Deanship of Graduate Studies
Al-Quds University

Design of Novel Tranexamic acid Prodrugs by Computational Methods

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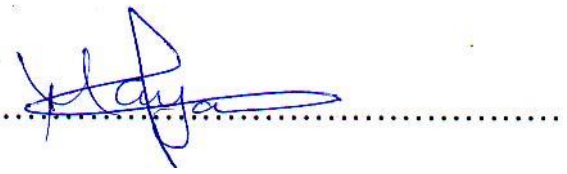
Dedication

I would dedicate this thesis to my family; mom, husband and kids. I am very grateful for their love, support and prayers.

Mariam Bader

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: 

Name: Mariam Mamoun Mahmoud Bader

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

Many thanks for each doctor that had taught me during my stay at Al-Quds University. Special thanks for Prof. Rafiq karaman who encouraged me to enter this master program and who gave me a great opportunity to work as a teaching assistant at the school of pharmacy.

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Abstract:

Nowadays computational chemistry has become a corner stone in the field of drug and prodrug design. Tranexamic acid which is a well known antifibrinolytic agent. Though, the drug suffers from a short half life and a low bioavailability as a result of being an amino acid derivative.

A new derivative of tranexamic acid with a higher bioavailability and a controlled release rate seems an attractive alternative. Designing tranexamic acid prodrugs *via* the computational pathway is a great pre step before beginning any experimental work. It gives us a hint on the expected experimental results while saving time and money.

In this thesis six Tranexamic acid prodrugs were designed depending on Kirby's proton transfer enzyme model. Calculations were made using the DFT method at B3LYP/6-31G (d,p) level. Calculations were run in the gas phase and in a dielectric constant of 79.38.

From the DFT calculation results it was revealed that the rate of a proton transfer in processes Tranexamic acid **ProD1**-**ProD6** is largely dependent on the geometric variations of the reactant (GM) mainly the distance between the two reactive centers, r_{GM}, and the angle of attack α. It was found that systems with low r_{GM} and high α values in their global minimum structures, such as **ProD1**, **ProD2** and **ProD3** exhibit much higher rates (lower $\Delta G^{\ddagger}$) than these with high r_{GM} and low α values, such as **ProD4-ProD6**. Thus, it is recommended that Tranexamic acid **ProD1-ProD3** should further precede into *in vitro* and *in vivo* testing.

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Abbreviations	Definition
EACA	ε-aminocaproic acid
ProD	Prodrug
CYP450	Cytochrome P450
Cmax	Maximum concentration
QM	Quantum Mechanics
DFT	Density Functional Theory
MM	Molecular Mechanics
CRASH-2	The 2010 Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2
HF	Hartree-Fock
Es_{INT}	Strain energy of the intermediate
B3LYP	Becke, 3-parameter, Lee-Yang-Parr.
HLB	Hydrophilic Lipophilic Balance
$t_{1/2}$	Half Life
IV	Intravenous
MO	Molecular Orbital
PCM	Polarizable Continuum Model (PCM)
GM	Global Minimum
TS	Transition State
INT	Intermediate
GP	Gas Phase
r_{GM}	Distance in the Global Minimum
A	Angle of Attack
S	Entropy
H	Enthalpy
$\Delta G^{\ddagger}$	Activation Energy
$\Delta H^{\ddagger}$	Enthalpy of activation energy
$T\Delta S^{\ddagger}$	Entropy of activation energy
Å	Angstrom

Chapter one

Introduction

Chapter one:

Introduction

1.1 Computational chemistry background

Computational chemistry is a branch of chemistry that uses equations encapsulating the behavior of matter on an atomistic scale. Equations are solved computationally to calculate structures and properties of molecules in order to explain or predict chemical phenomena.

In the recent few decades computational chemistry had put a fingerprint in the field of drug and prodrug design. Many computational methods are being used in the design and production of a wide variety of chemical compounds. Besides, they enable us to unravel the exact mechanism of reactions [1]. Contemporary drug design relies on these computational approaches for predicting experimental results.

Chemical computational methods are divided into two major subdivisions: Molecular Mechanics (MM) and Quantum Mechanics (QM) the latter includes: Density Functional Theory (DFT), ab initio and semi-empirical methods.

1.1.1. Quantum mechanics methods

1.1.1.1. Ab initio method [1]

Ab initio method refers to quantum chemistry; this term was first used by Robert Parr *et al* [1].

Ab initio molecular orbital methods include: HF, G1, G2, G2MP2, MP2 and MP3 which are based on rigorous use of the Schrodinger equation with a number of approximations.

Ab initio calculation is an important tool for investigating functional mechanisms of biological macromolecules based on their three-dimensional and electronic structures. Accordingly, isolated models of interesting parts of proteins (e.g., active sites) have been studied using ab initio calculations method.

Limitations of using ab initio method include treating only small-sized molecules, high cost and consumption of computer time, memory. Another disadvantage is ignoring proteins and solvents surrounding the catalytic centers, this implies that ab initio calculations using only the catalytic centers have difficulty in the understanding of biological systems.

1.1.1.2 Semi empirical method:

This method is based on Hartree-Fock Formalism but with many approximations and obtains some parameters from empirical data. Among the most used semi-empirical methods are MINDO, MNDO, MINDO/3, AM1, PM3 and SAM1. The semi-empirical methods have afforded vast information for practical application [2-5].

Semi empirical methods are considered beneficial for treating large molecules were the use of full Hartree-Fock Formalism is very expensive. It is much faster than ab initio and allows an inclusion of electron correlation effects. Calculations of molecules exceeding 60 atoms can be done using such methods. However, results can be very wrong if the molecule being computed is not similar enough to the molecules in the database used in parametrizing the method.

1.1.1.3 Density functional theory (DFT):

DFT is the most popular and commonly used method in physics and chemistry to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules and the condensed phases.

With this theory, the properties of a many-electron system can be determined by using functionals, that is, functions of another function, which in this case is the spatially dependent electron density. Hence the name DFT comes from the use of functionals of the electron density. It is used to calculate structures and energies for medium size molecules (30-60 atoms) [6].

1.1.2 Molecular mechanics (MM):

MM is a mathematical approach used for the computation of structures, energy, dipole moment and other physical properties and is widely used in calculating many diverse biological and chemical systems such as proteins, large crystal structures and relatively large solvated systems. However, this method is limited by the determination of parameters such as the large number of unique torsion angles present in structurally diverse molecules [7].

To overcome these difficulties, QM/MM calculations are utilized, in which the system is divided into QM and MM regions, where QM regions correspond to active sites to be investigated, and they are described quantum mechanically.MM regions correspond to the remainder of the system and are described molecular mechanically. The pioneer work of the QM/MM method was accomplished by Warshel and Levitt [8], and since then, there has been much progress on development of QM/MM algorithm and applications to biological systems [9, 10].

1.2 Tranexamic acid background:

Tranexamic acid; Trans-4-(aminomethyl)cyclohexanecarboxylic acid **(Figure 1)** , is a white crystalline powder. With a molecular formula of ($C_8H_{15}NO_2$) and a molecular weight of 157.21 g/mol.

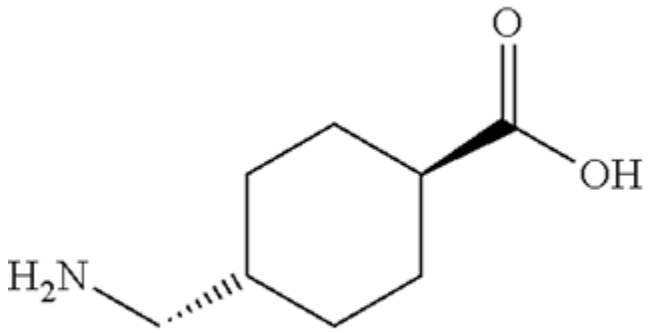


Figure 1: Chemical structure of tranexamic acid.

Tranexamic acid is a synthetic lysine amino acid derivative, which exerts its effects by competitively inhibiting the activation of plasminogen to plasmin, thereby inhibiting fibrin degradation. The drug use is considered attractive due to its minimal effect on blood clotting parameters. It is eight times more efficient than the older antifibrinolytic **ε-** aminocaproic acid [11].

1.2.1 Tranexamic acid uses:

Since it was introduced into clinical practice over 30 years ago, Tranexamic acid has been used for a wide variety of clinical conditions in which antifibrinolytic therapy has been deemed potentially beneficial.

Tranexamic acid was originally used in order to prevent excessive hemorrhage in hemophilia patients and to reduce the need for replacement therapy following tooth extraction.

In the recent years its use have expanded beyond hemophilia patients and tooth extracts to become an important agent which is used to decrease mortality rates due to bleeding in trauma patients which was proved by CRASH-2 clinical study [12]. Also, it reduces blood loss in women who undergo C- section, the need for intra-operative blood transfusion during heart, hip and knee replacement and liver transplant surgeries [13].

It is used to reduce blood loss in excessive menstrual bleeding [14]; the recommended dosage of tranexamic acid in this situation is two 650mg tablets three times daily for five days [15]. It is used orally to treat melasma; a hypermelanosis disease that occurs in Asian women [16].

Finally, it was found that tranexamic acid is effective in inhibiting urokinase in urine, so it has been used for treating severe hematourea in patients with chronic renal impairment who poorly respond to conventional therapies [17].

Recent studies have proved the ability of tranexamic acid to inhibit ultraviolet radiation induced pigmentation, thus it can be used topically as a bleaching agent [18].

1.2.2 Tranexamic acid pharmacokinetics:

Oral bioavailability of tranexamic acid is thirty five percent. The drug absorption after oral administration is not affected by food and he drug reaches C max in 3 hours. The initial volume of distribution is about 9 to 12 L. Ninety-five of the drug is excreted unchanged in the urine after intravenous administration. The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen [19-23].

The drug crosses the Blood Brain Barrier (BBB) and placenta with minimal excretion in breast milk. It is not detectable in saliva after oral administration [24-26]. The use of tranexamic acid mouthwash (5% w/v) results in plasma drug concentrations below 2 mg/L [27].

1.2.3 Tranexamic acid pharmacodynamics:

Tranexamic acid exerts its antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules and thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Although plasmin can still be formed under these circumstances, it is unable to bind to and degrade fibrin [28, 29].

Tranexamic acid is 6 to 10 times more potent in terms of binding to plasminogen/plasmin than ε-aminocaproic acid (EACA) [30].The drug has no effect on coagulation parameters. Concurrent administration of heparin does not influence the activity of Tranexamic acid [31].

1.2.4 Tranexamic acid associated side effects:

On general Tranexamic acid is well tolerated; nausea and diarrhea are the most common adverse events [32]. Increased risk of thrombosis with the drug has not been demonstrated in clinical trials.

The low bioavailability and short half-life of the drug (approximately 2 hours), which lead to poor patient compliance, had inspired us to search for a better alternative of the parent drug.

1.3 Problem statement:

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality, resulting in 100,000 deaths every year. PPH is usually managed by uterotonic agents including oxytocin and misopristol are used to reduce blood loss, and by replacing fluids and blood in severe cases [33, 34].

Providing blood for these patients is considered a problem in the third world countries, so an alternative oral agent to reduce blood loss such as Tranexamic acid is a crucial need in these developed countries.

Since Tranexamic acid is an amino acid derivative with a log P (partition coefficient) value of (-1.6), it undergoes ionization in physiologic environments and its oral bioavailability is low (35%) due to inefficient absorption through membranes resulting in the need for frequent administration leading to an increase in side effects and reducing patient compliance [34].

Hence, there is a necessity to design and synthesize relatively more lipophilic Tranexamic acid prodrugs that can provide the parent drug in a controlled release manner which mightresult in better clinical outcome, more convenient dosing regimens and potentially less side effects than the original medication.

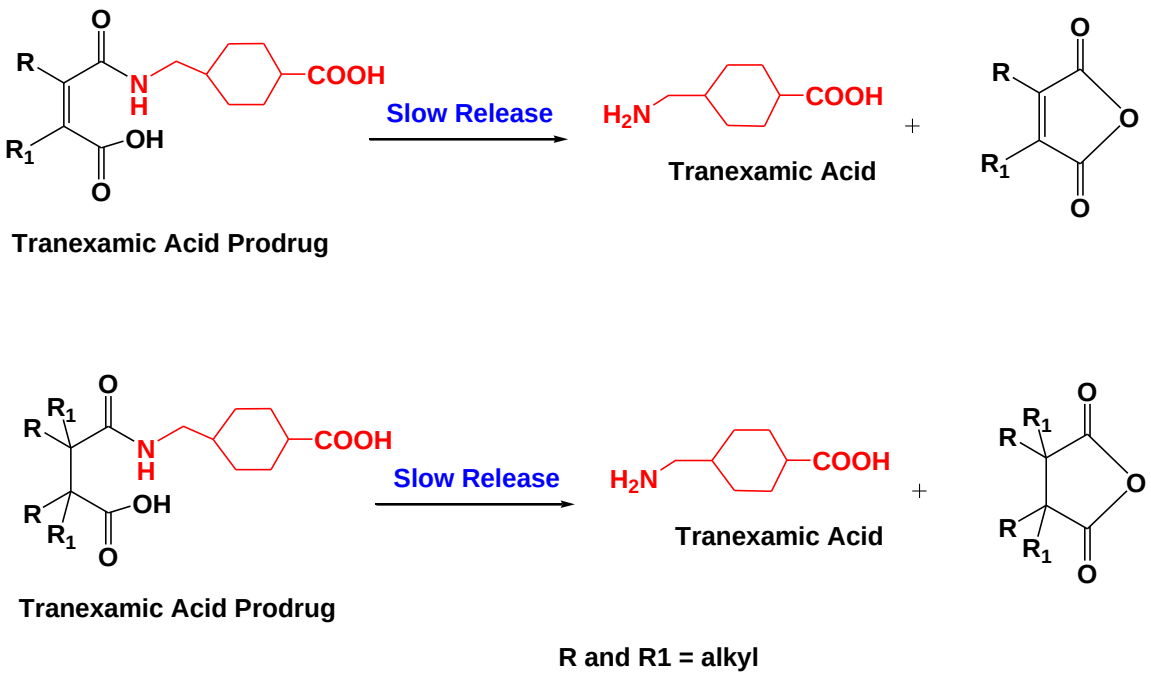


Figure 2: Conversion of Tranexamic acid prodrugs to their parent drug, Tranexamic Acid.

Nowadays the contemporary drug synthesis relies on computational approaches. Thus instead of starting the experimental work computational calculations are done for each drug giving a hint on the expected experimental results.

1.4 Thesis Objectives

1.4.1General objectives:

The main objective of this thesis was to complete the design of six Tranexamic acid prodrugs with a higher bioavailability and with the ability to release Tranexamic acid in the body in a controlled manner depending on solely intramolceular reactions (based on Kirby's enzyme model of intramolecular proton transfer using a variety of different molecular orbital and molecular mechanics).

1.4.2 Specific objectives:

To apply Kirby's enzyme model calculations on the design of six Tranexamic acid prodrugs. These prodrugs should fulfill the following properties:

1- To be able to release Tranexamic acid in a controlled manner.

2- To be able to increase the bioavailability of the drug.

3- To assure that the prodrug and the attached inactive linker is a safe manner.

1.5. Research questions:

- Would the DFT methods be capable of producing reaction rates similar to that obtained by Kirby?
- Do the DFT calculations offer good methods for designing of Tranexamic acid prodrugs that have the potential to provide the active drug with higher bioavailability and be cleaved in physiological environments to furnish the active drugs and a non-toxic moiety?
- How would the rate of release be affected by the surrounding environment?
- Can we provide a successful alternative to Tranexamic acid with higher bioavailability and fewer side effects?

Chapter Two

Literature Review

Chapter Two

Literature Review

2.1 Enzymes:

Enzymes are protein structures with crucial functions existing in our bodies. Their mechanism of action and interactions between enzymes and substrates had been explored extensively. The rate of a certain process is increased from 10^{10} to 10^{18} fold in the presence of enzymes when compared with their non-enzymatic bimolecular counterparts [35].

The majority of prodrugs are amides or esters which get activated by enzymatic action. Trypsin, chymotrypsin, elastase, carboxypeptidase, and aminopeptidase are considered the major enzymes responsible for amide prodrug activation. On the other hand, paraoxonase, carboxylesterase, acetylcholinesterase and cholinesterase are the major enzymes responsible for ester prodrugs activation. CYP450 enzymes are also engaged in prodrug activation [36].

One can control reaction rate by making slight changes in the structural features of enzyme model, thus, offering a wide range of reaction rates from 1 to 10^{15} folds [37]. Such a broad range enables prodrug design that is independent of enzymatic activation with varying release rates according to the main aim of the design.

Most of the existing prodrugs contain an ester or an amide bonds that occurs as a result of derivatizing a hydroxyl, carboxyl, or amine group present in the parental drug. Cleavage of these bonds occurs mainly by hydrolysis and oxidation. The main problem of enzymatic activation of prodrugs is unpredictable conversion rates which are affected by various factors such as: polymorphism, age, health, smoking and gender [38–40].

Both, enzymes and intramolecular processes are similar in that the reacting centers are held together (covalently with intra molecular systems, and non-covalently with enzymes) [41].

Mechanisms of some enzyme models that have been used to gain a better understanding of enzyme catalysis have been recently investigated and utilized by Karaman's group for the design of novel prodrug linkers [42-48].

2.2 Prodrugs:

In 1958 the term prodrug was first introduced by Albert *et al.* Prodrugs are reversible derivatives of drug molecules designed to overcome certain pharmaceutical, pharmacokinetic and pharmacodynamic problems, such as low oral absorption, lack of site specificity, insufficient chemical stability, poor solubility, toxicity, and unacceptable taste/odor [49].

Prodrug design has been more popular and successful than designing a novel drug. Prodrugs represent approximately 10% of the world's marketed medications and 20% of all small molecular medications that had been approved between 2000 and 2008 [50].

Prodrugs can be designed as targeted, chemically activated or intramolecularly activated prodrugs. Targeted prodrugs are designed to takes advantage from the physiological environment by attaching the drug to a moeity that have carrier/enzyme specifity. Targeted prodrugs need a wide knowledge of the functional and molecular characteristics of particular enzymes or carriers. Fora successful prodrug targeting the following requirements must befulfilled as suggested by Stella and Himmelstein: the drug must be

transported to its site rapidly, cleaved there selectively and retained at its site of action for a reliable time [51].

Intramolecularly activated prodrugs does not depend on enzymatic activation, they are solely dependent on the rate limiting step of the intramolecular reaction. These prodrugs are designed depending on calculations using molecular orbital (MO) and molecular mechanics (MM).

2.2.1. Conventional prodrug classification:

Prodrugs are classified based on the type of carriers and derivatization into:

(1) Carrier-linked prodrugs, in which the promoiety is covalently linked to the active drug but it can be easily cleaved by enzymes (such as an ester or labile amide) or non-enzymatically to provide the parent drug [52, 53].

(2) Bioprecursors which are chemical entities that are metabolized into new compounds that may be active or further are metabolized to active metabolites (such as amine to aldehyde to carboxylic acid). In this prodrug type there is no carrier but the compound should be readily metabolized to induce the necessary functional groups [54-56].

2.2.2. Prodrug approach associated disadvantages:

Although the prodrug approach is very popular, yet there are several challenges to be faced:

- Esterase hydrolysis: the most common approaches for prodrug design are aimed at prodrugs undergoing *in vivo* cleavage to the active drug by catalysis of hydrolyses such as peptidases, phosphates, and carboxyl-esterases[57]. Several hydrolyase activated prodrugs have bioavailability around 50% because of their premature hydrolysis during the absorption process in the enterocytes of the gastrointestinal tract [57]. Hydrolysis inside the enterocytes releases the active drug, which in most cases is more polar and less permeable than the prodrug and is more likely to be effluxes by passive and carrier-mediated processes back into the lumen than to proceed into blood, therefore limiting oral bioavailability.
- Bioactivation by cytochrome P450 enzymes: The CYP450 superfamily enzymes play a major role in drug metabolism that accounts for approximately 75% of enzymatic metabolism of drugs. The genetic polymorphisms of prodrug-activating P450s contribute substantially to the variability in prodrug activation and thus to the efficacy and safety of drugs using this bioactivation pathway [58,59].

To overcome such problems of the traditional prodrugs, the novel prodrug approach for drugs that contain hydroxyl, phenol, or amine groups is considered a great alternative. These drugs are designed based on intramolecular processes (enzyme models), that were advocated to assign the factors playing dominant role in enzyme catalysis. Prodrug design is based on computational calculations, using different molecular orbital and molecular

mechanics methods, and correlations between experimental and calculated rate values for some intramolecular processes.

Such approach does not require enzyme catalysis for the intra-conversion of a prodrug to its active parent drug. The release rate of the active drug is determined only by the factors playing dominant role in the rate limiting step of the intra-conversion process. Using this approach might have a potential to eliminate all disadvantages associated with prodrug interconversion by enzymes[60].

In the past five decades proposals have been made from attempts to interpret changes in reactivity versus structural variations in intramolecular systems. Many organic chemists and biochemists, such as Pandit and Bruice [61,62], Koshland[63],Kirby [64] and Menger [65-70], have been extensively engaged in studying a variety of intramolecular systems (enzyme models) for achieving a better understanding of biochemical enzyme catalysis.

As was mentioned previously, Karaman et al. had been engaged in the investigation of the mechanisms of some intramolecular processes. His group has been researching the mechanistic pathways of some intramolecular processes that was mentioned above, to be utilized in designing prodrugs for common drugs that suffer from poor bioavailability or/and have bitter sensation [71-77]. They have designed a variety of prodrugs that are independent of enzymatic catalysis for active drug release; instead, they are completely dependent on intramolecular chemical reactions for their release. This is because prodrugs that depends on enzyme catalysis are vulnerable and unpredicted because there are many intrinsic and extrinsic factors that can affect their bioconversion. For example, the activity of many prodrug activating enzymes may be flocculated due to genetic polymorphisms, age-related physiological changes or drug interactions, leading to adverse pharmacokinetics, pharmacodynamics and clinical effects. In addition, there are wide

interspecies variations in both the expression and function of most of the enzyme systems activating prodrugs which could lead to serious challenges in the preclinical optimization phase [78].

Utilizing DFT and ab initio molecular orbital calculation methods, Karaman et al. have studied intramolecular processes (enzyme models) to assign the factors affecting the rate-limiting step and playing dominant roles in governing the reaction rate. Among these enzyme models are:

(1) Proton transfer between two oxygens in Kirby acetals and between nitrogen and oxygen in Kirby's enzyme models [79].
(2) Intramolecular acid-catalyzed hydrolysis in Kirby's maleamic acid amide derivatives [44, 47-48].
(3) Proton transfer between two oxygens in rigid systems as investigated by Menger[64-67] and Cohen [80-82].
(4) S_N2-based-cyclization reactions of di-carboxylic semi-esters to yield anhydrides as studied by Bruice [61, 62].
(5) Intramolecular S_N2-based ring-closing reactions as researched by Brown and Mandolini[83,84].

From Karaman's studies on intramolecularity it was concluded that:

- Rate enhancement in intramolecular processes is a result of both entropic and enthalpy effects. In the cases by which enthalpy effects were predominant such as ring-closing and proton transfer reactions proximity or/and steric effects were the driving force for the rate accelerations.
- The distance between two reactive centers plays an important role too. If the distance exceeds 3Å an intermolecular reaction is preferred and vice versa.

- In S_N2-based ring-closing reactions leading to three-, four- and five-membered rings the *gem*-dialkyl effect is more dominant in processes involving the formation of an unstrained five-membered ring, and the need for directional flexibility decreases as the size of the ring being formed increases.
- An efficient proton transfer between two oxygens and between nitrogen and oxygen in Kirby's acetal systems were affordable when a strong hydrogen bonding was developed in the products and the corresponding transition states leading to them.

2.3. Intermolecular and intramolecular reactions:

Since we lay a complete dependence on intramolecular forces for the release of active drug from our designed prodrugs, a brief explanation on the difference between intra and intermolecular forces and their subdivisions had been clarified.

2.3.1. Intermolecular forces:

Intermolecular forces are defined as the forces that determine the properties of substances. They are particularly important in terms of how molecules interact together and form biological organisms and life [85].

2.3.1.1. Intermolecular forces include the following types of bonding:

- Strong ionic attraction; electrostatic attraction between oppositely charged ions. This type constitutes the major type of bonding in ionic compounds.
- Intermediate dipole-dipole forces; substances whose molecules have dipole moment, have higher melting point or boiling point than those of similar molecular mass with no dipole moment.
- Weak London dispersion forces or van der Waal's force: these forces always operate in any substance. The force arises in from induced dipole and the interaction is weaker than the dipole-dipole interaction. In general, the heavier the molecule, the stronger the van der Waal's force of interaction; boiling points of inert gases increase as their atomic masses increase due to stronger Landon dispersion interactions.
- Hydrogen bonding; It is a special type of dipole-dipole attraction that occurs when a hydrogen atom bonded to an atom with high electronegativity (such as N,O,F) exists in the vicinity of another electronegative atom with a lone pair of electrons.

- Covalent bonding; covalent is really intramolecular force rather than intermolecular force. However, some solids are formed due to covalent bonding example: silicon, quartz etc.. These solids are hard, brittle, and have high melting points. Covalent bonding holds atoms tighter than ionic attraction.
- Metallic bonding; forces between atoms in metallic solids belong to another category. Valence electrons in metals are rampant. They are not restricted to certain atoms or bonds. Rather they run freely in the entire solid, providing good conductivity for heat and electric energy. This behavior of electrons gives special properties such as ductility and mechanical strength to metals.

2.3.2. Intramolecular forces:

Intramolecular forces are defined as the forces that hold atoms together making up a molecule. They include all types of chemical bonds and are considered much more stronger than the intermolecular ones[86].

2.3.2.1. Intramolecular reactions:

In these reactions the functional groups bring together on the same molecule resembling what occurs when an enzyme brings together the same functional groups in its active site. From their *ab initio* calculations Karaman and Menger had demonstrated that when the distance between the two reacting centers is about 2.4A□, an intramolecular reaction is more preferable. However, when the distance exceeds 3A□, the reaction usually proceeds via the intermolecular pathway [87].

Chapter Three
Computational (Design) section

Chapter Three:

Computational (Design) section

3.1. Computation programs:

Calculations software used in the accomplishment of thesis calculations were:

3.1.1. Argus lab.

3.1.2. Gaussian.

3.1.3. Molden.

3.1.1. Argus lab:

A popular program that is commonly used for molecular modeling, graphic, and drug design. It is available for free on the World Wide Web. It is used to draw and edit molecular structures, visualize them in three dimensions, rotate, translate and modify atoms and molecules, and more importantly run Molecular Mechanics and semiempirical Quantum Mechanical calculations.

Argus lab is used for optimizing geometries of the wanted molecules, it allows for calculating Molecular Mechanics (UFF/Amber force fields) and QM semi-empirical (INDO, AMI, PM3) calculations such as evaluating single-point energies for fixed geometry, geometry optimization in the ground state, and more importantly obtain UV-VIS spectra of delocalized systems in gas phase and in several dielectric environments [88].

Argus lab writes its own format of molecule file like, .xml, but also it can write xyz files that are used as an input for other calculation programs such as Molden. Nevertheless, Argus lab leaves a lot of temporary files that need further managing.

Working with Argus lab is kind of easy, at first we click at the Argus lab item, after the Argus lab screen has opened click on new, or click on open for a previously saved file.

Our policy is to run AM1 and UFF calculations. It is noteworthy to save the molecule in two names one before any modification on the molecule and the other after geometrical optimization.

After completing the work with Argus lab click on file then exit [89].

3.2.2. Gaussian2009:

Gaussian2009 was first introduced in 1970 by John Pople and it was named Gaussian70. Pople's had received a noble prize in 1998 for his work in the field of quantum computational chemistry.Gaussian09 is the latest version of this program and it is also freely downloadable.

Gaussian predicts the energies, molecular structures, and vibrational frequencies of atomic or molecular systems, along with numerous molecular properties in the gas or liquids phase depending on the basis of the classical quantum mechanics. It can be used by chemists, chemical engineers, biochemists, physicists and others scientist for research in established and emerging areas of chemical interest. It allows performing virtual chemistry with a reasonable cost and saving much experimental time in the laboratory [90].

Experimental chemists can use it to study molecules and reactions of definite or potential interest, including both stable species and those compounds which are difficult or impossible to observe experimentally (short-lived intermediates, transition structures and so on)[91]. AM1, PM3, MINDO/3, MNDO, HF, DFT, MP2 and MP3 in all possible different levels can be run using Gaussian 09.

Steps for using Gaussain09:

At first, an input file is created either by hand or via molden software.

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

Using molden:

- Viewing output files from files run in Gaussian 09. Further, input files for use in Gaussian 09 can be generated using Molden program.
- Dissecting the output file:the Z-matrix represents how the software knows the molecular geometry (structure). Notice that the molecule has no charge and a multiplicity of 1 (all paired electrons). The structure is also represented as a more standard xyz coordinate system. The distance matrix shows the distance of each atom from the other atoms, in units of angstroms.

3.3.3. Molden:

Molden is a package for displaying Molecular density from ab initio packages GAMESS-UK, GAMESS-US, GAUSSIAN and the Semi-Empirical packages.

Molden is used as a standardizing method since it interprets information from all of these programs into its own format.

The Molden program can also be used as a visual Z-matrix molecule editor, thereby allowing users to create the molecule of their choice and being able to save the geometry in the Molden format[92].

It is capable of displaying Molecular Orbitals, the electron density and the Molecular minus Atomic density. Either the spherically averaged atomic density or the oriented ground state atomic density can be subtracted for a number of standard basis sets. Molden supports contour plots, 3-d grid plots with hidden lines and a combination of both.

It can write a variety of graphics instructions; *postscript, XWindows, VRML, povray, OpenGL, tekronix4014, hpgl, hp2392 and Figure*. Both X-windows and OpenGL versions of Molden are also capable of importing and displaying of Chemx, PDB, and a variety of Mopac/Ampac files and lots of other formats. Molden also can animate reaction paths and molecular vibrations. It can calculate and display the true or Multipole Derived Electrostatic Potential and atomic charges can be fitted to the Electrostatic Potential calculated on a Connolly surface. Atom typing can be done automatically and interactively from within Molden, as well as running optimization jobs. Molden has a powerful Z-matrix editor which gives full control over the geometry and allows you to build molecules from scratch, including polypeptides. Molden was also submitted to the QCPE (QCPE619), although the X-windows version is considerably running behind on the current one [93].

3.2 Calculation methods:

3.2.1 Tranexamic acid prodrugs:

The Becke three-parameter, hybrid functional combined with the Lee, Yang and Parr correlation functional (B3LYP), were employed in the calculations using DFT. All calculations were carried out using the quantum chemical package Gaussian-2009. Calculations were carried out based on the restricted Hartree-Fock method. The starting geometries of all calculated molecules were obtained using the Argus Lab program and were initially optimized at the AM1 and HF/6-31G levels of theory, followed by optimization at the B3LYP/6-31G(d,p). Total geometry optimizations included all internal rotations.

Second derivatives were estimated for all 3N-6 geometrical parameters during optimization. An energy minimum (a stable compound or a reactive intermediate) has no negative vibrational force constant. A transition state is a saddle point which has only one negative vibrational force constant.

Transition states were located first by the normal reaction coordinate method where the enthalpy changes were monitored by stepwise changing the inter-atomic distance between two specific atoms. The geometry at the highest point on the energy profile was re-optimized by using the energy gradient method at the B3LYP/6-31G(d,p) level of theory.

Full optimization of the transition states was accomplished after removing any constrains imposed while executing the energy profile. The activation energies obtained from the DFT for all molecules were calculated with and without the inclusion of water (dielectric constant of water, 78.39).

The calculations with the incorporation of a water molecule were performed using the integral equation formalism model of the polarizable continuum model. In this model, the cavity is created via a series of overlapping spheres. The radii type employed was the United Atom Topological Model on radii optimized for the PBE0/6-31G (d) level of theory.

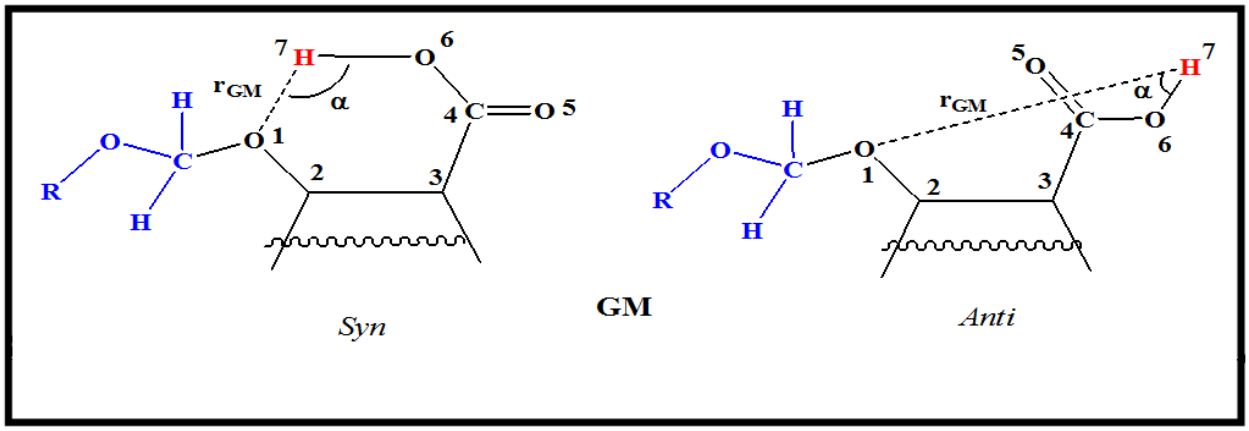


Chart 1: Schematic representation of the reactants in the proton transfers of Tranexamic acid. GM is the global minimum structure, r_{GM} is the O—H distance in the GM. α, is the angle of attack (hydrogen bonding) O1-H7-O6 in the GM.

Chapter Four
Results and Discussion

Chapter Four:

Results and Discussion

Continuing Karaman's work on the utilization of enzyme models as potential carriers for drugs containing amine and hydroxyl groups, and relying on Kirby's enzyme model of the proton transfer reactions in the acid-catalyzed hydrolysis of *N*-alkyl maleamic acids **1-7** (Figure 2); We have proposed six Tranexamic acid prodrugs, Tranexamic prodrugs **ProD1-ProD6** (Figure 3). Our strategy in prodrug design was by replacing the *N*-methyl amide group in 1–7 of Kirby's *N*-alkylmaleamic acid (Figure 4) with a Tranexamic acid entity, as shown for **ProD1-ProD6** in (Figure 2).

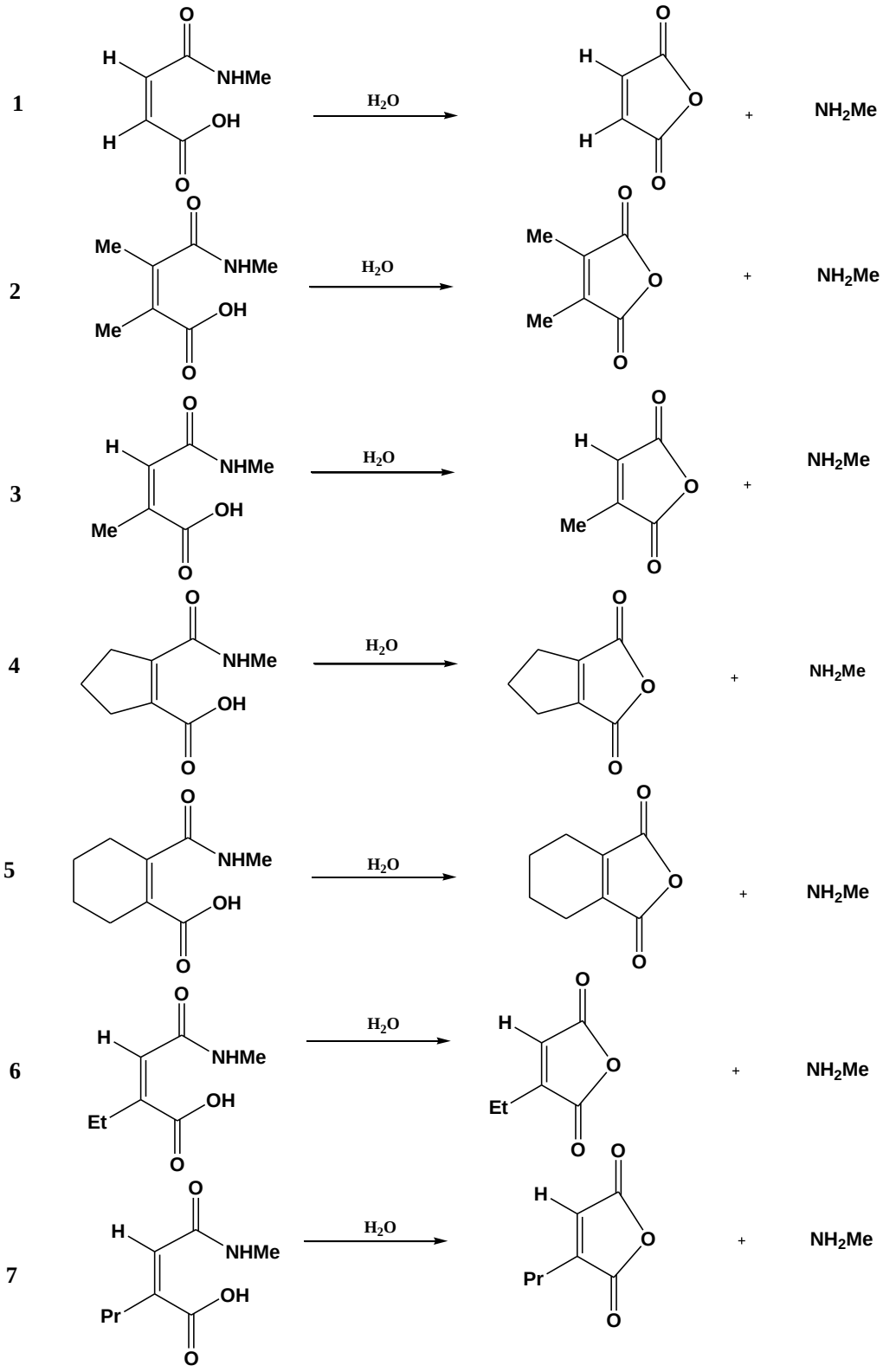


Figure 3: Acid-catalyzed hydrolysis of 1-7 *N*-alkylmaleamic acids.

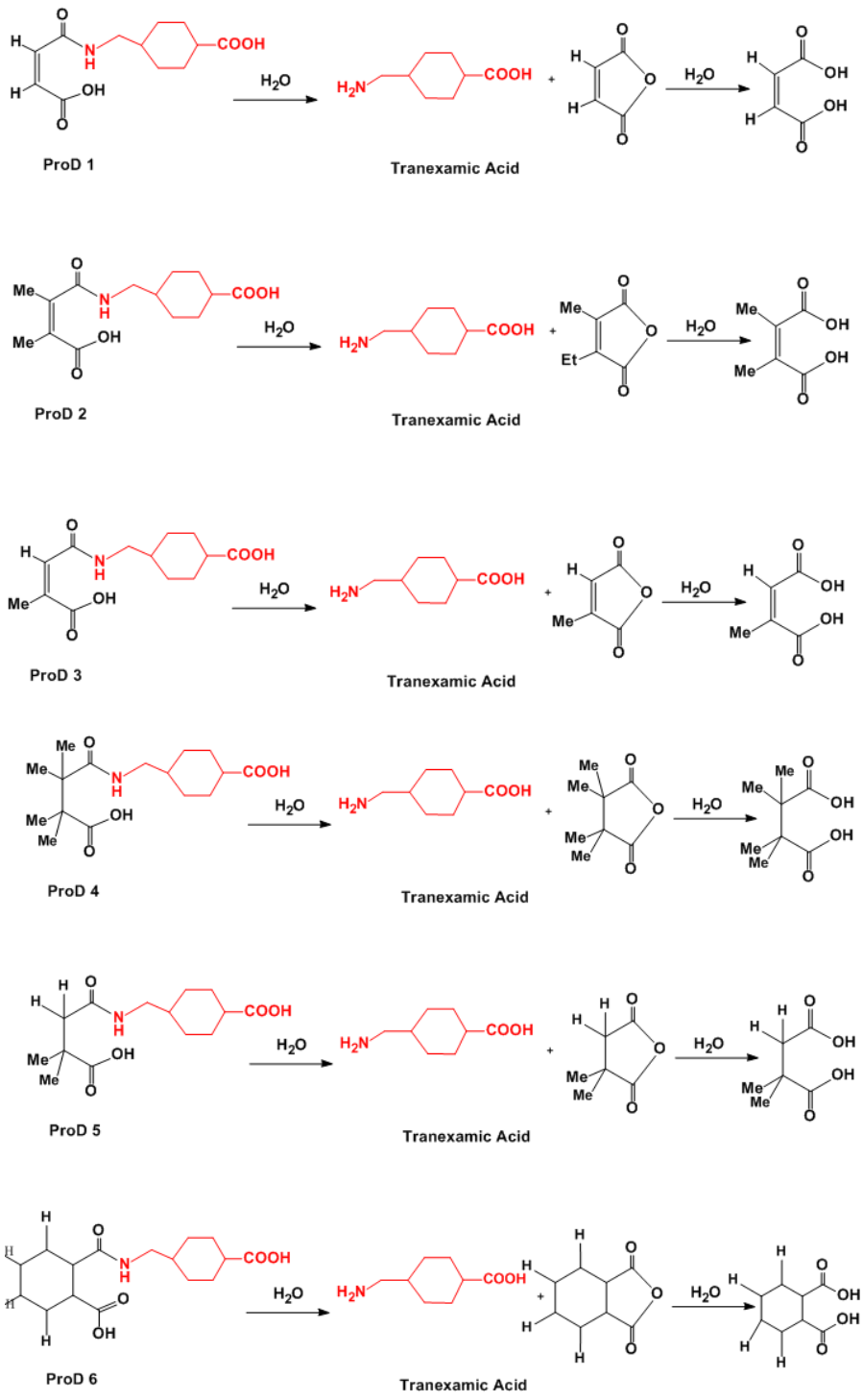


Figure 4: Structural formula of the proposed Tranexamic acid **ProD 1-ProD 6**.

As shown in Figure 4, Tranexamic acid prodrugs, **ProD1-ProD6** have a carboxylic group (hydrophilic moiety) and a lipophilic moiety (the rest of the prodrug), where the combination of both moieties secures a relatively moderate HLB.

Tranexamic acid itself will exist primarily as an ionized entity in most of the physiological environments (pH 1- 8.0) (Figure 5). However, our proposed prodrugs**ProD1-ProD6** will equilibrate between the ionic and the free acid forms (Figure 5) especially in the physiological pH environment of 5.5-6.8 (intestine).

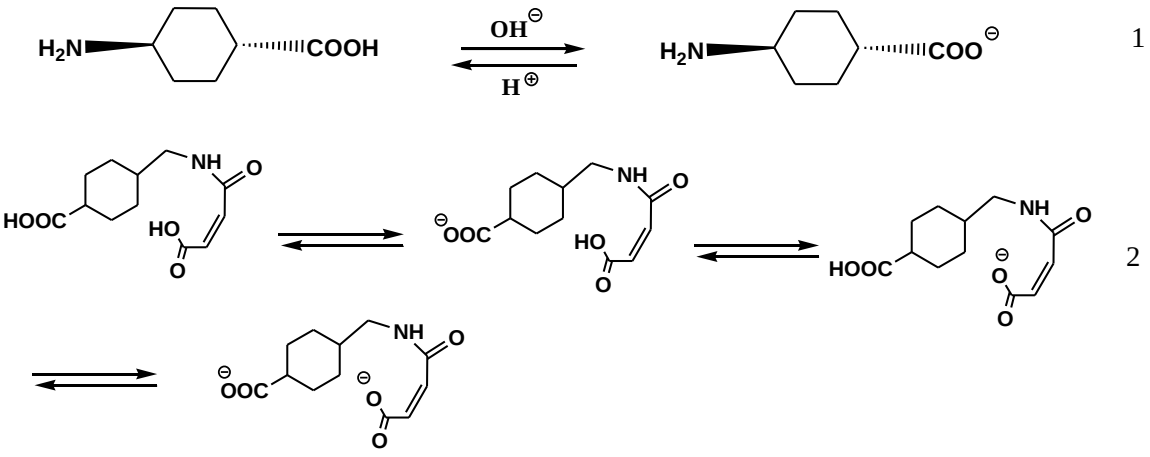


Figure 5: The ionization of Tranexamic acid and Tranexamic acid prodrug at the physiological environment.

As a result, it is expected that these designed prodrugs will improve the pharmacokinetic parameters of the parent drug including its bioavailability due to neutralizing the ionization of the amine group which results in the oral absorption improvement. In addition, these prodrugs may be used in different dosage forms (i.e. enteric coated tablets, topical use and etc.) because of their potential solubility in organic and aqueous media due to the ability of the carboxylic group to be converted to the corresponding carboxylate anion in a physiological pH of around 6.0.

It should be emphasized that at pH 5.5-6.5 (SC, skin, mouth cavity and intestine physiologic environments) the carboxylic group of the prodrugs will equilibrate with the corresponding carboxylate form (Figure 5). Subsequently, the free acid form will undergo

proton transfer reaction (rate limiting step) to yield the antifibrinolytic drug, tranexamic acid, and the inactive linker as a by-product (Figure 4).

From his study on Kirby's enzyme model of acid catalyzed proton transfer in seven *N*-alkylmaleamic acid derivatives, Karaman have revealed that the rate limiting step depends on the reaction media; in the gas phase the rate limiting step was found to be tetrahedral intermediate formation while, in the water phase the rate limiting step was tetrahedral intermediate collapse.

Also, He had revealed that other factors significantly affect the acid-catalyzed hydrolysis efficiency including; angle of attack(α), difference between the strain energies of the intermediate and product, as well as between the intermediate and reactant and the strain energy (Es_{INT}), and finally the distance between the hydroxyl oxygen of the carboxylic group and the amide carbonyl carbon(r_{GM}).

DFT calculations made by Karaman have proved that the acid catalyzed reaction proceeds in three consecutive steps:

(1) Proton transfer from the carboxylic group to the adjacent amide carbonyl oxygen.
(2) Nucleophilic attack of the carboxylate anion onto the protonated carbonyl carbon.
(3) Dissociation of the tetrahedral intermediate to provide products (Figure 6).

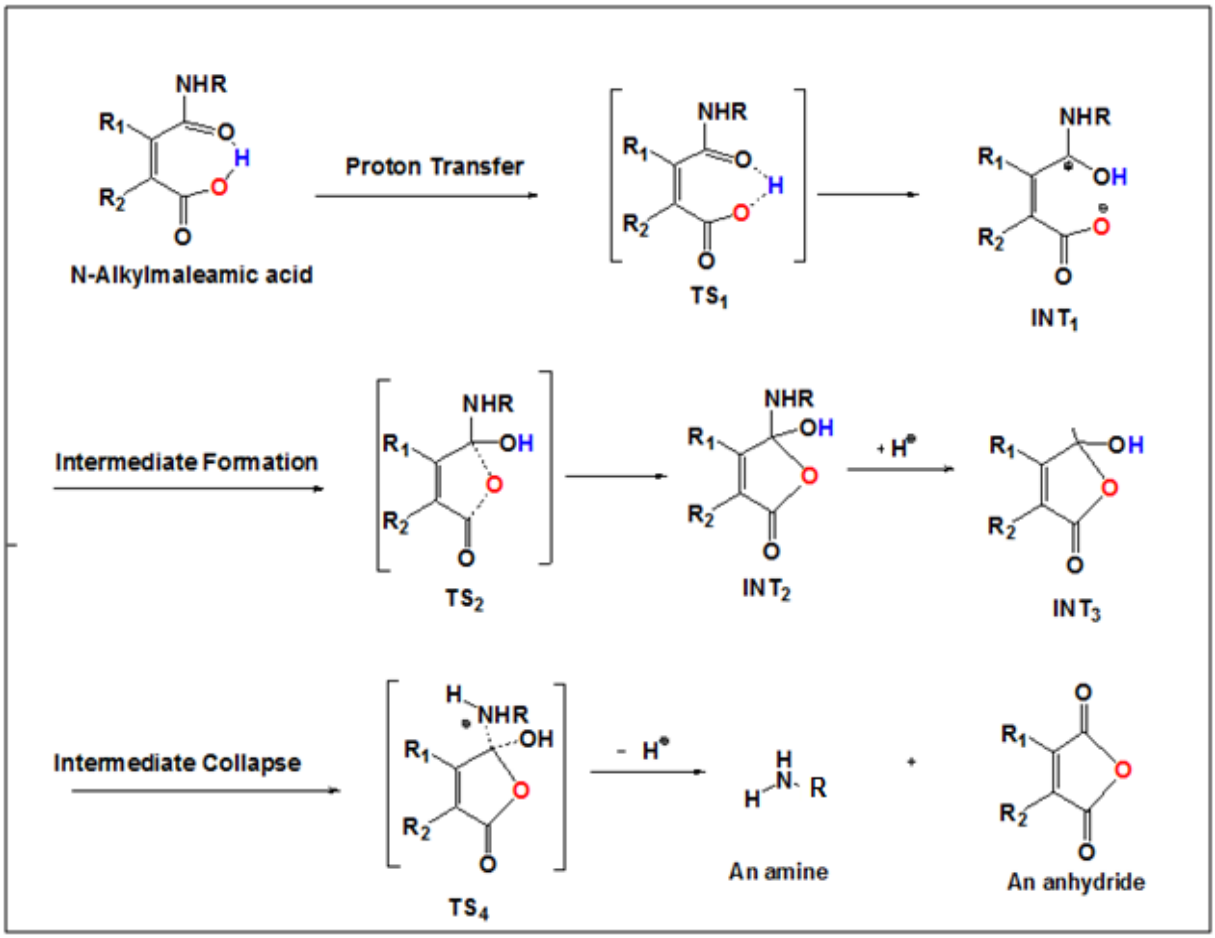


Figure 6: Proposed mechanism for the acid-catalyzed hydrolysis of *N*-alkylmaleamic acids.

In this section, we report DFT at B3LYP 6-31G (d,p) level calculations of ground state and transition state structures, vibrational frequencies, and reaction trajectories for intramolecular proton transfer in Tarnexamic acid prodrugs **ProD1- ProD6.**

Computations were directed toward elucidation of the transition and ground state structures for the acid-catalyzed hydrolysis of tranexamic acid **ProD1– ProD6** in the gas phase, dielectric constant of water (79.38). It is expected that the stability of the chemical entities will be different in the gas phase compared to that in water phase.

4.1 General Consideration

Because the energy of a carboxylic acid amide molecule is strongly dependent on its conformation and the latter determines its ability to be engaged in intramolecular hydrogen bonding, we were concerned with the identification of the most stable conformation (global minimum) for each of prodrugs **ProD1– ProD6** calculated in this study. This was accomplished by 360° rotation of the carboxylic group about the bond C6-C7 (i.e., variation of the dihedral angle O1C7C6C5, Chart 1), and 360° rotation of the carbonyl amide group about the bond C4-C5 (i.e., variation of the dihedral angle O3C4C5C6) in increments of 10° and calculation of the conformational energies (Chart 1).

In the DFT calculations for tranexamic acid **ProD1– ProD6**, two types of conformations in particular were considered: one in which the amide carbonyl is *syn* to the carboxyl group and another in which it is *anti*. The global minimum search for tranexamic **ProD1- ProD6** revealed that **ProD1, ProD2 and ProD3** exist in the *syn* orientation while **ProD4-ProD6** exists in the *anti*-orientation (Chart 1).

4.2. Optimized geometries of the entities involved in the proton transfers of tranexamic acid ProD1- ProD6.

4.2.1 Global minimum geometries (GM):

The calculated B3LYP/6-31G(d,p) geometries along with selected bond distances and bond angles for the global minimum structures of **ProD1GM-6GM** are illustrated in Figure7.

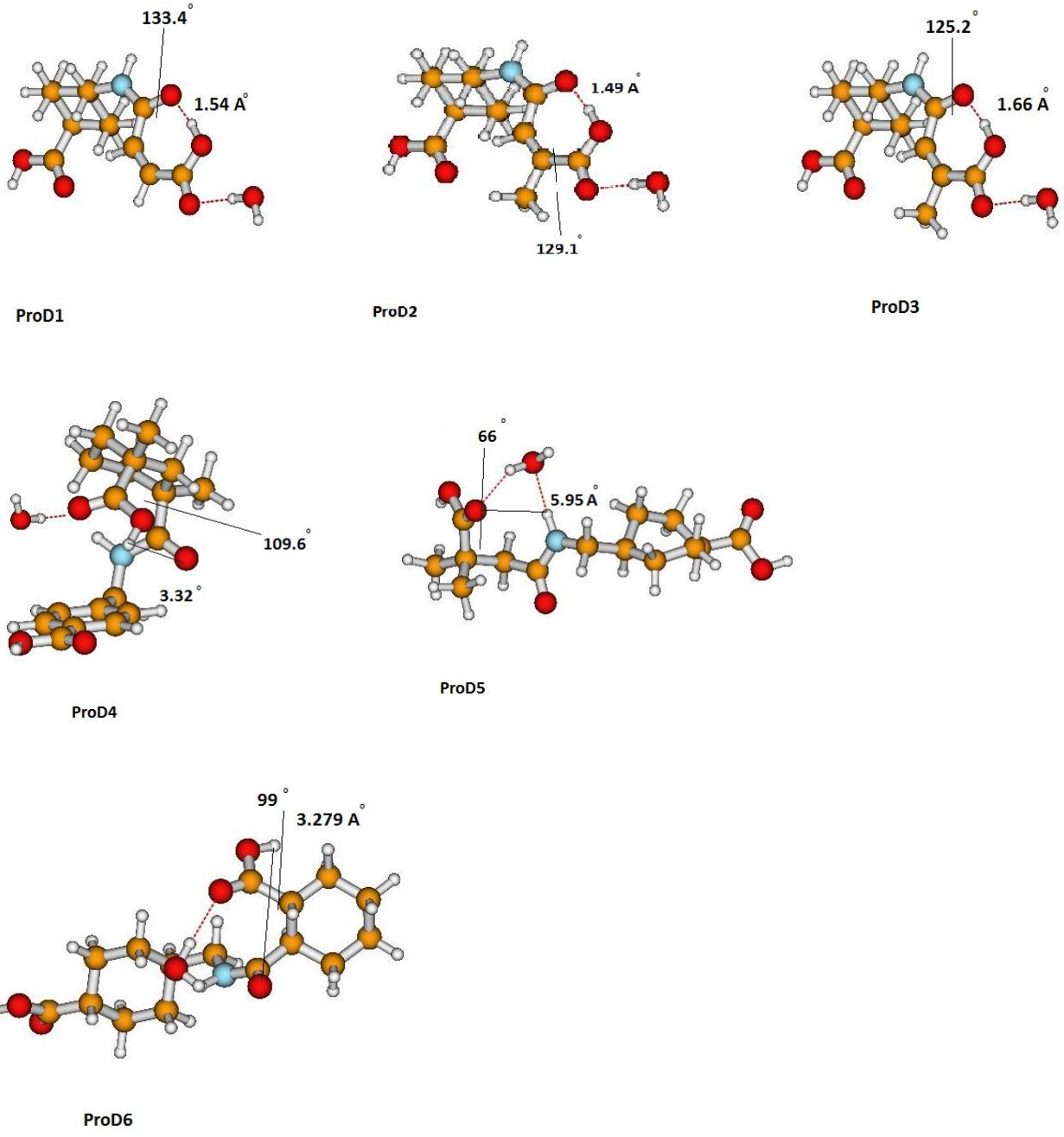


Figure 7: DFT optimized structures for the global minimum (**GM**) structures in the intramolecular proton transfer reaction of tranexamic **ProD 1-ProD 6**.

Examination of the calculated geometries of **ProD1GM-6GM** (Figure7) indicates that **ProD1**, **ProD2 and ProD3** exhibit conformation by which the carboxyl group is engaged intramolecular in a hydrogen bond with the neighboring amide oxygen.

The calculated B3LYP/6-31 G (d,p) intramolecular hydrogen bonding length r_{GM} (O1-H7) for these prodrugs was found to be less than 2.90Å for (**ProD1**, **ProD2**and**ProD3)**. Moreover, the hydrogen bond angle α (O1H7O6) was found to be the range of 125.2°-133.4°.

After the inspection of the optimized structures for**ProD4, ProD5** and**ProD6** in Figure 6 it was shown that have r_{GM} values of 3.32Å, 5.95Å and 3.27Å, and the hydrogen bond angle α values of 109.6°, 66.2° and 99° respectively.

4.2.2. Optimized tetrahedral intermediate geometries (INT):

The calculated properties for the tetrahedral intermediate geometries **(ProD1INT-ProD6INT**) are summarized in Table 1 and illustrated in Figure 8.

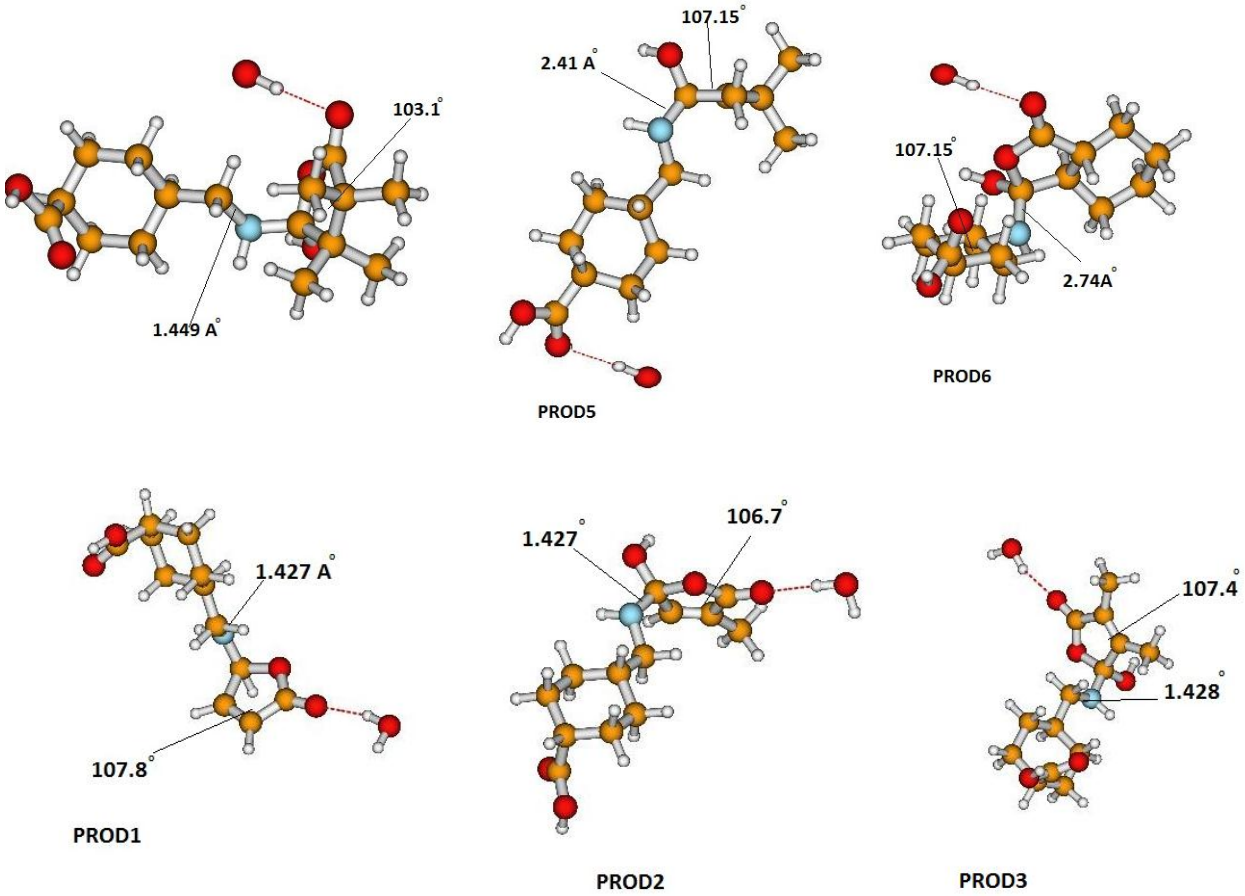


Figure 8: DFT optimized structures for the tetrahedral intermediate (INT) structures in the intramolecular proton transfer reaction of Tranexamic acid **ProD 1-ProD 6**.

4.2.2 Transition state geometries (TS):

The calculated properties for the transition state geometries of **(ProD 1TS-ProD 6TS**) are summarized in Table 1 and illustrated in Figure 9.

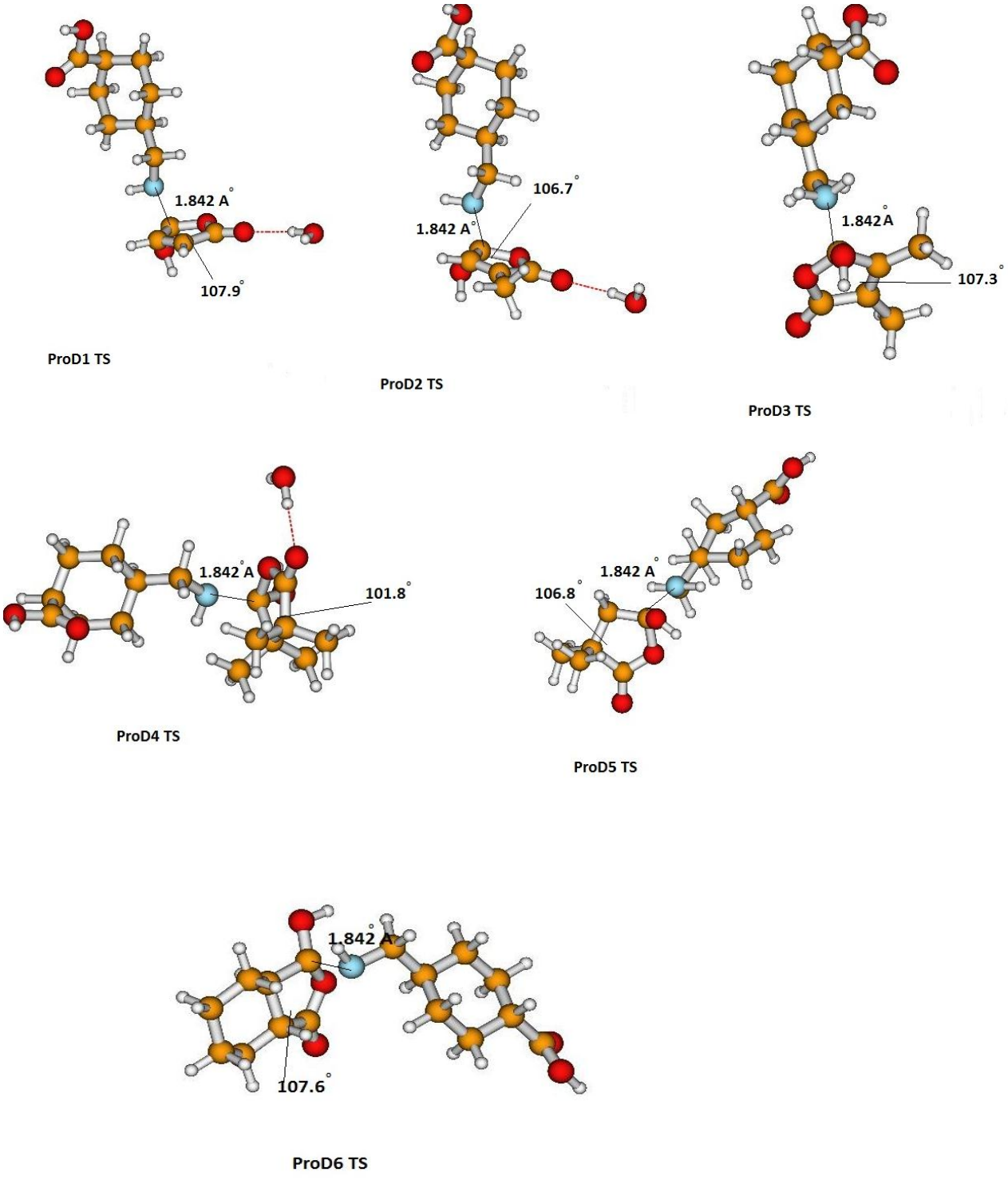


Figure 9: DFT optimized structures for the transition states in the intramolecular proton transfer reaction of Tranexamic acid **ProD1-ProD 6**.

4.3 DFT calculations of the kinetic and thermodynamic energies for the proton transfer reaction in Tranexamic acid ProD1- ProD6.

The kinetic and thermodynamic properties for the global minimum (GM), intermediate (INT) and transition state (TS) structures were calculated using the DFT at B3LYP/6-31 G (d,p) level of theory. The enthalpy and entropy energy values for all entities were calculated in both; the gas phase and the water phase. The data are shown in table1.

Table 1: DFT (B3LYP) calculated properties for the proton transfer reactions of in Tranexamic acid **ProD1- ProD6.**B3LYP refer to values calculated by B3LYP/6-31G (d, p). (GM) and (TS) are global minimumand transition state structures, respectively.

Compound	B3LYP, Enthalpy, H (gas phase) in Hartree	B3LYP (gas phase) Entropy, S, Cal/Mol-Kelvin	B3LYP Frequency Cm^{-1}
Tranexamic**ProD1GM**	-974.8819081	163.12	-------
Tranexamic**ProD1TS**	-974.8326548	148.66	145.69i
Tranexamic**ProD2GM**	-1014.2048171	171.51	-------
Tranexamic**ProD2TS**	-1014.1594626	156.97	115.95i
Tranexamic**ProD3GM**	-1053.5140615	179.62	-------
Tranexamic**ProD3TS**	-1053.4868204	171.73	102.39i
Tranexamic**ProD4GM**	-1133.3773287	177.52	-------
Tranexamic**ProD4TS**	-1133.3096986	171.68	145.69i
Tranexamic**ProD5GM**	-978.3127626	159.12	-------
Tranexamic**ProD5TS**	-978.2460971	151.16	-55,1342
Tranexamic**ProD6GM**	-1055.741283	162.53	-------
Tranexamic**ProD6TS**	-1055.680604	151.87	-78.2911

Using the calculated DFT values for the enthalpy and entropy of the global minimum structures of Tranexamic acid **ProD1**-**ProD6** and their corresponding transition states (Table 1) we have calculated the enthalpy activation energies ($\Delta H^{\ddagger}$), entropy activation

energies ($T\Delta S^{\ddagger}$), and the free activation energies ($\Delta G^{\ddagger}$) in the gas phase and water phase for the proton transfer reaction in these processes. The calculated energies are listed in Table 2.

Table 2: DFT (B3LYP/6-31G (d,p) calculated kinetic and thermodynamic properties for the proton transfers in kirby's 1-7 N-alkylmaleamic acids and in Tranexamic acid **ProD1-ProD 6**.

System	$\Delta H^{\ddagger}$ **(GP)**	$T\Delta S^{\ddagger}$ **(GP)**	$\Delta G^{\ddagger}$ **(GP)**	$\Delta H^{\ddagger}$ **(H_2O)**	$\Delta G^{\ddagger}$ **(H_2O)**
Tranexamic**ProD1**	33.52459878	-2.255715	35.78031378	33.74416208	36.81662708
Tranexamic**ProD2**	27.59055391	-2.220669	29.81122291	30.81535457	33.03602357
Tranexamic**ProD3**	37.73696366	-4.317489	42.05445266	40.88658947	45.20407847
Tranexamic**ProD4**	30.29145232	-3.320757	33.61220932	33.71209667	37.03285367
Tranexamic**ProD5**	41.83280125	-2.363526	44.19632725	38.83264665	42.15340365
Tranexamic**ProD6**	38.07619179	-3.168099	41.24429079	41.04628899	45.36377799

Table 3:DFT (B3LYP) calculated kinetic and thermodynamic properties for the acid catalyzed hydrolysis of 1-7 N-alkylmaleamic acid and Tranexamic acid**ProD 1- ProD6**.

System	Es_{INT}	Es_{GM}	$\Delta H^{\ddagger}$ (GP)	$\Delta G^{\ddagger}$ (GP)	$\Delta H^{\ddagger}$ (H_2O)	$\Delta G^{\ddagger}$ (H_2O)	log k_{rel} (Exp)
1	20.55	10.16	32.46	33.53	25.01	26.10	0
2	16.16	10.82	25.67	27.08	16.49	17.90	4.371
3	17.32	9.40	30.68	32.57	22.91	24.80	1.494
4	27.89	12.30	41.88	45.37	28.67	32.16	-4.377
5	19.25	9.18	24.55	26.87	15.57	17.89	2.732
6	17.59	5.12	30.11	32.12	21.86	23.87	1.516
7	18.55	6.20	30.76	32.30	22.86	24.40	1.648
TAProD 1	23.41	14.84	30.91	35.22	19.77	24.08	-----
TAProD 2	21.58	15.02	28.46	32.79	16.63	20.99	-----
TAProD 3	19.98	14.19	17.09	19.44	7.38	9.73	-----
TAProD 4	25.60	19.06	42.44	44.18	23.41	25.15	-----
TAProD 5	21.98	15.19	42.13	44.19	38.83	41.83	-----
TAProD 6	23.60	16.06	45.36	41.24	41.05	38.07	-----

4.3.1. The role of the distance O1-H7 (r_{GM}) and the angle O1H7O6 (α) on the rate of the proton transfer in processes Tranexamic acid ProD1- ProD6.

Careful inspection of Table 2 indicates that the distance between the two reactive centers r_{GM} (O1-H7) varies according to the conformation of the global minimum structure (GM). Short r_{GM} distance values were achieved when the values of the attack angle (α) in the GM conformations were high and close to 180°, whereas small values of α resulted in longer r_{GM} distances. In fact when the r_{GM} values were plotted against the corresponding α values linear correlation was obtained with $R^2 = 0.968$ (Figure 10).

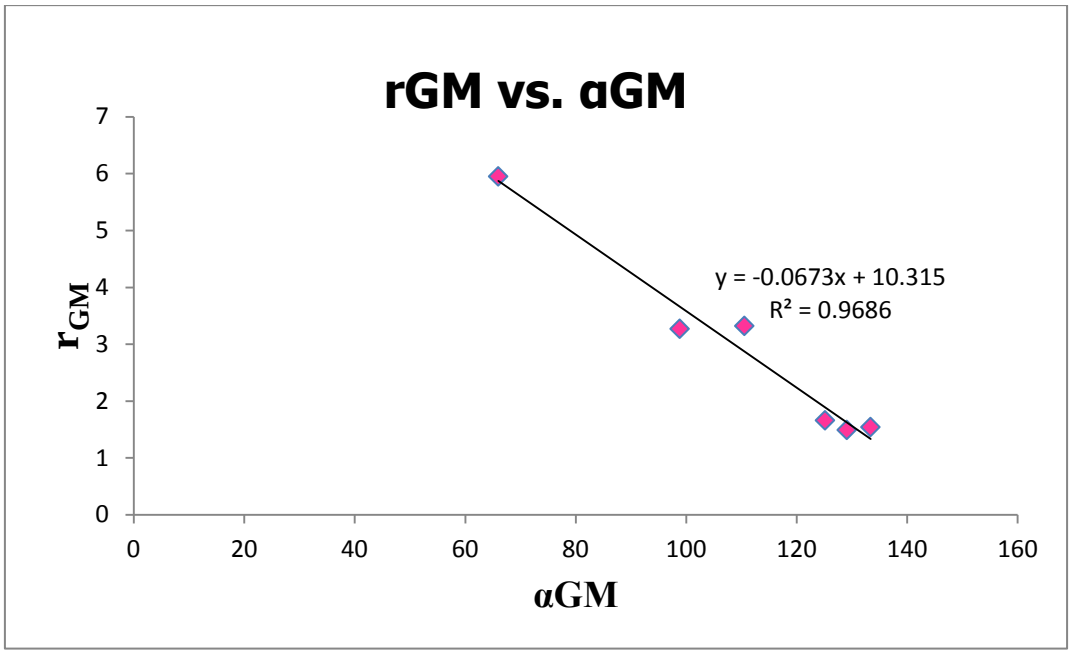


Figure 10: Plot of the DFT calculated r_{GM} (Å) vs. angle α (°) for tranexamic acid **ProD1**-**ProD6**, where (r_{GM}) and (α) are the distance between the two reactive centers and the attack (hydrogen bond) angle in the GM structure, respectively.

In addition, examination of the activation energy values ($\Delta G^{\ddagger}$) listed in Table 2 reveals that the energy needed to execute proton transfer in systems tranexamic acid **ProD1**- **ProD6**, is largely affected by both the distance between the two reactive centers r_{GM} (O1-H7), and the attack angle α (O1H7O6). Systems with low r_{GM} and high α values in their global minimum structures, such as **(ProD1, ProD2** and **ProD3)** exhibit much higher rates (lower $\Delta G^{\ddagger}$) than these with high r_{GM} and low α values, such as **ProD4, ProD5** and **ProD6** (figure 7).

4.3.2The role of the strain energy of the intermediates (Es_{INT}) on the rate of the proton transfer in processes Tranexamic acid ProD1- ProD5.

The strain energy values of the intermediates for tranexamic acid **ProD1-ProD6** (Es_{INT}) were calculated using Allinger's MM2 method, to examine the role of the (Es_{INT}) on the rate of the proton transfer in process tranexamic acid **ProD1-ProD6.**

The MM2 strain energies of the intermediates are listed in (Table 3). The calculated MM2 (Es_{INT}) values for the process tranexamic acid **ProD1-ProD6** were examined for correlation with the calculated DFT activation free energies ($\Delta G^{\ddagger}$), a linear correlation was found between $\Delta G^{\ddagger}$ and Es_{INT} with a satisfied correlation coefficient of R^2=0.694.

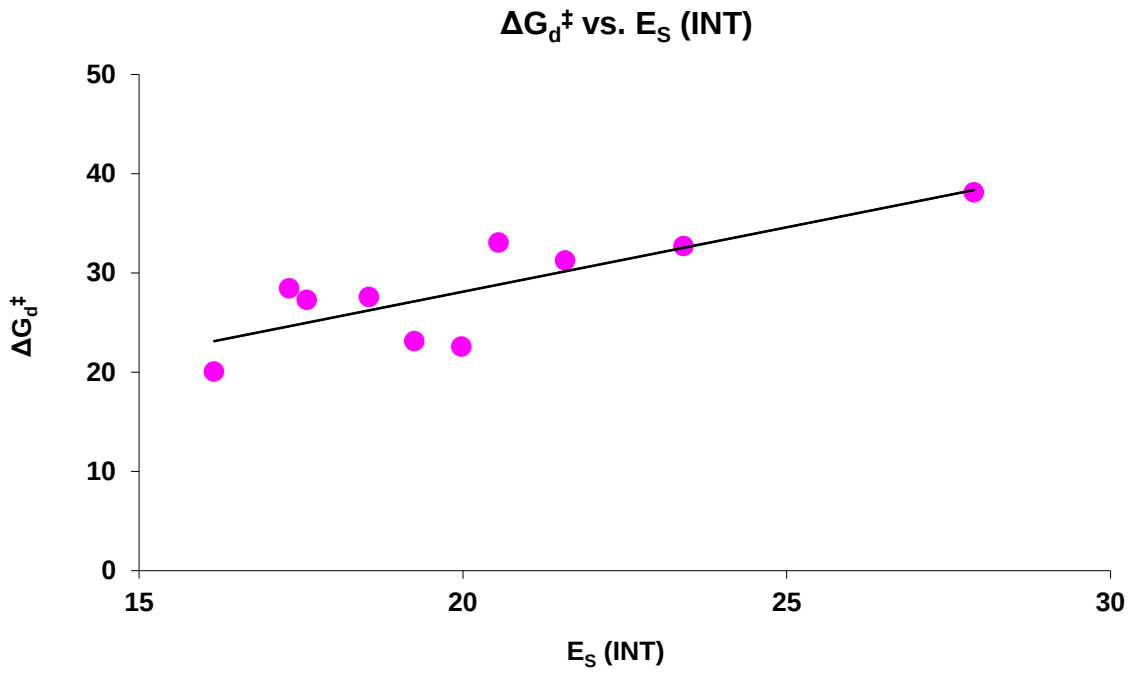


Figure 11: Plot of the DFT calculated $\Delta G^{\ddagger}$ vs. $Es_{INT}$for *N*-alkylmaleamic acid **1-7** and tranexamic acid**ProD1-ProD6.**

Examination of Figure 11 and Table 3 reveals thatthe rate of a proton transfer in processes tranexamic acid **ProD1**-**ProD6**is largely dependent on the strain energy of the tetrahedral intermediate. Systems having strained tetrahedral intermediates were found to be with low rates and *vice versa*.

In order to further support this conclusion, the B3LYP 6-31G (d,p)activation energy values for **1**-**7** *N*-alkylmaleamic acid calculated in water ($\Delta G^{\ddagger}_{H2O}$, see Table 3) were examined for correlations with log k_{rel} and the results are shown in(Figure 12). A linear correlation was found between $\Delta G^{\ddagger}_{H2O}$and log $k_{rel}$with a correlation coefficient of R^2= 0.9303.

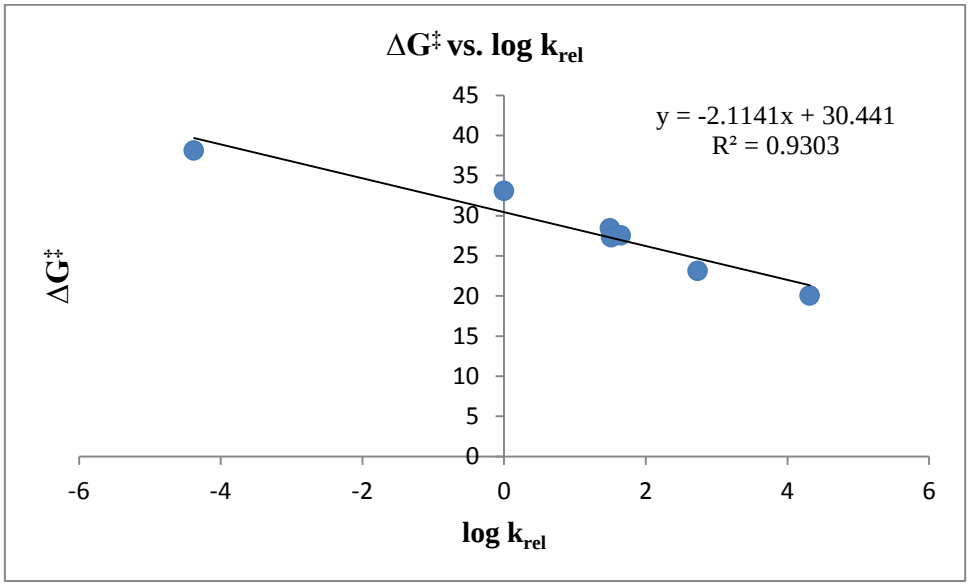


Figure 12: Plot of the DFT calculated $\Delta G^{\ddagger}$vs. relative rate (log $_{krel}$) in 1-7 N-alkylmaleamic 4acid.

Furthermore, a linear correlation was found between the strain energies for intermediates of 1-7 *N*-alkylmaleamic acid (Es_{INT}) and log k_{rel}(Figure 13) with a correlation coefficient of R^2= 0.885.

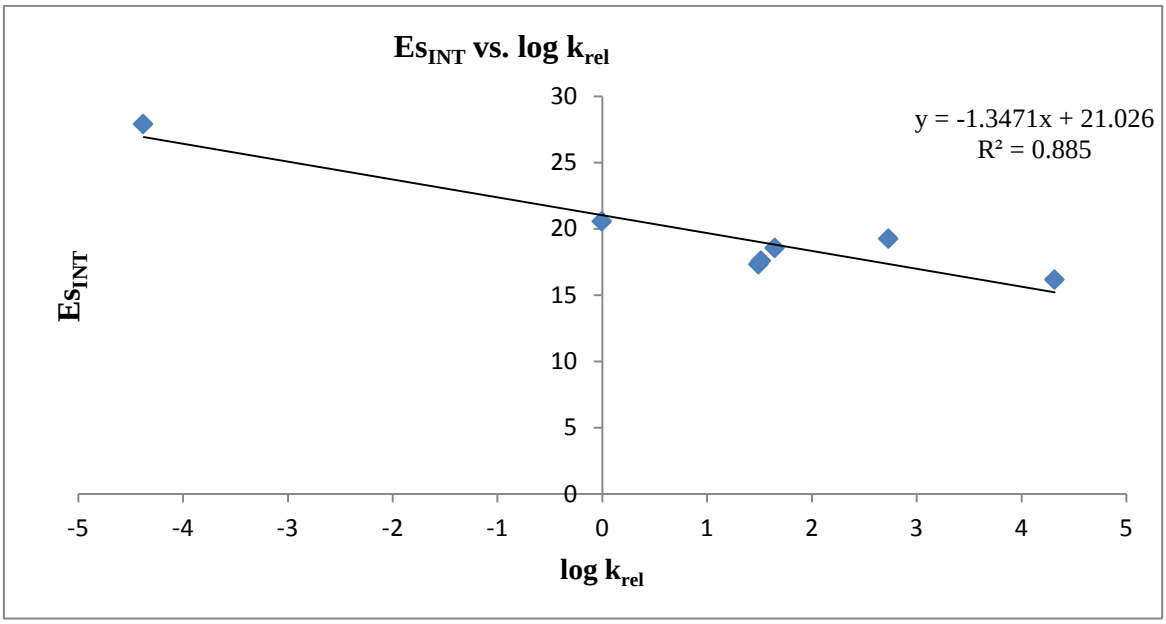


Figure 13: Plot of the Es_{INT} for intermediates of 1-7 *N*-alkylmaleamic acid vs. relative rate (log_{krel}).

Chapter Five

Conclusions and Future Directions

Chapter Five:

Conclusions and future directions

5.1. Conclusions:

Relying on the increased number of documented post-partum hemorrhage (PPH) mortality especially in the third world we were encouraged to design a number of Tranexamic acid prodrugs using the DFT calculations based on Kirby's model of acid catalyzed hydrolysis of N-alkylmaleamic acids.

As it is known Tranexamic acid is an amino acid derivative with a low bioavailability and short half-life. Each one of the designed prodrugs has a different linker moiety with a potential to provide the drug with a higher bioavailability and a controlled release pattern depending solely on intramolecular interactions based on Kirby's enzyme model (proton transfer in *N*-alkylmaleamic acids).

Our proposed prodrugs have a carboxylic group as a hydrophilic moiety and a hydrocarbon skeleton as a lipophilic moiety, where the combination of both groups ensures a moderate hydrophilic lipophilic balance value.

DFT calculations were made to find prodrug candidates to be used as efficient Tranexamic acid delivery systems. The DFT calculation results revealed that the rate of a proton transfer in processes Tranexamic acid **ProD1**-**ProD6** is largely dependent on the geometric variations of the reactant (GM) mainly the distance between the two reactive centers, r_{GM}, and the angle of attack α. It was found that systems with low r_{GM} and high α values in their global minimum structures, such as **ProD1**, **ProD2** and **ProD3**, exhibit much higher rates (lower $\Delta G^{\ddagger}$) than these with high r_{GM} and low α values, such as **ProD4, ProD5** and**ProD6**.

Moreover, it was found that the rate of a proton transfer in processes Tranexamic **ProD1**-**ProD6** is largely dependent on the strain energy of the tetrahedral intermediate. Systems having strained tetrahedral intermediates were found to be with low rates and *vice versa*.

Therefore, we conclude that the best candidates to fulfill the requirements needed to reach better bioavailability than the parent Tranexamicacid are the following: **ProD1**, **ProD2**and**ProD3.**

5.2. Future directions:

- According to the DFT calculations for 1-6 tranexamic acid designed prodrugs. It is recommended to synthesize tranexamic acid **ProD1, ProD2**and**ProD3** using Kirby's model for further experimental work. In vitro and in vivo testing should follow the synthetic procedure to determine pharmacokinetic and pharmacodynamics parameters for each prodrug.
- *In vitro* kinetics should be conducted at different pH's mimicking that of the physiological environment.
- *In vivo* studies each of these prodrugs should be administered to the animals via IV and *per os*. Samples should be collected and testes routinely. The concentration of Tranexamic acid should be determined by reliable controlled method.
- Finally, toxicological studies assuring the safety of the prodrug and the released linker must also be conducted.

References:

1. Karaman, R., Fattash, B., & Qtait, A. (2013). The future of prodrugs–design by quantum mechanics methods. *Expert opinion on drug delivery*, *10*(5), 713-729.
2. Dewar, M. J., & Thiel, W. (1977). Ground states of molecules. 38. The MNDO method. Approximations and parameters. *Journal of the American Chemical Society*, *99*(15), 4899-4907.
3. Bingham, R. C., Dewar, M. J., & Lo, D. H. (1975). Ground states of molecules. XXV. MINDO/3. Improved version of the MINDO semiempirical SCF-MO method. *Journal of the American Chemical Society*, *97*(6), 1285-1293.
4. Dewar, M. J., Zoebisch, E. G., Healy, E. F., & Stewart, J. J. (1985). Development and use of quantum mechanical molecular models. 76. AM1: a new general purpose quantum mechanical molecular model. *Journal of the American Chemical Society*, *107*(13), 3902-3909.
5. Dewar, M. J., Jie, C., & Yu, J. (1993). The first of a new series of general purpose quantum mechanical molecular models. *Tetrahedron*, *49*(34), 7393.
6. Parr, R. G. (1980). Density functional theory of atoms and molecules. In *Horizons of Quantum Chemistry* (pp. 5-15). Springer Netherlands.
7. Burkert, U., & Allinger, N. L. (1982). Pitfalls in the use of the torsion angle driving method for the calculation of conformational interconversions. *Journal of Computational Chemistry*, *3*(1), 40-46.
8. Warshel, A., & Levitt, M. (1976). Theoretical studies of enzymic reactions: dielectric, electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme. *Journal of molecular biology*, *103*(2), 227-249.
9. Field, M. J. (2002). Simulating enzyme reactions: challenges and perspectives. *Journal of computational chemistry*, *23*(1), 48-58.
10. Mulholland, A. J. (2005). Modelling enzyme reaction mechanisms, specificity and catalysis. *Drug discovery today*, *10*(20), 1393-1402.
11. Cyklokapron_ tranexamic acid injection prescribing information: http://www.pfizer.com/files/products/uspi_cyklokapron.pdf

12. Mayur, G., Purvi, P., Ashoo, G., & Pankaj, D. (2007). Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: a randomized case controlled prospective study. *J Obstet Gynecol India*, *57*(3), 227-230.
13. Liumbruno, G. M., Bennardello, F., Lattanzio, A., Piccoli, P., & Rossetti, G. (2011). Recommendations for the transfusion management of patients in the peri-operative period. II. The intra-operative period. *Blood Transfus*, *9*(2), 189-217.
14. Lukes, A. S., Kouides, P. A., & Moore, K. A. (2011). Tranexamic acid: a novel oral formulation for the treatment of heavy menstrual bleeding. *Women's Health*, *7*(2), 151-158.
15. Lukes, A. S., Moore, K. A., Muse, K. N., Gersten, J. K., Hecht, B. R., Edlund, M., ... & Rubin, A. (2010). Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. *Obstetrics & Gynecology*, *116*(4), 865-875.
16. Wu, S., Shi, H., Wu, H., Yan, S., Guo, J., Sun, Y., & Pan, L. (2012). Treatment of melasma with oral administration of tranexamic acid. *Aesthetic plastic surgery*, *36*(4), 964-970.
17. Turki, A., & Michael, W. (2011). Tranexamic acid treatment of lifethreatening hematuria in polycystic kidney disease (case report). *Int J Nephrol*, *203579*.
18. Maeda K., Naganuma M. (1998). Topical trans-4-aminomethylcyclohexanecarboxylic acid prevents ultraviolet radiation-induced pigmentation. *Journal of Photochemistry and Photobiology B: Biology*, *47*(2), 136-141.
19. Dunn, C. J., & Goa, K. L. (1999). Tranexamic acid. *Drugs*, *57*(6), 1005-1032.
20. Nilsson, I. M. (1980). Clinical pharmacology of aminocaproic and tranexamic acids. *Journal of Clinical Pathology*, *33*(Suppl 14), 41-47.
21. Pilbrant, Å., Schannong, M., & Vessman, J. (1981). Pharmacokinetics and bioavailability of tranexamic acid. *European journal of clinical pharmacology*, *20*(1), 65-72.
22. Andersson, L., Nilsson, I. M., Niléhn, J. E., Hedner, U., Granstrand, B., & Melander, B. (1965). Experimental and Clinical Studies on AMCA, the Antifibrinolytically Active Isomer of p-Aminomethyl Cyclohexane Carboxylic Acid. *Scandinavian journal of haematology*, *2*(3), 230-247.
23. Windlund, L., Strömberg, S., Hallström, H., & Osanius, B. (1979). The disposition of tranexamic acid (AMCA) in various animal species and in man after oral dosage. *Stockholm, Sweden: Kabi AB*.

24. Thulin, C. A. (1972). Ability of tranexamic acid to cross the blood-brain barrier and its use in patients with ruptured intracranial aneurysm. *Acta Neurol. Scan&*, *48*.
25. Eriksson, O., Kjellman, H., & Nilsson, L. (1971). Tranexamic acid in human milk after oral administration of Cyklokapron to lactating women. *Kabi AB, Stockholm*.
26. Kullander, S., & Nilsson, I. M. (1970). Human placental transfer of an antifibrinolytic agent (AMCA). *Acta obstetricia et gynecologica Scandinavica*, *49*(3), 241-242.
27. Sindet-Pedersen, S. (1987). Distribution of tranexamic acid to plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. *The Journal of Clinical Pharmacology*, *27*(12), 1005-1008.
28. Hoylaerts, M., Lijnen, H. R., & Collen, D. (1981). Studies on the mechanism of the antifibrinolytic action of tranexamic acid. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *673*, 75-85.
29. Dubber, A. C., McNicol, G. P., Douglas, A. S., & Melander, B. (1964). Some properties of the antifibrinolytically active isomer of amino-methylcyclohexane carboxylic acid. *The Lancet*, *284*(7373), 1317-1319.
30. Andersson, L., Nilsson, I. M., Niléhn, J. E., Hedner, U., Granstrand, B., & Melander, B. (1965). Experimental and Clinical Studies on AMCA, the Antifibrinolytically Active Isomer of p-Aminomethyl Cyclohexane Carboxylic Acid. *Scandinavian journal of haematology*, *2*(3), 230-247.
31. VANRIPER, D., Horrow, J., Strong, M. D., & Malik, N. (1993, September). Tranexamic acid is hemostatic when administered only during heparinization. In *Anesthesiology* (Vol. 79, No. 3 A, pp. A93-A93). 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106: LIPPINCOTT-RAVEN PUBL.
32. Albert, A. (1958). Chemical aspects of selective toxicity. *Nature*, *182*(4633), 421.
33. Ducloy-Bouthors, A. S., Jude, B., Duhamel, A., Broisin, F., Huissoud, C., Keita-Meyer, H.,& Depret-Mosser, S. (2011). High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Critical care*, *15*(2), 1.
34. Ayedi, M., Jarraya, A., Smaoui, M., Zouari, J., Smaoui, L., & Kolsi, K. (2011). Effect of tranexamic acid on post partum hemorrhage by uterine atony: a preliminary result of a randomized, placebocontrolled trial: 11AP4-7. *European Journal of Anaesthesiology (EJA)*, *28*, 165.
35. Lehninger Al, Nelson D., Cox M. Principles of Biochemistry Worth Publishers,2000.**book**

36. Karaman, R., Prodrugs Design-A New Era. Nova science publishers, 2014. **book**: p. 293.
37. Kirby, A. J., Hollfelder, F. (2009). *From enzyme models to model enzymes*. Royal Society of Chemistry.
38. Draganov DI., La Du BN. (2004). Pharmacogenetics of paraoxonases: a brief review. *Naunyn-Schmiedeberg's archives of pharmacology*, *369*(1), 78-88.
39. Ngawhirunpat, T., Kawakami, N., Hatanaka, T., Kawakami, J., & Adachi, I. (2003). Age dependency of esterase activity in rat and human keratinocytes. *Biological and Pharmaceutical Bulletin*, *26*(9), 1311-1314.
40. Moser, V. C., Chanda, S. M., Mortensen, S. R., & Padilla, S. (1998). Age-and gender-related differences in sensitivity to chlorpyrifos in the rat reflect developmental profiles of esterase activities. *Toxicological sciences*, *46*(2), 211-222.
41. Liebman, J. F. (1988). *Mechanistic principles of enzyme activity* (No. 04; QP601, L5.).
42. Karaman, R. (2008). Analysis of Menger's 'spatiotemporal hypothesis'. *Tetrahedron Letters*, *49*(41), 5998-6002.
43. Karaman, R. (2009). Cleavage of Menger's aliphatic amide: a model for peptidase enzyme solely explained by proximity orientation in intramolecular proton transfer. *Journal of Molecular Structure: THEOCHEM*, *910*(1), 27-33.
44. Karaman, R. (2010). The efficiency of proton transfer in Kirby's enzyme model, a computational approach. *Tetrahedron Letters*, *51*(16), 2130-2135.
45. Karaman, R., & Pascal, R. (2010). A computational analysis of intramolecularity in proton transfer reactions. *Organic & biomolecular chemistry*, *8*(22), 5174-5178.
46. Karaman, Rafik. "A general equation correlating intramolecular rates with 'attack'parameters: distance and angle." *Tetrahedron Letters* 51, no. 39 (2010): 5185-5190.
47. Karaman, R. (2011). Analyzing the efficiency of proton transfer to carbon in Kirby's enzyme model—a computational approach. *Tetrahedron Letters*, *52*(6), 699-704.
48. Karaman, R. (2011). Analyzing the efficiency in intramolecular amide hydrolysis of Kirby's N-alkylmaleamic acids–A computational approach. *Computational and Theoretical Chemistry*, *974*(1), 133-142.

49. Huttunen, K. M., Raunio, H., & Rautio, J. (2011). Prodrugs—from serendipity to rational design. *Pharmacological reviews*, *63*(3), 750-771.
50. Stella, V. J. (2011). Prodrugs: Some thoughts and current issues. J Pharm Sci 99: 4755–4765. *Journal of Pharmaceutical Sciences*, *100*(10), 4560-4560.
51. Stella, V. J., & Himmelstein, K. J. (1985). Prodrugs: a chemical approach to targeted drug delivery. In *Directed Drug Delivery* (pp. 247-267). Humana Press
52. Jana, S., Mandlekar, S., & Marathe, P. (2010). Prodrug design to improve pharmacokinetic and drug delivery properties: challenges to the discovery scientists. *Current medicinal chemistry*, *17*(32), 3874-3908.
53. Higuchi, T., & Stella, V. (Eds.). (1975). *Pro-drugs as novel drug delivery systems*. American Chemical Society.
54. Stella, V., Borchardt, R., Hageman, M., Oliyai, R., Maag, H., & Tilley. (2007). *Prodrugs: challenges and rewards*. Springer Science & Business Media.
55. Müller, C. E. (2009). Prodrug approaches for enhancing the bioavailability of drugs with low solubility. *Chemistry & Biodiversity*, *6*(11), 2071-2083.
56. Roche, E. B. (1977). *Design of biopharmaceutical properties through prodrugs and analogs: a symposium*. Amer Pharmacutical Assn.
57. Liederer, B. M., & Borchardt, R. T. (2006). Enzymes involved in the bioconversion of ester-based prodrugs. *Journal of pharmaceutical sciences*, *95*(6), 1177-1195.
58. Beaumont, K., Webster, R., Gardner, I., & Dack, K. (2003). Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist. *Current drug metabolism*, *4*(6), 461-485.
59. Gonzalez, F. J., & Tukey, R. H. (2006). Drug metabolism. *Goodman and Gilman's. The Pharmacological Basis of Therapeutics. 11ª ed. McGraw-Hill*, 71-91.
60. Testa, B., & Kraemer, S. D. (2007). The biochemistry of drug metabolism–an introduction. *Chemistry & biodiversity*, *4*(3), 257-405.
61. Bruice, T. C., & Pandit, U. K. (1960). The effect of geminal substitution ring size and rotamer distribution on the intramolecular nucleophilic catalysis of the hydrolysis of monophenyl esters of dibasic acids and the solvolysis of the intermediate anhydrides. *Journal of the American Chemical Society*, *82*(22), 5858-5865.
62. Bruice, T. C., & Pandit, U. K. (1960). INTRAMOLECULAR MODELS DEPICTING THE KINETIC IMPORTANCE OF „FIT" IN ENZYMATIC CATALYSIS. *Proceedings of the National Academy of Sciences*, *46*(4), 402-404.

63. Dafforn, A., & Koshland, D. E. (1973). Proximity, entropy and orbital steering. *Biochemical and biophysical research communications*, *52*(3), 779-785.
64. Menger, F. M., & Ladika, M. (1988). Fast hydrolysis of an aliphatic amide at neutral pH and ambient temperature. A peptidase model. *J Am Chem Soc*, *110*(20), 6794-6796.
65. Menger, F. M. (1985). On the source of intramolecular and enzymatic reactivity. *Accounts of chemical Research*, *18*(5), 128-134.
66. Menger, F. M., Chow, J. F., Kaiserman, H., & Vasquez, P. C. (1983). Directionality of proton transfer in solution. Three systems of known angularity. *Journal of the American Chemical Society*, *105*(15), 4996-5002.
67. Menger, F. M. (1983). Directionality of organic reactions in solution. *Tetrahedron*, *39*(7), 1013-1040.
68. Kirby, A. J., & Hollfelder, F. (2009). *From enzyme models to model enzymes*. Royal Society of Chemistry.
69. Menger, F. M., Galloway, A. L., & Musaev, D. G. (2003). Relationship between rate and distance. *Chemical Communications*, (18), 2370-2371.
70. Menger, F. M. (2005). An alternative view of enzyme catalysis. *Pure and applied chemistry*, *77*(11), 1873-1886.
71. Karaman, R. (2011). Computational-Aided Design for Dopamine Prodrugs Based on Novel Chemical Approach. *Chemical biology & drug design*, *78*(5), 853-863.
72. Karaman, R., Dokmak, G., Bader, M., Hallak, H., Khamis, M., Scrano, L., & Bufo, S. A. (2013). Prodrugs of fumarate esters for the treatment of psoriasis and multiple sclerosis—a computational approach. *Journal of molecular modeling*, *19*(1), 439-452.
73. Karaman, R. (2013). Prodrugs for masking bitter taste of antibacterial drugs—a computational approach. *Journal of molecular modeling*, *19*(6), 2399-2412.
74. Hejaz, H., Karaman, R., & Khamis, M. (2012). Computer-assisted design for paracetamol masking bitter taste prodrugs. *Journal of molecular modeling*, *18*(1), 103-114.
75. Karaman, R. (2014). Using predrugs to optimize drug candidates. *Expert opinion on drug discovery*, *9*(12), 1405-1419.
76. Karaman, R. (2013). Prodrugs Design Based on Inter-and Intramolecular Chemical Processes. *Chemical biology & drug design*, *82*(6), 643-668.

77. Karaman, R. (2014). Prodrugs for Masking the Bitter Taste of Drugs. In *Application of Nanotechnology in Drug Delivery*. InTech.
78. Karaman, R. (2013). Antimalarial Atovaquone Prodrugs Based on Enzyme Models-Molecular Orbital Calculations Approach. *Antimalarial Drug Research and Development, Banet, A C. & Brasier, P. Ed*, 1-67. Karaman, R., Prodrugs Design-A New Era. Nova science publishers, 2014. **Book**.
79. Kirby, A. J. (1997). Efficiency of proton transfer catalysis in models and enzymes. *Accounts of chemical research*, *30*(7), 290-296.
80. Milstien, S., & Cohen, L. A. (1970). Concurrent general-acid and general-base catalysis of esterification. *Journal of the American Chemical Society*, *92*(14), 4377-4382.
81. Milstien, S., & Cohen, L. A. (1970). Rate acceleration by stereopopulation control: models for enzyme action. *Proceedings of the National Academy of Sciences*, *67*(3), 1143-1147.
82. Milstien, S., & Cohen, L. A. (1972). Stereopopulation control. I. Rate enhancement in the lactonizations of o-hydroxyhydrocinnamic acids. *Journal of the American Chemical Society*, *94*(26), 9158-9165.
83. Brown, R., & Van Gulick, N. (1956). The geminal alkyl effect on the rates of ring closure of bromobutylamines. *The Journal of Organic Chemistry*, *21*(9), 1046-1049.
84. Galli, C., & Mandolini, L. (2000). The role of ring strain on the ease of ring closure of bifunctional chain molecules. *European Journal of Organic Chemistry*, *2000*(18), 3117-3125.
85. Hirschfelder, J.O. and W.J. Meath. (1967), The nature of intermolecular forces: Wiley Online Library.
86. Pitzer, K. S. (1993). Inter-and intramolecular forces and molecular polarizability. In *Molecular Structure And Statistical Thermodynamics: Selected Papers of Kenneth S Pitzer* (pp. 239-263).
87. Karaman, R. (2009). Reevaluation of Bruice's proximity orientation. *Tetrahedron Letters*, *50*(4), 452-456.
88. Oda, A. and O. Takahashi., (2009). Validation of ArgusLab efficiencies for binding free energy calculations. Chem-Bio Informatics Journal: p. 52-61.
89. http://www.chem.iitb.ac.in/latest/notices/CH831_newmanual.pdf
90. https://www.csuc.cat/sites/default/files/docs/treballantgaussian09.pdf

91. Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R. & Nakatsuji, H. (2010). Gaussian 09: EM64L-G09RevB. 01, Gaussian. *Inc., Wallingford*.
92. Schaftenaar, G., & Noordik, J. H. (2000). Molden: a pre-and post-processing program for molecular and electronic structures. *Journal of computer-aided molecular design*, *14*(2), 123-134.
93. http://www.cmbi.ru.nl/molden/

Supplementary Material

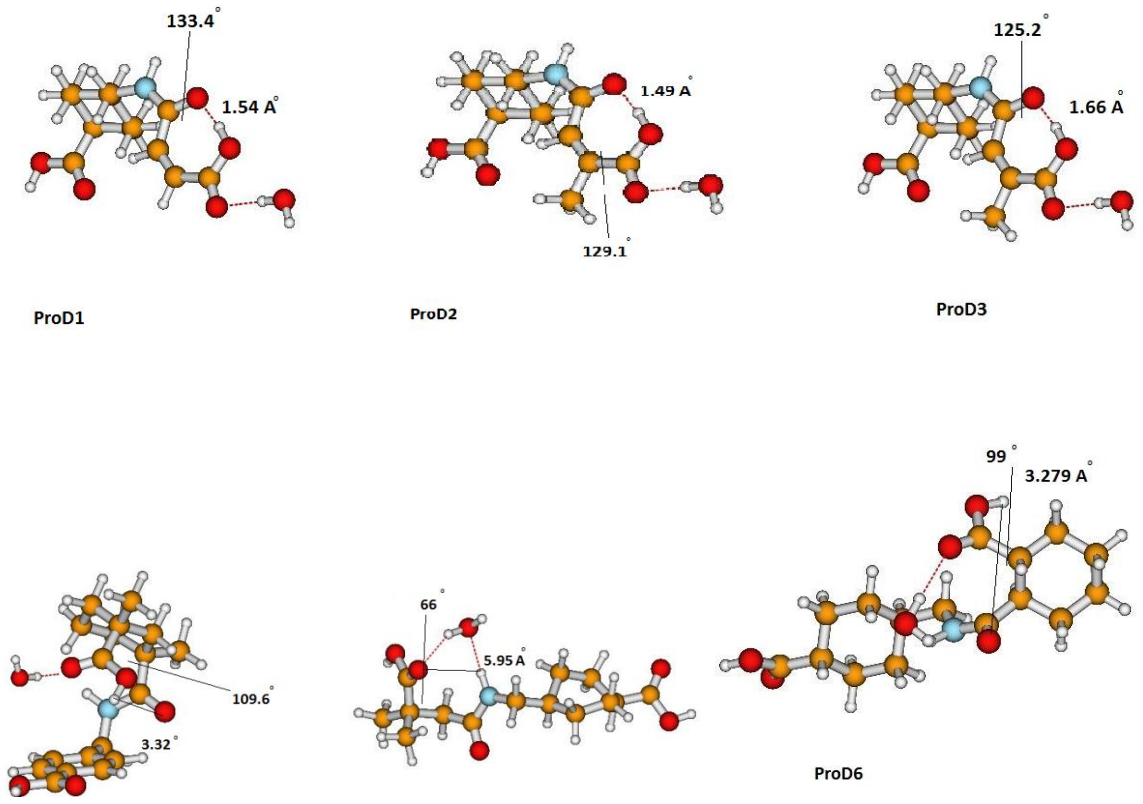
Content:

1- Figures of optimized structures of tranexamic acid prodrugs 1-6 GM.

2- DFT calculated energies for the proton transfers in Tranexamic acid **ProD1 – ProD6**.

3- Xyz Cartesian coordinates for the DFT optimized GM, TS and P in processes tranexamic acid**ProD 1- ProD6.**

Compound	B3LYP, Enthalpy, H (gas phase) in Hartree	B3LYP (gas phase) Entropy, S, Cal/Mol-Kelvin	B3LYP Frequency Cm^{-1}
Tranexamic**ProD1GM**	-974.8819081	163.12	-------
Tranexamic **ProD1TS**	-974.8326548	148.66	145.69i
Tranexamic **ProD2GM**	-1014.2048171	171.51	-------
Tranexamic **ProD2TS**	-1014.1594626	156.97	115.95i
Tranexamic **ProD3GM**	-1053.5140615	179.62	-------
Tranexamic **ProD3TS**	-1053.4868204	171.73	102.39i
Tranexamic **ProD4GM**	-1133.3773287	177.52	-------
Tranexamic **ProD4TS**	-1133.3096986	171.68	145.69i
Tranexamic **ProD5GM**	-978.3127626	159.12	-------
Tranexamic **ProD5TS**	-978.2460971	151.16	-55,1342
Tranexamic **ProD6GM**	-1055.741283	162.53	-------
Tranexamic **ProD6TS**	-1055.680604	151.87	-78.2911



Optimized GM structures of tranexamic**ProD1-ProD6.**

Prod 1 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.535313
C	1.429682	0.000000	2.106422
C	2.229731	-1.190989	1.553610
C	2.228367	-1.228705	0.016916
C	0.812419	-1.182718	-0.583682
C	1.388292	0.023322	3.645376
N	2.689257	0.239468	4.273121
C	3.530718	-0.600113	4.933046
O	4.583598	-0.129603	5.403692
C	0.074014	-2.500981	-0.400805
O	-1.113414	-2.501054	-1.057481
O	0.456079	-3.461992	0.232694

C	3.151557	-2.030261	5.048040
C	3.789644	-3.004457	5.724368
C	5.027998	-3.047364	6.589974
O	5.297866	-4.107145	7.124070
O	5.771780	-1.961301	6.741306
H	-0.554598	0.873203	1.901104
H	-0.537181	-0.885527	1.905028
H	1.921145	0.929763	1.776812
H	3.263436	-1.150609	1.914328
H	1.795046	-2.126300	1.926041
H	2.750560	-2.125514	-0.329012
H	2.784612	-0.364999	-0.369685
H	0.879309	-1.036192	-1.669462
H	-1.023305	-0.023079	-0.384998
H	0.455488	0.931123	-0.360158
H	0.952216	-0.903267	4.025728
H	0.725954	0.831668	3.978861
H	3.058942	1.182296	4.238376
H	-1.512817	-3.372302	-0.893592
H	2.259966	-2.333365	4.510540
H	3.348550	-3.996179	5.678448
H	5.389989	-1.189465	6.228524
H	6.967999	-3.902605	8.205189
O	7.757240	-3.853300	8.731657
H	7.954932	-4.687087	9.141801

Prod 1 INT

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.537591
C	1.446839	0.000000	2.085980
C	2.286207	-1.142351	1.497802
C	2.309152	-1.109465	-0.042047
C	0.870840	-1.118947	-0.594334
C	3.154172	-2.266988	-0.593342
N	3.319864	-2.153530	-2.041842
C	4.252454	-3.010039	-2.699825
O	5.595386	-2.684720	-2.235634
C	6.218184	-3.798549	-1.749060
C	5.284820	-4.950778	-1.868633
C	4.156415	-4.509088	-2.421474
O	4.110916	-2.721130	-4.055910
O	7.342796	-3.779617	-1.311433
C	-0.822933	-1.150801	2.099120
O	-1.429929	-1.984072	1.459966
O	-0.837419	-1.142343	3.456482
H	-1.393894	-1.893660	3.722779
H	2.700705	-3.225210	-0.282295
H	0.402545	-2.086619	-0.375711
H	1.434054	-0.053459	3.177864
H	-0.495994	0.909355	1.903909
H	0.379150	0.973424	-0.335584
H	2.796345	-0.176209	-0.359247
H	4.713354	-3.292181	-4.552952
H	2.442488	-2.176851	-2.548974
H	4.152359	-2.223001	-0.146239
H	3.259788	-5.068544	-2.663141
H	5.551959	-5.947949	-1.544948
H	1.882430	-2.108403	1.835450
H	0.879116	-1.002804	-1.684932

H	-1.024464	-0.092675	-0.372365	
H	3.309392	-1.082378	1.888146	
H	1.906306	0.959432	1.817173	

Prod 1 TS

C	2.063831	-2.112919	-0.062765	L H
O	2.691206	-0.145088	-1.074713	H
C	3.241551	0.468723	-0.091243	M H
O	3.708920	1.609448	-0.053411	H
H	4.339227	3.407917	0.020553	H
O	4.582708	4.335612	-0.134624	HH
H	4.510614	4.408238	-1.093788	HH
C	3.297714	-0.376767	1.173453	H
C	2.713152	-1.574705	1.164775	HH
H	2.699604	-2.239841	2.026420	H
H	3.803429	0.012692	2.052103	H
O	2.765415	-2.699373	-1.036033	HH
H	3.368235	-1.982226	-1.336004	M H
N	0.778762	-2.396614	-0.077791	HH
H	0.452282	-2.824190	-0.937524	H
C	-0.229342	-1.858695	0.842507	L H
H	0.234008	-1.759450	1.826831	H
H	-1.025816	-2.606105	0.920873	H
C	-0.797021	-0.505396	0.378776	H
H	0.050114	0.187891	0.287057	H
C	-1.766502	0.037373	1.444347	H
H	-1.246622	0.153069	2.403468	H
H	-2.570385	-0.694668	1.610729	H
C	-2.372439	1.384660	1.026833	H
H	-3.069978	1.744780	1.788243	H
H	-1.572103	2.130324	0.948619	H
O	-5.280076	1.144495	0.548845	HH

C	-2.134447	0.725417	-1.415239	H
O	-4.635178	-0.530831	-0.802502	L H
C	-1.489063	-0.604693	-0.992936	H
H	-2.264682	-1.379508	-0.959819	M H
H	-0.760533	-0.894188	-1.759479	H
H	-2.673709	0.586568	-2.356975	H
H	-1.346397	1.464852	-1.602406	H
H	-6.071159	0.579286	0.557784	HH
H	-3.371013	2.323064	-0.632268	H
C	-3.080033	1.303700	-0.348856	H
C	-4.380804	0.520584	-0.253049	HH

PROD 2 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.535313
C	1.429682	0.000000	2.106422
C	2.229731	-1.190989	1.553610
C	2.228367	-1.228705	0.016916
C	0.812419	-1.182718	-0.583682
C	1.388292	0.023322	3.645376
N	2.689257	0.239468	4.273121
C	3.530718	-0.600113	4.933046
O	4.583598	-0.129603	5.403692
C	0.074014	-2.500981	-0.400805
O	-1.113414	-2.501054	-1.057481
O	0.456079	-3.461992	0.232694
C	3.151557	-2.030261	5.048040
C	3.789644	-3.004457	5.724368
C	5.027998	-3.047364	6.589974
O	5.297866	-4.107145	7.124070
O	5.771780	-1.961301	6.741306
H	-0.554598	0.873203	1.901104
H	-0.537181	-0.885527	1.905028
H	1.921145	0.929763	1.776812
H	3.263436	-1.150609	1.914328
H	1.795046	-2.126300	1.926041
H	2.750560	-2.125514	-0.329012
H	2.784612	-0.364999	-0.369685
H	0.879309	-1.036192	-1.669462
H	-1.023305	-0.023079	-0.384998
H	0.455488	0.931123	-0.360158
H	0.952216	-0.903267	4.025728
H	0.725954	0.831668	3.978861
H	3.058942	1.182296	4.238376
H	-1.512817	-3.372302	-0.893592

H	2.259966	-2.333365	4.510540
C	3.176541	-4.382909	5.660541
H	5.389989	-1.189465	6.228524
H	6.967999	-3.902605	8.205189
O	7.757240	-3.853300	8.731657
H	7.954932	-4.687087	9.141801
H	3.781080	-5.076415	6.243210
H	2.167156	-4.350467	6.067985
H	3.139222	-4.715976	4.624397

PROD 2 INT

C	-2.886507	0.287352	-1.258472
C	-2.680121	-0.982066	-0.470897
O	-3.234890	-0.757369	0.793133
C	-3.786352	0.545613	0.831875
C	-3.563064	1.169983	-0.513157
N	-1.202985	-1.329392	-0.234872
C	-0.343608	-0.315893	0.490788
C	1.097373	-0.812386	0.647884
C	1.885788	0.251048	1.443983
C	3.361757	-0.138491	1.604948
C	4.054066	-0.398054	0.242935
C	3.260705	-1.446384	-0.562122
C	1.768415	-1.102843	-0.710947
C	4.210844	0.913331	-0.511457
O	5.421995	1.462815	-0.307570
O	-3.114510	-2.152101	-1.060762
O	-4.309163	0.978072	1.809508
C	-4.077097	2.533424	-0.816055
O	3.352755	1.446936	-1.190224
H	5.440829	2.309570	-0.787620

H	-0.381839	0.601722	-0.100811
H	1.674780	-0.221645	-1.354385
H	3.893933	0.641461	2.158188
H	5.059490	-0.781642	0.436980
H	3.362637	-2.408106	-0.044106
H	1.081513	-1.737289	1.246796
H	-4.066417	-2.101669	-1.238329
H	-0.786456	-1.553896	-1.145237
H	-0.826575	-0.144800	1.454307
H	-2.570950	0.383210	-2.291028
H	1.818285	1.211544	0.919426
H	1.282332	-1.949832	-1.219761
H	3.701015	-1.579194	-1.555098
H	1.432045	0.387914	2.432393
H	3.439351	-1.055047	2.202682
H	-3.682993	3.254048	-0.091869
H	-3.807684	2.851925	-1.823880
H	-5.167286	2.556050	-0.712859
H	-1.217796	-2.213200	0.289793

PROD 2 TS

N	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.842000
O	1.391148	0.000000	2.301836
C	1.599821	1.033149	3.162485
O	2.666971	1.246591	3.689311
H	4.415473	1.513955	4.476686
O	5.153434	1.829187	5.019732
H	5.226481	2.763766	4.793623
C	0.330776	1.806465	3.327598
C	-0.586320	1.208154	2.562674
C	0.264962	3.004273	4.214538

H	-0.741322	3.427146	4.238745
H	0.565210	2.740117	5.234349
H	0.969324	3.773569	3.881038
H	-1.626524	1.484476	2.429772
O	-0.645185	-1.183012	2.193749
H	-0.924860	-0.260698	-0.323528
C	0.537082	1.168023	-0.697059
H	-0.106829	2.060263	-0.600296
H	1.498282	1.412701	-0.233521
C	0.764135	0.871804	-2.186318
C	-0.543373	0.513916	-2.917417
C	-0.338750	0.291375	-4.426442
C	0.410698	1.435670	-5.132930
C	1.711025	1.792978	-4.361488
C	1.446686	2.067711	-2.875781
C	-0.429184	2.688966	-5.300785
O	0.136048	3.544362	-6.190571
H	0.699372	1.122474	-6.142893
H	0.249008	-0.623601	-4.578346
H	-1.307974	0.124254	-4.908621
H	-0.973522	-0.402038	-2.493842
H	-1.270856	1.320443	-2.775890
H	1.443178	0.008330	-2.242656
H	0.812251	2.959105	-2.767894
H	2.395054	2.298593	-2.375016
H	2.200772	2.649314	-4.837026
H	2.398198	0.942747	-4.456622
H	-0.776034	-1.183178	3.152735
O	-1.454757	2.964969	-4.712518
H	-0.426831	4.337309	-6.196874

PROD 3 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.546682
C	1.422992	0.000000	2.123255
C	2.256014	1.180194	1.588317
C	2.272776	1.176121	0.050277
C	0.857186	1.153606	-0.548116
C	3.664194	1.154059	2.201786
N	4.446074	2.344634	1.862699
C	5.779665	2.445578	1.641955
C	6.552549	1.205109	1.272833
C	6.109093	0.511682	-0.001455
C	0.438661	-1.344788	-0.564080
O	1.352133	-1.538031	-1.338236
O	6.336798	3.555947	1.681509
O	-0.342757	-2.356737	-0.111034
C	7.620672	0.762511	1.974543
C	8.359471	-0.491598	1.568049
C	8.150708	1.389315	3.246704
O	8.087651	2.710349	3.406620
O	8.664760	0.690400	4.105163
H	1.375699	0.035165	3.218492
H	1.926833	-0.943006	1.865472
H	1.765023	2.108506	1.925365
H	2.812939	2.054704	-0.319902
H	2.817340	0.293076	-0.304170
H	0.919500	1.085755	-1.638014
H	0.344327	2.094971	-0.312381
H	-1.038851	0.124740	-0.333941
H	-0.566741	-0.856144	1.922065
H	-0.524543	0.903197	1.883059
H	4.210765	0.270684	1.863608
H	3.582920	1.075709	3.294976

H	4.029652	3.239115	2.099099
H	-0.004963	-3.167045	-0.528965
H	7.626828	3.160181	2.652051
H	8.877823	-0.905308	2.432675
H	7.689080	-1.251356	1.159173
H	9.108122	-0.265237	0.796947
H	6.966061	0.337957	-0.658874
H	5.650192	-0.465846	0.197727
H	5.381262	1.109932	-0.551289

PROD 3 INT

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.540913
C	1.452036	0.000000	2.086206
C	2.295849	-1.131107	1.485290
C	2.333428	-1.060662	-0.052525
C	0.900068	-1.087026	-0.617158
C	3.205913	-2.188478	-0.620712
N	3.390689	-2.042109	-2.062026
C	4.343975	-2.884855	-2.710538
O	5.674507	-2.508645	-2.260763
C	6.331193	-3.607763	-1.792545
C	5.443929	-4.798006	-1.890932
C	4.282782	-4.390345	-2.424684
O	4.194427	-2.613634	-4.074444
O	7.469828	-3.564677	-1.387070
C	5.904873	-6.140153	-1.415122
C	3.046599	-5.162928	-2.744441
C	-0.786755	-1.165045	2.116955
O	-1.099559	-2.187403	1.541981
O	-1.112548	-0.949071	3.416935

H	-1.585880	-1.745942	3.710837
H	2.765880	-3.161453	-0.333878
H	0.452871	-2.068644	-0.423404
H	1.439538	-0.060799	3.178665
H	-0.494362	0.908417	1.905989
H	0.351239	0.987102	-0.326472
H	2.805777	-0.110514	-0.342088
H	4.842307	-3.146650	-4.556471
H	2.521725	-2.053185	-2.583039
H	4.196991	-2.138285	-0.157727
H	1.889265	-2.104444	1.794935
H	0.914925	-0.940990	-1.704751
H	-1.023254	-0.109914	-0.374475
H	3.315380	-1.076976	1.886397
H	1.904058	0.965509	1.826346
H	6.989669	-6.216198	-1.519301
H	5.675054	-6.281431	-0.352360
H	5.428268	-6.954688	-1.967582
H	2.743247	-4.979276	-3.780995
H	3.186865	-6.236173	-2.599648
H	2.211969	-4.842570	-2.107546
H	3.828260	-1.213016	-2.432429

PROD 4 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.530091
C	1.422978	0.000000	2.100567
C	2.421792	-0.969736	1.455721
C	2.325392	-0.891044	-0.065445
C	0.910678	-1.064770	-0.574775
C	-0.720255	1.257805	2.022456
C	-0.767899	-1.200667	2.042967

O	-1.209611	-2.169570	1.420228
C	3.836794	-0.546541	1.870101
C	2.239185	-2.373159	2.064975
O	2.106267	-2.498825	3.298316
O	-1.018577	-1.178869	3.380270
N	2.360971	-3.490479	1.254376
C	2.222337	-4.825220	1.779843
C	0.960101	-5.541545	1.379734
C	0.096925	-6.032072	2.365072
C	-1.055998	-6.726705	2.005167
C	-1.354455	-6.928925	0.650769
C	-0.493898	-6.437046	-0.338451
C	0.660518	-5.749292	0.028613
C	-2.580764	-7.655384	0.302079
O	-3.426789	-8.147084	1.055851
O	-2.813236	-7.807410	-1.034433
H	-1.741462	-7.116615	2.774307
H	-0.737066	-6.596892	-1.400261
H	0.323913	-5.863610	3.428409
H	1.338238	-5.371702	-0.750257
H	-3.645343	-8.289541	-1.160328
H	2.294123	-4.780826	2.904895
H	3.096744	-5.429717	1.396907
H	2.185895	-3.385632	0.283015
H	1.367663	-0.217033	3.201465
H	1.832148	1.037582	1.972737
H	3.011587	-1.633074	-0.546468
H	2.694442	0.124420	-0.375393
H	0.506538	-2.074809	-0.303088
H	-1.045930	-0.167437	-0.365452
H	0.332454	1.010393	-0.352809
H	3.934108	-0.585290	2.981124
H	4.044066	0.492398	1.522835
H	4.588995	-1.232951	1.416245

H	-0.747027	1.270698	3.137847
H	-1.766029	1.275839	1.636378
H	-0.188582	2.168220	1.659947
H	-1.469306	-1.997857	3.639679
H	0.907217	-0.989980	-1.692918

PROD 4 INT

C	-2.907562	-0.166880	-0.951316
C	-2.230129	-1.133319	0.104989
O	-2.465120	-0.635013	1.370491
C	-3.065780	0.656605	1.340640
C	-3.176816	1.143715	-0.098149
N	-0.655764	-1.304001	-0.050051
C	0.296019	-0.435101	0.740300
C	1.738327	-0.945269	0.640495
C	2.258696	-0.976026	-0.811821
C	3.752128	-1.336893	-0.886884
C	4.643215	-0.447099	0.003280
C	4.105043	-0.448089	1.456392
C	2.624926	-0.050341	1.534723
C	4.730210	0.980847	-0.512355
O	5.972949	1.482024	-0.388725
O	-2.621062	-2.460581	0.020145
O	-3.365307	1.183090	2.363031
C	-4.565722	1.789259	-0.294022
C	-2.127861	2.271947	-0.281304
C	-4.226826	-0.843261	-1.391099
C	-2.059965	0.064051	-2.213903
O	3.800161	1.631422	-0.952787
H	2.283839	-0.110956	2.574686
H	2.513462	0.992803	1.217068
H	1.768148	-1.967714	1.052718

H	1.704118	-1.712393	-1.412638
H	2.112867	0.009612	-1.266982
H	4.084363	-1.291224	-1.928593
H	3.891098	-2.374849	-0.559715
H	5.658995	-0.851353	0.011317
H	4.702495	0.222272	2.082357
H	4.239872	-1.458056	1.863165
H	0.218495	0.577583	0.341170
H	-0.065420	-0.437955	1.769100
H	-0.418305	-1.257777	-1.044591
H	5.946071	2.402932	-0.703535
H	-3.220846	-2.651074	0.758296
H	-4.657397	2.645487	0.377321
H	-5.388671	1.108785	-0.073042
H	-4.675583	2.148793	-1.320704
H	-4.885156	-1.073794	-0.549572
H	-4.021096	-1.777320	-1.915072
H	-4.769311	-0.182665	-2.069427
H	-1.093708	0.540591	-2.022746
H	-2.597678	0.720393	-2.902869
H	-1.897192	-0.876770	-2.752493
H	-2.314444	3.057572	0.453983
H	-2.221463	2.710949	-1.277413
H	-1.094914	1.943237	-0.154663
H	-0.512686	-2.281512	0.226184

PROD 4 TS

O	2.243827	1.794144	0.142161
C	1.994335	-0.082364	-1.164158
C	2.416731	-1.412053	-0.387818
C	2.853946	-0.901521	1.016690
C	2.880869	0.612331	0.871258

N	0.605067	0.059765	-1.598710
C	-0.295411	0.693722	-0.659593
C	-1.773612	0.606669	-1.072339
C	-2.581373	1.520476	-0.156910
C	-4.055859	1.474902	-0.503114
C	-4.617197	0.056660	-0.453748
C	-3.775051	-0.895736	-1.294286
C	-2.296129	-0.819711	-0.966781
C	-4.710967	-0.414403	0.972949
O	-5.975035	-0.353664	1.479702
O	2.863186	0.080322	-2.260231
C	3.559624	-2.086377	-1.137499
C	1.278309	-2.415646	-0.308393
C	4.231740	-1.383285	1.447274
C	1.862655	-1.238925	2.125683
O	3.261686	1.492346	1.630774
O	-3.840991	-0.834282	1.739266
H	-2.209924	2.572642	-0.249578
H	-2.438709	1.195469	0.907535
H	-1.887749	0.962364	-2.132223
H	-1.740137	-1.490006	-1.670847
H	-2.127833	-1.199362	0.076229
H	-4.135054	-1.945534	-1.142617
H	-3.931885	-0.633339	-2.373036
H	-5.664546	0.073424	-0.870820
H	-4.629841	2.128682	0.202321
H	-4.210590	1.872351	-1.539850
H	-0.193176	0.259118	0.377808
H	0.004308	1.778426	-0.599616
H	0.262183	-0.818549	-1.928618
H	-5.976140	-0.655530	2.401133
H	2.680766	0.936982	-2.669959
H	4.480968	-0.942945	2.443578
H	5.018481	-1.067014	0.723613

H	4.237944	-2.494862	1.532497
H	4.425627	-1.393547	-1.255751
H	3.215181	-2.375879	-2.159468
H	3.889251	-3.003240	-0.595677
H	0.358250	-1.984401	0.152957
H	1.599809	-3.291837	0.305113
H	1.022989	-2.789206	-1.330041
H	2.197252	-0.758643	3.077516
H	1.817022	-2.341927	2.280195
H	0.841395	-0.861116	1.885585
H	2.995068	3.277650	0.769608
O	2.887359	4.146754	0.401428
H	2.507703	4.078078	-0.466699

PROD 5 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.520475
C	1.411278	0.000000	2.083318
C	2.397741	-0.686102	1.141259
C	1.724685	-1.814605	0.370781
C	0.631710	-1.281181	-0.538038
C	3.581477	-1.209942	1.906654
O	3.297407	-2.161597	2.839212
C	-1.428071	0.120672	-0.565635
N	-2.054413	1.399254	-0.368241
C	-2.254435	2.293822	-1.399374
O	-2.024817	1.989107	-2.586020
O	4.767421	-0.892201	1.795599
C	-2.788741	3.675936	-1.047067
C	-4.270694	3.683137	-0.667574
C	-5.080630	2.801119	-1.609317

C	-4.448312	3.206747	0.758974
O	-3.591872	2.973125	1.617982
C	-4.788877	5.120325	-0.738585
O	-5.741831	3.044111	1.145504
H	-0.548780	-0.907489	1.883835
H	-0.544940	0.897249	1.910178
H	1.752901	1.052314	2.257700
H	1.409614	-0.522484	3.075017
H	2.795429	0.069259	0.406069
H	1.294756	-2.542851	1.106530
H	2.486705	-2.362751	-0.239714
H	-0.152781	-2.072878	-0.657442
H	1.050737	-1.074898	-1.556462
H	0.611068	0.874774	-0.355090
H	-1.392884	-0.096228	-1.671389
H	-2.072656	-0.660497	-0.070396
H	-2.137033	1.725538	0.567629
H	4.115979	-2.440706	3.278399
H	-2.185853	4.116151	-0.211017
H	-2.651166	4.317957	-1.957163
H	-5.771740	2.751941	2.070727
H	-4.170275	5.789583	-0.096458
H	-5.848426	5.159465	-0.390975
H	-4.741123	5.484113	-1.791761
H	-4.943891	3.153059	-2.659177
H	-6.162506	2.849560	-1.341304
H	-4.739670	1.740810	-1.544545

PROD 5 INT

O	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.463508
C	1.490186	0.000000	1.923430
C	2.323765	-0.054894	0.633151
C	1.288175	-0.016192	-0.481898
N	-0.822115	-1.074668	2.001158
C	-0.478839	-2.405431	1.535899
C	-1.450920	-3.483530	2.040351
C	-2.855036	-3.267364	1.485617
C	-3.626890	-4.568104	1.347642
C	-3.209627	-5.566298	2.422334
C	-1.745598	-5.968899	2.262043
C	-0.919742	-4.854497	1.644409
C	-4.093389	-6.781073	2.343744
O	-5.113450	-6.779355	3.246602
O	-0.530798	1.273185	1.750644
C	3.249867	1.143222	0.514772
C	3.118153	-1.347145	0.538646
O	1.402923	-0.002494	-1.698963
O	-4.030067	-7.755035	1.591134
H	-3.411961	-2.572185	2.165643
H	-2.799351	-2.776705	0.479337
H	-3.437797	-5.019715	0.339528
H	-4.725086	-4.364561	1.428367
H	-3.358106	-5.088864	3.431128
H	-1.671550	-6.882867	1.616013
H	-1.333388	-6.234926	3.268944
H	-0.936348	-4.946122	0.527544
H	0.145673	-4.959548	1.973473
H	-1.496014	-3.435208	3.163562
H	-0.437707	-2.456966	0.409072
H	0.551990	-2.642233	1.924159

H	-1.794252	-0.878750	1.863747
H	-5.649731	-7.579924	3.137882
H	1.709135	-0.865690	2.590935
H	1.680779	0.943040	2.492542
H	2.671000	2.094481	0.582415
H	3.782183	1.115938	-0.465825
H	4.002869	1.120656	1.337207
H	3.886700	-1.379309	1.346106
H	3.629760	-1.408157	-0.451400
H	2.443551	-2.229357	0.648962
H	-1.317307	1.410810	1.206182

PROD 5 TS

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.537051
C	1.462100	0.000000	2.059436
C	2.458438	0.673754	1.089200
C	1.780970	1.827046	0.312066
C	0.629185	1.289994	-0.568281
C	-0.811988	-1.172810	2.098643
N	-0.911446	-1.101314	3.560767
C	-1.990814	-2.323042	4.418270
O	-1.766904	-3.682404	3.906858
C	-2.941306	-4.385851	3.845173
C	-4.126110	-3.494597	4.246683
C	-3.496561	-2.088181	4.250530
O	-1.680331	-2.343574	5.787493
C	-4.586976	-3.932660	5.655198
C	-5.270214	-3.657931	3.236869
O	-2.976121	-5.544698	3.520141
C	2.817843	2.568148	-0.512372
O	3.033499	2.425230	-1.696391

O	3.543743	3.421744	0.254680
H	1.501978	0.506874	3.030845
H	1.791903	-1.034047	2.229802
H	2.833168	-0.056629	0.362492
H	3.328241	1.045971	1.638528
H	1.401083	2.541749	1.051873
H	1.014485	1.109694	-1.575653
H	-0.138096	2.067218	-0.659934
H	0.553298	-0.878777	-0.356798
H	-1.020877	-0.108460	-0.384022
H	-0.491119	0.921792	1.878088
H	-0.371709	-2.123493	1.757645
H	-1.825703	-1.131573	1.684436
H	0.008498	-1.118085	3.990734
H	4.206711	3.816647	-0.336862
H	-3.680905	-1.580449	3.300113
H	-3.853763	-1.439682	5.052597
H	-3.792579	-3.788072	6.391411
H	-4.877365	-4.986981	5.650064
H	-5.451879	-3.336261	5.964036
H	-6.127598	-3.043902	3.530855
H	-5.588645	-4.702572	3.191449
H	-4.963680	-3.355046	2.230263
H	-0.921606	-2.936048	5.895250

PROD 6 GM

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.521641
C	1.418529	0.000000	2.059187
C	2.192950	-1.201972	1.526089
C	2.179319	-1.230529	0.000237
C	0.758654	-1.206468	-0.530194

C	3.616812	-1.129108	2.006314
O	4.451851	-0.235756	1.851297
C	-1.423231	0.083733	-0.578768
N	-2.354184	-0.912514	-0.138753
C	-2.754868	-2.032085	-0.842983
O	-3.476795	-2.863282	-0.256583
C	-2.384675	-2.200607	-2.315548
C	-3.317160	-1.318581	-3.142928
C	-3.081546	-1.493876	-4.629378
C	-3.242415	-2.945980	-5.033177
C	-2.305159	-3.831450	-4.238653
C	-2.526412	-3.666249	-2.735171
C	-1.564383	-4.584616	-2.030554
O	-1.659565	-5.802407	-1.870200
O	4.021156	-2.221479	2.711569
O	-0.430182	-4.003898	-1.544081
H	-3.160363	-0.245462	-2.862269
H	-4.379492	-1.581402	-2.898293
H	-1.314238	-1.893707	-2.475503
H	-3.562977	-4.018187	-2.461305
H	-1.243193	-3.573489	-4.486803
H	-2.470319	-4.905444	-4.512862
H	-4.301700	-3.269137	-4.862805
H	-3.024787	-3.061775	-6.125603
H	-3.810263	-0.860837	-5.197331
H	-2.051020	-1.142032	-4.893071
H	-2.571208	-0.907266	0.833334
H	-1.345628	0.062607	-1.701176
H	-1.848322	1.087886	-0.283435
H	4.943851	-2.111290	2.988917
H	0.115515	-4.675866	-1.106389
H	-0.536491	-0.904466	1.908368
H	-0.541407	0.905194	1.897816
H	1.945490	0.941813	1.756699

H	1.396523	-0.035633	3.178154
H	1.726000	-2.147594	1.917972
H	2.697798	-2.155554	-0.359599
H	2.747824	-0.346008	-0.388476
H	0.785053	-1.173142	-1.650105
H	0.227565	-2.151067	-0.240938
H	0.531518	0.930149	-0.350046

PROD 6 INT

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.524287
C	1.413947	0.000000	2.071557
C	2.195993	-1.197523	1.539488
C	2.204721	-1.199536	0.014618
C	0.789883	-1.187661	-0.530677
C	3.607680	-1.138636	2.054042
O	4.531455	-0.386571	1.738607
C	-1.456385	-0.040045	-0.495953
N	-1.585593	0.138616	-1.929857
C	-1.777105	1.501304	-2.406225
C	-1.675766	1.652078	-3.958632
C	-0.180688	1.981992	-4.141856
C	0.137211	2.750203	-2.888051
O	-0.755549	2.399992	-1.880544
C	0.027914	2.593174	-5.506465
C	-0.399381	1.561005	-6.545783
C	-1.799087	1.008170	-6.319343
C	-2.043791	0.524932	-4.891791
O	-2.967150	2.125849	-1.969066
O	0.996348	3.556930	-2.571746
O	3.885297	-2.064918	3.014593
H	-3.119972	0.246720	-4.764233

H	-1.425570	-0.384717	-4.683687
H	-2.302512	2.550644	-4.217312
H	0.425469	1.031609	-4.076331
H	-0.578115	3.527557	-5.615219
H	1.103371	2.864670	-5.654217
H	0.334102	0.713310	-6.533253
H	-0.354433	2.029823	-7.562044
H	-1.970411	0.155620	-7.025196
H	-2.549970	1.803607	-6.564491
H	-2.319149	-0.429674	-2.304300
H	-2.035901	0.748911	0.064647
H	-1.892783	-1.041452	-0.221864
H	4.804944	-1.969524	3.306370
H	-2.810141	2.516882	-1.099732
H	-0.549435	-0.901288	1.899858
H	-0.538136	0.907436	1.900683
H	1.937338	0.945192	1.773333
H	1.384789	-0.039482	3.190068
H	1.717903	-2.145282	1.911946
H	2.742235	-2.109385	-0.355192
H	2.764959	-0.299739	-0.350461
H	0.829754	-1.144017	-1.648878
H	0.269634	-2.138710	-0.246624
H	0.482821	0.950579	-0.360204

PROD 6 TS

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.538835
C	1.417807	0.000000	2.126516
C	2.260199	-1.159103	1.576228
C	2.278193	-1.144839	0.028588

C	0.852185	-1.162729	-0.535840
C	3.670563	-1.131954	2.132322
O	4.174590	-0.230617	2.766264
C	-1.436235	-0.046817	-0.542738
N	-1.510847	0.072907	-2.012414
C	-2.119852	1.670034	-2.698899
C	-1.896676	1.790003	-4.211877
C	-0.433407	2.231274	-4.269040
C	-0.323189	3.124617	-3.049915
O	-1.288070	2.729796	-2.146755
C	-0.043539	2.755079	-5.645720
C	-0.322897	1.639562	-6.676187
C	-1.759213	1.080457	-6.590782
C	-2.155667	0.628296	-5.166809
O	-3.456072	1.974399	-2.412070
O	0.445650	4.017352	-2.812155
O	4.353493	-2.266643	1.825840
H	-3.208161	0.322458	-5.148607
H	-1.551733	-0.239693	-4.870074
H	-2.523572	2.637849	-4.519033
H	0.186946	1.352182	-4.033446
H	-0.633911	3.649359	-5.883204
H	1.009460	3.053133	-5.668329
H	0.389948	0.820342	-6.506939
H	-0.133671	2.008829	-7.690291
H	-1.870720	0.244945	-7.290958
H	-2.465697	1.855284	-6.918580
H	-2.081092	-0.668732	-2.404197
H	-2.023970	0.737342	-0.042200
H	-1.894517	-1.000577	-0.252226
H	5.243054	-2.150490	2.200457
H	-3.555138	2.038289	-1.451285
H	-0.542453	-0.888611	1.897560
H	-0.551819	0.870638	1.914323

H	1.922206	0.943313	1.886469
H	1.377936	-0.052893	3.219551
H	1.819556	-2.116758	1.889702
H	2.850439	-2.000113	-0.343553
H	2.797281	-0.238517	-0.311621
H	0.877063	-1.125935	-1.629757
H	0.371102	-2.115357	-0.263681
H	0.449782	0.942218	-0.341370

تصميم طلائع أدوية مبتكرة منحمض الترانيكساميك بالطرق الحسابية

إعداد: مريم مأمون محمد بدر

إشراف: أ.د رفيق قرمان

الملخص:

باستخدام الطرق الحسابية DFT molecular orbital على المستوى B3LYP 6-31G (d,p) وحسابات MM2لعملية نقل البروتون ضمن جزئي في عدد من نماذج الإنزيمللعالم كيربي واستغلال هذه النماذج لتصميم أدوية مقدمة لحمض الترانيكساميك التي لا تعتمد على انزيمات لتفعيلها و تمتاز بفاعلية أطول ذو مقارنة مع الدواء الأم.

لقد وجد أن معدل التحويل الداخلي لحمض الترانيكساميك prodrug أن القوة الدافعة لنقل البروتون تعتمد بشكل كامل على المسافة بين المركزين المتفاعلين r_{GM}،وزاويةالهجوم α حيث وجد ان الانظمة ذات المسافة المنخفضة (r_{GM}) وقيم الزاوية α المرتفعة مثل ProD1-ProD3في هياكلها تظهر معدلات اعلى بكثير (أقل$\Delta G^{\ddagger}$) من تلك التي لها مسافة مرتفعة (r_{GM}) و قيمة الزاوية α منخفضة مثل ProD4-ProD6.

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