

Physical-chemical and Biological Study of Fluorinated 6-Quinoline Chalcones

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Introduction

Hydrophobicity is recognized as an important parameter in the quantitative chemical structure and biological activity relationships (QSAR) studies, as well as to describe ADMET properties. The hydrophobicity can be expressed by their partition coefficient (LogP)¹. On the other hand, The $GAP_{HOMO/LUMO}$, is an important indication of chemical stability.² Herein, physical-chemical and biological studies for two fluorinated Chalcones are reported, including two different series, **1a-g** and **2a-g**, synthesized in our laboratories (Figure 1).

Results and Discussion

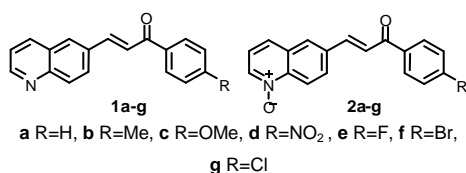


Figure 1. 6-Quinoline Chalcones **1a-g** and 6-Quinoline N-Oxide Chalcones **2a-g** structures.

The antifungal tests results for pathological *P. brasiliensis* indicate that **1e** (R=F) was one of the most active with MIC=7,8 µg/mL, in the **1a-g** series. In the N-Oxide series the **2e** (R=F) was the most significant activity with MIC=1,9 µg/mL. This compounds, **1e** e **2e**, was also the most cytotoxic activity for humam tumor cells lineage TK-10 (renal cell carcinoma).The IC₅₀ values was IC₅₀=1,0±0,05 µg/mL for **1e** and IC₅₀=0,19±0,1 µg/mL for **2e**. It was possible, not only to evidence that the N-Oxide **2e** has the most antifungal and cytotoxic potential activity between the 14 compounds, but also to verify through the two biological tests that both **1e** e **2e** show better potential activity than comparative drugs.

The physical-chemical parameters for both two series of compounds were calculated. For the partition coefficient (LogP) of **1a-g** and **2a-g** series, containing seven compounds each, the Chalcones **1a-g** shows a correlation $r = 0,994$ for CLogP

(partition coefficient calculated by ALOGPS 2.1 program) vs. SFLogP (experimental partition coefficient by the “Shake Flask” method), which means 99,4% of variation in the LogP results, for N-Oxide Chalcones **2a-g**, the $r = 0,984$ shows 98,4% of variation of results. The correlation of LogP data was obtained *in silico* by BILIN program.

The HOMO and LUMO orbital energies values were obtained *in silico* by the Orca program in a Beowulf-style compute cluster.

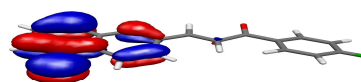


Figure 2. HOMO of **2e**.

The obtained value of **1e** Chalcone is 96,70 kcal/mol, and it is the highest value in between **1a-g** series, which means high stability and low reactivity beside the compounds of **1a-g** series. For the $GAP_{HOMO/LUMO}$ of **2e** compound was obtained 76,42 kcal/mol, in which stay in the 4th place in between the serie **2a-g** of N-Oxides, it shows a middle value for stability and reactivity in chemical reactions. The derived biopotential compounds **1e** e **2e** follow the Lipinski's Rule of Five that establish: MW ≤ 500, CLogP ≤ 5, H-bond acceptors ≤10 and H-bond donors ≤5, for a relevant oral bioavailability.

Conclusions

According to the results, the compound **1e** and **2e** are the most active compounds in the series. The observed biological activities and the correlation between physical properties suggest development of a QSAR model, which is in course in our group.

Thanks

FAPESC, CNPq, DQ-UFMG, DQ-UFSM, UFSC

¹ Santos, Elba V.M.; Tese de Doutorado Q.O.; IQ-USP; 2009.

² Karelson, et al.; *Chem. Rev.*; 96;1027-1043;1996.