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Computational Medicinal Chemistry to Design Novel Phosphoinositide 3-Kinase (PI3K) Alpha Inhibitors in View of Cancer

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Abstract: Phosphoinositide 3-kinase (PI3K) is an enzyme involved in the signaling and control of essential cell functions with respect to receptor tyrosine kinase (RTK), for which they are activated. PI3K is involved in some types of cancers in humans, as has been observed in breast, hepatocellular, and colorectal, where, in this latter one, it was only the gene whose mutation was showed. When this gene mutation occurs, overstimulation of this pathway may occur, resulting in an overexpression of tyrosine kinase pathway and inactivation of the Phosphatase and tensin homolog (PTEN), which is a tumor suppressor most frequently deregulated in cancer. The present study aimed to investigate the known inhibitors of PI3K-alpha, deposited in databases such as Binding DB and PDB, in order to draw a profile of physicochemical and pharmacokinetic properties of the most active inhibitors for this enzyme. From this, nine proposals of potential new PI3K inhibitors were developed, which were evaluated with respect to pharmacokinetic and physicochemical properties, activity and toxicity predictions, as well as synthetic accessibility. The results suggest that some of the proposals may be promising new PIK3 inhibitors, containing drug properties.

Keywords: Cancer therapy, medicinal chemistry, phosphoinositide 3-kinase (PI3K) inhibitors.

INTRODUCTION

Cancer is a condition that can be caused due to dysfunctioning of molecular and cellular levels by genetic mutations, genetic instability and due to deregulation in the mechanisms that maintain the balance between proliferation, growth, differentiation and apoptosis of various cell types [1-3]. If we deepen our knowledge on these mechanisms we can know more about cancer, besides enabling new opportunities for therapeutic interventions [4].

The phosphorylation, which is usually done by protein kinases, is a well elucidated mechanism that mediates protein functions and signal transduction. As important regulators of biological processes, the exaggerated expressions of kinases may be related to the onset of diseases like cancer [5].

Phosphoinositide - 3 - kinase (PI3K) is an enzyme involved in signaling and controlling of cell essential functions in relation to tyrosine kinase receptors (RTK), for which they are activated [6-8]. This family of enzymes has a function of lipid kinases and has three classes, and their classification depends on their structure, regulation and catalytic substrate [7]. The PI3K studied here is the PI3K alpha isoform (where there is the alpha, beta and gama isoforms of catalytic subunit) of IA class and has two subunits, one with 85kDa and other with 110KDa, with regulatory and catalytic functions, respectively, and is synthesized from gene PIK3CA [7]. Initially, mutations of PI3KCA in colorectal carcinomas were detected, allowing its classification as oncogene and since then more than 1500 mutations have been found in the enzyme in various types of tumors [9]. When the receptor is stimulated, the subunits migrate to the plasma membrane where they phosphorylate the lipid second messengers (since its action is to phosphorylate phosphoinositides at position 3' of hydroxy group) which have different functions and are related to the metabolism of a range processes such as survival, motility, progression of cell cycle and glucose metabolism [6].

It is known nowadays that PI3K is involved in some types of cancers in humans, as has been observed in PIK3CA, for example, breast cancer, hepatocellular and colorectal, where the latter was the only gene whose mutation was evidenced [7, 8]. When this gene mutation occurs, an overstimulation of this route may occur, generating an overexpression of tyrosine kinase pathway or inactivation of the phosphatase and tensin homolog (PTEN), which is a tumor suppressor most frequently deregulated in cancer [6].

The important role of the route of PI3K in various disease processes, such as neoplasms, has triggered the study and development of inhibitors. In 1957, a substance was isolated from *Penicillium wortmannii*, so-called wortimannin and later showed to be an inhibitor of PI3K. This molecule, by showing instability and toxicity, has not been used clinically, but led to the development of other derivatives with desirable pharmacological profiles and that they will be used in clinical studies [10].

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The present study aimed to investigate inhibitors of PI3K-alpha existing in databases such as the Binding DB (www.bindindb.org/bind/index.jsp) and PDB tracing a pattern for the physicochemical and pharmacokinetic properties to the existing inhibitors of this enzyme and therefore increase knowledge in this area, and develop new proposals for inhibitors that may be more active and selective, and have optimized physicochemical and pharmacokinetic properties, fewer side effects, or having higher synthetic viability.

METHODOLOGY

BindingDB and Select group of Inhibitors

This step started with the search of the enzyme PI3K-alpha in BindingDB [11] database where we found a list of 109 inhibitors, with a match score of 4.77, whose structures were divided into two groups: those that resemble steroidal nuclei, and pyrimidine derivatives with IC_{50} values of 2.7 nM to above 10.000nM. The first group was chosen to work, since it presents a molecule with crystal structure of the enzyme in the PDB database, 20 inhibitors were selected from there with different IC_{50}, values including the inhibitor with crystal structure in the PDB, in order to establish a pattern according to their physicochemical properties and how this influences on their pharmacological potential.

PharmaGist, Physicochemical Properties and Statistical Analysis

After selecting the 20 inhibitors, they were submitted to DS Visualizer (http://accelrys.com) program and prepared, hitting the links of aromatic rings and adding partial charge to the molecules when needed. After being set, the inhibitors were forwarded to PharmaGist server [12], in order to calculate the pharmacophore group present with the crystallographic inhibitor as a reference.

The physicochemical properties were calculated, such as ADME log P, structural volume, molecular refractivity, molecular flexibility (Phi), accessible surface area, average polarizability, homo eigenvalue, lumo eigenvalues and the total dipole, as a tool to observe the properties of rule 5 of C. Lipinski, as well as to characterize the different types of complementarity between ligand and receptor and for that DS Viewer Pro 6.0 program (www.accelrys.com) was used. Later, we also used this methodology to calculate the properties of our new proposals.

When measurements are made on a number of objects, the results are typically organized in a data matrix. The measures in this study (compounds) were organized in rows, and the objects (physico-chemical properties) were organized in columns. Statistical analysis was conducted with the Piroutte 3.10 [13] and Statistica 6.2 [14] programs.

Qikprop

In order to investigate, compare and analyze the pharmacokinetic parameters of both the crystallographic inhibitor and the most active inhibitors already described, the properties of the proposals developed used the QikProp program [15] since it predict such properties and alerts us of these parameters indicated for 95% of drugs. Thus, we selected the inhibitor with the crystallographic structure of the enzyme and the two most effective inhibitors found and submitted to the server QikProp, with intent to obtain and compare their pharmacokinetic properties.

Q-Site Finder

We use the Q-SiteFinder server [16] to detect cavities present in the enzyme (more specifically, the alpha subunit) and these are liable to be active sites for actions of inhibitors (enzyme-inhibitor). For this, we used the inhibitor with the crystallographic enzyme and selected only the last (and from it, only the alpha subunit without water molecules) with the DS Viewer Pro 6.0 program and submitted to the Q-SiteFinder server, as this server predicts binding sites to calculate the cavities found in the enzyme. Then joined the outputs of this program along with the PharmaGist in order to observe the pharmacophore pattern and its ligands within the active site, provided by Q-SiteFinder.

New Proposals

Based on the pharmacokinetic and physicochemical properties obtained, the ChemDraw program [17] was used to make changes in strategic groups in order to give new proposals with better values enzyme affinity, synthetic viability, and pharmacokinetics, as well as lower levels of toxicity.

Docking

We also used the Gold Solutions program [18] to make the docking of the structures studied. The process is initiated by opening the crystallographic inhibitor together with enzyme in DS Viewer Pro 6.0 program, has focused on inhibitor and created a radius of 12 angstroms from the center of molecule, to observe which amino acids (and in them, which atoms) could make interactions with the inhibitor or inhibitor potential. To accomplish this, the coordinates of the central atom were selected and reserved. In order to estimate the accuracy of Gold in docking the proposed inhibitors, redocking of the crystallographic inhibitor was perfomed and the best pose of the docked ligand was compared with the corresponding pose of the ligand co-crystallized with the target.

Distance Connections Calculation

After performing the docking of new proposals with the crystallographic inhibitor, we calculated the distance between the amino acids of the enzyme described in the literature that interacted with the inhibitor and compared with the proposals molecules in our work. For this calculation, we used the DS Viewer Pro 6.0 program.

Affinity of Enzyme

PASS server [19] was used to predict the biological activities of inhibitors and our modifications. The server indicated high efficiency, demonstrating an accuracy of 80%.

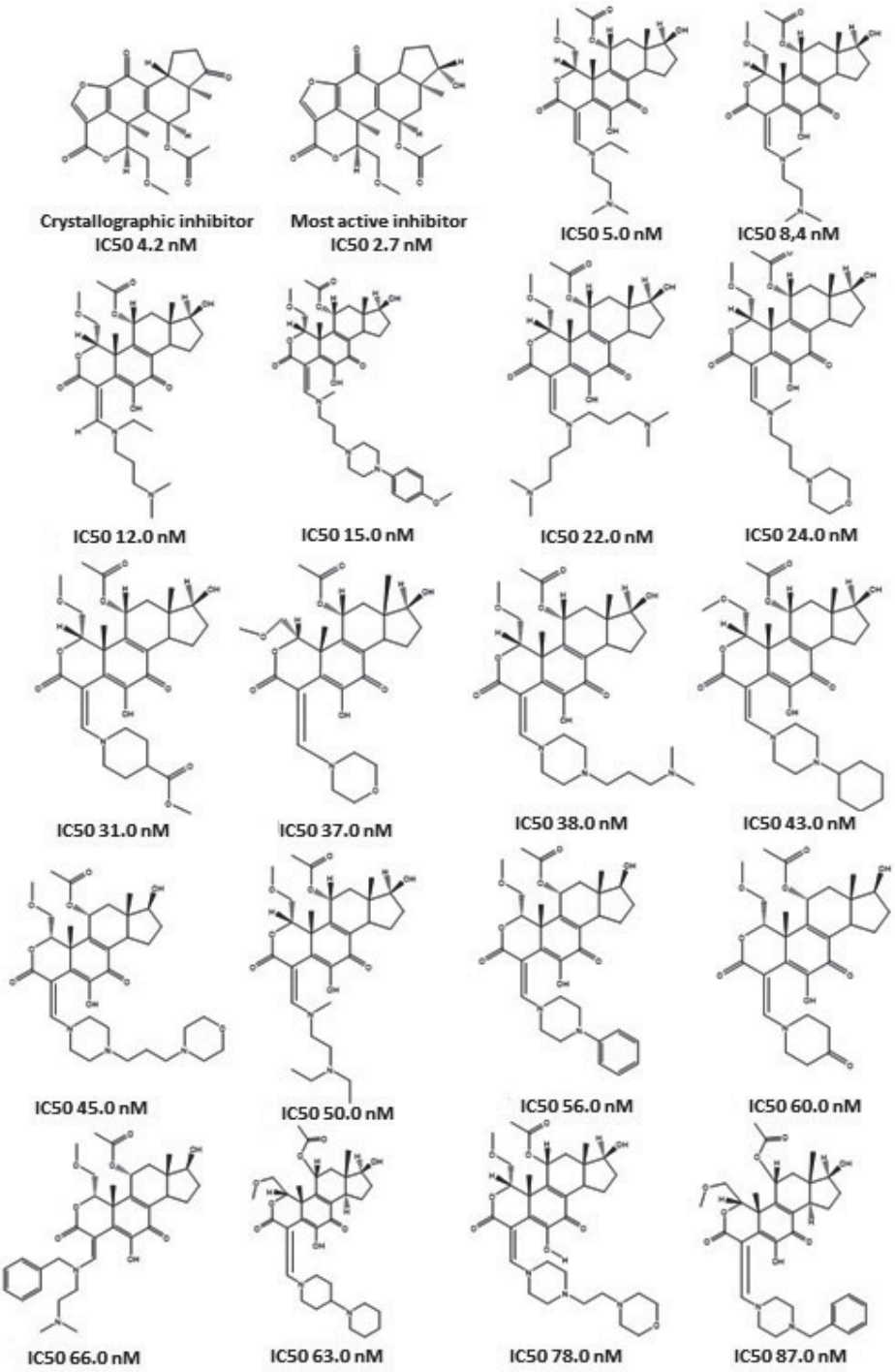

Fig. (1). Inhibitor from the Binding DB database. The first is the crystallographic inhibitor, from the second in the order from left to right and top to bottom are 19 inhibitors in decreasing order of activity.

Synthetic Viability

The SYLVIA - XT 1.4 software [20], demo version, has been used to predict the synthetic viability and degree of difficulty, both compounds were found to be the new proposals made.

Toxicity

The degree of toxicity was predicted from DEREK program [21], as well as the probability that occurs in humans, informing the group responsible for this effect, both in the most active crystallographic inhibitor as the new proposal.

RESULTS AND DISCUSSION

From the Binding DB database twenty molecules were selected in order of increasing activity for the enzyme complex PI3K-alpha (Fig. **1**). These molecules present by default, the presence of steroidal nuclei chosen, as stated in the methodology, for the existence of a crystallographic

complex in the PDB database. It is noteworthy that the crystallographic inhibitor is Wortmaninn.

Correlations between several physicochemical properties and the corresponding IC_{50} values (half maximal inhibitory concentrations) were estimated for each compound using the Pearson product-moment correlation coefficient, where 1 stands for a total positive correlation, 0 for no correlation, and -1 for a total negative correlation. Table **1** shows the Pearson correlation matrix between the physico-chemical properties and IC_{50} value and the correlation between pairs of physico-chemical properties is less than 0.997286, while the correlation between the physico-chemical properties and IC_{50} value is more than -0.443735. The molar volume of drugs causes higher steric hindrance, may block the receptor to interact with the corresponding substrate [22]. The range of variation of the molecular volume was 310.553 to 527.274 cm^3/mol, and compounds 2 and 6 had the lowest and the highest values, respectively. The value of the Pearson correlation of biological activity with the molar volume was 0.414813. The molar refractivity, MR, expresses a physicochemical property of additive-constitutive character, and is therefore highly dependent on the chemical structure of the compound [23-26]. The range of variation of the molar refractivity was 107.453 to 188.626 $Å^3$, and the compounds 1 and 6 had the lowest and highest values, respectively. The value of the Pearson correlation for the molar refractivity with biological activity was 0.432069.

The current concept of theory of action of drugs is based on the principle of fit between the molecular structure of the drug and its receptor and has, among other properties, the flexibility in biomacromolecules involved. Thus, the stereochemistry of bioactive compounds governs the principles of molecular recognition and discrimination, being the stereoselectivity an important aspect of this approach [27-29]. In Table **1**, the flexibility values for the studied compounds are shown, and the range of variation of the flexibility was 4.47468 to 10.8459. Compound 1 obtained the lowest value and the highest value was obtained by compound 7. The value of the Pearson correlation for the flexibility with the biological activity was 0.245076. The surface area is directly linked to the rate of dissolution and absorption, because the larger the contact area is the easier and faster dissolution will be, and hence its absorption by the body [30]. In this table, we observe that the range of variation in surface area of between 427.402 to 744.93 $Å^2$ for the compounds studied, and the compounds 1 and 6 showed the lower and higher values, respectively. The value of the Pearson correlation for the surface area with the biological activity was 0.357004.

The polarizability of physico-chemical properties is very important in studies of SAR/QSAR, it can be correlated with lipophilicity, molar volume and impediments stereos, aiding the interpretation of the mechanisms of interaction between a compound and their respective biological receptor [31, 32]. Table **1** shows the values of polarizability for the compounds studied, the minimum and maximum range was 53.709 to 85.765 $Å^3$ for compounds 1 and 6, respectively. The value of the Pearson correlation for the polarizability with the biological activity was 0.417974.

The Highest Occupied Molecular Orbital Energy (HOMO) is directly related to the ionization potential of the compound and characterizes the ability of the molecule to perform nucleophilic attacks [32]. The reason for this relates to the fact that this property provides information about the character electron donor and/or electron–acceptor compound and thereby forming a charge transfer complex (CTC) [33]. Table **1** shows the values of HOMO for the compounds studied, the maximum and minimum values were 4.4122 to -8.7677 eV for compounds 2 and 16, respectively. It is noteworthy that compound 2 showed the highest value of HOMO which present greater tendency to perform nucleophilic attacks, unlike compound 16. The value of the Pearson correlation for the HOMO with the biological activity was -0.443735.

Total Molecular Dipole Moment is a property that measures the magnitude of charge when displaced atoms of different electronegativity are interconnected. The direction of the dipole moment of a molecule is based on the relative electronegativities of the atoms of this molecules and the value is obtained by the vector resultant of the dipole moments of each bond present in the molecule. The presence of substituents with different electronegativities alters molecular properties as acidity and basicity of a compound so that the dipole moment can answer questions about the same reactivity [34, 35]. In Table **1** the values of total molecular dipole moment for compounds 1-20 are shown, the minimum and the maximum values were 2.05345 to 6.05556 Debye for compounds 1 and 3, respectively. It is noteworthy that compound 3 showed the highest value of the total dipole moment which presents greater tendency to dissolve in polar ways with ease, unlike compound 1 that had near zero. The value of the Pearson correlation for the total dipole moment with the biological activity was -0.254974.

The physico-chemical properties selected by Pearson correlations represent the characteristics necessary to quantify the anticancer activity of these compounds with 3-kinase (PI3K) alpha inhibitors in cancer therapy.

After analyzing the results obtained in the server PharmaGist (Fig. **2**), it could be seen that the pharmacophore is found mainly in the steroid rings, not in the side chains linked therein. The pharmacophore as seen in the figure, has a score 73.171, 12 hydrophobic bonds and 8 acceptors H bonds.

Based on this structure of the pharmacophore, we choose to make structural changes in other locations around the pivot molecule closer to the pharmacophore itself, as will be shown in the next steps of this article.

When submitted the alpha subunit of the enzyme to QSite-Finder server, it demonstrated the potential sites of enzymatic activity from cavities found in the enzyme, once the program fills the cavities, showing these volumes, as well as electronics or hydrophobic intensity.

Table 1. Physico-chemical properties selected by Pearson correlation matrix and IC_{50} experimental.

Compounds	CID	Volume	Refractivity	Flexibility	Surface área	Polarizability	Homo	Total dipole	IC_{50}(nM)
1	312145	310.909	107.453	4.47468	427.402	53.709	-4.81039	2.05345	4.2
2	10002774	310.553	108.275	4.63133	431.649	54.055	-4.41216	5.00977	2.7
3	24768371	415.959	146.217	8.5019	588.917	65.681	-8.58593	6.05556	5
4	24768370	402.756	141.469	7.99538	569.784	63.374	-8.53341	4.627	8.4
5	24768372	429.679	151.083	9.01995	609.533	67.966	-8.54344	5.11992	12
6	24768378	527.274	188.626	10.7714	744.93	85.765	-8.56852	3.5858	15
7	24768375	477.283	169.219	10.8459	692.798	76.059	-8.49382	5.19989	22
8	24768377	444.406	155.409	9.04751	627.389	69.638	-8.59965	5.14661	24
9	24768389	423.027	146.6	8.09737	588.289	65.56	-8.61898	5.87028	31
10	24768392	381.028	132.525	6.89252	523.616	59.287	-8.57586	3.85869	37
11	24768386	458.296	162.385	9.28889	652.239	73.08	-8.45782	4.79792	38
12	11642863	452.768	160.514	8.42788	633.071	73.487	-8.45633	4.17742	43
13	24768388	484.63	171.459	9.83956	683.66	77.075	-8.50688	2.97688	45
14	24768373	430.596	150.965	9.01995	614.693	67.917	-8.53951	4.81799	50
15	11692830	443.566	159.278	7.91488	613.312	72.743	-8.50534	3.94683	56
16	24768393	390.887	135.926	6.94501	537.947	60.824	-8.76771	3.69473	60
17	24768369	458.436	166.082	9.2627	646.809	75.668	-8.53141	3.31748	66
18	24768391	452.923	161.043	8.42788	631.769	73.562	-8.48382	5.28701	63
19	24768387	472.537	166.594	9.34106	660.823	74.796	-8.5174	3.81448	78
20	11721393	457.313	164.113	8.38123	631.567	74.959	-8.48097	3.86049	87
Volume		1.000000	0.997286	0.948206	0.995049	0.975743	-0.755936	0.062724	0.414813
Refractivity			1.000000	0.936611	0.991110	0.986020	-0.736743	0.037689	0.432069
Flexibility				1.000000	0.971201	0.890553	-0.770195	0.210652	0.245076
Surface area					1.000000	0.968380	-0.742640	0.101217	0.357004
Polarizability						1.000000	-0.621156	-0.031593	0.417974
Homo							1.000000	-0.258116	-0.443735
Total dipole								1.000000	-0.254974

In order to make our new proposals molecular, we used the two most active inhibitors, as well as crystallographic inhibitor, seeking changes that improve physicochemical, pharmacokinetic properties, as well as synthetic feasibility and toxicity. By doing molecular changes, the proposals were submitted for analysis of the PASS server that gave us a value of affinity of the enzyme inhibitor (Table **2**). Therefore, we got nine new proposals that followed for further analysis (Fig. **3**). We initiated the formulation of proposals to analyze the crystallographic inhibitor *in situ* and observed that this had a different structure found in the database of the Binding DB. In enzyme, molecule presented the opening of the furan ring and thereby generating a hydroxyl group and another methyl instead of the initial structure (Fig. **4**).

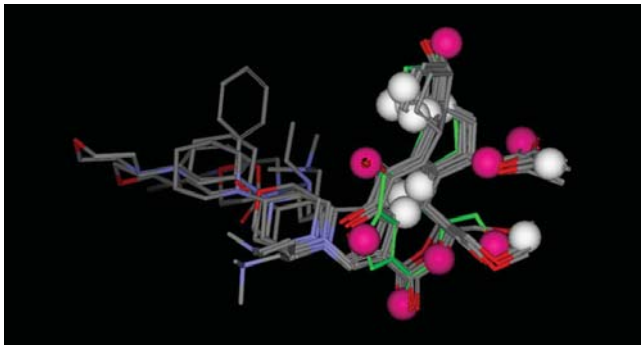

Fig. (2). Superposition of the 20 most active PI3K inhibitors and pharmacophore hypothesis generated in PharmaGist and visualized by DS Viewer Pro 6.0. Pharmacophore features are highlighted in Magenta (Hydrogen Bond Acceptor) and Light Gray (Hydrophobic).

Table 2. Affinity of the 9 proposed inhibitors, crystallographic inhibitor and the two most active inhibitors of the enzyme PI3K alpha obtained through PASS server.

Inhibitor	Prediction of affinity (Pa) to PI3K-alpha
Crystallographic	0,984
More active (Binding DB)	0,910
Second more active (Binding DB)	0,830
Proposal 1	0,826
Proposal 2	0,855
Proposal 3	0,882
Proposal 4	0,799
Proposal 5	0,829
Proposal 6	0,801
Proposal 7	0,836
Proposal 8	0,824
Proposal 9	0,964

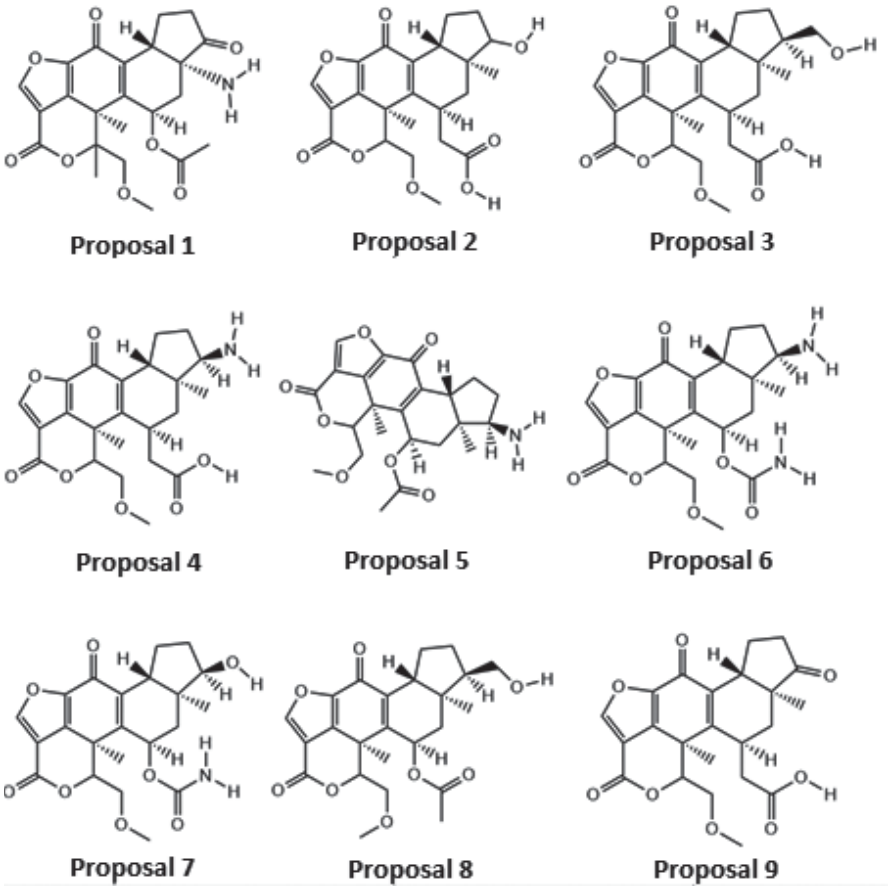

Fig. (3). Proposals made through changes in groups of crystallographic inhibitor and the most active inhibitor, taking into account the results of PharmaGist.

With this assumption, we based structures with the same open ring in order to resemble the behavior of the inhibitor *in situ*. To predict the activity of newly formulated proposals, the PASS server pointed to a degree of activity not compatible with the expected (both with proposals as to the crystallographic inhibitor itself - indicating extremely low and not selective value). Having realized this difference in activity, we decided to send back our proposals to the server, this time

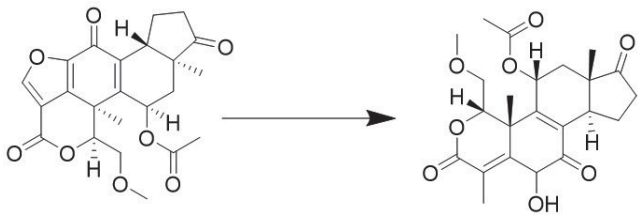

Fig. (4). Reaction proposal for opening the furan ring occurs within the enzyme.

with the ring closed, resulting in a high affinity for the expected enzyme subunit expected. Thus, it can be predicted that the inhibitor activity occurs with the closed enzyme and the inhibitor undergoes a reaction at the site of action that generates the ring opening, perhaps with this reaction step involving one of its mechanism of actions.

In QikProp program, both the crystallographic inhibitors as the two most active molecules had all their properties as expected, and showed no violation of the values of Molecular Weight, total SASA, Hydrophobic SASA, Hydrophilic SASA, Carbon Pi SASA, Weakly Polar SASA, Molecular Volume, vdW Polar AS, Number of Rotatable Bounds, Solute as Donor – Hydrogen Bounds, Solute as Acceptor – Hydrogen Bounds e Solute Globularity, and the polarizability in octanol/water. While analyzing the new synthetic proposals, the same parameters were used in order to calculate its properties and these, as well as molecules of the above analysis, showed values within the range that comprises 95% of known drugs, and no amount of any molecule showed to be abnormal.

As for the results involving the Gold Solutions program, we found that the prediction of the program was accurate in predicting where the crystallographic inhibitor would be, as well as its spatial position. Based on this result, we have confidence in the results obtained for our new proposals (Fig. **5**). In seven of our proposals [1, 3, 4, 5, 6, 7, 9], the program is able to predict the position in which the molecules would bind to the enzyme satisfactorily. In proposals 2 and 8, however, the program had difficulty in making the prediction requiring 10 attempts to do so, which in our criterion have been considered unsatisfactory. Importantly, due to the crystallographic inhibitor being in its open conformation, as mentioned above, the docking done to assess the accuracy of the Gold Solutions was done with the open ring. However, our objective was to evaluate the position in which our inhibitors would with a closed ring, which, as shown, have a higher affinity for the enzyme. Thus, observed in all proposals a

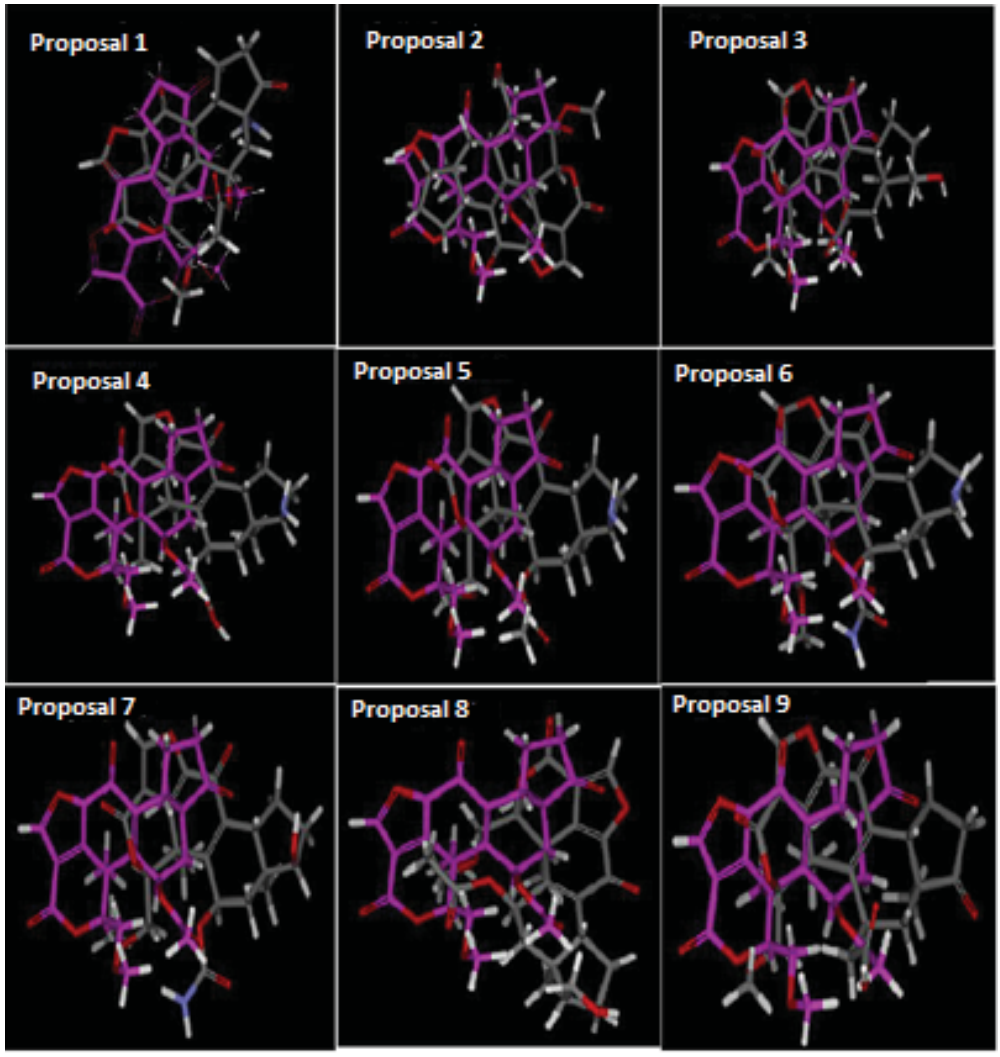

Fig. (5). Docking, made with Gold Solution program, our proposals with the crystallographic inhibitor.

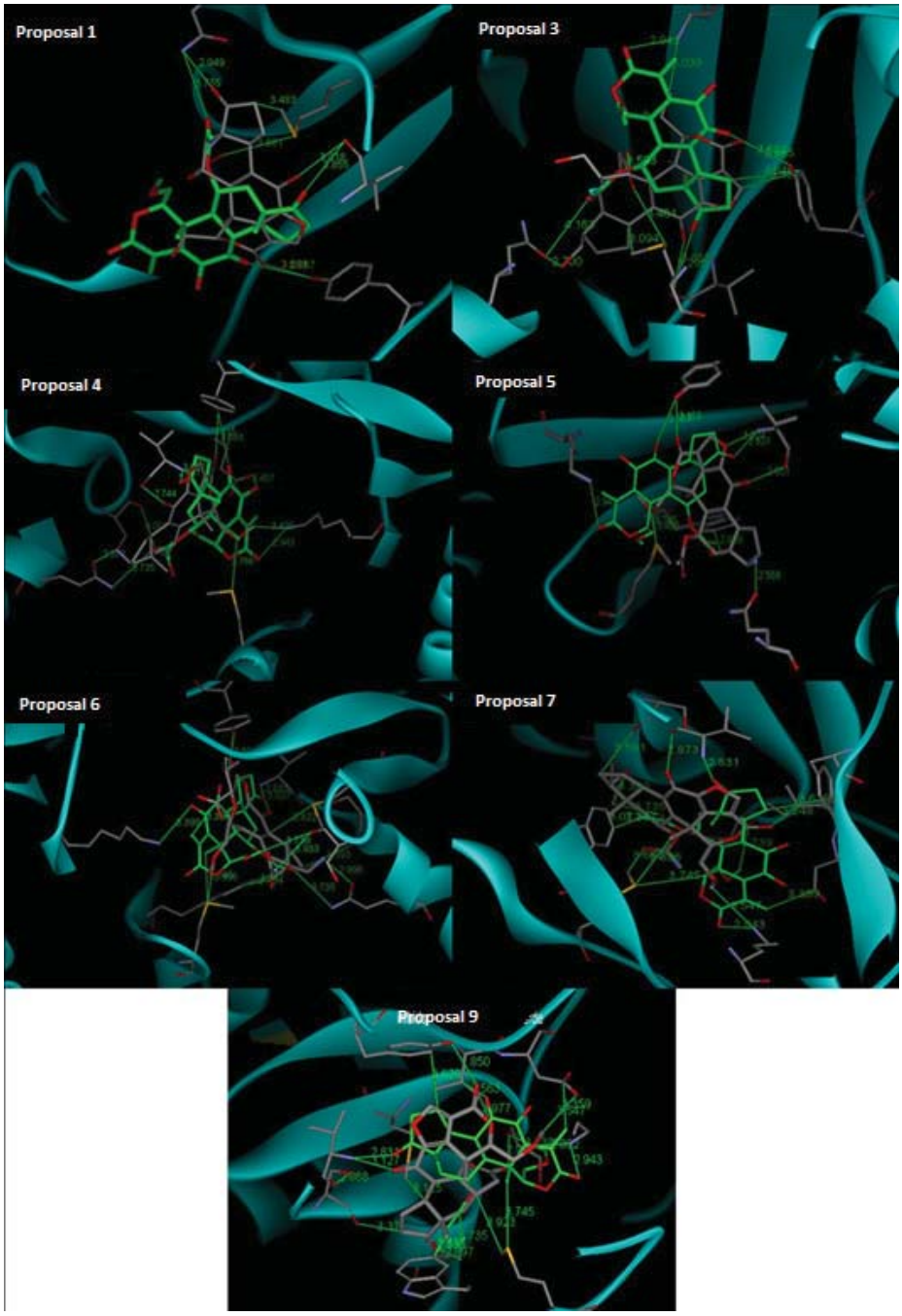

Fig. (6). Docking of the crystallographic inhibitor with each proposal and its values binding to amino acids in the PI3K-alpha binding site. Proposals in gray and crystallographic inhibitor in green.

small displacement, which could change the interactions of inhibitors with amino acids of the enzyme, which can generate approximations or distances and consequently changes the strength of connections.

To analyze these possible interaction changes, we used the DS Viewer Pro to calculate the distance between the proposed groups and the groups of amino acids. Therefore, seeking possible interactions in each of the seven proposals Gold Solutions could satisfactorily predict the position in site of the enzyme with the amino acids of PI3K-alpha (Fig. **6**). The results are shown in Table **3**, in which transcribed the value of the distances of the interactions proposed and compared with the distances found; there was the same procedure with the crystallographic inhibitor with an open ring. Thus, observed that the vast majority of proposals can interact with amino acids that were not previously involved as potential links to more in Tyr 836 and Ser 854, whose interactions occur with all proposals demonstrated.

Among the proposals analyzed, it was observed that the prediction of proposal 9 should be more active among the 9 proposals and compared it to the inhibitors described, we noted that the prediction activity was superior to those

Table 3. Comparison of distance in angstroms between atoms of the inhibitors proposed and crystallographic to amino acids PI3K enzyme. In dark grey those cases are observed where the distance for the proposal of the column was found to be smaller than the distance to the crystallographic inhibitor, the light grey column. (It makes no interaction = NF).

	Crystallographic	Proposal 1	Proposal 3	Proposal 4	Proposal 5	Proposal 6	Proposal 7	Proposal 9
Met 772	3,745	3,84	3,827	3,691	3,488	3,986	3,662	3,923
Trp 780	3,387	2,59	2,029	2,725	2,808	2,924	3,072	2,535
Lys 802	2,943	2,992	3,039	3,496	3,733	NF	3,547	2,892
Tyr 836	NF	2,867	2,855	3,115	3,163	NF	3,841	2,85
	3,620	3,370	3,055	NF	NF	3,496	NF	3,3325
Val 851	3,866	3,103	2,698	3,032	3,024	3,027	3,054	3,127
	2,831	NF	NF	2,744	2,851	NF	2,873	NF
Ser 854	NF	3,33	3,706	3,58	3,643	3,593	3,591	3,371
Gln 859	3,735	2,949	2,7	2,57	2,568	2,996	2,33	2,897
Ser 919	3,739	3,597	3,593	4,001	3,477	3,933	NF	2,992
Met 922	NF	3,881	3,461	NF	3,13	3,822	3,29	3,599
	4,133	3,087	3,094	3,494	NF	2,898	NF	3,125
Ile 932	3,563	NF	3,566	3,596	3,595	3,278	3,946	3,562
Asp 933	3,457	3,449	3,911	NF	NF	2,995	NF	3,344

already described, besides being slightly lower than the crystallographic inhibitor wormaninn. If this proposed molecule showed to be more stable and has a lower degree of synthetic difficulty, it can be forwarded for further studies *in vitro* and *in silico*, occasionally.

To examine the toxicity of each inhibitor and our proposals, we used the DEREK program and began the search for potential toxic effects, primarily in crystallographic enzyme inhibitor, followed by two active molecules found in the *DB Binding* database and finally tested the proposals developed during the job step. It was observed that all of the above molecules had two potential toxic effects, and this chromosomal damage with certainty was only plausible and a dubious chance of having nephropathy alpha-2-microglobulina. The first effect referred to may not be a harmful or deleterious effect, since the inhibitors are targets for cancer and chromosomal damage and a correct target may be a mechanism of valid action and can be selective and hence more efficient. Another existing potentially toxic effect, but with a low degree of certainty since the program indicated only as doubtful in mammals is the proliferation of peroxisomes, which are presented in the proposals 2, 3, 4, 8 and 9. Finally, the second most active molecule of Binding DB database, there is still a potential toxic effect of skin sensitization, whose degree of certainty displayed by the program is plausible. Despite the presence of these toxicities, it is known that chemotherapy drugs, which aim at decreasing the proliferation of tumor cells, alone, already have considerable side effects, thus, inhibitors of PI3K alpha, can be studied with the aim of lessening the severity of the treatment.

Table 4. Values of synthetic viability to crystallographic inhibitor, the two most active and the nine proposals inhibitors, obtained by SYLVIA-XT 1.4 program.

Molecule	Value obtained by SYLVIA-XT 1.4 program
Crystallographic inhibitor	8,8
More active inhbitor	8,25
Second more active inhbitor	8,43
Proposal 1	7,78
Proposal 2	7,82
Proposal 3	7,88
Proposal 4	7,85
Proposal 5	7,88
Proposal 6	7,92
Proposal 7	7,9
Proposal 8	7,91
Proposal 9	7,73

Finally, we start the analysis step of synthetic viability with SYLVIA-XT 1.4 program with the crystallographic inhibitor and the two inhibitors described in the literature with a greater degree of activity and all proved to have a complex and poorly functional synthetic viability. Subsequently, we

have submitted the proposals molecules in the same way and the results were found to be positive, as observed in Table **4**. To be a demo version, the results must be analyzed carefully, requiring further studies.

As can be seen, the molecular proposals have a lower degree of synthetic viability, since no value reaches 8. Also noted that the proposed inhibitor presents greater activity by PASS server, also, synthetic viability, which can lead to further study of the molecule viability as a drug.

CONCLUSION

Based on the results obtained so far can be seen that there is a need for further study involving both as enzyme and as new inhibitors in it is a promising and innovative area. Regarding our study, the efforts to raise the knowledge of the inhibitors already generated a new library of compounds of this class; they are proposals that demonstrated satisfactory *in silico* results, given the predictions of the programs as the physiochemical and pharmacokinetic properties. Therefore, further studies have to be done to evaluate the different proposals as well as their actions, toxicity, and potential use for inhibition of PI3K enzyme complex as well as the treatment of cancers, other diseases associated with this enzyme, and studies on its activity.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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