COMPARATIVE THEORETICAL STUDIES OF ENERGETIC AND STRUCTURAL PROPERTIES OF BETULINIC AND MELALEUCIC ACIDS AND THE STABILITY OF CLUSTERS OF THESE SPECIAL METABOLITES

Noam Gadelha da Silva[a] (PG), Kelson Mota Teixeira de Oliveira[a] (PQ), Jefferson Rocha Andrade Silva[a] (PQ)

[a]*DQ/ICE, UFAM, Block 10, North Sector, Avenue Rodrigo O. J. Ramos, 6200, Japiim, 69077-000, Manaus, Amazonas.*

Keywords: Computational Chemistry, Structure-Activity Relationship, Clusters.

INTRODUCTION

Drugs such as Betulinic acid gain attention because of their biological activity against several diseases such as various types of cancer, AIDS, and Malaria[1]. Many studies indicate the manner in which the drug acts on the disease, but is not detailed about which molecular characteristics have influence in these processes[1]. Combined theoretical and experimental studies can lead to answers about the real reason for activity of these biomolecules as inhibitors of diseases, and we can understand more about the structure-activity relationship and other influences on biochemical reactions[2,3]. In this work, theoretical calculations with the Gaussian 03 program package seek to explain the inactivity of Melaleucic acid, a very similar analogue of Betulinic acid, with just one difference regarding Betulinic acid, which is a carboxylic acid group at C-27 (**Figure 1**).

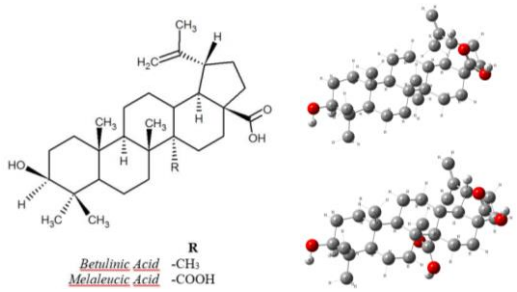

Figure 1. Structure of the substances and optimized geometry given by AM1 calculations.

RESULTS AND DISCUSSION

The methodologies used was semi-empirical AM1 (geometry optimization) and Ab Initio DFT/B3LYP 3-21G and 6-311+G(2d,p) (Single-Point energy and others). To AM1, the stabilizations by intermolecular interactions in systems with two (2MC2) and three (3MC7) molecules of both substances are close (see **Table 1**). In DFT level of theory, 2MC2 systems was not stabilized by these interactions, but the 3MC7 systems was. Structure and charges data indicate that coupling with an enzyme should be similar. A possible explanation to the relative inactivity of Melaleucic acid is the formation of clusters with a large number of hydrogen bonds stabilizing these macrostructures. Melaleucic acid may be forming more stable clusters, and, because of that, the substance tends to interact less with an enzyme active site. A theoretical molecular docking study showed similar affinity of the both substances with a specific enzyme active site (similar work can be seen in reference 2).

Table 1. Principal energetic results given by AM1 and DFT/B3LYP calculations.

Substance	E_T (kcal/mol)	Stab. 2MC2 (kcal/mol)	Stab. 3MC7 (kcal/mol)
Betulinic acid (AM1)	-190.64288	-7.22716	-22.75594
Betulinic acid B3LYP 6-311+G(2d,p)	-877151.98241	4.07525	-16.38562
Melaleucic acid (AM1)	-276.18145	-6.77567	-22.66992
Melaleucic acid B3LYP 6-311+G(2d,p)	-970820.01935	2.25227	-14.27433

CONCLUSIONS

This results indicates very similarity of these substances, and the reason for the difference in the bioactivity could be the possibility of more stable clusters in the Melaleucic acid. Experimental studies can confirm the presence of clusters or the incompatibility of the Melaleucic acid in the enzyme active site.

ACKNOWLEDGMENTS

For the support of FAPEAM and CNPq.

[1]M. G. Moghaddam, F. B. H. Ahmad and A. Samzadeh-Kermani. Pharmacology & Pharmacy 3 (2012) 119-123.
[2]P. Bernard, M. Pintore, J. Berthon, J. R. Chrétien. European Journal of Medicinal Chemistry 58 (2001) 1-19.
[3]W. J. Geldenhuys, K. E. Gaasch, M. Watson, D. D. Allen, C. J. Van der Schyf. Drug Discovery Today 11 (2006) 127-132.