THEORETICAL STUDY OF NEW INHIBITORS OF ENZYME HUMAN DHYDROOROTATE DESIDROGENASE.

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**Introduction**

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth committed step in the de novo biosynthesis of pyrimidines.¹ The rheumatoid arthritis (RA) is a chronic inflammation being characterized by strong pain in articularizations and progressions to irreversible articular injuries.² The class 2 DHODH from Homo sapiens enzyme (HsDHODH) has been studied as a promissor target to RA.¹ Recently, inhibitors have been synthetized based on the hydroxyfurazans (Fig. 1), which presented very satisfactory inhibitory activity against this enzyme, what showed potential benefit for RA treatment.² The drugs used in RA provide symptomatic relief, they don’t modify the illness course, causing collateral effects as gastric toxicity. This way, this work we performed Molecular Modeling (MM) and Theoretical Study of the inhibitors based the antiproliferative agents leflunomide and brequinar or understanding the mechanism of action theses molecules.

![Figure 1: General structure of the inhibitors based on the hydraxyfurazan.](image)

**Results and Discussion**

Here, the MM study was started with the 1D and 3D drawing of every structure with CS ChemOffice Ultra version 12 package followed by the structural minimization by the classical mechanics method MM² and finalized by B3LYP hybrid functional and 6-31G(d,p) base function with Gaussian 03 software.³ 3D structures were performed with VMD software⁴ and MEP surfaces were derived from BLYP/6-31G and generated by Moleké Molecular Visualization⁵ with an isodensity value of 0.05 a.u. The results have shown that between the twelve inhibitors synthetized, the most stable was Molecule 12 (Fig. 2a), with a value of energy equal to -968,1408 ha. This fact may be assigned by the quantity of total atoms, as well the absence of element Fluorine which present high electronegativity. In the MEP, the nucleophile regions represented negative electrostatic potential (red color) while the electrophile regions showed positive electrostatic potential (blue color). The Molecule 12 (Fig. 2b) evinced that the regions with negative potential are concentrated around the oxygen atoms. The positive electrostatic potentials can be found around the hydrogen atom. According to Lolli and co-workers, this present inhibitory activity (IC₅₀) of 45 µM, considered moderated inhibition.

From the analysis and the compounds most actives support two or four Fluorine atoms on the phениل ring adjacent to the Amide. The analysis of the structures can be gauged according to the literature, both (a) or (b) present Fluorine atoms constituting its molecule, for this reason, its activities become elevated. The MEP for Molecules 10 and A26 shown in Fig. 3 reveals a region of negative electrostatic potential around the oxygen atoms. Positive electrostatic potentials can be found around the hydrogen and nitrogen atoms. On the Table 1 are the values of energy and inhibitory activities of two new inhibitors considered as satisfactory inhibitors of the enzyme.

![Figure 3: Structure and MEP surface of the Molecules 10 and (b) A26 from BLYP/6-31G optimization.](image)

**Table 1. Values of energy optimizations (HF) and Inhibitory activities (IC₅₀).**

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>HF (Ha)</th>
<th>IC₅₀ (µM)</th>
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<tbody>
<tr>
<td>Mol 12</td>
<td>-968,1408</td>
<td>45±3</td>
</tr>
<tr>
<td>Mol 10</td>
<td>-1022,2369</td>
<td>0,12±0,02</td>
</tr>
<tr>
<td>A26</td>
<td>-1503,6693</td>
<td>0,020±0,002</td>
</tr>
</tbody>
</table>

The differences on the energy optimizations might be related to the quantity of atoms on each structure, another important factor may be attributed to the quantity of Fluorine presente, because it is an element that present electronegativity elevated.

**Conclusions**

The results showed that Molecule 12 despite of being the most stable has presented IC₅₀, that according to the literature considered moderate. However, the molecule 10 when compared on energy level and IC₅₀ to the natural inhibitor A26 of de HsDHODH has satisfactory values. Therefore, among the twelve inhibitors synthetized molecule 10 has a high potential for research and development of antirheumatic drugs with mitigation of adverse effects of conventional treatments.

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