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Characterization of the Molecular Lipophilicity of Mycolactones A/B and C, Infectious Factors of *Mycobacterium ulcerans* Agent of Buruli Ulcer

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Authors' contributions

This work was carried out in collaboration among all authors. Authors KFK, JME and MGRK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author GSD and NZ managed the analyses of the study. Author LO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The work was undertaken as part of the Buruli ulcer control program. It is particularly about the determination of the lipophilicity of mycolactones A/B and C, infectious factors of *Mycobacterium ulcerans*, the agent of Buruli ulcer. The REKKER method and some free software such as MOLINSPIRATION, ACD/ChemSketch and EPIWED were used for the determination of the lipophilicity of mycolactones A/B and C. Very high logP values were found and respectively ranged from 12.11 to 11.41 for mycolactone A/B and 11.69 to 11.58 for mycolactone C. These values obtained from this coefficient, show that mycolactones A/B and C are naturally lipophilic and that actually reflects their effective presence in the subcutaneous fat of the infected area. These results are very encouraging and promising. They are key factors for a better understanding of the biological activities of the two mycolactones and pave the way for the proposal of a mechanism to annihilate their destructive effects.

Keywords: Mycobacterium ulcerans; mycolactone; molecular lipophilia; partition coefficient.

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1. INTRODUCTION

Buruli ulcer is a disease caused by *Mycobacterium ulcerans*, a microorganism belonging to the family of bacteria responsible for tuberculosis and leprosy [1]. This long-neglected disease, is prevalent in humid tropical and subtropical countries and has shown a significant increase in West Africa since 1980 [2]. This situation has led the World Health Organization (WHO) to classify it as an emerging disease and to recognizing it as a serious public health and development problem [3]. *Mycobacterium ulcerans* secretes a toxin called mycolactone into skin tissue, which is responsible for extremely deep tissue damage due to its cytotoxic and immunosuppressive properties. Currently, six (06) different naturally occurring molecular structures of mycolactones have been isolated [4]. Among them, the most virulent A/B and C forms found in Africa, are the subject of our study. The therapeutic arsenal against Buruli ulcer remains limited, despite the progress observed in medical care [5]. Antibiotic therapy and reconstructive surgery, with its high cost and numerous relapses (16 to 28%) in case of serious infection, remain the reference treatments [6]. Unfortunately, the mode of action of the toxin remains unknown or poorly understood by the medical world.

Until a few years ago, Buruli Ulcer (BU), which is an ulcero-necrotic infectious disease, was very little known to health professionals. And since it occurs in most cases in low-income countries, little research had been done on it. At the instigation of the WHO, partially completed studies provided some knowledge of the therapy of the disease. However, many challenges remain. In particular, control of the disease remains a concern of the ministries of health of the countries concerned and of the scientific community. However, aspects such as the mode of action and the physico-chemical properties of mycolactones remain unknown to the medical community in most BU management programs, which is not likely to stimulate the search for a sustainable solution to this disease which is constantly on the rise in developing countries. For this reason, in a research dynamic carried out on bioactive molecules, it is important to identify and control the relevant biological and pharmacological properties that are easily calculable from the molecular structure. To this end, theoretical chemists have at their disposal a set of tools and approaches to evaluate the molecular properties of various systems. Thus, the development and improvement of increasingly high-performance computer tools facilitates the study of complex systems as well as the study of highly advanced techniques and levels of computation. The human body is subjected to multiple exogenous and endogenous pollutants, which contribute to its destruction. It is constantly working to eliminate these pollutants. To free itself from all its waste, the organism must face a process of detoxification, which consists, among other things; in transforming lipophilic substances into hydrophilic ones. Lipophilia is an important molecular parameter. It is intimately linked to the notion of the division of a molecule between an aqueous and a lipid phase. It is now known that the ability of a molecule to be shared between two phases; partly conditions its biological properties such as transport, its diffusion through membranes, bioavailability (distribution and accumulation), affinity for a receptor, protein binding, pharmacological activity, toxicity and accumulation in aquatic organisms. This work, which is part of the Buruli ulcer control program, focuses on A/B and C mycolactones. It aims to determine the lipophilicity of these two toxins using the REKKER method and some free software such as MOLINSPIRATION, ACD/ChemSketch and EPIWED [7, 8], in order to predict and better understand their biological activities. Through this study it will be possible to propose a mechanism to annihilate the destructive effects of mycolactones A/B and C.

2. MATERIALS AND METHODS

2.1 MATERIALS

In this study, two mycolactones are used. These are mycolactones A / B and C. These mycolactones consist of a lactone nucleus of twelve (12) elements attached to two side chains (Fig. 1).

Mycolactone A/B was first isolated in 1999 in Malaysia [9], from natural strains of *Mycobacterium ulcerans*. Mycolactones A and B are cis- and trans-isomers. They are strongly represented in *Mycobacterium ulcerans* found in Africa, particularly in West Africa. Their empirical formula, which is $C_{44}H_{70}O_9$, was elucidated by Gunawardana et al. [10] in 1999 using UV and NMR spectroscopic methods. Mycolactone C was isolated from natural strains of *Mycobacterium ulcerans* from Africa, Asia (Malaysia, Japan), Australia and Mexico [11]. It has a well-defined molecular structure like

mycolactones A and B but differs from them in the number and arrangement of hydroxyl and methyl groups along its highly unsaturated side chain. To fight against these more or less toxic substances for our organism, the studies carried out over the last few years have made it possible to determine an important parameter which is the logarithm of the partition coefficient P. Its knowledge allows us to effectively assess the molecular properties of various organic substances. The logarithm of the partition coefficient P of a compound between water and octanol. Hansch and Fujita [12] in 1964, based on the work of Richet [13], Meyer [14] and Overton [15] have proposed to use the logarithm of the partition coefficient log(P), (replacing the olive oil-water system [16]) to understand the interactions of this molecule with biological membranes.

$$logP = log\left(\frac{C_{octanol}}{C_{H_2O}}\right) \quad (1)$$

The higher this coefficient (p>1, log(P)>0), more the substance is considered to be lipophilic. On the other hand, the lower the coefficient (p<1, log(P) <0); the substance is considered hydrophilic. Various statistical studies have shown optimal logP values illustrated by a log(P) scale (Fig. 2) [17].

mycolactone A/B

mycolactone C

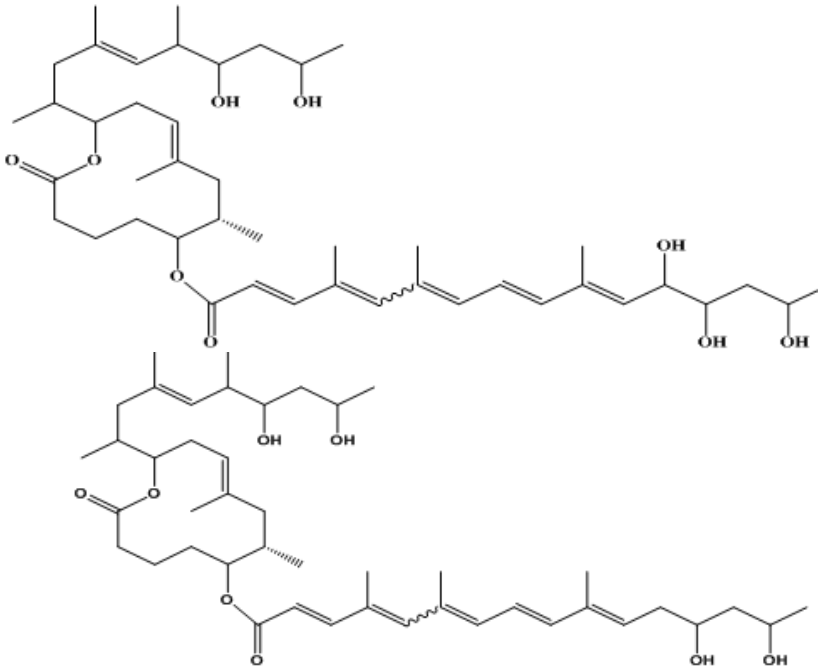


Fig. 1. Structure of mycolactones a / b and c

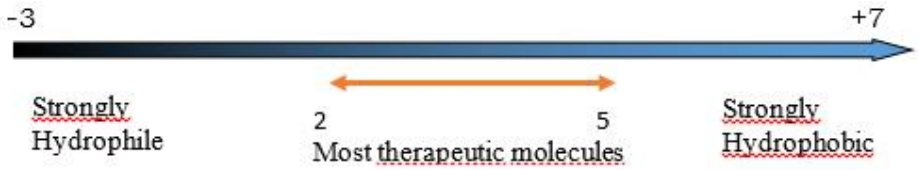


Fig. 2. Ladder of *log (P)*

2.2 METHODS

Most methods for determining the partition coefficient P suffer from the same disadvantage, namely that their field of application is relatively narrow. On the other hand, due to the intrinsic nature of some molecules, their logPs are inaccessible to the experiment. With the development of computational means, in particular computer science, the determination of logP in the field of computer-aided design has become possible. For this purpose, there are several methods of logP determination which differ from each other by the type of approximation performed. The main methods for determining the partition coefficient are as follows.

2.2.1 HANSCH method

HANSCH [18] considers that the substitution of a hydrogen of a radical R, which can be the benzene ring, by a substituent X (X = O, NH_2, CH_2 ⋯),, is equivalent to the insertion of a constituent of the type $X-H$ into this radical, i.e. OH for X = O, NH for X = NH_2, CH_3 for X = CH_2 ⋯, etc., which is the same as the substitution of a hydrogen of a radical X = O, $NH2$, · ⋯. He assigned to each substituent its own lipophilicity called the HANSCH parameter noted $\boldsymbol{\pi_X}$, so knowing the partition coefficient of the molecule RH, one can easily deduce the logP of the molecule RX using the following formula :

$$\boldsymbol{logP_{RX} = logP_{RH} + \pi X + \pi_{corr}} \qquad (2)$$

P_{RX} : partition coefficient of the molecule RX ;
P_{RH} : Partition coefficient of the molecule RH
π_X : Lipophilic parameter of substituent X ;
π_{Corr} : Corrective term taking into account the effect caused by branching, double bonds, ring closure, intramolecular bonds and molecule folding.

The HANSCH parameter π for benzene substituents is defined by :

$$\pi(X) = logP_{C_6H_5-X} - logP_{C_6H_6}$$

2.2.2 ABRAHAM equation

Abraham's equation [19] allows the logP to be expressed from a set of parameters characteristic of the solute, namely molecular volume (favoring lipophilicity), acidity and basicity by hydrogen bonding (favoring hydrophilicity) and polarity or polarisability (also favoring hydrophilicity). The form of this equation is :

$$logP = v.V + s.S + a.A + b.B + e.E + c$$

Capital letters indicate the properties of the solute :

- - V : molecular volume (ml/mol/100) ;
- - S: polarity/polarisability;
- - A: acidity by hydrogen bonding;
- - B: basicity by hydrogen bonding;
- -E: excess molar refraction (ml/mol/10) (depends on V and S).
- - Lower case letters indicate the properties of the solvent in relation to water:
- -v: Intensity of intermolecular bonds (v varies in the opposite direction);
- - s: Polarity/polarisability;
- - a: Hydrogen bond basicity;
- - b: Acidity by hydrogen bonding;
- - e: Combined influence of v and s

2.2.3 REKKER's method

According to REKKER, a molecule can be divided (theoretically) into elementary fragments; each having a partial hydrophobicity constant f_n and the number of identical fragments in the molecule is noted a_n. The logarithm of the partition coefficient P is obtained by adding the product of the constants a_n and f_n of all the fragments of the molecule [20]. It also takes into account some intermolecular effects (proximity of polar groups, hydrogen atom bound to a negative site, conjugation...). This contribution is the product of a constant called "magic constant" noted CM (C_M = 0.219), by a variable factor k_j called "key number". Thus, the expression of logP can be written as follows:

$$\log P = \sum_n a_n \,.\, f_n + C_M \sum_j k_j \qquad (3)$$

The value of k_j is fixed by empirical rules. On the other hand, f_n values have been tabulated for different organic solvent-water systems but are much more numerous for the octanol/water system. Indeed, this organic solvent presents many analogies between its physico-chemical properties and those of biological membranes. Table 1 gives the values of the hydrophobic constants for the main fragments. The constant is noted f_{al} when the fragment is bound to an

aliphatic chain and f_{ar} when it is bound to an aromatic ring.

2.2.4 Atomic method of GHOSE - VISWANADHAN [21]

$$\log P = \sum_i n_i \, . \, a_i \qquad (4)$$

$\mathbf{n_i}$: Number of atoms of type i ;
$\mathbf{a_i}$: Atomic constant of type i atoms.

2.2.5 Quantum method of KLOPMAN – IROFF

The quantum method of KLOPMAN - IROFF [22] (based on an approach to estimate the logarithm of the partition coefficient) is based on quantum chemistry calculations. For 61 simple organic compounds, atomic charge densities were determined using the MINDO/3 method and HÜCKEL method [23]. The mathematical model thus developed is as follows:

$$\begin{aligned} \log P = {} & 0.344 + 0.2078 n_H + 0.093 n_C \\ & - 2.119 n_N - 1.937 n_O \\ & - 1.389 q_C^2 - 17.28 q_N^2 \\ & + 0.731 q_O^2 + 2.844 n_A \\ & + 0.910 n_T \\ & + 1.709 n_M \end{aligned} \qquad (5)$$

- n_H, n_C, n_N, n_O : Number of atoms of hydrogen, carbon, nitrogen and oxygen respectively;

$-\ q_C^2, q_N^2, q_O^2$: Sum of the square of the charges of the respective atoms of carbon, nitrogen and oxygen or groups.

- n_A , n_T , n_M : Indicator variables that indicate the presence of respective acid/ester, nitrile and amide groups.

2.2.6 Quantum method of BODOR

The BODOR method [24] is a semi-empirical calculation method that uses certain properties calculated from molecular orbitals (SCF-MO) and certain geometrical properties (molecular surface area and a factor called "ovality" defined as the ratio of the occupied surface area to the minimum occupiable surface area) and structural properties (molecular weight, molecular volume, number of carbon atoms in the structure plus an additional variable for alkanes).

2.2.7 Computer methods

The development of computer tools contributes greatly to the availability of numerous means and automated methods of data processing. Thus, it becomes possible to find free software such as MOLINSPIRATION, ACD/ChemSketch and EPIWED adapted to the calculation of the partition coefficient [25,26]. These methods will be used to evaluate the molecular lipophilicity of mycolactones A/B and C. Indeed, KOWWIN/logP, Mi/logP and ACD/logP are substructure methods. KOWWIN/logP is a method that takes into account steric interactions between atoms, H-binding and polar substructure effects. Whereas the Mi/logP approach is based on functional groupings taking into account intramolecular H bonds and charge interactions. ACD/logP is based on the contributions of individual atoms and structural fragments and on the intramolecular interactions between the different fragments. During the ACD/logP computation, when fragment and interaction contributions are missing from the internal database, a special secondary algorithm is used to compute them. In any case, the computed values are provided with an uncertainty more or less equal to 0.6, a value indicated by the open-source ACD/ChemSketch software [26]. Beyond this uncertainty, it can be concluded that the compounds explored are new to the database of the ACD/logP program.

Two approaches were used to calculate the partition coefficient (logP) of mycolactones A/B and C in this work. The REKKER method is used not only for its simplicity of application, but also for its effectiveness in determining the lipophilicity of various molecules. The REKKER method is certainly effective in the rapid and simple determination of molecular lipophilicity, but it also has a number of shortcomings. These shortcomings include the incorrect description of the lipophilicity of complex molecules and the attribution of the same contribution to identical fragments belonging to different molecules. Therefore, these shortcomings indicate the limits of its application and the exploration of other new methods of calculation. The development of computer tools strongly contributes to the availability of numerous means and automated methods of data processing. Thus, it becomes possible to find free software such as MOLINSPIRATION, ACD/ChemSketch and EPIWED adapted to the calculation of the partition coefficient [10-12]. These methods will be used to evaluate the molecular lipophilicity of mycolactones A/B and C. Indeed, KOWWIN/logP, Mi/logP and ACD/logP are substructure methods. KOWWIN/logP is a

method that takes into account steric interactions between atoms, H-binding and polar substructure effects. Whereas, the Mi/logP approach is based on functional groups taking into account intramolecular H bonds and charge interactions. ACD/logP is based on the contributions of individual atoms and structural fragments and on the intramolecular interactions between the different fragments. During the ACD/logP computation, when the fragment and interaction contributions are missing from the internal database, a special secondary algorithm is used to compute them. In any case, the computed values are provided with an uncertainty more or less equal to 0.6, a value indicated by the open-source ACD/ChemSketch software [27]. Beyond this uncertainty, it can be concluded that the compound explored are new to the database of the ACD/logP program.

3. RESULTS AND DISCUSSION

3.1 Calculation of molecular lipophilicity by the REKKER method

The calculation of the logP partition coefficient was first performed on the lactone nucleus of mycolactones A/B and C, used as reference fragment. For the calculation of the coefficients of the other substituted compounds, the additivity rule of logP was applied to the two side chains noted respectively $\boldsymbol{R_1}$ and $\boldsymbol{R_2}$ contained in these molecules [9].

Table 1. Lipophilic fragment constant values according to REKKER

Fragment	$f_{aliphatic}$	$f_{aromatic}$
H	0.204	
C	0.110	
CH	0.315	
CH_2	0.519	
CH_3	0.724	
C_6H_5	-	1.902
N	-2.074	-0.979
O	-1.545	-0.450
F	-0.213	0.444
Cl	0.057	0.933
Br	0.258	1.134
NO_2	-0.915	-0.039
OH	-1.448	-0.353
CO	-1.633	-0.976
OCH_3	-0.821	0.274
Side by side aromatic rings	$+1C_m$	Pair of common vertices, as well as for each bond linking two cycles
Conjugated bonds	$+1C_m$	Double or triple bonds pair

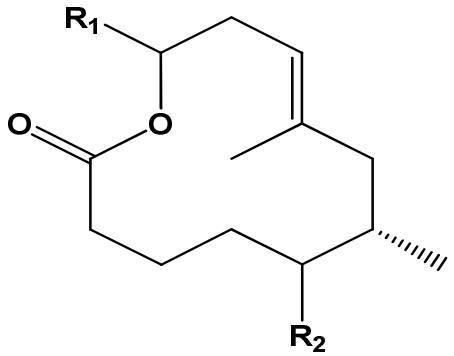


Fig. 3. Structure of the lactone nucleus of mycolactones A/B and C

The structure of the lactone nucleus consists of :

- (02) CH_3 groups
- (05) CH_2 groups
- (03) CH group
- (01) grouping O-C=O

Taking into account Table 1, the partition coefficient of the lactone nucleus of the two mycolactones is:

$$\log P(\text{lactone}) = 2.f_{al}(CH_3) + 5.f_{al}(CH_2) + 3.f_{al}(CH) + 1.f_{al}(O-CO) + C_M$$

$$\log P(\text{lactone}) = 2 \times 0.724 + 5 \times 0.519 + 3 \times 0.315 + 1 \times 0 + 0.219$$

$$\log P(\text{lactone}) = 5.207$$

For the calculation of mycolactone A/B and C partition coefficients, the lactone nucleus is considered as a fragment. Thus, the additivity of the logarithm of the partition coefficients of the lactone nucleus and the two side chains, allowed to determine the logarithm of the partition coefficients of the two mycolactones A/B and C.

- Side chain R_1

The structure of the side chain R_1 consists of:

- (04) CH_3 groups
- (02) CH_2 groups
- (05) CH groups
- (02) OH groups

$$\log P(R_1) = 4.f_{al}(CH_3) + 2.f_{al}(CH_2) + 5.f_{al}(CH) + 2.f_{al}(OH)$$

$$\log P(R_1) = 4 \times 0.724 + 2 \times 0.519 + 5 \times 0.315 + 2 \times (-1.448)$$

$$\log P(R_1) = 2{,}613$$

- Side chain R_2

The structure of the side chain R_2 consists of:

- (04) CH_3 groups
- (01) CH_2 group
- (10) CH groups
- (03) OH groups
- (01) O-C=O group

$$\log P(R_2) = 4.f_{al}(CH_3) + 1.f_{al}(CH_2) + 10.f_{al}(CH) + 3.f_{al}(OH) + 1.f_{al}(O-CO)$$

$$\log P(R_2) = 4 \times 0.724 + 5 \times 0.519 + 10 \times 0.315 + 3 \times (-1.448)$$

$$\log P(R_2) = 4{,}297$$

$$\log P(\text{mycolactone A/B}) = \log P(\text{lactone}) + \log P(R_1) + \log P(R_2)$$

$$\log P(\text{mycolactone A/B}) = 12{,}117$$

- Side chain R_1

The structure of the side chain R_1 consists of :

- (04) CH_3 groups
- (02) CH_2 groups
- (05) CH groups
- (02) OH groups

$$\log P(R_1) = 4.f_{al}(CH_3) + 2.f_{al}(CH_2) + 5.f_{al}(CH) + 2.f_{al}(OH)$$

$$\log P(R_1) = 4 \times 0.724 + 2 \times 0.519 + 5 \times 0.315 + 2 \times (-1.448)$$

$$\log P(R_1) = 2.613$$

- Side chain R_2

The structure of the side chain R_2 consists of :

- (04) CH_3 groups
- (02) CH_2 groups
- (09) CH groups
- (02) OH groups
- (01) O-C=O groups

$$\log P(R_2) = 4.f_{al}(CH_3) + 2.f_{al}(CH_2) + 9.f_{al}(CH) + 2.f_{al}(OH) + 1.f_{al}(O-CO)$$

$$\log P(R_2) = 4 \times 0.724 + 2 \times 0.519 + 9 \times 0.315 + 2 \times (-1.448)$$

$$\log P(R_2) = 3.873$$

$$\log P(\text{mycolactone C}) = \log P(\text{lactone}) + \log P(R_1) + \log P(R_2)$$

$$\log P(\text{mycolactone C}) = 11.693$$

All the lipophilicity values of both molecules are positive, so we can say that they are lipophilic: logP (mycolactone A/B) > logP(mycolactone C): This increase in lipophilicity is due to the

bstitution of a hydrogen by a hydrophobic OH fragment.

3.2 Calculation of logP According to free Software

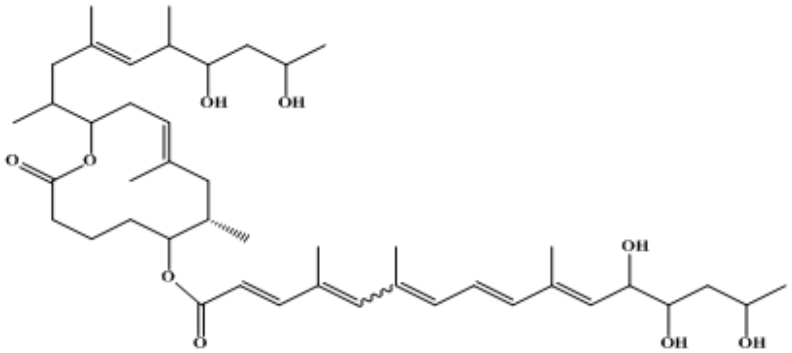
The values of logP obtained using an open source software are presented in the table below.

The lipophilicity values of both molecules are all positive. Thus, according to the software, we have lipophilic molecules. The arguments developed in the case of REKKER are valid here because the lipophilic character of the molecules are consistent in this case and shows a similar trend.

$$\mathbf{logP(mycolactone\ A/B)} > \boldsymbol{l}\mathbf{ogP(mycolactone\ C)}$$

The values predicted by the open source software are high (logP > 11) and are almost the same for each mycolactone. These values are clear indications that the different molecules are in the ACD/Labs database and are very lipophilic. Since biological membranes are lipophilic, the higher the degree of lipophilicity of the toxin, the better it passes through the membranes and evolves towards the lipoproteins in the blood, which are responsible for supplying the cells with lipidic substances. Analysis of the logP partition coefficient values obtained from the REKKER method and the free software used (Table 2), shows that the values are almost the same for each molecule regardless of the calculation method performed during our analyses. This shows that mycolactones A/B and C belong to the same family of toxins. The very high logP values of the molecules (12.11 to 11.41 for mycolactone A/B and 11.69 to 11.58 for mycolactone C), indicate that these the studied molecules are naturally lipophilic substances.

- **Mycolactone A/B Chemical Formula : $C_{44}H_{70}O_9$; $M_{A/B}$ = 742 g/mol**



- **Mycolactone C Chemical Formula : $C_{44}H_{70}O_8$; M_C = 726 g/mol**

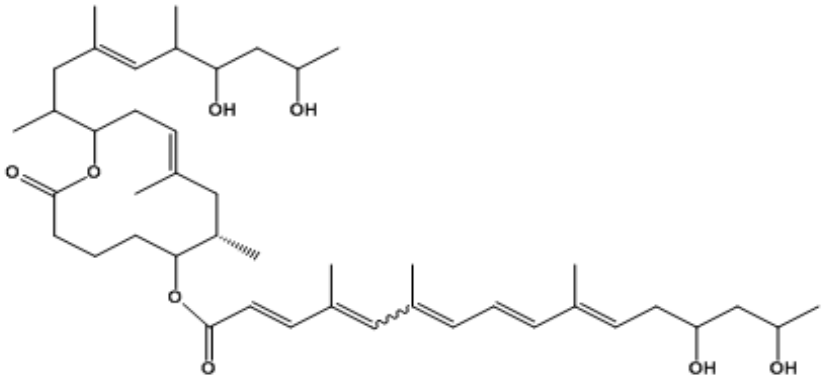


Table 2. logp values of mycolactones A/B and C according to open source software

Software (free)	ACD/logP	KOWWIN/logP	Mi/logP	logP (average)
Mycolactone A/B	11.45	11.35	11.43	**11.41**
Mycolactone C	10.57	10.60	10.58	**10.58**

The study conducted by Abgueguen et al. of the Infectious and Tropical Diseases Department of the University Hospital Center (CHU) of Angers (France) on the theme "Buruli ulcer or mycobacterium ulcerans infection", showed the lipophilic character of mycolactones [2]. Mycolactones, apolar molecules, consisting of a lactone nucleus and a highly unsaturated fatty acid side chain, have an affinity for apolar solvents such as lipids (fats) and are therefore soluble in skin and subcutaneous fat. The very high partition coefficient values (LogP > 7) obtained for mycolactones A/B and C in our work show that both molecules are lipophilic. These results are in harmony with those of Abgueguen et al. The presence of mycolactone in necrotic tissue is seen in the yellowish necrotic center observed at the periphery of the wounds.

Furthermore, these findings reflect their particularity to penetrate more easily into biological membranes and promotes their good affinity with the fats located in the necrotic part.

4. CONCLUSION

Using REKKER method and an open source software, the molecular lipophilicity of mycolactones A/B and C was investigated. Knowledge of the lipophilicity of these two toxins is primarily based on the interpretation of the partition coefficient (logP). The values obtained from this coefficient revealed that mycolactones A/B and C are naturally lipophilic. Lipophilic substances have the particularity to penetrate more easily all types of biological membranes. This reflects the actual presence of mycolactones A/B and C in subcutaneous fat in the infected area. These results are very encouraging and promising, as they could be used as strong baseline for some future investigations for the modification of the infected part which is rich in fat using , a medium dominated by polar solvents. This medium will contribute to the transformation of mycolactones A/B and C, lipophilic molecules into hydrophilic substances. The knowledge of the biological properties of these toxins and the transformation of the infected part of the patient into a medium rich in polar solvents will lead to a significant advance in the understanding of the mode of action of mycolactones, as well as the annihilation of their destructive effects.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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