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Investigation of Chemical stability of*metal-mycolacton A/B* complexes, using quantum chemicalONIOM method

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ABSTRACT
Mycolactons are responsible for Buruli Ulcer which (BU) is a necrotizing disease of the skin and soft tissue. In this work, up to five metals, meaning Lithium (Li), Sodium (Na), Magnesium (Mg), Calcium (Ca), and Aluminum (Al) are used to complex mycolacton A/B molecule. Quantum chemistry method, especially ONIOM two layers computation method, i.eONIOM(B3LYP/6-311+G(d,p):AM1)level, has led to determine the major interaction sites ofmycolacton A/B. Furthermore, geometric and energeticparameters of the above mentioned complexation reaction have been computed for each metal. Results showed that magnesium is the metal that possesses the strongest affinity with mycolacton A/B. The identification of such a metal constitutes a noticeable advance towards understanding the mode of action of the toxin. Its consideration in the design of drugs againstBuruli Ulcer will lead to annihilate destructive effects of mycolactonA/B.

Keywords:Buruli Ulcer,*Mycobacterium ulcerans*,mycolacton, ONIOM, quantum chemistry.

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I. INTRODUCTION

Buruli Ulcer, caused by *Mycobacterium ulcerans*, is the third most frequent mycobacterial disease in the world after tuberculosis and leprosy [1]. Longtime neglected, this disease, that rages in tropical and subtropical humid countries, has increased in West Africa since 1980 [2]. Its quick spread in this part of the african continent has led the World Health Organization (WHO) to initiate a global stuggle against this diseasesince 1997 [3]. Buruli Ulcer has been classified as an emerging disease and recognized as a public health and development problem [3].Nowadays, although no official estimation of global incidence is available, West Africa is the main endemic area, with more than 4.000 new cases reported in Côte d'Ivoire, Ghanaand Benin in 2010 [4]. Buruli Ulcer is a devastating necrotizing skin infection characterized by lesions (nodules, plaques, oedematous infiltration) that develop into deep ulcers with mined edges that can spread to a full member and disseminate to the bone. *Mycobacterium ulcerans* secretes in skin tissue, a toxin called mycolacton, responsible for tissue damage, because of its cytotoxic and immunosuppressive properties. Up to now, six different natural molecular structures of mycolacton, named A/B, C, D, E, F and G, have been isolated [5]. The particular structure namedA/B(Fig.1), the most virulent form met in Africa, is the subject of our study.

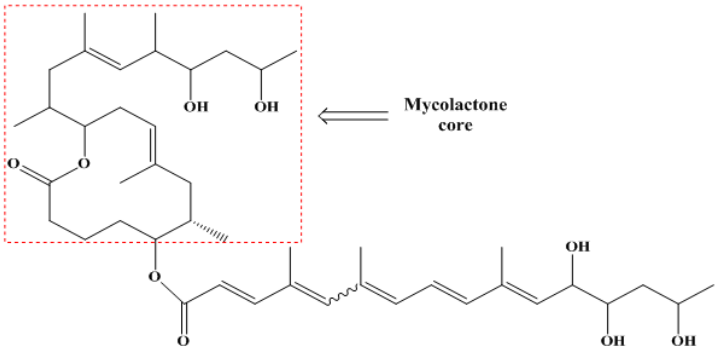


Figure 1: Structure of mycolactonA/B.

The raw structure of mycolactonA/B was founded by spectroscopic methods, and stereochemistry had already predicted this by the 2D NMR database approach [6]. Mycolactons are constituted of a lactone core attached to alateral ring which is highly unsaturated [7]. Up to now, the treatment of Buruli Ulcer remains limited, despite theobserved progress in the medical management [8]. Indeed, antibiotic therapy remains thetreatment of reference. One can also mention restorative surgery, with its high cost and numerous relapses (16 to 28%), in case of serious infection [9]. The mode of action of the toxin remains less or ill known until now. The relationship between mycolacton produced by *Mycobacterium ulcerans* and the proteins responsible for the onset of Buruli Ulcer is linked to the conformation of the molecules and the intermolecular interactions they can establish.

Knowledge of the interactions between metal ions and biological molecules is of paramount importance; because they allow to understand the usefulness role of metal ions in the vital functions of the human beings' organism [10]. Indeed, good operating of vital phenomena depends directly on the metals contained in humanbeings' body [10]. This interaction is one of the most important involved in supramolecular chemistry and in protein-ligand relationships. This work, part of the Buruli Ulcer control program, focuses on mycolacton A/B. It aims to determine, by means of quantum chemistry methods, some geometric and energetic parameters of the complexation reactions of mycolacton A/B with various metals. Calculations are carried out atONIOM(B3LYP/6-311+G(d,p):AM1) level. ONIOM method, developed by Morokuma and al. [11-13], has often been used successfully on large molecules [14-17]. We aimto identify a particular harmless metal that can strongly gather up mycolactonA/B molecules, in order to prevent their tissue damaging process, and finally, to propose an alternative treatment that can annihilate the destructive effects of the toxin.

II. COMPUTATION METHODS

2. 1. ONIOM Method

ONIOM method consists in cutting the studied system into several layers, each of them is treated at a different calculation level. In the case of a two-layer system (ONIOM2), the complete system will be the real system while the part that is of particular interest will be the model. The actual system will be calculatedat a low level (lower part). The model system will be treated with a high level of theory (higher part). The model system will also be treated at a low level, the final goal is to extrapolate the energy from the actual system to the high level. The total energy of the real system, determined by extrapolation from three independent calculations, will be computed according equation (1). The description of mycolactonA/B with the ONIOM2 method can be seen at Fig. 2.

$$E_{ONIOM\ 2} = \mathrm{E(high\,,real)} + \mathrm{E(low\,,real)} + \mathrm{E(high\,,model)} - \mathrm{E(low\,,model)} \quad (1)$$

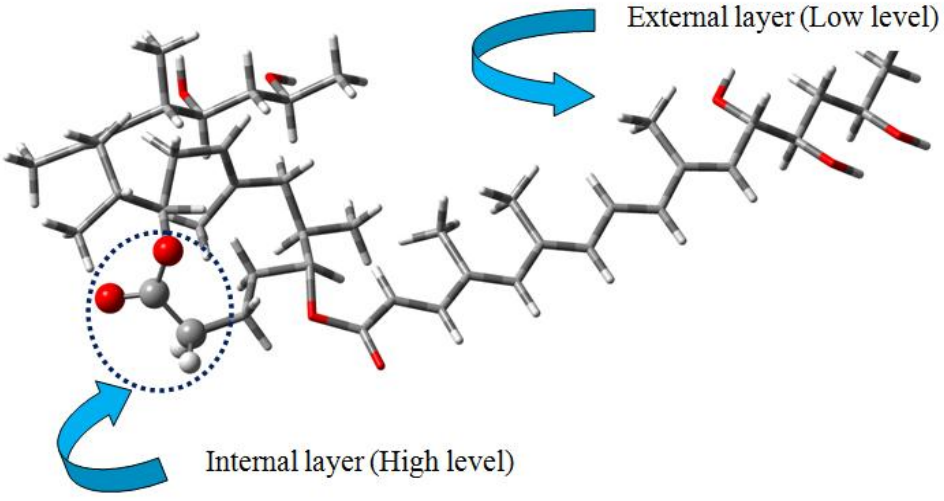


Figure 2: Description of a cutting model of mycolacton A/B with the ONIOM2 method. Image obtained from GaussViewsoftware. The part shown in the *tube* is the optimized part at the low level. And the surrounded part, presented in *ball and stick*, is the model system.

All calculations were performed using Gaussian 03 software [18]. Previous studies[19-21] have shown that the DFT/B3LYP method gives better relative energies and is in good agreement with high-level *ab initio* methods. As for the calculation high level, i.e. B3LYP/6-311+G(d,p), DFT is nowadays, widely used to study the properties of complex or even biological molecular systems. The presence of diffuse and polarization functions is useful to take into account the free lone pairs of the heteroatoms.

2.2. Geometry Optimization

The complexing reaction is a process in which a LEWIS base(ligand, L)fixes on a LEWIS acid (metal ion, M) to give an organometalliccomplex ion$[ML_n]^{n+}$, according to reaction (2), in which L stands for mycolacton A/B and M for metal ion. Thus, the complex formed is a polyatomic building composed from acentralmetallic cationsurrounded by n molecules of mycolactonA/B.

$$n(L) + (M^{n+}) \rightarrow [ML_n]^{n+} \quad (2)$$

The ionic and coordination links are electrostatic bonds which tend to form under both directional and energetic conditions. Indeed, observed directional preferences of the ionic or coordination binding are those predicted by Grignard [22] and Gillespie's theory.Thus, as initial guess complex geometry(Fig. 3), angle has been settled to 109.5° and 120°, respectively for $sp^3$and sp^2 hybridized oxygen atoms, whereas distance O…M depends on the metal. We performed a prior *single point* calculation, in order to determine the initial guess distance, assuming that this distance in the onethat corresponds to the minimum electronic energy of the complex. As results, initial distancesd_{min} have been settled to 1.9 Å, 2.3 Å, 2.0 Å, 1.9 Å and 2.0 Årespectively for Al, Ca, Li, Mg and Na metals.

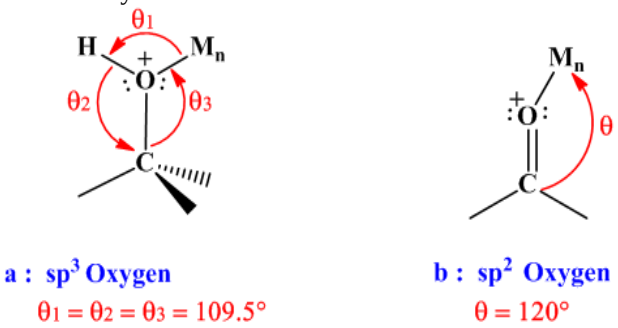


Figure 3:Initial guess geometry parameters of the complex before optimization.

MycolactonA/B has nine heteroatomscolored in red, the whole corresponding tosp^2orsp^3hybridized oxygen atoms (Fig. 4).The labelling of the heteroatoms of mycolacton A/B starts with thelateralchaingoing from the right to the left via the lactone ring. Thus, the numbers 1 to 9 refer to the different heteroatoms.In a former study [23], oxygen atom O_5sp^2surrounded in the molecule (Fig.4) has been undoubtedly identified as the major site for all intermolecular interactions. Thus, all complexes have been modeled involving only O_5sp^2oxygen atom.

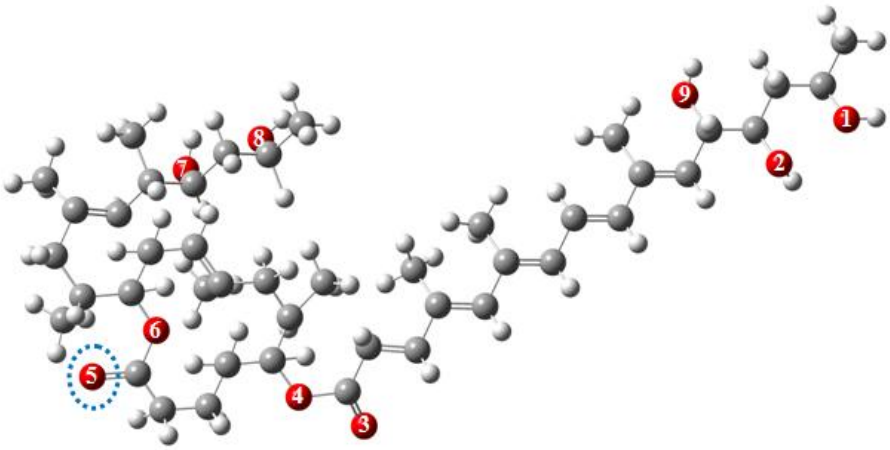


Figure 4: Structure of mycolacton A/B visualized with the GaussView software.

2.3. Energetic Parameters

Internal energy variation, ΔE^0, at 0 K, of the complex formed between the metal (M) and the ligand (L) can be calculated according to equation (3):

$$L + M \longrightarrow L \ldots M$$
$$\Delta E^0_{elec} = E^0_{elec}(L \ldots M) - [E^0_{elec}(L) + E^0_{elec}(M)] \quad (3)$$

This energy is the sum of the electronic, rotational, translational and vibrational contributions given in equation (4):

$$E_{298K} = E^0_{electronic} + E^0_{rotation} + E^0_{translation} + E^0_{vibration} \quad (4)$$

Geometry optimization of both complexes and free molecules, called monomers, provides the electronic contribution to the interaction energy (containing nuclear repulsion energies). In ideal gas approximation, rotational and translational contributions are given according equation (5):

$$\Delta E^0_{translation} = \Delta E^0_{rotation} = -\frac{3}{2}RT \quad (5)$$

ZPVE (Zero Point Vibrational Energy) contribution, i.e. lowest vibrational level energy, due to 3N-6 normal vibrational modes (3N-5 for the linear molecules), each with frequency ν_i, up to N kernels at 0 K, is defined according equation (6):

$$ZPVE = \frac{1}{2}R\sum_{i=1}^{3N-6}\frac{h\nu_i}{k} \quad (6)$$

To obtain the corresponding energy at 298.15 K, it is necessary to take into account the extra energy due to vibrational levels population during temperature rising from 0 to 298.15 K. Thus, equation (6) becomes equation (7):

$$E^0_{vib.thermal} = R\sum_{i=1}^{3N-6}\frac{h\nu_i/k}{e^{(h\nu_i/298K)}-1} \quad (7)$$

As a result, internal energy variation at 298.15 K is given by equation (8):

$$\Delta E^0_{298K} = \Delta E^0_{elec} + \Delta ZPVE + E^0_{vib.thermal} - 3RT \quad (8)$$

Enthalpy and free enthalpy variations, at 298.15 K,are given respectively by equations (9) and (10), and entropy variation, by equation (11):

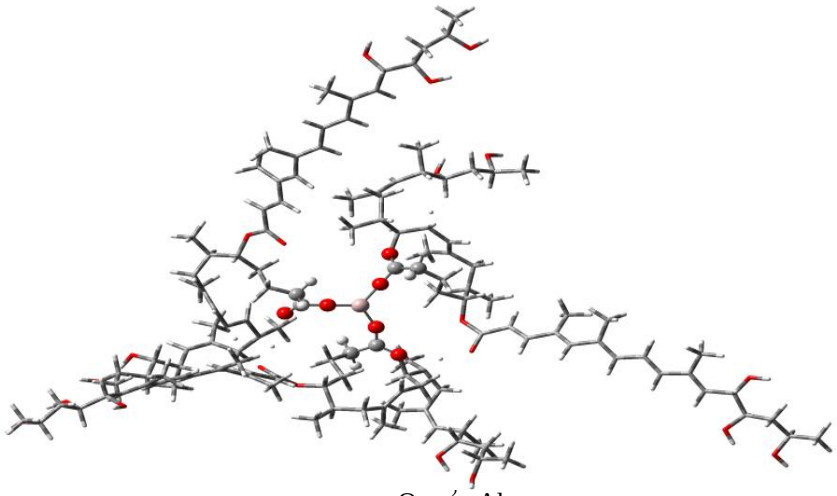
$$\Delta H^0_{298K} = \Delta E^0_{298K} - RT \quad (9)$$
$$\Delta G^0_{298K} = \Delta H^0_{298K} - T.\Delta S^0_{298K} \quad (10)$$
$$\Delta S^0_{298K} = \Delta S^0_{trans} + \Delta S^0_{rot} + \Delta S^0_{vib} \quad (11)$$

III. RESULTSAND DISCUSSION

3.1. Optimized Geometry

Optimized geometries are given at Fig.5.The absolute deviation of the interaction bond lengths(Δd) and the valence angle variation ($\Delta\theta$) between mycolacton A/B and metals stand for geometric parameters of the complexationprocess. These parameters were calculated according, respectively, equations (12) and (13).Our aim is to determine the better metal that strengthens the bond M-L. We assume that the smallertheseparameters are, the stronger a bond is.Results are given in table 1.

$$\Delta d = |d - d_{min}| \quad (12)$$
$$\Delta\theta = \theta - 120° \quad (13)$$

Metals	*Mycolacton-metal*A/BComplex
Aluminium (Al)	

O_5sp^2...Al

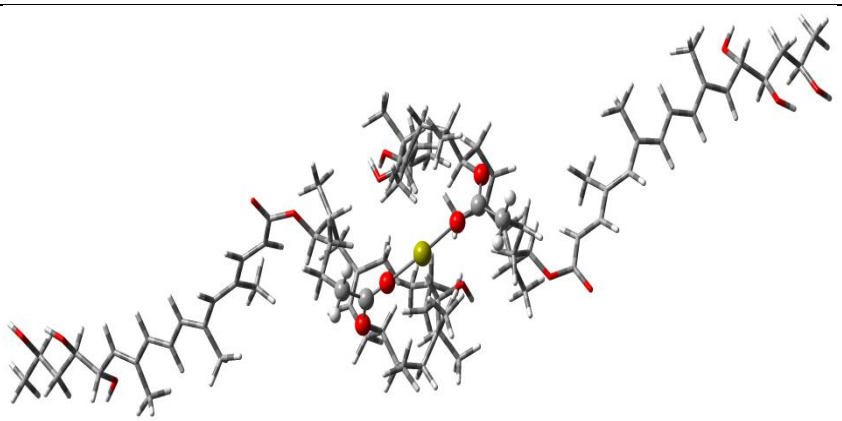
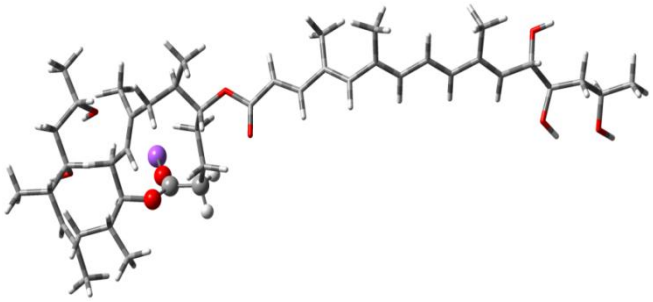
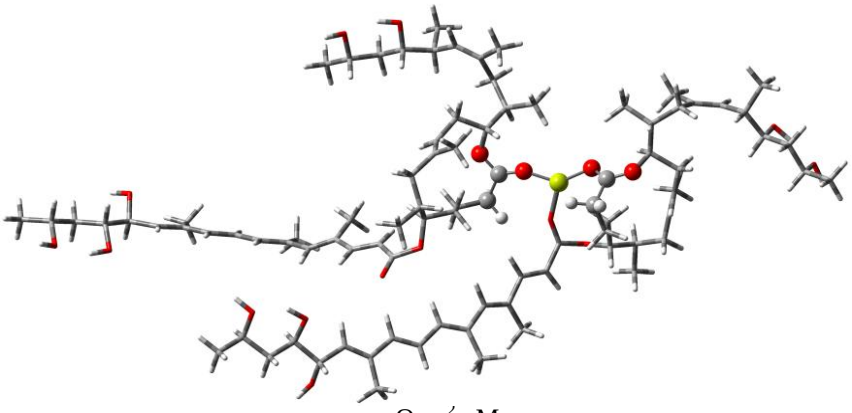
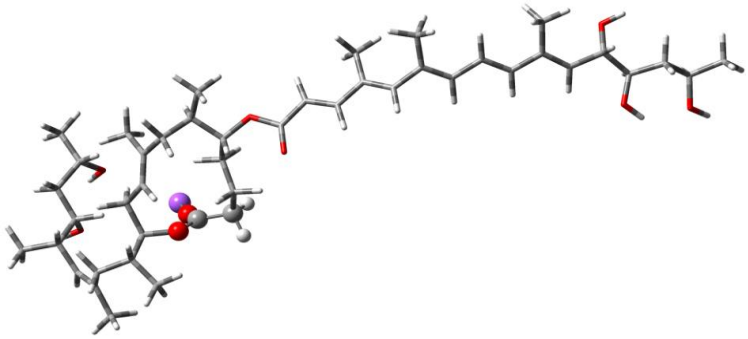
Calcium (Ca)	 $O_5sp^2...Ca$
Lithium (Li)	 $O_5sp^2...Li$
Magnesium (Mg)	 $O_5sp^2...Mg$
Sodium (Na)	 $O_5sp^2...Na$

Figure 5: Structures of optimized organometallic complexes formed withmycolacton A/B.

Coloured legend:

Table 1: Geometric Parameters of Complexes BetweenMycolacton A/B andStudied Metals Optimized at ONIOM (B3LYP/6-311+G (d, p): AM1) level.

	Aluminum (Al)	**Calcium (Ca)**	**Lithium (Li)**	**Magnesium (Mg)**	**Sodium (Na)**
d (Å)	1.75	2.17	1.68	1.83	2.13
d_{min}(Å)	1.9	2.3	2	1.9	2
|**Δd**(Å)|	0.15	0.13	0.32	**0.07**	0.13
Values of the angles of valences					
θ(°)	154.2	174.12	165.08	127.63	170.62
Δθ(°)	34.2	54.12	45.08	**7.63**	50.62

The lowest value of **Δd** corresponds to magnesium (0.07 Å). Furthermore, the smallest value of **Δθ, i.e.** 7.63°, equally corresponds to magnesium metal. All these results are obtained for an sp^2hybridized oxygen. According geometric parameters, there is a greater affinity of mycolacton with magnesium metal comparatively to the other checked metals.

3.2. Energetic Parameters

The computed energetic parameters (Table 2) are the variations of the thermodynamic quantities linked to the complexationreactions. All complexations are settled to involve the O_5sp^2oxygen atom of mycolacton A/B.We assume that the smaller the Gibbs free energy $\Delta_r G^\circ_{298}$is, the stronger the bond is, and the more stable the *mycolacton-metal*complexwillbe.Analysis of the energetic parameters (Table 2) shows that all of them correspond to negative values. So whatever the metal, all compexation reactions are spontaneous, carried out at 298.15 K under a pressure of 1 atm. However, most negative value of free enthalpy is computed for the magnesium, i.e.-1309.38 kJ/mol. The values computed for the other metals are very much higher. Thus, magnesium appears as the better metal needed to complex mycolacton A/B, in order to prevent its action. Furthermore, an increasing scale of reactivity can be settled (Fig. 6) apart from free enthalpy values for all five metals.

Table 2: Energetic Parameters $\Delta_r H^\circ_{298}$(kJ/mol), $\Delta_r G^\circ_{298}$(kJ/mol) and $\Delta_r S^\circ_{298}$(J/K.mol) of The ComplexingReactions of Mycolacton A/B with Metals, Computed at ONIOM(B3LYP/6-311+G(d,p):AM1) level.

	Aluminium (Al)	**Calcium (Ca)**	**Lithium (Li)**	**Magnesium (Mg)**	**Sodium (Na)**
$\Delta_r H^\circ_{298}$	-227.17	-1517.25	-72.26	-2624.41	-216.59
$\Delta_r S^\circ_{298}$	-0.21	-3.33	-0.15	-4.41	-0.14
$\Delta_r G^\circ_{298}$	-163.83	-524.78	-25.79	-1309.38	-174.3

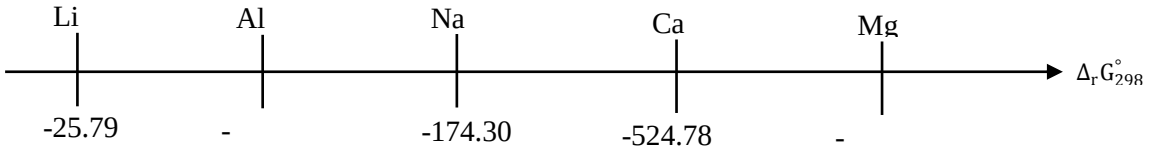


Figure6: Reactivity increasing scale of metals with mycolacton A/B.

IV. CONCLUSION

In this study, we have modelled five *mycolacton-metal* complexes by means of ONIOM

method, as complexes are large. The metals lithium (Li), aluminium (Al), sodium (Na), calcium (Ca) and magnesium (Mg) have been chosen, because of their supposed harmless properties toward human body. Geometric parameters, as well as energetic ones, show that, far away, magnesium can strongly complex the mycolacon A/B, and prevent itsaction, even if secreted in the tissue. Identification of this metal allowsto envisage a medical approach for the treatment of Buruli Ulcer. Indeed, the conception of anointment based on magnesium powder and applied to the infected part could help healing wounds and suffering people to recovery from this disease.

REFERENCES

[1]. WHOBuruliUlcer: Progress Report, 2004-2008, Weekly Epidemiological Record, 83,2008, 145-154. http://www.who.int/wer

[2]. Young, V.R. The role of skeletalandcardiac muscle in the regulation of proteinmetabolism. In: Munro, H.N., Ed., Mammalian Protein Metabolism, Vol. 4, Academic Press, New-York,1970,587-674. https://doi.org/10.1016/b978-0-12-510604-7.50018-9

[3]. Marston, B.J., Diallo, M.O. and Horsburgh Jr., C.REmergence of Buruli Ulcer Disease intheDaloa Region of Cote d'Ivoire.American Society of Tropical Medicine and Hygiene, 52,1995,219-224. https://doi.org/10.4269/ajtmh.1995.52.219

[4]. J. Guarner, J. Bartlett, E.A. Whitney, P.L. Raghunathan, Y. Stienstra, K. Asamoa, S. Etuaful, E. Klutse, E. Quarshie, T.S. van der Werf, W.T. van der Graaf, CH. King, D.A. Ashford, Histopathologic features of Mycobacterium ulcerans infection.Emerg. Infect, 9, 2003, 651-656.

[5]. Torrado, E., Adusumilli, S., Fraga, A.G., Small, P.L. and Castro, A.G. Mycolactone-Mediated Inhibition of Tumor Necrosis Factor Production by Macrophages Infected with Mycobacteriumulcerans Has Implications for the Control of Infection.Infection and Immunity,75, 2007, 3979-3988. https://doi.org/10.1128/IAI.00290-07

[6]. George KM, Chatterjee D, Gunawardana G, Welty D, Hayman J, Lee R, Mycolactone: apolyketide toxin from Mycobacterium ulceransrequired for virulence. Science, 5,1999, 854-857.

[7]. Stinear TP, Mve-Obiang A, Small PL, Frigui W, Pryor MJ, Giant plasmid- encoded polyketide synthases produce the macrolide toxin of Mycobacterium ulcerans. Proc NatlAcadSciUSA, 101, 2004, 1345–1349.

[8]. Stanford, J.L., Revill, W.D., Gunthorpe, W.J. and Grange, J.M. The Production and

[9]. Preliminary Investigation of Burulin, a New Skin Test Reagent for Mycobacterium ulcerans.Journal of Hygiene(London),74, 1974, 7-16. https://doi.org/10.1017/S0022172400046659

[10]. Amofah, G.K., Sagoe-Moses C, Adjei-Acquah C, Epidemiology of BuruliUlcerinAmansie West district of Ghana. Trans R Soc Trop Med Hyg, 87, 1993, 644-645.

[11]. R.J. Maldanis, J.S. Wood, A. Chandrasekaran, M.D. Rausch, J.C.W. Chien, The formation and polymerization behavior of Ni(II)-diimine complexes using various aluminum activators, Journal of Organometallic Chemistry, 645, 2002, 158-167.

[12]. Morokuma, K. New challenges in quantum chemistry: quests for accurate calculations forlarge molecular systems, Philosophical Transactions of the Royal Society of London A:Mathematical, Physical and Engineering Sciences, 360, 2002, 1149-1164.

[13]. Dapprich, S., Komáromi, I., Byun, K. S., Morokuma, K., and Frisch, M. J. A newONIOMimplementation in Gaussian98. Part I. The calculation of energies, gradients, vibrationalfrequencies and electric field derivatives, Journal of Molecular Structure: THEOCHEM, 461, 1999, 1-21.

[14]. Vreven,T., and Morokuma, K. On the application of the IMOMO (integrated molecularorbital+ molecular orbital) method. Journal of Computational Chemistry, 21, 2000, 1419- 1432.

[15]. Zheng, F., and Zhan, C.-G. Rational design of an enzyme mutant for anti-cocainetherapeutics.Journal of Computer-Aided Molecular Design, 22, 2008, 661-671.

[16]. Ruangpornvisuti, V. Recognition of carboxylate and dicarboxylates by azophenol–thiourea derivatives: a theoretical host–guest investigation.Journal of Molecular Structure:THEOCHEM, 686, 2004, 47-55.

[17]. Samanta, P. N., and Das, K. K. Prediction of binding modes and affinities of 4-substituted-2,3,5,6-tetrafluorobenzenesulfonamide inhibitors to the carbonic anhydrasereceptorby docking and ONIOM calculations.Journal of Molecular Graphics and Modelling,63, 2016, 38-48.

[18]. Promsri, S., Chuichay, P., Sanghiran, V., Parasuk, V., and Hannongbua, S. Molecular andelectronic properties of HIV-1 protease inhibitor C 60 derivatives as studied by the ONIOM method. Journal of Molecular Structure: THEOCHEM, 715, 2005, 47-53.

[19]. Gaussian 03, Revision C.01, Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, Jr., J.A., Vreven, T., Kudin, K.N., Burant, J.C., Mil-lam,J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N.,Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J.,Ishida,M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E.,Hratchian, H.P.,Cross, J.B., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev,O., Austin, A.J.,Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P.,Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick,D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V.,Cui, Q., Baboul, A.G., Clifford,S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A.,Piskorz, P., Komaromi, I., Martin, R.L.,Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill,P.M.W., Johnson, B., Chen, W., Wong, M.W.,Gonzalez, C. and Pople, J.A., Gaussian, Inc.,Wallingford, 2004.

[20]. Remko, M., Walsh, O. A., and Richards, W. G. Theoretical study of molecular structure,tautomerism, and geometrical isomerism of moxonidine: Two-layered ONIOM calculations.TheJournal of Physical Chemistry A, 105, 2001, 6926-6931.

[21]. Kapp, J., Remko, M., and Schleyer, P. v. R. H_2XO and $(CH_3)_2XO$ Compounds (X= C, Si,Ge, Sn, Pb): Double bonds vscarbene-like structures can the metal compounds exist atall?.Journal of the American Chemical Society, 118, 1996, 5745-5751.

[22]. Johnson, B. G., Gill, P. M., and Pople, J. A. The performance of a family of densityfunctional methods.The Journal of ChemicalPhysics, 98, 1993, 5612-5626.

[23]. V. Grignard. Action of methyliodide on ketones in the presence of magnesium to obtaintertiaryalcohols, doctoral thesis, 1901.

[24]. Kassi, K. F., Koné, M. G.-R., Affi, S. T., Ziao, N..ONIOM Method Characterization of Hydrogen Bonding Sites of MycolactoneA/B, a Buruli Ulcer Toxin. The Journal ofComputational Chemistry, 5,2017, 103-112.http://www.scirp.org/journal/cc

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