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Review Article

REVIEW OF COMPUTATIONAL STUDIES APPLIED IN NEW MACROLIDE ANTIBIOTICS

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ABSTRACT

Macrolide antibiotics have been the focus of widespread research due to increasing bacterial resistance. Structure elucidation of a large number of macrolides, shows the existence of two parts. The first one is a macrocyclic system from 12 to 40 links with a lactone function; the second part is a sugar. Conformational analysis indicates that each studied macrocycle presents eight families of privileged conformers. They result from the combination of the conformations of the two systems, diene and α,β-unsaturated ester. In presence of tricarbonyliron, the number of the privileged conformations was reduced to four. The study of stereochemical control in macrocycles was carried out using molecular mechanics and molecular dynamics. For complexing macrocycles, a high diastereoselectivity was obtained, this is the result from the combination of local control exerted by the methyl group and stereochemical control with tricarbonyliron.

Keywords: Macrolide, antibiotic**,** conformer, stereochemical, molecular mechanics.

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1. INTRODUCTION

Macrolide antibiotics play a therapeutically important role, particularly in the emergence of new pathogens. Among these products of major importance are macrocyclic antibiotics. The macrolide antibiotic family (14-, 15-, 16- membered ring derivates) shows a wide range of characteristics (antibacterial spectrum, side effects). The most commonly used macrolides are Azythromycine and Josamycin. Because of their biological interest many synthesis methods have been elaborated [1].

Molecular structure studies of these molecules show the existence of two parts [2]. The first one is a macrocyclic system from 12 to 40 links with several asymmetric centers and the lactone. The second part is a sugar. The two main classes of these macrolides are presented by two molecules , the first is erythromycin A which is an active antibiotic against a large number of bacteria, the second is amphotericin B which presents a strong anti-fungal.

Still et al. [3-4] demonstrated that the conformational properties of medium and large rings have profound consequences on the stereochemical course of their chemical reactions. More precisely, the macrocycles having a double bond (C=C, C=O), with substituents in a perfect position adopting preferred conformations. Peripheral attack of external reagents would occur largely from the less hindered peripheral face of the Π-system. This allows a highly stereoselective formation of new asymmetric centers. In this case, a substitute applies remote stereocontrol by conformational stability of a macrocycle. Grée et al. have shown also in some cases the existence of the remote stereocontrol induced by the tricarbonyliron [5].

In this paper we have three parts of study. The first part, we will study theα,β-unsaturated macrolides which represent the binding structure for many antibiotic families of 12- to 22-membered rings. Our object is to examine the relative importance of different contributions to total steric energy, and to determine preferred conformations of non-complexed macrocycles. The second part, we will try to evaluate the stereoselectivity of additions reactions carried out on functional groups appended to the tricarbonyliron moiety.

Finally, the last part we have studied some of QSAR proprieties of a series of 22-membered macrolides by HyperChem software.

2. COMPUTATIONAL METHODS

In our study, the main method of calculation, which we have used, is Molecular Mechanics. This is considered as the most appropriate method for larger molecules [6]. Programs that we have used are based on Allinger force field [7].

This method for structure determination includes a quantum mechanical (VESCF) π-system calculation in the iterative sequence. They use Metropolis algorithm [8].

We also used the molecular dynamics (HyperChem) for the conformational research, with following options: 1000°K, in vacuo, step size: 0.001ps, relaxation time: 0.1ps.

These calculations were carried out with two software packages; HyperChem (8.01) [9], for geometry optimization and conformational search and Chem3D (8.0) [10], for structural representation.

3. RESULTS AND DISCUSSION

3.1. Analysis of conformational exploration symmetric and dissymmetric for 12 to 22 membered Macrolides Antibiotics

In this part of our work we have undertaken a conformational study of macrocycles 12-22 membered[11-12] (Figure 1) , symmetrical which we will design 12s,14s,16s,18s,20s and 22s ($n_1 = n_2 = n$, m=2n), dissymmetrical which we will design 12d,14d,16d,18d,20d and 22d ($n=n_1 + n_2$), which represent the core group for many antibiotics.

3.1.1. Energetic Considerations

3.1.1.1. Variation of the total strain energy

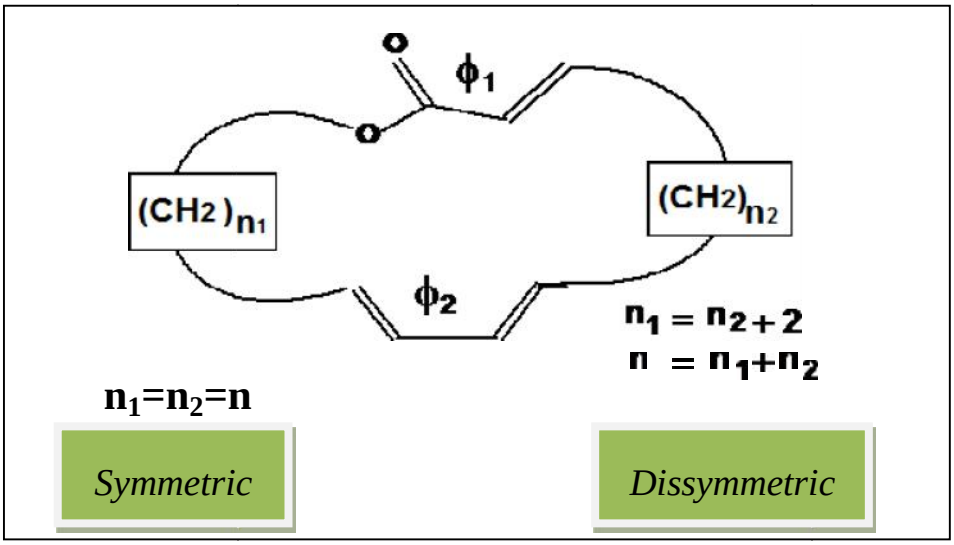


Fig.1. Scheme ofα,β-unsaturated symmetric and dissymmetric macrolides.

Conformational study is based on molecular mechanics. We will use the total and entire steric energy to compare the thermodynamic stability of conformation isomers of the same compound. The strain energy will be used for a comparison of the relative stability of different studied macrocycles [13]. Figure 2 presents an evolution of the strain energy per CH_2 group as a function of the entire amount of methylene (n) -A- (symmetric macrolides) and -B- (dissymmetric macrolides).

The strain energy per CH_2 group is relatively higher for macrocycle 12 (n = 4) of symmetric and dissymmetric macrolides.

The variation of strain energy per CH_2 group is similar to that obtained in anterior works concerning cycloalcanes studies C_4-C_{12} [14].

An important decrease in the strain energy per CH_2 group from n = 4 to n= 6 confirms perfectly the limit between the two classes of medium and large rings, as was mentioned in the literature [15].

In line with the above conclusions, the rate of cyclization increases with the size of the ring [16]. This is in good agreement with our results, which indicate that an evolution of strain energy per CH_2, group is opposite to the size of the ring.

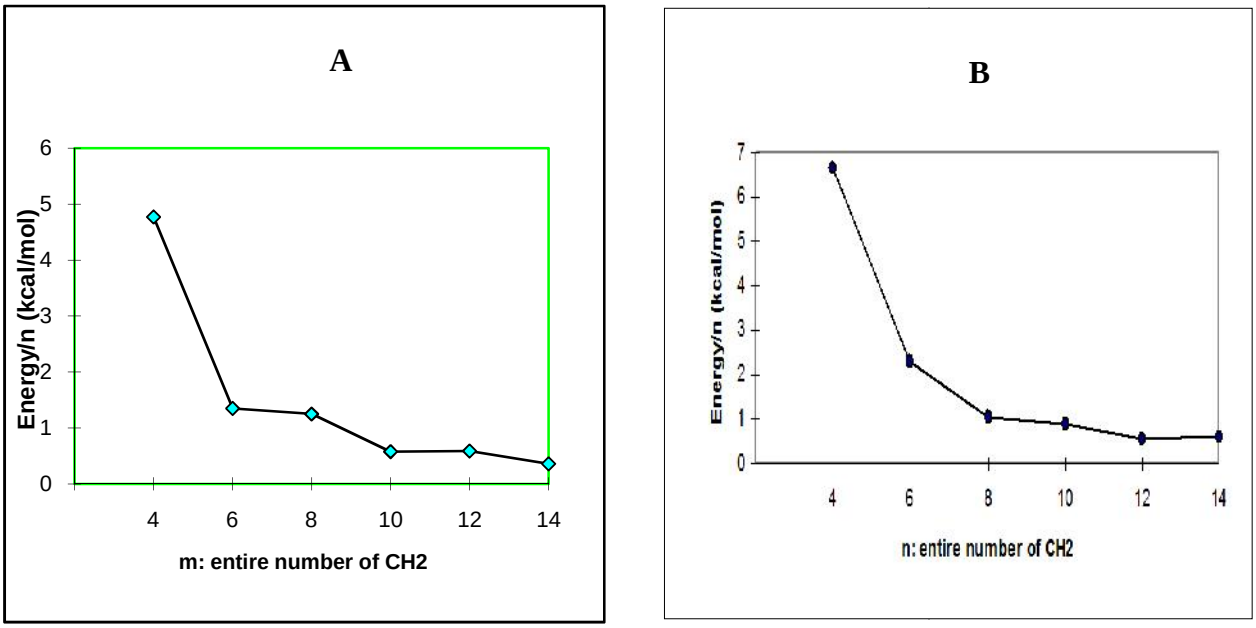


Fig.2. Evolution of the strain energy by (CH_2) group as a function of the entire number of methylene (n)

3.1.1.2.Contributions of different features to steric energy

The steric energy calculated [14] from the sum of different contributions such as stretching, bending, torsional, Van der Waals, and electrostatic energies:

$$E(steric) = E(stretch) + E(bend) + E(tors) + E(vdw) + E(electr) + \ldots\ldots(1)$$

We will investigate their contributions and influences on steric energy. Figure 3 present contribution of different component energies to the total steric energy of the most conformers.

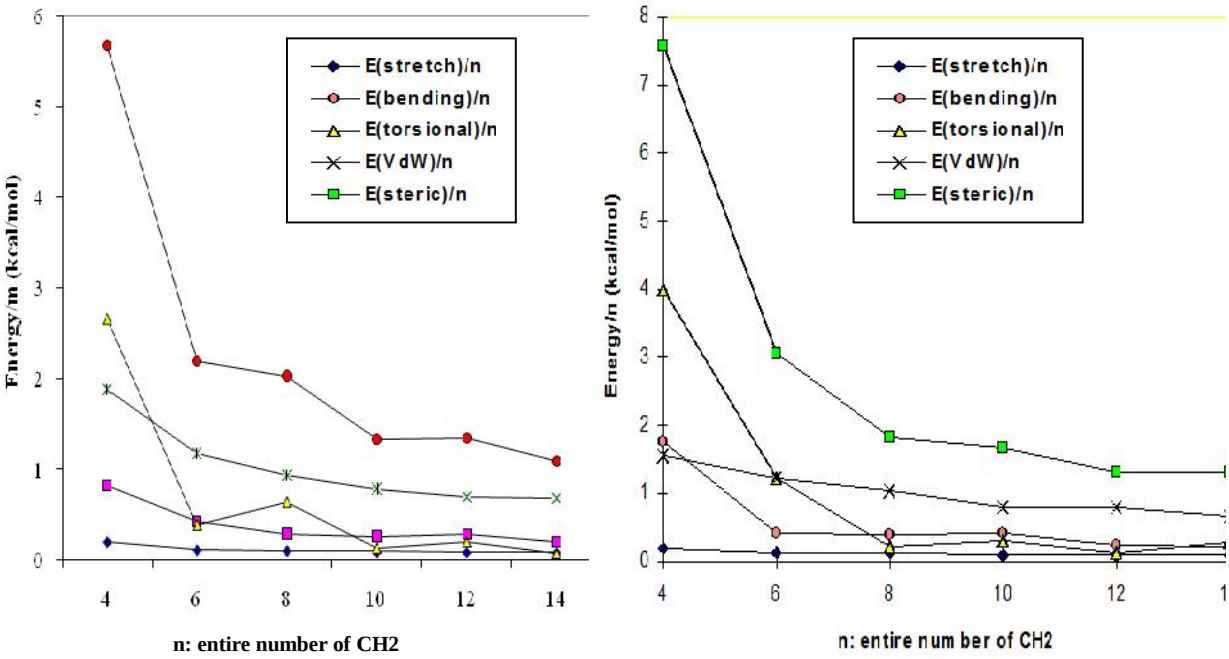


Fig.3. Contribution of different components to the total steric energy of the most stable conformers (symmetric and dissymmetric macrolides)

For the macrolide 12 (n= 4), the torsional energy contribution is superior to that of Van der Waals'. This is essentially due to unfavorable torsional angles because it is not possible to obtain the perfectly altered conformation on a majority of C-C bonds, as is the case with other macrocycles.

In conclusion, the contribution of the Van der Waals energy E (VdW /n) is higher in all examined macrocycles in their stable conformers ($n \geq 6$). Its variation as a function of (n) is, in general, proportional to a resultant of the bending and torsional constraint. In each ring, it

a compromise was established between the torsional, bending and Van der Waals energies in order that each molecule adopts the conformation which corresponds to the minimal total steric energy [17].

3.1.2. Geometrical and statistical study

The conformation searching operation was as follows: a crude starting geometry is produced and its structure is optimized by molecular mechanics energy minimization. The resulting minimum energy conformer is then compared with previously found conformers to test for possible duplication. If the conformer thus generated is a previously undiscovered one, it is added to an accumulating list of unique conformers, and the cycle is then repeated by obtaining new crude starting geometry energy minimization etc. When all given starting geometries have been used or when new minima cease to be found the search is terminated. Although several calculations were carried out in the conformational search we cannot be sure that other low energy conformers were not overlooked in some instances. This is in agreement with Still's work.

Conformational analysis using the statistical analysis software TSAR [18] (Tools for structure activity relationships) has led to an important number of conformers. Thus, the conformer number to explore is N^m, where N is the rotator number and m defines the angular increment (360/m).

A visual analysis of the first conformers shows that macrocycles possess three structural characters: the diene system,α,β-unsaturated ester group and the two saturated chains. As these two chains do not intervene in the reactivity problem that interests us, the conformation of these two chains is not to be taken as an important characteristic and will be ignored in our following reasoning. Finally, we found eight main conformational families for each set studied (Figure 4). Conformational families (2,4,6,8) have the two plans of the two sites: diene andα, β-unsaturated ester pseudo-parallels. For the rest of the families (1,3,5,7) the two plans are pseudo-antiparallels.

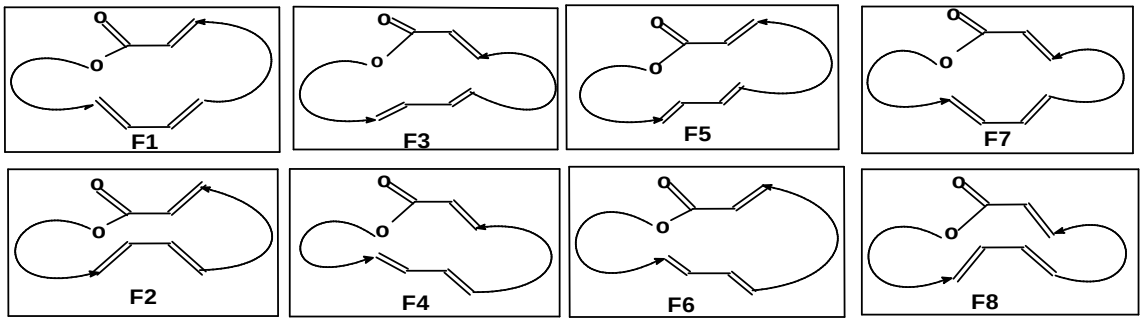


Fig. 4. Main conformational families

Conformers in each macrocycle with relative energies and their Boltzmann population at normal temperature [19] are listed in Tables (1a and 1b). Three conformational families, F5, F6 and F3 are preferred.

In an energy equal 1 Kcal/mol of symmetric macrocycles, we have 3 conformational families for macrolides 18s ,20s and 22s, 2 families for macrocycle 14s and 16s, only 1 family for macrocycle 12s. Also in an energy window of 2 Kcal/mol of dissymmetric macrocycles, we have 5 conformational families for macrolide 22d, 4 families for macrocycle 20d, 3 families for macrolides 12d, 16d, 18d and only one family for macrocycle 14d.

Table 1a. Energetic difference for different conformational families (12 to 16)

n	**4**						**6**						**8**					
Macrocycle	**12s**			**12d**			**14s**			**14d**			**16s**			**16d**		
	F	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**
To	**6**	0.00	34.0	**5**	0.00	18.8	**5**	0.00	19.4	**6**	0.00	26.6	**6**	0.00	18.7	**5**	0.00	19.6
1 kcal/mol							**4**	0.70	16.3				**4**	0.56	16.3			
				1	1.39	13.4				**3**	2.29	15.2				**4**	1.37	14.0
				4	1.69	12.5				**2**	2.44	14.7				**6**	1.83	12.5
Sup to				**8**	2.02	11.5				**4**	2.98	12.9				**7**	2.04	11.9
1 kcal/mol				**2**	2.14	11.2				**5**	3.79	10.6				**8**	2.17	11.5
				6	2.15	11.1				**1**	4.25	9.5				**3**	2.21	11.4
				3	2.28	10.8				**8**	5.65	6.7				**1**	2.68	10.2
				7	2.29	10.8				**7**	7.86	3.9				**2**	3.28	8.8
To	**5**	0.00	34.0				**3**	1.63	12.9				**3**	1.13	14.2			
2 kcal/mol							**1**	1.99	11.9				**5**	1.95	11.6			

Sup to	**3**	3.22	15.5	**8**	2.30	11.0	**1**	2.29	10.7
2 kcal/mol	**2**	4.39	11.7	**6**	2.68	10.1	**2**	2.47	10.2
	4	4.74	10.6	**7**	2.77	9.9	**7**	2.89	9.2
	1	4.87	10.3	**2**	3.36	8.6	**8**	2.99	9.0

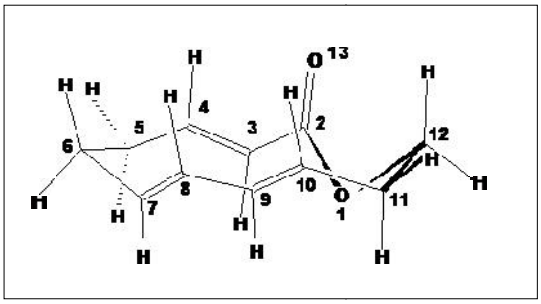
Table 1b. Energetic difference for different conformational families (18 to 22)

n	**10**						**12**						**14**					
Macrocycle	**18s**			**18d**			**20s**			**20d**			**22s**			**22d**		
	F	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**	**F**	**aE**	**%**
To 1 kcal/mol	**5**	0.00	17.2				**6**	0.00	19.8				**4**	0.00	17.9			
	3	0.58	15.0				**5**	0.50	17.5				**3**	0.08	17.5			
	4	0.84	14.1				**3**	0.96	15.7				**5**	0.36	16.4			
to 2 kcal/mol	**6**	1.07	13.3	**6**	0.00	21.4	**4**	2.06	12.0	**3**	0.00	17.5	**6**	1.47	12.5	**3**	0.00	18.3
	1	1.89	10.9	**3**	0.64	18.3				**5**	0.28	16.4				**4**	0.18	17.6
	8	1.90	10.9							**4**	0.29	16.3						
Sup to 2 kcal/mol	**7**	2.06	10.5	**5**	1.64	14.4	**1**	2.32	11.3	**6**	1.55	12.0	**7**	2.47	09.8	**6**	1.66	12.3
	2	3.05	08.2	**4**	2.68	11.2	**2**	3.43	08.6	**2**	2.16	10.4	**8**	2.69	09.3	**7**	1.70	12.1
				8	3.38	09.4	**7**	3.97	07.6	**7**	2.17	10.3	**1**	2.75	09.2	**8**	1.81	11.8
				7	3.39	09.4	**8**	4.03	07.5	**1**	2.74	09.0	**2**	3.55	07.5	**5**	1.95	11.4
				1	3.47	09.2				**8**	3.14	3.14				**2**	3.21	08.4
				2	4.72	06.8										**1**	3.37	08.1

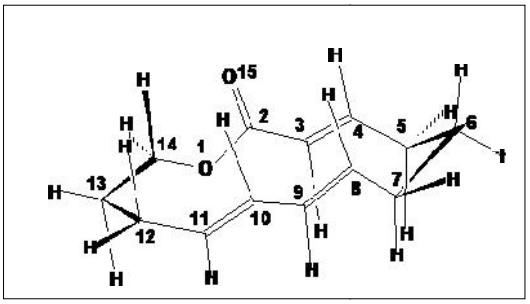
ΔE: Energetic difference to the absolute minimum % Boltzmann population

For symmetric macrocycles with n ≤ 12 and dissymmetric macrocycles with n ≤ 10, a conformation of the ester group is cisoid, and that of diene system is transoid for two families (F5 and F6) but the arrangement between these systems is a function of the parity of n or m. For even n or m, the strain constraints of methylene groups oblige the two systems to adopt a pseudo-parallel arrangement for the F6 family which is more favorable than the pseudo-antiparallel arrangement for the F5 family. For dissymmetric macrocycles with uneven m, from n = 12, the large size of the rings allows the F3 family to be the most stable of. Thus, for n ≤ 10, the most preferential conformer for rings with m even (m = n/2) belongs to the F5 family, then for (m) uneven it belongs to the F6 family. For n ≥ 12, only one family, F3, has the preferred conformer. Dissymmetric macrocycles with uneven n, from n=14, the large size of the rings allows the F4 family which a conformation of two systems is transoid

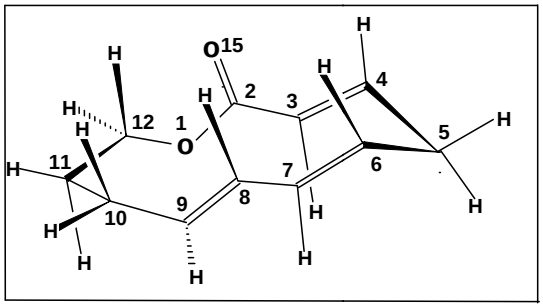
(Figure 5).



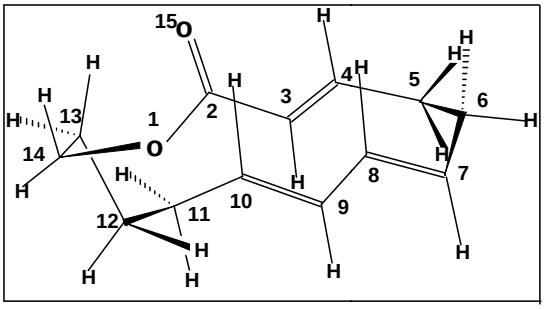
Macrocycle 12s (n = 4): Family 6



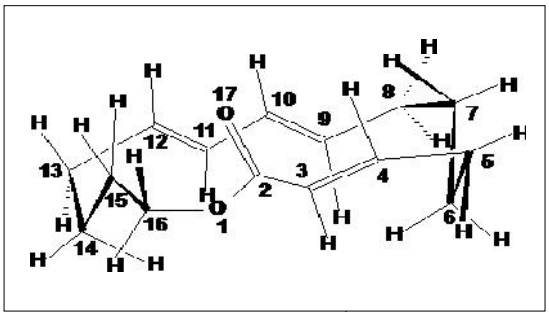
Macrocycle 14s (n= 6) : Family 5



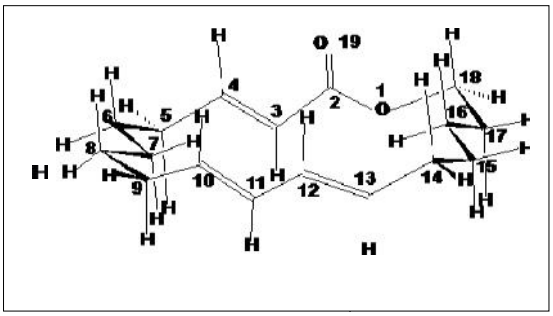
Macrocycle 12d (n = 4): Family 5



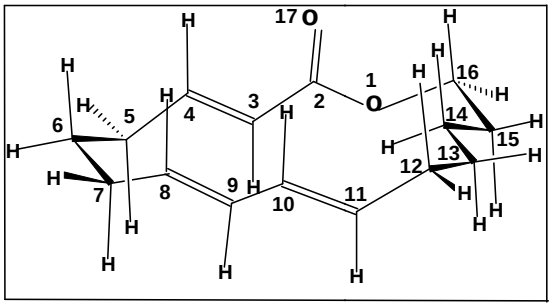
Macrocycle 14d (n = 6) : Family 6



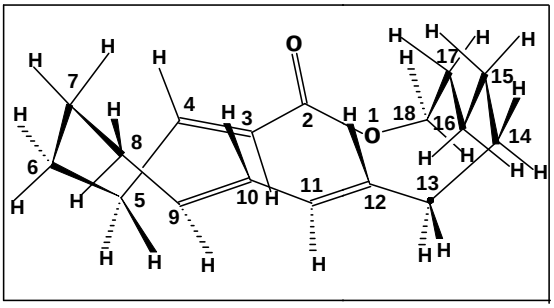
Macrocycle 16s (n = 8): Family 6



Macrocycle 18s (n = 10) : Family 5



Macrocycle 16d (n = 8): Family 5



Macrocycle 18d (n = 10): Family 6

Fig.5. Most favored conformers of macrocycles (symmetric and dissymmetric)

3.1.3. Complexing macrolides

The development of organometallic reagents derived from transition metals has been particularly successful and has had a deep effect on synthetic planning. The high natural abundance and ready accessibility of iron has resulted in the development of a wide and varied organometallic chemistry. These complexes constitute an intermediate compound usually used in organic synthesis [20]. The obtained complex must present all requisite conditions of thermal and chemical stability and mobility in order to have an efficient decomplexation. We note that the organometallic complex may intervene both by high steric hindrance and introducing rigidity in the structure. Tables 2a and 2b summarize conformational families of complexing macrocycles with the tricarbonyliron moiety, with relative energy less and more than 1 Kcal/mol, and the probability of each conformer calculated using the Boltzmann distribution.

Table 2a. Energetic difference and Boltzmann population for different conformational families (12 to 16)

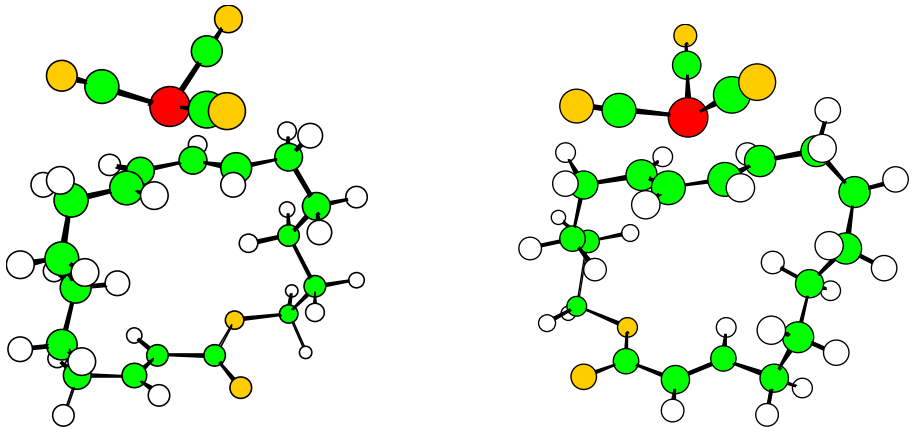
n	**4**						**6**						**8**					
Macrocycle	**12s**			**12d**			**14s**			**14d**			**16s**			**16d**		
	F	aE	**%**	**F**	aE	**%**	**F**	aE	**%**	**F**	aE	**%**	**F**	aE	**%**	**F**	aE	**%**
to 1 kcal/mol	**2**	0.00	39.1	**2**	0.00	29.2	**1**	0.00	29.7	**2**	0.00	40.3	**1**	0.00	29.2	**2**	0.00	27.6
	1	0.60	33.8	**1**	0.58	25.3	**8**	0.56	25.9	**1**	0.87	32.6	**2**	0.26	27.4	**1**	0.12	26.8
				8	0.90	23.4										**3**	0.14	26.7
Sup to 1 kcal/mol	**7**	4.17	14.2	**7**	1.15	22.1	**7**	1.08	22.8	**8**	3.81	16.0	**7**	1.12	22.2	**4**	1.57	18.9
	8	4.56	12.9				**2**	1.30	21.6	**7**	5.28	11.2	**8**	1.31	21.2			

Table 2b. Energetic difference and Boltzmann population for different conformational families (18 to 22).

n	**10**						**12**						**14**					
Macrocycle	**18s**			**18d**			**20s**			**20d**			**22s**			**22d**		
	F	aE	**%**	**F**	aE	**%**	**F**	aE	**%**	**F**	aE	**%**	**F**	aE	**%**	**F**	aE	**%**
to	**1**	0.00	28.5	**8**	0.00	31.7	**1**	0.00	33.0	**2**	0.00	26.6	**7**	0.00	28.1	**8**	0.00	30.5
1 kcal/mol	**8**	0.26	26.5	**7**	0.08	31.1	**2**	0.92	26.4	**7**	0.27	24.9	**1**	0.16	27.0	**7**	041	27.6
	7	0.54	25.1							**1**	0.35	24.4	**8**	0.63	24.1			
										8	0.42	24.0						

Sup to	**2**	1.47	19.9	**1**	1.17	23.9	**8**	1.79	21.3		**2**	1.23	20.8	**1**	1.35	22.0
				2	3.57	13.3	**7**	2.20	19.3					**2**	1.77	19.9
1 kcal/mol																

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



(a) (b)

Fig.6. 3D Privileged conformations of complexed macrocycles 18s (a) and 18d (b)

The majority of complexing macrolides with relative energy less than 1 Kcal/mol present two preferred conformers. The probability of the most stable conformers has increased in the case of complexing macrocycles compared with non- complexing rings. Macrocycle 20s, which was presented by a preferred conformer with 19.8% without complex, was populated with 33.0% in presence of $Fe(CO)_3$.Also Macrocycle 14d, which was presented by a preferred conformer with 26.6% without complex, was populated with 40.3% in presence of $Fe(CO)_3$. For all preferred conformers the dienic system has been fixed in an s-cis conformation by reason of the presence of the tricarbonyliron. A value of a dihedral angle of the dienic system (Φ2) is comprised between 0.24° and 15.36° (symmetric macrocycles) and for dissymmetric macrocycles is comprised between 1.6 and 17.6°.

The results of the conformational analysis of these complexing macrocycles show that the tricarbonyliron has a wide influence on the ring, because the number of conformers was reduced to four (Tables 2a and 2b). For all preferred conformers we found that the lactone function and the complexing diene are practically perpendicular to the medium plan of the ring. The lactone face was pointed towards the exterior of the ring, so the two faces of the enolate are diastereotopic [21]. Therefore, stereoselectivity is a result of two principles: the

tricarbonyliron stabilizes a ring under one or several preferential conformations and the addition of the reagent has been carried out by the less hindered face. This is in good agreement with Still and Takahashi [22] , who affirmed that the addition of CH_3X on enolate, was carried out by a peripheral attack on this face. This is due to a part of the tricarbonyliron, which has introduced an asymmetric element, and a steric effect that has increased the proportion of the peripheral attack. Our recent study [23-24] and Ley's work [25] on the complexes of $Fe(CO)_3$ show that the presence of this organometallic ligand induces a diastereoselectivity of addition reactions.

3.2. STEREOCHEMICAL CONTROL IN MEMBRED 16 AND 20 MACROCYCLES

3.2.1. Introduction of tricarbonyliron moiety

We have studied also the exerted effect by tricarbonyliron on conformational flexibility of these macrocycles. We note that organometallic complex can intervene by a very high steric hindrance and also introducing an important rigidification of skeleton. The results of conformational analysis of two complexed macrocycles 16 and two complexed macrocycles 20 show that tricarbonyliron has a considerable influence on cycles, because the number of possible conformations was reduced to four families [26].

In 1kcal/mol energetic difference, the complexed macrocycles 16s, 20s, 16d and 20d were presented two preferred conformers.

The peopling rate of the most stable conformers was increased for complexed macrocycles compared with these without tricarbonyliron (table 3).

Table 3. Energetic difference and Boltzmann population of different conformational families of complexed macrocycles (16 and 20)

Macrocycle	**16 symmetric (n_1 = n_2 = 4)**			**16 dissymmetric (n_1 = 5, n_2 = 3)**			**20 symmetric (n_1 = n_2 = 6)**			**20 dissymmetric (n_1 = 5, n_2 = 7)**		
	F	**aE**	%	**F**	**aE**	%	**F**	**aE**	%	**F**	**aE**	%
to 1 kcal/mol	**1**	0.00	29.2	**1**	0.00	30.5	**1**	0.00	33.0	**1**	0.00	40.2
	2	0.26	27.4	**8**	0.58	26.4	**2**	0.92	26.4	**2**	1.71	26.5

Sup to 1 kcal/mol		7	1.12	22.2	2	1.30	22.2	8	1.79	21.3	7	3.16	18.6
		8	1.31	21.2	7	1.55	20.9	7	2.20	19.3	8	4.13	14.7

For macrocycle 16s, which was presented by a preferred conformer with 18.7% without complex, was populated with 29.2% in presence of $Fe(CO)_{3.We}$ remark also that macrocycles 16s and 16d were presented the same type F1 respectively with 29.2% and 30.5% for the most favored conformers. Also for macrocycle 20d, which was presented by a preferred conformer with 22.4% without complex, was populated with 40.2% in presence of $Fe(CO)_3$. We remark also that macrocycles 20s and 20d were presented respectively in F1 type with 40.2% and F2 type with 26.5% for the most favored conformers.

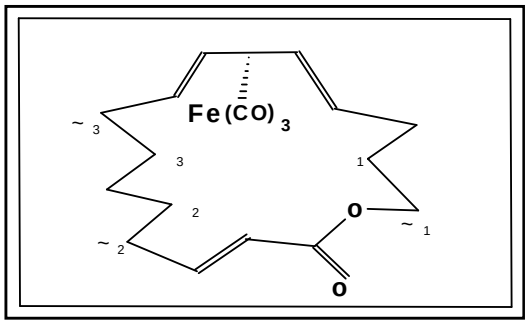
Dienic system was fixed in s-cis conformation for all preferential conformations. The dihedral angle value of dienic system was comprised between 3.1° and 11.9° for 16s cycle and between 7.0° and 11.3° for 16d cycle. Also the dihedral angle value of dienic system was comprised between 1.52° and 15.36° for 20s cycle and between 1.79° and 30.30° for 20d cycle.

The lower deviations of registered dihedral angles compared with normal values were imposed essentially by a cyclic chain.

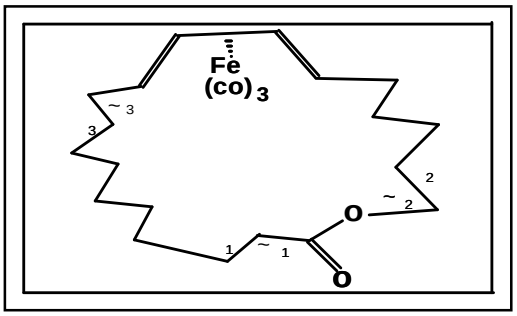
The study carried out by Cox and Ley [25], on Fe(CO)3 complexes has shown that the presence of complex, which has an important steric effect, induced a diastereoselectivity in addition reactions

3.2.2. Introduction of substituents

In order to study the role that a new substitute can play on stereochemical control [27-30], we have introduced methyl in various positions (scheme 1 and 2). The introduction of the substituent shows that the order of the types is variously modified according to the position of methyl in the carbon chain and the position of this one with compared to $Fe(CO)_3$.



Scheme 1 « Macrocycle 16 »



Scheme 2 «Macrocycle 20 »

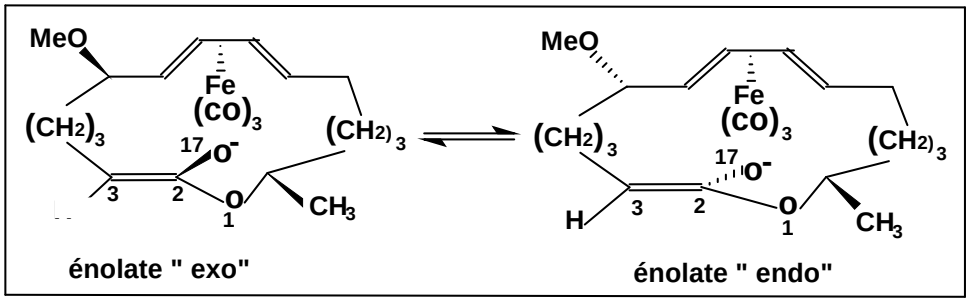
For the macrolide 16d, the first family F1 represents in the majority of the cases of the preferred conformers in a conformation (endo or exo). The family 8 (F8), as in the case of unsubstituted complexed macrolactones. The most influential position is α_2 (exo) for which the energy difference between the absolute minimum and the second minimum (1.3 kcal / mol) giving a probability to the F1 majority of the order of 35.4%, while this difference is only 0.58 kcal / mol in the case of unsubstituted complexed macrolactone with 30.5% Boltzmann population. Similarly, the positions α_3 (exo) and β_3 (endo) also have an influence because the preferred conformers are also in the majority with Boltzmann population (34.1% and 33.2% respectively).

Also the macrolide 20, the second family F2 represents in the majority of the cases the preferred conformers in a conformation (endo or exo) except for the substitution β_1 , where it is in second position in the case 'exo', with a weak energy difference of 0.13 kcal/mol per relation to the privileged conformers. The first family (F1), as in the case of unsubstituted complexed macrolactones. The most influential position is α_3 (endo) for which the energy difference between the absolute minimum (F1) and the second minimum (F2) is the largest (1.75 kcal/mol) giving a probability to the F1 majority of the order of 37.9%, while this difference is only 0.26 kcal/mol in the case of unsubstituted complexed macrolactone with 31.4% Boltzmann population. Similarly, the positions β_3 (endo) and α_2 (endo) also have an influence because the preferred conformers are also in the majority with Boltzmann population (36.9% and 33.7% respectively).

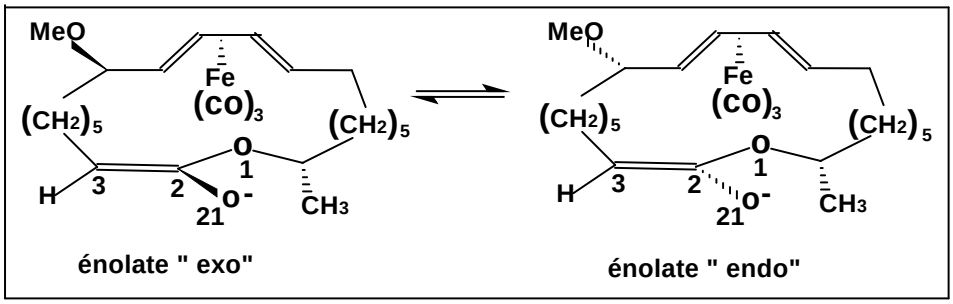
In conclusion, it appears, through this study on the complexes 16d and 20d, that stereochemical control is all the more effective since methyl is near to the asymmetric centre.

3.2.3. Type B macrocycles

Here we examine the case of a type B of macrocycle 16 and 20, after alkylation, it carries a methyl substituent in position (α_1) of the lactone, a methoxy substituent in position (α_3) of the diene and another methyl in position (α_2) of oxygen.The purpose of this part is to study the influence of the local conformational control provided by additional methyl on the diastereoselectivity of the alkylation reaction.



scheme 3

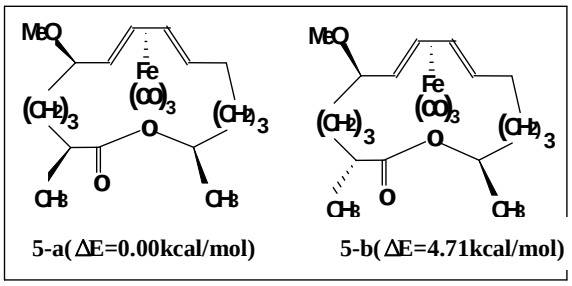


scheme 4

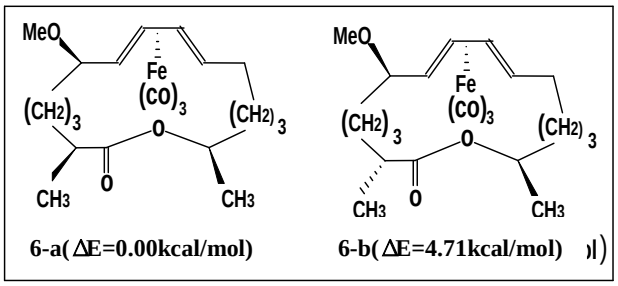
The formation of the intermediate enolate is stereoselective and leads to the derivative of geometry E for macrocycle 16 and the geometry Z for macrocycle 20 (scheme 3 and 4). Attempts to trap the same type of enolate have failed experimentally [31].

The enolate of geometry E (macrocycle 16) and geometry Z(macrocycle 20) exists in two privileged conformations " exo " and " endo " whose torsion angle of the exo configuration: O17-C2-C3-H (3) = 177.5 ° (macrocycle 16) and O21-C2-C3-H(3) =0.28°for macrocycle 20.

The two enolates "exo" and "endo" give respectively the majority diastereoisomer 5-a and 6-a and the minority diastereoisomer 5-b and 6-b (scheme 5 and 6). The two methyl groups are cis relative to each other for the most stable diastereoisomer; this result is in agreement with the work mentioned previously on other smaller size lactones ; these groups are "exo" with compared to the group Fe $(CO)_3$ for the majority diastereoisomer.



Scheme 5



Scheme 6

The reaction proceeds preferentially via the "exo" form of the enolate (scheme 5 and 6); The preferred diastereoisomer type 5-a (macrocycle 16) and type 7-a (macrocycle 20) is in the majority with 75.9% for macrocycle 16 and 73% for macrocycle 20; The other type 5-b (macrocycle 16) and type 7-b (macrocycle 20) is proportion lower at 24.1% for macrocycle 16 and 27% for macrocycle 20. The study we carried out on complexed type B macrolactones revealed a significant diastereoselectivity (76: 24) for macrocycle 16 and (73: 27) for macrocycle 20 . The methyl at position α_1 (macrocycle 16) and position α_2 (macrocycle 20) has the effect of increasing, presumably by local conformational control, the diastereoselectivity of the alkylation reactions.

For macrolactones type B, a high diastereoselectivity was obtained. This is the result from the combination of stereochemical remote control with Fe $(CO)_3$ and local control exerted by methyl substitute.

3.2. STRUCTURE ACTIVITY RELATIONSHIPS OF 12-MEMBERED MACROLIDES

In the present work, we have applied Structure-Activity Relationship (SAR) and rules of thumb (Lipinski's rules) [32-34] on thirteen conformers of 12-membred macrolides with respect to their antibiotics activity. The chemical structures of the studied macrolide are shown in Figure 7and for example, Figure 6 shows the favored conformation in 3D of cladospolide B.

The properties involved are: Partition coefficient octanol/water (log P), molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), Surface area grid (SAG), molar volume (V), hydration energy (HE), molar refractivity (MR) and polarizability (Pol). The results using HyperChem 8.0.8 software are shown in Table 4.

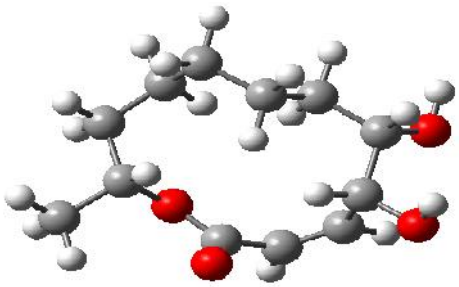


Fig.7. 3D Conformation of cladospolide B (Gauss View 3.09)

Table 4. QSAR proprieties for 12-membered macrolides

Macrolides	Energy of hydratation (Kcal/mol)	Pol ($Å^3$)	Volume ($Å^3$)	Surface ($Å^2$)	Mass (uma)	LogP	HBA	HBD	Lipinski score of 4
1-Cladospolide A	-7.656	23.825	696.538	414.994	228.288	1.591	4	2	4
2-Cladospolide B	-10.029	23.825	699.040	418.608	228.288	1.591	4	2	4
3-Cladospolide C	-8.770	23.825	689.945	414.379	228.288	1.591	4	2	4
4-Cladospolide D	-5.995	23.274	683.482	408.871	226.273	1.189	4	1	4
5-Methymycine	-5.694	49.617	1324.521	709.552	469.619	3.376	5	1	4
6-Neomethy-mycine	-5.304	49.617	1332.030	711.049	469.619	3.483	5	1	4
7-YC-17	-1.478	50.815	1351.548	721.440	467.646	4.727	4	0	4
8-Patulolide A	-0.330	22.637	656.943	397.729	210.273	2.763	3	0	4
9-Patulolide B	-0.981	22.637	646.126	389.778	210.273	2.763	3	0	4
10-Patulolide C	-5.437	23.188	675.196	411.752	212.289	2.360	3	1	4
11-Pandangolide 1	-9.242	24.103	713.430	423.606	244.288	1.341	5	2	4
12-Pandangolide 2	-3.760	30.859	837.203	474.734	318.385	1.603	6	2	4
13-Pandangolide 3	-8.267	37.001	1015.292	572.231	376.465	1.800	7	2	4
14-Sporiolide A	-5.375	35.684	970.017	557.306	348.396	3.383	6	1	4
15-Sporiolide B	-4.113	25.938	748.108	438.928	258.315	1.619	5	1	4

In the first part, we have studied Lipinski rules to identify "drug-like" compounds. Rich absorption or permeability is more likely when: [35]

1- There are less than 5 H-bond donors (expressed as the sum of OHs and NHs);

2- The molecular weight is under 500 DA;

3- The log P is under 5;

4- There are less than 10 H-bond acceptors (expressed as the sum of Ns and Os);

We used the Lipinski rules to identify compounds posing problems of absorption and permeability if these compounds don’t validate at least two of its rules.

The rules are based on a strong physicochemical rationale. 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 reduce partitioning from the aqueous phase into the lipid bilayer membrane for permeation by passive diffusion. The studied 12-membred macrolides are in accordance with rule 1 and rule 4 as shown in Table 4 so we can say that they probably less polar and easily absorbed.

Molecular weight (MW) is related to the size of the molecule. As molecular size increases, a larger cavity must be formed in water in order to solubilize the compound.

Increasing MW reduces the compound concentration at the surface of the intestinal epithelium, thus reducing absorption. Increasing size also impedes passive diffusion through the tightly packed aliphatic side chains of the bilayer membrane. We have all studied compounds with molecular weights less than 500 Da (rule number 2), so they are likely soluble and easily pass through cell membranes.

Increasing Log P also decreases aqueous solubility, which reduces absorption. Thus, membrane transporters can either enhance or reduce compound absorption by either active uptake transport or efflux, respectively. 12-membred macrolides satisfy also the rule number 3 so it has a consequence of a better solubility in aqueous and lipidic solutions too [36].

The majority (log*P*) of studied molecules have optimal values. For good oral bioavailability, 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.

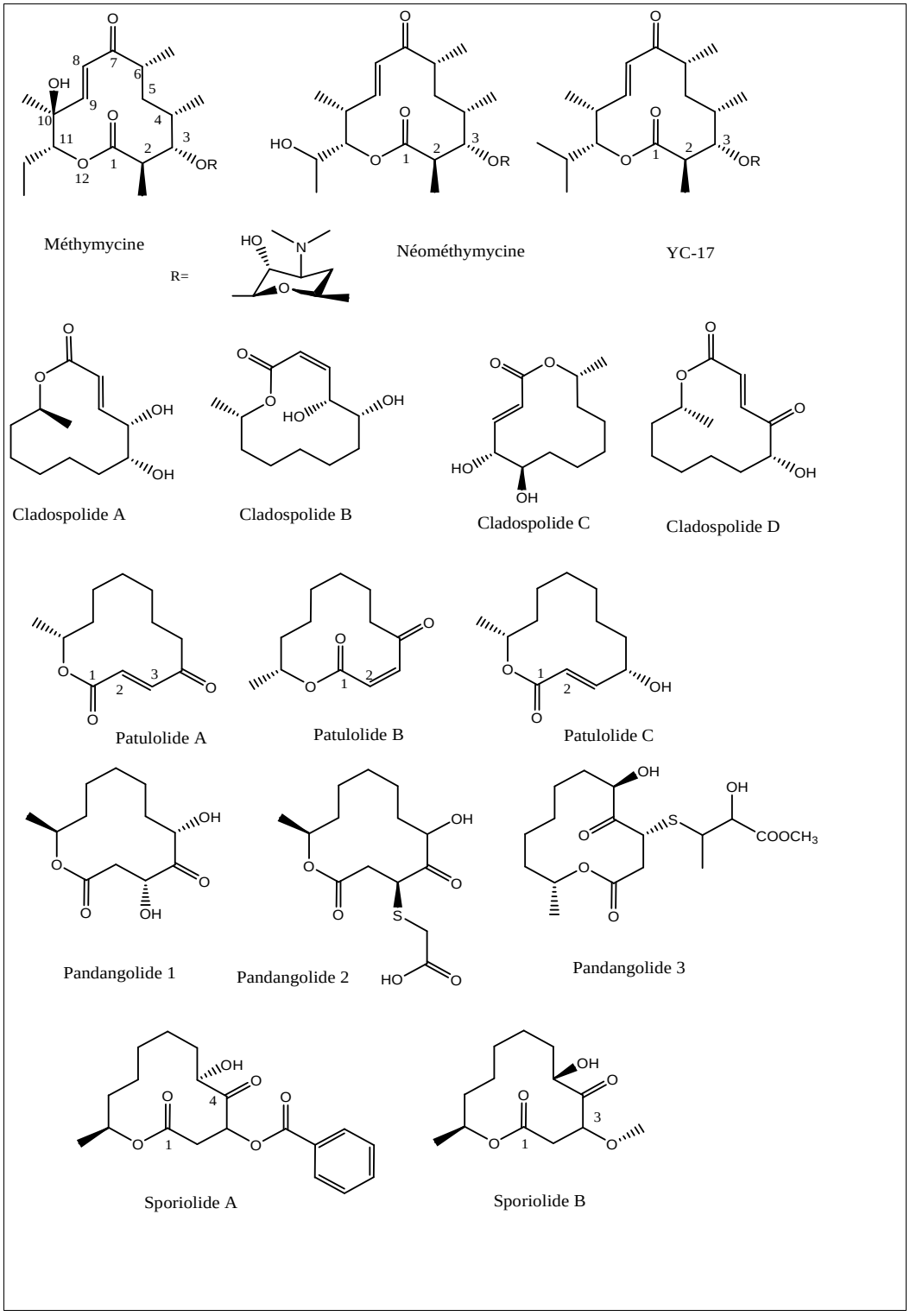


Fig.8. Chemical structure of the studied 12-membered macrolides

Compound 4 presents the low coefficient of division (1.189). When the coefficient of division is rather low, it has as a consequence a better gastric tolerance. Compounds 3 which has higher value (4.727), has capacity to be dependent on plasmatic proteins.

In the second part we perform the structure-activity relationship where we found that the polarizability values are generally proportional to the values of surfaces and volumes, the decreasing order of polarizability for these studied Macrolides (table 4).

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 [37].

Surface and distribution volume of these molecules are definitely higher than those of more polar molecules like the lipopeptides or beta-lactams. For example, Deleu et al. used Tammo software on the surfactins C13, C14 and C15 having cores similar to the macrolides [38]. They found that their surfaces vary from 129 to 157 $Å^2$, contrarily for these macrolides derivatives, surfaces vary from 389.778 to 721.440 $Å^2$.

The most important hydration energy in the absolute value is that of the compound 2: Cladospolide B (10.029 kcal/mol) and the weakest is that of compound 8: Patulolide A (0.330 kcal/mole). Indeed, in the biological environments the polar molecules are surrounded by water molecules.

Compound 2 has two donor site of proton (2OH), and four acceptor sites of proton (4O). Moreover, compound 8 has only three acceptor sites of proton (3O).

The first having higher value, it has one more acceptor site of protons.

This property supports the first compound, not only by fixing on the receiver, but also by activating. It is thus about an agonist. It has as a consequence i.e. a better distribution in fabrics. 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 [39].

4. CONCLUSION

The calculations carried out showed that these non-complexing macrocycles have a high conformational mobility. Also the mobility of dissymmetric macrocycles is lightly less important than that of symmetric macrocycles. They present many privileged conformations that do not a priori foresee a diastereoselection for envisaged reactions. This is in agreement with Still's works, on macrocycle 17, which yields many different conformations. The obtained diastereoselectivity for complexing macrolides is the result of the stereochemical control effect of the tricarbonyliron .This last factor constitutes a tool of the stereochemical remote control which permits us to foresee a priori the phenomenon of the stereoselectivity for envisaged reactions.

For macrolactones type B, a high diastereoselectivity was obtained. This is the result from the combination of stereochemical remote control with $Fe(CO)_3$ and local control exerted by methyl substitute.

The QSAR study, offers the ability to guide design and selection using Lipinski's rules to quickly identify compounds from the 12 membered macrolides series, which 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 relationship to search the preferred conformations to establish correlations between structural parameters and the various properties of the investigated macromolecules and improving the conception of new therapeutic drugs.

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