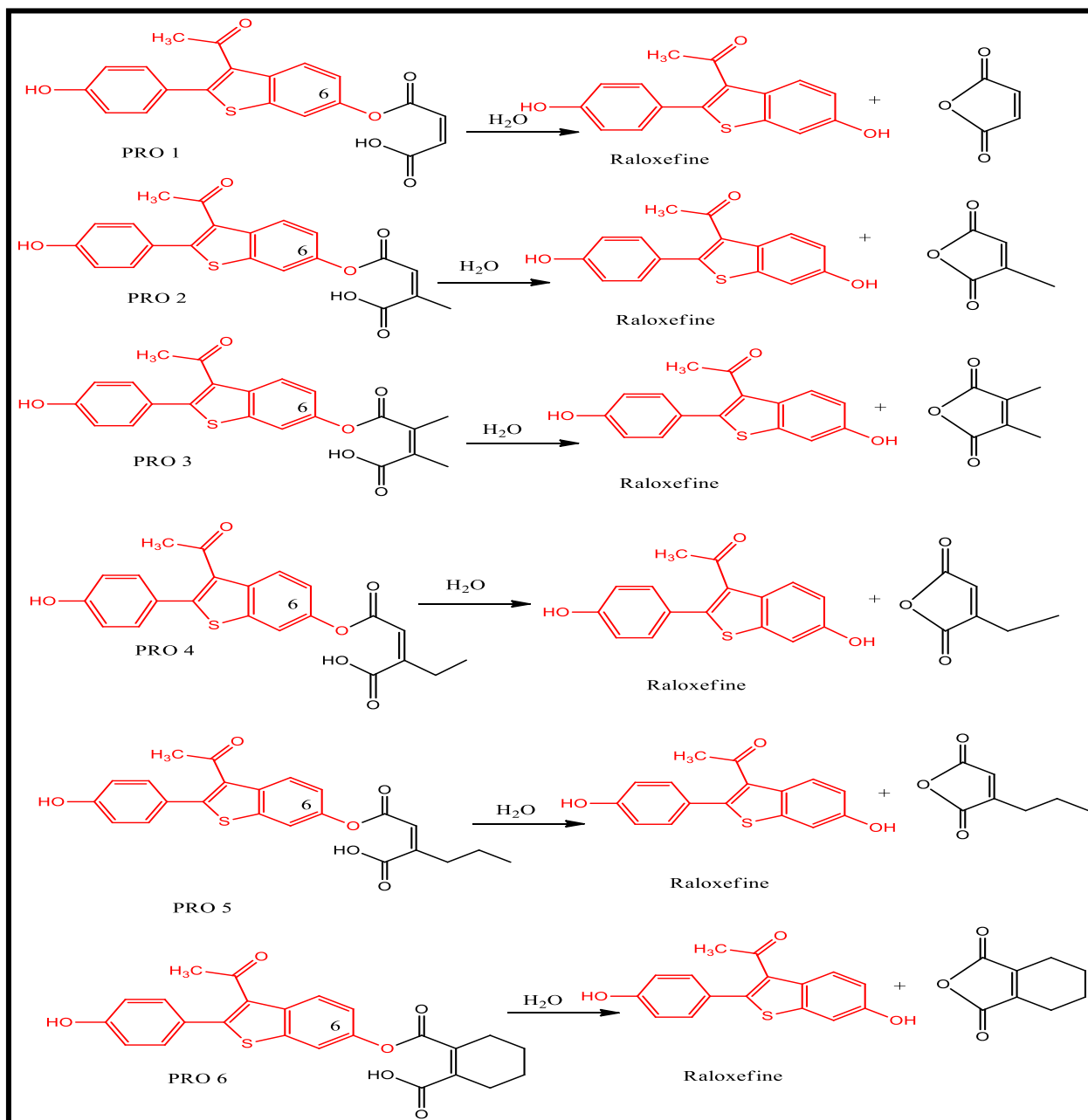


Figure 8b: Acid hydrolysis of the proposed Raloxifene Prodrugs Design on right side **ProD1-ProD6**.

Designed Raloxifene prodrugs on two sides (figure 8) are expected to have better bioavailability than the parent one because of a moderate HLB that had by a combination of two moieties a lipophilic (the hydrocarbon group) and a hydrophilic (carboxylic group). For ensuring that these prodrugs reached the intestine and release the parent drug (at pH not less than 5). Also, another plan includes to obtain these prodrugs as sodium or potassium salts as

enteric coated tablets dosage form because of their fast hydrolysis inside the stomach at low pH where both the carboxylate anion and the free acid form can be found inside the intestine. Subsequently, the free acid form will undergo proton transfer reaction (rate limiting step) to yield the active form of Raloxifene.

Karaman's study on Kirby's enzyme model proved that the tetrahedral intermediate (**INT**) has an effect on the rate limiting step of the reaction depending on its media where the rate limiting step in the water phase was the collapse of intermediate (**INT**), while in the gas phase was the formation of **INT**. Furthermore, they proved factors that clearly affect the efficiency of the hydrolysis for acid-catalyzed reaction which include, the strain energies ($E_{S_{INT}}$) and their differences between product or/ and reactant, angle of attack (α) and the distance between two reactive centers (r_{GM}). Also, Karaman studies that based on DFT calculations clarified these acid catalyzed reactions occur in three sequential steps (see figure 9):

- (1) Proton transfer from the carboxylic group to the adjacent carbonyl oxygen.
- (2) Nucleophilic attack of the carboxylate anion onto the protonated carbonyl carbon.
- (3) Dissociation of the tetrahedral intermediate to provide products.

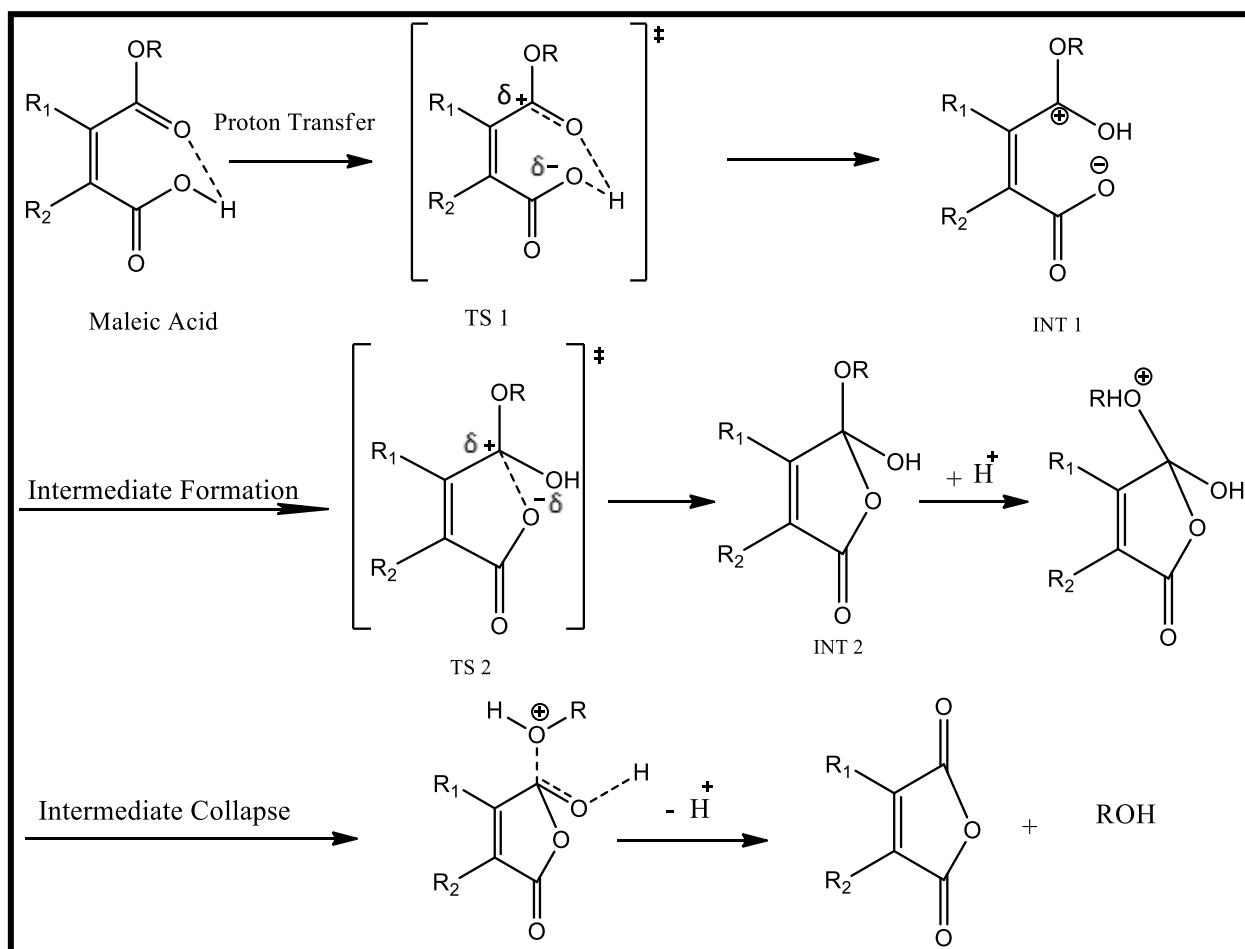


Figure 9: Proposed mechanism for the acid-catalyzed hydrolysis of maleic acids (R =Raloxifene, R_1 and R_2 =maleic acid substituent).

Our calculations for Raloxifene prodrugs were based on DFT at B3LYP 6-31G (d,p) level that reported the intramolecular proton transfer for ground state and transition state structures, also vibrational frequencies and reaction trajectories on both sides of Raloxifene prodrugs **ProD1-ProD6** (left and right sides). The calculations were carried out in the gas phase for the left side and in two phases for the right side, the gas and solvent phase with dielectric constant of water (79.38).

In this work, the calculation for the right side was carried out in both phases, gas phase and solvent phase with dielectric constant 79.38, while for the left side the calculation was done only for gas phase.

4.2 General Consideration

A six novel Raloxifene prodrugs were designed for both left and right sides by using Kirby's enzyme models (Acid-catalyzed hydrolysis), in order to increase the bioavailability of Raloxifene than the parent one (active form), with ability of programable the intra-conversion rate of Raloxifene prodrugs to the parent one depending on the nature of linker.

According to the major effect of the conformation on the free energy for the reactant, the exact orientation of the carboxylic group to the alkoxy moiety is very important and reflects the mode and rate of the cyclization reaction. So, it is very important to identify the most stable Global Minimum (**GM**) for all derivatives of maleic acids and Raloxifene prodrugs **ProD1–ProD6** on both sides. **GM** search was done by rotation of the carboxylic group about the C4-C5 bond increments of (i.e., the variation of the dihedral angle O6C5C4C3 see Chart 1) and calculation of the conformational energies.

There are two different types of conformations for Raloxifene **ProD1-ProD6** on starting geometries of DFT calculations: *syn* one where the carboxyl hydroxyl proton is *syn* to the alkoxy group and *anti*-one on their opposite orientation (Chart 1). On my search all **GM** of Raloxifene **ProD1- ProD6** on two sides were found to be arranged in the *syn*-orientation (figure 9).

4.3 DFT Optimized Geometries for all Raloxifene ProD1- ProD6 Entities Included in the Acid-Catalyzed Hydrolysis on Both Sides.

Based on DFT calculations for B3LYP/6-31 G (d, p) the optimized Raloxifene geometries for the Global Minimum (GM) **ProD1GM-ProD6GM** for both sides were illustrated in figure 10(a, b). Also, the attacking angle (α) and the distance between two reactive centers (r) were calculated and showed.

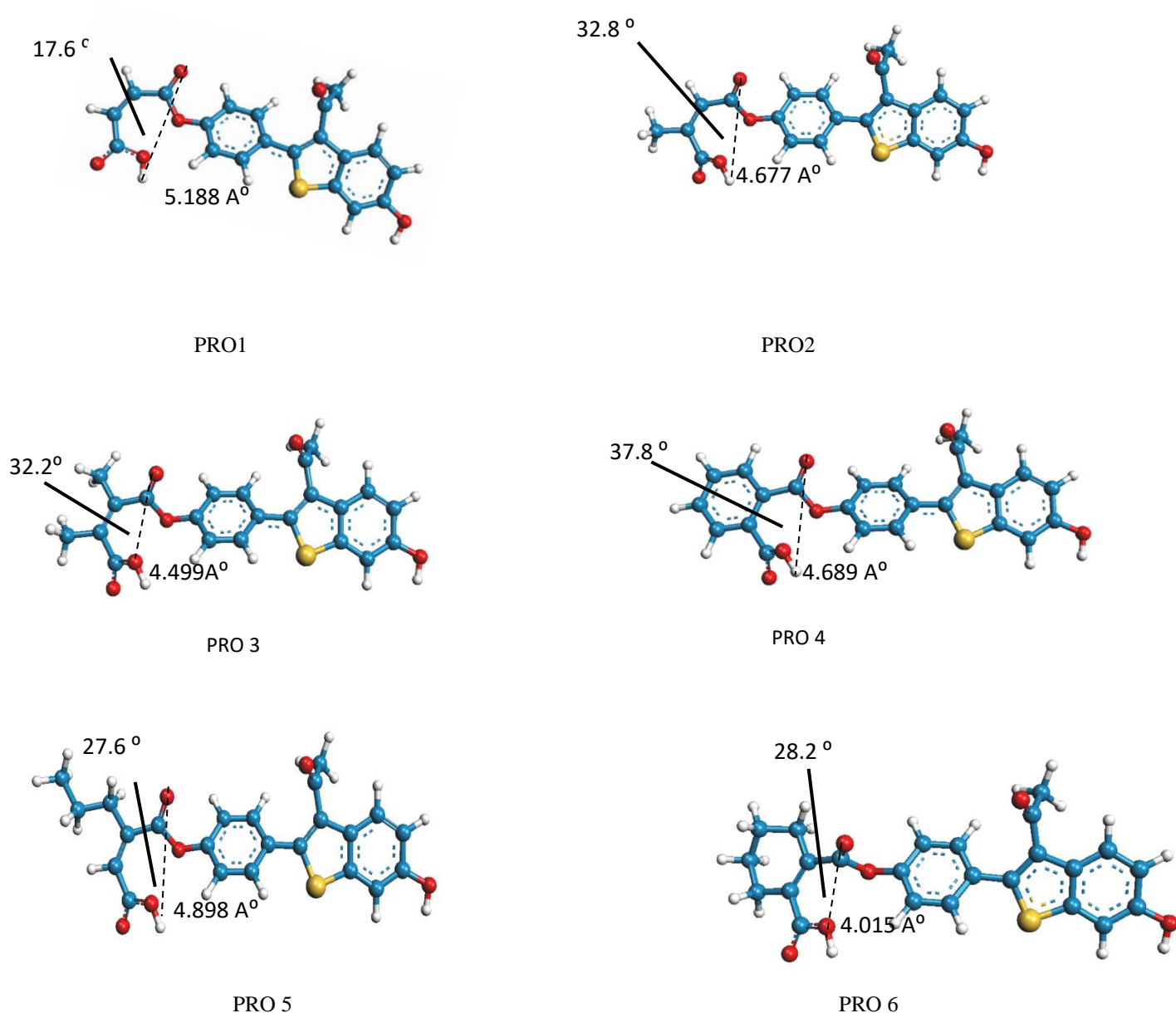


Figure 10a: DFT optimized structures for Raloxifene **ProD1GM-ProD6GM** at left side.

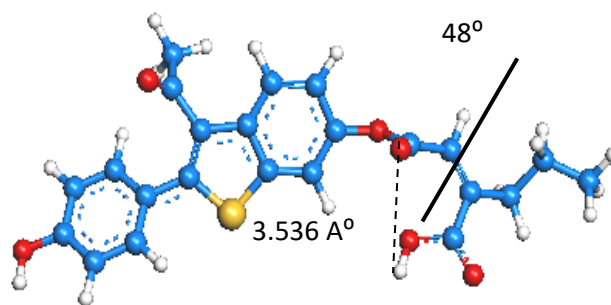
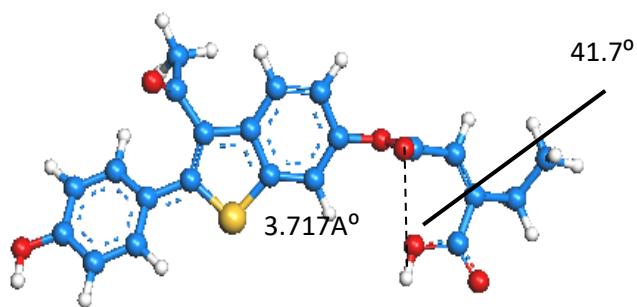
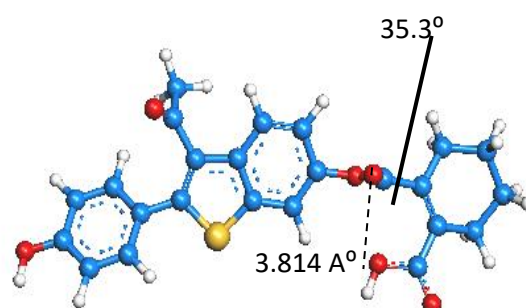
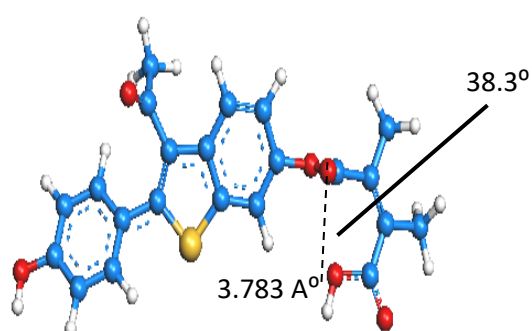
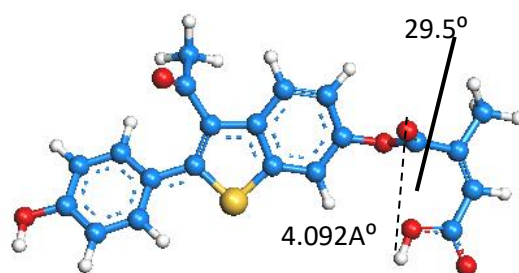
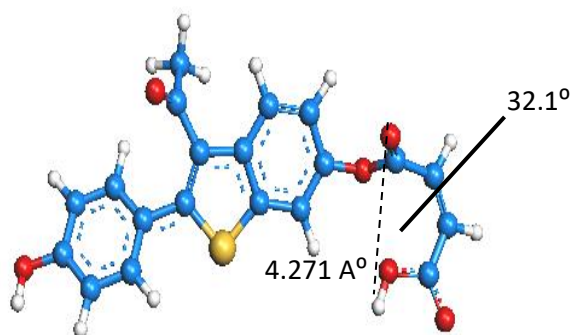


Figure 10b: DFT optimized structures for Raloxifene **ProD1GM-ProD6GM** at right side.

In view of above DFT optimized Raloxifene **ProD1GM-ProD6GM** values for the intermolecular distance (r_{GM}) (O1-H8) the range of these values were observed to be between 4.015 Å – 5.188 Å at left side (Figure 10 a) and at right side 3.536 Å - 4.271 Å (Figure 10 b). Where the shortest distance referred to **ProD6** at left side 4.015 Å and **ProD6** at right side 3.536 Å, meanwhile **ProD1** has the longest distance at left side 5.188 Å and **ProD1** at right side 4.271 Å. Furthermore, the angle α of attack for hydrogen bond (O1H8O7) was in the range of 17.6° – 37.8° on the left side and 29.5° – 48° on the right side.

The optimized tetrahedral intermediate geometries for Raloxifene prodrugs (**ProD1INT-ProD6INT**) for both sides, left and right are shown in the figure 11a, 11b, respectively. The formed bond distance between O and C are between 1.436 Å-1.450 Å for the left side. While, the distance varies between 1.426 Å-1.443 Å for the right side.

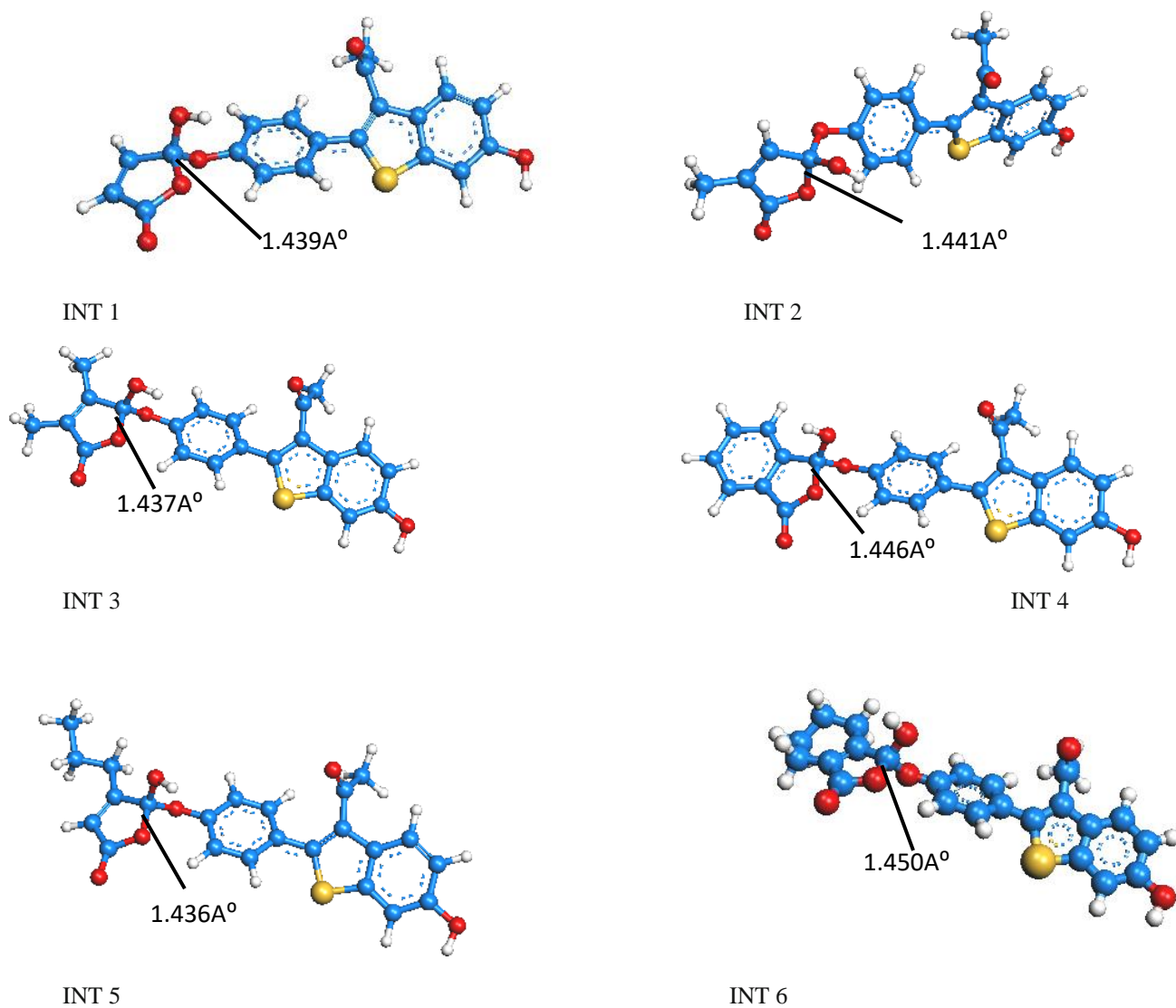
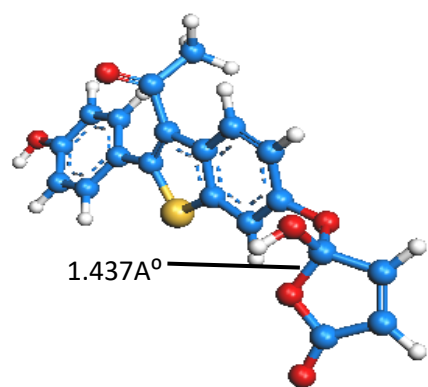
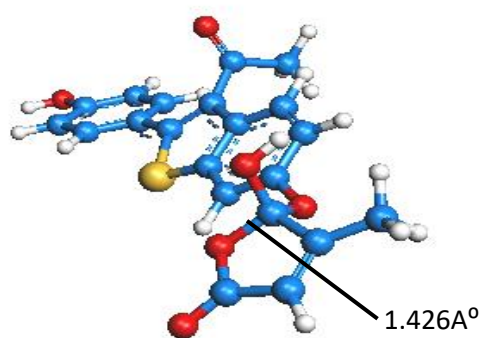


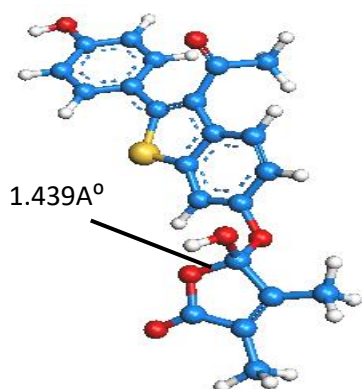
Figure 11a: DFT optimized structures for the tetrahedral intermediate (INT) of Raloxifene ProD1-ProD 6 in the intramolecular proton transfer reaction at the left side.



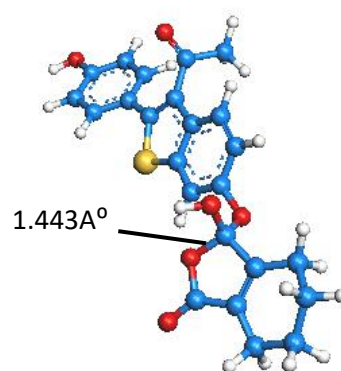
INT1



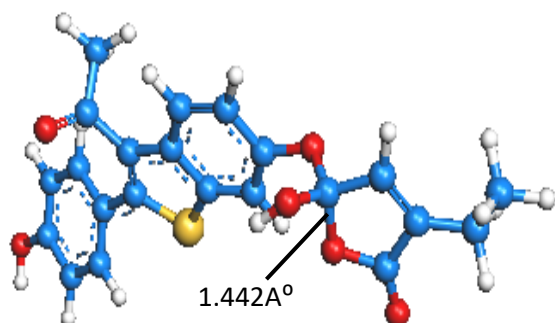
INT 2



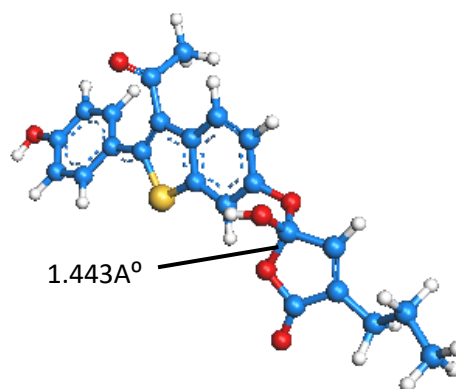
INT 3



INT 4



INT 5



INT 6

Figure 11b: DFT optimized structures for the tetrahedral intermediate (INT) of Raloxifene ProD1-ProD 6 in the intramolecular proton transfer reaction at the right side.

Figure 12a and 12b show the optimized transition state geometries for Raloxifene prodrug (**ProD1TS-ProD6TS**) for both sides. The distance of partially broken and formed bond in the intramolecular proton transfer reaction were calculated and shown.

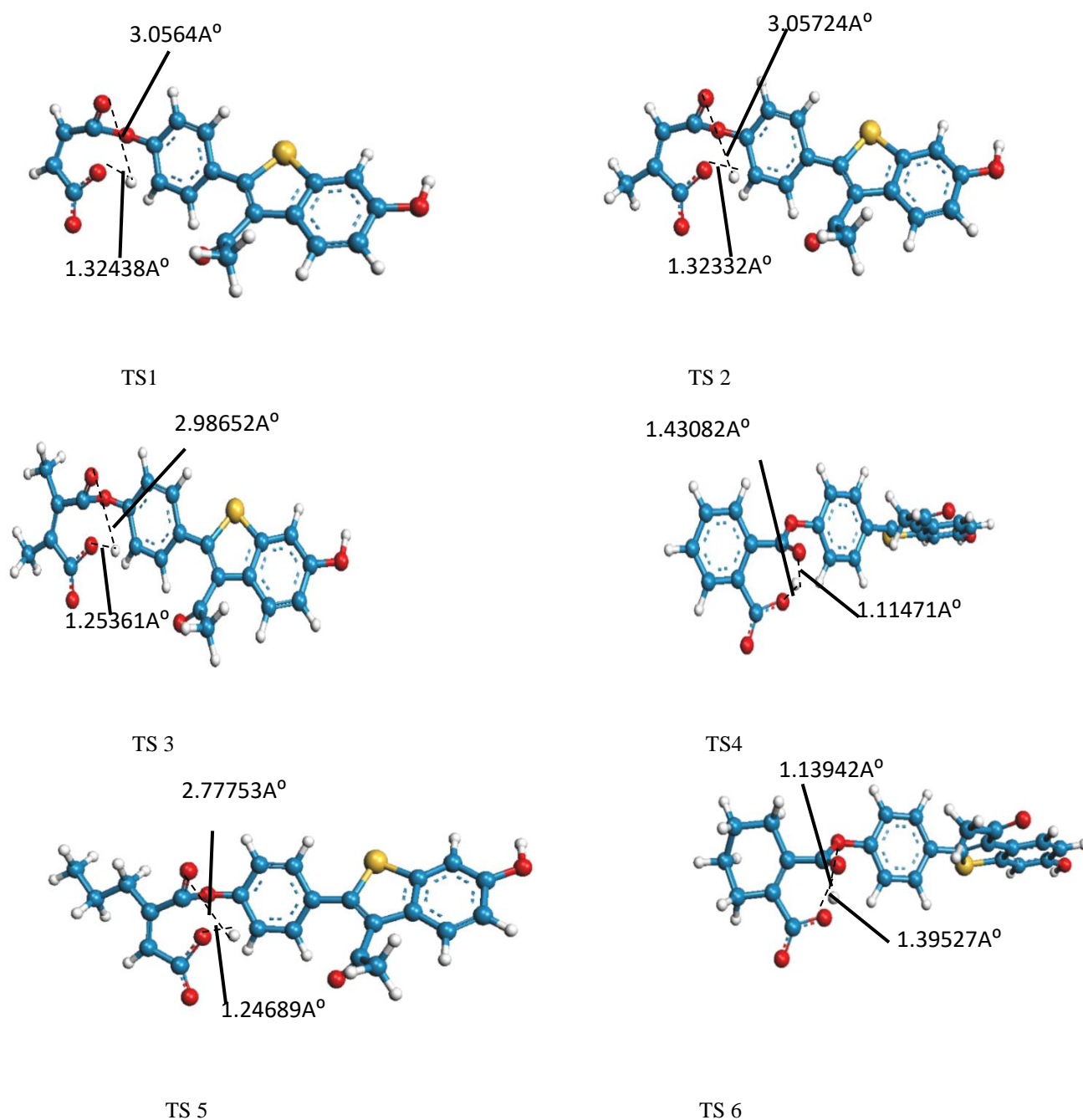


Figure 12a: DFT optimized structures for the transition state (TS) of Raloxifene **ProD1-ProD6** in the intramolecular proton transfer reaction on the left side.

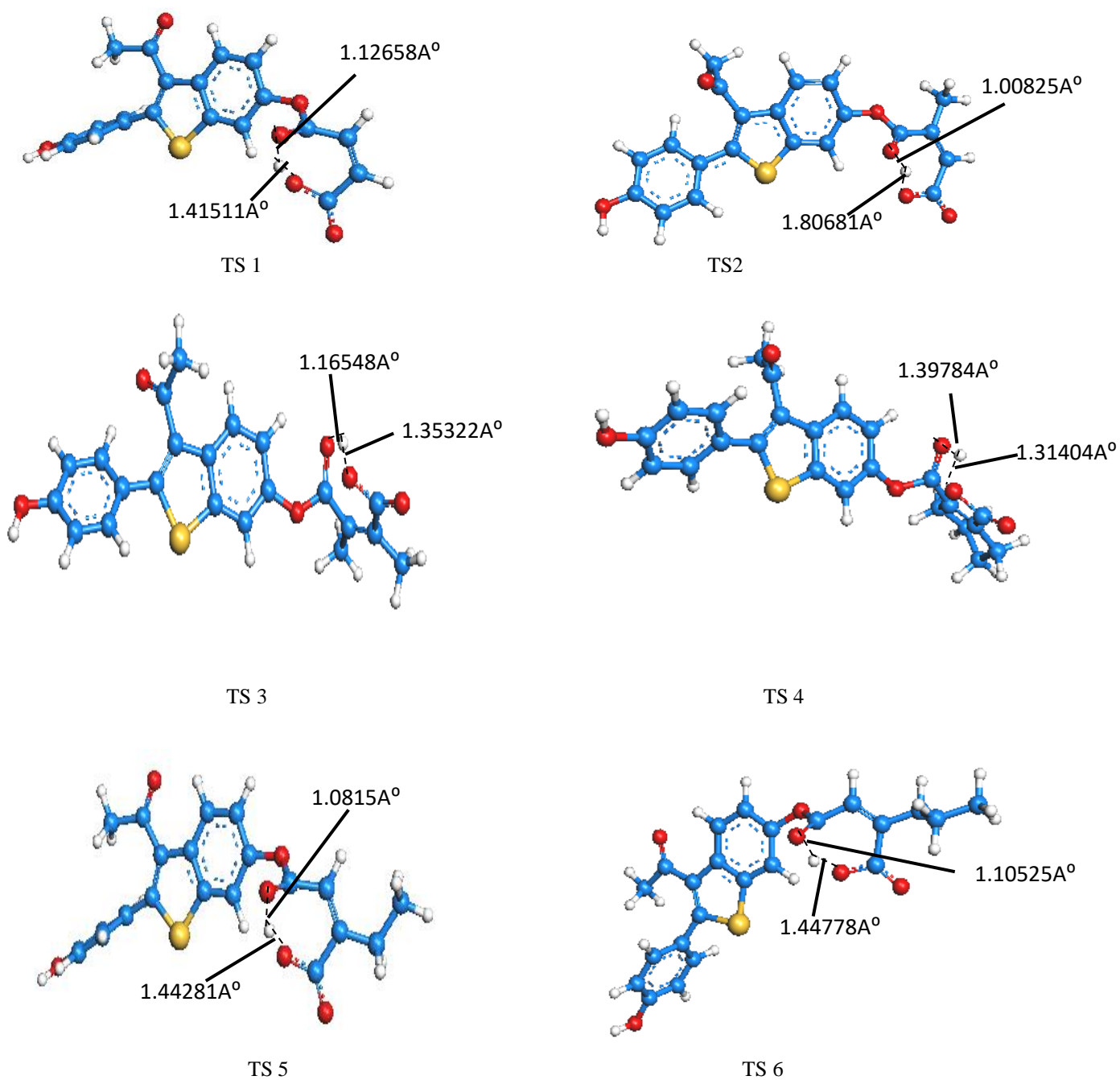


Figure 12b: DFT optimized structures for the transition state (TS) of Raloxifene **ProD1-ProD6** in the intramolecular proton transfer reaction on the right side.

4.4 The Thermochemistry Data of Energies and their Kinetics Based on DFT Calculation for the Proton Transfer Reaction on Raloxifene ProD1- ProD6 on Both Sides

Depending on DFT calculations at B3LYP/6-31 G (d, p) level of theory thermochemistry data and their kinetics properties which include the enthalpy (H) and entropy (S) energy values for all entities of global minimum (GM), intermediate (INT) and transition state (TS) structures were calculated in gas phase for the left side, see table 1a. Where table 1b shows the calculated data for the right side in the gas phase and solvent phase.

Table 1a: Calculated properties of DFT (B3LYP) for proton transfer reactions of Raloxifene at left side ProD1-ProD6.

System	B3LYP, Enthalpy, H (gas phase) in Hartree	B3LYP, Entropy, S (gas phase) Cal/Mol-Kelvin	B3LYP Frequency Cm ⁻¹
Raloxifene ProD1GM	-1619.754557	158.014	-----
Raloxifene ProD1TS	-1619.693831	155.174	743.30i
Raloxifene ProD2GM	-1659.054778	166.079	-----
Raloxifene ProD2TS	-1658.990791	162.850	784.90i
Raloxifene ProD3GM	-1698.343709	166.569	-----
Raloxifene ProD3TS	-1698.287797	169.648	782.75i
Raloxifene ProD4GM	-1773.378993	172.197	-----
Raloxifene ProD4TS	-1773.337812	171.574	1102.72i
Raloxifene ProD5GM	-1737.624043	179.575	-----
Raloxifene ProD5TS	-1737.565990	175.090	788.33i
Raloxifene ProD6GM	-1775.736557	163.434	-----
Raloxifene ProD6TS	-1775.699027	175.400	1144.28i

Table 1b: Calculated properties of DFT(B3LYP) for proton transfer reactions of Raloxifene at right side **ProD1-ProD6**.

System	B3LYP, Enthalpy, H (gas phase) in Hartree	B3LYP, Entropy, S (gas phase) in Cal/Mol- Kelvin	B3LYP Frequency in Cm^{-1}
Raloxifene ProD1GM	-1619.763958	163.762	-----
Raloxifene ProD1TS	-1619.724222	159.520	1366.36i
Raloxifene ProD2GM	-1659.060331	161.273	-----
Raloxifene ProD2TS	-1658.994339	154.744	734.94i
Raloxifene ProD3GM	-1698.349017	166.816	-----
Raloxifene ProD3TS	-1698.304573	174.181	1478.41i
Raloxifene ProD4GM	-1775.729747	165.698	-----
Raloxifene ProD4TS	-1775.672864	176.349	960.17i
Raloxifene ProD5GM	-1698.343369	167.643	-----
Raloxifene ProD5TS	-1698.308316	172.991	1171.30i
Raloxifene ProD6GM	-1737.623429	168.338	-----
Raloxifene ProD6TS	-1737.594747	180.034	1201.76i

Also, the enthalpy activation energies (ΔH^\ddagger), entropy activation energies ($T\Delta S^\ddagger$), and the free activation energies were calculated in the gas phase and (ΔG^\ddagger) for the proton transfer reaction at both left and right side also at water phase on the right side (Table 2).

Table 2: Calculated kinetic and thermodynamic properties of DFT (B3LYP/6-31G (d, p) for the proton transfer of Raloxifene **ProD1-ProD6** at right and left side.

System	ΔH^\ddagger (GP)	$T\Delta S^\ddagger$ (GP)	ΔG^\ddagger (GP)	ΔH^\ddagger (H ₂ O)	ΔG^\ddagger (H ₂ O)
Right Side					
Raloxifene ProD1	24.93	-1.25	26.18	28.37	28.96
Raloxifene ProD2	41.41	-1.92	43.33	30.81	31.41
Raloxifene ProD3	27.89	2.21	25.68	27.78	27.99
Raloxifene ProD4	35.69	3.19	32.50	29.41	28.55
Raloxifene ProD5	21.99	1.6	20.39	26.27	26.85
Raloxifene ProD6	17.99	3.49	14.5	24.19	24.26
Left Side					
Raloxifene ProD1	38.10	-2.09	40.19	-----	-----
Raloxifene ProD2	40.15	-0.96	41.11	-----	-----
Raloxifene ProD3	35.08	0.92	34.16	-----	-----
Raloxifene ProD4	25.84	-0.18	26.02	-----	-----
Raloxifene ProD5	36.42	-1.34	37.76	-----	-----
Raloxifene ProD6	23.55	3.57	19.98	-----	-----

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).

Then, the strain energy values (steric effect) of the intermediates and the global minimum for Raloxifene **ProD1-ProD6** ($E_{S(INT)}$, $E_{S(GM)}$) were calculated by using Allinger's MM2 method for ensuring about the effect of the ($\Delta E_{S(INT-GM)}$) on the rate of the proton transfer in process Raloxifene ProD1-ProD6 on two sides (see table 3).

Table 3: Calculated kinetic and thermodynamic properties of DFT (B3LYP) for the acid catalyzed hydrolysis of Raloxifene ProD1- ProD6 on two sides.

System	$E_{S(INT)}$	$E_{S(GM)}$	$\Delta E_{S(INT-GM)}$	$\Delta H^\ddagger (GP)$	$\Delta G^\ddagger (GP)$	$\Delta H^\ddagger (H_2O)$	$\Delta G^\ddagger (H_2O)$
Right side							
ProD1	62.51	23.03	39.53	20.29	18.58	19.45	19.12
ProD2	43.21	20.33	22.88	34.25	35.58	23.96	24.12
ProD3	39.71	28.58	11.13	25.68	23.39	29.87	28.87
ProD4	60.36	48.49	11.87	32.01	30.73	23.92	22.95
ProD5	44.74	26.07	18.67	19.01	16.85	22.80	22.64
ProD6	43.17	28.89	14.28	17.32	15.46	18.88	18.60
Left side							
ProD1	34.56	33.09	1.47	38.96	35.03	----	----
ProD2	36.75	35.22	1.53	38.60	37.57	----	----
ProD3	56.28	40.53	15.75	31.80	30.88	----	----
ProD4	79.01	49.37	29.64	25.84	26.02	----	----
ProD5	34.01	31.69	2.32	36.21	35.80	----	----
ProD6	69.72	41.87	27.85	23.55	19.89	----	----

4.4 The Effect of the Distance O1-H8 (r_{GM}) and the Angle O1H8O7 (α) on the Rate of Raloxifene ProD1- ProD6 Proton Transfer Process for Both Sides

Focusing on DFT results (figures of GM, Table 2) for Raloxifene proved and indicates the presence of an opposite relationship between the angle of attack (α) and the distance between the two reactive centers r_{GM} (O1-H8) depending on the conformation structure of GM where the shortest distance (r_{GM}) refers to higher value for angle of attack (α) and vice versa. So, a linear correlation was obtained once r_{GM} values plotted versus α values on two sides with $R^2 = 0.7079, 0.7485$ respectively (Figure 13a, b).

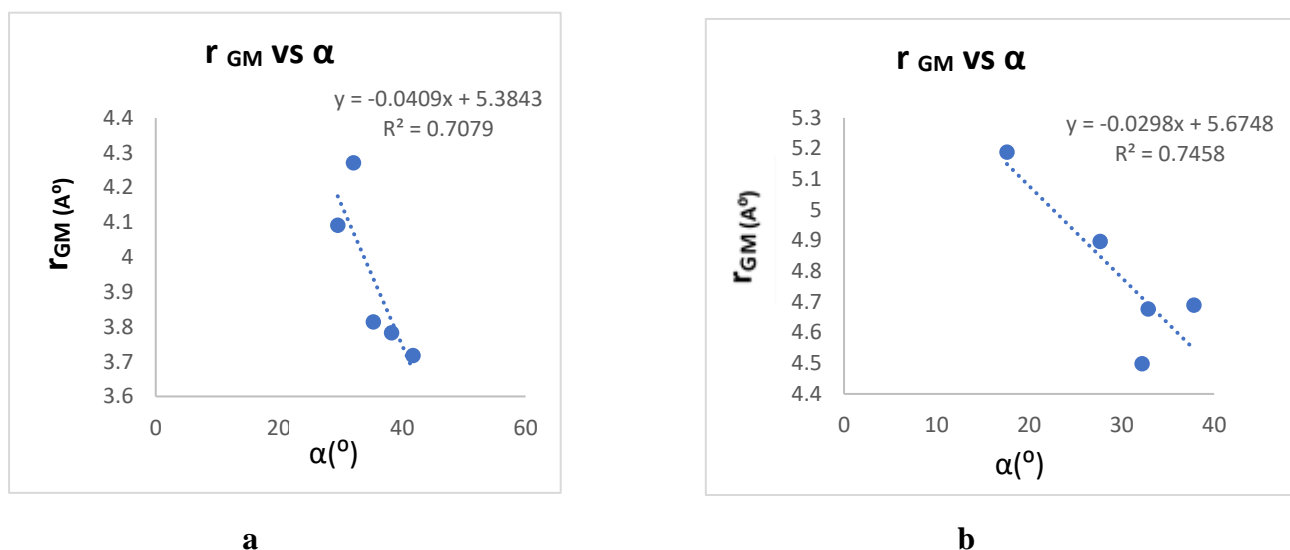


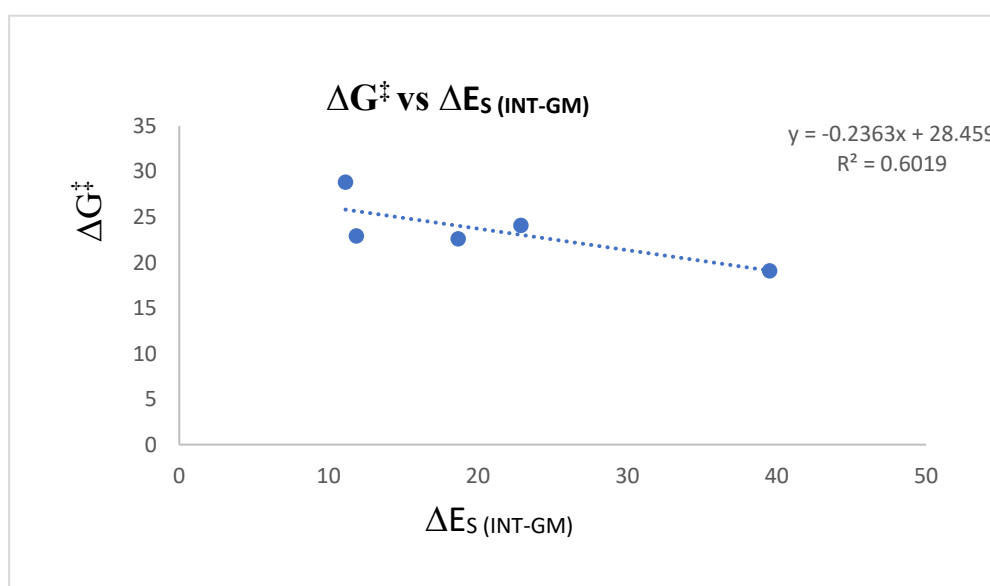
Figure 13(a, b): Plot of the DFT calculated r_{GM} (Å) vs. angle α (°) for Raloxifene **ProD1-ProD6**, where (r_{GM}) and (α) are the distance between the two reactive centers and the attack (hydrogen bond) angle in the GM structure, (a) at right side, (b) at left side.

Consequently, the activation energy values (ΔG^\ddagger) are major affected by these two factors r_{GM} (O1-H8) and α (O1H8O7) (see table 2, figure10a, b). To get a conclusion for their GM structures of Raloxifene **ProD1- ProD6** systems at gas phase including that the lower ΔG^\ddagger (higher rates) refer to system of low r_{GM} and high α values for examples (**ProD4, ProD6**) at left side and (**ProD5, ProD6**) at right side where the higher ΔG^\ddagger (lower rates) refer to system

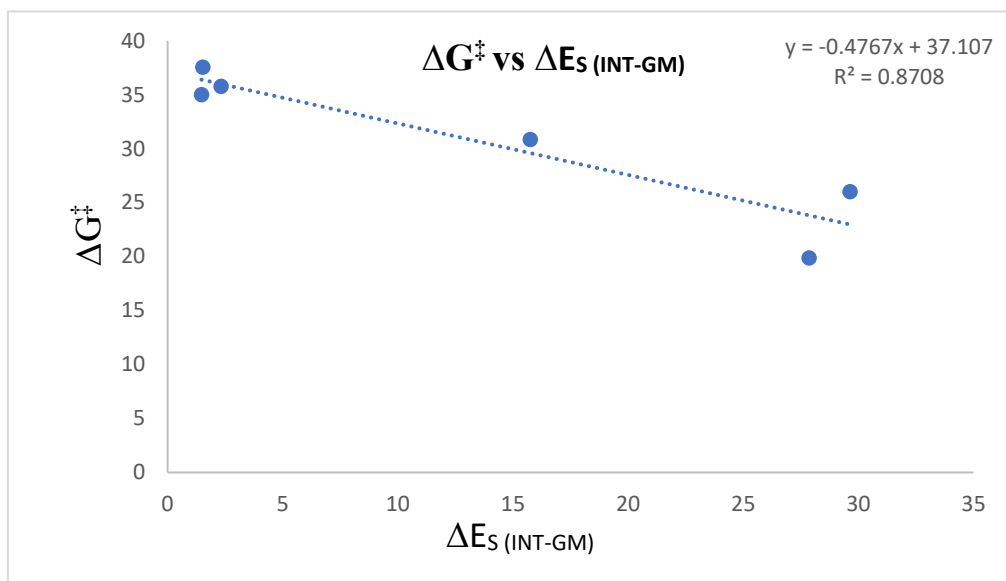
of high r_{GM} and low α values, for examples (**ProD1, ProD2, ProD3, Pro5**) at left side and (**ProD1, ProD2, ProD3, Pro4**) at right side (figure 13a, b).

4.5 The Effect of the Strain Energy (E_S) for the Intermediates (E_{SINT}) on the Rate of the Proton Transfer in Processes Raloxifene ProD1- ProD6 on Both Sides

The calculated MM2 (ΔE_S (INT-GM)) values for Raloxifene **ProD1-ProD6** were checked on both sides to plot a correlation between its values versus activation free energies (ΔG^\ddagger) that DFT calculated, to get a linear correlation between ΔG^\ddagger and ΔE_S (INT-GM) with a satisfied correlation coefficient of $R^2=0.609$ and 0.8708 for right and left sides respectively (figure 14a, b).



a



b

Figure 14(a, b): Plot of the DFT calculated ΔG^\ddagger vs. ΔE_S (INT-GM) for Raloxifen**ProD1-ProD6**(a)at right side in water(b)at left side.

Based on results of ΔG^\ddagger , ΔE_S (INT-GM) (figure 14a, b and table 3) that proved the largely effect of the strain energy of the tetrahedral intermediate on the rate of a proton transfer in processes Raloxifene **ProD1-ProD6** on two sides where strained tetrahedral intermediates system have low rates and *vice versa*.

Chapter Five

Conclusions and Future Directions

Chapter Five: Conclusions and Future Directions

5.1 Conclusions

A number of Raloxifene prodrugs were designed based on DFT calculations for Kirby's model with using of maleic acids and their derivatives to enhance poor bioavailability (2%) for the parent one via achieving a moderate HLB value which related for the combination of two moiety a lipophilic (hydrocarbon group) and a hydrophilic (carboxylic group).

Results approved that Raloxifene prodrugs are mainly affected by two factors of global minimum structures including the angle of attack α , and the distance between the two reactive centers, r_{GM} thus affecting the rate of proton transfer. Therefor at **GM** higher rates observed on system with low r_{GM} and high α values for examples **ProD5, ProD6** at right side and **ProD4, ProD6** at left side but lower rates related to system with high r_{GM} and low α values for examples **ProD1, ProD2, ProD3, ProD4** at right side and **ProD1, ProD2, ProD3, ProD5** at left side. Also, the steric effect for intermediate has an inverse relationship with the rate of proton transfer on Raloxifene prodrugs on both sides to conclude that systems with high values of difference between the strain energy of tetrahedral intermediate and the reactant have low rates and vice versa.

According to all above factors and to be ensure that the designed Raloxifene prodrugs are achieve better bioavailability than the parent one the best designed Raloxifene prodrugs are: **ProD4 and ProD6** at left and **ProD5 and ProD6** at right side.

5.2 Future Directions

The expected successful design of Kirby's model for Raloxifene prodrugs on both sides based on DFT calculations which must enter the manufacturing laboratories are **ProD4, ProD6** at left and **ProD5 and ProD6** at right side. Moreover, many parameters should be considered on synthesis for each prodrug including: *in vitro* kinetics test on different pH's that mimic the physiological environment and *in vivo* studies each one administered IV and *per os* to animals then collected and tested in controlled method and also, be ensure about the safety of the released prodrug and non- toxic released linkers that are used.

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Supplementary Material

Supplementary Material

XYZ cartesian coordinates format for the DFT optimized GM, INT and TS in processes

Raloxifene ProD1-ProD6 on two sides (right and left sides respectively).

At right side

ProD1 GM

C	0.61990	2.26790	0.06730
C	-0.22030	1.14490	-0.00200
C	0.31760	-0.15160	-0.23280
C	1.98020	2.11080	-0.12630
C	2.49460	0.82300	-0.38800
C	1.69590	-0.31810	-0.40860
C	-1.65770	1.10640	0.13980
C	-2.15840	-0.16840	0.00470
S	-0.91450	-1.30560	-0.26980
O	3.83200	0.65890	-0.74800
O	-7.52420	-1.81040	-0.14150
C	4.80640	0.91250	0.18640
C	6.14460	0.51510	-0.29330
C	6.61800	-0.73060	-0.34090
C	5.91730	-1.95850	0.05980
O	4.56700	-1.87290	0.20920
O	4.50900	1.45620	1.24400
O	6.42480	-3.06400	0.26500
O	-3.02810	2.53900	1.45550

C	-2.41280	2.34440	0.40530
C	-2.36840	3.37290	-0.68730
C	-4.54300	0.23070	-0.52650
C	-3.54030	-0.59480	0.01280
C	-3.89580	-1.85050	0.53150
C	-5.86670	-0.18660	-0.56610
C	-6.20320	-1.44940	-0.04770
C	-5.21940	-2.28050	0.50870
H	0.18650	3.25770	0.27530
H	2.67480	2.95910	-0.05880
H	2.14850	-1.30890	-0.56170
H	-7.64470	-2.65000	0.32220
H	4.21400	-2.73590	0.48000
H	7.64990	-0.93300	-0.68600
H	6.75910	1.37900	-0.60140
H	-3.35180	3.38060	-1.21700
H	-2.20060	4.38660	-0.25010
H	-1.55870	3.14850	-1.42120
H	-4.27370	1.22540	-0.91690
H	-3.11940	-2.50070	0.96530
H	-6.65490	0.44860	-0.99180
H	-5.49210	-3.25990	0.92400

ProD1 INT

C	0.70140	2.19290	0.08840
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C	-0.17850	1.10230	-0.00390
C	0.33120	-0.19880	-0.26320
C	2.05660	1.99780	-0.09470
C	2.54010	0.70540	-0.40030
C	1.70350	-0.40470	-0.45050
C	-1.61610	1.08590	0.13690
C	-2.14270	-0.17630	-0.03480
S	-0.91690	-1.32700	-0.33110
O	3.86070	0.60520	-0.83380
O	-7.55920	-1.67850	-0.12620
C	4.84620	0.28310	0.09890
C	6.23640	0.30500	-0.55690
C	6.73110	-0.94560	-0.53650
C	5.73730	-1.83710	0.12500
O	4.62720	-1.07670	0.51030
O	4.72000	1.08620	1.21950
O	5.71210	-3.01760	0.42040
O	-2.96150	2.48990	1.50320
C	-2.35680	2.32370	0.44220
C	-2.31360	3.37250	-0.63090
C	-4.52970	0.29190	-0.52570
C	-3.53780	-0.56610	-0.01720
C	-3.92580	-1.81590	0.49270
C	-5.86690	-0.08450	-0.54850

C	-6.22990	-1.34630	-0.04530
C	-5.25980	-2.21280	0.48100
H	0.30440	3.19300	0.30220
H	2.77670	2.82420	-0.02290
H	2.10160	-1.40940	-0.64880
H	-7.67580	-2.55460	0.26640
H	7.67370	-1.34580	-0.90830
H	6.65940	1.22950	-0.93760
H	-3.28470	3.36490	-1.18410
H	-2.17290	4.38620	-0.18550
H	-1.48010	3.17050	-1.34520
H	-4.23650	1.27720	-0.92000
H	-3.16390	-2.49580	0.90230
H	-6.63980	0.57440	-0.96910
H	-5.54940	-3.20250	0.86230
H	4.60580	0.51720	1.99840

ProD1 TS

C	0.58430	2.62330	-0.16130
C	-0.19470	1.45080	-0.11670
C	0.47190	0.20640	-0.14120
C	1.96930	2.53190	-0.22130
C	2.57360	1.27660	-0.23840
C	1.85430	0.09140	-0.19950
C	-1.65390	1.32470	-0.03610

C	-2.08390	0.02570	-0.03210
S	-0.70330	-1.16860	-0.09780
O	4.00730	1.23110	-0.38300
O	-7.26290	-2.26960	-0.10520
C	4.74270	0.42100	0.39090
C	6.14580	0.27780	-0.09800
C	6.61460	-0.93490	-0.38660
C	5.66670	-2.10030	-0.22600
O	4.45080	-1.66110	0.19120
O	4.31890	0.12470	1.60680
O	5.99280	-3.26530	-0.44100
O	-2.04110	3.67570	-0.04220
C	-2.52170	2.53460	0.07860
C	-3.99870	2.36330	0.39260
C	-4.22260	-0.55940	-1.18890
C	-3.43560	-0.56030	-0.02280
C	-3.94080	-1.17600	1.13040
C	-5.48750	-1.13010	-1.18980
C	-5.99580	-1.72580	-0.02740
C	-5.21170	-1.74680	1.13040
H	0.07620	3.57400	-0.15210
H	2.58700	3.41840	-0.26330
H	2.37170	-0.86030	-0.22280
H	-7.52100	-2.67560	0.76270

H	4.35340	-0.98770	1.43200
H	7.62540	-1.12490	-0.71920
H	6.71850	1.19270	-0.19750
H	-4.14650	1.72100	1.26540
H	-4.41090	3.35690	0.57910
H	-4.52790	1.89800	-0.44360
H	-3.82810	-0.11290	-2.09400
H	-3.33680	-1.20080	2.02960
H	-6.10220	-1.13800	-2.07980
H	-5.58940	-2.21190	2.03510

ProD2 GM

C	0.38290	2.25140	0.06500
C	-0.48750	1.15370	-0.04290
C	0.02900	-0.15060	-0.28430
C	1.74510	2.05820	-0.08440
C	2.23750	0.76000	-0.34160
C	1.40550	-0.35210	-0.42540
C	-1.92780	1.13060	0.07390
C	-2.43820	-0.13950	-0.07880
S	-1.21250	-1.28760	-0.36050
O	3.59040	0.57380	-0.63530
O	-7.80810	-1.76560	-0.00920
C	4.49290	0.61280	0.40120
C	5.87980	0.32140	-0.03720

C	6.37800	-0.91300	-0.19100
C	5.68220	-2.18990	-0.00920
O	4.36910	-2.13090	0.34740
O	4.10780	0.92280	1.52260
O	6.16470	-3.31840	-0.14160
O	-3.32350	2.52240	1.40260
C	-2.69670	2.35670	0.35410
C	-2.66750	3.40150	-0.72230
C	-4.83670	0.25440	-0.56260
C	-3.81940	-0.56320	-0.04290
C	-4.15820	-1.81040	0.50660
C	-6.16320	-0.15650	-0.54470
C	-6.48310	-1.40890	0.00770
C	-5.48130	-2.23730	0.53590
C	6.70580	1.53470	-0.26970
H	-0.02430	3.25260	0.27220
H	2.45320	2.89310	0.00720
H	1.82750	-1.35190	-0.59950
H	-7.89220	-2.63180	0.41260
H	4.02360	-3.03000	0.46770
H	7.43650	-1.05140	-0.48190
H	-3.60540	3.32310	-1.32450
H	-2.62480	4.42060	-0.26850
H	-1.79090	3.25950	-1.39660

H	-4.57540	1.23680	-0.98590
H	-3.36840	-2.45510	0.92290
H	-6.96210	0.47730	-0.95190
H	-5.74000	-3.21270	0.96890
H	6.67220	1.80930	-1.35460
H	7.76960	1.34690	0.01560
H	6.32330	2.39780	0.32860

ProD2 INT

C	0.46180	2.20850	0.03640
C	-0.41750	1.11640	-0.04990
C	0.08590	-0.19510	-0.27890
C	1.81940	2.00050	-0.11110
C	2.30300	0.69220	-0.35110
C	1.46210	-0.41230	-0.42020
C	-1.85560	1.11390	0.07910
C	-2.38170	-0.15100	-0.06930
S	-1.17060	-1.31510	-0.34340
O	3.66030	0.58740	-0.64430
O	-7.79220	-1.63660	-0.01490
C	4.48420	-0.04220	0.29900
C	5.96700	0.15560	-0.08210
C	6.50260	-1.06810	-0.27060
C	5.44010	-2.09210	-0.06530

O	4.23420	-1.44990	0.25390
O	4.12450	0.31410	1.59090
O	5.40440	-3.30830	-0.11840
O	-3.19490	2.54820	1.42500
C	-2.59930	2.35520	0.36310
C	-2.57440	3.38630	-0.72690
C	-4.76650	0.30310	-0.55520
C	-3.77160	-0.54520	-0.04090
C	-4.14400	-1.78820	0.49540
C	-6.10360	-0.07100	-0.54150
C	-6.45730	-1.31900	-0.00050
C	-5.47840	-2.17920	0.51980
C	6.54410	1.49490	-0.19550
H	0.06450	3.21590	0.22690
H	2.53340	2.83290	-0.05610
H	1.87780	-1.42120	-0.56350
H	-7.89850	-2.50060	0.40610
H	7.52270	-1.35190	-0.52510
H	-3.49670	3.27960	-1.34840
H	-2.55870	4.41300	-0.28880
H	-1.68230	3.24930	-1.38170
H	-4.47970	1.28170	-0.97020
H	-3.37190	-2.45710	0.90650

ProD2 TS

C	0.22300	2.50800	0.19780
C	-0.56090	1.35180	0.04020
C	0.05680	0.08800	-0.18920
C	1.60050	2.41840	0.11940
C	2.18340	1.15650	-0.12590
C	1.45060	-0.01230	-0.27600
C	-1.99610	1.22630	0.10020
C	-2.40390	-0.08080	-0.06590
S	-1.09090	-1.12970	-0.31250
O	3.58050	1.16810	-0.34420
O	-7.61050	-2.17600	-0.08690
C	4.37190	0.30000	0.29750
C	5.78720	0.29410	-0.06030
C	6.45960	-0.86130	-0.22890
C	5.81980	-2.23670	-0.12090
O	4.58230	-2.25930	0.19360
O	3.75370	-0.33820	1.25770
O	6.52730	-3.23410	-0.35470
O	-3.42210	2.61210	1.40890
C	-2.86280	2.39740	0.33100
C	-2.99980	3.32450	-0.83780
C	-4.83090	0.12150	-0.55290
C	-3.74470	-0.61860	-0.05790
C	-3.97150	-1.91160	0.44330

C	-6.11410	-0.40870	-0.55780
C	-6.32130	-1.70470	-0.05450
C	-5.24930	-2.45790	0.44800
C	6.38460	1.63610	-0.27560
H	-0.26320	3.47610	0.39300
H	2.24120	3.30430	0.23340
H	1.95270	-0.98250	-0.43550
H	-7.61670	-3.06450	0.29960
H	4.26290	-1.14630	1.58060
H	7.52970	-0.85840	-0.49970
H	-3.33040	2.75830	-1.74240
H	-3.74240	4.12890	-0.61570
H	-2.00900	3.79280	-1.05870
H	-4.66390	1.13930	-0.94050
H	-3.12850	-2.49820	0.84410
H	-6.96760	0.16680	-0.94330
H	-5.41900	-3.46870	0.84540
H	5.81110	2.19680	-1.05630
H	7.44570	1.53880	-0.61380
H	6.36910	2.23120	0.67130

ProD3 GM

C	0.00920	2.33060	0.16300
C	-0.82750	1.21060	0.02700
C	-0.26620	-0.07500	-0.21420

C	1.37800	2.18130	0.03130
C	1.91330	0.90400	-0.24450
C	1.11760	-0.23200	-0.34680
C	-2.26840	1.14540	0.11870
C	-2.73710	-0.13980	-0.04050
S	-1.47080	-1.24930	-0.30270
O	3.27180	0.79530	-0.54210
O	-8.05160	-1.93520	-0.14960
C	4.15860	0.60440	0.49300
C	5.54850	0.46590	-0.00190
C	6.15890	-0.72280	-0.17740
C	5.52070	-2.02640	0.08160
O	4.15830	-2.02710	0.12310
O	3.75020	0.61780	1.64800
O	6.07260	-3.11760	0.24610
O	-3.72590	2.52670	1.39700
C	-3.08140	2.35170	0.36120
C	-3.07170	3.36230	-0.74810
C	-5.13140	0.18370	-0.59310
C	-4.10630	-0.60310	-0.04120
C	-4.42410	-1.86050	0.49740
C	-6.44420	-0.26850	-0.62170
C	-6.74110	-1.53350	-0.08520
C	-5.73290	-2.33000	0.47910

C	6.23920	1.74690	-0.28980
C	7.56860	-0.80300	-0.64420
H	-0.42950	3.31450	0.38200
H	2.05710	3.03730	0.14090
H	1.57420	-1.21510	-0.52950
H	-8.12000	-2.80410	0.26960
H	3.83950	-2.92280	0.31870
H	-3.84470	3.07780	-1.50340
H	-3.31560	4.37730	-0.35300
H	-2.07420	3.38530	-1.24840
H	-4.88850	1.17550	-1.00550
H	-3.62930	-2.47880	0.94300
H	-7.24900	0.34380	-1.05090
H	-5.97620	-3.31270	0.90530
H	6.43670	1.82670	-1.38910
H	7.22170	1.77840	0.24550
H	5.62540	2.62440	0.02250
H	7.92780	-1.86100	-0.66270
H	7.65010	-0.37530	-1.67390
H	8.24090	-0.21480	0.02960

ProD3 INT

C	0.12640	2.21340	0.11930
C	-0.74380	1.11730	0.00230
C	-0.22280	-0.18700	-0.22300

C	1.48650	2.02410	-0.03410
C	1.98490	0.72970	-0.30900
C	1.15650	-0.38650	-0.36830
C	-2.18520	1.10360	0.10790
C	-2.70170	-0.16450	-0.04230
S	-1.47180	-1.31700	-0.30190
O	3.33850	0.62780	-0.63200
O	-8.09450	-1.74240	-0.12180
C	4.21260	0.17480	0.35710
C	5.67700	0.38020	-0.07730
C	6.24230	-0.84320	-0.22030
C	5.21810	-1.88040	0.11040
O	4.02730	-1.24770	0.47200
O	3.83560	0.73520	1.56620
O	5.21040	-3.09810	0.16220
O	-3.53380	2.58090	1.40460
C	-2.93700	2.34900	0.35160
C	-2.92110	3.33600	-0.77860
C	-5.08400	0.24730	-0.59330
C	-4.08830	-0.57850	-0.04300
C	-4.45980	-1.82100	0.49640
C	-6.41600	-0.14770	-0.61160
C	-6.76720	-1.39580	-0.06820
C	-5.78870	-2.23220	0.48940

C	6.21880	1.72000	-0.30180
C	7.58990	-1.24310	-0.63190
H	-0.27700	3.21450	0.32560
H	2.19400	2.85940	0.05780
H	1.57630	-1.39210	-0.51880
H	-8.19820	-2.61380	0.28620
H	-3.66470	3.02670	-1.55210
H	-3.19820	4.35220	-0.41220
H	-1.90910	3.37350	-1.24640
H	-4.80400	1.22510	-1.01550
H	-3.69090	-2.47640	0.93390
H	-7.19780	0.49270	-1.04150
H	-6.07090	-3.20350	0.91690
H	6.34160	1.88610	-1.40170
H	7.21920	1.83720	0.18270
H	5.53210	2.51090	0.08940
H	7.69490	-2.35460	-0.54800
H	7.77440	-0.94760	-1.69480
H	8.36690	-0.74870	0.00110
H	4.00770	0.09000	2.26910

ProD3 TS

C	0.16010	1.77200	-0.47700
C	-0.83670	0.79950	-0.27530
C	-0.43830	-0.55470	-0.22370

C	1.49750	1.40870	-0.58010
C	1.84650	0.05570	-0.49150
C	0.88970	-0.93960	-0.32210
C	-2.27830	0.98270	-0.16120
C	-2.98780	-0.18780	-0.07660
S	-1.86320	-1.65040	-0.06410
O	3.17290	-0.45790	-0.60820
O	-8.51730	-1.34190	0.35040
C	4.32670	0.21730	-0.46330
C	5.51140	-0.65750	-0.76370
C	6.47420	-0.75980	0.16110
C	6.22730	0.00480	1.44070
O	5.01240	0.62290	1.41460
O	4.33420	1.54780	-0.53680
O	7.04100	0.05870	2.36190
O	-3.82400	2.73120	-0.79600
C	-2.88760	2.34830	-0.08100
C	-2.34860	3.22260	1.04620
C	-5.39390	0.29040	-0.62410
C	-4.41710	-0.46820	0.05920
C	-4.85300	-1.54840	0.85250
C	-6.74000	-0.01990	-0.50610
C	-7.16030	-1.09340	0.28760
C	-6.20270	-1.85410	0.96830

C	5.48680	-1.31460	-2.12210
C	7.76350	-1.52520	0.05170
H	-0.10890	2.81570	-0.57630
H	2.27030	2.14150	-0.73480
H	1.20030	-1.97400	-0.27910
H	-8.69870	-2.12640	0.93070
H	4.83380	1.61690	0.51390
H	-2.97740	3.02700	1.92680
H	-1.32030	2.98470	1.31680
H	-2.45570	4.27890	0.78640
H	-5.07580	1.12900	-1.22560
H	-4.12620	-2.13860	1.39810
H	-7.49190	0.55500	-1.02980
H	-6.51140	-2.68500	1.59440
H	6.34650	-1.97580	-2.24850
H	5.50530	-0.55810	-2.91760
H	4.56440	-1.89540	-2.23180
H	8.34680	-1.21670	-0.82270
H	8.34120	-1.32720	0.95850
H	7.57960	-2.60410	-0.01830

ProD4 GM

C	-0.42140	2.23870	0.17070
C	-1.28760	1.14400	0.01840
C	-0.76740	-0.15150	-0.25160

C	0.94250	2.05480	0.03940
C	1.44360	0.76430	-0.23420
C	0.61370	-0.34400	-0.37210
C	-2.73040	1.12650	0.11120
C	-3.25020	-0.13300	-0.08020
S	-2.01740	-1.27790	-0.37610
O	2.80250	0.60960	-0.50180
O	-8.63640	-1.73270	-0.13320
C	3.68170	0.51010	0.55430
C	5.05980	0.28390	0.05830
C	5.60140	-0.93870	-0.08850
C	4.89310	-2.19610	0.20480
O	3.53730	-2.09480	0.29780
O	3.26720	0.62790	1.70010
O	5.36550	-3.32620	0.35180
O	-4.01230	2.59720	1.47500
C	-3.46380	2.37390	0.39500
C	-3.46270	3.37380	-0.72340
C	-5.63770	0.26260	-0.63140
C	-4.63570	-0.55320	-0.07770
C	-4.99780	-1.79570	0.46950
C	-6.96690	-0.14170	-0.64580
C	-7.30870	-1.38740	-0.09070
C	-6.32400	-2.21710	0.46650

C	5.81450	1.49990	-0.34740
C	6.96940	-1.11890	-0.64830
C	7.29990	1.37790	-0.06790
C	7.92350	0.03720	-0.40550
H	-0.83400	3.23080	0.40180
H	1.64370	2.89300	0.14130
H	1.04840	-1.33110	-0.57960
H	-8.73830	-2.59990	0.28270
H	3.16120	-2.97470	0.45250
H	-4.15230	3.02460	-1.52910
H	-3.80110	4.37140	-0.35660
H	-2.43630	3.46710	-1.15310
H	-5.36400	1.24000	-1.05820
H	-4.22660	-2.44470	0.91330
H	-7.75190	0.49250	-1.08030
H	-6.60060	-3.18920	0.89740
H	5.63930	1.66110	-1.44600
H	6.84670	-1.27100	-1.75590
H	5.41150	2.39870	0.18700
H	7.41630	-2.06740	-0.24010
H	8.61820	-0.24510	0.43140
H	8.55960	0.14970	-1.32460
H	7.47460	1.59570	1.01820
H	7.84150	2.17440	-0.64300

ProD4 INT

C	-0.36880	2.16720	0.19460
C	-1.25510	1.08940	0.03380
C	-0.75300	-0.21730	-0.21600
C	0.99140	1.96670	0.05390
C	1.47410	0.67450	-0.25890
C	0.62540	-0.42520	-0.35640
C	-2.69790	1.09690	0.11950
C	-3.23440	-0.15930	-0.06320
S	-2.01980	-1.32710	-0.33350
O	2.82120	0.56310	-0.60570
O	-8.66500	-1.61850	-0.16950
C	3.71800	0.10590	0.36360
C	5.17930	0.21790	-0.08520
C	5.69140	-1.03680	-0.15580
C	4.63650	-2.01550	0.21380
O	3.46550	-1.30760	0.51090
O	3.43570	0.69340	1.58570
O	4.57210	-3.22500	0.34710
O	-4.04320	2.57820	1.41940
C	-3.43500	2.34970	0.37240
C	-3.39410	3.34640	-0.74830
C	-5.60740	0.30070	-0.61830
C	-4.62990	-0.54820	-0.07040

C	-5.03450	-1.78360	0.46270
C	-6.94830	-0.06200	-0.64490
C	-7.33020	-1.30450	-0.10950
C	-6.37300	-2.16500	0.44850
C	5.98240	1.41230	-0.38590
C	7.07430	-1.36110	-0.52700
C	7.43590	1.15550	-0.00000
C	8.01140	-0.15370	-0.51680
H	-0.76590	3.16440	0.42830
H	1.70870	2.79020	0.17960
H	1.03060	-1.42890	-0.54490
H	-8.79180	-2.48930	0.23250
H	-4.04450	2.99300	-1.58500
H	-3.76610	4.33780	-0.39750
H	-2.34880	3.45100	-1.12420
H	-5.30370	1.27220	-1.03660
H	-4.28620	-2.46130	0.90050
H	-7.71080	0.60150	-1.07620
H	-6.68430	-3.13050	0.87100
H	5.90780	1.60600	-1.49100
H	7.06310	-1.79790	-1.56340
H	5.60360	2.32930	0.13450
H	7.44930	-2.15830	0.17020
H	8.89850	-0.41990	0.11790

H	8.40840	0.01720	-1.55210
H	7.52410	1.16820	1.11660
H	8.05420	2.00980	-0.38350
H	3.13050	0.00490	2.20020

ProD4 TS

C	-0.32160	1.99410	-0.04810
C	-1.25140	0.94330	-0.14160
C	-0.78210	-0.38240	-0.32270
C	1.03770	1.72050	-0.16200
C	1.45020	0.39070	-0.35730
C	0.56870	-0.69180	-0.43170
C	-2.70470	1.00820	-0.05820
C	-3.31500	-0.20400	-0.14150
S	-2.12700	-1.49850	-0.35710
O	2.79070	0.03160	-0.59050
O	-8.69170	-1.73600	0.10710
C	3.82830	0.60920	0.10860
C	5.14450	0.04680	-0.38230
C	5.79400	-0.67110	0.55710
C	5.08730	-0.71360	1.87370
O	3.82940	-0.09960	1.65880
O	3.68020	1.77530	0.67810
O	5.38890	-1.11700	2.95550
O	-4.05470	2.57520	1.09550

C	-3.42210	2.30840	0.09820
C	-3.33340	3.23920	-1.07370
C	-5.25890	-1.48330	-1.01010
C	-4.71370	-0.58040	-0.07280
C	-5.53010	-0.05340	0.94710
C	-6.59520	-1.85780	-0.93630
C	-7.38540	-1.31920	0.09570
C	-6.87170	-0.41900	1.04110
C	5.62690	0.27220	-1.76860
C	7.11180	-1.32880	0.34280
C	7.11160	-0.11440	-1.89780
C	7.43090	-1.42390	-1.16030
H	-0.66140	3.01580	0.12070
H	1.78360	2.51810	-0.08690
H	0.93600	-1.70770	-0.56430
H	-9.20770	-1.33320	0.84980
H	3.68520	1.17570	1.94080
H	-4.10510	2.98490	-1.81770
H	-3.51430	4.28170	-0.77400
H	-2.36870	3.19180	-1.59440
H	-4.63240	-1.88750	-1.80830
H	-5.10550	0.65670	1.66930
H	-7.03890	-2.55020	-1.64880
H	-7.49760	-0.01090	1.82900

H	5.00330	-0.32910	-2.46990
H	7.12340	-2.33950	0.80400
H	5.47780	1.33120	-2.07090
H	7.90230	-0.75180	0.87200
H	8.49730	-1.68430	-1.29860
H	6.85090	-2.25480	-1.60910
H	7.74210	0.70280	-1.49410
H	7.37890	-0.20870	-2.96730

ProD5 GM

C	-0.14380	2.40600	0.22450
C	-0.94810	1.26690	0.05400
C	-0.34790	0.00260	-0.20620
C	1.22990	2.30210	0.09500
C	1.80440	1.04620	-0.20070
C	1.04150	-0.11080	-0.32760
C	-2.38930	1.16310	0.11260
C	-2.82160	-0.13030	-0.08040
S	-1.52090	-1.20000	-0.34540
O	3.16060	0.98940	-0.52100
O	-8.10240	-2.03920	-0.11340
C	4.07720	0.73720	0.47490
C	5.43690	0.58970	-0.07810
C	6.08400	-0.57350	-0.22930
C	5.50880	-1.87740	0.16430

O	4.14850	-1.94260	0.18320
O	3.70990	0.71270	1.64320
O	6.10990	-2.91080	0.46700
O	-3.87010	2.50920	1.40370
C	-3.23750	2.34530	0.35880
C	-3.27350	3.35130	-0.75400
C	-5.22560	0.12060	-0.64210
C	-4.17740	-0.63460	-0.08980
C	-4.46260	-1.89700	0.45640
C	-6.52950	-0.35850	-0.64770
C	-6.79600	-1.61970	-0.08730
C	-5.76210	-2.39290	0.46220
C	7.45920	-0.66880	-0.80760
C	8.36970	0.46020	-0.38810
H	-0.61210	3.37120	0.46470
H	1.88030	3.17980	0.21270
H	1.52660	-1.07710	-0.52730
H	-8.14960	-2.90150	0.32180
H	3.87500	-2.81960	0.49720
H	-3.89190	2.95320	-1.59450
H	-3.72180	4.30980	-0.39930
H	-2.24190	3.54270	-1.13440
H	-5.01000	1.11080	-1.07170
H	-3.64970	-2.49810	0.89220

H	-7.35250	0.23050	-1.07450
H	-5.97860	-3.37770	0.89790
H	7.37020	-0.68520	-1.92810
H	7.91910	-1.64880	-0.50110
H	8.42320	0.53730	0.72360
H	9.39900	0.27240	-0.77750
H	5.90290	1.54750	-0.36640
H	8.01500	1.43750	-0.79350

ProD5 INT

C	-0.01340	2.32800	0.08330
C	-0.84500	1.19960	-0.01380
C	-0.28500	-0.08680	-0.25470
C	1.35060	2.18440	-0.08520
C	1.89110	0.90180	-0.33680
C	1.09810	-0.23900	-0.41110
C	-2.28400	1.13460	0.09400
C	-2.75580	-0.15040	-0.05720
S	-1.49180	-1.26090	-0.32300
O	3.24980	0.83540	-0.63520
O	-8.08550	-1.91020	-0.07760
C	4.10230	0.38460	0.38340
C	5.56490	0.55290	-0.03000
C	6.10690	-0.67480	-0.16810
C	5.05300	-1.69120	0.15760

O	3.87200	-1.03370	0.50690
O	3.80000	0.95530	1.60100
O	5.02500	-2.90880	0.17790
O	-3.65520	2.58910	1.39110
C	-3.08370	2.35260	0.32580
C	-3.12890	3.30110	-0.83580
C	-5.14920	0.16030	-0.62080
C	-4.12650	-0.61150	-0.04370
C	-4.44950	-1.85150	0.53130
C	-6.46410	-0.28570	-0.63000
C	-6.76850	-1.52670	-0.04480
C	-5.76170	-2.31310	0.53530
C	7.45780	-1.09080	-0.57930
C	8.50290	-0.02240	-0.35890
H	-0.44700	3.31580	0.29750
H	2.02590	3.05010	-0.03380
H	1.55540	-1.22630	-0.57810
H	-8.16340	-2.75330	0.38900
H	-3.63750	2.81170	-1.70040
H	-3.67960	4.23290	-0.56740
H	-2.08920	3.56480	-1.14740
H	-4.90680	1.13520	-1.07100
H	-3.65720	-2.46410	0.98900
H	-7.26810	0.31380	-1.07720

H	-6.00890	-3.27990	0.99400
H	7.42630	-1.36450	-1.67100
H	7.73820	-2.02430	-0.01830
H	8.59310	0.22600	0.72490
H	9.49370	-0.38400	-0.72300
H	5.98600	1.54480	-0.17480
H	8.24210	0.90960	-0.91480
H	2.94310	0.61200	1.89580

ProD5 TS

C	-0.11860	2.67620	-0.11670
C	-0.87240	1.48710	-0.08140
C	-0.17790	0.25760	-0.07850
C	1.26920	2.61510	-0.14120
C	1.90170	1.37380	-0.13200
C	1.20750	0.17310	-0.10040
C	-2.32990	1.32920	-0.03500
C	-2.73130	0.02090	-0.03290
S	-1.32340	-1.14280	-0.05450
O	3.33790	1.35760	-0.24370
O	-7.85230	-2.39300	-0.24260
C	4.07240	0.56240	0.54800
C	5.47930	0.43520	0.09270
C	5.99900	-0.77170	-0.15020
C	5.06250	-1.96050	0.02810

O	3.82650	-1.56360	0.38820
O	3.60560	0.26680	1.75070
O	5.45400	-3.11750	-0.13640
O	-2.77000	3.67070	-0.07210
C	-3.22610	2.52020	0.05500
C	-4.70220	2.31840	0.35610
C	-4.83540	-0.59020	-1.23820
C	-4.06920	-0.59470	-0.05820
C	-4.58020	-1.24430	1.07380
C	-6.08590	-1.19060	-1.27300
C	-6.60040	-1.82040	-0.13150
C	-5.83680	-1.84490	1.03990
C	7.40030	-1.08710	-0.58620
C	8.34740	0.12140	-0.67390
H	-0.64760	3.61530	-0.12940
H	1.86810	3.51480	-0.17620
H	1.74610	-0.76730	-0.10040
H	-8.11580	-2.82140	0.61290
H	3.67690	-0.83160	1.62250
H	-4.84460	1.67150	1.22630
H	-5.13600	3.30330	0.54020
H	-5.21470	1.84480	-0.48580
H	-4.43530	-0.11810	-2.12770
H	-3.99190	-1.27180	1.98340

H	-6.68400	-1.19650	-2.17420
H	-6.21930	-2.33570	1.92880
H	7.33720	-1.59670	-1.55730
H	7.79390	-1.83990	0.10940
H	8.43810	0.61880	0.29830
H	9.34550	-0.20280	-0.98490
H	6.02120	1.36370	-0.04490
H	7.98580	0.85130	-1.40730

ProD6 GM

C	-0.54820	2.48550	0.25150
C	-1.31510	1.32130	0.08250
C	-0.67960	0.06930	-0.15440
C	0.82890	2.41610	0.14460
C	1.43810	1.17390	-0.13980
C	0.71310	-0.00770	-0.25860
C	-2.75200	1.18120	0.12580
C	-3.14430	-0.12530	-0.06030
S	-1.81690	-1.16550	-0.29570
O	2.79320	1.17480	-0.46320
O	-8.35870	-2.17810	-0.21500
C	3.71260	0.77390	0.47940
C	5.04950	0.62540	-0.12380
C	5.67740	-0.55050	-0.26290
C	5.09170	-1.82180	0.21630

O	3.73310	-1.89330	0.12500
O	3.36640	0.63730	1.64620
O	5.66450	-2.80990	0.67790
O	-4.27020	2.49550	1.40370
C	-3.63760	2.33850	0.35790
C	-3.71220	3.32700	-0.76840
C	-5.53970	0.07220	-0.65500
C	-4.48540	-0.66040	-0.08580
C	-4.74510	-1.92780	0.45950
C	-6.82860	-0.44260	-0.69210
C	-7.06900	-1.71520	-0.14590
C	-6.02960	-2.45890	0.43400
C	7.01440	-0.67170	-0.91520
C	8.01130	0.35850	-0.40440
C	9.38230	-0.24090	-0.19870
H	-1.04790	3.44010	0.46990
H	1.45890	3.30720	0.26880
H	1.22650	-0.96430	-0.43480
H	-8.38740	-3.04310	0.21610
H	3.42230	-2.71770	0.53130
H	-4.26860	2.87660	-1.62560
H	-4.23980	4.25460	-0.44150
H	-2.68380	3.58760	-1.11440
H	-5.33940	1.07120	-1.07160

H	-3.92390	-2.50080	0.91760
H	-7.65700	0.12750	-1.13310
H	-6.22950	-3.44740	0.86880
H	6.87540	-0.55200	-2.02370
H	7.41190	-1.70750	-0.74760
H	5.49220	1.57300	-0.47260
H	9.31190	-1.16380	0.42580
H	9.86220	-0.50610	-1.17340
H	10.03610	0.49110	0.32790
H	7.64550	0.78640	0.56570
H	8.08260	1.20570	-1.13500

ProD6 INT

C	-0.43010	2.35570	0.13270
C	-1.24390	1.21490	0.03920
C	-0.66020	-0.07040	-0.13790
C	0.93820	2.23160	-0.00770
C	1.50180	0.95300	-0.23390
C	0.72850	-0.20400	-0.27180
C	-2.68510	1.14010	0.10430
C	-3.14000	-0.15530	-0.00660
S	-1.85280	-1.26010	-0.19270
O	2.85170	0.93040	-0.57540
O	-8.43530	-2.02900	-0.18830
C	3.76960	0.46800	0.37380

C	5.20880	0.65810	-0.11030
C	5.77090	-0.56010	-0.24830
C	4.74640	-1.59450	0.10950
O	3.56320	-0.95670	0.47950
O	3.54000	0.99800	1.62780
O	4.74730	-2.81190	0.14250
O	-4.10390	2.64330	1.29280
C	-3.50000	2.36100	0.25680
C	-3.52850	3.25540	-0.94740
C	-5.52590	0.10600	-0.63940
C	-4.50530	-0.63620	-0.01980
C	-4.82900	-1.86940	0.57020
C	-6.83180	-0.36580	-0.68730
C	-7.13260	-1.60640	-0.09810
C	-6.13180	-2.35700	0.53690
C	7.12990	-0.95530	-0.64480
C	8.18140	0.07540	-0.26780
C	9.54140	-0.57370	-0.19190
H	-0.88590	3.33970	0.30950
H	1.59740	3.11070	0.03510
H	1.19550	-1.19170	-0.40720
H	-8.51080	-2.88290	0.26000
H	-4.04390	2.73440	-1.78960
H	-4.06890	4.20490	-0.72120

H	-2.48300	3.49020	-1.26060
H	-5.28410	1.07920	-1.09410
H	-4.04510	-2.45950	1.06960
H	-7.62990	0.20980	-1.17650
H	-6.37920	-3.32090	1.00260
H	7.15800	-1.13340	-1.75450
H	7.36140	-1.94230	-0.15730

ProD6 TS

C	-0.65040	2.79760	-0.08750
C	-1.32750	1.56280	-0.09860
C	-0.55640	0.38070	-0.14400
C	0.73850	2.82540	-0.11650
C	1.44810	1.62740	-0.16150
C	0.83130	0.38490	-0.17840
C	-2.77270	1.31090	-0.08610
C	-3.08870	-0.02030	-0.08910
S	-1.60940	-1.09050	-0.14140
O	2.88240	1.70790	-0.26950
O	-8.01910	-2.80410	0.11090
C	3.66680	0.91950	0.47890
C	5.07950	0.91000	0.02480
C	5.68550	-0.24200	-0.28180
C	4.83440	-1.50200	-0.17100
O	3.57390	-1.21290	0.19910

O	3.21620	0.52110	1.65770
O	5.30440	-2.62280	-0.38850
O	-3.35880	3.61910	-0.01020
C	-3.74710	2.44190	-0.11690
C	-5.22310	2.14660	-0.32600
C	-4.92120	-1.34430	-1.16230
C	-4.38260	-0.72200	-0.02240
C	-5.07280	-0.82830	1.19340
C	-6.12980	-2.02430	-1.09380
C	-6.82390	-2.11190	0.11970
C	-6.28380	-1.51220	1.26280
C	7.11630	-0.40540	-0.70000
C	7.94870	-1.11750	0.40690
C	9.41530	-1.30940	-0.02780
H	-1.23710	3.70100	-0.04800
H	1.27950	3.76160	-0.11050
H	1.42740	-0.51900	-0.22080
H	-8.42070	-2.81570	1.01830
H	3.36660	-0.55830	1.47370
H	-5.64640	1.62690	0.53810
H	-5.73160	3.10290	-0.46350
H	-5.38030	1.50450	-1.19720
H	-4.38590	-1.28540	-2.10250
H	-4.65220	-0.37840	2.08500

H	-6.55860	-2.50130	-1.96470
H	-6.80320	-1.58580	2.21270
H	7.56440	0.56610	-0.93580
H	7.14270	-1.03540	-1.59730
H	5.55750	1.87950	-0.06560
H	9.46940	-1.91720	-0.93830
H	9.89340	-0.34340	-0.22970
H	9.98720	-1.81740	0.75630
H	7.47570	-2.08580	0.59130
H	7.90310	-0.52500	1.32840

At left side

ProD1 GM

C	5.17740	0.82870	0.13190
C	3.90250	0.24100	0.07380
C	3.78390	-1.16680	-0.09150
C	6.30530	0.03820	0.02780
C	6.16890	-1.36200	-0.15480
C	4.91880	-1.97240	-0.22410
C	2.60570	0.87270	0.18090
C	1.58490	-0.04620	0.11150
S	2.17080	-1.63600	-0.09370
O	7.34220	-2.06790	-0.25880
O	-3.99590	0.17890	-0.23790
O	1.96970	2.81910	1.38500
C	2.45360	2.32810	0.36260

C	2.91740	3.18430	-0.77850
C	-0.45250	1.24480	-0.48280
C	0.15250	0.13980	0.13010
C	-0.65570	-0.85430	0.71260
C	-1.84100	1.33460	-0.58530
C	-2.62170	0.30610	-0.04960
C	-2.03830	-0.77780	0.63130
C	-4.83040	1.25620	-0.13120
C	-6.27210	0.94760	-0.15590
C	-6.93030	-0.20960	-0.09100
C	-6.45340	-1.59600	-0.01310
O	-5.12440	-1.81190	0.14240
O	-7.17730	-2.59540	-0.06820
O	-4.35530	2.38740	-0.04500
H	5.26340	1.91730	0.26070
H	7.31730	0.46250	0.08150
H	4.82220	-3.05550	-0.38080
H	2.02340	3.52620	-1.35540
H	3.43820	4.08980	-0.38420
H	3.60130	2.62230	-1.45720
H	0.18290	2.04390	-0.89390
H	-0.18430	-1.70190	1.23350
H	-2.31130	2.20070	-1.07360
H	-2.68120	-1.55940	1.06110

H	7.12190	-3.00360	-0.36110
H	-6.86740	1.88340	-0.21580
H	-8.04160	-0.18790	-0.10260
H	-4.94230	-2.76500	0.11910

ProD1 INT

C	5.07960	0.87550	0.38470
C	3.84440	0.25730	0.12620
C	3.79140	-1.13070	-0.17820
C	6.23880	0.12770	0.34600
C	6.17360	-1.25340	0.02900
C	4.96360	-1.89030	-0.23820
C	2.52320	0.84110	0.16060
C	1.54590	-0.09030	-0.10500
S	2.20370	-1.63410	-0.41130
O	7.37440	-1.91820	0.02260
O	-3.96390	0.42960	-0.94120
O	1.78770	2.66490	1.50260
C	2.33100	2.27110	0.46880
C	2.85370	3.22300	-0.56620
C	-0.42320	1.23720	-0.79960
C	0.11380	0.08920	-0.19510
C	-0.75140	-0.91000	0.28460
C	-1.79550	1.36440	-0.98260
C	-2.63460	0.32680	-0.54990

C	-2.12880	-0.80130	0.10890
C	-4.95360	0.45200	0.04660
C	-6.32230	0.70440	-0.59760
C	-7.07440	-0.39580	-0.41400
C	-6.27560	-1.40580	0.34090
O	-5.01570	-0.86590	0.62340
O	-6.47940	-2.53630	0.74370
O	-4.64170	1.32840	1.06340
H	5.11150	1.94750	0.63060
H	7.21660	0.57460	0.56880
H	4.92670	-2.95990	-0.48380
H	2.05700	3.38340	-1.33300
H	3.11030	4.20540	-0.10200
H	3.75730	2.80010	-1.06650
H	0.24940	2.04000	-1.13720
H	-0.33750	-1.79270	0.79790
H	-2.23400	2.24400	-1.47670
H	-2.81270	-1.59070	0.46170
H	7.20220	-2.84230	-0.20380
H	-6.53160	1.64550	-1.10150
H	-8.09680	-0.59670	-0.73080
H	-3.96640	0.91560	1.62370

ProD1 TS

C	-4.55110	1.47770	0.12580
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C	-3.51430	0.52780	0.01300
C	-3.88640	-0.82810	-0.07070
C	-5.87200	1.06970	0.18670
C	-6.21190	-0.29430	0.12680
C	-5.20820	-1.25200	-0.01150
C	-2.07330	0.74440	-0.09180
C	-1.34790	-0.40630	-0.28870
S	-2.44330	-1.88900	-0.30040
O	-7.55860	-0.60200	0.19790
O	4.18080	-1.53500	-0.61730
O	-0.51860	2.50850	-0.62330
C	-1.45550	2.08960	0.07580
C	-1.98130	2.93570	1.23580
C	0.63800	-1.85760	0.17090
C	0.08840	-0.66950	-0.40790
C	0.94710	0.16110	-1.11800
C	1.97060	-2.18510	0.06940
C	2.87500	-1.36160	-0.64750
C	2.34310	-0.11880	-1.19020
C	4.74980	-0.73970	0.99480
C	6.15220	-0.53450	0.55220
C	6.38260	0.63650	-0.03720
C	5.15100	1.45030	-0.18100
O	4.10950	0.77860	0.50220

O	4.98320	2.49450	-0.78340
O	4.21710	-1.24500	1.94570
H	-4.32340	2.53440	0.15000
H	-6.67720	1.78650	0.27210
H	-5.45250	-2.30600	-0.08080
H	-1.11540	3.28310	1.80950
H	-2.48550	3.83010	0.84910
H	-2.65890	2.38350	1.88580
H	-0.02130	-2.50370	0.74040
H	0.55030	1.05250	-1.58070
H	2.36220	-3.07400	0.54390
H	2.90530	0.33710	-2.00740
H	-7.69400	-1.58310	0.13730
H	6.87100	-1.31820	0.73940
H	7.32160	0.98430	-0.43730
H	3.02930	0.54570	-0.22780

ProD2 GM

C	5.46540	0.88780	0.12530
C	4.20930	0.25880	0.08510
C	4.13140	-1.15560	-0.04650
C	6.61700	0.13230	0.03030
C	6.52430	-1.27550	-0.11040
C	5.29350	-1.92620	-0.15080
C	2.89430	0.85580	0.16180

C	1.89920	-0.09170	0.08510
S	2.53060	-1.67120	-0.05800
O	7.72080	-1.94270	-0.20390
O	-3.68200	0.16510	-0.46540
O	2.19710	2.82560	1.30150
C	2.70890	2.31270	0.30410
C	3.18480	3.14420	-0.85090
C	-0.12730	1.17130	-0.59490
C	0.46320	0.07240	0.04810
C	-0.36310	-0.91370	0.61920
C	-1.51080	1.25420	-0.74250
C	-2.30740	0.22750	-0.22610
C	-1.74480	-0.84190	0.48500
C	-4.47850	1.17660	0.01960
C	-5.92360	1.00200	-0.19160
C	-6.63350	-0.13310	-0.13030
C	-6.03530	-1.47870	-0.00240
O	-5.05050	-1.58350	0.93020
O	-6.34050	-2.50810	-0.60940
O	-3.94120	2.13640	0.56830
C	-8.11860	-0.12150	-0.16970
H	5.52360	1.98060	0.23420
H	7.61310	0.59320	0.06370
H	5.23760	-3.01630	-0.26180

H	2.31480	3.36970	-1.51500
H	3.60650	4.10920	-0.47950
H	3.95860	2.60320	-1.44420
H	0.50730	1.98470	-0.97920
H	0.07910	-1.74490	1.19100
H	-1.97620	2.11960	-1.23440
H	-2.41010	-1.60000	0.92060
H	7.53520	-2.88890	-0.27650
H	-6.43410	1.97020	-0.35290
H	-4.66580	-2.47280	0.89640
H	-8.50240	-1.00720	-0.73340
H	-8.49980	-0.16950	0.88190
H	-8.49740	0.81910	-0.63820

ProD2 INT

C	5.43110	0.84010	0.35480
C	4.18470	0.23850	0.10850
C	4.10670	-1.16070	-0.13370
C	6.57820	0.07200	0.34780
C	6.48750	-1.32080	0.09450
C	5.26470	-1.94490	-0.14400
C	2.87690	0.85180	0.07720
C	1.88190	-0.06760	-0.16630
S	2.51120	-1.64000	-0.37530
O	7.67820	-2.00430	0.10230

O	-3.66310	0.72240	-0.67150
O	2.22860	2.76990	1.33120
C	2.70360	2.30090	0.29540
C	3.16440	3.17210	-0.83530
C	-0.07390	1.34080	-0.76540
C	0.45440	0.14250	-0.26070
C	-0.42660	-0.87350	0.14890
C	-1.44880	1.53170	-0.85710
C	-2.30960	0.50210	-0.44650
C	-1.80440	-0.70330	0.05800
C	-4.57100	0.41730	0.35190
C	-5.97340	0.91360	-0.00910
C	-6.78210	-0.15940	-0.13240
C	-5.97430	-1.39240	0.13820
O	-4.66030	-1.01890	0.43140
O	-6.21540	-2.58600	0.15900
O	-4.12940	0.86550	1.57850
C	-8.20790	-0.23250	-0.46070
H	5.48390	1.91960	0.55930
H	7.56660	0.51230	0.53770
H	5.20840	-3.02490	-0.33290
H	2.62190	2.89780	-1.77150
H	2.97830	4.24770	-0.60440
H	4.25760	3.01590	-1.00280

H	0.60760	2.14450	-1.08420
H	-0.02200	-1.81710	0.54810
H	-1.86590	2.46800	-1.25280
H	-2.48860	-1.50850	0.36780
H	7.49100	-2.93770	-0.06820
H	-6.17350	1.97620	-0.12250
H	-3.36420	0.33150	1.84180
H	-8.35800	-0.84990	-1.38210
H	-8.77000	-0.71890	0.37620
H	-8.63300	0.78520	-0.63580

ProD2 TS

C	-4.82950	1.53230	0.12850
C	-3.81010	0.56490	0.00760
C	-4.20770	-0.78180	-0.10360
C	-6.15870	1.14910	0.17110
C	-6.52430	-0.20660	0.08390
C	-5.53790	-1.18080	-0.06310
C	-2.36410	0.75510	-0.08020
C	-1.65900	-0.40610	-0.29110
S	-2.78360	-1.86640	-0.33980
O	-7.87730	-0.48950	0.13820
O	3.84770	-1.64260	-0.58640
O	-0.76780	2.49640	-0.56170
C	-1.72180	2.08410	0.11820

C	-2.24520	2.92130	1.28610
C	0.29160	-1.90720	0.16000
C	-0.22760	-0.69660	-0.40100
C	0.65570	0.12890	-1.08650
C	1.61750	-2.26040	0.06560
C	2.54860	-1.44260	-0.62580
C	2.04610	-0.17830	-1.14970
C	4.41790	-0.91010	1.07340
C	5.83010	-0.72370	0.67920
C	6.10550	0.43960	0.08710
C	4.87880	1.27010	-0.09440
O	3.81360	0.65060	0.57690
O	4.76570	2.30020	-0.73770
O	3.83310	-1.41670	1.98950
C	7.40510	0.95300	-0.44500
H	-4.58190	2.58390	0.17380
H	-6.95050	1.87990	0.26260
H	-5.80190	-2.22850	-0.15350
H	-1.37930	3.24700	1.87230
H	-2.73230	3.82870	0.90810
H	-2.93710	2.37020	1.92170
H	-0.38720	-2.55070	0.70930
H	0.28210	1.03640	-1.53690
H	1.98480	-3.16700	0.52590

H	2.62710	0.28390	-1.95010
H	-8.03050	-1.46660	0.05790
H	6.53190	-1.51720	0.89200
H	2.73670	0.45320	-0.16650
H	7.26960	1.29340	-1.47760
H	7.73900	1.81930	0.13950
H	8.18160	0.18540	-0.41540
H	3.76926	-0.49917	0.38389
H	3.95913	-0.14105	1.05658
H	3.35670	0.45320	-0.16650

ProD3 GM

C	5.68230	0.94540	0.14260
C	4.43520	0.29860	0.10340
C	4.37730	-1.11480	-0.04630
C	6.84520	0.20950	0.03020
C	6.77070	-1.19690	-0.13700
C	5.54910	-1.86420	-0.18360
C	3.11120	0.87340	0.19000
C	2.13330	-0.09070	0.10720
S	2.78700	-1.65780	-0.05100
O	7.97480	-1.84650	-0.25210
O	-3.43950	0.06060	-0.57220
O	2.37130	2.81590	1.34630
C	2.89770	2.32450	0.34580

C	3.35880	3.17330	-0.80220
C	0.09410	1.12710	-0.60530
C	0.69650	0.04020	0.04370
C	-0.11500	-0.98150	0.56600
C	-1.28600	1.17290	-0.78840
C	-2.06970	0.12200	-0.30220
C	-1.49380	-0.94540	0.39810
C	-4.25710	0.92860	0.11550
C	-5.70480	0.73860	-0.11220
C	-6.34660	-0.44340	-0.05020
C	-5.65000	-1.74100	0.05780
O	-4.64820	-1.80210	0.97820
O	-5.86950	-2.76920	-0.58570
O	-3.74050	1.79530	0.81600
C	-6.43760	2.00850	-0.35740
C	-7.82820	-0.53900	-0.11290
H	5.72160	2.03790	0.26090
H	7.83470	0.68540	0.06700
H	5.50380	-2.95000	-0.33430
H	2.47930	3.40650	-1.45080
H	3.77930	4.13620	-0.42570
H	4.12930	2.64390	-1.41060
H	0.72340	1.95400	-0.96460
H	0.34580	-1.81200	1.12140

H	-1.75960	2.02120	-1.29770
H	-2.12920	-1.74330	0.80100
H	7.80110	-2.79460	-0.33130
H	-4.22660	-2.67600	0.93460
H	-5.74040	2.87980	-0.39280
H	-7.17160	2.17900	0.46810
H	-6.98760	1.95090	-1.32930
H	-8.26950	0.23850	-0.78420
H	-8.25110	-0.39330	0.91320
H	-8.13660	-1.54590	-0.48650

ProD3 INT

C	5.59290	0.96460	0.28930
C	4.37700	0.26780	0.16710
C	4.38070	-1.13700	-0.05460
C	6.78720	0.28330	0.16770
C	6.77740	-1.11590	-0.06580
C	5.58820	-1.83540	-0.17240
C	3.03050	0.79070	0.20170
C	2.08380	-0.18800	-0.01030
S	2.80480	-1.72370	-0.19310
O	8.01230	-1.70060	-0.20340
O	-3.45300	0.59030	-0.79870
O	2.18300	2.63320	1.44870
C	2.77190	2.22190	0.44680

C	3.28750	3.15460	-0.60970
C	0.15890	1.14350	-0.80120
C	0.65490	-0.00910	-0.16530
C	-0.25550	-0.99520	0.24500
C	-1.20570	1.33020	-0.99570
C	-2.10260	0.34960	-0.54190
C	-1.62380	-0.83110	0.04120
C	-4.36300	0.38580	0.25290
C	-5.83410	0.59100	-0.15990
C	-6.43600	-0.62420	-0.13160
C	-5.44480	-1.64000	0.32060
O	-4.25270	-0.99230	0.64580
O	-5.42930	-2.85160	0.44230
O	-4.02400	1.15270	1.34470
C	-6.40500	1.92450	-0.35890
C	-7.81430	-0.97870	-0.47100
H	5.59250	2.05100	0.46820
H	7.75400	0.80180	0.22860
H	5.59410	-2.91720	-0.36690
H	2.46240	3.39210	-1.32380
H	3.64290	4.10580	-0.14790
H	4.12460	2.69090	-1.18200
H	0.86020	1.91500	-1.15600
H	0.09480	-1.91850	0.73320

H	-1.58760	2.22570	-1.50510
H	-2.30800	-1.64080	0.34000
H	7.87870	-2.64600	-0.35400
H	-3.12430	0.91830	1.62640
H	-5.59150	2.68510	-0.26150
H	-7.19530	2.10890	0.41870
H	-6.88140	2.03240	-1.36510
H	-8.22930	-0.17940	-1.13320
H	-8.44400	-1.04040	0.45270
H	-7.84600	-1.97480	-0.98190

ProD3 TS

C	-5.10810	1.46290	0.17520
C	-4.06700	0.52270	0.02780
C	-4.43370	-0.83020	-0.11030
C	-6.42790	1.04770	0.21770
C	-6.76200	-0.31390	0.10390
C	-5.75390	-1.26110	-0.07020
C	-2.62620	0.74940	-0.06430
C	-1.89440	-0.38980	-0.30620
S	-2.98620	-1.87510	-0.37980
O	-8.10810	-0.63050	0.16000
O	3.63570	-1.49240	-0.68270
O	-1.07670	2.54410	-0.50610
C	-2.01700	2.08820	0.16520

C	-2.55600	2.88110	1.35750
C	0.09150	-1.86110	0.08180
C	-0.45930	-0.64630	-0.43540
C	0.40170	0.22080	-1.10320
C	1.42480	-2.17600	-0.03430
C	2.33410	-1.31350	-0.70540
C	1.79040	-0.05770	-1.19470
C	4.18610	-0.65870	1.00260
C	5.57980	-0.48490	0.51820
C	5.80960	0.71570	-0.03520
C	4.57380	1.51960	-0.11170
O	3.52580	0.79400	0.56170
O	4.36700	2.58610	-0.65400
O	3.67050	-1.23300	1.92530
C	6.47270	-1.66920	0.68050
C	7.06160	1.27240	-0.64120
H	-4.88490	2.51890	0.24100
H	-7.23590	1.75770	0.32930
H	-5.99370	-2.31260	-0.18180
H	-1.69560	3.20760	1.95140
H	-3.06250	3.78860	1.00630
H	-3.23470	2.29780	1.97830
H	-0.56620	-2.53770	0.61680
H	0.00400	1.13440	-1.51910

H	1.82010	-3.08650	0.39480
H	2.36630	0.46570	-1.95900
H	-8.23750	-1.60910	0.05950
H	2.50760	0.58500	-0.13910
H	6.47680	-2.00180	1.72500
H	7.49460	-1.45960	0.35960
H	6.05340	-2.47960	0.07050
H	7.36340	2.18830	-0.11940
H	6.88610	1.53560	-1.69080
H	7.88170	0.55320	-0.59070
H	3.49807	-0.17194	0.40704
H	3.71354	-0.02722	0.97198
H	3.12760	0.58500	-0.13910

ProD4 GM

C	4.06000	0.26440	0.17300
C	3.28930	-0.18170	0.11770
C	3.29830	-1.07880	0.01610
C	4.82080	-0.16770	0.12030
C	4.81930	-1.06060	0.00710
C	4.06570	-1.51930	-0.04510
C	2.43080	0.14190	0.14660
C	1.84160	-0.49860	0.06850
S	2.30760	-1.47120	-0.02680
O	5.60330	-1.43690	-0.05050

O	-1.71850	-0.49770	-0.17300
O	1.91020	1.34010	0.90160
C	2.25170	1.05460	0.25820
C	2.51330	1.62060	-0.46160
C	0.50520	0.22370	-0.35540
C	0.92600	-0.45700	0.03330
C	0.44500	-1.12720	0.37470
C	-0.37730	0.23880	-0.41220
C	-0.84080	-0.43740	-0.07240
C	-0.43560	-1.12160	0.32790
C	-2.22720	0.12260	0.17310
C	-3.14680	-0.03690	0.07380
C	-3.52030	-0.84450	0.04980
C	-3.02180	-1.63520	0.10330
O	-2.48100	-1.68540	0.77540
O	-3.05580	-2.26050	-0.36620
O	-1.89050	0.74670	0.49700
C	-3.66560	0.68380	0.00860
C	-4.54190	0.60020	-0.07760
C	-4.91110	-0.20400	-0.09530
C	-4.40220	-0.92570	-0.03700
H	4.05260	0.95730	0.25730
H	5.43320	0.16260	0.16340
H	4.07170	-2.20940	-0.13730

H	1.96250	1.69870	-0.90160
H	2.69560	2.26050	-0.21710
H	3.05660	1.34160	-0.81930
H	0.87570	0.75380	-0.61690
H	0.76760	-1.66110	0.68840
H	-0.70850	0.77700	-0.70710
H	-0.81410	-1.64230	0.59630
H	5.52160	-2.04180	-0.11650
H	-2.15760	-2.20820	0.73470
H	-3.37150	1.31690	0.03750
H	-4.93930	1.17200	-0.12690
H	-5.60330	-0.27210	-0.15250
H	-4.68610	-1.56400	-0.06770

ProD4 INT

C	5.935800001	1.068800000	0.292100000
C	4.756500001	0.316100000	0.160500000
C	4.823300001	-1.083900000	-0.077000000
C	7.164200001	0.451800000	0.170800000
C	7.219400001	-0.943600000	-0.076300000
C	6.065600001	-1.716400000	-0.200800000
C	3.390200000	0.776400000	0.208900000
C	2.487200000	-0.243000000	0.004500000
S	3.272100000	-1.740300000	-0.210100000
O	8.480700001	-1.473000000	-0.200800000

O	-3.045100000	0.478000000	-0.819400000
O	2.476800000	2.595800000	1.445700000
C	3.062500000	2.194900000	0.438300000
C	3.510000000	3.123600000	-0.652800000
C	0.555300000	1.042800000	-0.805900000
C	1.055500000	-0.084600000	-0.132700000
C	0.152000000	-1.032300000	0.365300000
C	-0.810200000	1.236700000	-0.964500000
C	-1.698300000	0.260400000	-0.491500000
C	-1.219000000	-0.878900000	0.170200000
C	-3.972800000	0.288900000	0.210100000
C	-5.452600001	0.444600000	-0.132700000
C	-6.035200001	-0.856100000	-0.081900000
C	-4.954900001	-1.820700000	0.234900000
O	-3.831900000	-1.097100000	0.598400000
O	-4.816900001	-3.031900000	0.230300000
O	-3.515400000	1.032600000	1.285100000
C	-6.249500001	1.565300000	-0.270400000
C	-7.648000001	1.390100000	-0.293500000
C	-8.211800001	0.119800000	-0.225700000
C	-7.403500001	-1.031300000	-0.166300000
H	5.870300001	2.151500000	0.473300000
H	8.102100001	1.020600000	0.238600000
H	6.132700001	-2.792800000	-0.407700000

H	2.714900000	3.190600000	-1.433300000
H	3.690600000	4.145100000	-0.245900000
H	4.437800001	2.744100000	-1.142800000
H	1.248000000	1.790400000	-1.218700000
H	0.520700000	-1.909600000	0.916400000
H	-1.189400000	2.137500000	-1.461600000
H	-1.899900000	-1.660500000	0.540400000
H	8.393900001	-2.429800000	-0.307600000
H	-4.195100001	1.033200000	1.969100000
H	-5.816100001	2.576900000	-0.311100000
H	-8.299600001	2.282200000	-0.323500000
H	-9.309500001	0.023100000	-0.176900000
H	-7.871000001	-2.029500000	-0.162300000

ProD4 TS

C	6.05950	0.96660	0.50310
C	4.85980	0.31340	0.14770
C	4.95180	-1.02390	-0.28020
C	7.26510	0.29370	0.42510
C	7.32690	-1.04480	-0.00480
C	6.15630	-1.71220	-0.36220
C	3.48680	0.82740	0.16460
C	2.56190	-0.08760	-0.25560
S	3.31870	-1.69120	-0.69730
O	8.58090	-1.62860	-0.04780

O	-3.06080	0.10730	-1.05750
O	4.11290	2.99670	0.92610
C	3.19160	2.21480	0.63390
C	1.74500	2.65870	0.77990
C	0.56380	0.56340	-1.60370
C	1.09870	-0.00470	-0.43730
C	0.23130	-0.54330	0.52770
C	-0.81730	0.62530	-1.78920
C	-1.64500	0.10170	-0.80720
C	-1.14960	-0.48730	0.35190
C	-3.91470	0.49720	-0.09500
C	-5.33340	0.18700	-0.41770
C	-6.08220	-0.51480	0.53010
C	-5.35040	-1.00630	1.74860
O	-4.03980	-0.65420	1.67890
O	-5.89830	-1.62770	2.65780
O	-3.49510	1.37880	0.79870
C	-5.92080	0.60670	-1.61250
C	-7.27640	0.34340	-1.82950
C	-8.03060	-0.34100	-0.86980
C	-7.42800	-0.77910	0.31130
H	6.00390	1.99320	0.82750
H	8.19400	0.77920	0.69220
H	6.18280	-2.74320	-0.69640

H	1.75140	3.65770	1.22020
H	1.24210	2.68890	-0.19090
H	1.18070	1.97180	1.41710
H	1.23260	0.95380	-2.36060
H	0.64400	-1.00270	1.41740
H	-1.24820	1.05780	-2.68190
H	-1.84010	-0.89310	1.08170
H	8.51440	-2.56810	-0.36020
H	-3.73590	0.74390	1.68270
H	-5.33310	1.12950	-2.35650
H	-7.74200	0.66840	-2.75210
H	-9.07880	-0.54410	-1.05320
H	-7.96820	-1.33870	1.06540
H	-3.72137	-0.17818	0.93730
H	-3.11590	0.74390	1.68270

ProD5 GM

C	4.31520	0.52600	0.09230
C	3.52880	0.04250	0.06180
C	3.56360	-0.88410	-0.04580
C	5.11240	0.10160	0.01330
C	5.13540	-0.82190	-0.10170
C	4.36840	-1.31830	-0.13420
C	2.63150	0.34890	0.13060
C	2.03390	-0.32750	0.07780

S	2.54660	-1.31720	-0.04880
O	5.95800	-1.18310	-0.17500
O	-1.64080	-0.51600	-0.27230
O	2.06910	1.57420	0.91650
C	2.42270	1.28720	0.24770
C	2.66390	1.87940	-0.50100
C	0.62070	0.37420	-0.34460
C	1.08250	-0.30950	0.06620
C	0.60280	-1.00770	0.43510
C	-0.28930	0.34010	-0.43930
C	-0.74620	-0.38480	-0.11040
C	-0.30540	-1.04970	0.34870
C	-2.23490	0.07200	0.06830
C	-3.17420	-0.18370	0.00050
C	-3.50290	-0.99870	0.00610
C	-3.03860	-1.84010	0.02030
O	-2.28740	-1.87750	0.50050
O	-3.28680	-2.52680	-0.33170
O	-1.95510	0.76560	0.37160
C	-3.75840	0.60340	-0.08150
C	-4.73100	0.40010	-0.05360
C	-5.28770	1.21410	-0.13650
H	4.29540	1.24220	0.18200
H	5.73810	0.45960	0.04040

H	4.39400	-2.03260	-0.22710
H	2.06730	1.99410	-0.91190
H	2.89430	2.52680	-0.24630
H	3.18720	1.58130	-0.91650
H	0.98310	0.94880	-0.59080
H	0.94320	-1.52570	0.80690
H	-0.65070	0.87690	-0.75670
H	-0.68360	-1.59550	0.63050
H	5.89600	-1.81090	-0.24320
H	-4.22440	-1.09670	-0.02170
H	-2.01520	-2.44780	0.42380
H	-5.01480	1.77390	0.24770
H	-5.35720	1.41430	-0.83670
H	-5.95800	1.07630	0.12140
H	-4.88370	0.06020	0.58160
H	-4.89770	-0.06420	-0.60000
H	-3.58960	0.92520	-0.72130
H	-3.59670	1.08210	0.45510

ProD5 INT

C	5.86930	1.11000	0.48580
C	4.69010	0.44150	0.10750
C	4.75320	-0.91190	-0.32680
C	7.08240	0.44900	0.43500
C	7.12700	-0.90030	-0.00200

C	5.97650	-1.58620	-0.38770
C	3.32530	0.92390	0.12390
C	2.42950	-0.04820	-0.26180
S	3.21760	-1.50210	-0.68470
O	8.36720	-1.49040	-0.02280
O	-3.18830	0.14350	-0.59950
O	2.43730	2.56360	1.60030
C	3.00950	2.30520	0.53950
C	3.44650	3.38380	-0.40930
C	0.30900	1.17510	-0.70590
C	0.98450	0.00720	-0.32300
C	0.23440	-1.13140	0.02070
C	-1.08220	1.21740	-0.73370
C	-1.81520	0.07010	-0.38710
C	-1.15700	-1.10780	-0.00750
C	-4.07370	-0.26960	0.40480
C	-5.53570	-0.19990	-0.09070
C	-6.02180	-1.46110	-0.09600
C	-4.97140	-2.39090	0.39460
O	-3.81850	-1.65290	0.69610
O	-4.90160	-3.59090	0.59290
O	-3.86640	0.43480	1.57340
C	-6.16350	1.08480	-0.43030
C	-7.67890	1.00130	-0.51270

C	-8.33190	2.35520	-0.37800
H	5.81920	2.15430	0.83260
H	8.02120	0.94050	0.73100
H	6.02650	-2.63090	-0.72680
H	2.67100	3.50080	-1.20590
H	3.55940	4.35590	0.12970
H	4.41650	3.11440	-0.89180
H	0.89060	2.06740	-0.98580
H	0.75570	-2.05790	0.31190
H	-1.59940	2.13090	-1.05640
H	-1.73050	-2.01010	0.25460
H	8.24720	-2.42440	-0.24730
H	-7.01360	-1.81410	-0.38110
H	-3.06590	0.09410	2.00100
H	-8.08050	2.81710	0.60700
H	-7.99100	3.04390	-1.18650
H	-9.44190	2.24320	-0.44590
H	-8.05970	0.32900	0.29910
H	-7.97320	0.53690	-1.48890
H	-5.74590	1.43080	-1.41570
H	-5.86210	1.84720	0.34050
ProD5 TS			
C	-4.09480	0.47480	0.14690
C	-3.35080	-0.08660	0.04910

C	-3.51440	-1.00450	-0.02800
C	-4.94270	0.12180	0.18940
C	-5.08390	-0.79990	0.12860
C	-4.36170	-1.36800	0.01310
C	-2.41150	0.14750	-0.02570
C	-1.86170	-0.56540	-0.18190
S	-2.49730	-1.61300	-0.20960
O	-5.95510	-1.08860	0.18010
O	1.85580	-0.99770	-0.48060
O	-1.49590	1.42140	-0.34970
C	-2.08610	1.07160	0.10850
C	-2.48070	1.57710	0.89680
C	-0.46280	-1.42560	0.06730
C	-0.89810	-0.65420	-0.27690
C	-0.38090	-0.03630	-0.73160
C	0.43570	-1.56250	-0.02160
C	0.98420	-0.94620	-0.48120
C	0.55220	-0.14730	-0.80640
C	2.19020	-0.38270	0.62450
C	3.09640	-0.21440	0.26520
C	3.17640	0.58560	-0.11640
C	2.33020	1.06450	-0.15030
O	2.11330	1.75580	-0.49960
C	3.74890	-0.95360	0.36530

C	4.69390	-0.74870	0.03090
C	5.31420	-1.55620	0.15110
H	-4.01050	1.18750	0.17870
H	-5.51880	0.54450	0.26360
H	-4.45820	-2.07900	-0.04990
H	-1.92650	1.85380	1.27840
H	-2.87540	2.14150	0.65870
H	-2.88750	1.15710	1.32280
H	-0.85620	-1.90620	0.43240
H	-0.69770	0.54490	-1.00800
H	0.75110	-2.14150	0.26350
H	0.89700	0.22610	-1.32280
H	-5.98340	-1.74470	0.12470
H	3.76290	0.85710	-0.42410
H	5.36170	-1.74120	0.85360
H	5.06190	-2.12990	-0.21930
H	5.98340	-1.40540	-0.09040
H	4.96180	-0.17760	0.39590
H	4.66540	-0.56700	-0.67430
H	3.46170	-1.51500	-0.00480
H	3.76390	-1.15370	1.06770
O	1.68870	0.54580	-0.15030
O	2.40370	-1.17960	0.62450

ProD6 GM

C	6.19570	1.00030	0.14140
C	4.96940	0.31630	0.08340
C	4.94620	-1.08290	-0.16790
C	7.37560	0.31330	-0.06280
C	7.33830	-1.08130	-0.31890
C	6.13770	-1.78700	-0.36570
C	3.63430	0.84820	0.23450
C	2.67510	-0.12620	0.08260
S	3.36570	-1.65940	-0.20770
O	8.55630	-1.68280	-0.51910
O	-2.88640	0.11830	-0.52330
O	2.96640	2.67790	1.60040
C	3.41400	2.27780	0.52420
C	3.78870	3.22400	-0.57860
C	0.63120	1.15160	-0.46970
C	1.23600	0.00150	0.06000
C	0.42920	-1.05720	0.51280
C	-0.75220	1.23150	-0.59930
C	-1.53050	0.13990	-0.19890
C	-0.95520	-0.99090	0.39520
C	-3.79320	0.59530	0.39330
C	-5.19560	0.47060	-0.06920
C	-5.89520	-0.67890	-0.04550
C	-5.32810	-1.98930	0.33160

O	-4.13730	-1.96730	0.99400
O	-5.80880	-3.10660	0.12190
O	-3.38510	1.10400	1.43100
C	-5.79210	1.75900	-0.53110
C	-7.29680	1.76890	-0.33630
C	-7.35100	-0.74400	-0.38080
H	6.20320	2.08120	0.34590
H	8.34930	0.82090	-0.03200
H	6.12420	-2.86770	-0.55730
H	2.88560	3.43150	-1.20270
H	4.15210	4.18940	-0.15220
H	4.58140	2.78240	-1.22730
H	1.25920	1.99560	-0.79220
H	0.89920	-1.94680	0.95960
H	-1.22870	2.12880	-1.01550
H	-1.60000	-1.80620	0.75300
H	8.40320	-2.62340	-0.68400
H	-3.85840	-2.87600	1.19340
C	-7.90980	0.53760	-0.97220
H	-5.55740	1.88670	-1.62370
H	-5.32320	2.61330	0.02320
H	-7.72570	2.69750	-0.79280
H	-7.53610	1.78830	0.75760
H	-7.90110	-0.99960	0.56630

H -7.51860 -1.59220 -1.09910

H -7.71140 0.55640 -2.07460

H -9.02080 0.55320 -0.83140

ProD6 INT

C 3.979300000 0.260500000 0.182500000

C 3.230200000 -0.179900000 0.024400000

C 3.257700000 -1.031600000 -0.227600000

C 4.743200001 -0.147200000 0.102300000

C 4.761400001 -1.004300000 -0.137700000

C 4.025200000 -1.451100000 -0.311900000

C 2.372700000 0.132300000 0.087800000

C 1.782600000 -0.460700000 -0.111300000

S 2.249900000 -1.434100000 -0.393800000

O 5.545400001 -1.358600000 -0.190200000

O -1.744900000 -0.226800000 -0.362000000

O 2.066100000 1.217100000 1.071000000

C 2.210500000 1.019500000 0.347400000

C 2.251800000 1.647100000 -0.365100000

C 0.474000000 0.340900000 -0.443800000

C 0.866400000 -0.377000000 -0.117200000

C 0.369800000 -1.035800000 0.195100000

C -0.398700000 0.393900000 -0.480100000

C -0.884800000 -0.282700000 -0.189100000

C -0.502900000 -0.995300000 0.160600000

C	-2.332200000	-0.366500000	0.279800000
C	-3.228200000	-0.158100000	-0.034100000
C	-3.695100000	-0.866400000	-0.017000000
C	-3.155600000	-1.564900000	0.310800000
O	-2.359400000	-1.252300000	0.500300000
O	-3.259100000	-2.302100000	0.451000000
O	-2.036500000	0.060700000	0.976300000
C	-3.539800000	0.673600000	-0.309000000
C	-4.503600001	0.670900000	-0.339600000
C	-4.590600001	-0.918500000	-0.267200000
C	-4.850100001	-0.126100000	-0.751200000
H	3.952100000	0.924000000	0.370000000
H	5.334300001	0.188200000	0.224200000
H	4.042900000	-2.112800000	-0.507700000
H	1.693500000	1.568800000	-0.770600000
H	2.266900000	2.302100000	-0.148700000
H	2.814900000	1.535600000	-0.749800000
H	0.857400000	0.872000000	-0.672300000
H	0.673800000	-1.595000000	0.464500000
H	-0.700300000	0.957800000	-0.739900000
H	-0.876900000	-1.521300000	0.406200000
H	5.479200001	-1.937100000	-0.330200000
H	-2.446500000	0.033100000	1.410800000
H	-3.268400000	0.816500000	-0.936600000

H	-3.308600000	1.169800000	0.123300000
H	-4.726500001	1.232400000	-0.685100000
H	-4.759200001	0.728200000	0.307000000
H	-4.978900001	-0.995200000	0.308000000
H	-4.701300001	-1.489100000	-0.651800000
H	-4.626700001	-0.166700000	-1.410800000
H	-5.545400001	-0.092000000	-0.785000000

ProD6 TS

C	6.20510	0.93010	0.46610
C	4.99020	0.29820	0.12430
C	5.05760	-1.02750	-0.34270
C	7.40160	0.24830	0.33830
C	7.43870	-1.07830	-0.12950
C	6.25260	-1.72450	-0.47460
C	3.62320	0.82340	0.19390
C	2.67850	-0.06920	-0.23000
S	3.40780	-1.66670	-0.73720
O	8.68530	-1.67240	-0.22110
O	-2.95240	0.22000	-0.93310
O	4.28990	2.96810	0.99020
C	3.35410	2.19450	0.72260
C	1.91760	2.62720	0.96930
C	0.66610	0.69340	-1.49450
C	1.21390	0.03690	-0.38140

C	0.35580	-0.56610	0.55340
C	-0.71680	0.77760	-1.65420
C	-1.53590	0.18730	-0.70240
C	-1.02680	-0.48900	0.40190
C	-3.79620	0.53880	0.07000
C	-5.21780	0.25840	-0.27560
C	-5.91660	-0.57210	0.50680
C	-5.18780	-1.17770	1.67810
O	-3.89370	-0.75320	1.71570
O	-5.72400	-1.94990	2.47110
O	-3.37340	1.35250	1.02190
C	-5.76770	0.92020	-1.52580
C	-7.30880	0.78950	-1.58830
C	-7.35540	-0.93560	0.26890
C	-7.76550	-0.63260	-1.19000
H	6.16840	1.94840	0.81810
H	8.34190	0.71770	0.59380
H	6.26030	-2.74610	-0.83750
H	1.38810	1.90540	1.59780
H	1.94850	3.60120	1.46160
H	1.36270	2.70940	0.03050
H	1.32700	1.13300	-2.23130
H	0.77740	-1.09260	1.40080
H	-1.15730	1.27760	-2.50610

H	-1.71080	-0.94370	1.10870
H	8.60100	-2.60240	-0.55680
H	-3.62810	0.61010	1.84790
H	-5.30200	0.43890	-2.39670
H	-5.47900	1.97900	-1.54560
H	-7.64920	1.03210	-2.60090
H	-7.75900	1.51540	-0.89990
H	-7.98730	-0.36210	0.96240
H	-7.48990	-1.99270	0.52150
H	-7.29810	-1.36600	-1.85890
H	-8.85160	-0.72310	-1.29790

تصميم طلائع أدوية مبتكرة من الرالوكسيفين بالطرق الحسابية

إعداد: نيرمين نادر إبراهيم حجاج

إشراف: الدكتور صالح جبور

الملخص:

تم إنجاز هذه الأطروحة باستخدام المدار الجزيئي DFT عند مستوى (B3LYP 6-31G (d, p وحسابات الميكانيكا الجزيئية (2MM) لنقل البروتون داخل الجزيء في عدد من نماذج إنزيم Kirby لتصميم العقاقير الأولية من الرالوكسيفين على الجانبين (اليسار واليمين). لتوفير دواء لديه القدرة على إطلاق الرالوكسيفين بطريقة قابلة للبرمجة والتحكم مع توافر بيولوجي أعلى من الدواء الأصلي. هناك ستة عقاقير أولية من الرالوكسيفين على الجانبين (الجانب الأيسر والأيمن) تم تصميمها اعتمادًا على نموذج إنزيم نقل البروتون في كيربي. بطريقة DFT عند (B3LYP / 6-31G (d, p تم إجراء حسابات مستوى في الطور الغازي وفي ثابت العزل الكهربائي 79.38 (طور الماء) للجانب الأيمن وفي الطور الغازي للجانب الأيسر.

تم الكشف عن أن معدل نقل البروتون في عمليات 6ProD1-ProD الرالوكسيفين على الجانبين يعتمد إلى حد كبير على الاختلافات الهندسية للمتفاعل (GM) بشكل أساسي المسافة بين المركزين المتفاعلين (r_{GM}) وزاوية الهجوم (α). لاستنتاج أن الأنظمة التي تحتوي على قيم r_{GM} منخفضة وقيم α عالية في هيكلها الدنيا العالمية، مثل 4ProD و 6ProD في الجانب الأيسر 5ProD و 6ProD في الجانب الأيمن تظهر معدلات أعلى بكثير (أقل G) من هذه مع قيم r_{GM} عالية وقيم α منخفضة، مثل 1ProD و 2ProD و 3ProD و 5ProD على اليسار 1ProD و 2ProD و 3ProD و 4ProD على الجانب الأيمن. وبالتالي، فمن المستحسن أن الرالوكسيفين 4ProD و 6ProD في الجانب الأيسر و 5ProD و 6ProD على الجانب الأيمن يجب أن تسبق الاختبار في المختبر وفي الجسم الحي.

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