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CONFORMATIONAL ANALYSIS AND QSAR MODELING OF 14-MEMBERED MACROLIDE ANALOGUES AGAINST MYCOBACTERIUM TUBERCULOSIS

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ABSTRACT

Electronic structures, effect of the substitution and structure physical-chemistry properties relationship for macrolide derivatives, have been studied by PM3 and ab initio methods. In the present work, the calculated values, namely net charges, bond lengths, MESP, dipole moments, electron-affinities, heats of formation, then, we treated the structural, physical and chemical relationships for a series of macrolide derivatives with inhibition activity against Mycobacterium tuberculosis. QSAR studies were done for these macrolide derivatives using a combination of various physicochemical descriptors. A multiple linear regression procedure was used to design the relationships between molecular descriptor and the activity of macrolide derivatives. Results validate the derived QSAR model.

Keywords: Macrolide, Conformational**,** MESP, QSAR studies, MLR.

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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 medicinal activity. The new finding in the field of antitumor 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 pathogens has 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 undergo clinical development, represent a new family of antimicrobials that are derived chemically from the macrolides and have been developed for use against respiratory pathogens.[11]

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 Falzari et al [32] and Zhaohai et al [33].

1. MATERIAL AND METHODS

Initial calculations were optimized using HyperChem 8.03 software [34]. The geometries of 14-membered macrolide analogues 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 [35]. 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. The calculation of QSAR properties is performed by the module (QSAR Properties, version8.0). QSAR Properties is a module that, together with HyperChem, allows several properties commonly used in QSAR studies to be calculated. Multiple linear regression analysis of molecular descriptors was done using the stepwise strategy in SPSS (version 19 for Windows) [36].

2. RESULTS AND DISCUSSION

2.1.Conformational Analysis of 14-membered α, β-unsaturated macrolides

The most stable structures can be characterized by three structural characters: the diene group, the, β –unsaturated ester group, and the two saturated chains [37]. Thus, we have obtained eight types of conformations which are present in the majority of cases in a 5 kcal/mol energy range above the global minimum. The conformation types are classed from 1 to 8 [38]. 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. 1)[37].

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%. Then, the macrocycle 14d (Figure. 2) is presented preferably in the type T3 with 24.9%. The percentages of other conformers are listed in Table 1.

Table 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.

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

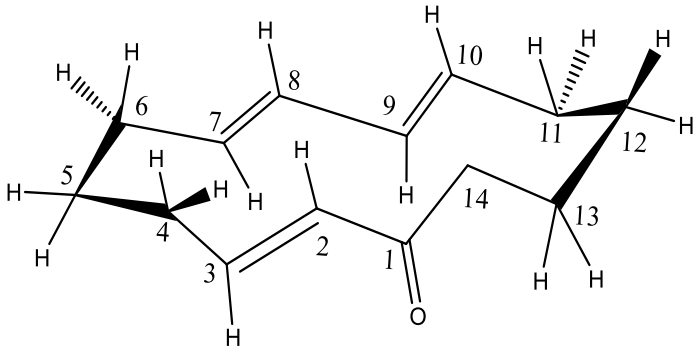


Fig.1. Privileged Conformations of the macrocycle 14s (T6)

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 2.

The geometric study allow to see that ester α, β–unsaturated system for the 14S macrolide type 6 (Figure 3) 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.2 Bond lengths (in Å) and valence angles (in degree) of the macrocycle 14s (T6) as computed at different levels of theory. See Fig. 1 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 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.

Table 3. Mulliken charges of basic structure of macrolide T6.

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

1.2. 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.[39-44] In this study; the electrostatic potentials at the surface are presented by different colors in Figure 2.

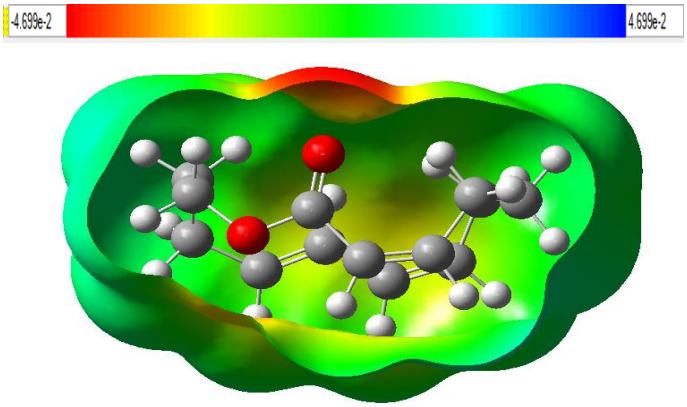
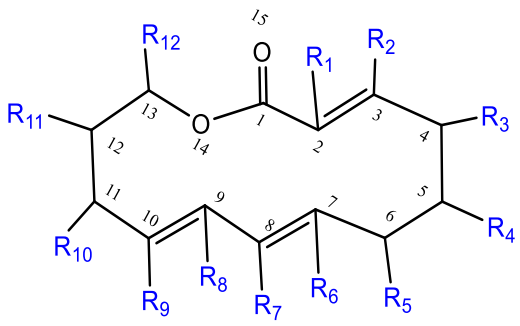


Fig.2. 3D MESP contour map for 14 macrolide T6.

Red color parts represent the regions of negative electrostatic potential while blue 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.

1.3. 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 4 and Table 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.



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

Fig.3. Scheme of macrolide systems.

Table 4. Energies of macrolide and di-methyl substituted 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-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 5. Energies of macrolide and di-fluorine substituted macrolides (Series 2)

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.

The heat of formation is decreased at each addition of di-methyl groups. Compound 2 (2, 8-dimethylmacrolide) 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-fluorinemacrolide (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.

2.2. 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 4 shows the favored conformation in 3D of the clarithromycine. We will continue this work in the future by a quantitative calculation.

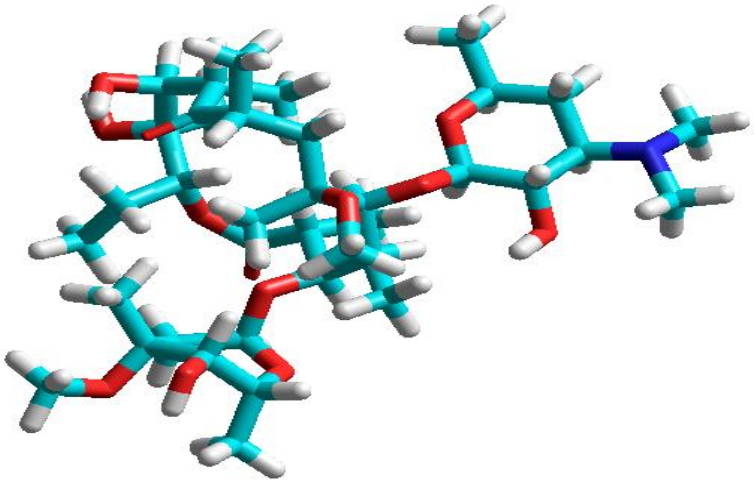


Fig.4. 3D Conformation of clarithromycine (HyperChem 8.03).

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.[46] 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.

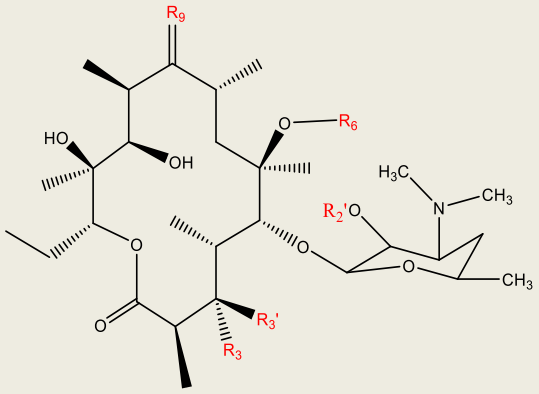
Computation of molar refractivity was made via the same method as log P. Ghose and Crippen presented atomic contributions to the refractivity.[47] Solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bodor et al.,[48] using the atomic radii of Gavezotti.[49] Polarizability was estimated from an additivity scheme given by Miller with a 3% in precision for the calculation,[50] 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.[51] The calculation is based on exposed surface area as computed by the approximate method (above), weighted by atom type.

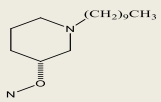
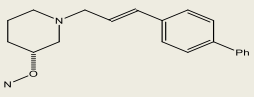
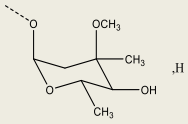
2.3. Structural comparison of the 14-membered macrolide derivatives

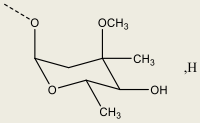
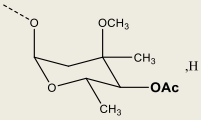
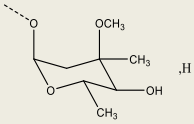
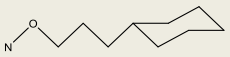
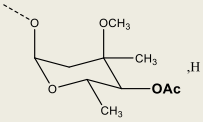
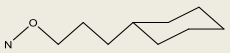
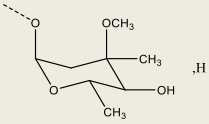
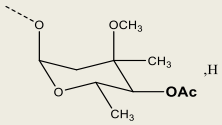
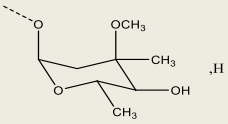
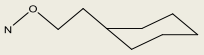
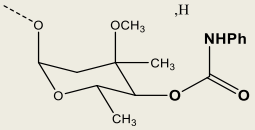
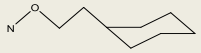
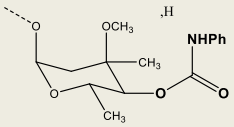
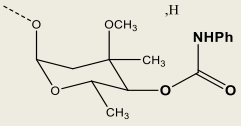
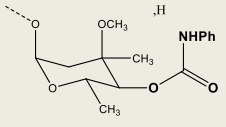
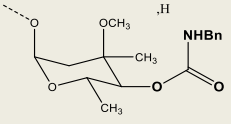
Based on our conclusions on the effect of substitution on the 14-membered macrolides molecules. We chose a series of 14-membered macrolide derivatives in Table 6, Table 7 and Table 8; some of them have a biological activity. Initially, we performed a structural comparison of this series. We used molecular 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 difference in specific sites: C2, C3, C6, C9, C11, C2' and C4" as shown in the references [32] and [33].

Table 6. 14-membered macrolide derivatives (Structure A).



Structure A

Compound	Macrolide	IC50	$R_3R'_3$	$R_{2'}$	R_6	R_9
A1	RU60887[39]	27.58	=O	H	Me	
A2	RU61804[39]	9.12	=O	H	Me	
A3	RU29558[39]	28.15		H	H	$NOCH_2OBn$

A4	Clarithromycine[39]	40.99		H	Me	O
A5	ITR054[40]	35.6		H	Me	O
A6	ITR051[40]	9.03		H	H	
A7	GI-448[40]	13.6		H	H	
A8	ITR159[40]	45		Ac	Me	
A9	ITR160[40]	39		Ac	Me	
A10	TR077[40]	16.3		H	Me	
A11	ITR120[40]	115		C(O)NHPh	Me	
A12	ITR126[40]	48.0		C(O)NHPh	Me	NOC_2H_4Ph
A13	ITR138[40]	107		C(O)NHPh	Me	NOC_3H_6Ph
A14	ITR121[40]	6.8		C(O)NHPh	Me	O
A15	ITR083[40]	39		H	Me	O
A16	ITR163[40]	73	H, OC(O)NHHexyl	H	Me	O

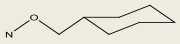
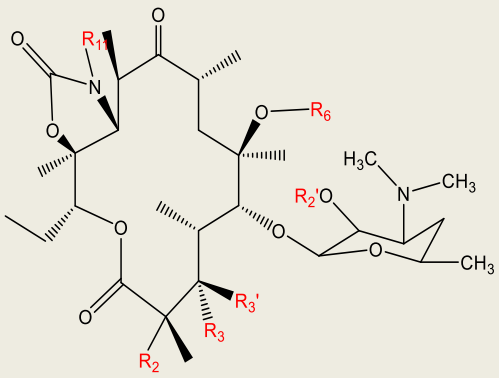
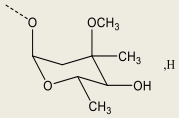
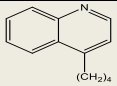
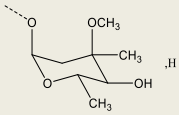
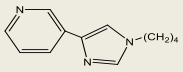
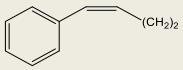
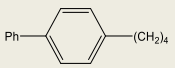
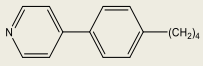
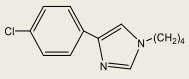
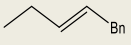
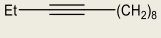
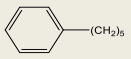
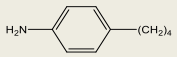
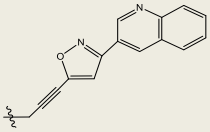
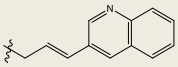
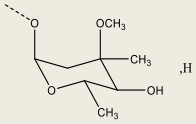
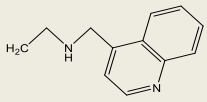
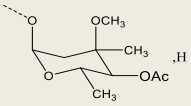
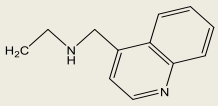
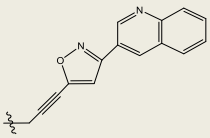
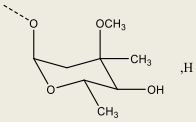
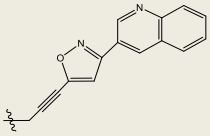
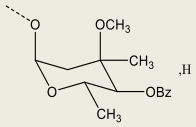
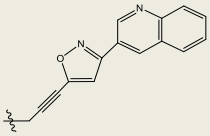
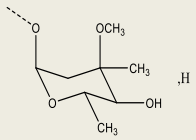
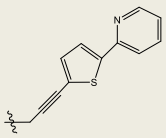
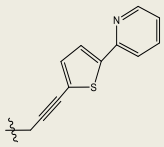
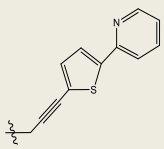
A17	ITR157[40]	45	H, OH	H	Me	

Table 7. 14-membered Macrolides derivatives (Structure B).



StructureB

Compound	Macrolide	IC50	R_2	$R_3R'_3$	$R_{2'}$	R_6	R_{11}
B1	RU66080[39]	8.1	H		H	Me	
B2	RU69874[39]	26.96	H		H	Me	
B3	RU60856[39]	104.8	H	=O	H	Me	
B4	RU61143[39]	24.25	H	=O	H	Me	
B5	RU63013[39]	7.37	H	=O	H	Me	
B6	RU66898[39]	6.93	H	=O	H	Me	
B7	RU62041[39]	8.19	H	=O	H	Me	
B8	RU62543[39]	8.71	H	=O	H	Me	
B9	RU60849[39]	8.84	H	=O	H	Me	

B10	RU70332[39]	26.04	H	=O	H	Me	
B11	A323348[39]	24.29	F	=O	H		H
B12	Cethromycine[39]	102.4	H	=O	H		H
B13	ITR049 [40]	38.8	H		H	Me	
B14	ITR048[40]	13.5	H		H	Me	
B15	ITR250[40]	35.0	H	=O	H		H
B16	ITR286[40]	12	H		H		H
B17	ITR258[40]	37.0	H		H		H
B18	ITR285[40]	27.7	H		H		H
B19	ITR248[40]	11.9	H	=O	H		H
B20	ITR278[40]	44	F	=O	H		H

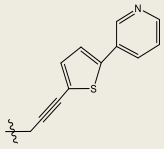
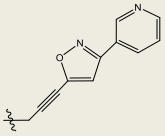
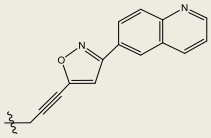
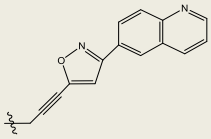
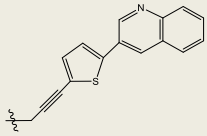
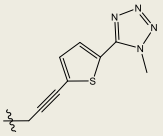
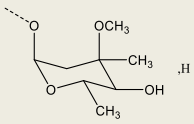
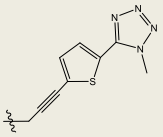
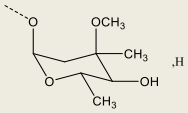
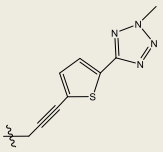
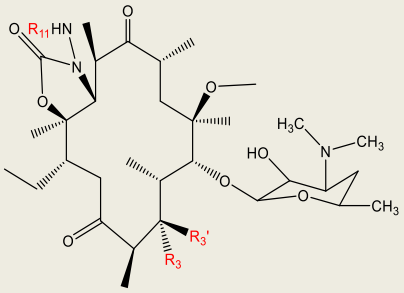
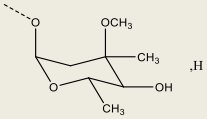
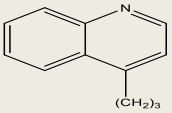
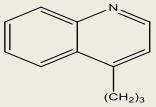
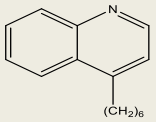
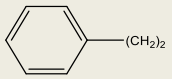
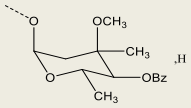
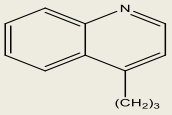
B21	ITR257[40]	15.0	H	=O	H		H
B22	ITR273[40]	35.4	F	=O	H		H
B23	ITR266[40]	51.3	F	=O	H		H
B24	ITR276[40]	42.4	F	=O	Bz		H
B25	ITR275[40]	14.07	H	=O	H		H
B26	ITR263[40]	51.1	H	=O	H		H
B27	ITR270[40]	18.9	H		H		H
B28	ITR271[40]	48.2	H		H		H

Table 8. 14-membered Macrolides derivatives (Structure C).



StructureC

Compound	Macrolide	IC50	$R_3R'_3$	R_{11}
C1	RU66252[39]	24.93		
C2	RU004[39]	26.34	=O	
C3	RU69697[39]	7.32	=O	
C4	RU70645[39] Rifampin	46.7	=O	
C5	ITR053[40]	5.5		

3.7. Structure Property/Activity Relationships

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretionproperties

2.4. 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 [52-53].

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 [54]**.**

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 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 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 [55].

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 [52].

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 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 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 [55].

Compound A3 has five proton donor sites (5 OH) and 16 proton acceptor sites. On the contrary, B3 has only one donor sites and it has 12 proton acceptor sites. 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 9. QSAR Proprieties for 14-membered macrolide derivatives.

Com.	V (Å^3)	S (Å^2)	Mass (uma)	Log(P)	EH (kcal/mol)	Pol (Å^3)	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

2.5. 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.[56-57] 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[58].

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

Com.	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

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 10 shows that all compounds have a LogP comprised between 2 and 8. LogP values in the range of 1 to3 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 in to 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 $pIC50 = -\log (IC_{50})$ [59].

LELP = log P/LE. The optimal LELP scores are -10 < LELP < 10 [60].

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)[61-62]. 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[63]. Note that compounds with high LE and LLE interact efficiently with biological targets[64].

In the studied series, LLE is changing during optimization (Table 10). All compounds have negative LLE values which are clearly unfavorable.

The above mentioned parameters were calculated for A1- C5 and the results were presented in Table 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 [65], macrocycles can demonstrate drug like physicochemical

and pharmacokinetic properties such as good solubility, lipophilicity, metabolic stability and bioavailability.

2.6.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 [66].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 [67].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}), with 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 9 and 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 log P and HBD explain that any increase in hydrogen bond donors or log P 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 %95 level, 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} =0.898and 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 [68] ,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 are as on ably good model as established in Ref .[69] .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.Figure6 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 pIC_{50} against the experimental values does not show any systematic error (Fig. 5) positive and negative residuals are randomly distributed. Thus this confirms further that our QSAR model can be successfully applied to predict anti-TB activity.

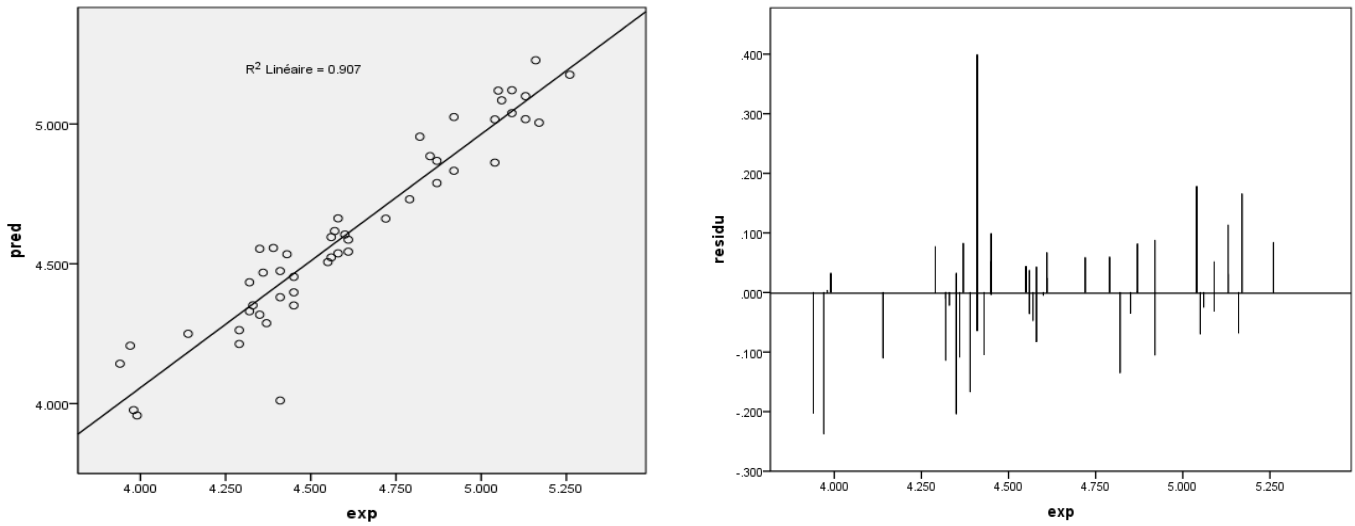


Fig. 5. Left: Plots of predicted (y-axis) versus experimentally (x-axis) observed pIC50. Right: Plots of residual against experimental values pIC50

3. CONCLUSION

The present work studied the molecular proprieties of 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

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

The QSAR modelis 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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