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Rational Computational Study for New Kinase Inhibitors

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Abstract: The development of new drugs can present several problems, it is a important obstacle the ability to adapt a molecule that is a potent pharmacological inhibitor and that is also possible to execute its synthesis. Quinazolines are known to be capable of inhibiting kinases. Thus, a detailed study was carried out to propose new quinazolines with already known synthetic routes, and that were promising for the ability to inhibit kinases. A drug candidate molecule shall be proposed to have a good absorption, an extensive distribution so it's capable of reaching the desired therapeutic targets. Lipinski's Rule of 5 in computational studies has been applied to select more promising molecules. In this study, the molecules proposed for the synthesis were systematically designed in appropriate computational programs to test several substituents of the quinazoline nucleus on the capacity of these molecules to be considered inhibitors of kinases. Six molecules were selected with the best results to inhibit kinases. In the study to evaluate the variation of substituents, the result obtained for the 8-position of the quinazoline ring and with the -Cl substituent at that ring position presented 60% of the 10 best molecules capable of inhibiting kinases. The molecular docking study confirmed that the two most promising molecules to inhibit kinase also obtained the best results to inhibit AKT kinase. Therefore, through this study it was possible to select six more promising molecules to be synthesized and available in large screening tests for several therapeutic targets known as High-Throughput Screening.

Keywords: Kinase Inhibitor, Quinazoline, Molecular Docking

1. Introduction

In the development of new drugs it's possible to find several problems, and an important obstacle is to adapt a molecule that is potent, that is, capable of inhibiting a certain target and that it is also capable of having known synthetic routes and possibility of execution [1]. Thus, a drug candidate molecule must be proposed to have a good absorption, an extensive distribution, so it's capable of reaching the desired target and so it's not toxic [2]. In addition, these molecules must be able to have their synthesis easily executed. One of the major problems in drug development has been to synthesize the most promising molecules. Previous computational studies can be performed to select molecules with good pharmacokinetic parameters [3], high biological activity and also have a possibility of being synthesized. In this context, computational studies can help if drug candidate molecules have good pharmacokinetic parameters [4]. Molecular docking studies allow us to evaluate if certain molecules have the capacity to inhibit their molecular targets [5], so, this computational tool corroborates the selection of more promising molecules. Kinases are promising targets for various types of cancer and other diseases [6], thus, some molecules capable of inhibiting kinases may be considered promising in studies for the discovery and development of new drugs.

2. Method

2.1. Evaluation of Quinazolines for Syntheses by Well-Established Synthetic Routes

Due to the great importance of quinazolinones and quinazolines, many methods for their syntheses have been reported in the literature [7]. The main synthetic routes use 2-

aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenyl isocyanate, N-arylnitrilium salts and 4H-3, 1-benzoxazinones as starting materials (Figure 1) [8].

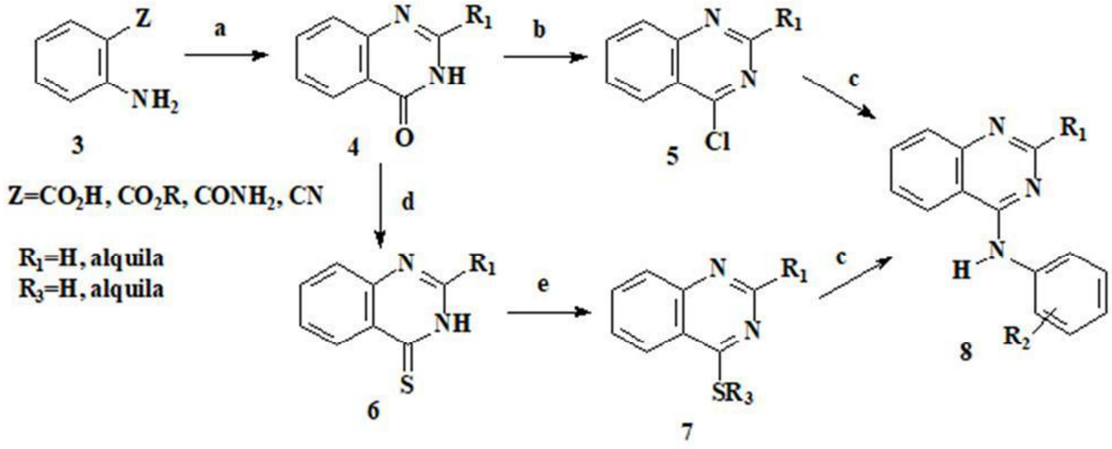

Figure 1. *Steps for the preparation of 4-anilinoquinazolines [8].*

According to methodology which can be seen in Figure 1, the first step involves adding a carbon atom to an anthranilic acid derivative (3), and this leads to the cyclization to the quinazolinone represented by the number 4 in Figure 1 [7]. This reaction may be carried out using reagents such as formic acid, formamide and amidines [8]. The second step in derivatization involves the conversion of intermediate 4 to 4-chloroquinazoline 5, through the reaction with phosphoryl chloride (POCl 3) or with thionyl chloride containing a catalytic amount of DMF. Through the proposed quinazoline synthesis seen in Figure 1, it is possible to propose several modifications in the quinazoline ring through variations of substituents at the R_1, R_2, R_3 and R_4 positions which can be seen in Table 1.

2.2. Study of Several Substituents of Quinazolines to Have a Good Oral Bioavailability and High Capacity to Inhibit Kinases

The molecules of the quinazolines were drawn with variations of substituents at the R_4 position of the quinazoline ring which can be seen in Table 1. Each molecule was tested with various substitutions at the R_4 position and fixed at R_1 (O-Me, H, Cl); R_2 (H and OMe) and R_3 (H and OMe). All molecules were drawn using the ChemSketch [9] program, then converted to the SMILE format and introduced into the computational platform Molinspiration [3]. This platform allowed to calculate the possibility of violation of the *Rule of 5 of Lipinski* [10] and the capacity of each molecule to have inhibited kinases.

2.3. Studies by Molecular Docking to Confirm the Most Promising Molecules of Having the Ability to Inhibit a Specific Kinase

The method is based on the use of atomic coordinates to represent a docking molecule with other molecules using computationally simulated atomic force fields. Several representations of molecular surface and volume have been drawn. In this study, the protein database (PDB) [11] was used to obtain the crystal coordinates of the enzyme under study (AKT) bound to a selective inhibitor. The quinazoline molecules selected for synthesis were then submitted to docking studies within the active site of AKT. The three-dimensional (3D) structures of the compounds were obtained from the *Molegro Virtual Docker* program (MVD) [12], using the crystals of the structures containing the selective inhibitor of AKT as template. Subsequently, the fully optimized geometries and the calculations of the atomic charge distribution of the ligands were performed with the same program using the semi-empirical method AM1 [12]. The quinazoline was analyzed by interactions within the active site of the AKT enzyme, using the MVD. This program allows to predict the most likely conformation with which a ligand could bind to a macromolecule. The MolDock scoring function (Mol Dock score), used by the MVD program, is derived from the Linear Potential Piecewise PLP and extended in the Generic evolutionary method for molecular DOCK (GEMDOCK) with a new term of hydrogen bonds and new schemes of charges. The search algorithm of the docking study was the MVD based on interactive techniques of optimizations, inspired by the evolutionary theory of Darwin (evolutionary algorithms - EA) [12]. The potential binding site of the AKT receptor was calculated using the program algorithm for detecting the receptor cavity. Binding molecules and a set of composite regions of all amino acid residues (side chain), having at least one atom distant at 12 Å from the center of the selective binder, were considered flexible during the docking simulation. The conformation of each compound was then selected using its best spatial similarities with the selective inhibitor, which were represented by the structures with the energies of the most favorable interactions between the positioning of the ligand and the protein.

3. Results

Figure 2 shows the positions of the substituents R1, R2, R3 and R4 that have been tested in this study. This figure can be used for the results in Tables 1, 2 and 3.

The Table 1 shows a variation of substituents in the quinazoline ring to select the most promising molecules for inhibiting kinases and oral bioavailability.

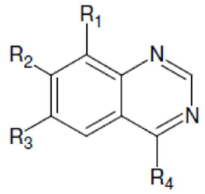

Figure 2. *Substituentes R1, R2, R3 and R4 in quinazoline ring.*

Table 1. *Study of 150 quinazolines with variations of substituents at the R_4 position; R_1 (O-Me, H, Cl); R_2 (H and OMe) and R_3 (H and OMe) for the possibility of violating the Lipinski's Rule of 5 (in red) and high capacity to inhibit kinases (in green).*

Molecule	R1	R2	R3	R4	Violation of Lipinski's Rule	Kinase Inhibition
1.0	OMe	H	H	3-nitro-5-(trifluoromethyl)aniline	No	0.41
1.1	H	OMe	OMe	3-nitro-5-(trifluoromethyl)aniline	No	0.48
1.2	Cl	H	H	3-nitro-5-(trifluoromethyl)aniline	Yes	0.51
2.0	OMe	H	H	1,3-benzodioxol-5-amine	No	0.53
2.1	H	OMe	OMe	1,3-benzodioxol-5-amine	No	0.62
2.2	Cl	H	H	1,3-benzodioxol-5-amine	No	0.62
3.0	OMe	H	H	3,5bis(trifluoromethyl)aniline	Yes	0.53
3.1	H	OMe	OMe	3,5bis(trifluoromethyl)aniline	No	0.59
3.2	Cl	H	H	3,5bis(trifluoromethyl)aniline	Yes	0.63
4.0	OMe	H	H	3-(methylthio)aniline	No	0.41
4.1	H	OMe	OMe	3-(methylthio)aniline	No	0.54
4.2	Cl	H	H	3-(methylthio)aniline	No	0.51
5.0	OMe	H	H	4-(4-chlorophenoxy)aniline	Yes	0.53
5.1	H	OMe	OMe	4-(4-chlorophenoxy)aniline	Yes	0.59
5.2	Cl	H	H	4-(4-chlorophenoxy)aniline	Yes	0.64
6.0	OMe	H	H	4-(methylthio)aniline	No	0.44
6.1	H	OMe	OMe	4-(methylthio)aniline	No	0.57
6.2	Cl	H	H	4-(methylthio)aniline	No	0.53
7.0	OMe	H	H	4-(trifluoromethyl)aniline	No	0.61
7.1	H	OMe	OMe	4-(trifluoromethyl)aniline	No	0.68
7.2	Cl	H	H	4-(trifluoromethyl)aniline	Yes	0.72
8.0	OMe	H	H	4-chloro-3-(trifluoromethyl)aniline	Yes	0.57
8.1	H	OMe	OMe	4-chloro-3-(trifluoromethyl)aniline	No	0.64
8.2	Cl	H	H	4-chloro-3-(trifluoromethyl)aniline	Yes	0.70
9.0	OMe	H	H	4-aminobenzenesulfonic acid	No	0.43
9.1	H	OMe	OMe	4-aminobenzenesulfonic acid	No	0.51
9.2	Cl	H	H	4-aminobenzenesulfonic acid	No	0.53
10.0	OMe	H	H	2-(methylthio)aniline	No	0.44
10.1	H	OMe	OMe	2-(methylthio)aniline	No	0.57
10.2	Cl	H	H	2-(methylthio)aniline	No	0.53
11.0	OMe	H	H	2-(phenylsulfonyl)aniline	No	0.34
11.1	H	OMe	OMe	2-(phenylsulfonyl)aniline	No	0.41
11.2	Cl	H	H	2-(phenylsulfonyl)aniline	Yes	0.43
12.0	OMe	H	H	2-(phenylthio)aniline	Yes	0.53
12.1	H	OMe	OMe	2-(phenylthio)aniline	Yes	0.46
12.2	Cl	H	H	2-(phenylthio)aniline	Yes	0.57
13.0	OMe	H	H	2-methoxyaniline	No	0.55
13.1	H	OMe	OMe	2-methoxyaniline	No	0.66
13.2	Cl	H	H	2-methoxyaniline	No	0.61
14.0	OMe	H	H	2-(trifluoromethyl)aniline	No	0.71
14.1	H	OMe	OMe	2-(trifluoromethyl)aniline	No	0.64
14.2	Cl	H	H	2-(trifluoromethyl)aniline	Yes	0.61
15.0	OMe	H	H	3-(1,1,2,2-tetrafluoroethoxy)aniline	No	0.65
15.1	H	OMe	OMe	3-(1,1,2,2-tetrafluoroethoxy)aniline	No	0.70
15.2	Cl	H	H	3-(1,1,2,2-tetrafluoroethoxy)aniline	Yes	0.75
16.0	OMe	H	H	4-(2-aminoethyl)aniline	No	0.72
16.1	H	OMe	OMe	4-(2-aminoethyl)aniline	No	0.80
16.2	Cl	H	H	4-(2-aminoethyl)aniline	No	0.84
17.0	OMe	H	H	3-(difluoromethoxy)aniline	No	0.32
17.1	H	OMe	OMe	3-(difluoromethoxy)aniline	No	0.41
17.2	Cl	H	H	3-(difluoromethoxy)aniline	No	0.41

Molecule	R1	R2	R3	R4	Violation of Lipinski's Rule	Kinase Inhibition
18.0	OMe	H	H	3-methoxyaniline	No	0.57
18.1	H	OMe	OMe	3-methoxyaniline	No	0.67
18.2	Cl	H	H	3-methoxyaniline	No	0.63
19.0	OMe	H	H	3-(trifluoromethyl)aniline	No	0.61
19.1	H	OMe	OMe	3-(trifluoromethyl)aniline	No	0.68
19.2	Cl	H	H	3-(trifluoromethyl)aniline	Yes	0.73
20.0	OMe	H	H	1-(4-aminophenyl)ethanone	No	0.37
20.1	H	OMe	OMe	1-(4-aminophenyl)ethanone	No	0.48
20.2	Cl	H	H	1-(4-aminophenyl)ethanone	No	0.47
21.0	OMe	H	H	3-nitro-5-(trifluoromethyl)aniline	No	0.41
21.1	H	OMe	OMe	3-nitro-5-(trifluoromethyl)aniline	No	0.48
21.2	Cl	H	H	3-nitro-5-(trifluoromethyl)aniline	Yes	0.51
22.0	OMe	H	H	1,3-benzodioxol-5-amine	No	0.53
22.1	H	OMe	OMe	1,3-benzodioxol-5-amine	No	0.62
22.2	Cl	H	H	1,3-benzodioxol-5-amine	No	0.62
23.0	OMe	H	H	3,5bis(trifluoromethyl)aniline	Yes	0.53
23.1	H	OMe	OMe	3,5bis(trifluoromethyl)aniline	Yes	0.59
23.2	Cl	H	H	3,5bis(trifluoromethyl)aniline	Yes	0.63
24.0	OMe	H	H	3-(methylthio)aniline	No	0.41
24.1	H	OMe	OMe	3-(methylthio)aniline	No	0.54
24.2	Cl	H	H	3-(methylthio)aniline	No	0.51
25.0	OMe	H	H	4-(4-chlorophenoxy)aniline	Yes	0.54
25.1	H	OMe	OMe	4-(4-chlorophenoxy)aniline	Yes	0,59
25.2	Cl	H	H	4-(4-chlorophenoxy)aniline	Yes	0.64
26.0	OMe	H	H	4-(methylthio)aniline	No	0.44
26.1	H	OMe	OMe	4-(methylthio)aniline	No	0.57
26.2	Cl	H	H	4-(methylthio)aniline	No	0.53
27.0	OMe	H	H	2-methoxy-5-(trifluoromethyl)aniline	No	0.54
27.1	H	OMe	OMe	2-methoxy-5-(trifluoromethyl)aniline	No	0.60
27.2	Cl	H	H	2-methoxy-5-(trifluoromethyl)aniline	Yes	0.63
28.0	OMe	H	H	2-morpholin-4-ylaniline	No	0.52
28.1	H	OMe	OMe	2-morpholin-4-ylaniline	No	0.58
28.2	Cl	H	H	2-morpholin-4-ylaniline	No	0.62
29.0	OMe	H	H	4-aminobenzenesulfonic acid	No	0.43
29.1	H	OMe	OMe	4-aminobenzenesulfonic acid	No	0.51
29.2	Cl	H	H	4-aminobenzenesulfonic acid	No	0.53
30.0	OMe	H	H	2-(methylthio)aniline	No	0.44
30.1	H	OMe	OMe	2-(methylthio)aniline	No	0.57
30.2	Cl	H	H	2-(methylthio)aniline	No	0.53
31.0	OMe	H	H	4-(4-fluorophenoxy)aniline	Yes	0.58
31.1	H	OMe	OMe	4-(4-fluorophenoxy)aniline	Yes	0.64
31.2	Cl	H	H	4-(4-fluorophenoxy)aniline	Yes	0.68
32.0	OMe	H	H	4-(4-nitrophenoxy)aniline	Sim	0.38
32.1	H	OME	OMe	4-(4-nitrophenoxy)aniline	No	0.44
32.2	Cl	H	H	4-(4-nitrophenoxy)aniline	Yes	0.47
33.0	OMe	H	H	4-(difluoromethoxy)aniline	No	0.31
33.1	H	OMe	OMe	4-(difluoromethoxy)aniline	No	0.40
33.2	Cl	H	H	4-(difluoromethoxy)aniline	No	0.40
34.0	OMe	H	H	4-(trifluoromethoxy)aniline	No	0.52
34.1	H	OMe	OMe	4-(trifluoromethoxy)aniline	No	0.58
34.2	Cl	H	H	4-(trifluoromethoxy)aniline	Yes	0.63
35.0	OMe	H	H	2,6-dichloro-4-(trifluoromethyl)aniline	Yes	0.63
35.1	H	OMe	OMe	2,6-dichloro-4-(trifluoromethyl)aniline	Yes	0.69
35.2	Cl	H	H	2,6-dichloro-4-(trifluoromethyl)aniline	Yes	0.76
36.0	OMe	H	H	2-bromo-4-(trifluoromethyl)aniline	Yes	0.48
36.1	H	OMe	OMe	2-bromo-4-(trifluoromethyl)aniline	No	0.56
36.2	Cl	H	H	2-bromo-4-(trifluoromethyl)aniline	Yes	0.60
37.0	OMe	H	H	2-chloro-4-(trifluoromethyl)aniline	Yes	0.62
37.1	H	OMe	OMe	2-chloro-4-(trifluoromethyl)aniline	No	0.68
37.2	Cl	H	H	2-chloro-4-(trifluoromethyl)aniline	Yes	0.75
38.0	OMe	H	H	2-fluoro-6-(trifluoromethyl)aniline	No	0.60
38.1	H	OMe	OMe	2-fluoro-6-(trifluoromethyl)aniline	No	0.66
38.2	Cl	H	H	2-fluoro-6-(trifluoromethyl)aniline	Yes	0.72
39.0	OMe	H	H	4-(4-fluorophenoxy)aniline	Yes	0.58

Molecule	R1	R2	R3	R4	Violation of Lipinski's Rule	Kinase Inhibition
39.1	H	OMe	OMe	4-(4-fluorophenoxy)aniline	Yes	0.64
39.2	Cl	H	H	4-(4-fluorophenoxy)aniline	Yes	0.68
40.0	OMe	H	H	4-(4-bromophenoxy)aniline	Yes	0.51
40.1	H	OMe	OMe	4-(4-bromophenoxy)aniline	Yes	0.57
40.2	Cl	H	H	4-(4-bromophenoxy)aniline	Yes	0.61
41.0	OMe	H	H	4-(4-fluorophenoxy)aniline	Yes	0.58
41.1	H	OMe	OMe	4-(4-fluorophenoxy)aniline	Yes	0.64
41.2	Cl	H	H	4-(4-fluorophenoxy)aniline	Yes	0.68
42.0	OMe	H	H	4-(4-nitrophenoxy)aniline	Yes	0.38
42.1	H	OMe	OMe	4-(4-nitrophenoxy)aniline	No	0.45
42.2	Cl	H	H	4-(4-nitrophenoxy)aniline	Yes	0.47
43.0	OMe	H	H	4-(difluoromethoxy)aniline	No	0.31
43.1	H	OMe	OMe	4-(difluoromethoxy)aniline	No	0.40
43.2	Cl	H	H	4-(difluoromethoxy)aniline	No	0.40
44.0	OMe	H	H	4-(trifluoromethoxy)aniline	No	0.52
44.1	H	OMe	OMe	4-(trifluoromethoxy)aniline	No	0.58
44.2	Cl	H	H	4-(trifluoromethoxy)aniline	Yes	0.62
45.0	OMe	H	H	2,6-dibromo-4-(trifluoromethyl)aniline	Yes	0.50
45.1	H	OMe	OMe	2,6-dibromo-4-(trifluoromethyl)aniline	Yes	0.57
45.2	Cl	H	H	2,6-dibromo-4-(trifluoromethyl)aniline	Yes	0.62
46.0	OMe	H	H	2-bromo-4-(trifluoromethyl)aniline	Yes	0.48
46.1	H	OMe	OMe	2-bromo-4-(trifluoromethyl)aniline	No	0.56
46.2	Cl	H	H	2-bromo-4-(trifluoromethyl)aniline	Yes	0.60
47.0	OMe	H	H	2,6-dichloro-4-(trifluoromethoxy)aniline	Yes	0.41
47.1	H	OMe	OMe	2,6-dichloro-4-(trifluoromethoxy)aniline	No	0.48
47.2	Cl	H	H	2,6-dichloro-4-(trifluoromethoxy)aniline	Yes	0.52
48.0	OMe	H	H	2-fluoro-3-(trifluoromethyl)aniline	No	0.73
48.1	H	OMe	OMe	2-fluoro-3-(trifluoromethyl)aniline	No	0.79
48.2	Cl	H	H	2-fluoro-3-(trifluoromethyl)aniline	Yes	0.86
49.0	OMe	H	H	4-(4-fluorophenoxy)aniline	Yes	0.58
49.1	H	OMe	OMe	4-(4-fluorophenoxy)aniline	Yes	0.64
49.2	Cl	H	H	4-(4-fluorophenoxy)aniline	Yes	0.68
50.0	OMe	H	H	4-(4-bromophenoxy)aniline	Yes	0.51
50.1	H	OMe	OMe	4-(4-bromophenoxy)aniline	Yes	0.57
50.2	Cl	H	H	4-(4-bromophenoxy)aniline	Yes	0.61

The synthesis of quinazolines were submitted to the Molinspiration computational platform to select the most promising molecules that were grouped in Table 2 and Figure 3.

Table 2. *Classification of the top ten quinazolines for the ability to inhibit kinases.*

Molecule	R1	R2	R3	R4	Violation of Lipinski's Rule	Kinase Inhibition	Classification
48.2	Cl	H	H	2-fluoro-3-(trifluoromethyl)aniline	Yes	0.86	1[a]
16.2	Cl	H	H	4-(2-aminoethyl)aniline	No	0.84	2[a]
16.1	H	OMe	OMe	4-(2-aminoethyl)aniline	No	0.80	3[a]
48.1	H	OMe	OMe	2-fluoro-3-(trifluoromethyl)aniline	No	0.79	4[a]
35.2	Cl	H	H	2,6-dichloro-4-(trifluoromethyl)aniline	Yes	0.76	5[a]
15.2	Cl	H	H	3-(1,1,2,2-tetrafluoroethoxy)aniline	Yes	0.75	6[a]
37.2	Cl	H	H	2-chloro-4-(trifluoromethyl)aniline	Yes	0.75	6[a]
19.2	Cl	H	H	3-(trifluoromethyl)aniline	Yes	0.73	7[a]
48.0	OMe	H	H	2-fluoro-3-(trifluoromethyl)aniline	No	0.73	7[a]
7.2	Cl	H	H	4-(trifluoromethyl)aniline	Yes	0.72	8[a]
16.0	OMe	H	H	4-(2-aminoethyl)aniline	No	0.72	8[a]
38.2	Cl	H	H	2-fluoro-6-(trifluoromethyl)aniline	Yes	0.72	8[a]
14.0	OMe	H	H	2-(trifluoromethyl)aniline	No	0.71	9[a]
8.2	Cl	H	H	4-chloro-3-(trifluoromethyl)aniline	Yes	0.70	10[a]
15.1	H	OMe	OMe	3-(1,1,2,2-tetrafluoroethoxy)aniline	No	0.70	10[a]

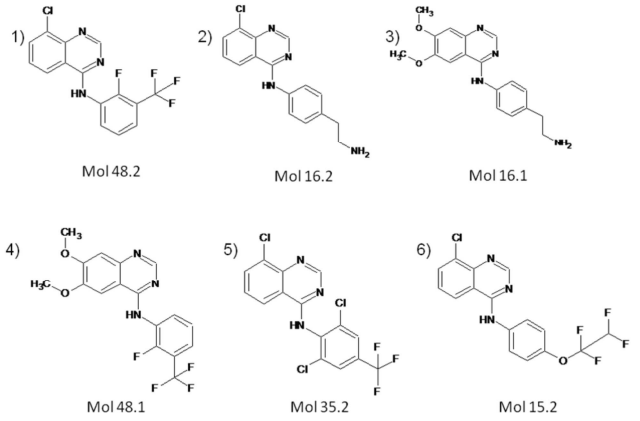

Figure 3. *The six molecules with the best results to inhibit kinases.*

Calculations performed in this study demonstrated that 8-Cl substitution showed a better result to inhibit kinase than 8-OMe and 6, 7-di-OMe (Figure 4).

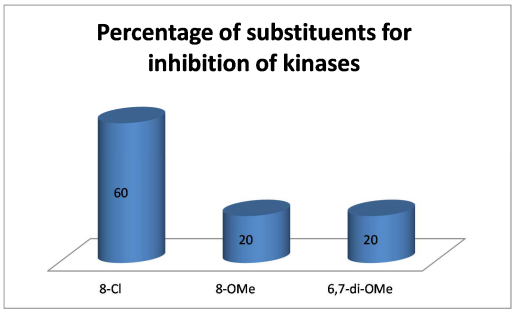

Figure 4. *Percentage of substituents in the quinazoline ring to inhibit kinase. At the 8-position (R_1) of the substituent in the quinazoline ring the 8-Cl substituent was present in 60% of the 10 best molecules with the ability to inhibit kinase. However, only 20% of the top ten molecules analyzed had the ability to inhibit kinases when the 8-OMe (Oxy-methyl) and 6, 7-di-OMe substituents were used.*

The ability to inhibit kinases of the most promising molecules was tested by a molecular docking study. The result of this study can be seen in Table 3 and Figure 5.

Table 3. *Result of the study of molecular docking with AKT kinase to test the results of two more promising molecules to inhibit kinases.*

MOL	R1	R2	R3	R4	ΔEgrid (kcal/mol)
48.2	Cl	H	H	2-fluoro-3-(trifluoromethyl)aniline	- 23.87
16.2	Cl	H	H	4-(2-aminoethyl)aniline	- 20.53
15.1	H	OMe	OMe	3-(1,1,2,2-tetrafluoroethoxy)aniline	-19.12

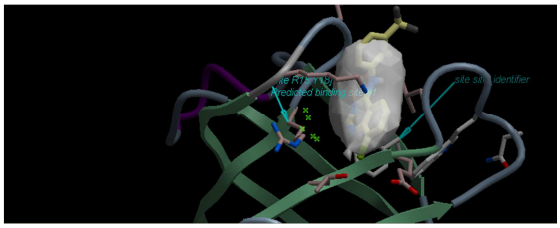

Figure 5. *Molecule 48.2 was considered the most promising to inhibit kinase. It is observed that this molecule can occupy most of the active site of AKT kinase by the study of molecular docking.*

4. Discussion

The Lipinski's Rule of 5 [10] says that for a molecule to present with good oral bioavailability it must obey certain parameters considered as rule of five and this molecule can not violate more than one of these parameters. These parameters are: Log P <5, Molecular Mass <500Da; numbers of hydrogen bond acceptors <10 and hydrogen bonding donors <5. This rule is one of the most widely used strategies in the organization of databases containing molecules with adequate properties of ADME (Absorption, Distribution, Metabolism and Excretion) [13]. This rule is supported by robust statistical parameters and serves as an available tool for filtering molecules in initial screenings for the discovery of new drugs [13]. The Molinspiration platform [3] allows you to perform calculations to evaluate each drawn molecule and test the ability of these molecules to violate Lipinski's rule of five. This platform also allows calculating for each molecule the ability to inhibit kinase [14]. Thus, all molecules proposed for the synthesis of quinazolines were submitted to the Molinspiration computational platform to select the most promising molecules that were grouped in Table 2 and Figure 3.

The positions of the substitutions at 6, 7 and 8 (R_3, R_2 and R_1) respectively of the quinazoline ring have been well explored in an attempt to modify the molecules and improve the enzymatic inhibition profile for various pharmacological targets [15]. Thus, in this study three substituents at the R_3, R_2 and R_1 positions were investigated. At position 8 (R_1) the 8-Cl and 8-OMe (*i.e.* 8-OCH_3) substituents were tested. In positions 6 (R_3) and 7 (R_2) the 6, 7-di-OMe substituents were also explored. Calculations performed in this study demonstrated that 8-Cl substitution showed a better result to inhibit kinase than 8-OMe and 6, 7-di-OMe (Figure 4). This result can be explained by the increase of the electronegativity of the chlorine atom in relation to Oxy-methyl. Probably the catalytic pocket of most kinases is interacted with very electronegative atoms with chlorine at the 8-position of pharmacophore groups such as quinazolines.

In this study, one hundred and fifty molecules of quinazolines with variation of substituents at position R_4 and substitution in R_1 (O-Me, H, Cl); R2 (H and OMe) and R3 (H and OMe) were also evaluated, as it can be seen in Table 1. All 150 molecules were evaluated for violation of Lipinski's Rule of 5 [10] and ability to inhibit kinases [3]. One of the studied quinazolines (Mol 48.2) showed a greater ability to inhibit kinase (0.86), this result implies that this molecule is practically 86% likely to be a strong inhibitor of kinases. On the other hand, these same molecules had low capacity to inhibit G-protein-coupled receptors. The best result to inhibit the G-protein-coupled receptor was 0.31, i.e., 31% probability to inhibit this receptor. This result can be explained by the fact that the G-protein-coupled receptors are classified as different from kinase receptors. [15]. According to Peng Wu *et al.*, 2016, various quinazolines have the ability to inhibit pharmacological targets such as kinases. Quinazolines have

advantages over other small bioactive molecules in pharmacokinetic properties [4] and some of them are already well established drugs, such as Pazosin® [17].

The use of medicinal chemistry allows evaluating various substituents if such substituents can increase or decrease the biological activity of these molecules [17]. Thus, in this study it is found that when the substituent at the 4-position of the quinazoline ring is made and the variation of substituents at other positions is performed, it resulted in a greater inhibition always when the substituent was the Cl and this was at position 8. This has always been compared with the other possibilities for substitutions in the quinazoline ring. According to our studies 60% of the most promising molecules to inhibit kinases were with chlorine substitution at the 8-position of the quinazoline ring, as it can be seen in Figure 4. Probably the chlorine substituent at the 8-position of the quinazoline ring may act as an anchor for the pharmacophoric group of these inhibitors to bind within the active site of the kinases or may contribute to the specific inhibition of the active site of these enzymes for a chlorine-containing inhibitor at that position.

The molecular docking study allows to evaluate interactions between ligand and active site of enzymes to evaluate if the ligand is considered a strong inhibitor of some pharmacological target [5]. Thus, a study to confirm the inhibition of the most promising quinazolines in this study was performed and to test their inhibition with regard to a kinase. AKT kinase along with PI3K (Protein kinase b / Phosphatidylinositol 3-kinase) is one of the main signaling pathways for growth, survival and cell division factors [18] and was chosen to be the target for the study of molecular docking among the most promising quinazolines, as it can be seen in Table 3. The result of the molecular docking study confirmed the inhibition of the most promising quinazoline to inhibit kinase (molecule 48.2) which showed lower interaction energy between the active site amino acids and the tested quinazolines. These interactions can be represented by ΔE grid representing the major interactions in the already stabilized binding enzyme complex [11]. In the same study the molecule less promising to inhibit kinase (molecule 15.1) showed a higher value for *ΔE grid* confirming the lower potential to inhibit AKT kinase.

5. Conclusion

The use of computer tools to study promising new drug candidate molecules has been widely used. In this study, it was allowed to select six most promising molecules to inhibit kinases. Such studies allow reducing time and money for the discovery of new drugs.

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