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Structural exploration and study of the QSAR properties of several series of macrolide antibiotics.

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To my beloved parents

To my children

To my siblings

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List of Abbreviations

Ac	=	Acetyl
AUCs		Area under the curve
Bn	=	Benzyl
CYP 3A4	=	Cytochrome P450 3A4 (enzyme)
CYP 2D6	=	Cytochrome P450 2D6 (enzyme)
Cbm	=	Carbomycin
DFT	=	Density-functional theory
HOMO	=	Highest Occupied Molecular Orbital
1D, 2D, 3D	=	One-Dimensional, Two-Dimensional, Three-Dimensional
ADMET	=	Absorption, Distribution, Metabolism And Excretion – Toxicity
ANOVA	=	Analysis of Variance
BLYP	=	Becke's Lee, Yang and Parr
CNS	=	The Central Nervous System
GETAWAY	=	Geometry, Topology and Atom-Weights Assembly
GGA	=	Generalized Gradient Approximation
GROMOS	=	Gronigen Molecular Simulation
Et	=	Ethyl
Erm	=	Erythromycin
IR	=	Infrared
IUPAC	=	International Union of Pure and Applied Chemistry
HF	=	Hartree-Fock
HSAB	=	Hard and Soft Acids and bases
IC50	=	The Half Maximal Inhibitory Concentration
LDA	=	Local Density Approximations
LUMO	=	Lowest Unoccupied Molecular Orbital
LOO	=	Leave one out
Me	=	Methyl
mRNA	=	Messenger RNA

MES model	=	The Maximal Electroshock Seizure
MESP	=	Electrostatic Potential Surface
MLR	=	Multiple Linear Regression
MM	=	Molecular Mechanics
MLS_B	=	Macrolides-Lincosamides-Streptogramins B
MP	=	Møller-Plesset
MPA	=	Mulliken Population Analysis
MR	=	Molecular Refractivity
MW	=	Molecular Weight
PCA	=	Principal Component Analysis
Ph	=	Phenyl
Pol	=	Polarizability
PRESS	=	Predicted Residual Sum of Squares
PTZ	=	Pentylenetetrazol
QSAR	=	Quantitative Structure-Activity Relationship
rRNA	=	Ribosomal ribonucleic acid
SAG	=	Surface Area Grid
SPR	=	Structure-Propriety Relationship
SSY	=	Sum of the Squares of the Response Value
WHIM	=	Weighted Holistic Invariant Molecular
ΔE	=	HOMO-LUMO energy gap
ΔH_f	=	Heat of Formation
tRNA	=	Transfer RNA
Tyl	=	Tylosin
Tel	=	Telithromycin

General introduction

The advent of high-speed computers, availability of sophisticated algorithms, and state of-the-art computer graphics have made plausible the use of computationally intensive methods such as quantum mechanics, molecular mechanics, and molecular dynamics simulations to determine those physical and structural properties most commonly involved in molecular processes. The power of molecular modeling rests solidly on a variety of well established scientific disciplines including computer science, theoretical chemistry, biochemistry, and biophysics. Molecular modeling has become an indispensable complementary tool for most experimental scientific research [1].

Molecular modeling is focused on applying the fundamental laws of physics and chemistry to the study of molecules. The ultimate aim is to create models and simulations, which can help by predicting, rationalizing, and estimating the properties of molecules and their interactions. Today, computational techniques performed by powerful computers have revolutionized molecular modelling to the extent that most calculations could not be performed without the use of a computer [2].

It allows chemists to study chemical phenomena by running calculations on computers rather than by examining reactions and compounds experimentally. Some methods can be used to model not only stable molecules, but also short-lived, unstable intermediates and even transition states. In this way, they can provide information about molecules and reactions, which is impossible to obtain through observations. Molecular modelling and computational chemistry is therefore both an independent research area and a vital adjunct to experimental studies [2].

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties [3]. To obtain highly accurate geometries and physical properties for molecules that are built from electronegative

elements, expensive ab initio/HF electron correlation methods are required [4-6]. Density functional theory methods offer an alternative use of inexpensive computational methods, which could handle relatively large molecules. [7-16]

Quantitative structure – activity relationships (QSARs), as one of the most important areas in chemometrics [17]. QSARs are a suite of tools used to link chemical activities with molecular structure and composition [18], and is actively used in drug design [19, 20]. The concept of using QSARs to link structure and activity was introduced over 100 years ago and subsequently widely used in medical and biological research [21,22]. To develop a QSAR model, several statistic methods can be used [23].

Druglikeness is a qualitative concept used in drug design, which is estimated from the molecular structure before the substance is even synthesized and tested. The calculation of drug-like property can give us better assumption of biological activity of certain molecule. The theoretical calculation and maintain of certain properties of a molecule can fulfill the parameters which are essential to show certain biological activity. Lipinski's rule of five is a rule of thumb to evaluate druglikeness or determine a chemical compound with a certain pharmacological or biological activity that would make it a likely orally active drug in humans [24].

Drug-likeness appears as a promising paradigm to encode the balance among the molecular properties of a compound that influences its pharmacodynamics and pharmacokinetics and ultimately optimizes their absorption, distribution, metabolism and excretion (ADME) in human body like a drug [25, 26].

Molecular physicochemical and the drug-likeness are the two most significant properties to be considered for a compound to become a successful drug candidate. It is also important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski’s rule [27].

Nowadays the main objective of these studies is to predict biological activity of In-silicodesigned compounds on the basis of already synthesized compounds [28]. The molecular modeling and QSAR calculations are used in many fields specially, physics, chemistry, biology, material science as well as tissue engineering and drug design [29-36].

Multiple linear regression (MLR), which is one of the most common and simplest method for constructing QSAR models, was used in this study [37 –39]. The advantage of MLR is that it is simple to use and the derived models are easy to interpret.

The useful properties of macrolides range from perfumery to biological and medecinal activity. The new finding in the field of antitumour active and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration to chemists to study macrolides. The term “macrolide” is used to describe drugs with a macrocyclic lactone ring of 12 or more elements. [40]

Our work is placed in the context of fundamental and original research on 14-membered macrolides and their derivatives, the main objective of this work is the application of different methods of molecular modeling to predict the chemical reactivity and biological activities expected in new bioactive molecules studied.

The structure of the memory, composed by three chapters, has been conceptually divided into two differentiated parts. On one hand, the theoretical background section, which is composed by chapter 1 and chapter 2. On the other hand, chapter 3 and chapter 4 devoted to applications and results, deepens into specific practical applications.

Next, the content of the chapters is briefly described

❖ **CHAPTER 1:** *Classification and pharmacological properties of macrolides and ketolides*.

The first chapter is divided into three parts: in the first part, we present generalities of the macrolides. In the second part, we will show, on generalities regarding Discovery and physicochemical properties of Erythromycin. The third part studies the ketolides and the structural comparison between the macrolides and the ketolides.

- ***CHAPTER 2**: Molecular Modeling*

This chapter contains the main concepts and definitions related to computational methods (quantum mechanics methods, Semi - empirical methods and molecular mechanics methods).

- ***CHAPTER 3:** Geometric, Electronic Structure and Substituent effects of 14- Membered α, β -Unsaturated Macrolides.*

The third chapter contains a structural, electronic and energetic study of 14-membered macrolides and its derivatives. In this chapter we present the results of a comparative study on two methods used in the calculation of PM3 and ab initio, as well, the substitution effect on energy and electronic parameters of the basic nucleus of 14- membered macrolide.

- ***CHAPTER 4:** Drug-likeness properties and Structure activity Relationships of 14- Membered Macrolides.*

In the last chapter, We highlights the importance of a qualitative study of structure-property relationships and drug likeness proprieties of a bioactive series of 14- membered macrolide derivatives.

Finally, we establish a quantitative relationship between physiochemical properties and biological activity of a series of bioactive derivatives of 14- membered macrolides (QSAR Model).

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K. Zitouni, S. Belaidi, A. Kerassa, CONFORMATIONAL ANALYSIS AND QSAR MODELING OF 14-MEMBERED MACROLIDE ANALOGUES AGAINST MYCOBACTERIUM TUBERCULOSIS, *J Fundam Appl Sci.*, 12(3), 1035-1066, (2020).

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CHAPITER 01

Classification and pharmacological properties of macrolides and ketolides

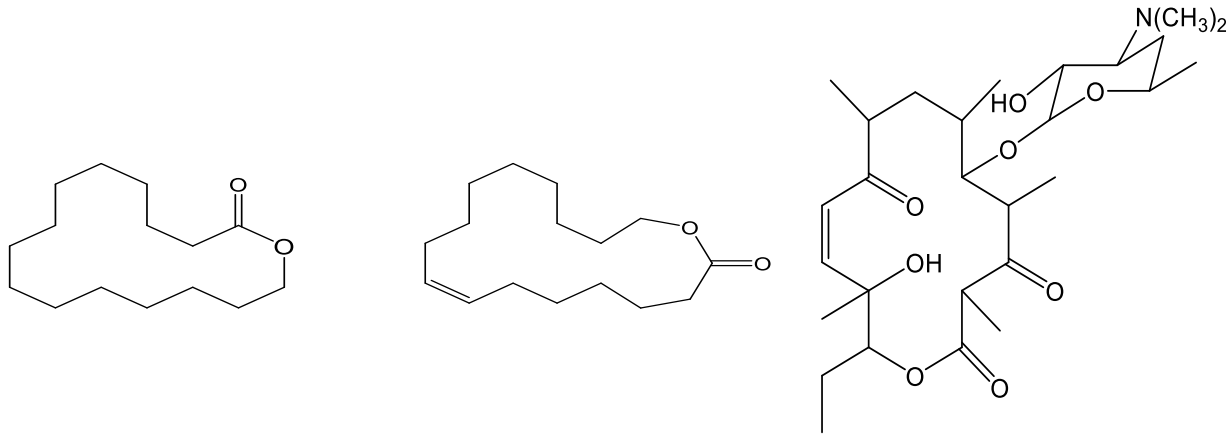
1. THE MACROLIDES

1.1 Introduction

The term macrocycle refers to medium- and large-ring compounds, with, respectively, 8–11 and 12 or more atoms in the ring. Macrocyclic structures that have one or more ester linkages are generally referred to as macrolides or macrocyclic ring lactones. In some cases, macrocyclic lactams have also been described as macrolides. Originally macrolides denoted a class of antibiotics derived from species of Streptomyces and containing a highly substituted macrocyclic lactone ring aglycone with few double bonds and one or more sugars, which may be aminosugars, non-nitrogen sugars or both [1]. To our knowledge the largest naturally occurring macrolides are the 60-membered quinolidomicins6 and the largest constructed macrolide is the 44-membered swinholide [2].

In 1927 Kerschbaum isolated the first macrocyclic lactones, Exaltolide®**1** and ambrettolide **2**, from angelica root and ambrette seed oil, respectively [3]. The discovery of these vegetable musk oils aroused interest in finding synthesis routes to these and related macrolides owing to their commercial importance in the fragrance industry [4]. Even today Exaltolide® **3** is one of the most widely produced macrocyclic musk lactones. The production was estimated at 200 tons in 1996. The importance of macrocyclic musks is increasing due to their ready biodegradability [5].

The great breakthrough in macrolide chemistry came in 1950 when Brockmann and Henkel isolated the first macrolide antibiotic picromycin **3** from an Actinomyces culture [6]. Après les années 1970, la découverte des nouveaux macrolides augmente rapidement. Le nombre des macrolides isolés à partir des sources naturelles est environs de 400 composés, ce nombre devenu plus de 2000 composés dans les années 2000 [7].



Exaltolide 1 **ambrettolide 2** **picromycin 3**

Figure 1.1 : chimical Structure of macrolides (1), (2) and (3)**.**

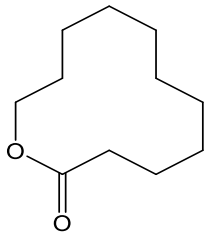
The tremendous interest in macrolide chemistry can be understood if one takes a look at the diversity of the structures and physiological effects of macrolides. Natural products containing a macrolactone framework are found in plants, insects, and bacteria and they may be of terrestrial or marine origin. The useful properties of macrolides range from perfumery to biological and medicinal activity. The new findings in the field of antitumour active and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration to chemists to study macrolides [1].

Macrolide antibiotics play a therapeutically important role. They are regarded as among the safest of antibiotics and they have successfully been used to treat infections caused by gram-positive organisms and certain gram-negative and anaerobic bacteria. Natural macrolide antibiotics can be classified according to the size of the aglycone ring [8].The most commonly used macrolide antibiotics, erythromycin and josamycin, belong to the groups of 14-membered and 16- membered ring derivatives, respectively [9].

1.2. Nomenclature of macrolides

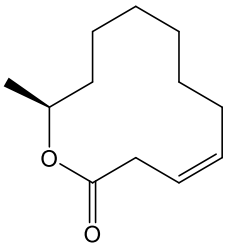
The nomenclature of macrolides is anything but straightforward. Trivial names are widely used, especially for naturally occurring macrocyclic lactones.

According to IUPAC rules, macrolides as well as other lactones formed from aliphatic acids should be named by adding "olide" as a suffix to the name of the hydrocarbon with the same number of carbon atoms. The numbering starts from the ester carbonyl carbon. The IUPAC rules also give an alternative way of naming lactones based on the rules for naming heterocycles. According to this rule the lactones are named as oxacyclo ketones and the numbering starts from the ring oxygen (table 1.1). The AutoNom [10] naming program uses this latter rule although the "olide" naming is generally used in the literature. By way of example, Figure 1.2 shows the alternative names of two macrolides. The macrolide structures of this work are sometimes identified by their trivial names.



Undecanolide

Oxacyclododecan-2-one



(3Z,11S)-3-Dodecen-11-olide

(4Z,12S)-12-Methyl oxacyclododec-4-en-2-one

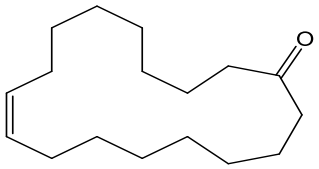
Ferrulactone II (trivial name)

Figure 1.2 Examples of naming simple macrolides.

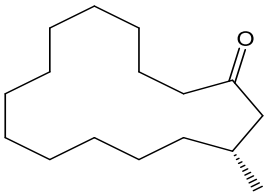
Trivial name	*IUPAC name*
Ambrettolide	(Z)-7-hexadecenolide
Civetone	(Z)-9-cycloheptadecen-1-one
Muscone	3-methylcyclopentadecan-1-one
Exaltolide	pentadecanolide

Table 1.1 systematic names of selected macrolides

The chemistry of macrocyclic compounds originated in 1926 when Ruzicka [11] elucidated the structures of civetone 4 and muscone 5 as large-ring ketones (figure 3). Before this time it was believed on the basis of Baeyer's strain theory [12] that large-ring compounds would be too unstable to exist because the internal bond angles in large planar rings do not have tetrahedral geometry. In fact, large rings are able to adopt non-planar conformations and they are flexible and almost strain free [4].



civetone 4



muscone 5

Figure 1.3 structures of civetone and muscone

1.3 Chemical structure of macrolides and classification

The macrolides having a monolactone ring can have various ring sizes up to a 62 membered ring (figure I.5). The macrolides can be classified into four classes : simple macrolides, polyenic macrolides, macropolylides and nitrogenous macrolides (azalides).

The tremendous interest in macrolide chemistry can be understood if one takes a look at the diversity of the structures and physiological effects of macrolides. Natural products containing a macrolactone framework are found in plants, insects, and bacteria and they may be of terrestrial or marine origin. The useful properties of macrolides range from perfumery to biological and medicinal activity. The new findings in the field of antitumour active and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration to chemists to study macrolides [1]

Antibacterial agents, or antibiotics, are a class of a much larger group of compounds called antimicrobial agents. Antibiotics used to refer to only naturally occurring molecules produced by a variety of microorganisms [13]. Macrolides belong to one of the most commonly used families of clinically important antibiotics used to treat infections caused by

Gram-positive bacteria such as Staphylococcus aureus, Streptococcus pneumoniae and Streptococcus pyogenes. [14; 15] Chemically, macrolides are represented by a 14-, 15- or 16-membered lactone ring carrying one or more sugar moieties and additional substitutions linked to various atoms of the lactone ring, (Figure 1.4) [14].

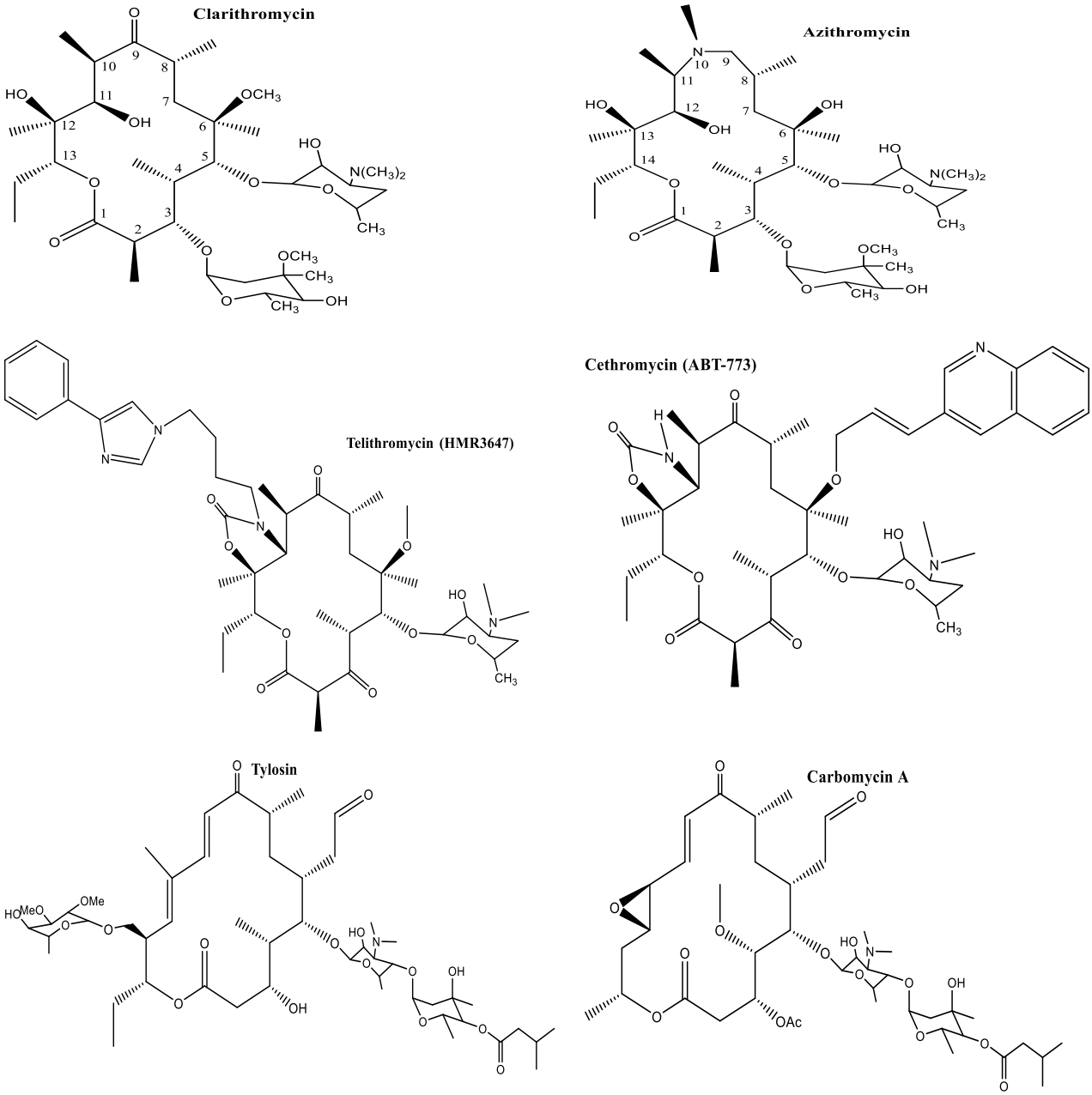


Figure 1.4: Chemical structures of the 14-, 15- or 16-membered macrolide antibiotics.

First row: drugs of the first generation (erythromycin) and second generation (14-membered ring clarithromycin and 15-membered ring azithromycin). Second row: ketolides, the macrolides of the third generation. Third row: examples of 16-membered ring macrolides. The wide variety of macrolide structures in nature can be appreciated just by looking at some examples of different types of macrolide antibiotics (Figure 1.5) [16; 17].

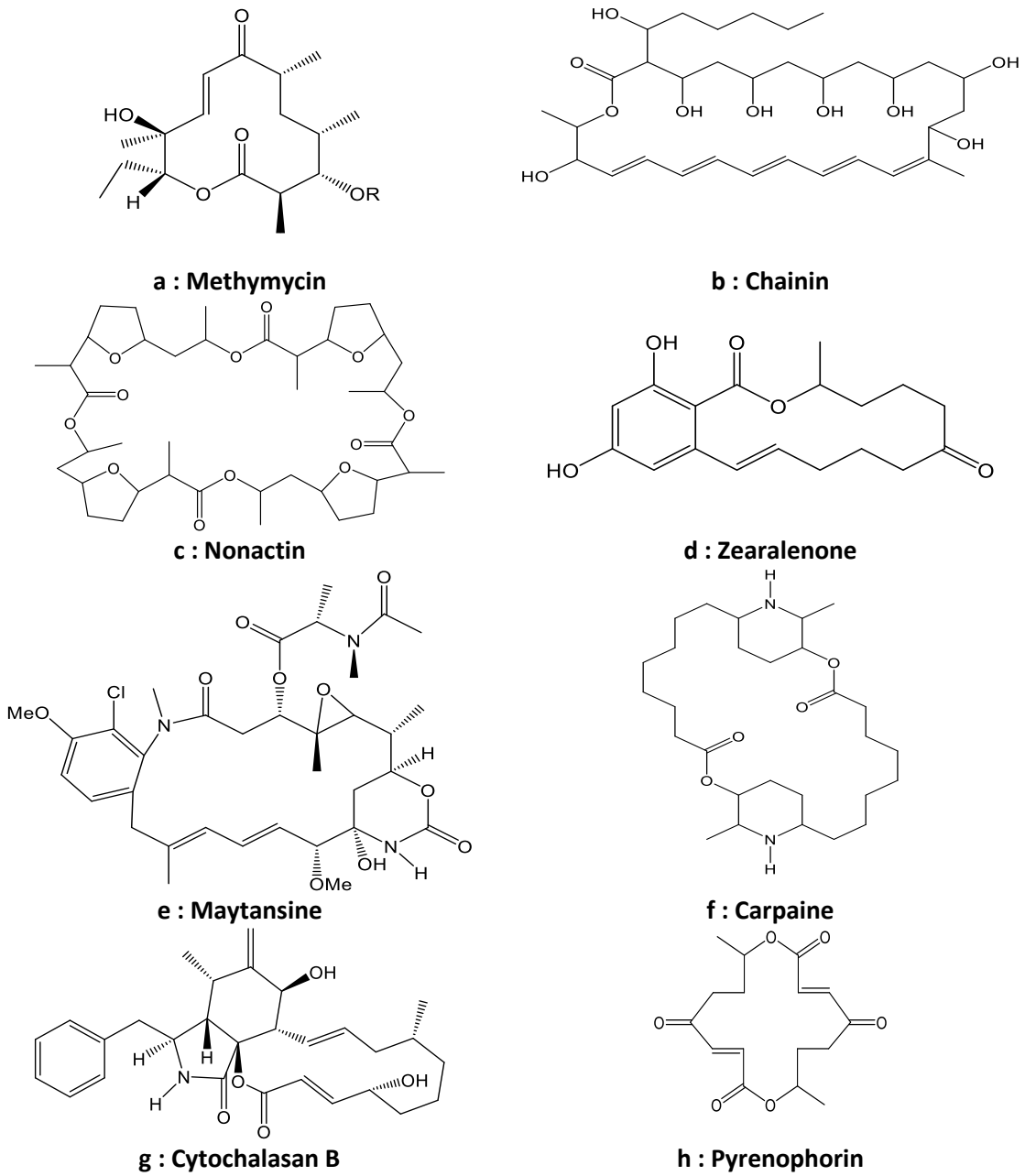


Figure 1.5 Examples of macrolide antibiotics**: a:** polyoxo-macrolide, **b:** polyene-macrolide , **C:** ionophore-macrolide, **d**: β-resorcyclic acid macrolides, **e**: ansamycins , **f:** alkaloid macrolides, **g:** macrolide cytochalasans, and **h:** macrotetranolides.

1.4 The need for novel antibacterial agents

The prevalence of drug resistant bacteria is growing at an alarming rate in both developing and developed countries [18]. From this statement alone, it should be clear that the need for the development of novel antibacterial agents is of utmost importance. In the current antibacterial drug pipeline, there is only a miniscule glimmer of hope. This rapid increase in resistant bacteria coupled with the slow development of novel agents has lead some experts to call this time the "dawn of the post-antibiotic era." [13] There exists a perpetual need for new antibiotics. Most drugs will be just as effective in the future as they are today, but that is not the case with antibiotics. Eventually, the inevitable rise of resistance will erode the utility of today's antibiotics. There are three factors that intensify this supply problem by discouraging antibiotic development [19].

First, antibiotics are used in smaller quantities than other drugs. The standard antibiotic course lasts only weeks compared to treatment for chronic illness which can last a lifetime. Therefore, antibiotics yield lower revenues than most drugs. Second, the use of newly approved antibiotics is often limited to serious bacterial infections. The third reason is an increase in regulatory requirements to get a drug licensed, which makes clinical trials cost prohibitive. However, most newly approved drugs can be prescribed to all who may benefit from their use. These factors ultimately result in this quandary: Resistance is on the rise while antibiotic discovery and development are on the decline. Having new antibiotics approved for use is a great thing, but those antibiotics which utilize the same mechanism of action as previously approved drugs always run the risk of increasing the rate of resistance [13].

1.5 Macrolide-binding site in the ribosome

The discovery of the significance of (hetero) aryl anchored at the terminus of a suitable linker enable us design the novel macrolides capable of interacting with a new binding site of bacterial ribosome [20]. The general location of the macrolide binding site on the large ribosomal subunit has been initially mapped using a combination of biochemical

and genetic methods [14]. Nonetheless, the details of the molecular interactions of the various classes of macrolides with the ribosome have just started to emerge with the release of several crystallographic structures of the archaeal and bacterial large ribosomal subunits and their complexes with antibiotics [14]. Because the polar groups locate on the frontal face of the aglycone and most of the alkyl groups install on the other face, the two sides of the macrolides present hydrophilic and hydrophobic properties, respectively. The hydrophobic side is believed to make van der Waals contacts with hydrophobic areas on the peptide tunnel wall. Recently, comparison of reduced efficacy of 4,8,10-tridemethyl telithromycin and 4,10- didemethyl telithromycin with parent telithromycin undoubtedly gave new sight into the important function of these methyl groups [20].

A macrolide molecule is coordinated in its binding site by multiple hydrophobic and hydrogen bonds (and possibly, a covalent bond in case of some 16-membered ring macrolides) between its functional groups and 23S rRNA [14]. These interactions with RNA account for most of the free energy of drug binding. In addition, some macrolides can reach ribosomal proteins L4 and/or L22. The mucinose sugar of tylosin interacts with L22 and the furosamine residue of spiramycin interacts with L4. The proximity of these proteins to the macrolide binding site explains why mutations in L22 and L4 protein genes can render cells resistant to macrolides [14].

1.6 Modes of inhibition of protein synthesis by macrolides

The precise mechanism of protein synthesis inhibition by macrolides depends on the specific chemical structure of the drug molecule. This affects its interaction with the ribosome as well as the mode of the inhibitory action. Four modes of inhibition of protein synthesis have been ascribed to macrolides [14]:

1) Inhibition of the progression of the nascent peptide chain during early rounds of translation [21];
2) Promotion of peptidyl tRNA dissociation from the ribosome [22];
3) Inhibition of peptide bond formation;
4) Interference with 50S subunit assembly [15].

All of these mechanisms have some correlation with the location of the macrolide binding site on the ribosome [14].

Most macrolides are weak bases and are unstable in acids. The action of macrolides can be bactericidal or bacteriostatic, the effect depending on the concentration and the type of microorganism targeted by the drug.

Macrolides bind to the 50S subunit of the bacterial ribosome and inhibit the transpeptidation and translocation process, causing premature detachment of incomplete polypeptide chains. The antimicrobial spectrum of erythromycin is very similar to penicillin; it has proved to be a safe and effective alternative for penicillin-sensitive patients.

Macrolides are effective against Gram-positive bacteria and spirochetes but not against most Gram-negative organisms, the exceptions being Neisseria gonorrhoeae and Haemophilus influenzae. Mycoplasma pneumoniae, Legionella species and some chlamydial organisms are also susceptible.

The macrolides are administered orally and intravenously. They diffuse readily into most tissues, but do not cross the blood-brain barrier; additionally there is poor penetration into synovial fluid. The majority of side effects associated with macrolides are mild and transient. As a class they are generally welltolerated. The most common complaints involve the gastrointestinal tract and include diarrhea, nausea, vomiting and abdominal pain. Patients may complain of an abnormal or metallic aftertaste. Hepatotoxicity is a very rare but serious side effect associated with the estolate salt of erythromycin [23].

1.7 Antibiotic Resistance

Resistance is defined as the relative insusceptibility of a microorganism to a particular treatment under a particular set of circumstances [24]. Some researchers believe that resistance is an ecological phenomenon stemming from the response of bacteria to the widespread use of antibiotics and their presence in the environment.

They believe that the rise in the frequency of antibiotic resistance among pathogens should be a “cause of great concern” and suggest “a commitment to act responsibly” [23].

Macrolides inhibit protein synthesis by interacting with bacterial ribosomal RNA. Two distinct mechanisms have been responsible for the majority of macrolide resistance observed in clinical isolates. The first mechanism involves the production of a ribosomal methylase. This enzyme methylates a specific adenine residue on the ribosomal RNA thus preventing binding of the macrolide, lincosamide and streptogramin B (MLSB) and conferring MLSB resistance. The methylase is the product of a family of genes called erm that can be inducibly regulated or constitutively expressed. The second mechanism involves a family of genes called mef and is commonly referred to as efflux resistance [25].

Bacteria resist macrolide and lincosamide antibiotics in 3 ways:

- Through target-site modification by methylation or mutation that prevents the binding of the antibiotic to its ribosomal target,
- Through efflux of the antibiotic,
- And By drug inactivation. These mechanisms have been found in the macrolide and lincosamide producers, which often combine several approaches to protect themselves against the antimicrobial that they produce. In pathogenic microorganisms, the impact of the 3 mechanisms is unequal in terms of incidence and of clinical implications [26].

The extensive use of these antibiotics has led inevitably to the spread of resistant strains. Expression of some of the resistance determinants is inducible by macrolides. Of particular interest are Erm methyltransferases, which specifically methylate a unique nucleotide within the macrolide binding site. The mechanism of Erm induction depends on ribosome stall within the translated regulatory open reading frame preceding the Erm cistron, and is apparently closely related to the general mode of macrolide action on protein synthesis. However, the details of the mechanism of Erm induction are not known [14]. Equally important, the study of arising macrolide resistance shed light on how to fight against mutation of pathogens [20].

1.7.1 Macrolide action and drug resistance:

Macrolides inhibit protein synthesis by interacting with bacterial ribosomal RNA. Two distinct mechanisms have been responsible for the majority of macrolide resistance observed in clinical isolates. The first mechanism involves the production of a ribosomal methylase. This enzyme methylates a specific adenine residue on the ribosomal RNA thus preventing binding of the macrolide, lincosamide and streptogramin B (MLSB) and conferring MLSB resistance. The methylase is the product of a family of genes called erm that can be inducibly regulated or constitutively expressed. The second mechanism involves a family of genes called mef and is commonly referred to as efflux resistance [25].

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2. Discovery and physicochemical properties of Erythromycin

2.1 Discovery

Erythromycin is a macrolide antibiotic, first discovered in 1952. It is produced by an actinomycete originally isolated from a soil sample from the island of Panay in the Phillipine Archipelago. The actinomycete was identified as a strain of Streptomyces erythreus by Waksman and Henrici [27, 28]. The antibiotic, erythromycin, was isolated from this actinomycete by McGuire et al in the Lilly Research Laboratories, U.S.A. [29].

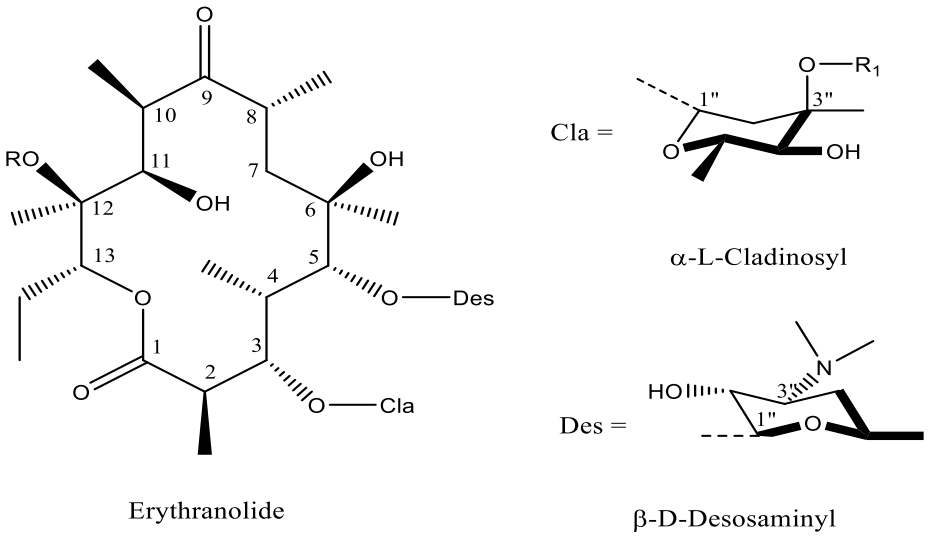
2.2 Chemistry

Not only does Streptomyces erythreus produce erythromycin (known as erythromycin A), it has also been found to produce other antibiotics, namely erythromycin B [30]. and erythromycin C [31]. Thus, erythromycin base occurs as a mixture of erythromycin A, which is the major component, and smaller amounts of erythromycin B and erythromycin C. By means of chromatography and the specific preparative techniques, erythromycin A, B or C may be selectively extracted from the mixture [32].

The work of a number of authors has lead to the elucidation of the chemical structure and stereochemistry of erythromycin [31]. Erythromycin is a polyhydroxylactone containing two sugars. The aglycone portion of the molecule is erythranolide, a 14-membered macrocyclic lactone ring. Attached to the lactone ring, via B-glycosidic linkages are two sugars: L-cladinose (2,3,6-trideoxy-3-methoxy-3-C-methyl-L-ribo-hexose), a sugar unique to the erythromycin molecule and D-desosamine (3,4,6-trideoxy-3- dimethylamino-D-xylo-hexose), the portion conferring the basic character to erythromycin, attached at positions C3 and C5 respectively [31] The hydroxyl groups at positions ell and C12 are in the cis position [31]. Figure 1.6 depicts the chemical structure of erythromycin A and its components.

Erythromycin B differs from erythromycin A by a hydrogen attached to the C9 position as opposed to the hydroxyl group found in erythromycin A. In erythromycin C the L-

cladinose sugar found in erythromycin A is replaced by a nonrnethoxylated mycarose [31]. Hung, Marks and Tardrew have synthesized erythromycin A, Band C from erythranolide A [33]. Figure 1.6 depicts the proposed pathway for the synthesis of erythromycins A, Band C.



	R	***R₁***
Erythromycin A	OH	CH_3
Erythromycin B	H	CH_3
Erythromycin C	OH	H

Figure 1.6 Chemical structure of erythromycin A and its components

2.3 Physical Properties

The active form of the drug is erythromycin base. Erythromycin base, (C37H67N013.H20, molecular mass = 733.90) is an odourless, bitter-tasting, white crystalline compound [34]. It is very slightly soluble in water (2mg/ml) and ether, but is freely soluble in alcohols, methanol, acetone, chloroform, acetonitrile and ethyl acetate [31, 34]. A list of solubilities of erythromycin are depicted in Table 1.2.

Whilst there is some controversy over the states of the polymorphic forms of erythromycin base, it is generally accepted that erythromycin occurs in a number of polymorphic forms: as an amorphous form, a hydrate (both mono- and di-) or as an anhydrate crystalline form [35]. In addition, the dihydrate has been shown to exist in three

polymorphic forms [36]. However, Bauer et al [37] have Buggested that the so-called mono- and dihydrates are in fact pseudomorphs containing entrapped water.

solvent	***mg/ml***
Isooctane	0.477
Petroleum ether	4.69
CycIohexane	0.2
Carbon disulfide	5.05
Carbon tetrachloride	>20
Toluene	>20
Benzene	>20
diethyl ether	>20
Chloroform	>20
Ethylene chloride	>20
Methyl ethyl ketone	>20
Acetone	>20
1,4 -Dioxane	>20
Isoamyl acetate	>20
Ethyl acetate	>20
Isoamyl alcohol	9.65
Pyridine	>20
Formamide	>20
Benzy l alcohol	>20
Isopropanol	>20
Ethanol	>20
Methano	>20
Ethylene glycol	>20
Water	2.1

Table 1.2 Solubilities of Erythromycin

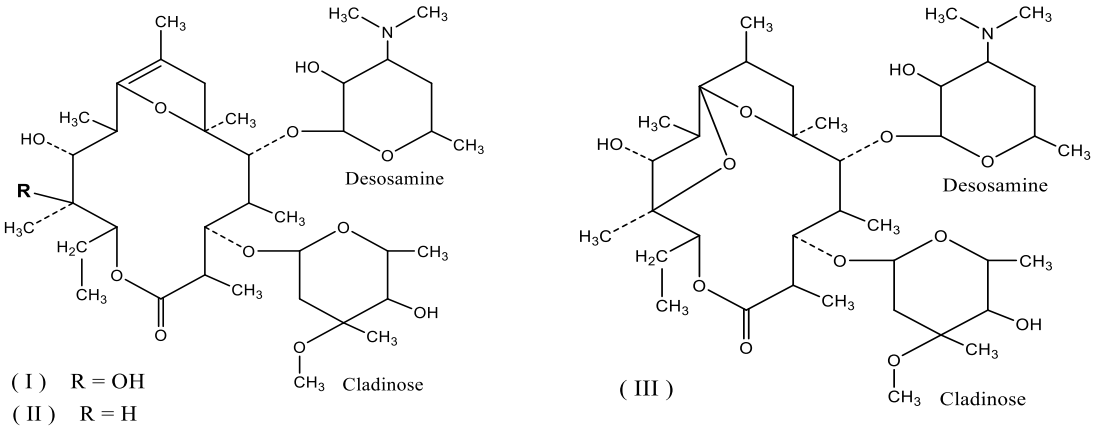
The various polymorphic forms have been reported to affect the solubility of erythromycin, with the dihydrate rapidly dissolving whilst the anhydrate is poorly soluble due to its hydrophobic nature and poor wettability [35]. Erythromycin base has a melting point of between 137°C - 140°C and a specific rotation, [a)250 = - 7PC and - 78° (c = 2' · ethanol). The anhydrous base has a melting point of 190°C - 193°C [31]. Erythromycin estolate has also been shown to exist in two polymorphic forms: crystalline and amorphous, with a slightly crystalline intermediate phase [38].

As a result of the N,N-dimethylarnino group, erythromycin has a basic character [31], being a relatively weak base with a pka = 8.6 [34].

2.4 Stability

It has been well established that erythromycin is unstable in acidic media. Until recently, the proposed mechanism of degradation of erythromycin in acidic solutions followed one of two pathways depending on the acid conditions. Under mild acid conditions (glacial acetic acid) erythromycin enol ether (EEE) is initially formed. Subseguent treatment of EEE with acid (methanolic hydrochloric acid) yields anhydroerythromycin (AE). Under strong acid conditions (hydrochloric acid) degradation of erythromycin yields only AE. Irrespective of the acid strength, no cleavage of the glycosidic linkages has been observed [39]. A recent report by Vinckier et al suggests an alternative mechanism for the acid degradation of erythromycin. This alternative mechanism was based on the simple observation that when EEE was placed in an acidic solution erythromycin base (EB) was formed as a degradation product. Therefore, the new mechanism proposes that the degradation of erythromycin is not unidirectional, but rather that there is an equilibrium between erythromycin and EEE with a simultaneous pathway by which erythromycin directly decomposes to AE without having to pass through EEE [40]. Figure 1.7 represents the chemical structures of the acid degradation products of EB, AE and EEE.

It has also been established that erythromycin is unstable in strong alkaline solutions, with the major degradation product being dihydroerythromycin. As a result of all these investigations, it would appear that the pH of maximum stability is between 7 and 8.8 [41], although one report has cited the maximum stability to be between pH 6.0 - 9.5 [34].



(I) 6,9 - hemi-acetal of 8,9 - anhydroerythromycin A

(II) 6,9 - hemi-acetal of 8,9 - anhydroerythromycin B

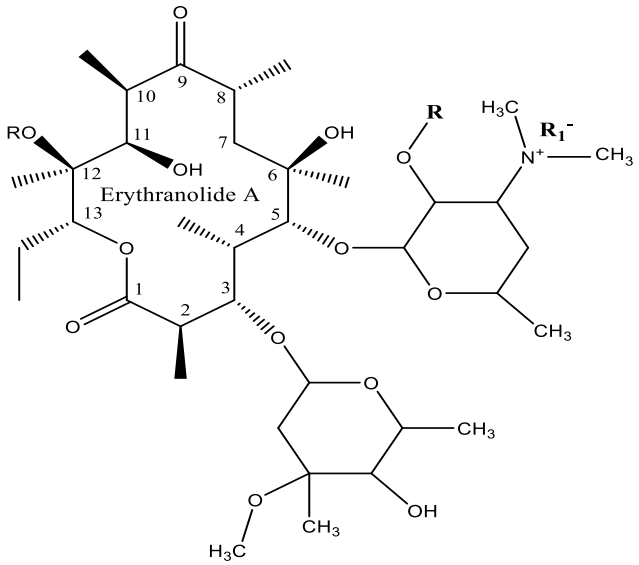
(III) 8,9 - anhydroerythromycin A

Figure 1.7 Chemical structures of the acid degradation products of erythromycin base

Since erythromycin is an acid labile drug, passage through the gastrointestinal tract will result in gastric acid inactivation of the drug, causing decreased absorption and low serum concentration levels. These problems associated with gastric acid inactivation of the drug may be overcome in a number of ways. Firstly, erythromycin base may be protected by enteric or film coating of the dosage fornl. This coating protects the drug from the acidic environment of the stomach, but allows the release of the active medicament in the more favorable environment of the intestine.

Secondly, the drug may be modified by preparing a salt (stearate), an ester (ethylsuccinate (EES) or propionate (PE», or a salt of the ester (estolate (EE) which is the lauryl sulphate salt of the propionyl ester and erythromycin acistrate which is the stearic acid salt of the 2'- acetyl ester) (38). However, propionyl erythromycin and erythromycin stearate have been shown to be unstable in acidic media. When PE is exposed to the acidic solution

of the stomach, the carboxylic acid portion is released, leaving behind the soluble hydrochloride salt. However, since EE is the salt of a strong acid (lauryl sulphuric acid), unlike PE, when it is exposed to the acidic contents of the stomach it does not release the acidic portion of the drug and therefore remains insoluble. These salts and esters are also used to overcome the bitter taste and water in solubility of erythromycin [43]. Figure 1.8 depicts the structural formulae of erythromycin and its most commonly used derivatives.



	R	***R1***
Erythromycin base	H	
Propionyl erythromycin	CH_2CH_2CO	
Erythromycin estotate	CH_2CH_2CO	$C_{12}H_{25}OSO_3$
Erythromycin stearate	H	$C_{17}O_{35}COO$
Erythromycin ethylsuccinate	$CH_2CH_2OOCCH_2CH_2COO$	
Erythromycin lactobionate	H	$C_{11}H_{19}O_9COO$
Erythromycin glucoheptonate	H	$C_6H_{13}O_6COO$

Figure 1.8 structural formulae of erythromycin and its most commonly used derivatives

Not only does pH affect the stability of erythromycin, buffer type and concentration, temperature and the presence of metal ions have also been shown to affect erythromycin stability [44,45].

2.5 Erythromycin derivatives

Recently, new derivatives of erythromycin have been synthesized which inhibit or retard the acid degradation process whilst retaining potent antimicrobial activity and offering comparative or improved pharmacokinetic properties.

Modification of the functional groups involved in the degradation mechanism is the principle upon which inhibition of the acid degradation of these compounds is based. These groups include the ketone at C9, hydroxyl at C6, the proton at C8 and the diol moiety at C11 and C12. Several modifications have been made to the ketone at the C9 position. The first of these modifications, an oximation of the ketone group at C9, resulted in roxithromycin (erythromycin, 9-[o-{(2-methoxyethoxy)-methyl}oxime]) .Its acid stability is largely due to the inhibition of the internal ketal formation of the aglycone ring (associated with erythromycin acid degradation) by the oxime function. The effect of pH on roxithromycin has been reported to be similar to that on erythromycin, with roxithrornycin also showing less activity at pH = 6 . 5 than at pH = 8.0 [46].

Another new derivative is dirithromycin (9-deoxo-ll-deoxy-9,11- [imino[2-(2-methoxyethoxy)ethylidene]-oxy]-(9S)-erythromycin), an oxazine formed from erythromycylamine and (2- methoxyethoxy) acetaldehyde. Erythromycylarmine, derived from reductive amination of the C9 ketone of erythromycin is no longer considered as an acid stable alternative to erythromycin as it yields extremely low blood levels [46].

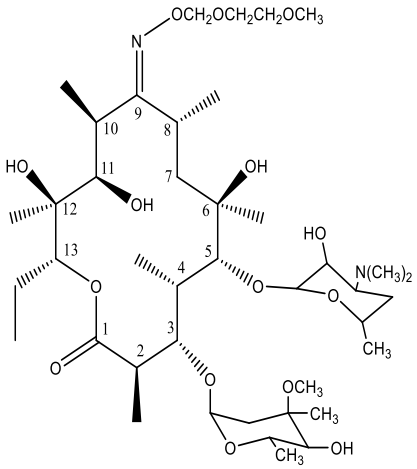
Dirithromycin, however, achieves sufficiently high concentrations in the blood and has a long serum half life. A novel new l5-membered ring compound, azithromycin (a 9-deoxo-9a-aza-9a-homoerythromycin A derivative), has been developed as a result of modification of the ketone group at position C9 in the erythromycin lactone ring. Utilizing a Beckmann rearrangement of the 9-oxime derivative followed by reduction and N-methylation the I5-membered macrocyclic ring containing a tertiary amino group has been synthesized [46].

However, a recent report by Fiese and Steffen [47] has shown azithromycin to be unstable in aqueous acidic media, although more stable than erythromycin under those conditions. Furthermore, unlike erythromycin, there is cleavage of the ether bond resulting in the neutral cladinose sugar and a compound CP-66,458 [46].

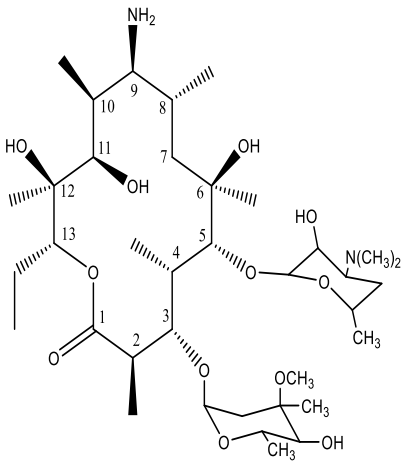
Modification of the hydroxyl group at position C6 (which is involved in the initial cyclization step) by means of alkylation has resulted in the formation of 6-0-methylerythromycin, named clarithromycin [46].

Flurithromycin (S-fluoroerythromycin), synthesized by using both chemical and bioconversion methods inhibits acid degradation by preventing the dehydrati on step that leads to the formation of the anhydrohemiketal[46].

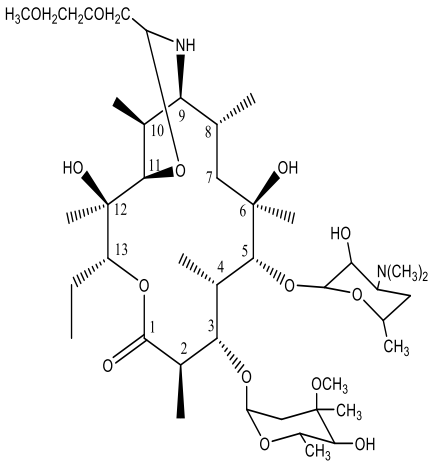
The various derivatives of erythromycin are depicted in Figures 1.9. Research continues on the modification of erythromycin to yield derivatives that will have oral efficacy, fewer gastrointestinal side effects and remain acid stable. These modifications include reductive amination with aliphatic aldehydes of erythrornycylarnine, formation of cyclic 11,12-carbamate derivatives of erythromycin, modification of the hydroxyl group at C11 as well as chemical modification of the 11,12-diol moiety and the 4" position [46].



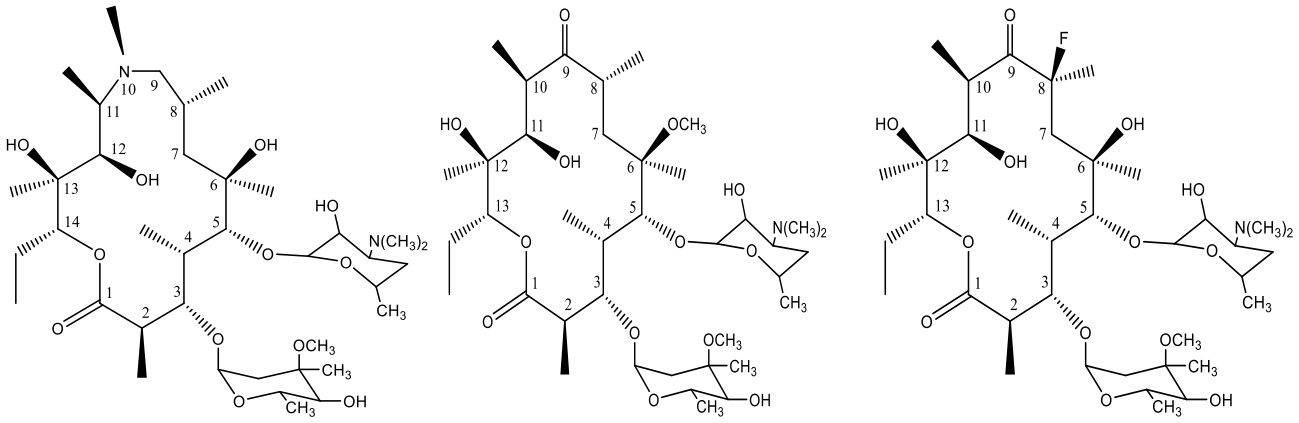
Roxithromycin



Erythromycylamin



Dirithromycin



Azithromycin **Clarithromycin** **Flurithromycin**

Figure 1.9 Semisynthetic derivatives of erythromycin

This review is confined to erythromycin and those newer macrolide antibiotics synthesized from erythromycin. However, there are a number of other macrolide drugs available. These include josamycin, spiramycin as well as the newer semi-synthetic 16-membered antibiotics rokitamycin and miokamycin. The latter two drugs appear to have improved activity against some resistant organisms as well as improved oral bioavailability (41).

2.6 Clinical pharmacology

2.6.1 Spectrum of antimicrobial activity

Erythromycin is a broad spectrum antibiotic, active against most grampositive and some gram-negative bacteria. In addition, it is also effective against Treponema pallidum, many strains of rickettsiae and chlamydia and certain non-tuberculosis mycobacteria [48].

Although few reports appear in the literature on the antimicrobial spectrum of the new semisynthetic macrolide antibiotics, with the possibility of a few exceptions, it is generally accepted that they have a very similar antimicrobial spectrum to erythromycin.

A list of comparative in vitro activities of erythromycin and five new semisynthetic macrolide antibiotics is tabulated in Table 2.2. Although it is evident that there is very little or no difference between erythromycin and the newer macrolide antibiotics as far as antimicrobial spectrum of activity is concerned, the potentially favourable differences in the pharmacokinetic properties (longer half-life, thus having the potential for once-daily dosing) of the newer macrolides might make them clinically more advantageous than erythromycin [46].

Table 1.3 Comparative in vitro activities of ERYTHROMYCIN and five new semisynthetic macrolide antibiotics

Microorganism	Compound	n	MIC (µg/ml) RANGE
Staphylococcus aureus (MS)	***Erythromycin***	16	0.06 - > 128
	Roxithromycin		0.12 - > 128
	Dirithromycin		0.12 - > 128
	Azithromycin		0.06 - > 128
	Clarithromycin		0.03 - > 128
	Flurithromycin		0.06 - > 128
Staphylococcus aureus (MR)	***Erythromycin***	13	> 128
	Roxithromycin		> 128
	Dirithromycin		128 - > 128
	Azithromycin		> 128
	Clarithromycin		> 128
	Flurithromycin		128 - > 128
Staphylococcus epidermidis	***Erythromycin***	15	0.06 - > 128
	Roxithromycin		0.12 - > 128
	Dirithromycin		0.06 - > 128
	Azithromycin		0.06 - > 128
	Clarithromycin		0.03 - > 128
	Flurithromycin		0.06 - > 128
Streptococcus pogenes	***Erythromycin***	15	0.015 - 0.06
	Roxithromycin		0.03 – 0.06
	Dirithromycin		0.03 – 0.12
	Azithromycin		0.015 – 0.12
	Clarithromycin		0.015 – 0.015
	Flurithromycin		0.03 – 0.06

Streptococcus pneumoniae	***Erythromycin***	13	≤ 0.004 - 0. 015
	Roxithromycin		0.03 – 0.03
	Dirithromycin		0.03 – 0.06
	Azithromycin		≤ 0.004 - 0. 12
	Clarithromycin		≤ 0.004 - 0. 015
	Flurithromycin		0.03 – 0.06
Streetococcus species,	***Erythromycin***	13	0.015 - 0.12
viridans group	***Roxithromycin***		≤ 0. 008 - 0.03
	Dirithromycin		0.06 – 0.25
	Azithromycin		0.015 - 0.12
	Clarithromycin		≤ 0. 008 - 0.03
	Flurithromycin		0.015 – 0.06
Enterococcus species	***Erythromycin***	15	0.06 - > 128
	Roxithromycin		0.25 - > 128
	Dirithromycin		0.12 - > 128
	Azithromycin		0.25 - > 128
	Clarithromycin		0.03 - > 128
	Flurithromycin		0.25 - > 128
Corynebacterium species	***Erythromycin***	12	0.008 – 16
	Roxithromycin		0.015 – 32
	Dirithromycin		0.03 - 64
	Azithromycin		0.008 - > 128
	Clarithromycin		0.008 - 8
	Flurithromycin		≤ 0. 015 - 32
Legionella pneumophila	***Erythromycin***	14	0.5 – 2
	Roxithromycin		0.12 – 0.5
	Dirithromycin		1 – 16
	Azithromycin		0.12 – 2
	Clarithromycin		0.12 – 0.25
	Flurithromycin		0.5 - 2

n = number of strains / MS = methicillin sensitive / MR = methicillin resistant

It is evident from Table 2.2 that there is some controversey over the range of minimum inhibitory concentrations of erythromycin required to inhibit the growth of various microorganisms.

2.6.2 Mode of action

Erythromycin interferes with protein synthesis at the ribosomes. Erythromycin penetrates the cell wall of sensitive bacteria and binds to the 50S ribosomal subunit in a 1:1 stoichiometry. Penetration of the cell wall of sensitive bacteria is dependent on the presence of ammonium or potassium salts [49].The exact mechanism by which erythromycin inhibits protein synthesis is not known with certainty, but it has been proposed that it inhibits the translocation reaction stage of bacterial protein synthesis. Inhibition of translocation is primarily due to the detachment of peptidyl-tRNA from the ribosome during translocation [50].

During translocation, the growing peptide chain moves from the acceptor site to the donor thought that erythromycin binds to the translocation of the peptide chain. site on the ribosome. It is donor site, thus preventing certain amino acids, in the presence of erythromycin, are prevented from being incorporated into polypeptide linkages, but erythromycin has no effect on nucleic acid synthesis [51].

Although erythromycin acts by inhibiting protein synthesis, it may be bacteriostatic or bactericidal depending on the microbial species, sensitivity of the micro-organism, the phase of growth of the sensitive pathogen, inoculum density and concentration of erythromycin used . At high concentrations of the drug, erythromycin may be bactericidal, but at lower concentrations it appears to be bacteriostatic [52].

2.6.3 Resistance

There are a number of mechanisms by which pathogens are resistant to erythromycin. These include inability of the macrolide to penetrate the cell, chemical inactivation of the macrolide and inability of the macrolide to bind to the ribosome target as a result of target site modification [53,54].

Conflicting reports appear in the literature with respect to the inability of the macrolide to enter the cell. Several reports suggest lack of penetration into the cell causes resistance to the macrolide antibiotic. However, other reports indicate that erythromycin may enter bacterial cells by means of passive diffusion across the lipid bilayer of the cell membrane. Goldman and Kadam, as a result of unpublished observations, suggest that further studies in this regard be performed before this mechanism of resistance is generally accepted [53].

Target site modification, as a result of a number of enzymes which result in mono- or di-methylating the N6 amino group of the adenine residue 2058 in 23S rRNA, is the best known mechanism of erythromycin resistance . This methylation does not seem to perturb ribosomal function, but results in the binding site on the ribosome becoming inaccessible to the antibiotic[53].

Resistance due to target site modification may be constitutive (presence of erythromycin is not required for resistance), but most frequently it is inducible (resistance to erythromycin as a result of the presence of subinhibitory concentrations of the drug) . The third mechanism of resistance is inactivation of erythromycin by enzymes produced by the micro-organism itself [54].

2.7 Pharmacokinetics of ERYTHROMYCIN

Until recently, microbiological assays were the most frequently used technique to determine the serum concentrations of erythromycin. Thus, the majority of pharmacokinetic parameters for erythromycin have been determined microbiologically [55]. Unfortunately, these assays cannot differentiate between parent drug and its metabolites or the free drug and its protein-bound or unhydrolysed ester forms. It is thus difficult to compare erythromycin bioavailability data from different formulations and from studies using different protocols or analytical methods. Similarly, the evaluation of the clinical significance of antibiotic concentrations from different dosage forms is also not meaningful [56].

Data obtained from bioavailability studies on erythromycin and its derivatives may only be compared if the products are assessed under the same conditions [57].

2.7.1 Absorption and bioavailability

The free base is the only biologically active in vivo form of erythromycin. The stearate and the esters of erythromycin have to dissociate and/or hydrolyse to the free base in vivo in order to be biologically active [56]. Studies carried out by Lee et al, in rats, show erythromycin to be marginally absorbed from the stomach but extensively absorbed from all parts of the small intestine. The authors showed erythromycin to be mainly absorbed in the small intestine, with lesser amounts being absorbed in the caecum and large intestine [58].

As has been previously mentioned (Section 1.1.4), erythromycin base is unstable in acidic media, rapidly degrading to its inactive metabolites, resulting in decreased absorption of active drug and thus erratic bioavailability. Erratic bioavailability has been reported with film coated (90) and enteric coated erythromycin base tablets [56], whilst better and more regular absorption is seen from enteric coated base pellets [59]. Large intersubject variability has been reported [60], whilst higher erythromycin serum concentrations have been detected in subjects with pernicious anaemia and/or achlorhydria [56].

2.7.2 Metabolism

Both erythromycin A and clarithromycin are metabolised through CYP450 3A4. However, there are differences in their abilities to bind to and inhibit the cytochrome P450 isoform CYP 3A4. On the basis of these differences, macrolides (in general) are classified into three groups on the basis of data provided by in vitro experiments:

1) Group 1 include erythromycin A and troleandomycin. Both drugs bind strongly to and markedly inhibit CYP 3A4.

2) Clarithromycin belongs to Group 2 agents. This drug exhibits a lower affinity for CYP 3A4 compared to erythromycin A, and form complexes to a lesser extent.

3) Group 3 include azithromycin and dirithromycin. These compounds have been shown to interact poorly with the cytochrome P-450 system in vitro. However, results obtained from some clinical studies showed that clarithromycin is similar to erythromycin A in some drug interactions (e.g. with psychotropic agents) [61].

The emergence and broad spread of resistance prompted the development of the new generation of macrolides. Ketolides , representing the third generation, show improved potency against many sensitive and some resistant strains and are often associated with bactericidal activity. Macrolide antibiotics with an extended macrolactone ring, such as 16-membered macrolides , find extensive use in veterinary medicine and are sometimes also used in humans [62].

3. THE KETOLIDES

3.1 Introduction

The emergence of antibiotic-resistant bacterial strains is driving the search for new antimicrobial agents and will hopefully lead to the widespread application of new antibiotics in the future. Within the last 3 years, a number of new agents, such as the newer fluoroquinolones and the oxazolidinones, reached the market. They show significantly improved activity against bacteria that have acquired resistance or show limited susceptibility to older agents [63].

Penicillin resistance in pneumococci has already reached alarming levels worldwide [64]. Additionally, the lack of activity against atypical pathogens limits the usage of penicillins in lower respiratory tract infection. Also the resistance and crossresistance of macrolides, which initially offered a good activity against a wide spectrum of respiratory pathogens, is increasing among agents of the class [65].

Macrolides were introduced to the field of anti-infectives, beginning with erythromycin A, in the early 1950s [29]. Advantages over existing drugs were their value in patients with β-lactam intolerance and activity against penicillin-resistant pathogens.

Drawbacks were rapidly evolving resistance, instability of the drug in acid environment, poor absorbance by the oral route and gastrointestinal side-effects [66]. New substances ideally have activity against key pathogens and overcome resistance problems. A new or extended mechanism of action is needed to fulfil these requirements. Telithromycin (HMR 3647) is the first antibiotic belonging to a new class of 14-membered ring macrolides, named ketolides, to reach clinical use. This new addition to the macrolide–lincosamide–streptogramin B (MLSB) group was developed specifically for the treatment of community acquired respiratory tract infections. Telithromycin was developed at Aventis (Romainville, France) and reached the market (Germany and Spain) as Ketek late in 2001 [67].

3.2 From macrolides to ketolides (Chemistry and structure–activity relationship).

The structural characteristics responsible for this property are (Figure 1.10) [68]:

i) removal of the cladinose normally present at position 3 and its replacement by a keto-group (hence the name ketolides);

ii) incorporation of an 11,12- or 6,11-cyclic moiety

iii) addition of a heteroaryl-alkyl side chain attached to the macrocyclic ring by a suitable linker.

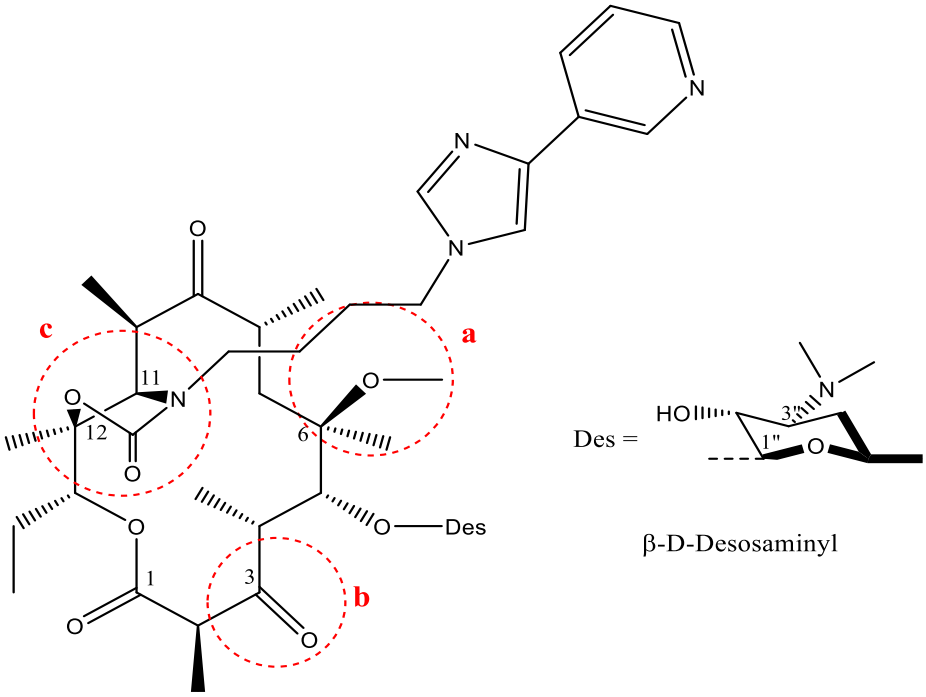


Figure 1.10 Chemical structure of telithromycin; **(a)** the methoxy-group at C6 improves acid stability and prevents internal hemiketalization; **(b)** 3- keto-function avoids MLS_B resistance induction and improves ribosome binding; **(c)** C11/12 carbamate side-chain increases affinity for the ribosomes and improves interaction with MLS_B-resistant ribosomes.

The L-cladinose sugar was long thought to be essential for the antimicrobial activity of the 14-membered ring macrolides, since its removal from clarithromycin, azithromycin and roxithromycin leads to loss of antimicrobial activity. However, with the ketolides, modifications at other positions of the macrolactone ring compensate the loss of cladinose (C3, C6, C11/12) [69]. Telithromycin is differentiated from other known ketolides by the introduction of a large aromatic N-substituted carbamate extension at position C11–C12. This ring also has an imidazo-pyridyl group attachment. Telithromycin possesses a 6-OCH3 group (like clarithromycin), avoiding internal hemiketalization with the 3-keto function and giving the ketolide molecule excellent acid stability [70].

Like erythromycin, roxithromycin, clarithromycin and azithromycin, the ketolides belong to the MLS_B group of antimicrobials [67].

3.3 Mechanism of action

MLS_B antimicrobials target the bacterial ribosomes, which consist of two subunits, 30S and 50S. The two subunits are made of ribosomal RNA (rRNA) and numerous protein (r-protein) components. The 30S ribosomal subunit interacts with the messenger RNA (mRNA) and translates in conjunction with transfer RNAs (tRNAs) the genetic code on the mRNA. The large subunit (50S) provides the catalytic centre (peptidyl transferase centre) where a peptide bond is formed between the amino acid and the peptide chain previously synthesized. The growing peptide passes through a peptide exit channel within the 50S subunit to emerge on the back of the ribosome [69].

Ketolides inhibit the synthesis of new proteins by preventing the bacterial ribosome from translating its mRNA. This process is blocked in two different ways.

(1) The peptidyl transferase centre in the 50S subunit is the site of interaction of MLSB antibiotics and of chloramphenicol and puromycin. The structure of the 50S subunit has recently been resolved by visualizing molecular details at atomic resolution using X-ray crystallography. The peptidyl transferase centre appears to be constructed entirely from elements of 23S rRNA, which is composed of six domains. This indicates that peptide bonds are catalysed by rRNA and that the catalytic centre is formed mainly from structures in domain V of the 23S rRNA. MLS_B drugs, such as chloramphenicol and puromycin, bind to closely related sites on the 50S ribosomal subunit and interact with an internal loop structure within domain V of bacterial 23S rRNA in the upper portion of the peptide exit channel close to the peptidyl transferase centre (figure 1.11) [69,71].

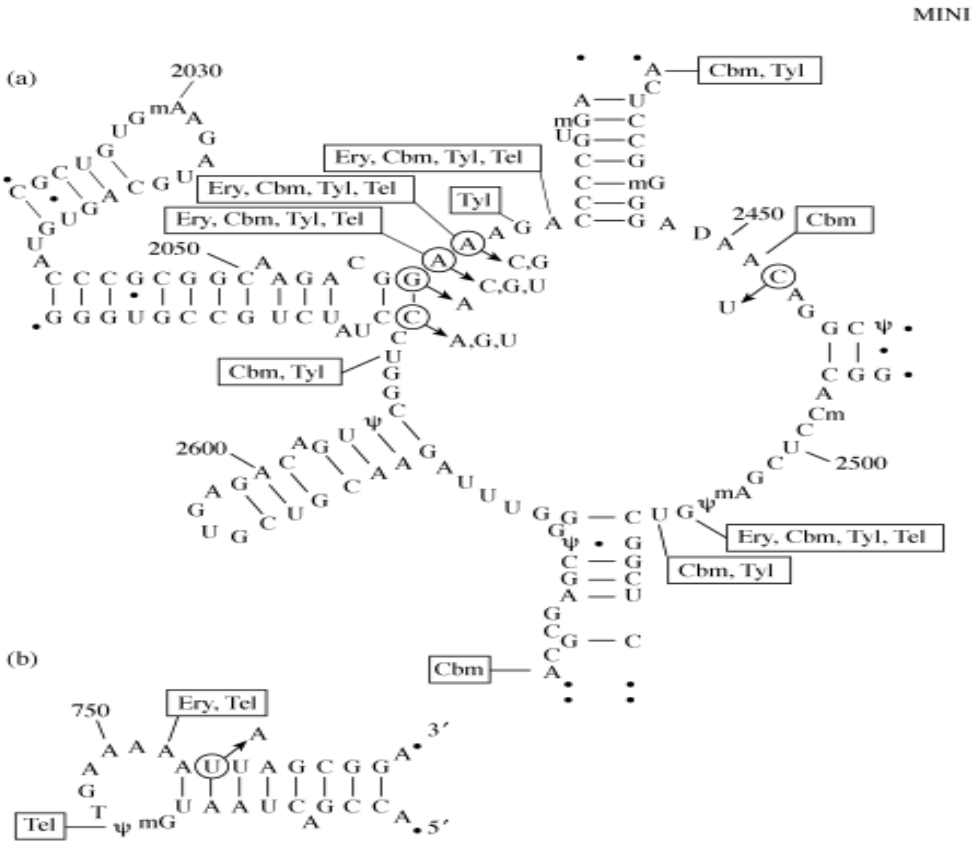


Figure 1.11 Secondary structure models of the peptidyl transferase centre in domain V of 23S rRNA **(a)** and hairpin 35 in domain II **(b)** Positions of macrolide interactions and of mutations that confer macrolide resistance are indicated and nucleotides are circled, respectively. **Ery**, erythromycin; **Cbm**, carbomycin; **Tyl**, tylosin; **Tel**, telithromycin [72].

Macrolides and ketolides bind to the same region of 23S rRNA. Because of the C11/12 carbamate arm in ketolide antimicrobials, the strength of interaction is different from those of macrolides. The drugs bind to the ribosome and interact with specific nucleotides in the rRNA, preventing these nucleotides from reacting with chemical reagents [69,71].

The drug-binding sites in hairpin 35 of domain II and the peptidyl transferase loop of domain V of the 23S rRNA are folded close to each other, forming a binding pocket for macrolides and other drug types [69,71].

The alkyl–aryl extension at C11–C12 in the ketolide lactone ring produces the dominant effect in protecting position A752 in hairpin 35 of domain II. The cladinose moiety influences this position by expressing a less strong binding. The binding affinity for

telithromycin evaluated as dissociation constants is ~10-fold stronger than that for erythromycin [71].

Hairpin 35 and the peptidyl transferase loop act as a single drug-binding site on the ribosome, binding one ketolide molecule [69,71].The distance between the nucleotides involved in drug binding is probably spanned by the C11/12 carbamate compounds, whereas erythromycin and clarithromycin might not be capable of making direct contact with the base of A752 [69].

(2) The numerous r-protein components of rRNAs are required to create the two subunits of newly formatted ribosomes. Some 34 r-proteins and two rRNA molecules (5S and 23S) form a functionally active 50S subunit. Macrolides and ketolides interact with partially assembled 50S subunit precursors to block this process, leading to nucleolytic degradation of the unassembled precursor particles. In cells treated with erythromycin, a 50S precursor particle accumulates. Erythromycin is bound by this particle that contains 23S and 5S rRNAs but only 18 of the 34 large subunit r-proteins. Cellular ribonucleases degrade the unassembled 50S subunit particle[69].

3.4 Antibacterial activity

The microbiological profile of telithromycin is characterized by high in vitro activity against many common and atypical/ intracellular respiratory pathogens, including MLS_B-resistant strains [67].

Telithromycin has improved in vitro activity against Gram-positive aerobes compared with macrolides and azalides. High activity of telithromycin against atypical respiratory pathogens (Bordetella spp., Legionella spp., Chlamydia pneumoniae, Mycoplasma pneumoniae) was demonstrated [73,74]. Its potency against key community-acquired Gram-negative respiratory pathogens such as Moraxella catarrhalis and Haemophilus influenzae appeared similar to that of azithromycin [75,76].

Telithromycin was found to be active against several Gram-positive and -negative anaerobic bacteria such as Clostridium spp., Peptostreptococcus spp. and Bacteroides spp [77]. Telithromycin is inactive against Enterobacteriaceae, nonfermentative Gram-negative

bacilli, Acinetobacter baumanii and constitutively MLSB-resistant Staphylococcus aureus. In a study from Spain, telithromycin displayed significant in vitro activity against Streptococcus pneumoniae isolates regardless of the presence of different macrolide resistance determinants [erm(B), mef(A)] [78]. Telithromycin is two to five times more active than clarithromycin against Gram-positive cocci susceptible to erythromycin A. Telithromycin is bactericidal against S. pneumonia [79].

3.5 Resistance

Three main mechanisms of resistance account for acquired resistance to MLSB antimicrobials:

(i) target site modification, (ii) reduced intracellular accumulation due to decreased influx or increased efflux of the drug and (iii) production of inactivating enzymes.

(i) Target site modification

Target site modification occurs as a mutation on 23S rRNA or on ribosomal proteins, or is due to mono- or dimethylation of 23S rRNA at positions A2058 and A2059. Methylation is usually governed by the acquisition of erm genes. erm genes encode methyltransferases that N6-dimethylate specific adenine residues within a conserved region of the rRNA. Ribosomal methylation confers cross-resistance to MLSB antibiotics because the binding sites of these drugs overlap. The methylation leads to a conformational change in the ribosome, resulting in decreased affinity for all MLS_B antibiotics. Numerous erm genes have been described for different clinically important bacterial species [80]. Methylation or substitution of A2058 alters the major contact site for the drugs. Binding of clarithromycin and erythromycin to Escherichia coli ribosomes is reduced over 10000-fold by the 23S rRNA A2058G mutation. Binding of telithromycin is reduced by the A2058G mutation, but this mechanism is clearly less efficacious than for other MLSB drugs[67].

(ii) Efflux pumps

Efflux pumps for erythromycin A have been described for several Gram-positive cocci. The efflux-mediated resistance pattern, known as M phenotype, is encoded by different genes: mef (A) or mef (E) in streptococci, and msr(A) and msr(B) in staphylococci[78]. The phenotype of macrolide resistance in S. pyogenes is differentiated by the so-called double- or triple-disc assay [81]. The conventional double-disc assay uses erythromycin and clindamycin to identify strains expressing the M phenotype, which is characterized by susceptibility to lincosamides, even after induction, and 16-membered macrolides. This resistance pattern has also been observed in S. pneumoniae [82].

(iii) Production of antibiotic inactivating enzymes

Degradation due to hydrolysis of the macrolide lactone ring by an esterase and modification due to macrolide phosphorylation and lincosamide nucleotidylation appear to play a minor role in MLS_B resistance. Only a few strains have been reported to harbour corresponding genes and to produce inactivating enzymes [83].

3.6 Stability

Ketolides are highly stable in acidic media. The C11–C12 carbamate substituent is responsible for improved activity in comparison with erythromycin A. Differences in the side chains fixed to the C11–C12 carbamate residues characterize numerous carbamate ketolides such as HMR 3004, ABT 773 and telithromycin [84]. In addition, the C11–C12 fixed side chain defines in vitro activities, pharmacodynamics, intracellular uptake, accumulation and efflux, and tolerance[85].

Namour et al. [86] evaluated the single- and multiple-dose pharmacokinetics and dose proportionality of telithromycin given once daily over the dose range of 400–1600 mg/day in healthy human subjects. Absorbance after oral administration was rapid, reaching C_{max} within 1 h of dosing.

Food intake did not affect absorption. Steady-state plasma concentrations were reached within 2–3 days of multiple dosing, regardless of the dose. Total plasma protein binding was ~70% with an absolute bioavailability of telithromycin of 57%.

3.7 Metabolism and drug interaction

Telithromycin undergoes hepatic metabolization and is eliminated primarily through the faeces (~80%)[86]. RU 76363, an alcohol resulting from hydrolysis of the aryl rings of the carbamate side chain of telithromycin, is the major hepatic metabolite, and is 4- to 16-fold less active than telithromycin in vitro. Its AUC represents ~10–12% that of telithromycin [85]. Excretion of telithromycin is almost complete in urine after 24 h and in faeces after 72 h [87].

Telithromycin is an inhibitor of CYP3A4 and in vitro of CYP2D6. Telithromycin should not be used in combination with drugs such as simvastatin, midazolam and cisaprid. Plasma concentrations of cyclosporin, tacrolimus and sirolimus need to be monitored during telithromycin therapy. An increase in QTc interval (< 500 ms) in special patients has been described [85]. The increase in the AUC of telithromycin due to therapy with itraconazole and ketoconazole does not indicate a dose adjustment. AUCs of theophylline, digoxin and levonorgestrel are increased in the presence of telithromycin [88].

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CHAPITER 02

Molecular modeling

1. Introduction

In recent decades, computer simulation has become an important tool in various fields such as mechanical engineering, chemistry, physics and materials [1-3]. In particular, computer simulations that take account of electronic structures [4].

At the present time, the computer simulation is one of the main tools to identify the regularities of behavior of the molecular systems under various external influences. [5]

Molecular modeling is the computer simulation of molecular structures, which concerns the distances and angles of bonds in chemical molecules, also the results of introduction and substitution of atoms or groups of atoms in the molecule.

Molecular modeling is the sum of theoretical methods and computational techniques that is used to predict molecular behaviours specifically interactions between molecules. [6]

Molecular modeling has been introduced as a valuable methodology for scientific research providing useful tools for the analysis and estimate of the physicochemical parameters and/or biological activity. [7]

Molecular modeling can be considered as a range of computerized techniques based on theoretical chemistry methods and experimental data that can be used either to analyze molecules and molecular systems or to predict molecular, chemical, and biochemical properties [8-10]. It serves as a bridge between theory and experiment to:

1. Extract results for a particular model.

2. Compare experimental results of the system.

3. Compare theoretical predictions for the model.

4. Help understanding and interpreting experimental observations.

5. Correlate between microscopic details at atomic and molecular level and macroscopic properties.

6. Provide information not available from real experiments.

All molecular calculation techniques can be classified under three general categories:

- ab initio and density functional electronic structure calculations,
- semi-empirical methods, and
- Molecular Mechanics

2. Quantum Mechanical Methods

2.1 Schrödinger equation

The starting point of the following overview is the Schrödinger equation [11 - 14] in its time dependent and time independent forms (1) and (2) respectively

$$\frac{\partial \Psi}{\partial t} = -\frac{i}{\hbar}\hat{H}\Psi \qquad (1)$$

$$\hat{H}\,\Psi = E\Psi \qquad (2)$$

where the wave functions Ψ and Ψ are functions of all coordinates of the relevant system and Ψ is also a function of time. In our case of a molecular Hamiltonian $\hat{H}$ is given by:

$$\hat{H} = -\frac{\hbar^2}{2}\sum_I \frac{1}{m_I}\nabla_I^2 - \frac{\hbar^2}{2m_e}\nabla_i^2 + \sum_I \sum_{J<I} \frac{Z_I Z_J e^2}{r_{IJ}} - \sum_I \sum_i \frac{Z_I e^2}{r_{iI}} + \sum_j \sum_{i>j} \frac{e^2}{r_{ij}} \qquad (3)$$

where I and J refer to the nuclei i and j refer to electrons. The first term in (3) is the operator of the kinetic energyof the nuclei. The second term is the operator of the kinetic energy of the electrons. The third term is the potential energy of repulsions between the nuclei, r_{IJ} is the distance between the nuclei I and J with atomic numbers Z_I and Z_J. The fourth term is the potential energy of the attractions between the electrons and the nuclei and $r_{iI}$is the

distance between electron i and nucleus I. The last term is the potential energy of the repulsions between the electrons, r_{ij} is the distance between electrons i and j .

2.2 The Born-Oppenheimer Approximations:

simplifies the general molecular problem by separating nuclear and electronic motions. This approximation is reasonable since the mass of a typical nucleus is thousands of times greater than that of an electron. The nuclei move really slowly with respect to the electrons. Thus, the electronic motion can be described as occurring in a field of fixed nuclei.

We can use the Born-Oppenheimer approximation to construct an electronic Hamiltonian, which neglects the kinetic energy termof the nuclei,

$$\hat{\mathrm{H}} = -\frac{\hbar^2}{2m_e}\nabla_i^2 + \sum_I \sum_{J<I} \frac{Z_I Z_J e^2}{r_{IJ}} - \sum_I \sum_i \frac{Z_I e^2}{r_{iI}} + \sum_j \sum_{i>j} \frac{e^2}{r_{ij}} \qquad (4)$$

This Hamiltonian is used in the Schrödinger equation describing the motion of the electrons in the field of the fixed nuclei:

$$\hat{\mathrm{H}}^{elec}\Psi^{elec} = E^{eff}\,\Psi^{elec} \qquad (5)$$

Solving this equation for the electronic wave function will produce the effective-nuclear potential function E^{eff} that depends on the nuclear coordinates and describes

the potential energy surface of the system. For bond electronic problem, Ψ should satisfy two requirements: antisymmetricity and normalization. Ψ should change sign when two electrons of the molecule interchange and the integral of Ψ over all space should be equal to the number of electrons of the molecule.

3. Hartree-Fock Self-Consistent Field Method

Much of the difficulty of solving the Schrödinger equation stems from the need to simultaneously determine the energy of eachelectron in the presence all other electrons. In the Hartree-Fock (HF) method this is avoided by calculating the energy of each electron in the averaged staticfield of the others. Initially a guess is made of the electron energies.

The energy of each electron is then calculated in the field of the initial electron configuration. This procedure is repeated in an iterative loop until convergence (Self-Consistent referring to this iterative calculation).

The Hartree-Fock method can therefore be thought of as a kind of mean-spherical approximation at the electron level. The difference between the Hartree-Fock energy and the energy for the full Schrödinger equation is called the correlation energy. Hartree-Fock calculations are sufficiently accurate to provide insight into many problems and they are widely used. As Hartree-Fock calculations have been applied to different problems it has however become increasingly clear that the correlation energy is of great significance in determining the properties of a system. Efforts have therefore been made to improve on the Hartee-Fock energy.

3.1 Post-HF Methods

There a number of different methods that go beyond Hartree-Fock calculations, one of the widely used approaches is perturbation theory. In perturbation theory the Hartree-Fock solution is treated as the first term in a Taylor series. Theperturbation terms added involve the electron repulsion. One of the more common forms was developed by Møller and Plesset.The second order perturbation form is referred to as MP2. This form will be utilized in the present work.

It should be noted that the electron-electron repulsion energy is not necessarily a small perturbation. In cases in which this term is large the application of perturbation theory can become more difficult.

There are a number of other techniques to include electron correlation that can potentially provide very accurate results, such calculations can however become very time consuming and at present they tend to be used for small molecules with maybe 3-4 heavy (non-hydrogen) atoms. The molecules studied in the present work are somewhat larger and the decision has been made not to use such time-consuming methods.

3.2 Moller-Plesset perturbation theory (MP)

The Moller-Plesset (MP) Perturbation Theory attempts to correct the HF theory, which as mentioned earlier provides an approximation for the repulsion term between electrons and determines the position of an electron solely with respect to the atom's nucleus and the average of other electrons. As this model is not quite accurate, the MP theory uses HF as a starting point and then corrects it for the attraction term between the nucleus and the electron as well as the position of an electron with respect to another electron.

The number following MP, such as MP2 or MP3, indicates the number of perturbations, or approximation terms, used in the theory. Generally, the higher this number, the greater the accuracy of the method.

3.3 Density-Functional Theory (DFT)

DFT theory models electron correlation as a functional of the electron density, ρ. The functional employed by current DFT methods partitions the electronic energy via the Kohn-Sham equations [9, 10] into several terms :

$$\boldsymbol{E = E^T + E^V + E^J + E^{XC}} \qquad \textbf{(6)}$$

where E^T is the kinetic energy term (arising from the motion of the electrons), E^V is the potential energy term that includes nuclear-electron and nuclear-nuclear interactions, E^J is the electron-electron repulsion term and E^{XC} is the electron correlation term. All terms except nuclear-nuclear repulsions are functions of the electron density.

The terms $E^T + E^V + E^J$ represent the classical energy of the electron distribution, while E^{XC} represents both the quantum mechanical exchange energy, which accounts for electron spin, and the dynamic correlation energy due to the concerted motion of individual electrons.

Pure DFT methods calculate E^{XC} by pairing an exchange functional with a correlation functional and so are designated by the choice of combination. For example, BLYP combines Becke's gradient-corrected exchange functional with the gradient-corrected correlation functional of Lee, Yang and Parr [15].

DFT calculations fall into three general categories: local density approximations (LDA), generalised gradient approximations (GGA), and "hybrid" combinations of DFT and Hartree-Fock terms. LDA exchange and correlation functionals only contain terms related to electron density- an approach that works for some bulk materials, but fails to accurately predict properties in isolated molecules. GGA ("nonlocal") functionals contain terms that depend upon both the electron density and the density gradients.

The gradient-corrected density functional method BLYP is capable of predicting intramolecular bond dissociation energies to within a few kJ/mol [16]. However, the generalised gradient approximation severely underestimates activation barriers for some reactions due to neglect of Coulomb "self-interaction" of the electrons [17].

This problem is remedied with hybrid methods that combine Hartree-Fock self-interaction corrections with density functional exchange and correlation. Examples of hybrid methods are B3LYP and B3PW91, where B3 denotes Becke's three-parameter hybrid functional [18,19], while'PW91' and 'LYP' are gradient-corrected correlation functionals of Perdew and Wang [20] and, as above, Lee, Yang and Parr.

3.4 Quantum methods: Ab initio :

Having established the importance of the electronic wave function (ψ) in Eq. (2), it is now necessary to discuss the methods that enable the derivation of the electronic states for

which Eq. (2) holds true, the following discussion is an outline of the fundamentals of Hartree–Fock theory from which both semi-empirical and density functional methods have been developed [21]. In this theory, the wave function [22], is considered as a series of molecular orbitals, which are occupied by electrons. One of these sets of molecular orbitals will correspond to the ground state and hence have the lowest energy. [21]

Ab initio methods are derived from theoretical principles, with no inclusion of experimental data, it take account both, electron and core in treatment.

practical *ab initio* calculations are severely limited by the types of atoms and size of molecules. [23]. these calculations are really time consuming and need large CPU memories.

4. Semi-empirical method

Most molecular computations done by organic chemists, especially those examining minimum energy geometries, are done using this method because it provides the best compromise between speed and accuracy. This method can be thought of as a hybrid of molecular mechanics-type models based on experimentally measured empirical data and pure theory quantum chemical, thus the name semi-empirical. It uses the Schrödinger equation approximations, but in order to make the calculations less time-consuming, it only calculates the locations of valence electrons, not all electrons. For the inner shell electrons, empirical data from typical organic molecules is used to estimate their locations.

The semi empirical methods are presented by :

- **MNDO method (Modified Neglect of Diatomic Overlap)** [24] which takes in account the repellencies between the electrons pairs and the electron-electron perellence directions;

- **ZDO method (zerodifferential overlap)** is based on the Huckel method for the π electrons;

❖ **CNDO method (Complete Neglect of Differential Overlap)** which takes inaccount only the atomic orbital of spherical symmetry and assesses therepellence integrals as the orbital would be sphere. In this case are two methodsCNDO/1 and CNDO/2 which are used for the spectrum parameters;

❖ **INDO method** [25] (Intermediate Neglect of Differential Overlap) which includes the monoelectronic repellence integrals between atomic orbital of the same atom;

❖ **NDDO method (Neglect of Differential diatomic orvelap)** which takes in account the orientation direction of the orbital; MINDO/3 [26] method is an particular case of the NNDO method which assesses the monoelectronic repellence integrals;

❖ **SAM1 (Semi-Ab-Initio Model 1)**

The final 1993 offering in Michael Dewar's name was Semi-Ab-Initio Model 1 [27].

In SAM1, two-electron integrals are calculated using a standard STO-3G basis set (and hence the appearance ofab initioin the title). The resulting integrals were then scaled, and the Gaussian terms in the core–core repulsions were retained in order to fine-tune the calculations.

❖ **AM1 (Austin Model 1)**

Next came Austin model 1 (AM1), due to M. J. S. Dewar et al. [28]. AM1 was designed to eliminate the problems from MNDO caused by a tendency to overestimate repulsions between atoms separated by the sum of their van der Waals radii. The strategy adopted was to modify the core–core terms by multiplication of the Coulomb term with sums of Gaussian functions.

In the original AM1 paper there are four terms in the Gaussian expansion. Each Gaussian is characterized by its position along the A–B vector and by its width. This significantly increased the number of parameters for each atom.

The performances of the semi empirical method consist in the smaller cost of them and it their speed, but also in the fact they can determine some properties that can not be established experimentally.

❖ **PM3 (parameterized method 3)**

PM3 is the third parameterization of MNDO, and the PM3 model contains essentiallyall the same terms as AM1. The parameters for PM3 were derived by J. J. P. Stewart [29] in a more systematic way than for AM1, many of which were derived by 'chemical intuition'. As a consequence, some of the parameters are quite different from those of MNDO but the two models seem to predict physical properties to the same degree of accuracy.

5. Molecular Mechanics (MM)

Molecular mechanics describes molecules in terms of "bonded atoms", which have been distorted from some idealized geometry due to non-bonded van der Waals and Coulombic interactions. [30, 31]

Molecular mechanics calculates the energy of a molecule and then adjusts the energy through changes in bond lengths and angles to obtain the minimum energy structure.

Molecular mechanics models are useful in studying structures, conformational energies and other molecular properties, including vibrational frequencies, conformational entropies and dipole moments, etc. [32].

5.1 Steric Energy

A molecule can possess different kinds of energy such as bond and thermal energy. Molecular mechanics calculates the steric energy of a molecule (the energy due to the geometry or conformation of a molecule). Energy is minimized in nature, and the conformation of a molecule that is favored is the lowest energy conformation. Knowledge of the conformation of a molecule is important because the structure of a molecule often has a great effect on its reactivity. The effect of structure on reactivity is important for large

molecules like proteins. Studies of the conformation of proteins are difficult and therefore interesting, because their size makes many different conformations possible.

Molecular mechanics assumes the steric energy ofa molecule to arise from a few, specific interactions within a molecule. These interactions include the stretching or compressing of bonds beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that come close together, and the electrostatic interactions between partial charges in a molecule due to polar bonds. To quantify the contribution of each, these interactions can be modeled by a potential function that gives the energy of the interaction as a function of distance, angle, or charge [30,33].

The total steric energy of a molecule can be written as a sum of the energies of the interaction:

$$\boldsymbol{E_{steric\ energy} = E_{str} + E_{bend} + E_{tor} + E_{VdW} + E_{qq}} \qquad (7)$$

The bond stretching, bending and torsion interactions are called bonded interactions because the atoms involved must be directly bonded or bonded to a common atom. The Van der Waals and electrostatic (qq) interactions are between non-bonded atoms.

$$\boldsymbol{E_{steric\ energy} = E_{tot}}$$

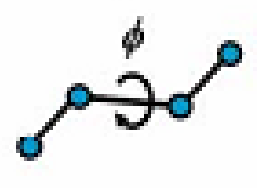
$$= \sum_{bonds} \boldsymbol{k_r}\left(\boldsymbol{r - r_{eq}}\right)^2 + \sum_{bonds} \boldsymbol{k_\vartheta}\left(\boldsymbol{\vartheta - \vartheta_{eq}}\right)^2 + \sum_{bonds} \frac{\boldsymbol{V_n}}{\boldsymbol{2}}[\boldsymbol{1 + cos(n\Phi -}$$

$$+ \sum_{i<j} \frac{\boldsymbol{A_{ij}}}{\boldsymbol{R_{ij}^{12}}} - \frac{\boldsymbol{B_{ij}}}{\boldsymbol{R_{ij}^{6}}} + \sum_{i<j} \frac{\boldsymbol{q_i q_j}}{\boldsymbol{\varepsilon R_{ij}}} \quad (8)$$

$$\boldsymbol{E_{str}} = \sum_{bonds} \boldsymbol{k_r}\left(\boldsymbol{r - r_{eq}}\right)^2 \quad (9)$$

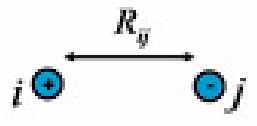
$$E_{bend} = \sum_{bonds} k_{\vartheta}(\vartheta - \vartheta_{eq})^2 \quad (10)$$

$$E_{tor} = \sum_{bonds} \frac{V_n}{2}[1 + cos(n\Phi - \gamma)] \quad (11)$$



$$E_{VdW} = \sum_{i<j} \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} \quad (12)$$

$$E_{qq} = \sum_{i<j} \frac{q_i q_j}{\varepsilon R_{ij}} \quad (13)$$



5.2 Examples of MM force fields :In Common use are:

- ✓ **AMBER**

(Assisted Model Building with Energy Refinement) - primarily designed forthe study of biomolecules such as proteins and nucleotides [34].

- ✓ **CHARMM**

(Chemistry at HARvard Molecular Mechanics) - primarily designed for biological and pharmaceutical study, but has also been applied to micelles and self-assembling macromolecules [35].

- ✓ **MMx** (MM2, MM3, etc)

Optimised for structural and thermodynamic studies of small non-polar molecules [47]. MMx force fields include third- and fourth-order corrections to standard quadratic fits for

the potential energy surfaces of bonds and bond angles, thus allowing for non-harmonic effects in molecular vibrations. The various MMx versions differ primarily in their parameterisations. The higher versions tend to be more modern and address deficiencies in their predecessors. However, for the newer versions such as MM4, parameters may not be available for all classes of molecules.

✓ OPLS

(Optimised Potentials for Liquid Simulations)-optimised for reproducing the physical properties of biomolecules in liquid solutions [36].

The authors are not aware of any published study discussing the use of AMBER, CHARMM, MMx or OPLS with energetic materials. Since these packages are optimised for biochemistry and pharmaceutical applications, it is unlikely that they will accurately reproduce the behaviour of energetic materials without further modification. However, it is likely they can be used for limited applications with only slight modification.

✓ CFF

The consistent force field (CFF) [37-40] was developed to yield consistent accuracy of results for conformations, vibrational spectra, strain energy, and vibrational enthalpy of proteins. There are several variations on this, such as the Ure-Bradley version (UBCFF), a valence version (CVFF), and Lynghy CFF. The quantum mechanically parameterized force field (QMFF) was parameterized From ab initio results. CFF93 is a rescaling of QMFF to reproduce experimental results. These force fields use five to six valence terms, one of which is an electrostatic term, and four to six cross terms.

✓ DREIDING [41]

DREIDING is an all-purpose organic or bio-organic molecule force field. It has been most widely used for large biomolecular systems. It uses five valence terms, one of which is an electrostatic term. The use of DREIDING has been dwindling with the introduction of improved methods.

- ✓ **MMFF**

The Merck molecular force field (MMFF) is one of the more recently published force fields in the literature. It is a general-purpose method, particularly popular for organic molecules. MMFF94 [42] was originally intended for molecular dynamics simulations, but has also seen much use for geometry optimization. It uses five valence terms, one of which is an electrostatic term, and one cross term.

- ✓ **MOMEC**

MOMEC [40] is a force field for describing transition metal coordination compounds. It was originally parameterized to use four valence terms, but not an electrostatic term. The metal-ligand interactions consist of a bond-stretch term only. The coordination sphere is maintained by non bond interactions between ligands. MOMEC generally works reasonably well for octahedrally coordinated compounds.

- ✓ **GROMOS**

(Groningen Molecular Simulation) developed at the University of Groningen and the ETH (Eidgenössische Technische Hochschule) of Zurich [41] is quite popular for predicting the dynamical motion of molecules and bulk liquids, also being used for modelling biomolecules. It uses five valence terms, one of which is electrostatic [45]. Its parameters are currently being updated [46].

5.3 Energy Minimization and Geometry Optimization

The basic task in the computational portion of MM is to minimize the strain energyof the molecule by altering the atomic positions to optimal geometry. This meansminimizing the total nonlinear strain energy represented by the force field equation with respect to the independent variables, which are the Cartesian coordinates of the atoms [47]. The following issues are related to the energy minimization of a molecular structure:

- The most stable configuration of a molecule can be found by minimizing its free energy, G.
- Typically, the energy E is minimized by assuming the entropy effect can be neglected.
- At a minimum of the potential energy surface, the net force on each atom vanishes, therefor the stable configuration.

Because the energy zero is arbitrary, the calculated energy is relative. It is meaningful only to compare energies calculated for different configurations of chemically identical systems.

- It is difficult to determine if a particular minimum is the global minimum, which is the lowest energy point where force is zero and second derivative matrix is positive definite. Local minimum results from the net zero forces and positive definite second derivative matrix, and saddle point results from the net zero forces and at least one negative eigenvalue of the second derivative matrix.

6 Research Methods of Global Minimum

The most widely used methods fall into two general categories:

(1) steepest descent and related methods such as conjugate gradient, which use first derivatives, and

(2) Newton Raphson procedures, which additionally use second derivatives.

6.1 The Steepest Descent Method : [48] depends on:

1- either calculating or estimating the first derivative of the strain energy with respect to each coordinate of each atom and

2- moving the atoms.

The derivative is estimated for each coordinate of each atom by incrementally moving the atom and storing the resultant strain energy change. The atom is then returned to its original position, and the same calculation is repeated for the next atom. After all the atoms have been tested, their positions are all changed by a distance proportional to the derivative calculated instep 1. The entire cycle is then repeated. The calculation is

terminated when the energy is reduced to an acceptable level. The main problem with the steepest descent method is that of determining the appropriate step size for atom movement during the derivative estimation steps and the atom movement steps. The sizes of these increments determine the efficiency of minimization and the quality of the result. An advantage of the first-derivative methods is the relative ease with which the force field can be changed.

6.2 The Conjugate Gradient Method :

is a first-order minimization technique. It uses both the current gradient and the previous search direction to drive the minimization. Because the conjugated gradient method uses the minimization history to calculate the search direction and contains a scaling factor for determining step size, the method converges faster and makes the step sizes optimal as compared to the steepest descent technique.

However, the number of computing cycles required for a conjugated gradient calculation is approximately proportional to the number of atoms (N), and the time per cycle is proportional to N.

The Fletcher-Reeves approach chooses a descent direction to lower energy by considering the current gradient, its conjugate, and the gradient for the previous step. The Polak- Ribiere algorithm improves on the Fletcher-Reeves approach by additional consideration of the previous conjugate and tends to converge more quickly.

6.3 The Newton-Raphson Methods : of energy minimization [30] utilize the curvature of the strain energy surface to locate minima. The computations are considerably more complex than the first-derivative methods, but they utilize the available information more fully and therefore converge more quickly. These methods involve setting up a system of simultaneous equations of size(3N-6)(3N-6) and solving for the atomic positions that are the solution of the system. Large matrices must be inverted as part of this approach.

The general strategy is to use steepest descents for the first 10-100 steps(500-1000 steps for proteins or nucleic acids) and then use conjugate gradients or Newton-Raphson to complete minimization for convergence(using RMS gradient or/and energy difference as an indicator). For most calculations, RMS gradient is set to 0.10 (you can use values greater than 0.10 for quick, approximate calculations).

The calculated minimum represents the potential energy closest to the starting structure of a molecule. The energy minimization is often used to generate a structure at a stationary point for a subsequent single-point calculation or to remove excessive strain in a molecule, preparing it for a molecular dynamic simulation.

7 Types of Calculations

Computational chemistry (also called molecular modelling; the two terms mean about the same thing) is a set of techniques for investigating chemical problems on a computer. Questions commonly investigated computationally are:

7.1 Molecular Geometry: The shapes of molecules – bond lengths, angles and dihedrals.

7.2 Geometry Optimization [49] is a standard computational chemistry calculation to find the lowest energy or most relaxed conformation for a molecule. The approach is the same for all levels of calculation, involving an iterative "jiggling" process like that described for molecular mechanics.

At each step, the molecular geometry is modified slightly and the energy of the molecule is compared with the last cycle. The computer moves the molecule a little, calculates the energy, moves it a little more, and keeps going until it finds the lowest energy. This is the energy minimum of the molecule and is obtained at the optimized geometry. Recall that the energies from molecular mechanics can only be used in a relative sense, while those from quantum electronic structure methods can be compared in an absolute sense, like heats of formation.

7.3 Single Point Calculations [49] are often used in combination with a geometry optimization to investigate steric hindrance. In this case the method only performs one computational cycle to calculate the energy of a particular fixed geometry. In a thermodynamically controlled reaction, the energetic difference between two conformations is often due to steric hindrance. If the product molecule optimizes in one conformation, you can use single point calculations to determine how much more energy is needed to form the non-preferred conformation.

The structure drawing and manipulation part of the software will allow you to move only that part of the molecule that changes in the higher energy form, leaving the rest of the molecule optimized.

The single point calculation performed on this modified molecule will give an energy that you can directly compare with the optimized energy to find the energy difference between the lower and higher energy conformers. For example, the energetic difference between having a constituent in the axial or equitorial position on a cyclohexane ring can be determined.

7.4 Transition State Calculations [49] can be thought of as the reverse of geometry optimizations. In this case, the method searches for a structure of maximum energy, a transient intermediate which cannot be isolated experimentally. For example, this type of calculation allows one to examine transition state energies and geometries of intermediates involved in carbocation rearrangements.

The literature contains standard models that should use as the starting point for these calculations. It takes a far amount of effort and experience to properly analyze transition state structures and energies.

7.5 Electronic Density and Spin Calculations, Graphical Models and Property Maps [49] Allow visualization of electronic properties such as electron densities, electrostatic potentials, spin densities and the shapes and signs of molecular orbitals.

The values for a particular property at each point in the 3-dimensional space around a molecule are displayed on the 2-dimensional computer screen as a surface of constant numerical value, often called an isosurface which can be rotated in any direction to study it.

Alternately, numerical variations of a given property (such as electron density) at a defined distance from the molecule can be displayed as property maps using color as a key yielding what is called a property map. Carrying out surface calculations and viewing their graphical representations are major activities in computational chemistry and can provide useful insight into the mechanisms of organic reactions.

7.6 Chemical Reactivity : [50]

For example, knowing where the electrons are concentrated (nucleophilic sites) and where they want to go (electrophilic sites) enables us to predict where various kinds of reagents will attack a molecule.

7.7 IR, UV and NMR spectra : [50] these can be calculated, and if the molecule is unknown, someone trying to make it knows what to look for.allow the calculation of infrared stretching and bending absorption frequencies and it is a lot of fun to view animations of these types of motions in molecules.

The vibrational frequency of a two-atom system is proportional to the square root of the force constant (the second derivative of the energy with respect to the interatomic distance) divided by the reduced mass of the system (which depends on the masses of the two atoms).

8. Scope of application of molecular modeling :

Molecular modeling methods are used to investigate the structure, dynamics, surface properties and thermodynamics of inorganic, biological and polymeric systems.

Molecular modeling methods are used in the fields of computational chemistry, drug design, computational biology and materials science for studying molecular systems (small and large chemical systems). Also are used to predict molecular behaviours specifically interactions between molecules.

Molecular mechanics calculates the energy of a molecule, like the steric energy, the energy due to the geometry or conformation of a molecule.

8.1 QSAR Methods :

8.1.1 Introduction:

It has been nearly 40 years since the quantitative structure-activity relationship (QSAR) paradigm first found its way into the practice of agrochemistry, pharmaceutical chemistry, toxicology, and eventually most facets of chemistry [51]

If we can understand how a molecular structure brings about a particular effect in a biological system, we have a key to unlocking the relationship and using that information to our advantage, formal development of these relationships on this premise has proved to be the foundation for the development of predictive models, if we take a series of chemicals and attempt to form a *quantitative relationship* between the biological effects (i.e. the *activity*) and the chemistry (i.e. the *structure*) of each of the chemicals, then we are able to form a *quantitative structure–activity relationship* or QSAR. [52]

QSAR, a quantum chemical technique [53,54] , is known to relate the biological activity of compounds with their molecular structure [55] and has been extensively used as predicting tool in rational drug design [56-61].

Computational evaluation to give predictive QSAR models is an important tool to avoid unnecessary experimental assays and find an optimum drug target. [62]

8.1.2 Historical Development of QSAR :

More than a century ago, Crum-Brown and Fraser expressed the idea that the physiological action of a substance was a function of its chemical composition and constitution [63].

A few decades later, in 1893, Richet showed that the cytotoxicities of a diverse set of simple organic molecules were inversely related to their corresponding water solubilities [64].

At the turn of the 20th century, Meyer and Overton independently suggested that the narcotic (depressant) action of a group of organic compounds paralleled their olive oil/water partition coefficients [65,66].

In 1939 Ferguson introduced a thermodynamic generalization to the correlation of depressant action with the relative saturation of volatile compounds in the vehicle in which they were administered [67].

In 1962 Hansch and Muir published their brilliant study on the structure-activity relationships of plant growth regulators and their dependency on Hammett constants and hydrophobicity [68].

The Free-Wilson approach addresses structure-activity studies in a congeneric series as described in Equation 14 [69].

$$\mathbf{BA = \Sigma\ a_i\ x_i + u} \qquad \mathbf{(14)}$$

BA is the biological activity, *u* is the average contribution of the parent molecule, and *ai* is the contribution of each structural feature; *xi* denotes the presence *Xi*= 1 or absence *Xi*= 0 of a particular structural fragment.

Limitations in this approach led to the more sophisticated Fujita-Ban equation that used the logarithm of activity, which brought the activity parameter in line with other free energy-related terms [70].

$$\mathbf{Log\ BA = \Sigma\ G_i\ x_i + u} \qquad \mathbf{(15)}$$

In Equation 15, *u* is defined as the calculated biological activity value of the unsubstituted parent compound of a particular series. *I* represents the biological activity contribution of the substituants, whereas *Xi* is ascribed with a value of one when the substituent is present or zero when it is absent.

8.1.3 Tools and techniques of QSAR:

8.1.3 .1 Biological parameters:

In QSAR analysis, it is imperative that the biological data be both accurate and precise to develop a meaningful model, it must be realized that any resulting QSAR model that is developed is only as valid statistically as the data that led to its development, biological data are usually expressed on a logarithmic scale because of the linear relationship between response and log dose in the midregion of the log dose-response curve, inverse logarithms for activity (log 1/*C*) are used so that higher values are obtained for more effective analogs, it is also important to design a set of molecules that will yield a range of values in terms of biological activities. Generally, the larger the range (>2 log units) in activity, the easier it is to generate a predictive QSAR [71].

8. 1.3. 2. Molecular descriptors :

These are truly structural descriptors because they are based only on the two-dimensional representation of a chemical structure [71]. The most widely known descriptors are those that were originally proposed by Randic [72]. and extensively developed by Kier and Hall [73].

Molecular descriptors are formal mathematical representations of a molecule, obtained by a well-specified algorithm, and applied to a defined molecular representation or a well-specified experimental procedure: *the molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment* [74].

Molecular descriptors play a fundamental role in developing models for chemistry, pharmaceutical sciences, environmental protection policy, toxicology, ecotoxicology, health research, and quality control [21].

Evidence of the interest of the scientific community in molecular descriptors is provided by the huge number of descriptors that have been proposed: more than 5000 descriptors [74]. derived from different theories and approaches are defined and computable by using dedicated software of chemical structure. [21]

Molecular descriptors are numerical indexes encoding some information related to the molecular structure, they can be both experimental physico-chemical properties of molecules and theoretical indexes calculated by mathematical formulas or computational algorithms, they are derived by applying principles from several different theories, such as quantum-chemistry, information theory, organic chemistry, graph theory, they are used to model several different properties of chemicals in scientific fields such as toxicology, analytical chemistry, physical chemistry, medicinal, pharmaceutical, and environmental chemistry [21].

8. 1. 3. 3. Statistical methods :

Quantitative structure activity relationships (QSAR) in the past 50 years have been considered a versatile tool for the activities prediction of drug and drug-like molecules, the aim of developing a QSAR model is to construct a relation (using statistical methods) between structures and activities. [75]

In most cases, it is more convenient to consider a linear relationship between activity/property and descriptors.[76]

The most commonly used modeling methods are [76]:

- Multiple linear regression (MLR),

- principal component regression (PCR),

- partial least squares (PLS) regression,

- artificial neural networks (ANN).

The most widely used method is the multiple linear regression (MLR) approach originally proposed by Bartlett and Youd (1995). [77]

8. 1. 3. 4. Multi-linear regression :

Multi-linear regression (MLR) is a statistical method for studying the relationship between a dependent variable and two or more independent variables.

In this method, a dependent variable Y is described in terms of a series of explanatory variables X1, . . ., Xn, as given in Eq 16 :

$$\mathbf{Y= Y_0 + a_1 X_1 + a_2 X_2 + \cdots + a_n X_n} \qquad \mathbf{(16)}$$

It is assumed that all the explanatory variables are independent of each other [78].

✓ **Description of the method :**

The analysis of multiple linear regression (MLR) is a statistical method that examine cause-effect relationships between dependent and independent variables, in MLR, the relationship between input variable more than one (x1 ,x2, . . .xn) and a dependent variable (y) is examined [79].

If it is assumed that the relationship is well represented by a model that is linear in the regressed variables, a suitable model may be [76]:

$$\mathbf{y = b_0 + b_1 x_1 + b_2 x_2 \ldots.+e} \qquad \mathbf{(17)}$$

In Eq 17, the b's are unknown constants called regression coefficients and the objective of regression analysis is to estimate these constants, the algebraic MLR model is defined in Eq 17, and in matrix notation. [76]:

$$\mathbf{y = X \beta + \varepsilon} \qquad \mathbf{(18)}$$

The matrix X is referred to as the *design matrix :*

$$y = \begin{bmatrix} y_1 \\ y_2 \\ . \\ . \\ . \\ y_n \end{bmatrix} \quad X = \begin{bmatrix} 1 & x_{11} & x_{12} & . & . & . & x_{1n} \\ 1 & x_{21} & x_{22} & . & . & . & x_{2n} \\ . & . & . & & & & . \\ . & . & . & & & & . \\ . & . & . & & & & . \\ 1 & x_{n1} & x_{n2} & . & . & . & x_{nn} \end{bmatrix} \quad \beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ . \\ . \\ . \\ \beta_n \end{bmatrix} \quad \text{and } \epsilon = \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ . \\ . \\ . \\ \epsilon_n \end{bmatrix}$$

Multiple linear regression (MLR) techniques based on least-squares procedures are very often used for estimating the coefficients involved in the model equation [80,81].

✓ Test of the total significance of the regression :

a. Determination coefficient (R^2) :

The *coefficient of determination (R^2)* is a measure of how well the regression line represents the data on the scatter plot. R^2 is a measure of the fit of the regression model [66].

The R^2 can be used to determine the linear relationship between the measured and estimated values. [79]. R^2 ranges from 0 to 1.

The coefficient of determination R^2 is the ratio of the explained sum of squares to the total sum of squares.

$$\boldsymbol{R^2 = \frac{ESS}{TSS} = \frac{TSS-RSS}{TSS} = 1 - \frac{RSS}{TSS}} \qquad \textbf{(18)}$$

where:

TSS is the total sum of squares: $\boldsymbol{TSS = \sum (Y_{obs} - \overline{Y})^2}$ **(19)**

ESS ist he explained sum of squares: $$\boldsymbol{ESS} = \sum(\boldsymbol{Y_{cal}} - \overline{\boldsymbol{Y}})^2 \qquad \textbf{(20)}$$

RSS is the residual sum of squares: $$\boldsymbol{RSS} = \sum(\boldsymbol{Y_{obs}} - \boldsymbol{Y_{cal}})^2 \qquad \textbf{(21)}$$

b. Correlation coefficient (R)

The quantity *R*, called the *correlation coefficient*, it is a correlation coefficient between observed and predicted values of dependant variable Y, where 0 < R < 1

$$\mathbf{R= (ESS/TSS)^{0.5} = (1-RSS/TSS)^{0.5}} \qquad \textbf{(22)}$$

c. Test Fisher-Snedecor (F)

F the Fisher test, reflects the ration of the variance explained by the model and variance due to error in the model, high values of F-test indicate the significance of the equation. [82]

$$\mathbf{F = [ESS/ (k)] / [RSS / (n-k-1)]} \qquad \textbf{(23)}$$

Where n, and (k-1) are degrees of freedom associated to ESS and RSS respectively.

d. Standard deviation (s)

S is called the standard deviation

$$\boldsymbol{s} = \sqrt{\frac{\boldsymbol{RSS}}{\boldsymbol{n-k-1}}} \qquad \textbf{(24)}$$

Where *k* is the number of independent variables.

e. Prediction coefficient (Q^2)

it measures the predictive capacity of a model $$Q^2 = 1 - \frac{PRESS}{SSY} \quad (25)$$

8.1.4 Models Validations :

The best multiple linear regression model is one that has high R and F-values, low standard error, the least number of variables and high prediction ability [83].

To test the validity of the predictive power of model we use some techniques:

Cross-validation *LOO* (leave-one-out) is a model validation technique, for assessing how the results of a statistical analysis will generalize to an independent data set, in which we use these statistical parameters:

PRESS (predicted residual sum of squares) $$\mathbf{PRESS} = \sum(\mathbf{Y_{obs}} - \mathbf{Y_{cal}})^2 \quad (26)$$

TSS (total sum of squares) $$\mathbf{TSS} = \sum(\mathbf{Y_{obs}} - \bar{\mathbf{Y}})^2 \quad (27)$$

R^2_{adj} (adjusted R-squared) $$\mathbf{R^2_{adj}} = (1 - \mathbf{r^2})\left(\frac{\mathbf{n-1}}{\mathbf{n-p-1}}\right) \quad (28)$$

R^2_{CV} (cross-validated correlation coefficient) $$\mathbf{R^2_{CV}} = 1 - \frac{\mathbf{PRESS}}{\mathbf{TSS}} \quad (29)$$

S_{PRESS} (standard validation of the prediction errors) $$\mathbf{S_{PRESS}} = \sqrt{\frac{\mathbf{PRESS}}{\mathbf{n}}} \quad (30)$$

PE (Prediction error) $$\mathbf{PE} = 0.6745\,(1 - \mathbf{r^2})/\sqrt{\mathbf{n}} \quad (31)$$

The PRESS (predicted residual sum of squares) statistic appears to be the most important parameter accounting for a good estimate of the real predictive error of the models. Its small value indicates that the model predicts better than chance and can be considered statistically significant [76].

9. Programs and materials used:

This work was carried out within team of Computational and pharmaceutical chemistry of the laboratory of molecular chemistry and environment (LMCE) at the university of Biskra.

The first calculations were optimized by using a software HyperChem 8.03 [84]

The geometry of macrolides and its derivatives initially were entirely optimized by molecular mechanics, with the force field MM + (rms = 0.001 Kcal / A). Further geometries were fully re-optimized by using PM3 method.

Then a parallel study was made by using the Gaussian software 09 [85]. One based on *ab* initio of Hartree-Fock (HF) type HF/6-31++G (d,p), and the density functional theory DFT with functional calculus B3LYP, by using the following base : 6-31++G (d,p).

DFT with B3LYP/6-31G, this theory was used to calculate a number of electronic descriptors: dipole moment (DM), energy of frontier orbital's, E_{HOMO} and E_{LUMO}.

Multiple linear regression analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows [86].

All calculations are carried out in a Station in a PC (SAMSUNG Intel inside™ Micro-processor ® Core™ i7 Quad CPU Q8300 4Go of RAM).

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CHAPITER 03

Geometric, Electronic Structure and Substituent effects of 14-Membered α, β -Unsaturated Macrolides

1. Introduction

Molecular modeling can be defined as the generation, manipulation, calculation, and prediction of realistic molecular structures and associated physicochemical as well as biochemical properties by the use of a computer. It is primarily a mean of communication between scientist and computer, the imperative interface between human-comprehensive symbolism, and the mathematical description of the molecule.[1]

The types of predictions possible for molecules and reactions include [2]:

- Heats of formation
- Bond and reaction energies
- Molecular energies and structures (thermochemical stability)
- Energies and structures of transition states (activation energies)
- Reaction pathways, kinetics and mechanisms
- Charge distribution in molecules (reactive sites)
- Substituent effects • Electron affinities and Ionization potentials
- Vibrational frequencies (IR and Raman spectra)
- Electronic transitions (UV/Visible spectra)
- Magnetic shielding effects (NMR spectra)

Prediction of these properties has many applications in energetic materials research, including studies of synthesis pathways, reaction products and initiation mechanisms.

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties [3]. To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive ab initio/HF electron correlation methods are required [4-6]. Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules [7-16].

2. Mulliken population analysis (MPA)

This population analysis is the oldest and one of the most widely used. MPA divides bond orbital populations equally between the two atoms of a bond.

This approach is very simplified and does not take into consideration that one of bonded atoms can attract electrons markedly more than the second one. On the other hand, the simplicity of MPA is sometimes an advantage because the method can be easily used.[17]

3. Electrostatic Potential Surface (MESP)

The molecular electrostatic potential is the potential energy of a proton at a particular location near a molecule.

- Negative electrostatic potential corresponds to an attraction of the proton by the concentrated electron density in the molecules (from lone pairs, pi-bonds, etc.) (colored in shades of red).
- Positive electrostatic potential corresponds to repulsion of the proton by the atomic nuclei in regions where low electron density exists and the nuclear charge is incompletely shielded(colored in shades of blue).

The more red / blue differences, the more polar the molecule. If the surface is largely white or lighter color shades, the molecule is mostly non-polar. The MESP may be employed to distinguish regions on the surface which are electron rich (subject to electrophilic attack) from those which are electron poor (subject to nucleophilic attack) and has been found to be a very convenient tool in exploration of correlation between molecular structure and the physiochemical property relationship of molecules including bio molecules and drugs [18-23].
The electrostatic potential V(r) at any point in space around a molecule by charge distribution is given by:

$$V(r) = \sum \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')}{|r' - r|} dr' \qquad (1)$$

Where the summation runs over all the nuclei A in the molecule and polarization and reorganization effects are neglected. ZA is the charge of the nucleus A, located at RA and ρ(r') is the electron density function of the molecule.

4. Dipole Moment

An electric dipole consists of a pair of charges of equal magnitude and opposite signs (+q and –q), separate by a distance (r). The dipole moment of an electric dipole is a vector directed from the negative to the positive charge. The magnitude of the dipole moment is measured in Coulomb meters (Cm) or in debye (D), where 1D = 3.338*10-30 Cm. [24]

If the positive and negative charges in a molecule do not overlap, the molecule possesses a permanent dipole moment (μ) (polar molecule). Molecular dipole moment is usually calculated using the following formula:

$$\boldsymbol{\mu = \sum q_i \times r_i} \qquad (2)$$

Where r is the radius-vector of an atom i from the origin of the coordinate system (Centre of charge or Centre of mass)

- is the partial charge of atom i
- The summation is over all atoms in the molecule.

5. Heat of Formation (ΔH_f)

The heat of Formation is known as the change in enthalpy accompanying the formation of one mole of a compound from its elements in their natural and stable states, under standard conditions of one atmosphere at a given temperature [25].

The quantum chemical and energy descriptors are useful parameters for describing QSAR of a chemical system. A more useful quantity the heat of formation of the compound from its elements in their standard state. This is equal to the energy required to ionize the valence electrons of the atoms involved. The heat of formation is defined as:

$$\boldsymbol{\Delta H_f = E_{elec} + E_{nuc} - E_{iso} + E_{atom}} \qquad (3)$$

Where E_{elec} is the electronic energy, E_{nuc} is the nuclear-nuclear repulsion energy, E_{iso} is the energy required to strip all the valence electrons of all the atoms in the system and E_{atom} is the total heat of atomization of all the atoms in the system.

6. Energies of the Frontier Molecular Orbitals HOMO and LUMO

The energies of the frontier orbitals HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are commonly used descriptors in QSAR analysis. They reflect the reactivity of a molecule. A higher HOMO energy suggests higher affinity of a molecule to react as a nucleophile, a lower LUMO energy suggests stronger electrophilic nature of a molecule.

Additionally, electrophilic and nucleophilic attack will most likely occur at atoms where the coefficients of the corresponding atomic orbitals in HOMO and LUMO, respectively, are large. [24]

7. Substituent Effects on the Electronic Structure

The measure of some important electronic properties such as ionization energy, electron affinity, etc., through the introduction of electron donating (ED) or electron withdrawing (EW) substitutions follows a long established method in bio-chemical and molecular electronics engineering. [26-30]

ED substituents (donor Substituents) can increase the energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) relative to that of bare molecule (M), allowing a significant modification of the molecular electronic properties (Figure 3.1).

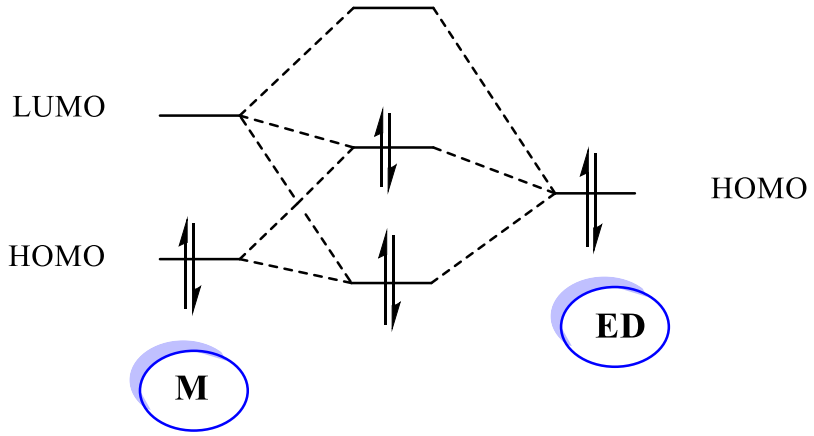


Figure 3.1. Influence of energy level of the donor group (ED)

EW substituents (Acceptor Substituents) can decrease the energies of lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) relative to that of bare molecule (M), allowing a significant modification of the molecular electronic properties. (Figure 3.2).

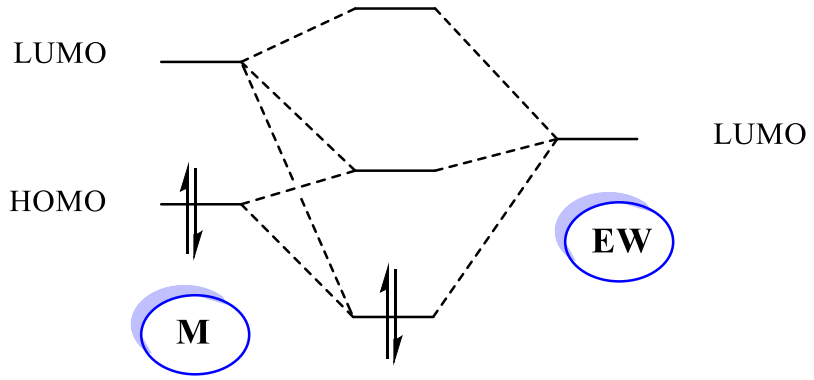


Figure 3.2. Influence of energy level of the acceptor group (EW)

8. Material and methods

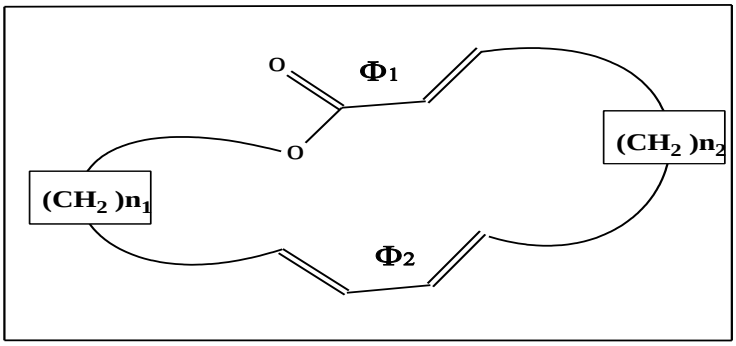


Figure 3.3 α, β unsaturated macrolactone.

Initial calculations were optimized using HyperChem 8.03 software [31]. The geometries of macrolides and its derivatives were first fully optimized by molecular mechanics, with MM+ force-field (rms = 0.001 Kcal/Å). Further, geometries were fully re-optimized by using PM3 method [32]. In the next step geometries were fully re-optimized by using Ab initio/HF (STO-3G). The calculated results have been reported in the present work.

9. Results and discussion

9.1. Conformational Analysis of 14-Membered *α, β* -Unsaturated Macrolides

The most stable structures can be characterized by three structural characters: the diene group, the *α, β* –unsaturated ester group, and the two saturated chains (Figure 3.3) [33]. Thus, we have obtained eight types of conformations which are present in the majority of cases in an 5 kcal/mol energy range above the global minimum. The conformation types are classed from 1 to 8 [34].

For types (2, 4, 6, 8), the two planes of two conformational sites, diene and *α, β* -unsaturated ester group are pseudo parallels; but for types (1, 3, 5, 7), the two planes of the two sites are pseudo antiparallels (Figure 3.4) [33].

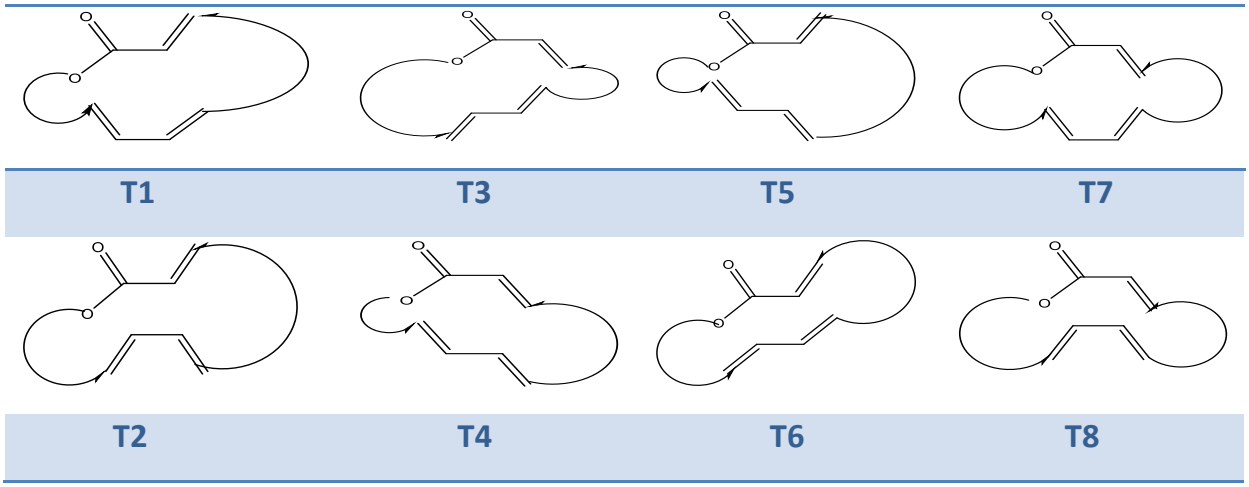


Figure 3.4. Main conformational types of macrolides.

In 2 kcal/mol difference, the macrocycle 14s is characterized by the first conformer type 6, which is the most favored with 23.7% rate followed by a type 4 with 16.6%, this is done using the Boltzmann statistical method.

Then, the macrocycle 14d (Figure 3.1) is presented preferably in the type T3 with 24.9%. The percentages of other conformers are listed in Table 3.1.

Table 3.1. Energetic difference and Boltzmann population for different macrolide types.

Macrolides	*14 symmetric ($n_1 = n_2 = 3$)*			*14 dissymmetric ($n_1 = 2, n_2 = 4$)*		
to 2 kcal/mol	***Type***	***ΔE***	***%***	***Type***	***ΔE***	***%***
	6	0.00	23.7	3	0.00	24.9
	4	1.58	16.6			
Sup to 2 Kcal/mol	3	2.49	13.3	6	2.03	15.2
	2	3.12	11.4	4	2.61	13.2
	7	3.35	10.8	7	3.35	11.1
	1	4.45	08.2	1	3.49	10.7
	5	4.48	08.2	5	3.64	10.3
	8	4.72	07.7	8	4.52	08.3
				2	5.78	06.2

Note: ΔE: Energetic difference to the absolute minimum, %: Boltzmann population.

9.2. Geometric and Electronic Structure of Basic Structure of Symmetric 14-membered Macrolide Type 6 (T6)

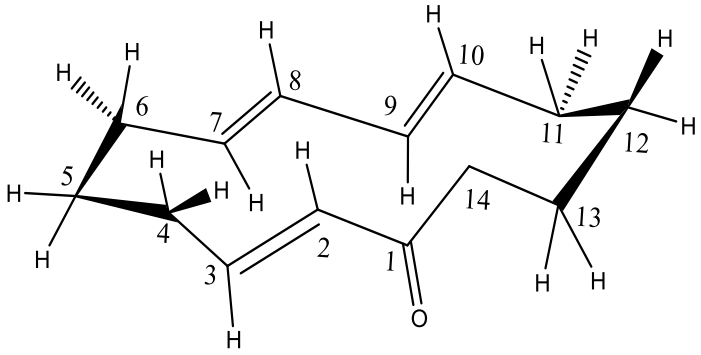


Figure 3.5. The privileged Conformations of the macrocycle 14s (T6)

The efficiency of PM3 method may be scrutinized by comparison with the results obtained by more elaborate calculation such as ab initio/HF(STO- 3G).

Present results concerning from these results a good correlation can be seen between the ab initio, and PM3 for bond lengths, also the charge densities calculated by these methods are approximately similar, Table 3.2.

The geometric study allow to see that ester *α*, *β* –unsaturated system for the 14S macrolide type 6 (Figure 3.5) has an S-CIS form with a dihedral angle $\Phi_1 = O_{15}\text{-}C_1\text{-}C_2\text{-}C_3 =$ 2.861° using molecular mechanic calculation; 046.395° using PM3 method and 018.671° via ab-initio/HF method. Also it allows to see that the diene system, it has an S-TRANS form, with a dihedral angle of Φ_2 = C7-C8-C9-C10 = 175.583° using MM calculation, 175.195° via PM3 method and 163.269 ° using ab-initio method.

Finally, we conclude that ester *α*, *β* -unsaturated and diene systems for the two macrocycles are perpendicular on medium plans of cycles.

Table 3.2 Bond lengths (in Å) and valence angles (in degree) of the macrocycle 14s (T6) as computed at different levels of theory. See Figure 3.5 for the numbering of the atoms.

Distance	*MM+*	*PM3*	*ab initio /HF*	*Distance*	*MM+*	*PM3*	*ab initio /HF*
C_1-O_{15}	1.2095	1.2168	1.2196	C_7-C_8	1.3449	1.3387	1.3176
C_1-O_{14}	1.3501	1.3709	1.3958	C_8-C_9	1.3434	1.4516	1.4871
C_1-C_2	1.3594	1.4809	1.5119	C_9-C_{10}	1.3437	1.3372	1.3168
C_2-C_3	1.3447	1.3349	1.3165	C_{10}-C_{11}	1.5101	1.4891	1.5293
C3-C_4	1.5094	1.4854	1.5224	C_{11}-C_{12}	1.5391	1.5237	1.5483
C_4-C_5	1.5537	1.5243	1.5492	C_{12}-C_{13}	1.5387	1.5294	1.5499
C_5-C_6	1.5540	1.5248	1.5517	C_{13}-O_{14}	1.4085	1.4198	1.4383
C_6-C_7	1.5120	1.4869	1.3165				
Angle	*MM+*	*PM3*	*ab initio /HF*	*Angle*	*MM+*	*PM3*	*ab initio /HF*
C_1-C_2-C_3	127.451	124.782	125.218	C_9-C_{10}-C_{11}	124.023	123.025	125.004
C_2-C_3-C_4	129.921	126.343	126.816	C_{10}-C_{11}-C_{12}	115.791	114.488	114.463
C_3-C_4-C_5	111.84	113.109	113.820	C_{11}-C_{12}-C_{13}	114.822	113.574	114.004
C_4-C_5-C_6	113.224	113.157	114.614	C_{12}-C_{13}-O_{14}	113.540	113.022	114.031
C_5-C_6-C_7	111.908	112.899	113.537	C_{13}-O_{14} -C_1	119.859	119.674	113.292
C_6-C_7-C_8	128.120	124.513	127.794	O_{14}-C_1-O_{15}	119.703	119.571	122.775
C_7-C_8-C_9	126.105	123.292	127.077	C_2-C_1-O_{15}	121.920	128.808	127.588
C_8-C_9-C_{10}	123.275	122.989	123.033				
Torsion angle	*MM+*	*PM3*	*ab initio /HF*	*Torsion angle*	*MM+*	*PM3*	*ab initio /HF*
C_1-C_2-C_3-C_4	002.052	002.809	002.594	C_9-C_{10}-C_{11}-C_{12}	046.313	032.791	054.751
C_2-C_3-C_4-C_5	116.788	113.966	123.816	C_{10}-C_{11}-C_{12}-C_{13}	068.295	084.717	068168
C_3-C_4-C_5-C_6	063.701	87.496	70.818	C_{11}-C_{12}-C_{13}-O_{14}	057.525	076.327	056.740
C_4-C_5-C_6-C_7	075.170	092.997	076.652	C_{12}-C_{13}-O_{14}-C_1	067.379	080.478	075.409
C_5-C_6-C_7-C_8	120.784	120.741	120.059	C_{13}-O_{14} –C_1-C_2	170.332	168.061	176.267
C_6-C_7-C_8-C_9	001.039	003.591	001.359	C_{13}-O_{14}-C_1-O_{15}	007.330	013.693	003.566
C_7-C_8-C_9-C_{10}	175.583	175.195	163.269	O_{15}-C_1-C_2-C_3	002.861	046.395	018.671
C_8-C_9-C_{10}-C_{11}	178.497	177.621	178.995				

The Table 3.3 shows that the atoms C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, O_{14} and O_{15} have negative Mulliken charges which leads to electrophilic substitution, whereas the atom C_1 and C_{13} have positive Mulliken charge which lead to preferential site nucleophilic attack.

Atoms	*PM3*	*ab initio/HF*
C_1	0.418	0.310
C_2	-0.194	-0.097
C_3	-0.046	-0.027
C_4	-0.092	-0.116
C_5	-0.085	-0.093
C_6	-0.077	-0.108
C_7	-0.143	-0.060
C_8	-0.101	-0.068
C_9	-0.141	-0.078
C_{10}	-0.119	-0.050
C_{11}	-0.061	-0.106
C_{12}	-0.138	-0.106
C_{13}	0.074	0.012
O_{14}	-0.264	-0.258
O_{15}	-0.385	-0.275

Table 3.3. Mulliken charges of basic structure of macrolide T6.

9.3. The molecular electrostatic potential MESP of basic structure (T6)

The molecular electrostatic potential surface MESP which is a plot of electrostatic potential mapped onto the iso-electron density surface simultaneously displays molecular shape, size and electrostatic potential values and has been plotted for both the molecules.

Molecular electrostatic potential (MESP) mapping is very useful in the investigation of the molecular structure with its physiochemical property relationships [35-40].

In this study, the electrostatic potentials at the surface are presented by different colors Figure 3.6.

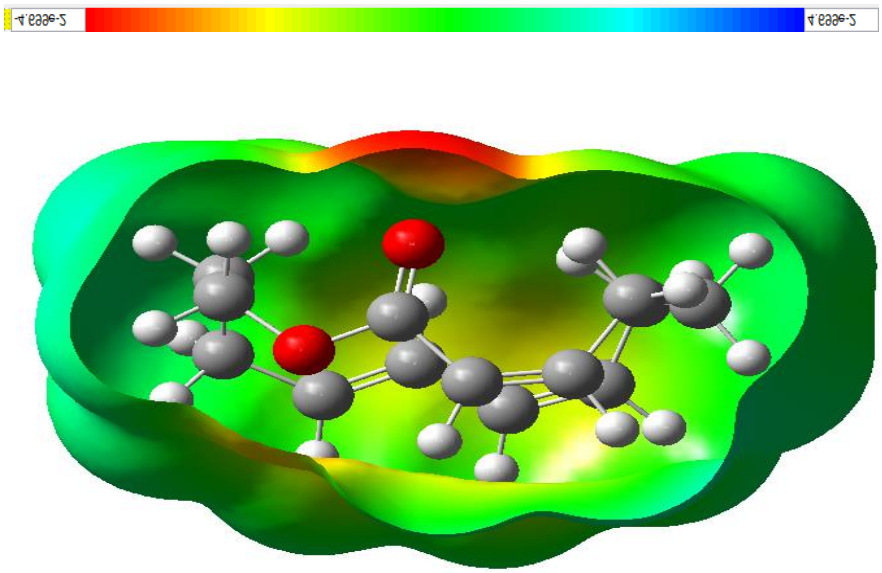


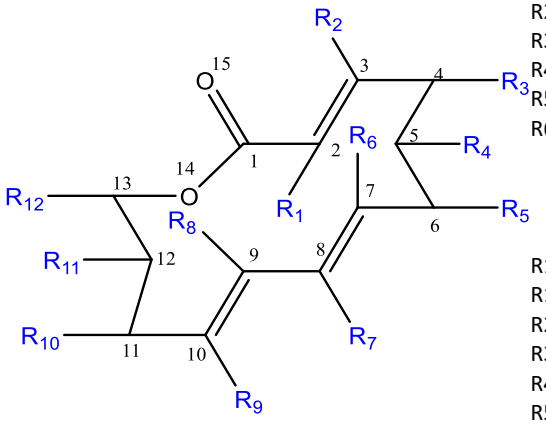
Figure 3.6. 3D MESP contour map for 14 macrolide molecule (Gaussian 09).

Red color parts represent the regions of negative electrostatic potential while yellow ones represent regions of positive electrostatic potential. Green color parts represent also regions of zero potential. A portion of the molecule that has a negative electrostatic potential is susceptible to electrophilic attack while the positive ones are related to nucleophilic reactivity.

9.4. Substituent effects on the electronic structure in symmetric 14-membered macrolides

Ab initio/HF method with (STO-3G) basis set was used to investigate the effects of a variety of substituents (-CH3 and -F) on the electronic and structural properties of macrolide.

In Table 3.4 and Table 3.5, HOMO and LUMO energies, energy gaps ΔE, heat of formation and dipole moments are reported for macrolide and its derivatives. The chemical structures of the studied macrolide and its derivatives are shown in Figure 3.7.



Series 1

R1=R2=R3=R4=R5=R6=R7=R8=R9=R10=R11=R12=H
R1=R7=CH_3,R2=R3=R4=R5=R6=R8=R9=R10=R11=R12=H
R2=R8=CH_3,R1=R3=R4=R5=R6=R7=R9=R10=R11=R12=H
R3=R9=CH_3,R1=R2=R4=R5=R6=R7=R8=R10=R11=R12=H
R4=R10=CH_3,R1=R2=R3=R5=R6=R7=R8=R9=R11=R12=H
R5=R11=CH_3,R1=R2=R3=R4=R6=R7=R8=R9=R10=R12=H
R6=R12=CH_3,R1=R2=R3=R4=R5=R7=R8=R9=R10=R11=H

Series 2

R1=R2=R3=R4=R5=R6=R7=R8=R9=R10=R11=R12=H
R1=R7=F, R2=R3=R4=R5=R6=R8=R9=R10=R11=R12=H
R2=R8= F, R1=R3=R4=R5=R6=R7=R9=R10=R11=R12=H
R3=R9= F , R1=R2=R4=R5=R6=R7=R8=R10=R11=R12=H
R4=R10= F, R1=R2=R3=R5=R6=R7=R8=R9=R11=R12=H
R5=R11= F, R1=R2=R3=R4=R6=R7=R8=R9=R10=R12=H
R6=R12= F, R1=R2=R3=R4=R5=R7=R8=R9=R10=R11=H

Figure 3.7 Scheme of macrolide systems.

Nº	*System*	*Heat of formation (kcal/mol)*	*HOMO (eV)*	*LUMO (eV)*	*ΔE (eV)*	*μ(D)*
1	macrolides	-54.5684	-5.6027	-1.0296	4.5731	1.101
2	2,8-dimethyl macrolide	-70.7862	-5.5480	-0.9132	4.6348	1.313
3	3,9-dimethyl macrolide	-67.2676	-5.5456	-0.8666	4.6790	0.997
4	4,10-dimethyl macrolide	-67.5177	-5.4356	-1.0215	4.4141	1.252
5	5,11-dimethyl macrolide	-64.6269	-5.5899	-1.0468	4.5431	1.124
6	6,12-dimethyl macrolide	-65.1767	-5.6035	-0.9972	4.6063	1.085
7	7,13-dimethyl macrolide	-67.9773	-5.4286	-0.9698	4.4588	1.135

Note: Heat of formation by PM3 by HyperChem 8.06. HOMO, LUMO, ΔE and μ by Ab initio/HF (STO-3G).

Table 3. 4 Energies of macrolide and di-methyl substitute macrolides (Series 1)

Nº	*System*	*Heat of formation (kcal/mol)*	*HOMO (eV)*	*LUMO (eV)*	*ΔE (eV)*	*μ(D)*
1	macrolides	-54.5684	-5.6027	-1.0296	4.5731	1.101
2	2,8-difluorine macrolide	-139.1277	-5.7815	-1.2601	4.5214	1.486
3	3,9- difluorine macrolide	-139.9724	-5.8465	-1.0432	4.8033	1.214
4	4,10- difluorine macrolide	-138.3979	-5.7306	-1.4843	4.2463	2.218
5	5,11- difluorine macrolide	-137.8738	-6.0830	-1.3782	4.7048	1.513
6	6,12- difluorine macrolide	-136.5750	-6.1690	-1.4174	4.7516	3.000
7	7,13- difluorine macrolide	-148.3032	-5.6715	-1.3692	4.3023	0.904

Note: Heat of formation by PM3 by HyperChem 8.06. HOMO, LUMO, ΔE and μ by DFT/B3LYP.

Table 3.5 Energies of macrolide and di-fluorine substitute macrolides (Series 2).

The heat of formation is decreased at each addition of di-methyl groups. Compound 2 (2, 8-dimethyl macrolide) has the smallest value of the heat of formation. This compound (2) is more stable compared to other derivatives.

As has been seen by calculating the effect of a substituent donor increase the energy of the HOMO and that of the LUMO, while we see by calculating the effect of a substituent acceptor decrease the energy of the HOMO and that of the LUMO, Results in a stabilization of the HOMO and LUMO.

In the substituted di-methyl group category, the 4,10-dimethylmacrolide (compound 4) has smaller HOMO-LUMO energy gap (4.4141) Table 4 depicts the chemical reactivity of the compound; higher is the HOMO-LUMO energy gap, lesser is the flow of electrons to the higher energy state, making the molecule hard and less reactive. On the other hand in smaller HOMO-LUMO gap, there is easy flow of electrons to the higher energy state making it softer and more reactive (HSAB principle: hard and soft acids and bases).

Hard bases have highest-occupied molecular orbitals (HOMO) of low energy, and hard acids have lowest-unoccupied molecular orbitals (LUMO) of high energy [45].

The heat of formation is decreased at each addition of di-fluorine groups. Compound 7 (7,13- difluorine macrolide) has the smallest value of the heat of formation. This compound (7) is more stable compared to other derivatives.

As has been seen by calculating the effect of a substituent donor increase the energy of the HOMO and that of the LUMO.

In the substituted di- fluorine group category, the 4,10-fluorine macrolide (compound 4) has smaller HOMO-LUMO energy gap (4.2463) Table 5 depicts the chemical reactivity of the compound; higher is the HOMO-LUMO energy gap, lesser is the flow of electrons to the higher energy state, making the molecule hard and less reactive.

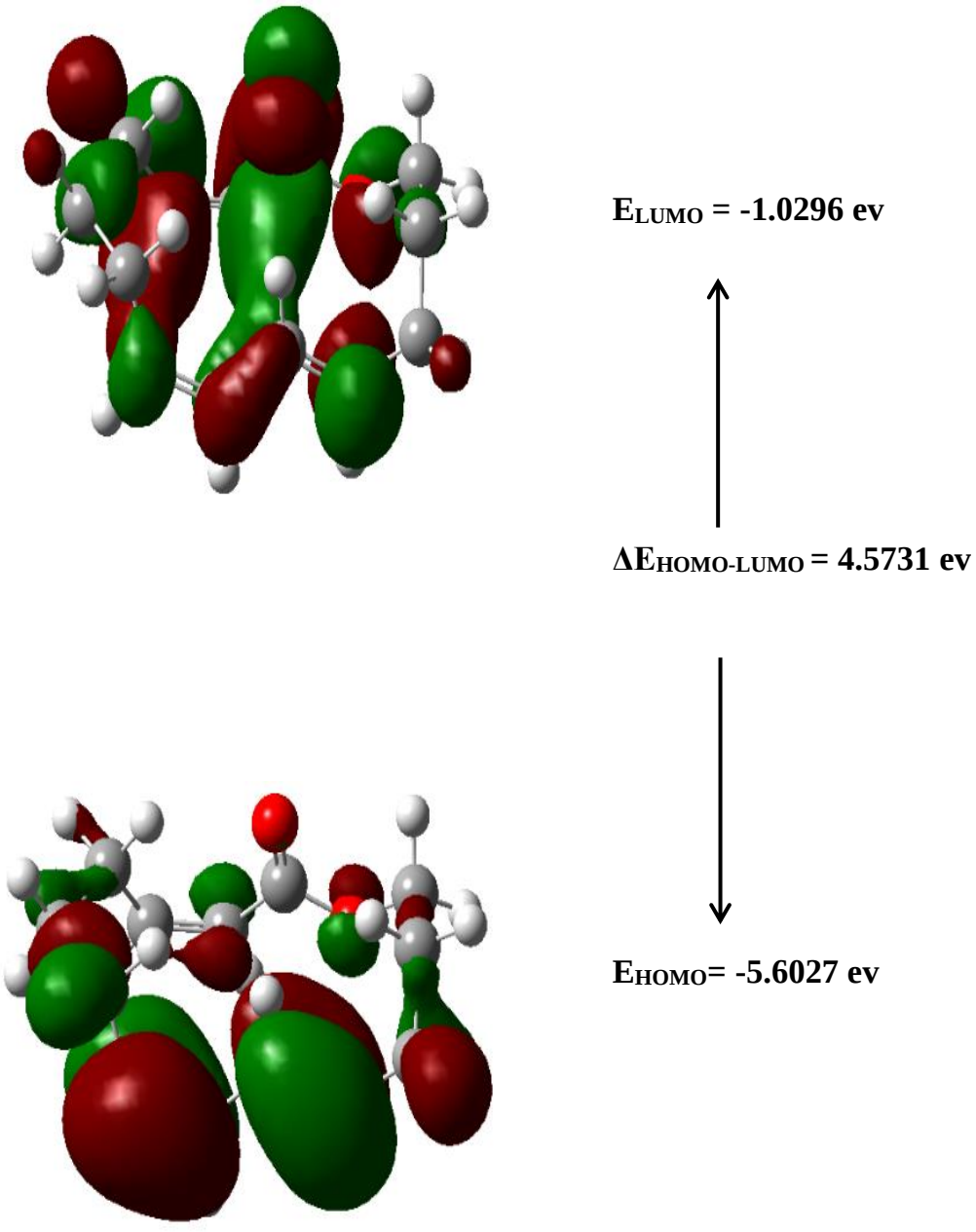


Figure 3.8. Schematic drawings of the HOMO and LUMO of compound 1(Gaussian 09).

The contour plots of the π-like frontier orbital's for the ground state of compound B1 are shown in (Figure 3.8), The positive phase is red and the negative one is green. from the plots, one can find that the HOMO mainly concentrates on the diene group, whereas, the LUMO distributes over the α, β –unsaturated ester group with some delocalization along the diene group. These further demonstrate that there exists the delocalization of the conjugated π-electron system in the molecule of compound 1.

10. Conclusion

The present work studied the molecular proprieties of 14-membered macrolides. The PM3, and ab initio method can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either donor or acceptor electron.

The 4, 10-di-methyl macrolide is predicted to be the most reactive with least HOMO-LUMO energy gap (4.4141) of all macrolide systems substituted by di-methyl, and in the substituted di-fluorine group category, the 4,10-fluorinemacrolide has smaller HOMO-LUMO energy gap (4.2463). depicts high chemical reactivity of the compounds.

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CHAPITER 04

Drug-likeness properties and Structure activity Relationships (SPR) of 14- Membered Macrolides.

1. Introduction

The idea that the physiological effects of a substance depend on its chemical composition and structure was first formulated more than a hundred years ago [1] . Today this approach is widely used in biochemical, pharmaceutical and other fields of science where predicting properties of chemical compounds is necessary. The popularity of this approach is based on the now obvious statement that the biological or physicochemical activity of the compound is a function of its structure, represented by a set of directly measurable or computable parameters [2-6]. Heterocyclic compounds hold a special place among the major pharmaceutical natural products and synthetic drugs having different biological activities [7].

The useful properties of macrolides range from perfumery to biological and medecinal activity . The new finding in the field of antitumour active and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration to chemists to study macrolides. The term “macrolide” is used to describe drugs with a macrocyclic lactone ring of 12 or more elements. [8] The 14-, 15-, and 16-membered macrolides are a widely used family of antibiotics. They have excellent tissue penetration and antimicrobial activity, mainly against Gram-positive cocci and atypical pathogens.

Macrolide concentrations are at least 10-fold higher in the epithelial lung fluid than in serum. Erythromycin A, a 14-membered macrolide, was isolated more than 50 years ago from cultures of *Streptomyces* and was the first macrolide introduced into clinical practice. [8-10]

However, increasing macrolide resistance among respiratory tract pathogensh as led to a search for new agents that are more effective against macrolide-lincosamide-streptogramin group B (MLSB)-resistant strains, and have low potential to select for or induce resistance and cross-resistance. The ketolides of which telithromycin (HMR 3647) is the first to undrgo clinical development, represent a new family of antmicrobials that are derived chemically from the macrolides and have been developed for use against respiratory pathogens.[11]

CHAPITER 4: Drug-likeness properties and Structure activity Relationships of 14- Membered Macrolides.

A successful drug that passes the hurdles of clinical trials to gain approval and a strong market position must exhibit a delicate balance of biological and physicochemical properties[12,13].

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties.[14] To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive *ab initio*/HF correlation methods are required.[15–17] Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules.[13], [18–25]

Quantitative and qualitative Structure-Activity Relationships (QSAR) are attempts to correlate molecular structure, or properties derived from molecular structure [5], [20], [25] with a particular kind of chemical or biochemical activity.

The kind of activity is a function of the interest of the user: QSAR is widely used in pharmaceutical, environmental, and agricultural chemistry in the search for particular properties. The molecular properties used in the correlations relate as directly as possible to the key physical or chemical processes taking place in the target activity [26].

QSAR has done much to enhance our understanding of fundamental processes and phenomena in medicinal chemistry and drug design[27–31].

The ability of a drug to penetrate various biological membranes, tissues and barriers is a primary factor in controlling the interaction of drugs with biological systems.

In quantitative structure activity relationship models (QSAR) in which physicochemical parameters of drugs are correlated with biological activities, lipophilicity (partition Coefficient) has a major role. Other important parameters are polarizability, electronic and steric parameters, molecular weight, geometry, etc.

In this work, we have investigated the geometry, electronic structure and substituent effect for 14-membered macrolides derivatives. Finally, we have studied some of QSAR proprieties and drug likeness proprieties of a series of 14-membered macrolides and ketolides derivatives reported by K. falzari and al [32] and J. Zhu. Zhaohai and al [33].

2. Structure-Property Relationships (SPR) Properties

2.1. Molecular Volume And Surface Area

Molecular volumes are often calculated by a numerical integration grid technique [34] that I can illustrate by considering the trivial problem of finding the volume of an atom whose van der Waals radius is R (the volume is of course $\frac{4}{3}\pi R^3$)

Figure 4.1 shows a two-dimensional representation of the atom whose van der Waals radius is R, surrounded by a three-dimensional grid of equally spaced points.

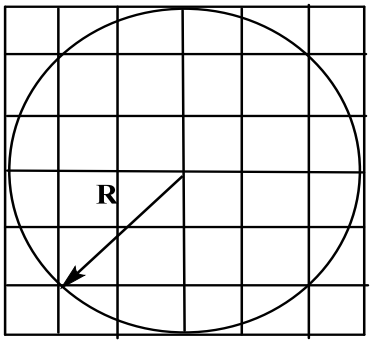


Figure 4.1: Grid around atom

The grid has its centre at the atom centre, and the edges of the grid correspond to the van der Waals radius. For each grid point in turn we calculate its distance from the centre and determine whether the grid point lies inside or outside the atom. If n is the total number of grid points and na the number that lie within the atom whose volume is V, then we have

$$\frac{V}{8R^3} = \frac{n_a}{n} \qquad (1)$$

For a polyatomic, we have to give special consideration to grid points that lie in the overlap region. Figure 4.2 shows two atoms, A and B, with radii RA and RB. The overlap region is labelled X.

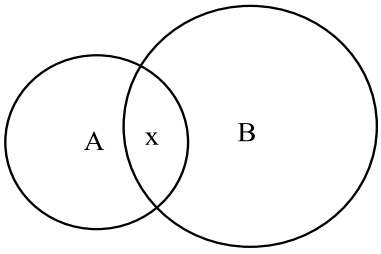


Figure 4.2. Atoms A, B and overlap region X.

For atom A, we know that the volume is $\frac{4}{3}\pi R^3$. We now surround atom B with a grid, as described above, and test each grid point in turn. If the grid point lies within sphere B, then we test to see if it lies in region X and so has already been counted as part of the volume of atom A. The algorithm proceeds until all atoms have been considered in turn. The molecular volume is found by adding all atomic contributions. There are similar methods for the estimation of molecular surface area.

2.2. Molecular Refractivity (MR)

The molar refractivity is a steric parameter that is dependent on the spatial array of the aromatic ring in the synthesized compounds. The spatial arrangement also is necessary to study the interaction of the ligand with the receptor [35].

This parameter is a measure of the volume occupied by an atom or group of atoms. The molar refractivity is a constitutive-additive property that is calculated by LorenzLorentz formula:

$$MR = \frac{n^2-1}{n^2+2} \times \frac{Mw}{\rho} \qquad (2)$$

where n is the refraction index, Mw is the molecular weight, and ρ is the density. The (n^2-1)/(n^2 + 2) term provides a correction factor by defining how easily the substituent can be poralized, whereas the Mw/ρ term defines a volume. Molar refractivity is related to the lipophilicity, volume, and steric of the molecules. Moreover, it has been correlated with the London dispersive force that acts in the drug-receptor interaction.

2.3. Molecular Polarizability (Pol)

Molecular Polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities [36].

It is widely used to describe the inductive and dispersive interaction of a molecule or molecular system. In addition, polarizability values have been shown to be related to hydrophobicity and thus to other biological activities. It is one of the descriptors that are extensively used in QSAR study.

Highly polarizable molecules can be expected to have strong attractions with other molecules. The molecular polarizabity (α) is also related to molecular refractivity (MR) by the Lorentz-Lorenz equation (3) where N_0 is the Avogadro constant.

$$MR = \frac{4}{3}\pi N_0 \alpha \qquad (3)$$

2.4. Molecular Weight (MW)

Molecular weight descriptor has been used as a descriptor in systems such as transport studies where diffusion is the mode of operation. It is an important variable in QSAR studies pertaining to cross resistance of various drugs in multi-drug resistant cell lines [37]. Molecular weight is correlated with the size of the molecule [38].

High molecular weight compounds are likely to show high toxicity as promiscuity of compounds is also likely to increase [39]. Additionally, the systemic clearance of a compound is inversely proportional to the molecular weight [40].

2.5. Hydration Energy (HE)

Hydration energy is very important in the selectivity filter of ion channels where the drug is almost entirely strip from the hydration water [41]. Indeed, in the biological environments the polar molecules are surrounded by water molecules. They are established hydrogen bonds between a water molecule and these molecules. The donor sites of the proton interact with the oxygen atom of water and the acceptor sites of the proton interact with the hydrogen atom. The first corresponds to the complex with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible [42].

2.6. Partition Coefficient (Log P)

One of the most important physicochemical properties much interest in QSAR studies is lipophilicity (or hydrophobicity). Because it directly relates to solubility in aqueous phase, to membrane permeation (an important factor contributing to the toxicity of chemicals), and to its contribution to ligand binding at the receptor site.

The ability of a molecule to cross the biological membranes (permeability) is a very important bio-pharmaceutic parameter that governs the absorption, distribution, metabolism and excretion (pharmacokinetics) of a drug. Enroute to its bio-phase, the drug has to partition between the lipid bio-membranes and the aqueous biological fluids. Although constituents vary from one membrane to the other, major constituents of bio-membranes are phospholipids, cholesterol, sphingolipids, and glycolipids (Figure 4.3).

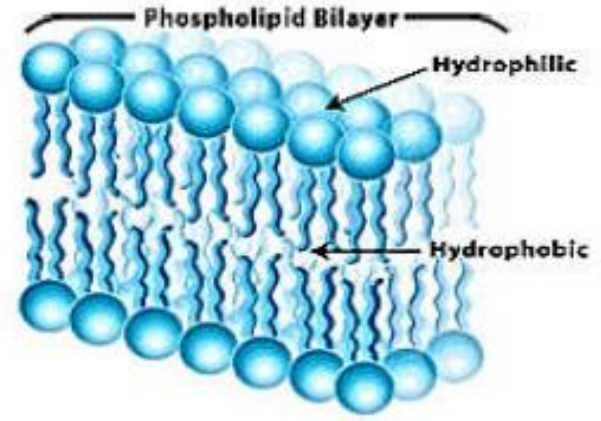


Figure 4.3. Polarity of different cellular milieus.

All of these lipids are amphipathic in nature. Therefore, to successfully cross the various bio-membranes and to reach its site of action, any drug molecule should have a balance between hydrophilic and lipophilic properties.

The partition coefficient P, defined as the ratio of molar concentration of a chemical dissolved at equilibrium in octanol phase C_{oct} to its molar concentration in aqueous phase C_{aq} [43-45], (Figure 4.4), and is given by the equation:

$$\mathbf{P} = \left(\frac{C_{oct}}{C_{aq}}\right)_{equilibrium} \qquad (4)$$

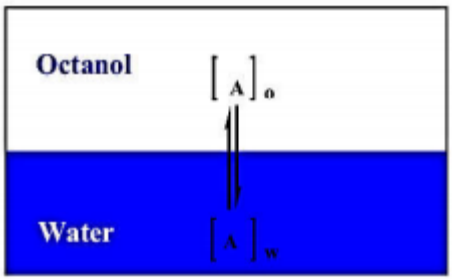


Figure 4.4. Schematic depictions of the partition of species between octanol and water**.**

Which $[A]_O$ and $[A]_W$ are the concentrations of the compound A in organic and aqueous phases, respectively.

The best choice out of various non-polar and slightly polar solvents available is noctanol [46] because, it mimics the biological membranes in several aspects:

- n-octanol has a saturated alkyl chain,
- it has a hydroxyl group that can act as both hydrogen bond donor as well as acceptor, it dissolves water to the extent of 1.7 M,
- and its solubility parameter ($\delta_{octanol}$=10) is close to that of biological membranes, for example skin (δ_{skin}=10).

This combination of lipophilic chains, hydrophilic groups, ability to take up water molecules and similar solubility parameter gives n-octanol properties very close to those of natural membranes.

LogP values between 0 and 3 constitutes an optimal window for passive drug absorption. A logP value below 0 means that the compound is hydrophilic, and hence it will have a good solubility but it may have poor permeability. Whereas, a logP value far higher than 3 means that the compound is highly lipophilic, hence, tends to favour absorption, and renders the compounds more susceptible to metabolism and / or biliary clearance [47, 48]. The influence of lipophilicity on the metabolic clearance of drugs is attributed mainly to the increased affinity of drugs for the enzymes [49].

2.7. Number of Hydrogen Bond Donors and Bond Acceptors

Hydrogen bonding is now seen as an important property related to membrane permeation. Various scales have been developed [50]. Some of these scales describe total hydrogen bonding capability of a compound, while others discriminate between donors and acceptors [51].

Hydrogen bonds increase solubility in water and must be broken in order for the compound to permeate into and through the lipid bilayer membrane. Thus, an increasing number of hydrogen bonds reduces partitioning from the aqueous phase into the lipid bilayer membrane for permeation by passive diffusion [38]. Thus, the number of hydrogen bond donors and acceptors should be limited in order to minimize the stability of compound in aqueous media.

2.8. Druglikeness

The term drug-like captures the concept that certain properties of compounds are most advantageous in their becoming successful drug products. The term became commonly used following the pivotal work of Lipinski and his colleagues at Pfizer [52]. Their work examined the structural properties that affect the physicochemical properties of solubility and permeability and their effect on drug absorption. The term drug-like property has expanded and has been linked to all properties that affect ADME/Tox. Although medicinal chemists and pharmaceutical scientists had used structural properties in various ways for many years, rules became more prominent and defined in the field with the report by Lipinski et al [52] of the “rule of 5,” or what has become known as the “Lipinski rules.” These rules are a set of property values that were derived from classifying key physicochemical properties of drug-like compounds. The rule of five is based on four properties of molecules; namely, molecular weight (MW), logP, number of hydrogen-bond donors (HBD) taken as equivalent to the number of –OH and –NH groups, and the number of hydrogen-bond acceptors (HBA) taken as equivalent to the number of oxygen and nitrogen atoms.

A 'flag' is set if a molecule's MW is greater than 500, its logP is greater than 5, the number of its HBDs exceeds 5 and the number of its HBAs exceeds 10.

Because the values of the decision points for all of the property values are multiples of five, the above set of rules has been called the 'Rule of Five'[52].

2.9. Lipinski Rules

Although medicinal chemists and pharmaceutical scientists had used structural properties in various ways for many years, rules became more prominent and defined in the field with the report by Lipinski et al. [53] of the "rule of 5," or what has become known as the "Lipinski rules." These rules are a set of property values that were derived from classifying the key physicochemical properties of drug-like compounds. The rules were used at Pfizer for a few years prior to their publication and since then have become widely used. The impact of these rules in the field has been very high. This acceptance can be attributed to many factors:

- The rules are easy, fast, and have no cost to use.
- The "5" mnemonic makes the rules easy to remember.
- The rules are intuitively evident to medicinal chemists.
- The rules are a widely used standard benchmark.
- The rules are based on solid research, documentation, and rationale.
- The rules work effectively.

The rule states that the compounds are more likely to be orally bioavailable if they obey the following criteria :

- ✓ hydrogen bond donors ≤5 (expressed as the sum of all OHs and NHs)
- ✓ MW ≤ 500
- ✓ logP ≤ 5
- ✓ hydrogen bond acceptors ≤10 (expressed as the sum of all Ns and Os).

Molecules that violate more than one of these rules may have problems with bioavailability.

Therefore, this rule establishes some structural parameters relevant to the theoretical prediction of the oral bioavailability profile, and is widely used in designing new drugs. However, classes of compounds that are substrates for biological transporters such as antibiotics, antifungals, vitamins, and cardiac glycosides, are exceptions to the rule [53].

3. Results and Discussion

3.1 Study of Structure - activity Relationships for 14-membered Macrolides

We have studied seven physical and chemical proprieties of a series of fifty Macrolides derivatives using HyperChem 8.03 software. For example , in Figure 5 shows the favored conformation in 3D of the Clarithromycine. We will continue this work in the future by a quantitative calculation.

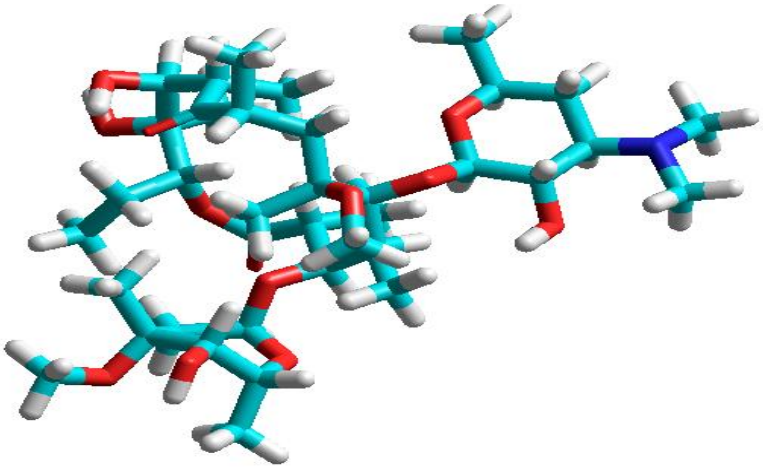


Figure 4.5. 3D Conformation of Clarithromycine (HyperChem 8.03).

QSAR proprieties are van der Waals surface molecular volume (V), octanol-water partition coefficient (log *P*), polarizability (pol), Refractivity (Ref), hydration energy (EH), solvent-accessible surface (S) bounded molecular volume and molecular mass (M). Calculation of log P is carried out using atomic parameters derived by Viswanadhan and coworkers [54].

Log *P* is one criterion used in medicinal chemistry to assess the drug likeness of a given molecule, and used to calculate lipophilic efficiency, a function of potency and log *P* that evaluate the quality of research compounds. For a given compound lipophilic efficiency is defined as the pIC50 (or pEC50) of interest minus the log *P* of the compound.

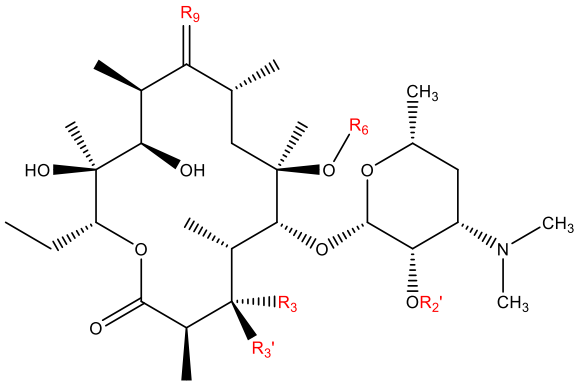
Computation of molar refractivity was made via the same method as log *P*. Ghose and Crippen presented atomic contributions to the refractivity [55]. Solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bodor et al.,[56] using the atomic radii of Gavezotti [57]. Polarizability was estimated from an additivity scheme given by Miller with a 3% in precision for the calculation [58], where different increments are associated with different atom types.

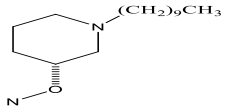
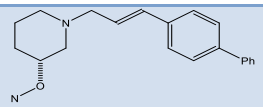
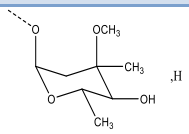
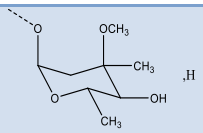
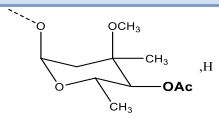
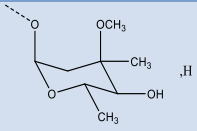
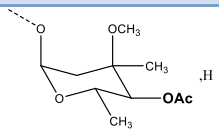
Hydration energy is a key factor determining the stability of different molecular conformations in water solutions[59]. The calculation is based on exposed surface area as computed by the approximate method (above), weighted by atom type.

3.2. Structural Comparison of the 14-membered Macrolide Derivatives

Based on our conclusions on the effect of substitution on the 14-membered Macrolides molecules. We chose a series of 14-membered Macrolide derivatives in Table 4.6, Table 4.7 and Table 4.8.; some of them have a biological activity (anti-tuberculosis). Initially, we performed a structural comparison of this series. We used molecular mechanics, with MM+ force-field to calculate the stable conformations of this series. In a window of 40 kcal/mol, only one favored conformations is found, for each structure. These molecules have a structural differences in specific sites : C2, C3, C6, C9, C11, C2' and C4" as shown in the references [32] and [33].

Table 4.6 14-membered Macrolide derivatives (Structure A).



N°	*Macrolide*	IC_{50}	$R_3R'_3$	$R_{2'}$	R_6	R_9
A1	***RU60887*** [32]	27.58	=O	H	Me	
A2	***RU61804*** [32]	9.12	=O	H	Me	
A3	***RU29558*** [32]	28.15		H	H	$NOCH_2OBn$
A4	***Clarithromycine*** [32]	40.99		H	Me	O
A5	***ITR054*** [33]	35.6		H	Me	O
A6	***ITR051*** [33]	9.03		H	H	
A7	***GI-448*** [33]	13.6		H	H	

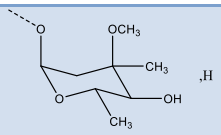
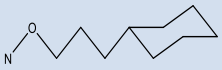
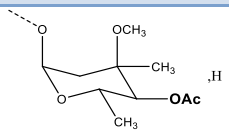
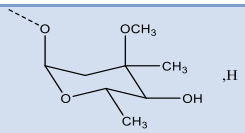
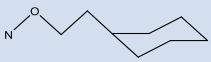
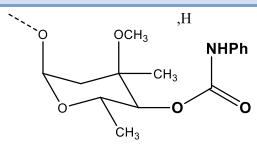
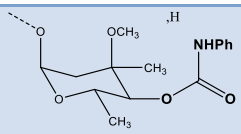
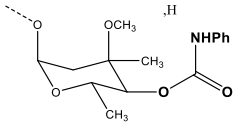
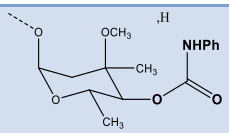
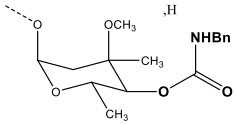
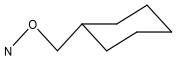
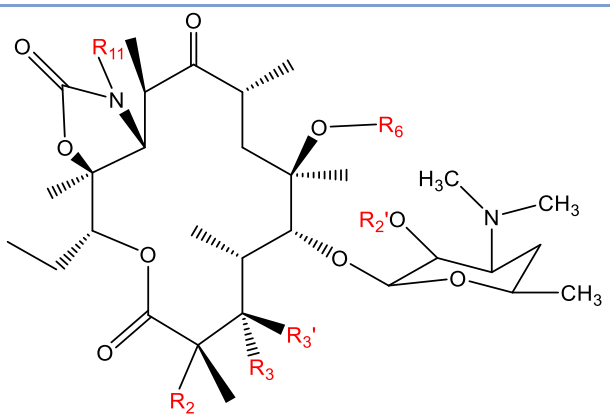
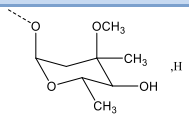
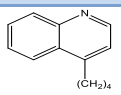
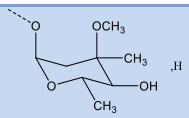
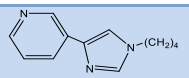
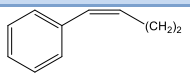
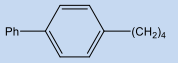
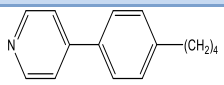
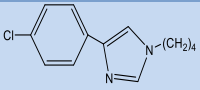
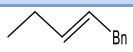
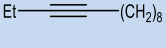
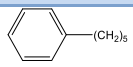
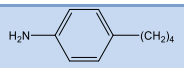
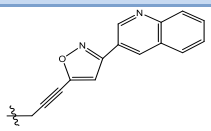
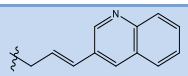
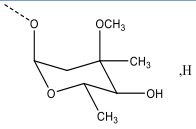
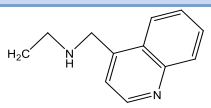
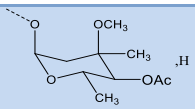
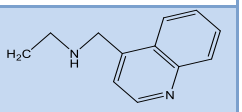
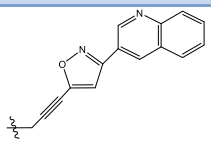
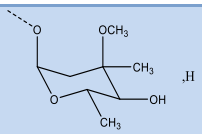
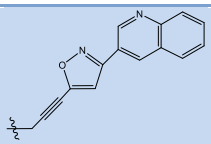
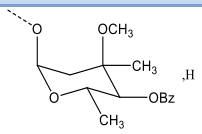
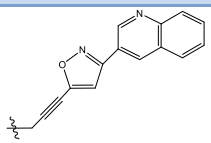
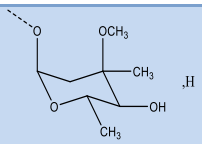
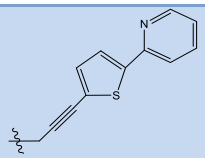
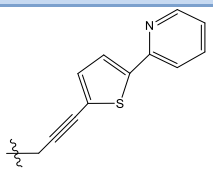
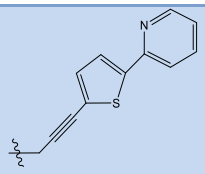
A8	***ITR159*** [33]	45		Ac	Me	
A9	***ITR160*** [33]	39		Ac	Me	
A10	***ITR077*** [33]	16.3		H	Me	
A11	***ITR120*** [33]	115		C(O)NHPh	Me	
A12	***ITR126*** [33]	48.0		C(O)NHPh	Me	NOC_2H_4Ph
A13	***ITR138*** [33]	107		C(O)NHPh	Me	NOC_3H_6Ph
A14	***ITR121***[33]	6.8		C(O)NHPh	Me	O
A15	***ITR083*** [33]	39		H	Me	O
A16	***ITR163*** [33]	73	H, OC(O)NHHexyl	H	Me	O
A17	***ITR157*** [33]	45	H, OH	H	Me	

Table 4.7 14-membered Macrolide derivatives (Structure B).



N°	Macrolide	IC_{50}	R_2	$R_3R'_3$	$R_{2'}$	R_6	R_{11}
B1	***RU66080*** [32]	8.1	H		H	Me	
B2	***RU69874*** [32]	26.96	H		H	Me	
B3	***RU60856*** [32]	104.8	H	=O	H	Me	
B4	***RU61143*** [32]	24.25	H	=O	H	Me	
B5	***RU63013*** [32]	7.37	H	=O	H	Me	
B6	***RU66898*** [32]	6.93	H	=O	H	Me	
B7	***RU62041*** [32]	8.19	H	=O	H	Me	
B8	***RU62543*** [32]	8.71	H	=O	H	Me	
B9	***RU60849*** [32]	8.84	H	=O	H	Me	

B10	***RU70332*** [32]	26.04	H	=O	H	Me	
B11	***A323348*** [32]	24.29	F	=O	H		H
B12	***Cethromycine*** [32]	102.4	H	=O	H		H
B13	***ITR049*** [33]	38.8	H		H	Me	
B14	***ITR048*** [33]	13.5	H		H	Me	
B15	***ITR250*** [33]	35.0	H	=O	H		H
B16	***ITR286*** [33]	12	H		H		H
B17	***ITR258*** [33]	37.0	H		H		H
B18	***ITR285*** [33]	27.7	H		H		H
B19	***ITR248*** [33]	11.9	H	=O	H		H
B20	***ITR278*** [33]	44	F	=O	H		H

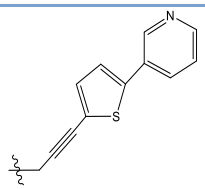
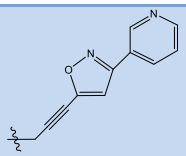
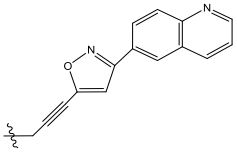
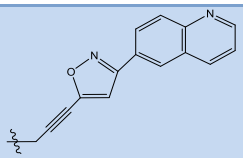
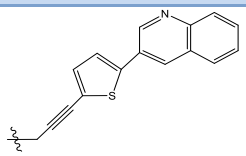
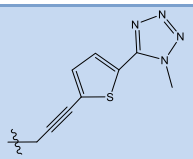
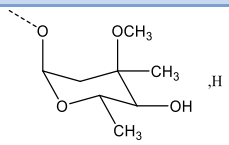
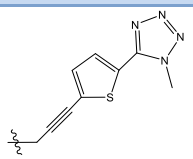
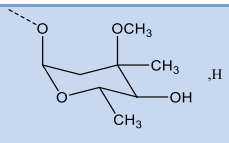
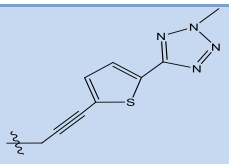
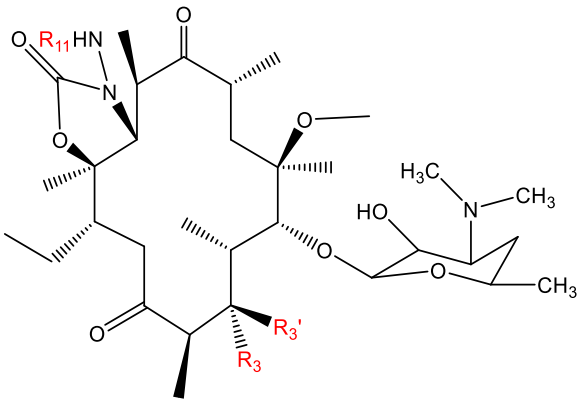
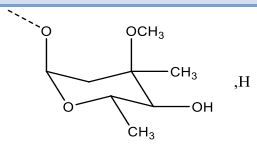
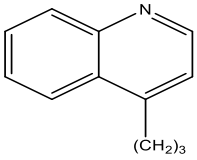
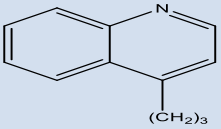
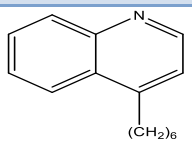
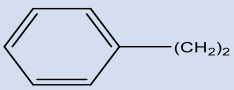
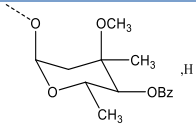
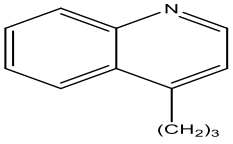
B21	***ITR257*** [33]	15.0	H	=O	H		H
B22	***ITR273*** [33]	35.4	F	=O	H		H
B23	***ITR266*** [33]	51.3	F	=O	H		H
B24	***ITR276*** [33]	42.4	F	=O	Bz		H
B25	***ITR275*** [33]	14.07	H	=O	H		H
B26	***ITR263*** [33]	51.1	H	=O	H		H
B27	***ITR270*** [33]	18.9	H		H		H
B28	***ITR271*** [33]	48.2	H		H		H

Table 4. 8. 14-membered Macrolide derivatives (Structure C).



Nº	*Macrolide*	*IC50*	*$R_3R'_3$*	*R_{11}*
C1	**RU66252** [32]	24.93		
C2	**RU004** [32]	26.34	=O	
C3	**RU69697** [32]	7.32	=O	
C4	**RU70645** [32] **Rifampin**	46.7	=O	
C5	**ITR053** [32]	5.5		

3.3 Structure Property/Activity Relationships

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity. Lipophilicity has been studied and applied as an important drug property for decades. It can be quickly measured or calculated.

Lipophilicity has been correlated to many other properties, such as bio availability, storage in tissues, permeability, volume of distribution, toxicity, plasma protein binding and enzyme receptor binding [60-61].

Polarizability values are generally proportional to the values of surfaces and of volumes, the order of polarizability is approximately the same one for volume and surface. This also is explained by the relation between polarizability and volume, for the relativity non polar molecules. They are directly linked, for the centers of gravity of negative and positive charges in the absence of external fields to coincide, and the dipole moment of the molecule is zero. The polarizability of a molecule depends only on its volume, which means that the thermal agitation of non polar molecules does not have any influence on the appearance of dipole moments in these molecules.

On the other hand, for the polar molecules, the polarizability of the molecule does not depend solely on volume but also depends on other factors such as the temperature because of the presence of the permanent dipole [62]**.**

We found for these macrolides that their surfaces vary from 875 to 1226 Å2. These macrolides have a considerable variation of distribution volume, in particular compound A11, A13 and compound A12 which have respective volumes: 2739.69, 2647.39 and 2643.51 $Å^3$ (Table 4.9).

The most important hydration energy in the absolute value, is that of the compound B27 (-18.89 kcal/mol) and the weakest is that of compound B7 (-1.01 kcal/mol) (Table 4.9). Indeed, in the biological environments the polar molecules are surrounded by water molecules. They are established hydrogen bonds between a water molecule and these molecules. The donor sites of the proton interact with the oxygen atom of water and the acceptor sites of the proton interact with the hydrogen atom.

The first corresponds to the complex with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible [63]**.**

All (log P) of studied molecules have optimal values. For good oral bio availability, the log *P* must be greater than zero and less than 3 ($0 < \log P < 3$). For log *P* too high, the drug has low solubility and a log *P* too low; the drug has difficulty penetrating the lipid membranes [60].

All the studied compounds Log *P* have a positive value higher than 3 except two compounds: A4 and B2 with Log P values: 3 and 2.44 (Table 4.9), respectively. These two Compounds present the low coefficient of division. Order, these molecules possess a good solubility. When the coefficient of division is rather low, it has as a consequence a better gastric tolerance. Compound A1, B8 and A11 which have, respectively, higher values 7.89, 7.75 and 7.10 (Table 4.9); these molecules are the most absorbent products and have important the capacities to be dependent on plasmatic proteins**.**

They are established hydrogen bonds between a water molecule and these molecules. The donor sites of the proton interact with the oxygen atom of water and the acceptor sites of the proton interact with the hydrogen atom. The first corresponds to the complex with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible [63].

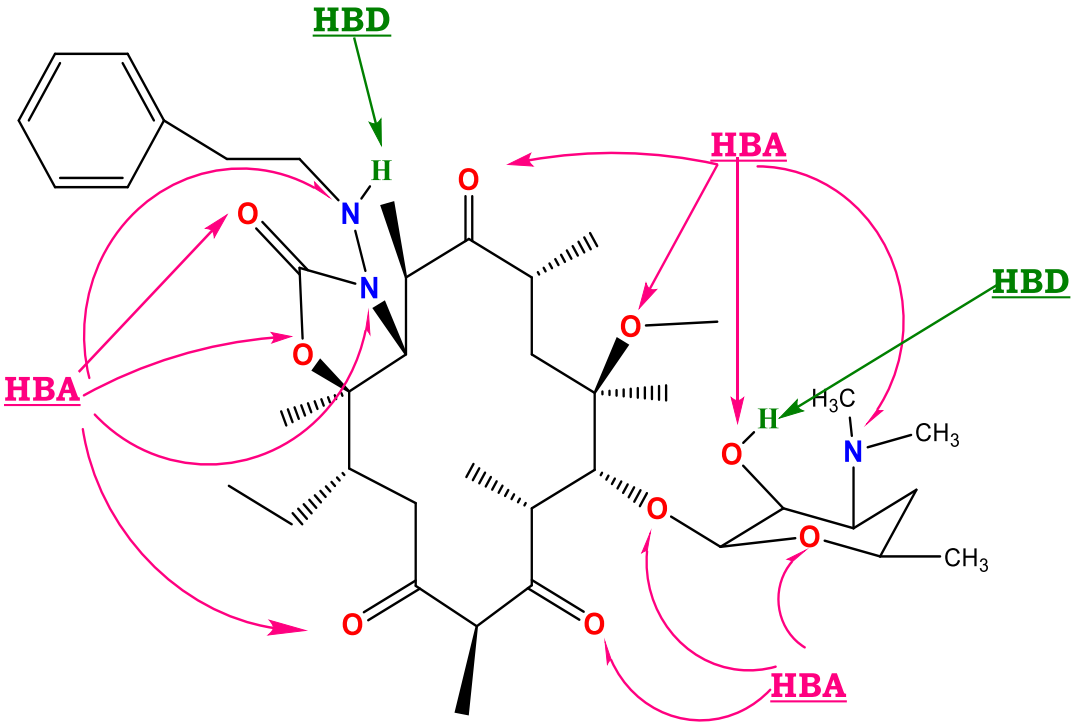


Figure 4.6. Donor and acceptor sites of compound C4

Coumpound A3 has five proton donor sites HBD (5 OH) and 16 proton acceptor sites HBA. On the contrary, B3 has only one donor sites HBD and it has 12 proton acceptor sites HBA. This property supports the first compound, not only by fixing the receiver, but also activates it. It is thus about an agonist. It has as a consequence a better distribution in fabrics.

Table 4.9 QSAR Proprieties for 14-membered macrolide derivatives.

Macrolides	*V (Å³)*	*S (Å²)*	*Mass (uma)*	*Log(P)*	*EH (kcal/mol)*	*Pol (Å³)*	*Ref*	*IC_{50} uM*
A1	2270.24	1106.61	826.17	7.89	-2.78	89.68	215.53	27.58
A2	2343.45	1190.89	878.16	6.46	-7.41	96.21	252.38	9.12
A3	2143.96	1014.46	869.10	4.62	-10.91	90.33	228.94	28.15
A4	1827.35	875.28	747.96	3	-11.03	76.71	190.78	40.99
A5	1988.81	957.34	790.00	3.13	-6.05	80.47	199.94	35.6
A6	2236.38	1058.71	873.18	6.03	-6.03	92.10	229.36	9.03
A7	2304.10	1079.35	915.21	6.16	-4.29	95.86	238.51	13.6
A8	2313.69	1061.24	929.24	6.43	-5.16	97.69	243.26	45
A9	2413.50	1122.91	971.28	6.56	-2.99	101.45	252.41	39
A10	2201.17	1029.99	873.18	5.91	-6.31	92.10	229.51	16.3
A11	2739.69	1281.60	1111.42	7.10	-8.85	117.97	304.13	115
A12	2643.51	1200.37	1105.38	6.14	-11.15	117.39	307.22	48.0
A13	2647.39	1153.65	1119.40	6.54	-11.09	119.23	311.82	107
A14	2359.49	1059.25	986.21	4.19	-10.96	102.58	265.41	6.8
A15	2190.01	1049.17	881.11	4.11	-9.28	91.48	232.26	39
A16	1797.83	869.88	714.94	4.15	-5.55	74.40	185.78	73
A17	1834.32	897.61	700.95	5.05	-5.69	74.45	186.09	45
B1	2271.71	1039.66	956.23	4.36	-4.75	101.05	258.75	8.1
B2	2309.10	1061.75	972.23	2.44	-7.64	101.69	258.81	26.96
B3	1865.23	897.83	742.95	5.66	-2.21	79.01	204.45	104.8
B4	2036.77	951.69	821.06	6.53	-3.56	88.87	231.85	24.25
B5	2013.71	948.81	822.05	5.05	-4.93	88.16	228.28	7.37
B6	2060.82	1019.90	845.47	3.94	-4.50	87.96	227.58	6.93
B7	1971.64	981.00	756.98	5.96	-1.01	80.85	208.58	8.19
B8	2107.06	1076.61	777.05	7.75	2.08	83.12	210.67	8.71
B9	1935.85	932.56	758.99	6.31	-3.51	81.04	207.93	8.84
B10	1920.42	937.56	759.98	4.20	-8.01	80.56	206.88	26.04
B11	2142.51	1090.01	853.00	3.37	-10.89	86.53	225.38	24.29
B12	1883.92	892.31	765.94	3.98	-5.85	80.82	210.77	102.4
B13	2281.52	1051.19	957.21	2.94	-6.77	100.56	257.52	38.8
B14	2342.81	1057.68	999.25	3.07	-3.82	104.32	266.67	13.5
B15	1950.10	903.19	830.98	4.21	-6.54	86.01	226.54	35.0
B16	2354.64	1113.10	991.19	3.97	-11.59	102.38	266.06	12
B17	2604.01	1226.50	1095.3	5.25	-10.76	113.96	299.53	37.0
B18	2257.98	1055.55	956.20	4.02	-8.39	99.27	256.35	27.7
B19	1895.45	908.85	795.99	4.27	-5.79	82.90	216.83	11.9
B20	1922.60	930.89	813.98	4.08	-5.27	82.81	216.61	44
B21	1875.81	896.79	795.99	2.77	-5.16	82.90	216.56	15.0
B22	1913.98	933.85	798.91	3.74	-9.50	79.74	206.78	35.4
B23	2027.11	986.08	848.97	3.90	-9.50	85.92	226.25	51.3
B24	2238.18	1080.74	953.07	5.18	-10.68	97.50	259.71	42.4
B25	1999.39	951.82	846.05	4.34	-4.79	89.09	235.03	14.07
B26	1888.72	904.79	800.97	4.37	-16.66	81.19	214.21	51.1

B27	2311.64	1116.73	961.18	4.12	-18.89	97.56	253.74	18.9
B28	2321.25	1123.44	961.18	4.12	-14.99	97.56	253.74	48.2
C1	2277.58	1035.21	957.21	3.92	-5.66	100.56	257.45	24.93
C2	1950.02	915.10	797.00	4.17	-3.24	84.19	217.93	26.34
C3	2085.33	973.70	839.08	5.36	-4.10	89.70	231.73	7.32
C4	1868.78	933.64	731.93	5.08	-3.23	76.89	197.43	46.7
C5	2474.24	1122.57	1061.32	5.20	-4.65	112.14	290.92	5.5

3.4 Drug likeness screening of 14-membered macrolide derivatives

Drug-likeness appears as a promising paradigm to encode the balance among the molecular properties of a compound that influences its pharmacodynamics and pharmacokinetics and ultimately optimizes their absorption, distribution, metabolism and excretion (ADME) in human body like a drug [64-65]. The empirical conditions to satisfy Lipinski's rule and manifest a good oral bio availability involve a balance between the aqueous solubility of a compound and its ability to diffuse passively through the different biological barriers.

Drug-likeness is a qualitative property of chemicals. This concept is useful in guiding early-stage drug discovery. It is based on observations of correspondences between pharmacological activity of molecular agents and their physicochemical properties. It allows connecting the impact of physicochemical properties on molecular behaviors *in vivo*, with a special focus on solubility, permeability, metabolic stability and transporter effects. The best compromise results from a subtle balance between physiochemical and pharmacokinetic properties. This is critical for designing new drugs [66].

These parameters allow to ascertaining oral absorption or membrane permeability that occurs when the evaluated molecule follows Lipinski's rule of five, evaluated molecule follows Lipinski's rule of five, molecular weight (MW) ≤ 500 Da, an octanol-water partition coefficient log *P* ≤ 5, H-bond donors, nitrogen or oxygen atoms with one or more hydrogen atoms (HBD) ≤ 5 and H-bond acceptors, nitrogen or oxygen atoms (HBA) ≤ 10.

Table 10 lists the pharmacological activities and properties we deduced for 14-membered macrolides derivatives under study. They correspond to partition coefficient octanol/water (LogP), molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), ligand efficiency (LE) and lipophilic ligand efficiency (LLE). These results were calculated using HyperChem 8.0.8.

Also, we have studied Lipinski rule to identify “drug-like” compounds. Table 4.10 shows that all compounds have a LogP comprised between 2 and 8. LogP values in the range of 1 to 3 are connected with a good oral bioavailability.

The drug has hence sufficient aqueous solubility to dissolve in the gastrointestinal contents and also adequate lipid solubility to facilitate its partitioning into the lipoid membrane. For LogP > 3, the drug has low solubility and for LogP < 1 the drug has difficulty penetrating the lipid membranes.

Ligand efficiency (LE) and lipophilic ligand efficiency (LLE) are defined as

$LE=1.4 * pIC_{50}/N_H$, and LLE = pIC50−LogP where N_H is the number of heavy atoms and

$pIC50 = - \log (IC_{50})$ [67].

LELP = log P/LE. The optimal LELP scores are -10 < LELP<10 [68].

LE is introduced as an important metric in drug discovery, and as a tool of assessing a compound’s potency relative to its size. It is dependent on ligand size (with smaller ligands having greater efficiencies, on average, than larger ligands) [69-70]. Also, we took advantage of LLE to gain a deeper understanding of the effect of structural changes in the series. As a rough guide, medicinal compounds in drug-like space have LLE values in the range 5–7 [71]. Note that compounds with high LE and LLE interact efficiently with biological targets [72].

In the studied series, LLE is changing during optimization (Table 4.10). All compounds have negative LLE values which are clearly unfavorable.

above mentioned parameters were calculated for A1- C5 and the results were presented in Table 4.10. From the data obtained, it was observed that all derivatives were found doesn't obey the Lipinski rule, suggesting that these compounds theoretically would have problems with oral bioavailability.

There is much evidence that despite having molecular mass that are above ‘rule of 5’-compliant small molecules [73], macrocycles can demonstrate drug like physicochemical and pharmacokinetic properties such as good solubility, lipophilicity, metabolic stability and bioavailability.

Table 4.10 Drug-likeness parameters and lipophilicity indices of 14-membered macrolide derivatives.

Cpds	*MW (Da)*	*log P*	*HBD*	*HBA*	*No. of violations*	*pIC50*	*LLE*	*N_H*	*LE*	*LELP*
A1	826.17	7.89	03	13	03	4.56	-3.33	58	0.110	71.73
A2	878.16	6.46	03	13	03	5.04	-1.42	64	0.110	58.72
A3	869.10	4.62	05	16	02	4.55	-0.07	61	0.104	44.42
A4	747.96	3	04	14	02	4.39	1.39	52	0.118	25.42
A5	790.00	3.13	03	15	02	4.45	1.32	56	0.111	28.19
A6	873.18	6.03	04	15	03	5.04	-0.99	61	0.116	51.98
A7	915.21	6.16	04	16	03	4.87	-1.29	64	0.106	58.11
A8	929.24	6.43	03	16	03	4.35	-2.08	65	0.093	69.13
A9	971.28	6.56	02	17	03	4.41	-2.15	68	0.090	72.88
A10	873.18	5.91	04	15	03	4.79	-1.12	61	0.109	54.22
A11	1111.42	7.10	04	20	03	3.94	-3.16	79	0.069	102.89
A12	1105.38	6.14	04	20	03	4.32	-1.82	79	0.076	80.78
A13	1119.40	6.54	04	20	03	3.97	-2.57	80	0.069	94.78
A14	986.21	4.19	04	19	02	5.17	0.98	70	0.103	40.68
A15	881.11	4.11	04	16	02	4.41	0.3	68	0.090	45.66
A16	714.94	4.15	04	14	02	4.14	-0.01	50	0.116	35.77
A17	700.95	5.05	04	12	03	4.35	-0.7	49	0.124	40.72
B1	956.23	4.36	02	16	02	5.09	0.73	68	0.105	41.52
B2	972.23	2.44	02	18	02	4.57	2.13	69	0.093	26.23
B3	742.95	5.66	01	12	03	3.98	-1.68	53	0.105	53.90
B4	821.06	6.53	01	12	03	4.61	-1.92	59	0.109	59.91
B5	822.05	5.05	01	13	03	5.13	0.08	59	0.122	41.39
B6	845.47	3.94	01	14	02	5.16	1.22	59	0.122	32.29
B7	756.98	5.96	01	12	03	5.09	-0.87	54	0.131	45.49
B8	777.05	7.75	01	12	03	5.06	-2.69	55	0.129	60.07
B9	758.99	6.31	01	12	03	5.05	-1.26	54	0.131	48.17
B10	759.98	4.20	03	13	02	4.58	0.38	54	0.119	35.29
B11	853.00	3.37	02	15	02	4.61	1.24	61	0.106	31.79
B12	765.94	3.98	02	13	02	3.99	0.01	55	0.101	39.40
B13	957.21	2.94	03	17	02	4.41	1.47	68	0.091	32.30
B14	999.25	3.07	03	18	02	4.87	1.8	71	0.096	31.98
B15	830.98	4.21	02	15	02	4.45	0.24	60	0.104	40.48
B16	991.19	3.97	04	18	02	4.92	0.95	71	0.097	40.92
B17	1095.30	5.25	03	19	03	4.43	-0.82	79	0.078	67.30
B18	956.20	4.02	04	17	02	4.56	0.54	67	0.095	42.31
B19	795.99	4.27	03	13	02	4.92	0.65	56	0.123	34.71
B20	813.98	4.08	03	13	02	4.36	0.28	57	0.107	38.13
B21	795.99	2.77	03	13	02	4.82	2.05	56	0.120	23.08
B22	798.91	3.74	03	15	02	4.45	0.71	57	0.109	34.31

B23	848.97	3.90	03	15	02	4.29	0.39	61	0.098	39.79
B24	953.07	5.18	02	16	03	4.37	-0.81	69	0.088	58.86
B25	846.05	4.34	03	13	02	4.85	0.51	60	0.113	38.40
B26	800.97	4.37	03	16	02	4.29	-0.08	56	0.107	40.84
B27	961.18	4.12	04	19	02	4.72	0.6	67	0.098	42.04
B28	961.18	4.12	04	19	02	4.32	0.2	67	0.090	45.77
C1	957.21	3.92	03	17	02	4.60	0.68	68	0.095	41.26
C2	797.00	4.17	02	14	02	4.58	0.41	57	0.112	37.23
C3	839.08	5.36	02	14	03	5.13	-0.23	60	0.119	46.20
C4	731.93	5.08	02	13	03	4.33	-0.75	52	0.116	43.79
C5	1061.32	5.20	02	18	03	5.26	0.06	76	0.097	53.61

4. Quantitative structure-activity relationships studies

The field of quantitative structure–activity relationships (QSARs) deals with development of predictive models correlating biological activity of a compound with its physicochemical properties [74]. The quantitative approach depends upon expression of a structure by numerical values and then relating these values to the corresponding changes in the biological activity by using statistical methods [75]. The series of fifty macrolides derivatives was used for multi linear regression model generation using the SPSS software package. Different physicochemical descriptors were used as independent variables and were correlated with anti-TB activity (pIC_{50}) Pearson's correlation matrix has been performed on all descriptors. The analysis of the matrix revealed five descriptors for the development of MLR models. The values of the descriptors used in MLR analysis are presented in Tables 4.9 and 4.10.

The correlation between the biological activity (IC_{50}) and the descriptors can be expressed by the following relation:

$$pIC_{50} = -3.785 - 0.036 \times \text{Logp} + 0.006 \times \text{Mass} + 41.429 \times \text{LE} - 0.041 \times \text{HBD}$$

To derive this equation, 50 Compounds were considered. In this equation, the negative coefficients of logp and HBD explain that any increase in hydrogen bond donors or logp of the compounds causes a decrease in the biological activity.

The values of fraction variance, r, may vary between 0 and 1.

QSAR models having r 0.6 <^{2}will only be considered for validation. Here, r is equal to 0.952 and r^2 =0.907 , which allows us to indicate firmly the correlation between the independent variables with respect anti-TB activity. The F-value has found to be statistically significant at % 95level, since the obtained F value (of 109.268) is relatively high.

The positive value of quality factor (Q = 8.424) for this QSAR model suggests its high predictive power and lack of over fitting.

In order to confirm the validity of the predictive power of selected MLR models, the leave-one-out technique (LOO technique) was used. The developed model was validated by calculation of the following statistical parameters: predicted residual sum of squares (PRESS), total sum of squares deviation (SSY), S_{PRESS}(predicted squares error) the predictive error of the coefficient of correlation (PE) and cross-validated correlation coefficients (R^2_{adj} and R^2cv). We computed the following cross-validation parameters:

PRESS = 0.573, SSY = 6.137, PRESS/SSY = 0.093, S_{PRESS} =0.107 , R^2_{cv} = 0.907 , R^2_{adj} =0.898 and 6 × PE = 0.017.

PRESS is a good estimate of the real predictive error of the model. If PRESS is smaller than the sum of the squares of the response values (SSY), then the model can be considered statistically significant [76] ,which is the case presently. The ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of a new compound. This ratio is equal to 0.093, which is smaller than 0.4, indicating that we have a reasonably good model as established in Ref [77] . Also, the high values of r^2_{cv} and r^2_{adj} are essential criteria for the best qualification of the QSAR model.

Our results for these two values are 0.907 and 0.898, respectively. Finally, we show that the condition r > 6 × PE is satisfied. Again, this confirms the good predictive power of the model. Figure 3.6 shows the plots of linear regression of predicted versus experimental values of the biological activity outlined above. The plots for our model show a good correspondence with experimentally reported data (r^2 = 0.907) .The plot of residuals of predicted values of the biological activity pMIC against the experimental values does not show any systematic error (Figure 4.7) positive and negative residuals are randomly distributed. Thus, this confirms further that our QSAR model can be successfully applied to predict anti-TB activity.

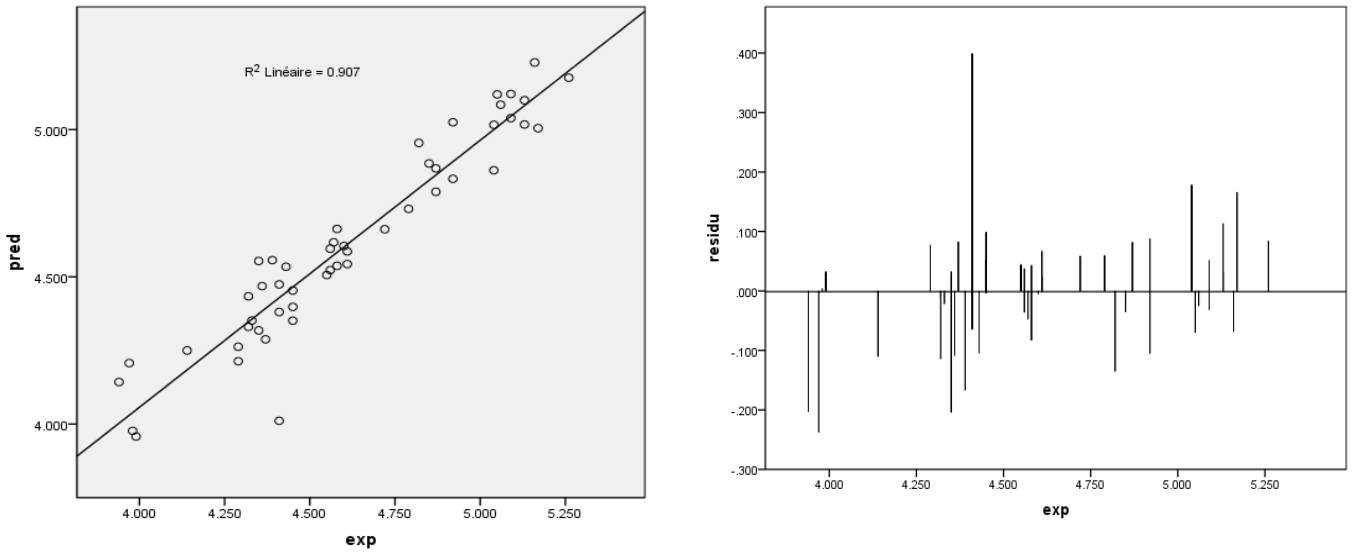


Figure 4.7 Left: Plots of predicted (y-axis) versus experimentally (x-axis) observed pIC50. Right: Plots of residual against experimental values pIC50

5. Conclusion

The present study, offers the ability to guide design and selection to quickly identify compounds from the 14-membered macrolide derivatives. Series that are likely to achieve outcome in the clinic and occupy a strong market position. Also, it provides a discussion of several qualitative approximations of the structure activity/property relationship.

The compounds A1-C5 doesn't obey the Lipinski rule, suggesting that these compounds theoretically would have problems with oral bioavailability.

The QSAR model is used to predict inhibitory activity of the macrolide derivatives investigated and close agreement between experimental and predicted values was obtained.

$$pIC_{50} = -3.785 - 0.036 \times \text{Logp} + 0.006 \times \text{Mass} + 41.429 \times \text{LE} - 0.041 \times \text{HBD}$$

The validity of the model has been established by the determination of suitable statistical parameters. A low residual activity and a high cross-validated values are obtained. These suggest a good predictive ability of the developed QSAR model.

Also, they indicate that the activity of the studied macrolide derivatives can be successfully modeled using various molecular descriptors.

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General Conclusion

In this work, we applied the methods of computational chemistry on 14-membered macrolide molecules, this study include:

- Geometric, electronic structure and substituent effects.
- Computational study of structure -property relationships (SPR) for 14-membered macrolide derivatives.
- QSAR modeling of some 14-membered macrolide derivatives

Firstly, the results demonstrate that the structural and electronic comparison of nucleus of 14-membered macrolides present similar results using different calculation methods: semi-empirical method (PM3) and Ab initio quantum methods.

The 4, 10-di-methyl macrolide is predicted to be the most reactive with least HOMO-LUMO energy gap (4.4141) of all macrolide systems substituted by di-methyl, and in the substituted di-fluorine group category, the 4,10-fluorinemacrolide has smaller HOMO-LUMO energy gap (4.2463). depicts high chemical reactivity of the compounds

Then, the results of research on the structure-property relationship (SPR) of the 14-membered macrolides derivatives series have shown that structural units involved in the biological activity.

The compounds A1, A11 and B8 which have higher values of partition coefficient. These lipophilic compounds penetrate in various membranes, including cellular membranes as well as tissues with high lipoid content, to arrive at the receptor site. Compound B27 has important hydration energy leading to a better distribution in fabrics.

Molecular properties such as membrane permeability and oral bioavailability are usually associated with some basic molecular descriptors, such as log P (partition coefficient), molecular weight (MW), and the acceptors and donor for hydrogen bonding in a molecule. Using these molecular properties, Lipinski established a controversial rule for drug design.

The compounds A1-C5 doesn't obey the Lipinski rule, suggesting that these compounds theoretically would have problems with oral bioavailability.

Finally, Quantitative structure activity relationship (QSAR) studies were performed on a series of 14-membered macrolides as antibiotiques, multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally for the prediction of activity. The developed models were cross-validated by the ‘leave one out’ technique as well as by the calculation of statistical parameters.

The QSAR model is used to predict inhibitory activity of the macrolide derivatives investigated and close agreement between experimental and predicted values was obtained.

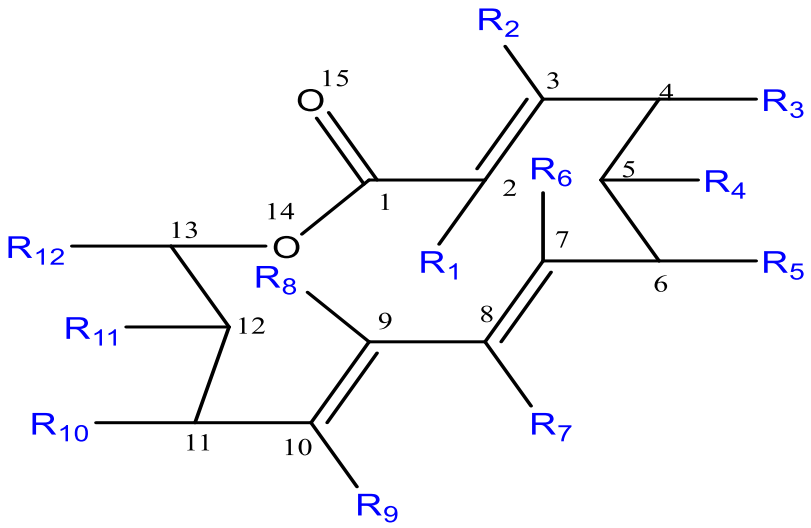
The validity of the model has been established by the determination of suitable statistical parameters. A low residual activity and a high cross-validated values are obtained. These suggest a good predictive ability of the developed QSAR model.

Also, they indicate that the activity of the studied macrolide derivatives can be successfully modeled using various molecular descriptors.

Appendix (A)

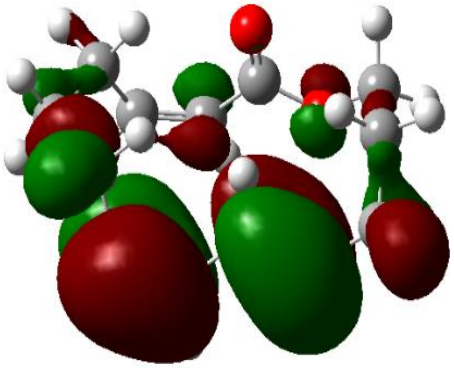
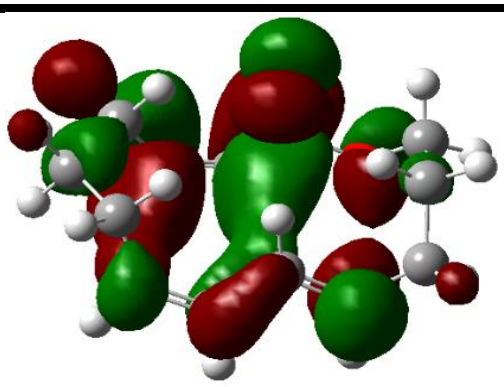
The frontier molecular orbitals HOMO and LUMO of *14- Membered Macrolide* derivatives

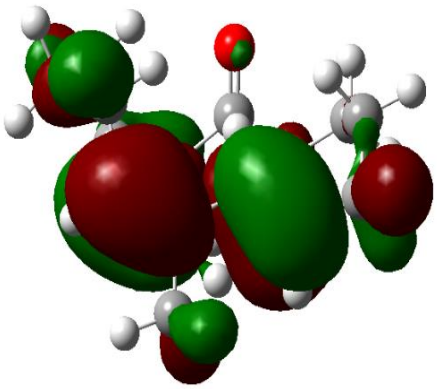
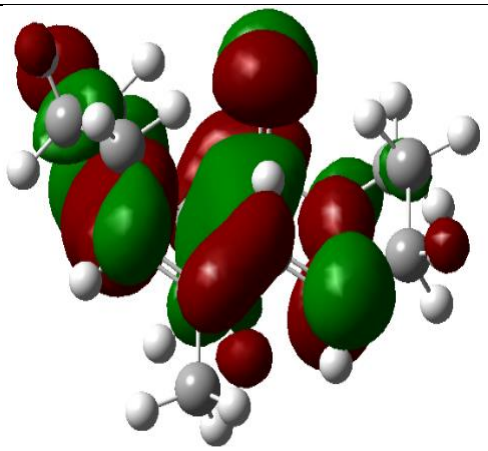
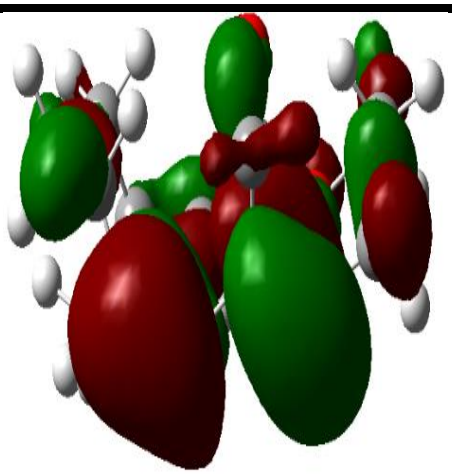
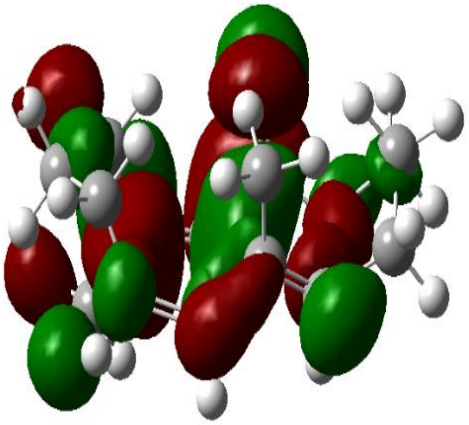
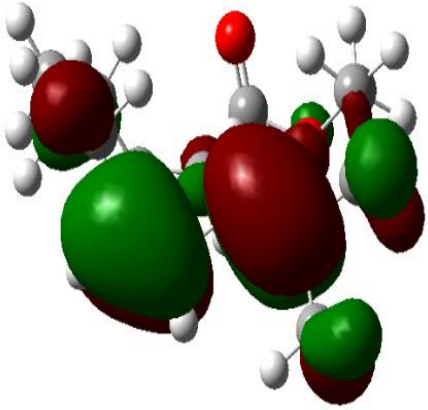
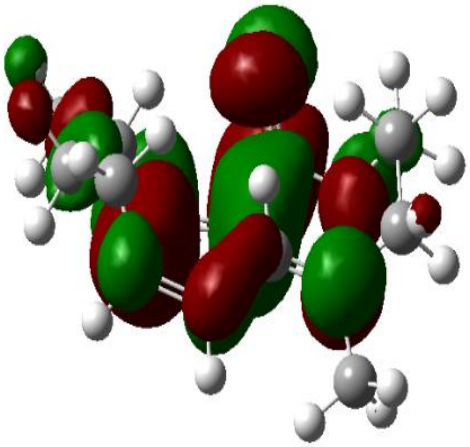
The frontier molecular orbitals HOMO and LUMO of 14-membered Macrolide derivatives (series 1)

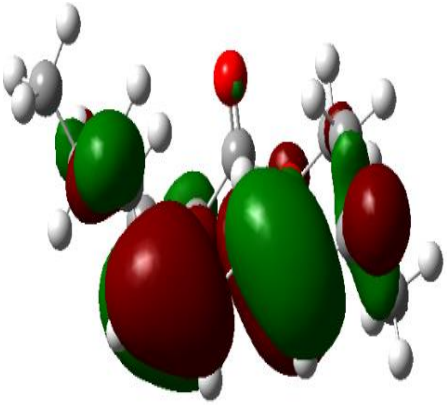
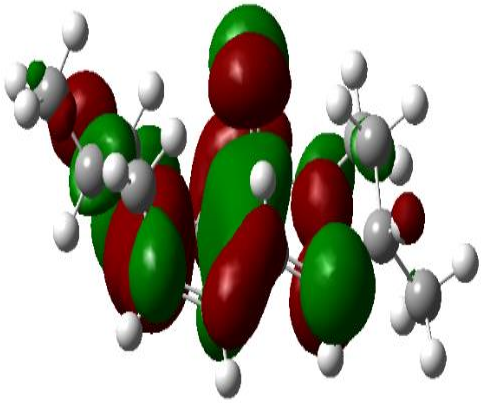
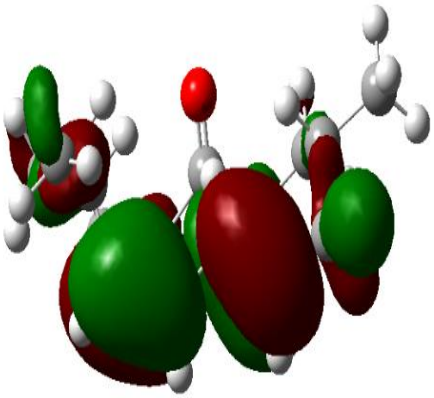
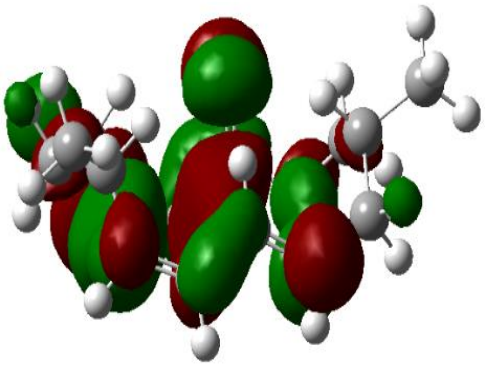
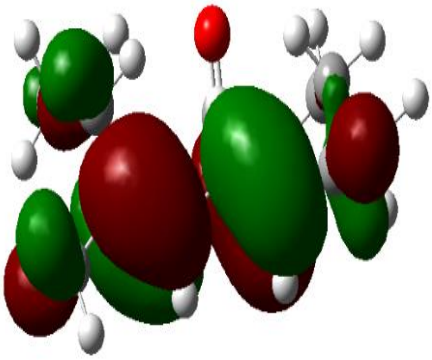
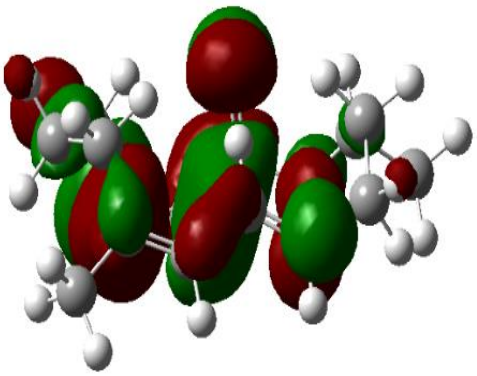


Comp.1 **R1=R2=R3=R4=R5=R6=R7=R8=R9=R10=R11=R12=H**

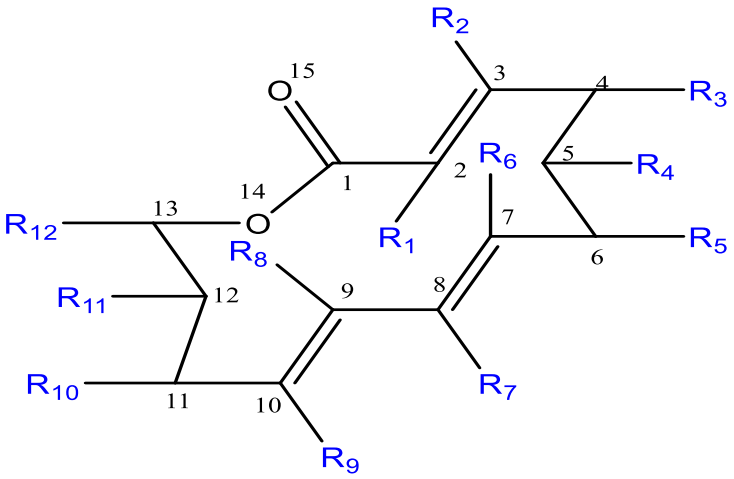
Comp.2 **R1=R7=CH_3, R2=R3=R4=R5=R6=R8=R9=R10=R11=R12=H**
Comp.3 **R2=R8=CH_3, R1=R3=R4=R5=R6=R7=R9=R10=R11=R12=H**
Comp.4 **R3=R9=CH_3, R1=R2=R4=R5=R6=R7=R8=R10=R11=R12=H**
Comp.5 **R4=R10=CH_3, R1=R2=R3=R5=R6=R7=R8=R9=R11=R12=H**
Comp.6 **R5=R11=CH_3, R1=R2=R3=R4=R6=R7=R8=R9=R10=R12=H**
Comp.7 **R6=R12=CH_3, R1=R2=R3=R4=R5=R7=R8=R9=R10=R11=H**

Comp.	HOMO	LUMO
1		

2		
3		
4		

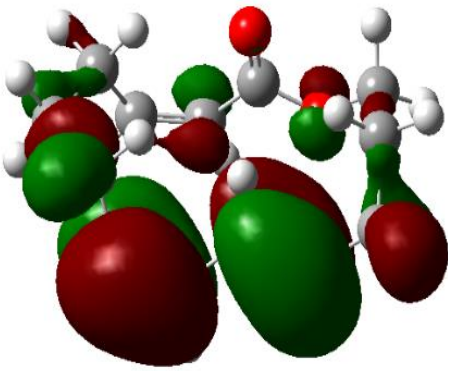
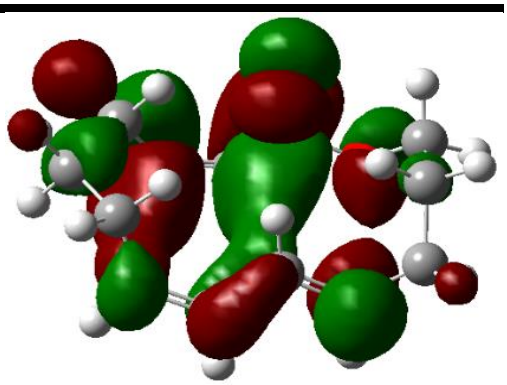
5		
6		
7		

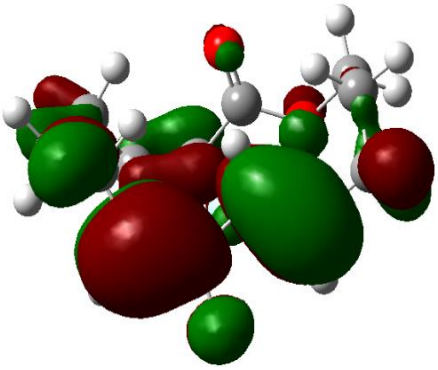
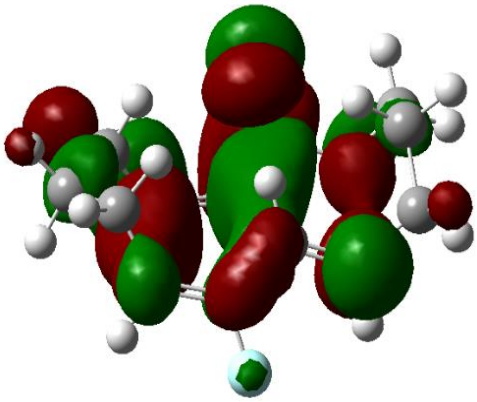
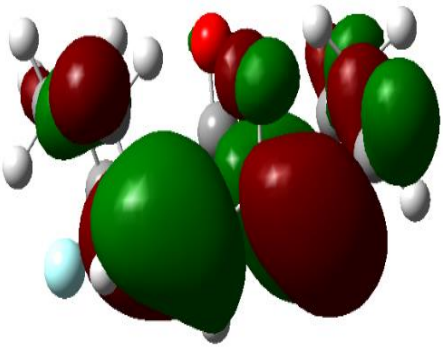
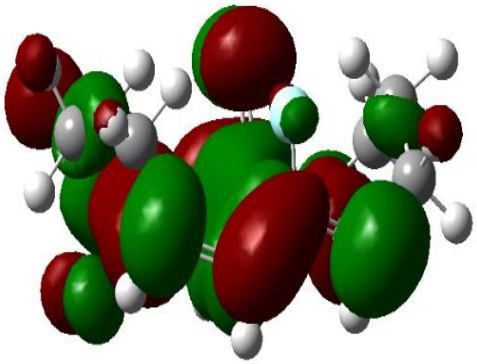
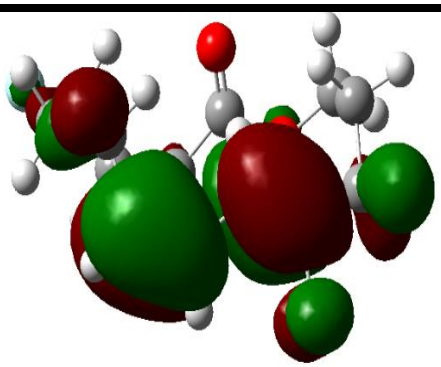
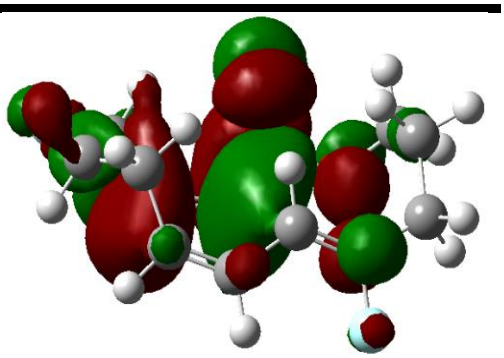
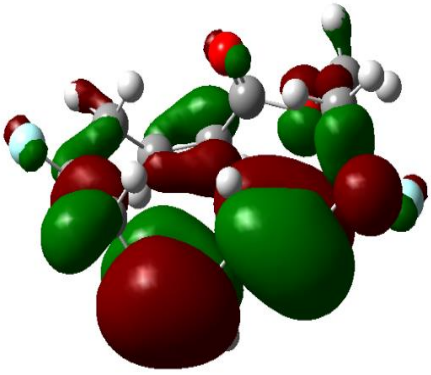
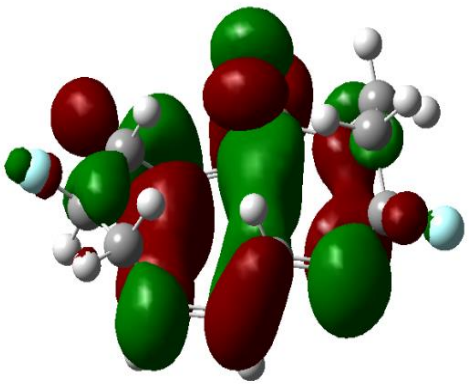
The frontier molecular orbitals HOMO and LUMO of 14-membered Macrolide derivatives (series 2)

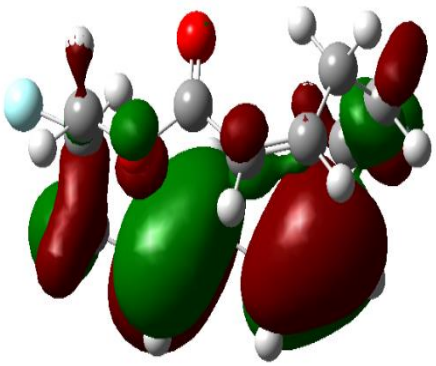
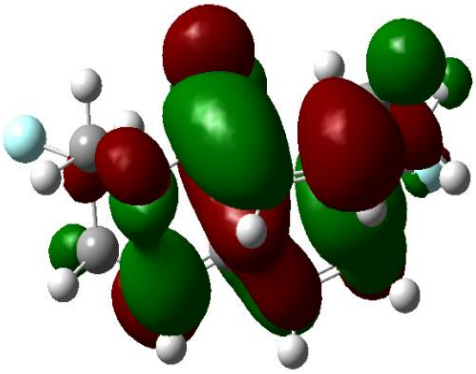
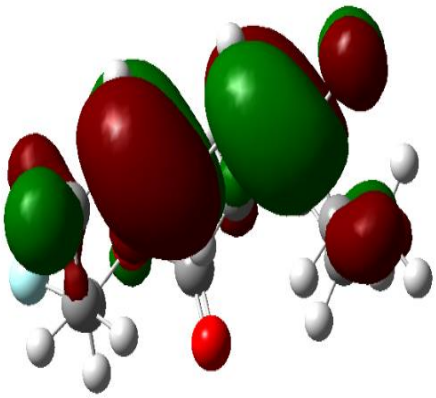
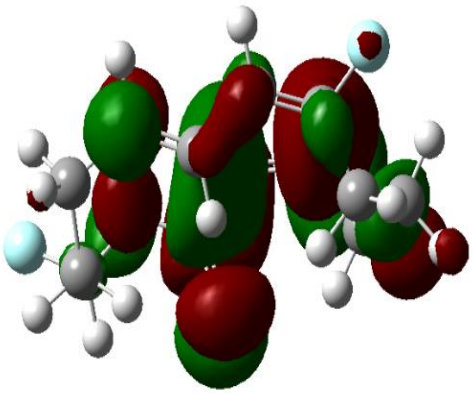


Comp.1 **R1=R2=R3=R4=R5=R6=R7=R8=R9=R10=R11=R12=H**

Comp.2 **R1=R7=F, R2=R3=R4=R5=R6=R8=R9=R10=R11=R12=H**
Comp.3 **R2=R8= F, R1=R3=R4=R5=R6=R7=R9=R10=R11=R12=H**
Comp.4 **R3=R9= F, R1=R2=R4=R5=R6=R7=R8=R10=R11=R12=H**
Comp.5 **R4=R10= F, R1=R2=R3=R5=R6=R7=R8=R9=R11=R12=H**
Comp.6 **R5=R11= F, R1=R2=R3=R4=R6=R7=R8=R9=R10=R12=H**
Comp.7 **R6=R12= F, R1=R2=R3=R4=R5=R7=R8=R9=R10=R11=H**

Comp.	HOMO	LUMO
1		

2		
3		
4		
5		

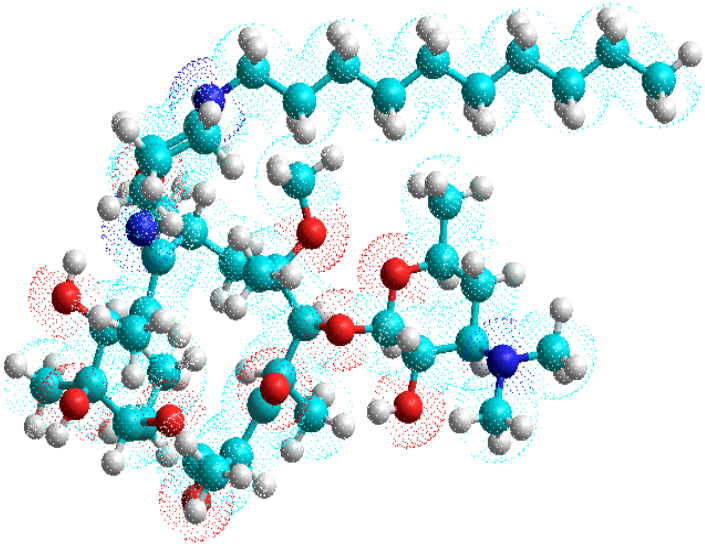
6		
7		

Appendix (B)

3D Structure of 14- Membered Macrolide derivatives

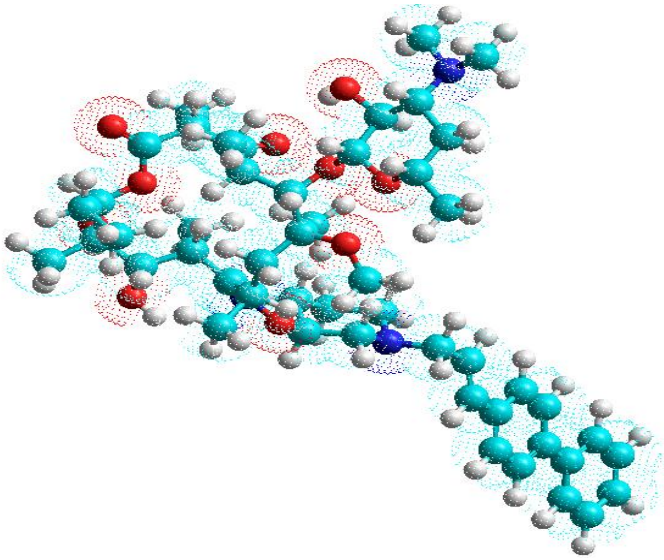
(HyperChem 8.03)

Compound A1



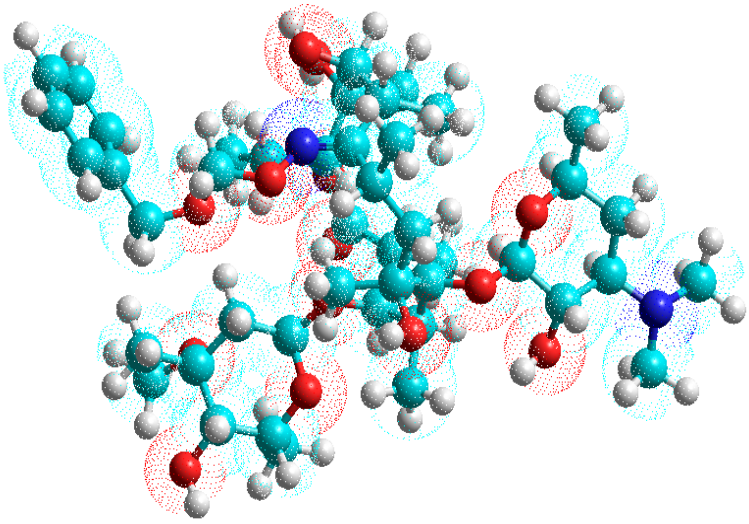
RU60887

Compound A2



RU61804

Compound A3



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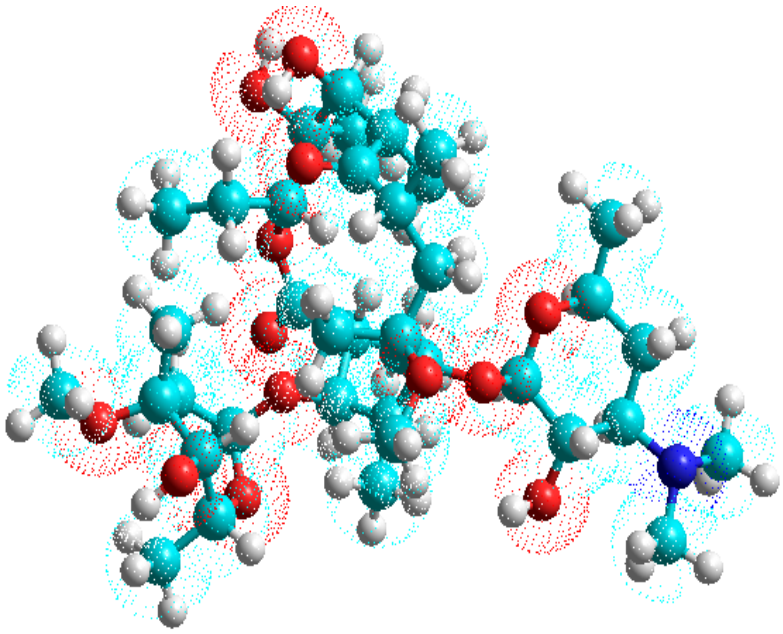
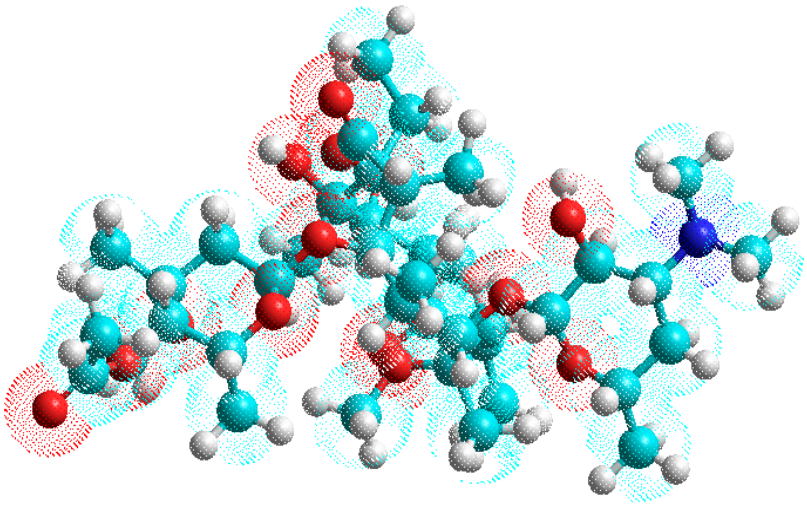
Compound A4



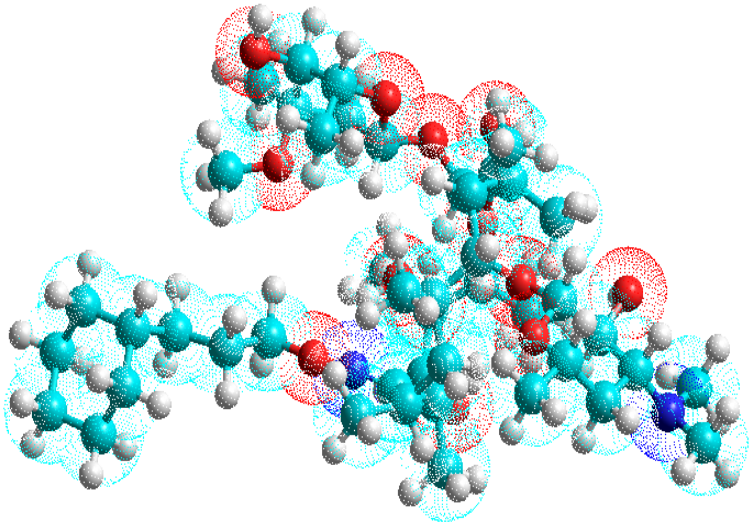
Clarithromycine

Compound A5



ITR054

Compound A6



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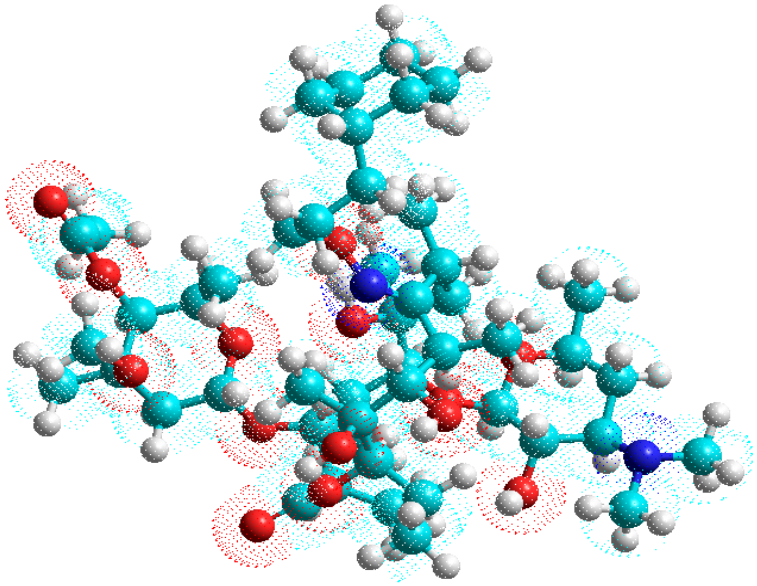
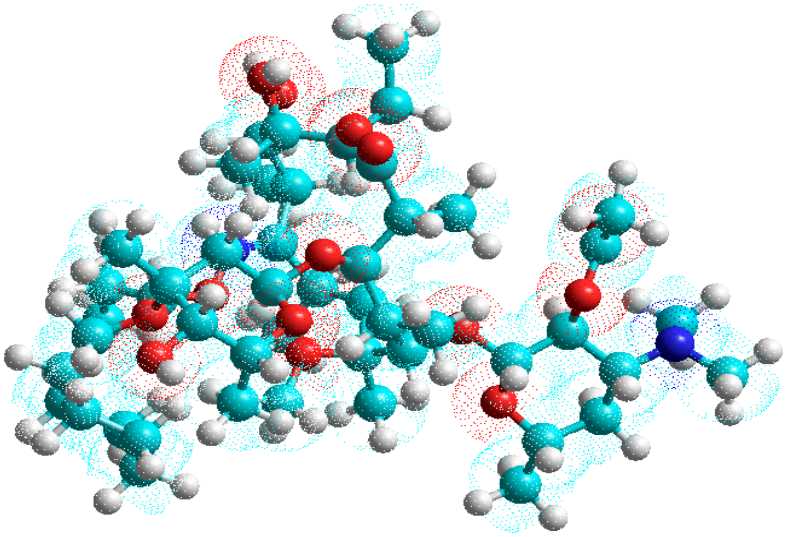
Compound A7



GI-448

Compound A8



ITR159

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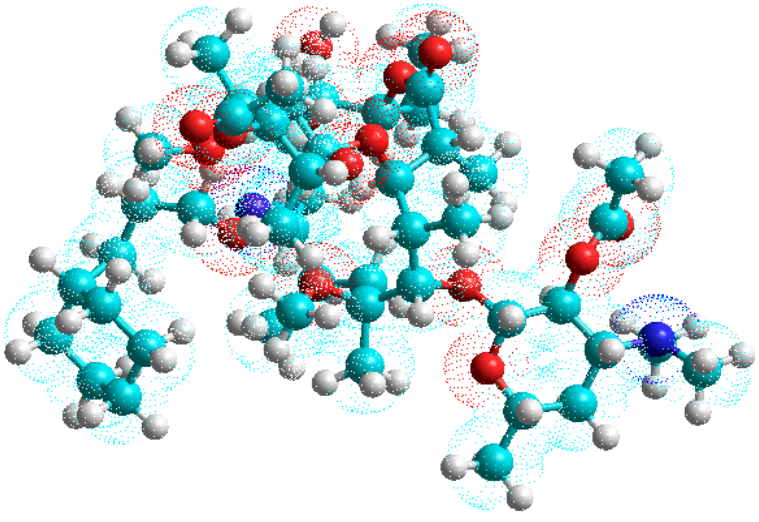

ITR160

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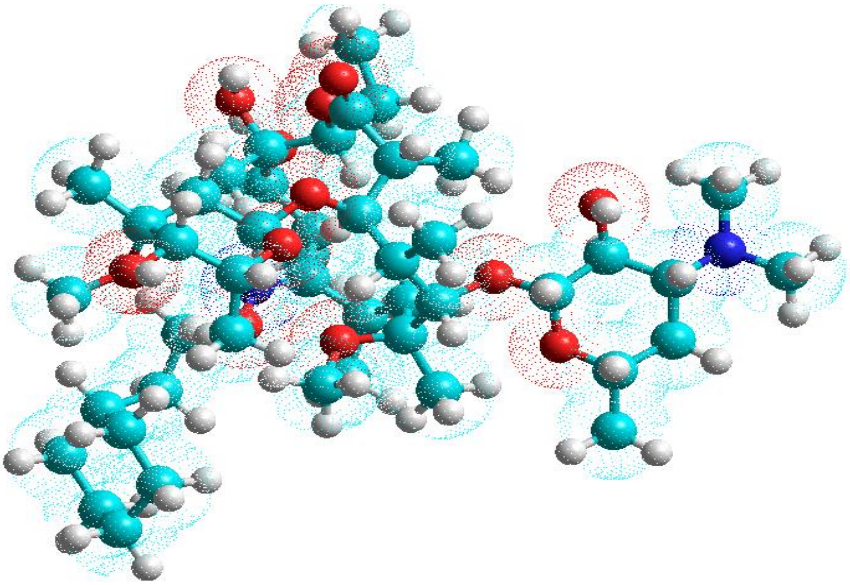

ITR077

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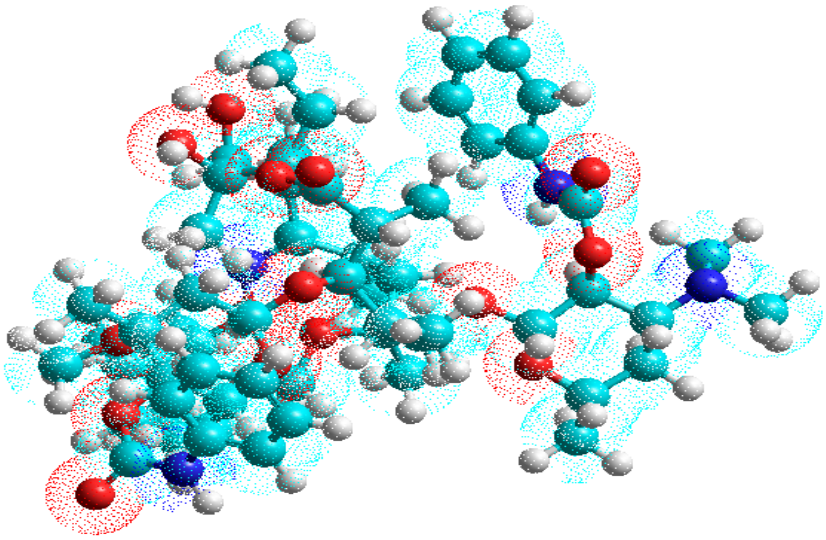

ITR120

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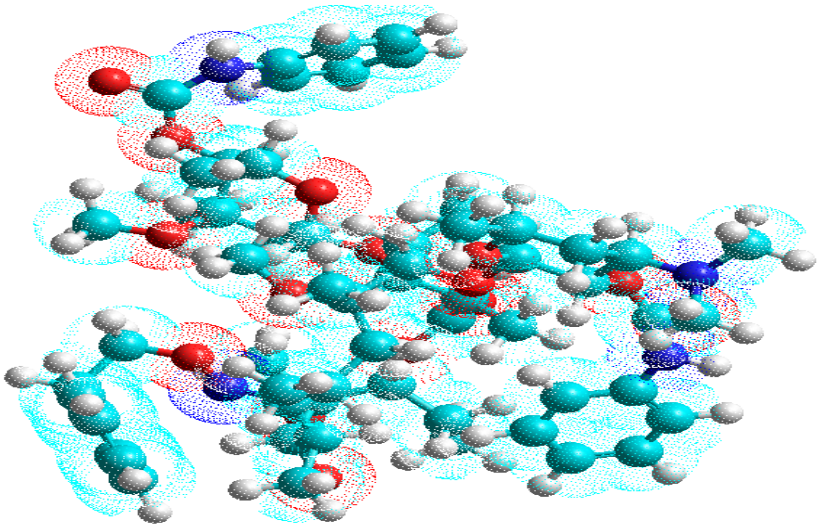

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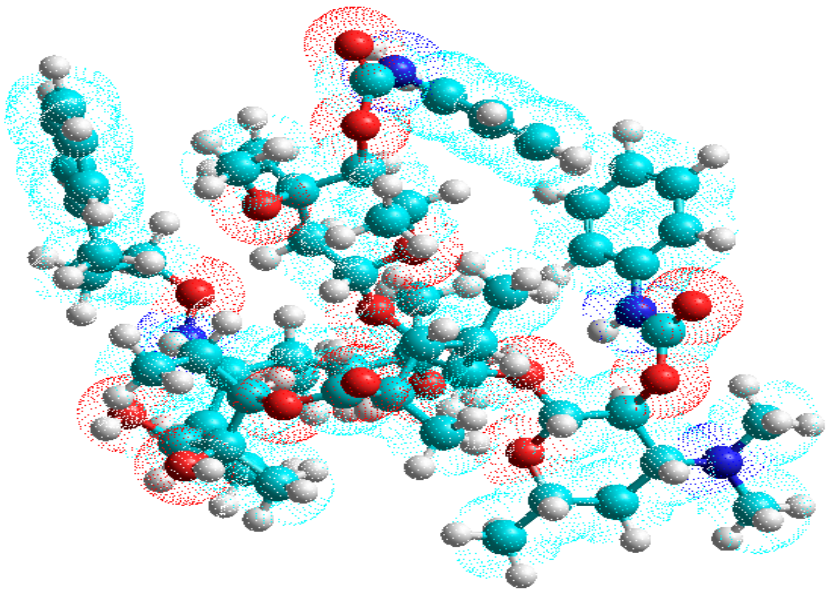

ITR138

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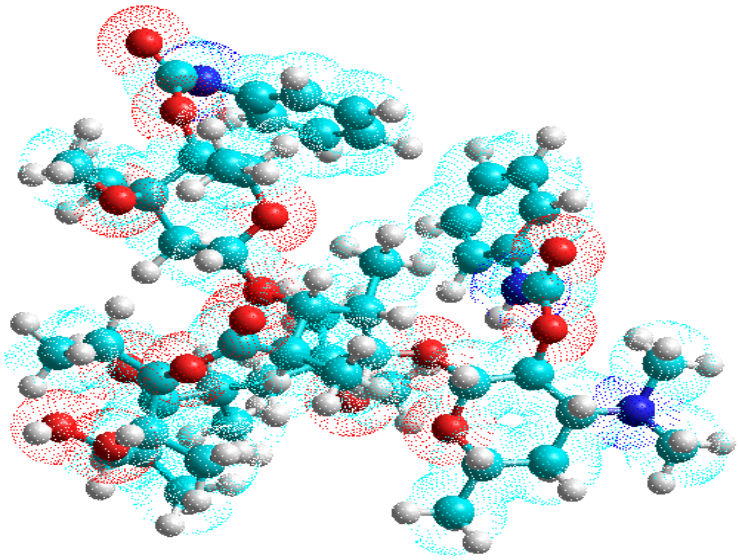

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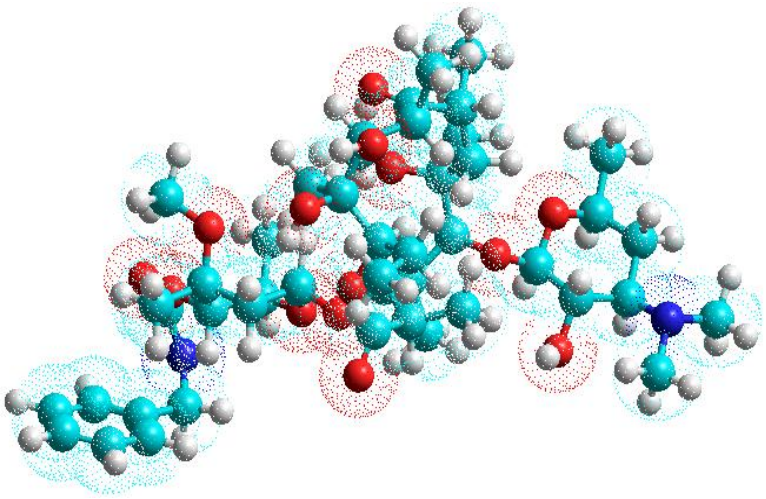

ITR083

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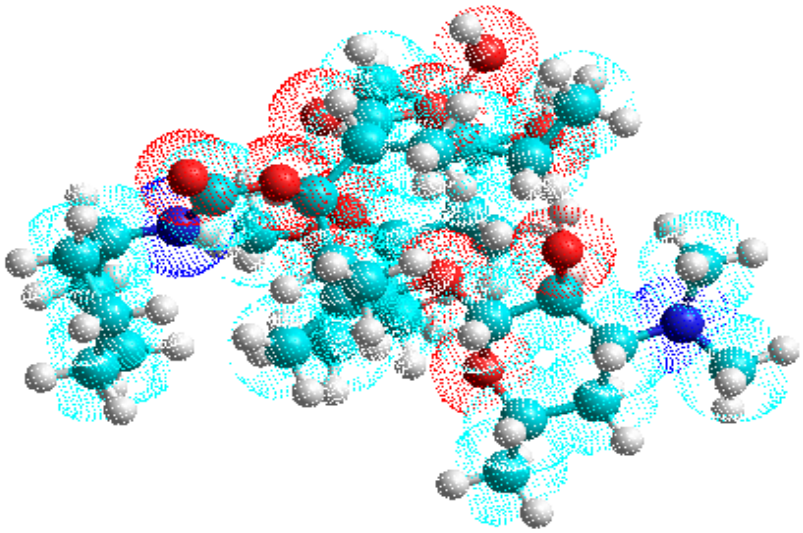

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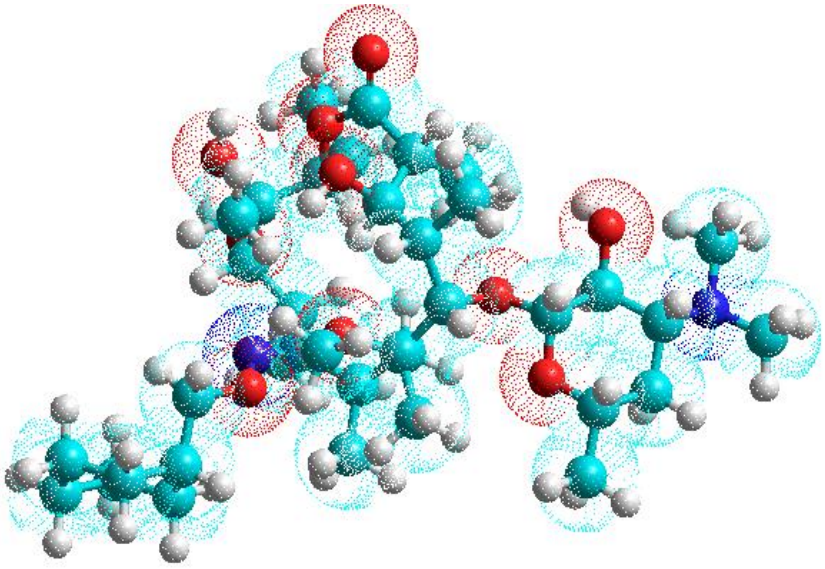

ITR157

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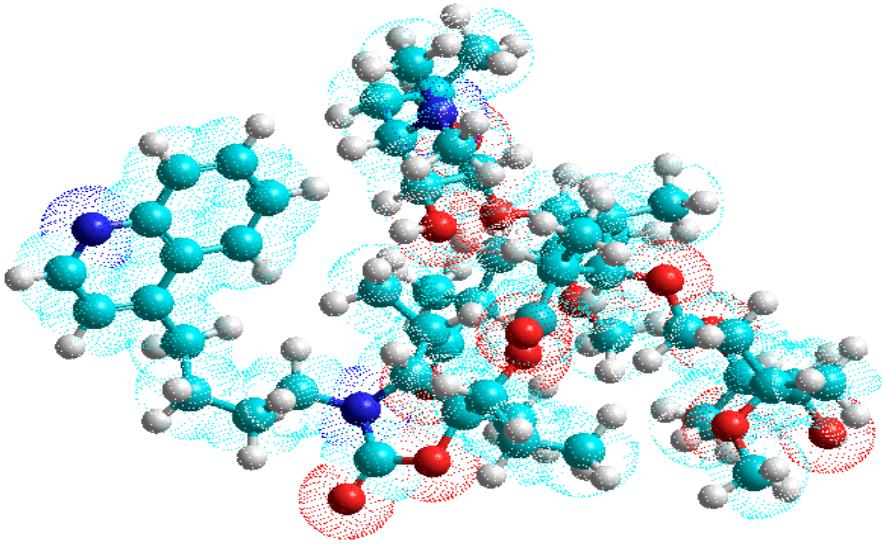

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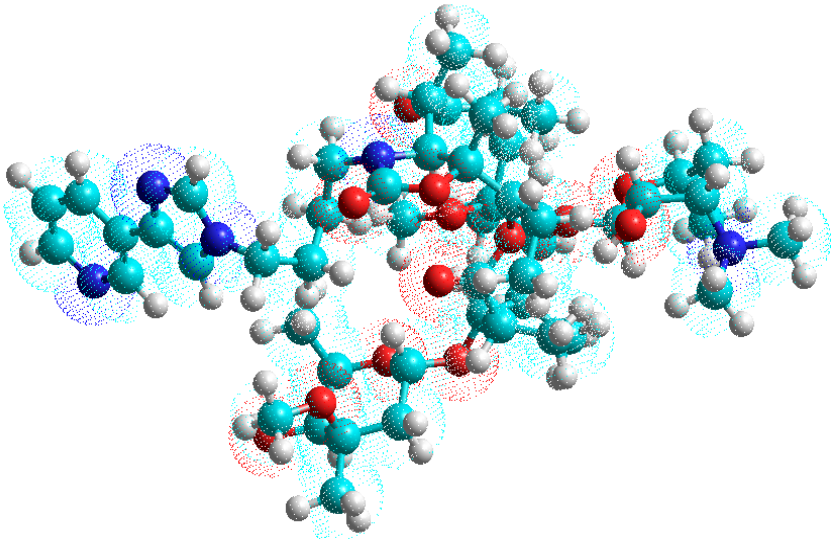

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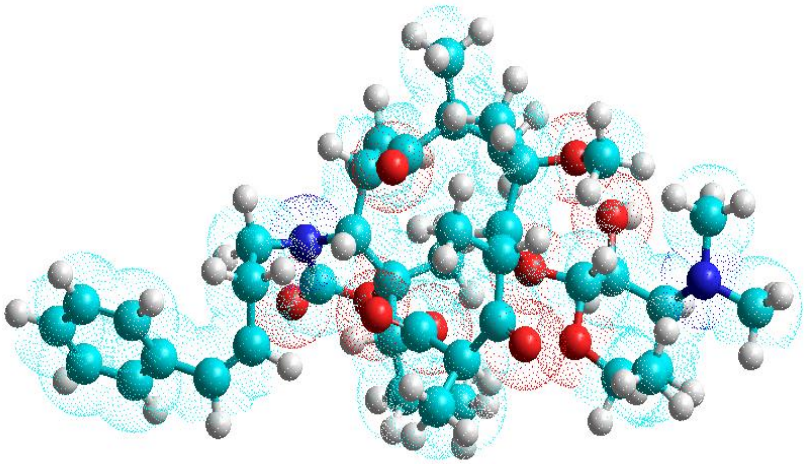

RU60856

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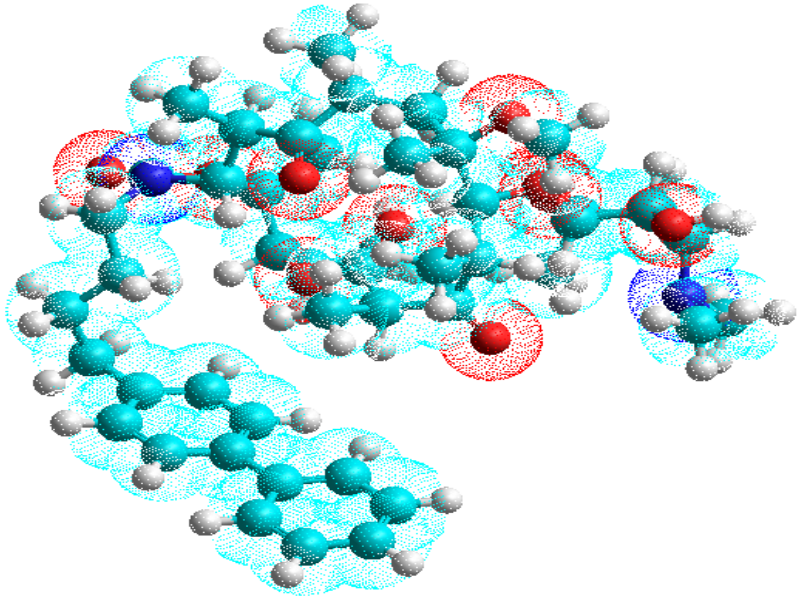

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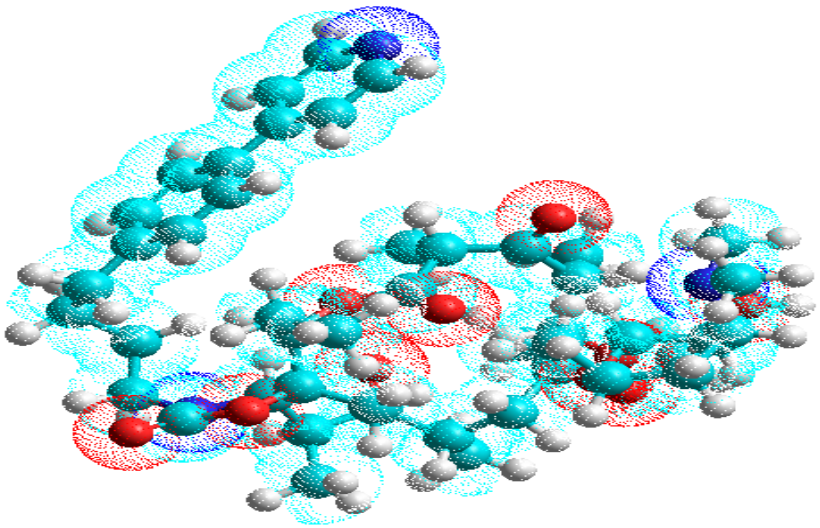

RU63013

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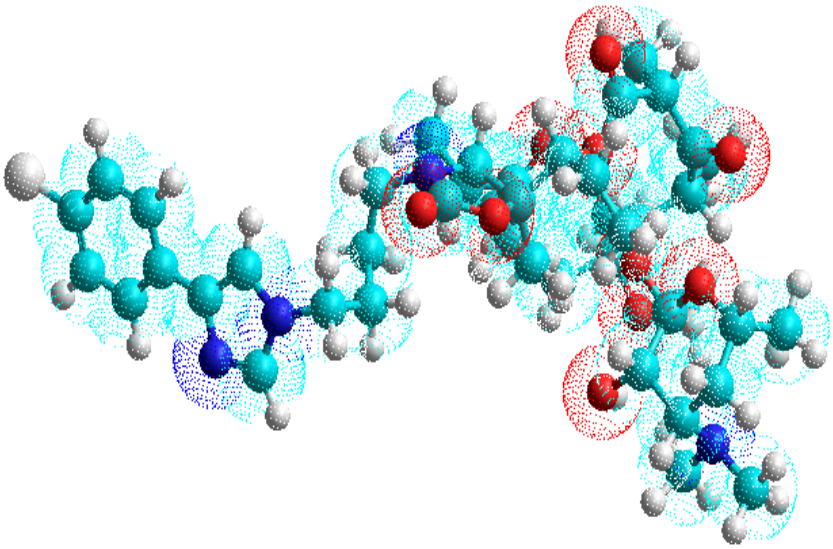

RU66898

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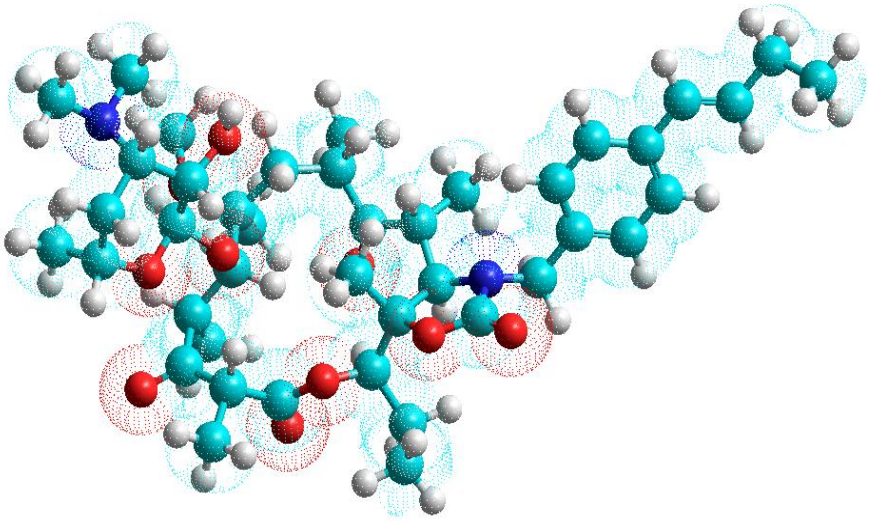

RU62041

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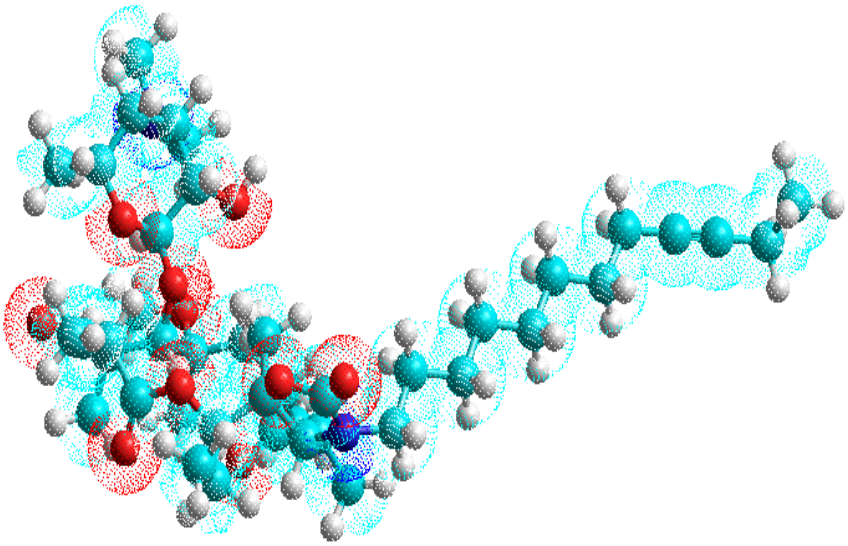

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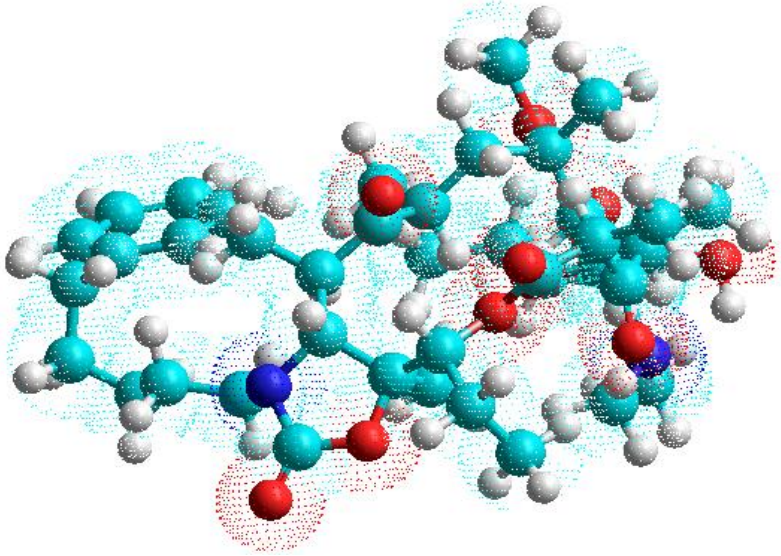
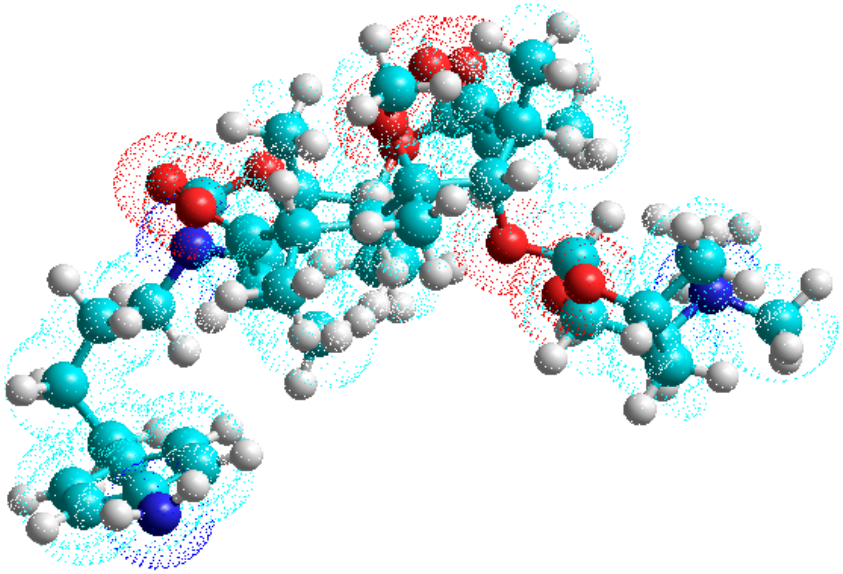


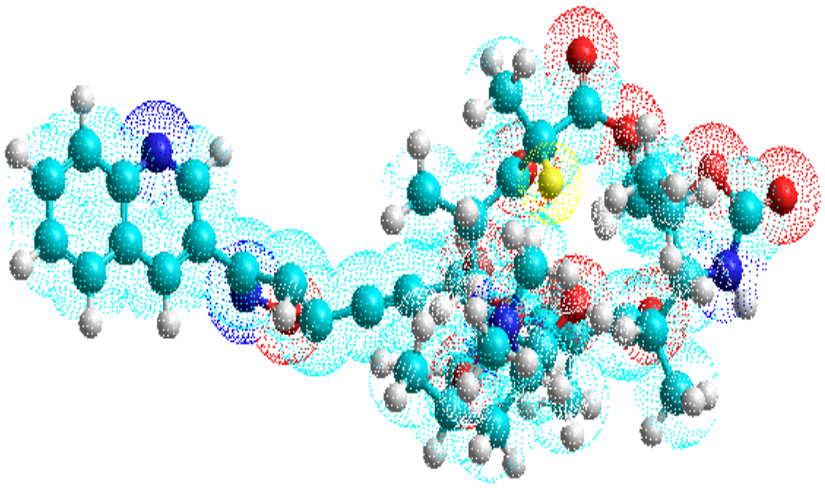
RU60849

Compound B10



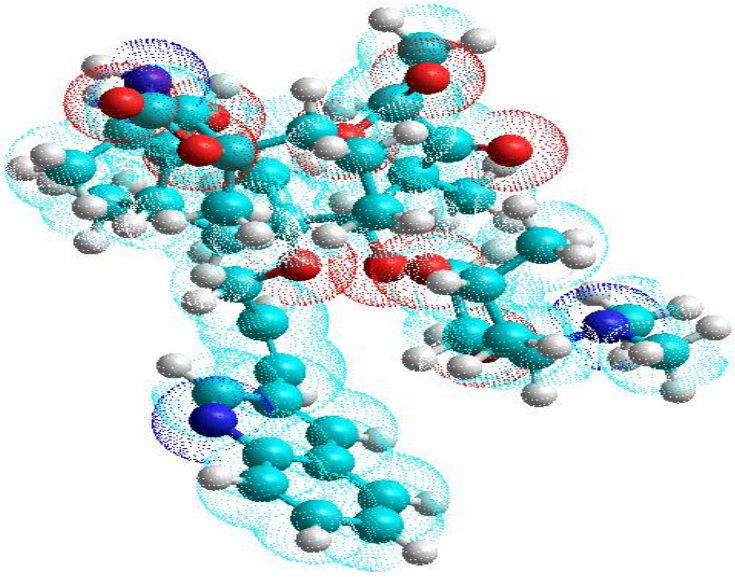
RU70332

Compound B11



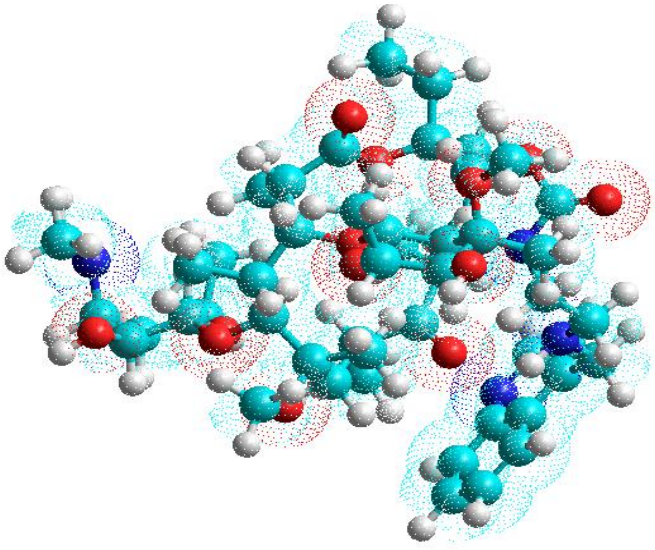
A323348

Compound B12



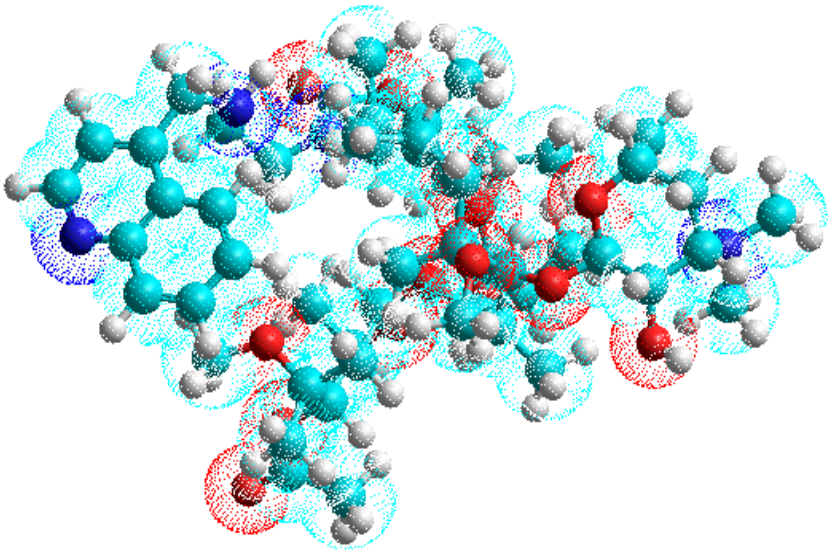
Cethromycine

Compound B13



ITR049

Compound B14



ITR048

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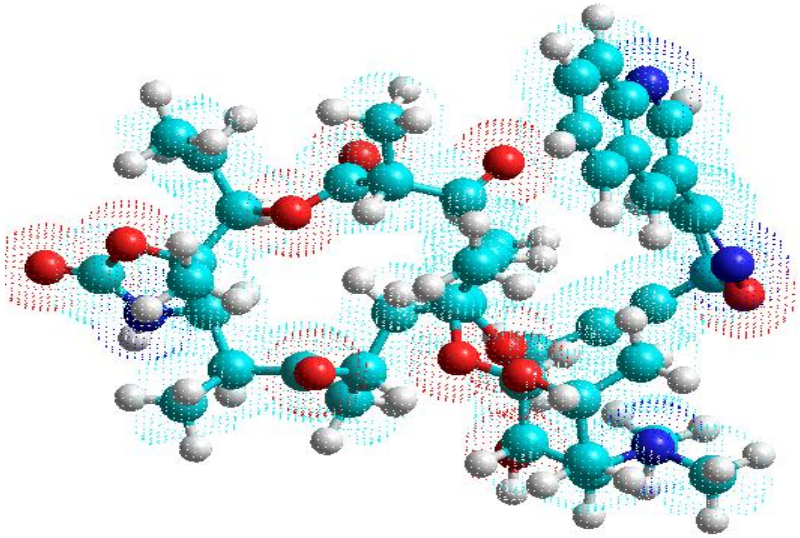

ITR250

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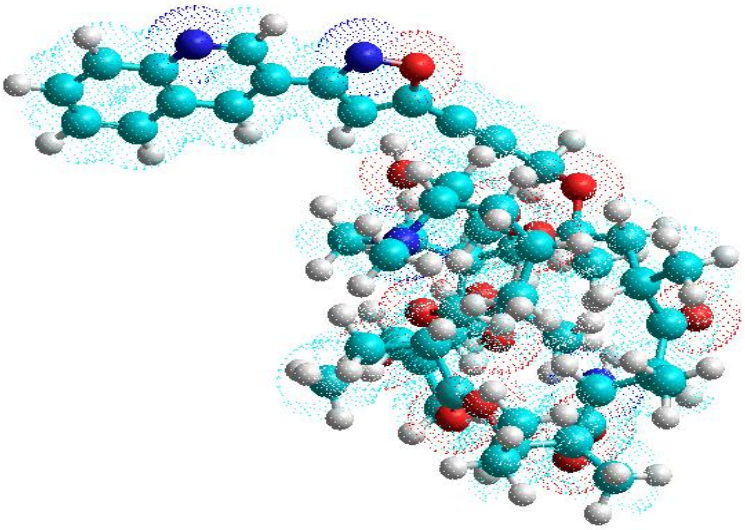

ITR286

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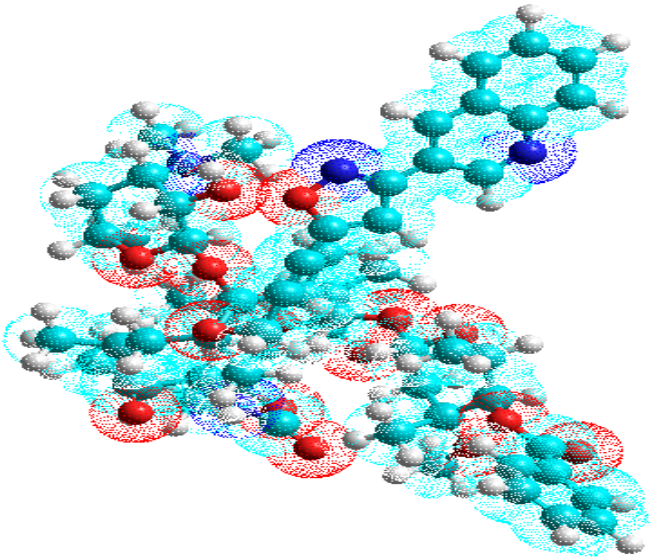

ITR258

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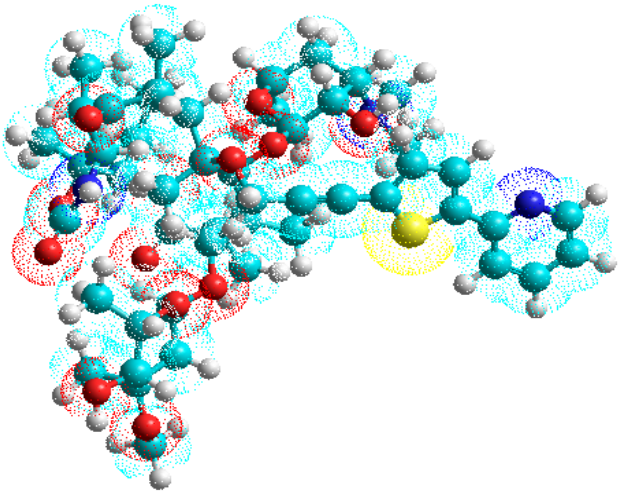

ITR285

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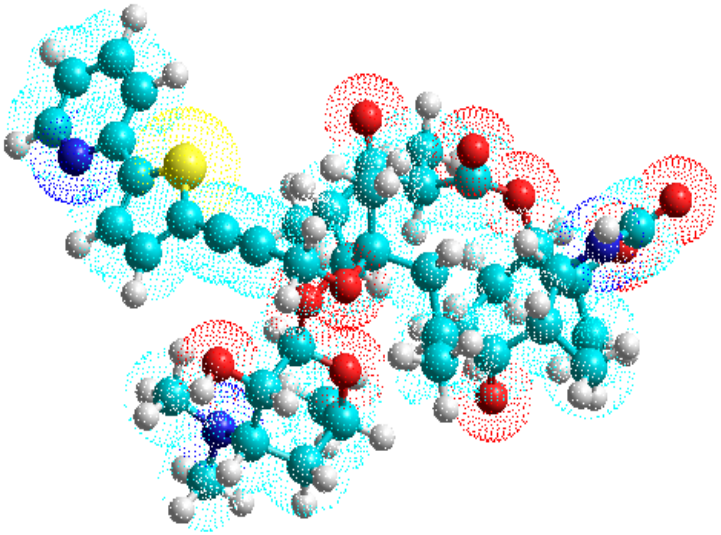

ITR248

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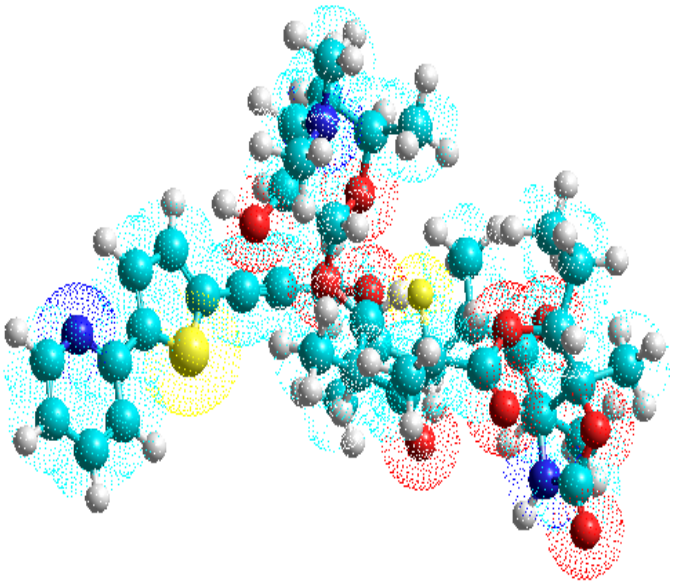

ITR278

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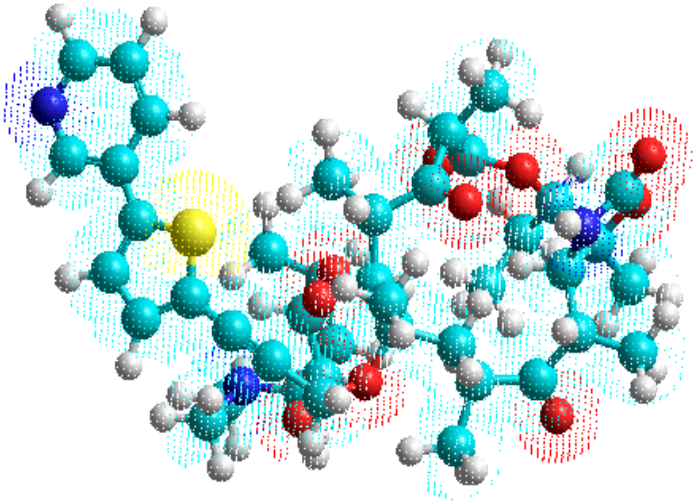

ITR257

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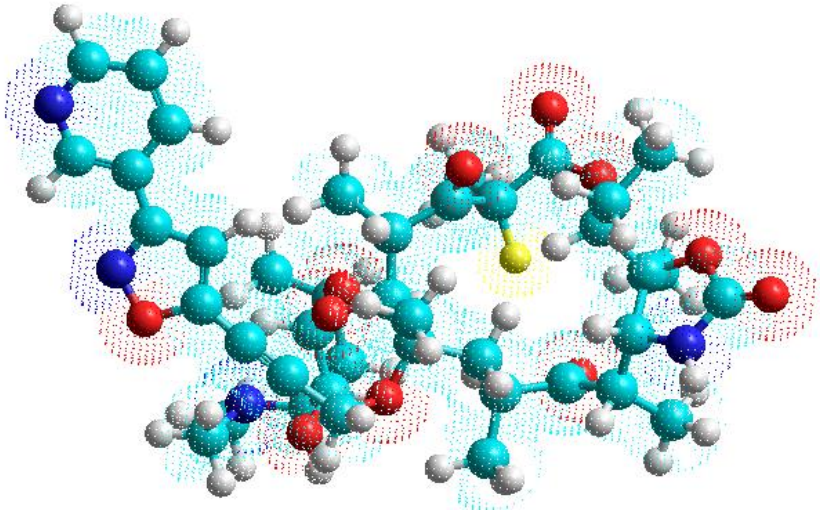

ITR273

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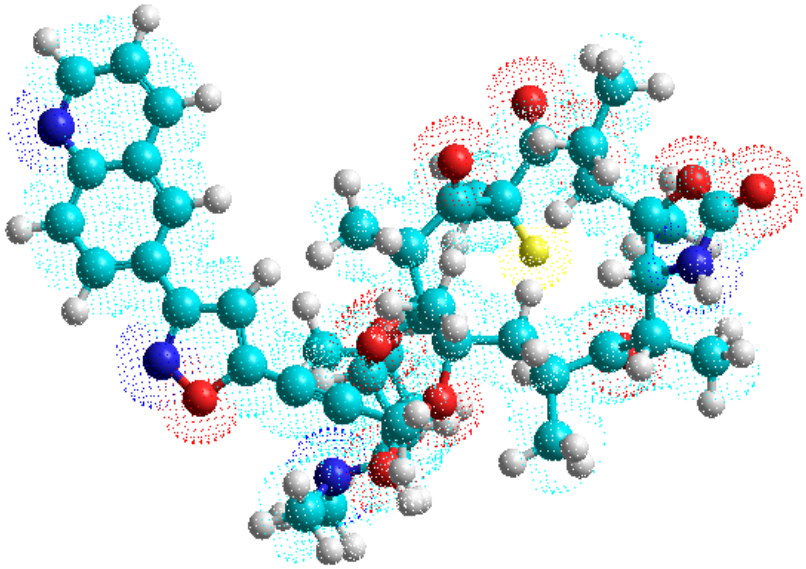

ITR266

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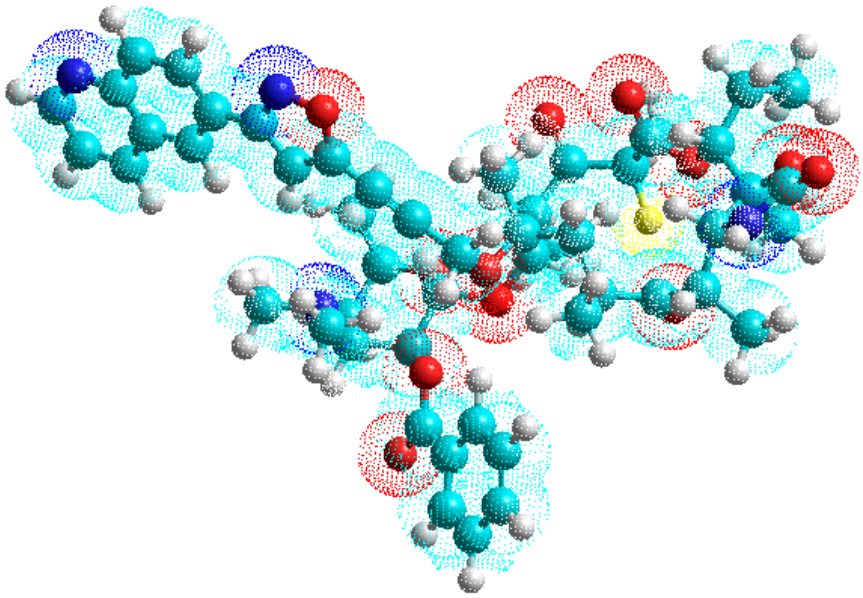

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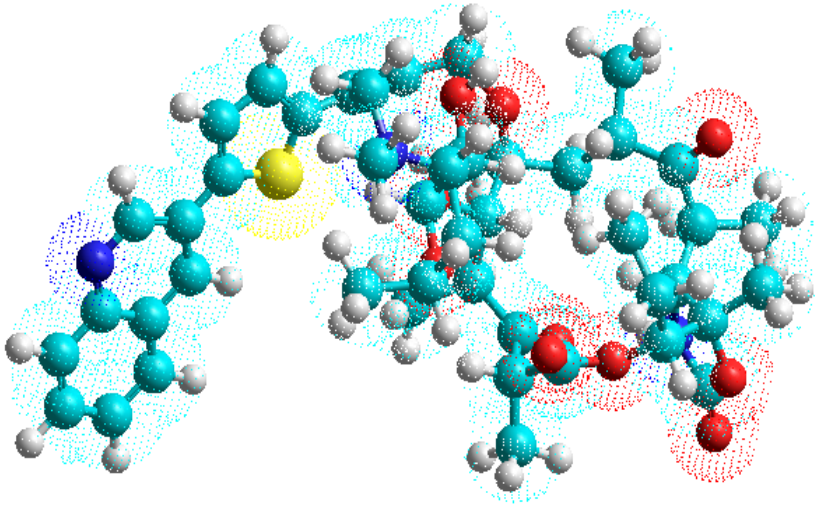

ITR275

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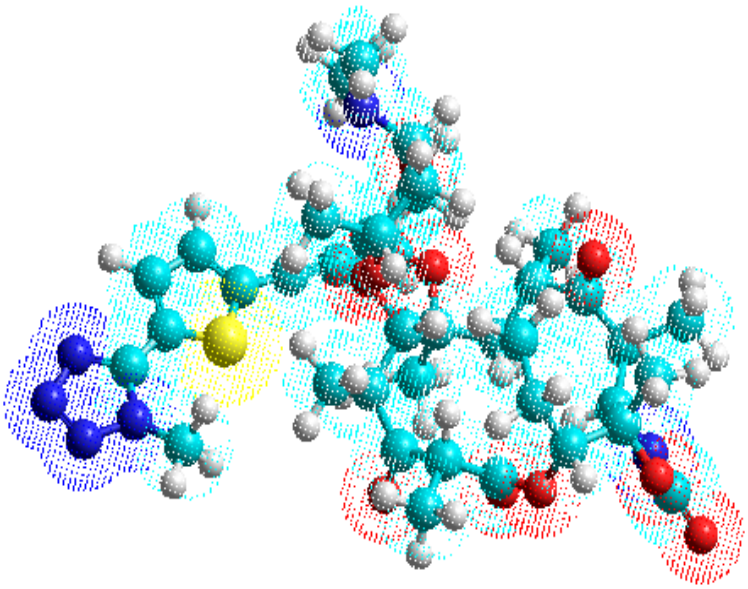

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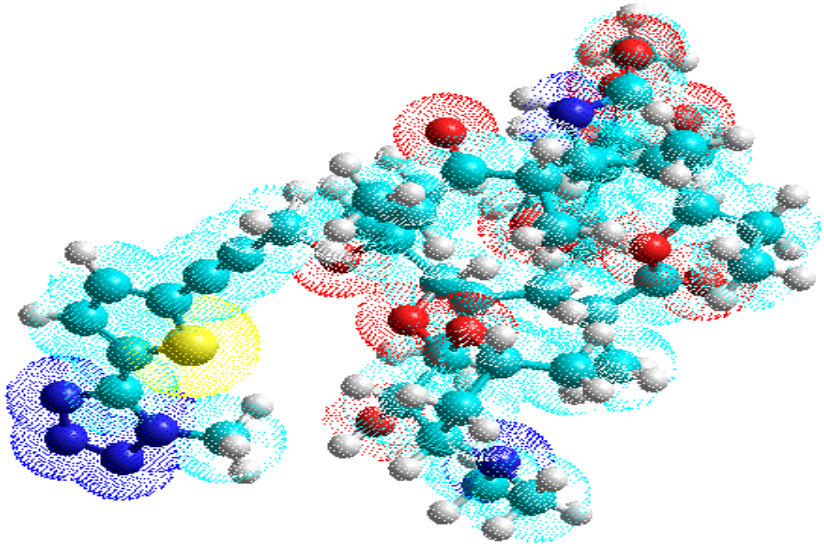
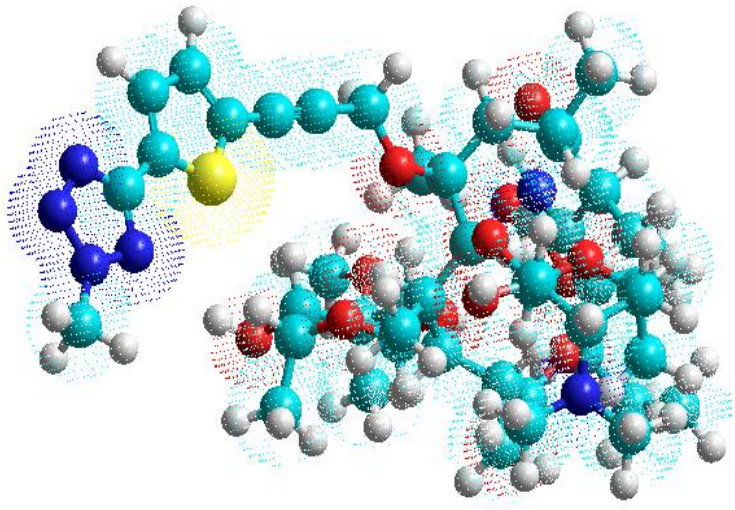


ITR270

Compound B28



ITR271

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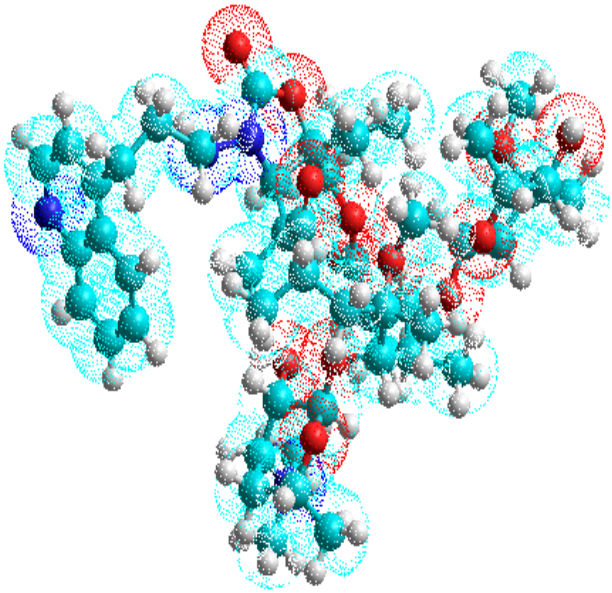

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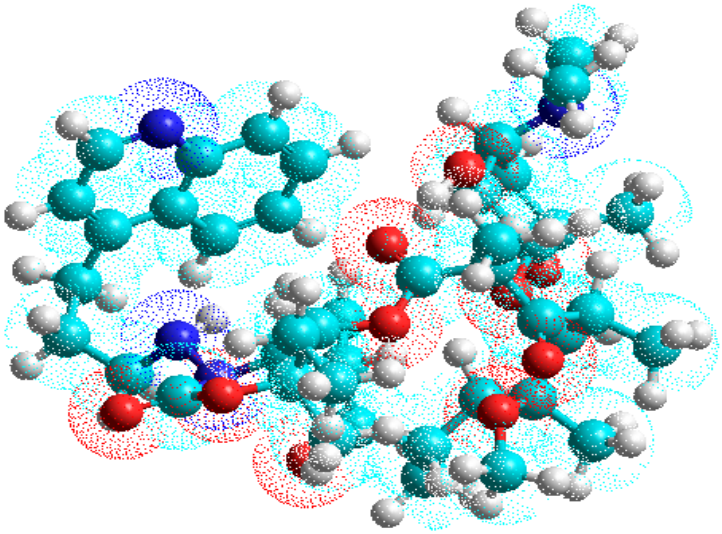
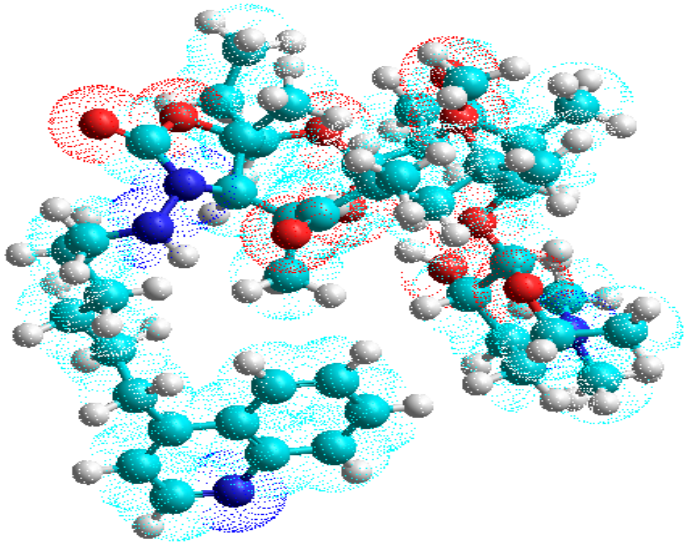


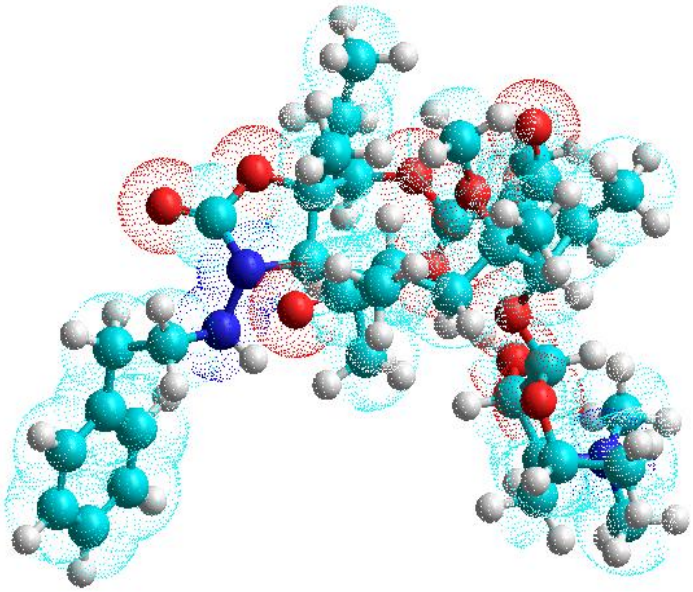
RU004

Compound C3



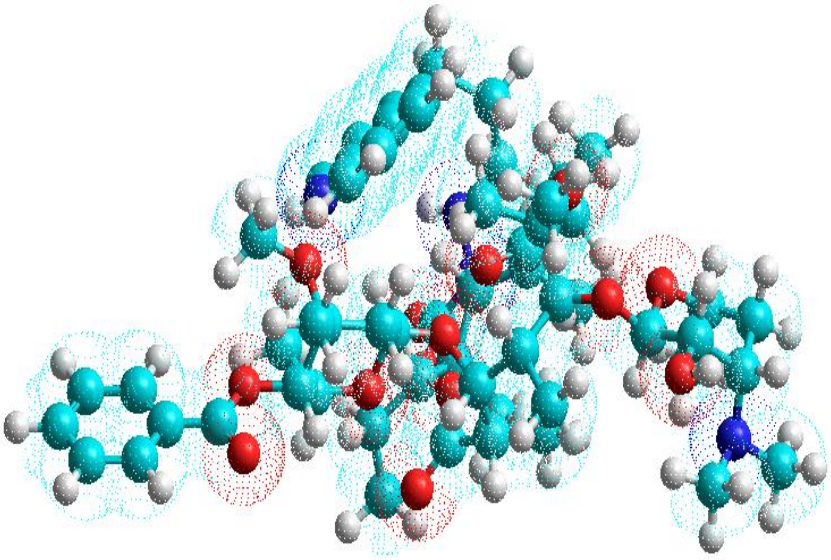
RU69697

Compound C4



RU70645 (Rifampin)

Compound C5



ITR053

الملخص :

في هذا العمل بحث أساسي و أصلي حول حلقة المكروليد ذات 14 ذرة و الهدف من ذلك هو توقع الفعالية والنشاط البيولوجي للمركب المدروس و مشتقاته .المعايير الهيكلية و الالكترونية لنواة المكروليد ذات 14 ذرة في حالتها الأساسية و في حالة وجود المستبدل تم حسابها باستخدام الطرق التالية : MM+, ab initio/HF(STO- 3G) و PM3, . هذه الطرق استعملت من اجل تحديد العوامل البنيوية ,الالكترونية و الطاقوية المشتركة للجزيئات المدروسة. طبيعة نمط المستبدل (مانح ، مستقبل) تؤثر على العوامل الالكترونية و الطاقوية للنواة الأساسية للمكروليد. في الواقع فانَ هذه الدراسة الأخيرة تسمح لنا بتوقع الفعالية الكيميائية لمشتقات للمكروليدات ذات 14 ذرة و كذا الكيتوليدات. وقد تم أيضا القيام بدراسة نوعية بنية – خصائص(SPR) لسلسلة من مشتقات المكروليدات ذات 14 ذرة النشطة بيولوجيا . وأخيرا قمنا بدراسة العلاقة الكمية بنية – فعالية البيولوجية (QSAR) لخمسين مركب من مشتقات المكروليد ذات 14 ذرة لهم فعالية بيولوجية (مضادات حيوية) وقد استخدمنا الطريقة الإحصائية MLR وذلك لتصميم نموذج رياضي QSAR لغرض التنبؤ بالقيم النظرية للفعالية البيولوجية عن طريق هذا النموذج .ولتأكد من صحة و فعالية هذا النموذج استخدمنا طريقة LOO وكذلك بعض المعايير الاحصائية. ولقد لاحظنا شدة التقارب بين القيم النظرية و التجريبية للفعالية البيولوجية مما يؤكد فعالية و جودة النموذج QSAR المتحصل عليها.

Résumé :

Dans ce travail, une recherche fondamentale et originale sur les macrolides à 14 chaînons a est réalisée dans le but est de prédire de la réactivité et de l'activité biologique du composé étudié et ses dérivés. Les méthodes de modélisation moléculaire utilisées dans notre travail sont :MM+, PM3 et ab initio/HF(STO- 3G). Ces méthodes ont été utilisées pour déterminer les paramètres structuraux, électroniques et énergétiques associés aux molécules étudiées. La nature de type de substituant (donneur, accepteur) influe sur les paramètres électroniques et énergétiques de noyau de base de macrolide. En effet, cette étude nous a permet de prédire la réactivité chimique des dérivés des macrolides à 14 chaînons. Une étude qualitative de la relation structure-propriétés (SPR) a été effectuée également pour une série bioactive de dérivés des macrolides à 14 chaînons et aussi des kétolides. Une étude QSAR a été effectuée sur une cinquantaine de molécules analogues de les macrolides à 14 chaînons. Les composés utilisés sont caractérisés par son effet des antibiotiques. La régression linéaire multiple (MLR) a été utilisée pour quantifier les relations entre les descripteurs moléculaires et la propriété de l'activité antibiotique des dérivés des macrolides à 14 chaînons. La prédiction des modèles obtenus a été confirmé par la méthode de validation croisée LOO. Une forte corrélation a été observée entre les valeurs expérimentales et les valeurs prédites de l'activité antiproliférative, ce qui indique la validité et la qualité des modèles QSAR obtenus.

Abstract:

In this work a fundamental and original research on the 14- membered macrolide, the aim is to predict the reactivity and biological activity of the compound studied and its derivatives. The molecular modeling methods used in our work are: MM+, PM3 and ab initio/HF(STO- 3G). These methods were used to determine the structural parameters, electronics and energy associated with molecules studied. The nature of such substituent (donor, acceptor) affects the electronic and energy parameters of basic core of the 14-membered macrolide. Indeed, this qualitative study allows us to predict the chemical reactivity of derivatives of the 14- membered macrolide and also the ketolides. A study of structure - property relationships (SPR) for the 14- membered macrolide derivatives has been carried out for a series of bioactive derivatives of the 14-membered macrolide. QSAR studies have been performed on fifty molecules of the 14- membered macrolide as the antibiotics, multiple linear regression analysis was performed to derive QSAR models which were further evaluated internally for the prediction of activity. The developed models were cross-validated by the 'leave one out' technique as well as by the calculation of statistical parameters LOO. High correlation between experimental and predicted activity values was observed, indicating the validation and the good quality of the derived QSAR models.