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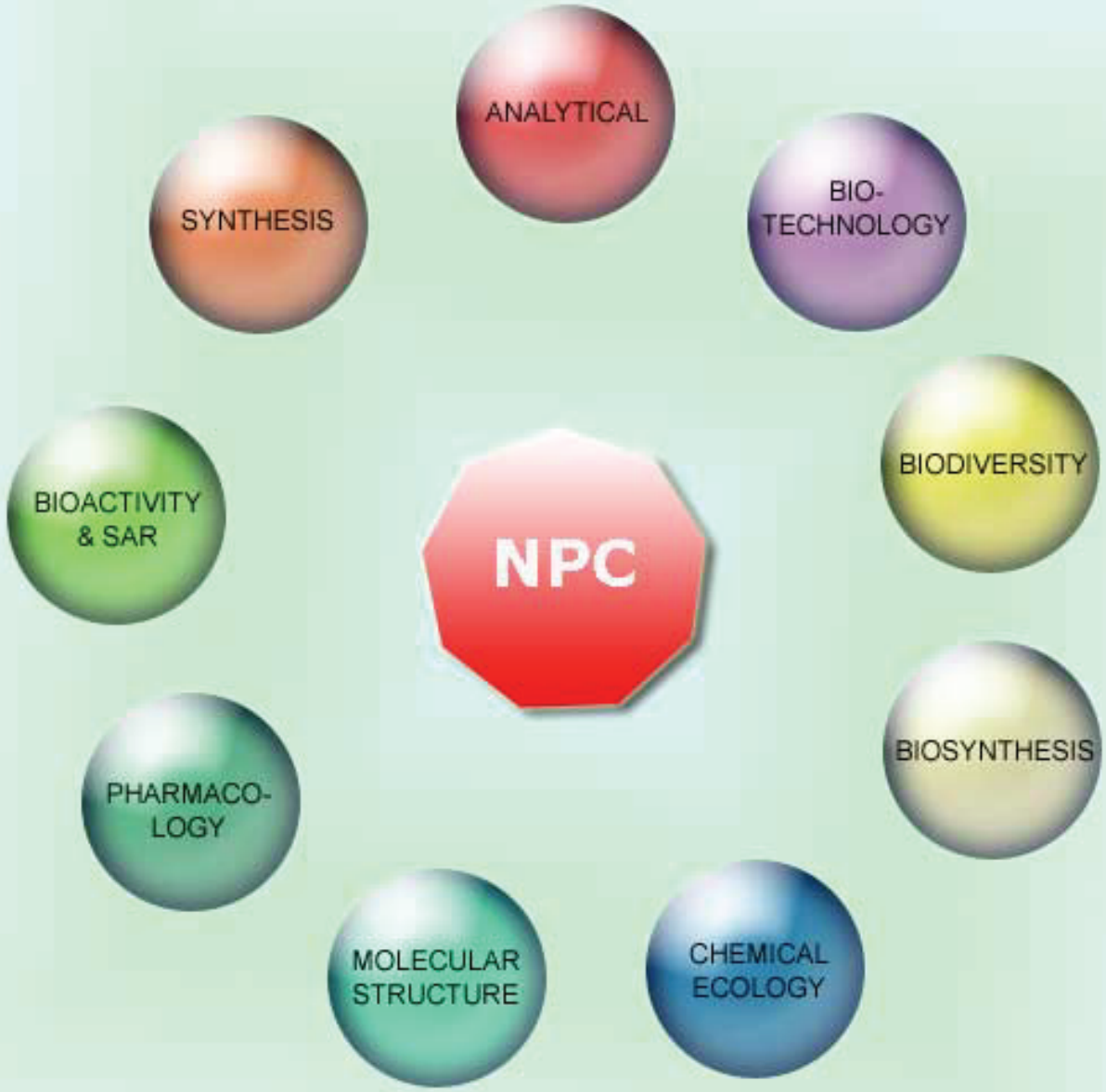

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Professor Alejandro F. Barrero
On the Occasion of his 68th Birthday

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Study of Anti-Tuberculosis Activity Behaviour of Natural Kaurane and Trachylobane Diterpenes Compared with Structural Properties Obtained by Theoretical Calculations

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A set of seven diterpenes, three kauranes and four trachylobanes, isolated from the African plant *Psiadia punctulata* were assayed against *Mycobacterium tuberculosis* and reached activity comparable with cycloserine, a second line drug used to treat tuberculosis (TB). Several structural properties of those diterpenes, such as lipophilicity, HOMO and LUMO energies, charge density, and intramolecular hydrogen bond (IHB) formation, were obtained by theoretical calculations and compared with their activities. Peculiar correlations were observed, especially between activity, lipophilicity and IHB formation.

Keywords: Diterpenes, Kauranes, Trachylobanes, *Psiadia punctulata*, Structure-activity relationship, Lipophilicity, Computational study.

The chronic disease called tuberculosis (TB) is predominantly caused by *Mycobacterium tuberculosis* and is transmitted through air [1], which can be considered as an additional problem for the control of this pathology. TB ranks as the second leading cause of death from a single infectious agent and killed 1.5 million people in 2013 [2]. At least 9 million people fell ill with TB in the same year [2]. From the active TB cases, 75% are pulmonary, while the other 25% affects meninges, lymphatic system, bones, pleura, joints and so on [1].

Some *M. tuberculosis* strains have developed resistance to the current drug treatments and so now there is Multi-Drug Resistant TB (MDR-TB) [3], which can be considered as a worsening of the TB problem. Moreover, latent infection can be seen as an additional difficulty while dealing with this disease [3]. In this case, most of the anti-mycobacterial agents are ineffective against this metabolically dormant pathogen [3]. The typical treatment for latent TB is monotherapy with isoniazid, which is really the only effective drug in this case [4]. The drugs in use for acute TB treatment are mostly the first line anti-TB drugs streptomycin, isoniazid, pyrazinamide, rifampicin and ethambutol [1]. The resistance to first line drugs and the availability of drugs also lead to the use of second and third line anti-TB drugs [1]. Another serious matter that one has to take into account when dealing with TB treatment is the possibility of mild to severe hepatotoxicity induced by isoniazid [4]. Due to this side effect researchers had to seek another form of administration of isoniazid to avoid the liver issue [4].

However, in the last five decades only two new anti-TB drugs have been introduced to the market [5]. Some practical obstacles to the search for new anti-TB agents are the lack of financial incentive, slow growth and highly contagious nature of *M. tuberculosis* [6]. Despite these difficulties and taking into account what was known about TB treatment, there is a consensus between several researchers about the urgent need to develop new anti-TB agents [5, 6].

Diterpenes constitute an important class of Natural Products (NP). Several substances from this class are known to display a great variety of biological activities, going from antibacterial through anti-inflammatory to antitumor activity [7]. Their potential is highlighted by the dedication of several researchers to understand better the chemistry and to synthesize bioactive diterpenes [8]. Either for a more detailed biological study or for a more accurate spectroscopic structure assignment, researchers have concentrated efforts on the synthesis of compounds of this Natural Product (NP) class [8]. As well as other terpenoids, some diterpenes have already shown remarkable antituberculosis activity [6]. Nevertheless, only a limited number of components of this class of NP have been assayed against *M. tuberculosis* [6]. Due to this, diterpenes can be placed as promising structures in the search for new antituberculosis agents.

Psiadia punctulata (DC) Vatke is an African, erect round-topped shrub whose leaves are covered by an exudate, mainly when they are young [9, 10]. This exudate seems to be responsible for the plant's drought resistance and also for the grazing-deterrent effect which makes browsing herbivores like giraffes and goats avoid it, even during severe drought [10,11]. This plant is popularly used for treatment of colds and fever, for the removal of ectoparasites from cattle [12] and for the relief of abdominal pain [10] in Kenyan ethno-medicine. Some proven effects of the plant exudates are antifungal and anti-feedant activities [11].

Plant leaf exudates are known often to contain mixtures of terpenoids and flavonoids [10]. The chemistry of the diterpenes of this exudate could explain the cited activities [10]. As shown in previous works, the exudate from leaves of *P. punctulata* indeed is comprised of terpenoids, among them diterpenes from the classes of kauranes and trachylobanes [9, 11, 12]. Kauranes have already been reported for several families of higher plants and some of them have been cited as anti-inflammatory, antibacterial, antifungal, antitumor,

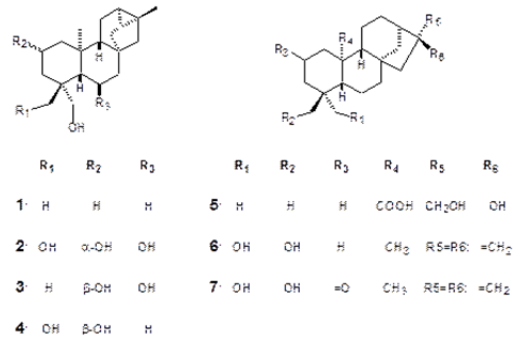

Figure 1: Structures of the diterpenes isolated from *Psiadia punctulata*.

and cytotoxic agents [13]. On the other hand, the biological activities of trachylobanes are poorly investigated, although they already presented vasorelaxant and cytotoxic properties [13]. Due to our research interest in terpenoids [14-17], especially diterpenes and their biological activities [18-20], we worked with kaurane and trachylobane diterpenes that were available in the leaf exudate of *Psiadia punctulata* [9, 11, 12], and shown in Figure 1.

The main goal was to verify the relationship between structure properties and activity level, aiming to understand a bit more about the structure-activity relationship. We were mostly interested in verifying if the anti-tuberculosis activity of each molecule has any relation to some specific aspects of the structures, like lipophilicity, that could influence the molecule's mechanism of action. These structures were initially considered interesting due to their differences with the number of oxygenated groups. The difference between trachylobane and kaurane diterpene skeletons is certainly also an interesting issue for this evaluation.

All seven compounds were assayed against *M. tuberculosis*, as described above, and furnished some interesting results. Results of the anti-tuberculosis activity are summarized in Table 1.

Despite the fact that three of the assayed diterpenes displayed weak activity, with MIC results of 200 $\mu g.mL^{-1}$, three others presented a very interesting value of 50 $\mu g.mL^{-1}$. The anti-tuberculosis activities of compounds **1**, **6** and **7** are comparable with the activity of the "second line" anti-TB drug cycloserine [21]. When μM values are compared, these diterpenes activities are closer to the lower value in cycloserine's range of activity. Moreover, one diterpene (**2**) presented also an intermediate value of activity. This can be highlighted as a relevant set of results. One of the main goals is to verify if this activity variation can be related to some specific structure property.

Table 1: Anti-tuberculosis activity for the assayed compounds **1** to **7**.

Compound	*MIC (μg.mL^{-1})*	*MIC (μM)*
1	50	173.3
2	100	297.2
3	200	624.1
4	200	624.1
5	200	594.4
6	50	164.2
7	50	157.0
Cycloserine [41]	12.5 - 50	122.4 - 489.8
Isoniazid	0.06	0.44

Theoretical calculations were undertaken in an effort to find molecular properties that could be correlated with the anti-tuberculosis activity of the diterpenes. Lipophilicity was taken into account, as this property is suggested by some authors to be responsible for the antibacterial activity [22]. It is considered an important parameter in medicinal chemistry and is pointed out as a very relevant requisite in understanding drug action [23]. There is a hypothesis that bacterial lysis caused by diterpenoids occurs due to the insertion of those structures into the cell membrane with consequent disruption [22]. The present comparison could clarify if this relevance to activity could also be validated for *M tuberculosis*.

Lipophilicity for compounds **1** to **7** was considered through log*P* calculated values, presented on Table2.

The calculated log*P* is defined as the ratio of the concentration of a substance in organic and aqueous phase [23]. Thus, a higher value suggests a higher lipophilicity. However, the partial miscibility of octanol in water can lead to different results from those obtained with a nonpolar solvent such as hexane [24]. Thus, both models were taken into account in the present work – octanol/water and hexane/water.

A comparison of log*P* values considering only compounds **1** to **4** shows a clear correlation between activity and lipophilicity. In this group of compounds with a trachylobane skeleton, the higher the lipophilicity, the higher was the activity. Only a peculiar detail is noted for compounds **3** and **4**, when considering both solvent/water systems: compound **3** presented a slightly higher lipophilicity in the octanol/water system, while compound **4** was a little more lipophilic in hexane/water. This could be considered in agreement with the lipophilicity/activity relationship presented above, taking into account that **3** and **4** showed the same activity level and that their lipophilicities are of the same magnitude in both systems. For the diterpenes with a trachylobane skeleton, it seems that lipophilicity is relevant to the anti-tuberculosis activity.

Further comparison can be made considering compounds **1** to **4**, **6** and **7** and the log*P* values obtained in the hexane/water system. Excluding only compound **5**, the three more active compounds presented the three higher values of log*P* (positive values). Compound **2**, with intermediate activity, comes next and the less active compounds presented the lowest value for log*P*. It is noteworthy that, even with this new group, there is still some order relating activity and lipophilicity. Another relevant consideration to be taken into account is that the log*P* values obtained in the octanol/water model may be overestimated when compounds are able to form hydrogen bonds [24, 25]. As all compounds in the present work have at least one hydroxyl group, the hexane/water model is the most reliable, as pointed out [24, 25]. This reinforces the probability of the relevant contribution of lipophilicity to the activity against *M. tuberculosis* for all those compounds.

The frontier molecular orbitals HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) constitute a structural property that can be considered for the understanding of molecular interactions. These orbitals play an important role in the chemical reactivity of molecules and participate in chemical reactions and interactions [26]. Thus, these orbitals could probably play a role also in biological activity, since several mechanisms of action are dependent on effective interactions between an active compound and an interaction site in a biological organism. The HOMO acts as an electron donor [26] and higher values of the energy for this orbital (E_{HOMO}) indicate a greater ease of electron donation to the receptor [27]. The LUMO acts as an electron acceptor [26] and lower values for this orbital's energy (E_{LUMO}) determines that the receptor would accept electrons [27]. The difference between both energies (ΔE_{gap}) reflects the molecule's chemical reactivity and stability [26, 27]. The ΔE_{gap} could also be related to activity in some cases. The values found

Table 2: Calculated lipophilicities, HOMO and LUMO energies and ΔE_{gap} for compounds **1** to **7***.

Compound	log*P*		E_{LUMO}	E_{HOMO}	ΔE_{gap}
	hexane/water	octanol/water	(Hartree)		(eV)
1	4.81	5.93	-0.000388	-0.213398	5.80
2	-0.45	3.82	-0,006041	-0,214256	5.67
3	-1.41	3.51	-0,001558	-0,215157	5.81
4	-1.17	3.46	-0,005666	-0,214265	5.68
5	0.40	4.80	-0,048895	-0,219353	4.64
6	3.43	4.85	-0,022311	-0,21178	5.16
7	0.19	2.79	-0,074741	-0,211261	3.71

* lipophilicities expressed by their log*P* values – COSMO-RS methodology; E_{HOMO} and E_{LUMO} in Hartree units; $\Delta E_{gap} = E_{LUMO} - E_{HOMO}$ in eV. Calculations performed at BP/TZP level of theory.

and presented in Table 2 showed that this is not the case. They could not be related to activity in our samples. Nevertheless, the HOMO and LUMO distribution in the molecule should be somehow relevant to activity. If they are electron donors and receptors, respectively [26], they could be directly related to interactions with the pharmacophoric group in active molecules. Therefore, the calculated HOMO and LUMO for compounds **1** to **7** are depicted in Figure 2.

A close observation of the individual figures above may enable some speculation about some behaviors previously observed. For substances **1** to **4**, HOMO and LUMO distribution in the molecules present the same pattern. HOMO is always mostly located at the extreme right of the molecule, in the complex polycyclic system C, near positions 12, 15, 16 and 17. LUMO, on the other hand, always appears in the A ring, near positions 1 to 4, more specifically involving substituents in positions 2, 18 and 19.

For substances **5**, **6** and **7**, there are different distributions in comparison with the four other compounds and also a different distribution between them is observed. There is a similar distribution of HOMO for all compounds, but LUMO appears in different regions in compounds **5** to **7**. In all cases, including compounds **5** to **7** the HOMO concentrates mostly near the bicyclic system C. Nevertheless, for compound **5,** LUMO is concentrated near ring B, probably due to the carboxyl group. This is the only configuration of LUMO in this ring in all the studied systems. Compound **6** is the only one that presents LUMO exactly in the same region that it presents HOMO. Although compound **7** presents the most similar distribution of LUMO in comparison with compounds **1** to **4**, there is a considerable difference. In this case, LUMO is concentrated near position 3, probably involving the carbonyl group.

Despite the fact that the mechanism of action is either not known or has not been taken into account, these HOMO and LUMO distributions may somehow influence the activity.

Compounds **1** to **4** present a direct correlation between activity and lipophilicity calculated in both systems, as discussed earlier. These compounds are also the ones that show the same distribution of HOMO and LUMO orbitals. Maybe this distribution of orbitals has some influence on the molecular interactions that leads to this activity.

Compounds **5**, **6** and **7**, which showed different HOMO and LUMO distributions, also showed different behavior due to activity related to lipophilicity, as highlighted before. Both compounds **6** and **7** were in agreement with the relation between activity and lipophilicity, but only for the hexane/water model. Compound **5**, on the other hand, could not fit in any lipophilicity comparison. It is possible that a more detailed study of molecular interactions could clarify the influence of HOMO and LUMO orbitals distribution with lipophilicity and molecular-membrane interactions.

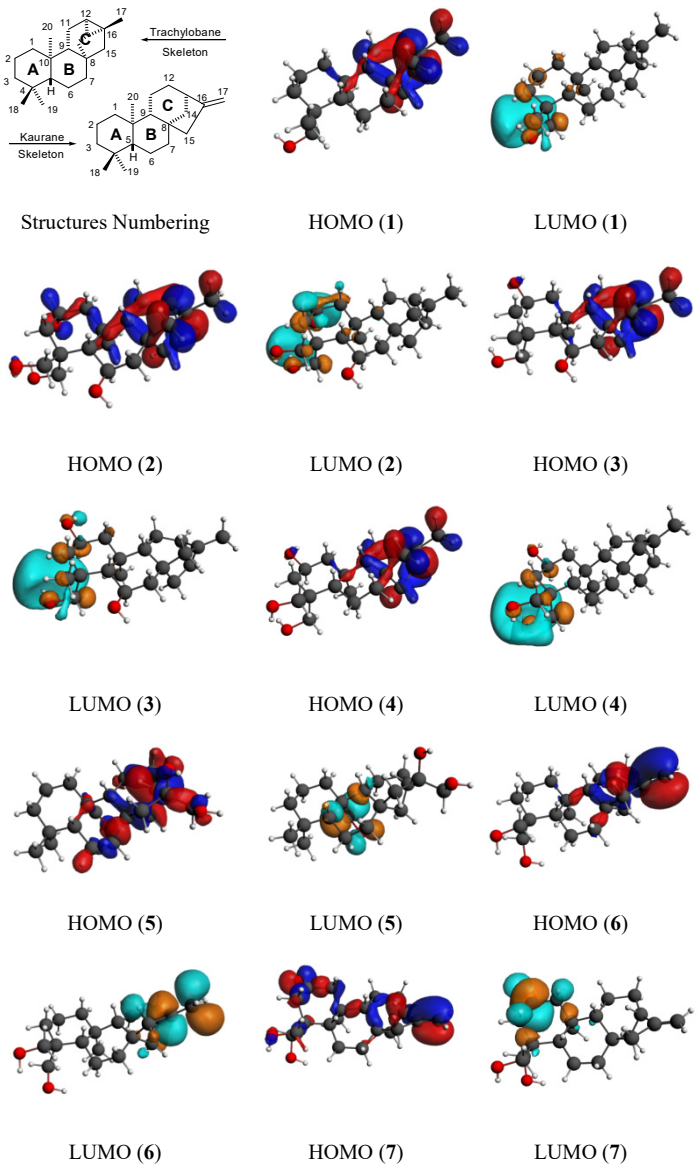

Figure 2: Structure numbering; HOMO and LUMO for compounds **1** to **7**. All molecules plotted in the same orientation as depicted in Figure 1.

The exact relationship between activity, lipophilicity and HOMO and LUMO distribution in the molecules is not yet clear. However, when lipophilicity was considered, the molecules were grouped in a manner considerably resembling that in which they were grouped after these HOMO-LUMO considerations. These interactions may be somehow related to each other. Further study could make this subject even clearer.

Molecular interactions between active compounds and target organisms as cited above could certainly depend on many other factors. The size of a molecule, expressed as its area, as well as its volume, is certainly important for interaction at the active site. If this interaction depends on the insertion of the molecule inside a given cavity, or if the interaction surface is of a certain area, there could be a molecular size limitation for activity. In those cases, if a molecule does not fit the area or the cavity, probably no other molecular feature would matter. However, if several molecules fit the assumed cavity or contact area, other factors would be more relevant to each molecule's activity. All area and volume calculated values for compounds **1** to **7** are plotted in Table 3.

Table 3: COSMO surface area and COSMO volume for substances **1** to **7**. Area given in $(Å)^2$ and Volume given in $(Å)^3$.

Compd.	Volume $(Å)^3$	Area $(Å)^2$
1	372.40	302.81
2	400.05	320.81
3	392.42	318.78
4	392.15	318.47
5	405.26	327.59
6	387.29	315.29
7	391.16	319.10

The attempt was not successful to find a direct correlation between activity and the area of the molecules of compounds **1** to **7**. Nevertheless, evaluation of the volumes brings interesting information: the three more active molecules are exactly the three less bulky ones. This can suggest that at least one probable mechanism of action could involve some kind of interaction that is limited by molecular volume.

Another structural property is related to the charge density of the molecules. Even if the mechanism of action is not clarified and the interaction between the active compound and the interaction center in the biological organism is unknown, it cannot be denied that charge density influences molecular interactions. The challenge is to find a relationship between these structural properties and molecular behavior, which can lead to a better structure-activity comprehension. Therefore, charge density surfaces were calculated for all compounds, as shown in Figure 3.

The red part represents positive COSMO charge density (the underlying molecular charge is negative), the blue part negative COSMO charge density (the underlying molecular charge is positive). It is also possible to look at the COSMO surface points themselves. The small spheres represent the COSMO surface points that are used for the construction of the COSMO surface

Initially it is worth mentioning that all molecules were plotted in the same orientation as in Figure 1. Thus, the stereochemistry of the basic skeleton is always the same, providing easier comprehension.

The most evident difference observed in all plotted charge density surfaces is that six of these molecules exhibit their most negative region in the left side of the figure, corresponding to the ring A region (see Figure 2). Only compound **5** exhibits the most negative region on the right side, corresponding to its bicyclic system C. Compound **5** is the only one that did not fit the correlation between lipophilicity and activity previously presented, not even for the hexane/water model. Moreover, if not only the most negative region is observed but any negative region, another interesting result can be attained. The only compounds that present a significant negative surface on the right side of the plotted molecule are compounds **5** to **7**. This is due to compound **5** having both OH groups in positions 16 and 17, and compounds **6** and **7** their double bond in the same region. Compounds **5**, **6** and **7** are the ones that were not in

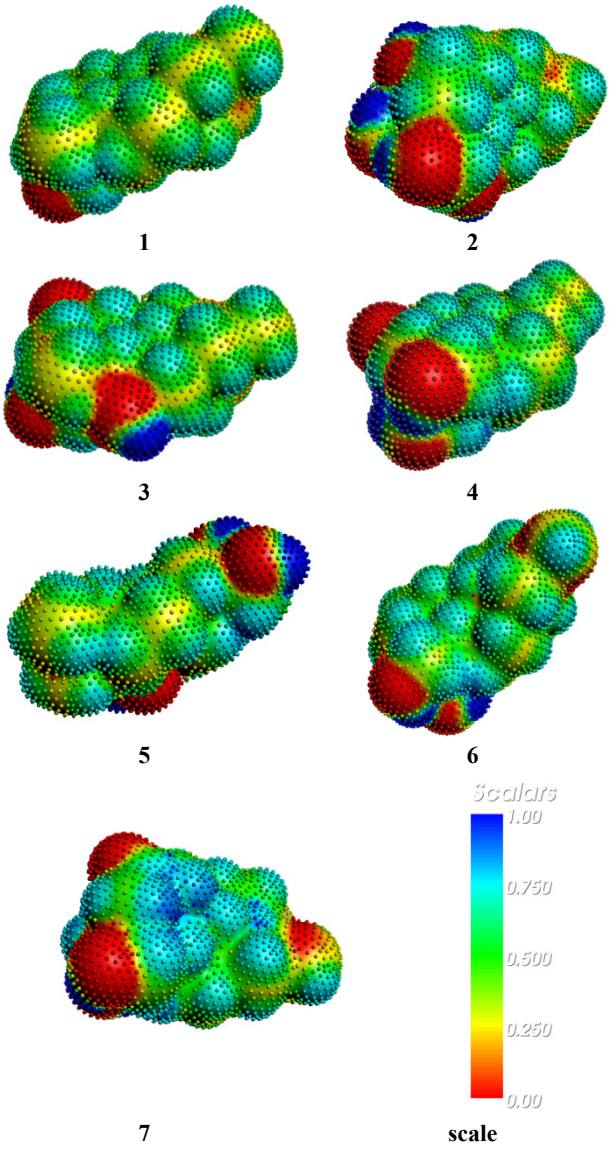

Figure 3: COSMO-RS (Conductor-like Screening Model for Real Solvents) surfaces (BP/TZP level) for compounds **1** to **7**. All molecules plotted in the same orientation as depicted in Figure 1.

agreement with the lipophilicity-activity considerations taking into account both systems (octanol/water and hexane/water). Once again the molecular grouping is similar to that obtained previously.

Another structural property that could be related to activity concerns the possibility of intramolecular hydrogen bond formation. To consider this possibility, calculations were undertaken and results are summarized in Figure 4 and Table 4.

Considering the QTAIM theory, one of the characteristics of hydrogen bonds is the existence of a bond path (BP) between the hydrogen donor and acceptor atoms containing an interatomic surface (IAS) and a Bond Critical Point (BCP). Considering compound **2**, it is observed that three –OH groups are involved in (two) intramolecular hydrogen bonds of the type O-H···O, while another group interacts via a weak C-H···O hydrogen bond. On the other hand, only C-H···O hydrogen bonds are observed for compounds **3** and **5**. Compounds **6**, **4**, and **7** exhibit only one O-H···O intramolecular hydrogen bond between the –OH groups. The characterization of intramolecular and/or intermolecular interactions

can be performed in terms of local properties at critical points. According to the criteria established by Popelier, the electron density (ρ_b) of a hydrogen bond should be in the range between 0.002 a.u, and 0.034 a.u. [48-50]. For the Laplacian of the electron density ($\nabla^2\rho_b$), this range should be around 0.024-0.139 a.u. [28-30]. For all studied compounds the values of the electron density and the Laplacian of the electron density obeyed the limits proposed by Popelier for hydrogen bonds (Table 4).

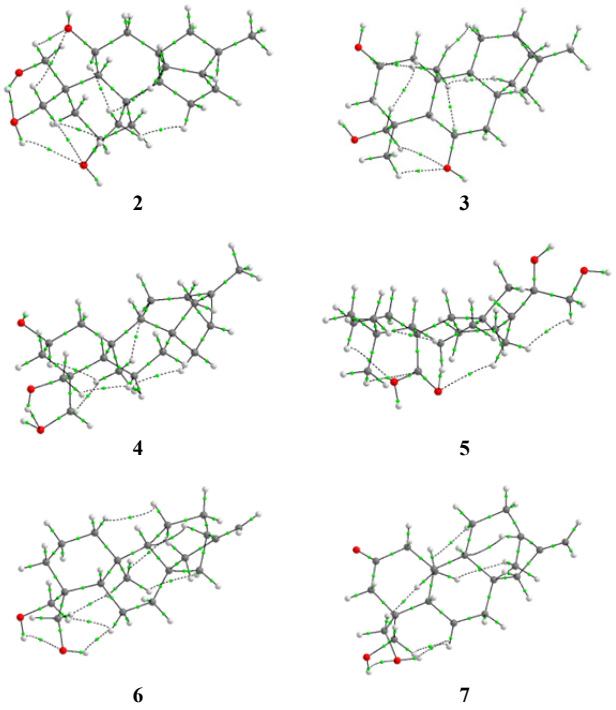

Figure 4: Molecular graphics for compounds **2** to **7**. Black lines represent the Bond Paths (BPs) and green spheres depict the Bond Critical Points (BCPs).

Table 4: Bond Critical Points (BCP) properties for the O-H···O and C-H···O hydrogen bonds in compounds **2** to **7**.

Compd.	Prop.	BCP			
		O-H···O (a)	O-H···O (b)	C-H···O (a´)	C-H···O (b´)
2	ρ_b	0.0060	0.0262	0.0191	0.0154
	$\nabla^2\rho_b$	0.0226	0.0841	0.0724	0.0522
3	ρ_b			0.0170	0.0083
	$\nabla^2\rho_b$			0.0656	0.0326
4	ρ_b	0.0294			
	$\nabla^2\rho_b$	0.0919			
5	ρ_b			0.0085	0.0119
	$\nabla^2\rho_b$			0.0297	0.0465
6	ρ_b	0.0147			
	$\nabla^2\rho_b$	0.0573			
7	ρ_b	0.0118			
	$\nabla^2\rho_b$	0.0493			

*a.u. where ρ_b = electron density; and $\nabla^2\rho_b$ = Laplacian of the electron density.

This property must be considered when seeking a better comprehension of the relevance of lipophilicity in anti-tuberculosis activity. This was initially considered starting from Urzúa and coworkers proposition about antibacterial activity of terpenoids [22].

However, this proposed hypothesis [22] includes further considerations involving the presence of hydrogen-bond-donor (HBD) groups. As proposed by the hypothesis, an HBD group strategically positioned in the molecule was an important requirement for activity. Nevertheless, the presence of a second HBD group would reduce the lipophilicity and thus reduce activity [22]. Moreover interactions between HDB groups through intramolecular hydrogen bonds might compete with intermolecular interactions and change activity [22].

Furthermore, the formation of intramolecular hydrogen bonds (IHB) in drug molecules is hypothesized to facilitate improvement of membrane permeability [31]. There seems to be a modulation of lipophilicity through intramolecular hydrogen bonding [31]. The delicate balance of size, solubility and lipophilicity is required for cell penetration and is dependent on the IHB [32]. Although it is uncertain how physicochemical properties exactly influence permeability of natural products, in a few cases intramolecular hydrogen bonding was found to improve membrane permeability of small molecule drug candidates [32].

Our group of substances initially seems to follow the hypothesis of Urzúa [22]. The most active compounds, **1**, **6** and **7** present a decalinic ring system with one or two strategically positioned HBD. In compounds **6** and **7**, the presence of two HBD groups did not decrease too much either the lipophilicity or the activity. This probably occurs exactly due to their hydrogen bonds between the OH groups. It is also possible to infer that this IHB is partially responsible for keeping compounds **6** and **7** lipophilicities in considerably high values.

It is also expected that lipophilicity decreases with the increase of the number of HBD groups in molecule. Thus, if activity is related to lipophilicity, it is also expected a decrease of activity in this case.

In fact, the less active molecules, compounds **3**, **4** and **5**, present three HBD each and only one of them presents a single IHB. Due to the weakness of C-H···O hydrogen bonds, they are only being considered for their O-H···O hydrogen bonds.

The most peculiar case is related to compound **2**. This molecule presents four HBD groups and a higher activity than compounds **3**, **4** and **5**. Moreover, compound **2**, with four OH groups, is more lipophilic than **3** and **4** with only three each. This can also be explained by the formation of two IHB in compound **2**. Both IHB formations leave the OH groups less available for intermolecular interactions, decreasing hydrophilicity and consequently increasing the lipophilicity and activity.

A better understanding of the structure-activity relationship is crucial to enhance the chance to reach effective anti-tuberculosis agents. Some of the results presented in this work suggest that lipophilicity can play an interesting role in anti-tuberculosis activity of diterpenes, as suggested before for antimicrobial activity. HOMO and LUMO distributions showed a probable reason for diterpenes activity behaviour regarding lipophilicity, while charge density also showed a possibility of influence. Further considerations regarding intramolecular hydrogen bonding showed that those bonds influence HBD group availability and thus influence lipophilicity and activity.

Several inferences could be made and a series of structural properties of the diterpenes were related to anti-tuberculosis activity. This could be considered as an initial structure-activity-relationship. Therewith, a relevant data set on this activity and diterpenes structural properties is being provided.

Experimental

Diterpene isolation and identification: All diterpenes were isolated from *Psiadia punctulata* as described in previously published works [9, 11, 12]. A rinse extract from the leaves of *P. punctulata* was prepared to give a complex mixture of diterpenes and flavonoids, components of the plant's exudate. Submitting this extract to

sequential column chromatography with different eluents as described [9, 12] and performing careful purification, substances **1** to **7** can be achieved in good yields and in adequate purity. The identification of all studied compounds was undertaken by comparison of ^{1}H and ^{13}C NMR data from those substances with data reported in the literature [9, 12, 13].

Anti-mycobacterial assays: Compounds **1** to **7** were assayed against *M. tuberculosis* in the Research Laboratory of Applied Microbiology (LAPEMA), University of Franca, under the supervision of Prof. Dr Carlos Henrique Gomes Martins. The activity was determined by the minimum inhibitory concentration (MIC). These values were determined in triplicate, using the microdilution technique on a REMA, adapted from a procedure reported in the literature [33].

The sample quantity used for each compound was 1 mg, dissolved in 125 μL of dimethylsulfoxide (DMSO) and with addition of 1875 μL of Mueller Hinton broth. The final concentration of DMSO did not exceed 5% and this percentage of solution was used as negative control. The 24-hour cultures of microorganisms were transferred to tubes containing 10 mL of sterile saline solution. The suspension was standardized by comparing it with the McFarland tube 0.5 (0.1 mL of a 1% solution of $BaCl_2$ in 9.9 mL of 1% H_2SO_4). After that, serial dilutions in saline and finally in Mueller Hinton were performed to provide an inoculum of 5 x 10^5 CFU/mL (colony forming unit/mL).

In the sterilized 96 holes microplates, a total of 100 μL Mueller Hinton was added, with suspensions of micro-organisms and the solutions of the substances to be evaluated. All compounds were evaluated at different concentrations, allowing determination of the concentration required to inhibit the growth of the evaluated micro-organism. One hole of each plate contained the control culture, which must provide bacterial growth due to the absence of antimicrobial agents. Another hole was used for sterility control of the medium and Mueller Hinton, and another one for solvent control (DMSO) used to solubilize the substances. As a positive control, isoniazid was used.

The plates were incubated at 37°C for 24 h. Subsequently, to each well, 30 μL of 0.02% aqueous solution of resazurin was added. After waiting for 18 h, the presence of blue coloration (coloring resazurin solution) was interpreted as lack of bacterial growth and a pink color signified the presence of viable micro-organisms.

Computational methods: Gas phase geometry optimizations and COSMO-RS calculations were performed with a TZP small core basis set [34] in conjunction with a GGA:BP exchange correlation functional (Becke-Perdew) [35, 36]. The ZORA (zeroth order regular approximation) approximation to the Dirac equation was also considered [37-41]. The nature of the stationary points was determined by the absence of imaginary eigen values in the Hessian matrix. The vibrational frequency calculations were carried out using the Gaussian 09 program [42] employing the BP86/TZP [43] model. The lipophilicity of the studied compounds was calculated with use of the COSMO-RS (Conductor-like Screening Model for Real Solvents) [44-46] methodology, which is implemented in the ADF (Amsterdam Density Functional) package [47-50].

Topological analysis of the electron density was made using the QTAIM (Quantum Theory of Atoms in Molecules) theory [51]. Calculations were carried out with the software AIMAll (Version 13.02.26) [52].

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