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Design of Novel Gabapentin Prodrugs by Computational Methods

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Dedication

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

To my colleagues and friends in the Department of Pharmaceutical Sciences.I thank them for their companionship.

Last, but not least, Special thanks to my husband, my daughters Bushra and Eleen for their support; they were always with me and in close proximity to help and without their assistance and support this work would not have been possible.

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Declaration

I certify that the thesis submitted for the degree of master is a 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: ……..

Hanadi Abd Alkareem Sinokrot

Date: 25/May/2019

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Abstract

The anti-epileptic Gabapentin has a dose-dependent bioavailability as it is absorbed from the limited distributed and saturable L-amino acid transporter. Drug derivatization using prodrug approach has been demonstrated as a very important means to overcome such related pharmacokinetic and pharmaceutical drawbacks. However, in this approach, enzymes are mandatory for the interconversion of many prodrugs and many prodrug-activating enzymes may be decreased or increased due to genetic polymorphism and age-related physiological changes. Unraveling the mechanisms of a number of enzyme models (intramolecular processes) has contributed to the design of efficient prodrug linkers that can be covalently attached to commonly used drugs; these drugs have the ability to release the active drug chemically, but not enzymatically. Such enzyme models were utilized in my prodrug design approach which was accomplished using computational calculations based on molecular orbital and molecular mechanics methods.

Using DFT molecular orbital at B3LYP 6-31G (d, p) level and molecular mechanics (MM2) calculations of the intramolecular proton transfer in a number of Kirby's enzyme models four Gabapentin prodrugs were designed to provide a medicine with higher bioavailability than its parent drug (Gabapentin), and to provide systems having the potential to release Gabapentin in a controlled matter.

It was found that the intramolecular proton transfer rate of the designed Gabapentin **ProD1-ProD4** is largely determined on the strain energies of the reactions' tetrahedral intermediates; no correlation was found between the cyclization rate and distance between the two reactive centers (r_{GM}). Therefore, the intra-conversion rates of the Gabapentin prodrugs can be programmed according to the nature of the prodrug linker.

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Abbreviations	Definition
GM	Global Minimum
TS	Transition State
INT	Tetrahedral Intermediate
P	Product
ProD	Prodrug
Es	Strain Energy
GP	Gas Phase
H_2O	Water Phase
r_{GM}	Distance in the Global Minimum
$\Delta G^{\ddagger}$	Activation Energy
MM	Molecular Mechanics
QM	Quatum Mechanics
DFT	Density Functional Theory
SN_2	Nucleophilic Substitution Reaction

Chapter One

Introduction

Chapter One

Introduction

1.1 Background

Generally, a drug is characterized by its biological and physicochemical properties. Drugs, with unsuitable physicochemical properties, might provide inefficient and undesirable therapeutic profiles. Nowadays, finding a drug with good physicochemical properties and pharmacokinetic profile is considered as one of the most important issues in the drug discovery field.

Presently several known oral medicines suffer from poor pharmacokinetic and bioavailability profiles. Therefore, for drugs clinical profiles to be improved, the physicochemical properties of those parent drugs should be modified. The pharmacokinetic or pharmacological barrier's such as low absorption, lack of site specificity, insufficient chemical stability, poor solubility, toxicity, and unacceptable taste/odor should be greatly eliminated [1].

Among the various approaches to minimize the undesirable drug properties while retaining the desirable therapeutic activity is the prodrug approach [2, 3]. Prodrug design is an efficient approach which is based on transiently modified drug's pharmaceutical properties to overcome some of the related pharmacokinetic and pharmaceutical problems [4]. The prodrug approach has been successfully applied to a wide variety of drugs; about 10% of worldwide marketed drugs can be classified as prodrugs [1, 5, 6].

Generally, prodrugs can release their active drugs by two main prodrugs approaches: the traditional approach by which a prodrug interconversion occurs via enzymatic reaction and the novel approach which is based on enzyme models (intramolecular process) that have been advocated to assign the factors playing a dominant role in enzyme catalysis [7-9]. In this approach, there is no need for an enzyme to catalyze the prodrug interconversion. The interconversion rate is determined only by the factors govern rate-limiting step of the intramolecular process [7, 10, 11]. In this novel approach, the design of prodrug is accomplished using computational calculations (computational chemistry) based on

molecular orbital and molecular mechanics methods and correlations between experimental and calculated rate values for some intramolecular processes [7, 10].

Computational chemistry uses the principles of computer science to assist in solving chemical problems. It uses the theoretical chemistry results incorporated into efficient computer programs for calculating the structures, physical and chemical properties of molecules. Few decades ago, the world has viewed an increasing number of medicinal chemists, biochemists and further researchers in various fields who have started using computational methods to better understand the mechanism of intramolecular processes for a number of enzyme models as well as calculating molecular properties of ground and transition states and design of some novel prodrug linkers. The application of computational chemistry has many advantages mainly by helping to reduce the need for access to expensive laboratory time, test equipment and chemicals [10, 12, 13].

Today, modern computational methods such as those based on quantum mechanics (QM) and molecular mechanics (MM) methods could be exploited for the design of innovative prodrugs for common use drugs [10].

Quantum Mechanics (QM):

Quantum Mechanics (QM also known as Quantum Physics, or Quantum Theory) is the laws of physics for very small and light objects, such as electrons and nuclei. It can provide a mathematical description of the behavior of electrons and thus of chemistry. In QM, the Schrodinger equation is solved for the wave-functions of our particles, giving information about the probability of measuring various values for its physical properties [14, 15].

$$\hat{H}\,\Psi = E\,\Psi \rightarrow$$ Schrodinger Equation

The Hamiltonian operator, H, depends on the kinetic and potential energies of the nuclei and electrons in the atom or molecule. The wave-function,Ψ, will give us information about the probability of finding the electrons in different places in the molecule. The energy, E, is related to the energies of individual electrons which can be used to help interpret electronic spectroscopy.