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ANALYSIS OF THE LIGAND EFFICIENCY OF 4-THIAZOLIDINONE DERIVATIVES WITH ANTITUMOR ACTIVITY

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ABSTRACT

Ligand efficiency analysis has been shown to be useful in the selection and optimization of new bioactive compounds. In order to direct the planning for new 4-thiazolidinones as regards in vitro antitumor activity, ligand efficiency (LE) calculations, fit quality (FQ) and ligand lipophilic efficiency (LipE) were conducted for 121 4-thiazolidinone derivatives found in the literature. Average values for LE and LipE were found to be below adequate minimum values. 14% of compounds studied showed an LE ≥ 0.3 and only one compound had a LipE ≥ 5 -7. 29% of the compounds had FQ values above 0.8 and three compounds with values above 1 showed exceptional LE.

Keywords: Ligand efficiency; Ligand lipophilic efficiency; 4-Thiazolidinones; Cytotoxicity; Anticancer

INTRODUCTION

Cancer is commonly defined as a group composed of more than 100 diseases characterized by uncontrolled growth of abnormal cells in the body which is the leading cause of deaths in the world **[1]**. In 2012, 14 million new cases and 8.2 million deaths caused by cancer took place. More than 70% of the deaths occurred in Africa, Asia and South and Central America **[2]**. Advanced therapies have been used in the treatment of cancer patients but cells have quickly acquired multidrug resistance (MDR) **[3].** The main MDR mechanism is

overexpression of the P-glycoprotein (Pgp), a carrier protein that acts as an anti-carcinogenic drug efflux pump **[4].**

4-thiazolidinones (**Figure 1**) have continued to be of interest to the pharmaceutical industry due to their hypoglycemic, anti-inflammatory, anticonvulsant, antidiabetic, antitumor, antiviral and cardiovascular pharmacological activities, among others **[5]**. Several compounds containing the 4-thiazolidine nucleus with substitutes at positions 2, 3 and 5 have demonstrated good cytotoxicity against cancer cell lines including cells with Pgp overexpression **[6-9**]. Ligand efficiency metrics quantify molecular properties needed to ensure compound affinity by the therapeutic target. Ligand efficiency calculations have been applied with success in fragment selection and optimization, bioactive molecules and lead compounds **[10]**. The concepts of ligand efficiency (LE), binding free energy by heavy atoms and ligand lipophilic efficiency (LipE) which combines potency and lipophilicity are the most used in the discovery of drugs **[11-14]**.

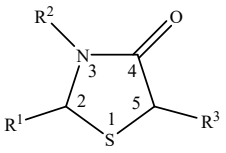


Figure 1: 4-Thiazolidinone nucleus

In LE calculation, NHAs are handled without distinction even if the sizes and binding properties are different. In anticipation of this inconvenience, the fit quality (FQ) proposes a correction of LE values making this metric independent of the influence of differences in the size of atoms **[9, 10]**. There are already several published studies using ligand efficiency analysis as an aid in the planning of new drugs **[15-19]**.

Based on the need to direct the planning of new 4-thiazolidinones for better cytotoxicity against cancerous cells, the present study had as its objective the analysis of LE, FQ and LipE of molecules with proven activity containing the 4-thiazolidinone nucleus in their chemical structure.

MATERIALS AND METHODS

To carry out the research, a database of 4-thiazolidinone compounds from the literature was generated **[20-34]**. Only articles that presented the IC_{50} of 4-thiazolidinone derivatives for cytotoxic activity in vitro were incorporated into the database. Some compounds showed the (IC_{50}) average inhibitory concentration in weight/volume units. In these cases, it was necessary to perform the IC_{50} conversion to molarity units. LogP values were calculated using a ChemAxon computer program (online

version 5.4 chemicalize.org). Compounds with negative cLogP were not included in the database. For the calculation of ligand efficiency (LE) **[35]**, Fit Quality (FQ) **[9]** and ligand lipophilic efficiency (LipE) **[10]** the following formulas were used:

Equation 1: $LE = 1{,}4 \times pIC_{50}/NHA$

Equation 2:

$$FQ = \frac{LE}{0.0715 + (7.5328 \times NHA^{-1}) + (25.7079 \times NHA^{-2}) - (361.4722 \times NHA^{-3})}$$

Equation 3: $LipE = pIC_{50} - cLogP$

Where NHA is the number of different hydrogen atoms; $pIC_{50} = -LogIC_{50}$; cLogP is the calculated partition coefficient. The database was created and analyzed using Microsoft Excel® software. The charts were generated using OriginPro 8 SR2 v 8.0891 (B891) software.

RESULTS AND DISCUSSION

A ligand efficiency analysis of 121 4-thiazolidinone compounds with cytotoxic activity was calculated. **Table 1** shows the average values found for the compounds studied. The average value calculated for LE was 0.26, lower than the 0.3 LE acceptable minimum.10 When FQ was applied for correction of the LE average value, the new average value found was 0.75.

The average cLogP found was 4.51 which obeyed the Rule of Five proposed by Lipinski.36 However, the average pIC_{50} (5.42) was not very different from the average cLogP and so the LipE average (0.91) was well below ≥ 5-7, an ideal value for this metric **[10]**. In addition, Schultes et al. showed that successful compounds have, on average, pIC_{50} equal to 8 **[37]**. The histogram (**Figure 2**) shows the number of compounds based on the values calculated for LE. Only 14% of the compounds have LE values ≥ 0.3, i.e., they have greater chances in succeeding **[38]**. The vast majority of compounds had LE calculated values below the ideal due to NHA. It is known that NHA can influence lipophilia and is considered a risk factor in the planning for drugs. The majority of compounds with high lipophilia has inadequate pharmacokinetics and toxicology. On the other hand, the affinity for the compound target also increases based on lipophilia **[39, 40]**.

In order to verify the influence of NHA on LE values, six 4-thiazolidinone derivatives present in the database were selected and their LE, pIC_{50} and NHA values were compared **(Table 2)**. Compounds 1 **[20]**, 2 **[20]** and 3 **[31]** have pIC_{50} equal to 0.9 μM, however, only compound 3 has an acceptable LE. This is due to NHA. In compound 3, it took 27 NHA to produce a pIC_{50} equal to compounds 1 and 2 which needed 34 and 33 NHA, respectively. Compounds 4 **[31]**, 5 **[24]** and 6 **[27]** fit the same profile. Both have a pIC_{50} of 9 μM and only compound 4 has an acceptable LE, i.e., compound 4, with 0.37 Kcal•mol-1

per NHA, requires 19 different atoms of hydrogen to produce an pIC_{50} equal to compounds 5 and 6. On the other hand, the latter require more heavy atoms to produce pIC_{50} equal to compound 4.

FQ values near 1.0 indicate a wonderful molecule binding affinity for the therapeutic target. So, removing the influence of the difference in molecular size, we have 29% of the compounds with an FQ > 0.8 **(Figure 3)**. Still, compounds with FQ values > 1 have an exceptional affinity for the molecular target **[10]**. In **Figure 3** three FQ compounds above 1 are marked.

According to Lipinski, LogP values for compounds with good oral bioavailability must be equal or less than 5. **Figure 4** shows charts for cLogP x pIC_{50} **(Figure 4a)** and NHA x pIC_{50} **(Figure 4b)**. A total of 37% of the compounds studied have cLogP values greater than 5, i.e., they disobey one of the Lipinski rules for drugs with good oral bioavailability **[36]**. Analyzing **Figure 4a**, we did not notice a tendency to increase pIC_{50} in the cLogP function. This demonstrates that the pIC_{50} for cytotoxicity of 4-thiazolidinones is not dependent on a lipophilia increase and that it is possible to synthesize new chemical entities according to Lipinski's LogP value rule with excellent cytotoxic activity against cancer cells. We also came to the same conclusion when we observed the NHA x pIC_{50} chart **(Figure 4b)**. We realized that most of the compounds that have NHA between 25 and 35, however, do not have a tendency to increase the pIC_{50} based on NHA.

In **Figure 4a**, two compounds synthesized by Wang et al. **[20]** are marked. These compounds **(Figure 5)** are examples of bioactive molecules with LogP within Lipinski's standards36 with pIC_{50} exceeding 8 **[37]**. In addition, they have values for LE ≥ 0.3 and FQ > 1 which fit into the select group of molecules that possess an exceptional affinity for the therapeutic target.

The LE x LipE chart **(Figure 6)** allows us to analyze LE and LipE together. With cLogP greater than pIC_{50}, 31% of the compounds had LipE values less than zero. This means that these molecules have a greater affinity for n-octanol than for the molecular target **[10]**. Two lines divide the compounds with minimal favorable LE and LipE values.

From 121 compounds studied we observed only one that stood out for LE and LipE values **(Figure 6)**. This compound **(Figure 7)** was synthesized by Feitoza et al. **[21]**. It has a better

chance of being successful than the other compounds under study.

The LE metric penalizes compounds with the same potency and different NHA, whereas heavier compounds have worse physicochemical and ADME properties. Yet the LipE metric penalizes compounds that have increased potency based on increased lipophilia. High LogP values are associated with low solubility, absorption and metabolic stability in addition to an increased risk of non-specific interactions and toxicity **[40]**.

Table 1: Average values calculated for ligand efficiency (LE), fit quality (FQ) and lipophilic efficiency (LipE) for 121 compounds studied containing a 4-thiazolidinone nucleus.

Quantity of compounds	pIC_{50}	NHA	LE	FQ	cLogP	LipE
121	5.42 ± 0.62	30.12 ± 4.33	0.26 ± 0.05	0.75 ± 0.08	4.51 ±1.44	0.91 ± 1.59

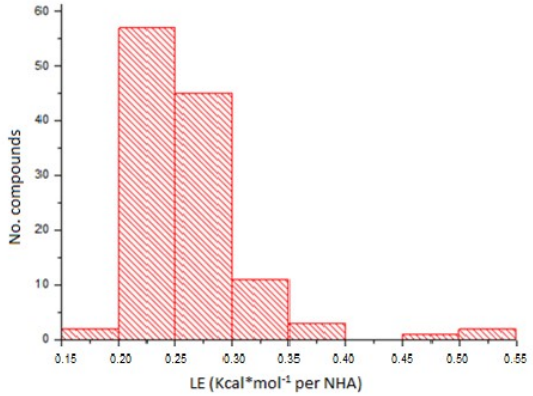


Figure 2: Distribution of ligand efficiency values for 121 4-thiazolidinone derivatives

Table 2: Values for the ligand efficiency (LE), minimum inhibitory concentration (pIC_{50}) and the number of different hydrogen atoms (NHA) for 6 selected 4-thiazolidinone derivatives

Compound	LE (Kcal•mol^{-1} per NHA)	IC_{50} (µM)	NHA
1	0.24	0.9	34
2	0.26	0.9	33
3	0.31	0.9	27
4	0.37	9	19
5	0.27	9	26
6	0.17	9	41

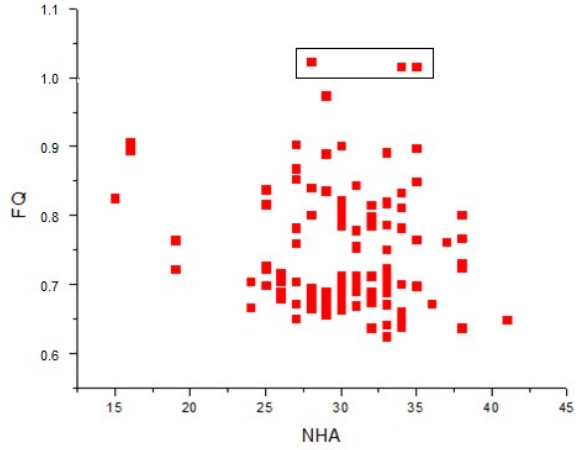


Figure 3: Fit quality values (FQ) x the number of different hydrogen atoms (NHA) for 121 4-thiazolidinone derivatives

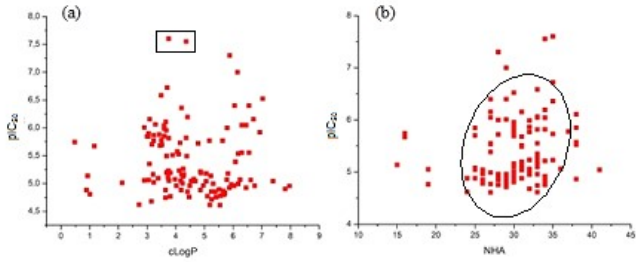
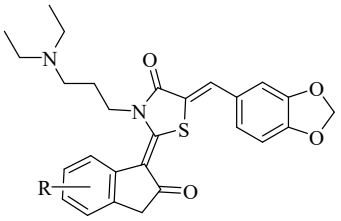


Figure 4: cLogP values x pIC_{50} (3a) and the number of different hydrogen atoms (NHA) x pIC_{50} (3b) for 121 4-thiazolidinone derivatives.



(7) R= 5F (8) R= 6F

IC_{50} 25nM	IC_{50} 28nM
pIC_{50} 7.60	pIC_{50} 7.55
cLoP 4.36	cLogP 3.75
LE 0.30	LE 0.31
FQ 1.02	FQ 1.02
LipE 3.19	LipE 3.85

Figure 5: Synthesized compounds by Wang et al.[20] with cLogP within Lipinski's standards

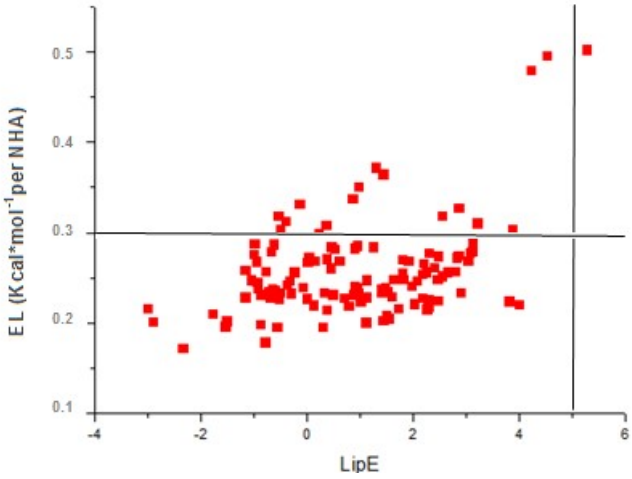
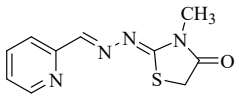


Figure 6: Ligand efficiency (LE) x ligant lipophilic efficiency (LipE) for 121 4-thiazolidinone derivatives



pIC_{50} 5.74
cLogP 0.48
LE 0.50
FQ 0.73
LipE 5.26

Figure 7: Chemical structure and data of compound synthesized by Feitoza et al..[34]

CONCLUSION

The ligand efficiency analysis and lipophilic efficiency of 121 4-thiazolidinone cytotoxic compounds under study showed that 14% of them have LE ≥ 0.3, 29% have an FQ above 0.8. Only one compound has a LipE ≥ 5-7, this is due to a disproportion between the pIC_{50} and the cLogP, or i.e., in general, the compounds studied have high lipophilia in relation to potency. However, the data showed that the increase in potency is independent of lipophilia and the NHA. Even being aware of the Rule of Five there were 37% of the compounds which had a cLogP exceeding five. Consequently, we must stress the necessity for adequate

use of an efficiency analysis of the ligand during the planning of new 4-thiazolidinone antitumor analogs.

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