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Molecular Properties and Bio-Activity Score of 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides

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Abstract

Molecular properties and bio-activity score of 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides were calculated using molinspiration software. Mi Log P values of these compounds were found to be in the range of 5 that means these compounds have good permeability across cell membrane. TPSA in the range of 76.02 to 121.85 (well below 160) and molecular mass <500. Number of violations is 0 and rotb < 7. Number of hydrogen bond donors < 5 (The sum of OHs and NHs) and hydrogen bond acceptor <7 (The sum of Os and Ns). These observation showed that the compounds can easily bind to receptor and were taken further for the calculation of bioactivity score. However, the result of bioactivity score of GPCR ligand, ion channel modulator, nuclear receptor ligand, inhibitor activities towards kinase, protease and enzymes indicated that the compounds exhibit moderate score towards all the receptors.

Keywords: {[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides; Molecular properties; Bioactivity score

Introduction

The ever growing resistance to antibiotics leads to continuous screening for new biologically effective compounds of either natural or synthetic origin. Quinazoline derivatives are extensively used in pharmaceutical industry, medicine and in agriculture for their wide scope of biological activity [1]. Quinazolinone analogs have been reported for various biological activities such as anti-inflammatory [2], antimicrobial [3], antioxidant [4], anticancer [5] and antihypertensive activities [6]. In the drug discovery study the development of new molecule depends on various parameters and one such is `the rule of 5' that predicts absorption or permeation. The other descriptors include H-bond donors, H-bond acceptors, molecular weight and the calculated Log P (CLogP) value.

The present investigation is to evaluate the molecular properties and the bioactivity score of 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides (4a-p) that has been reported earlier [7].

Materials and Methods

The molecular structure of 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides (Figure 1) were drawn using online molinspiration software (www.molinspiration.com) for calculation of molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors).

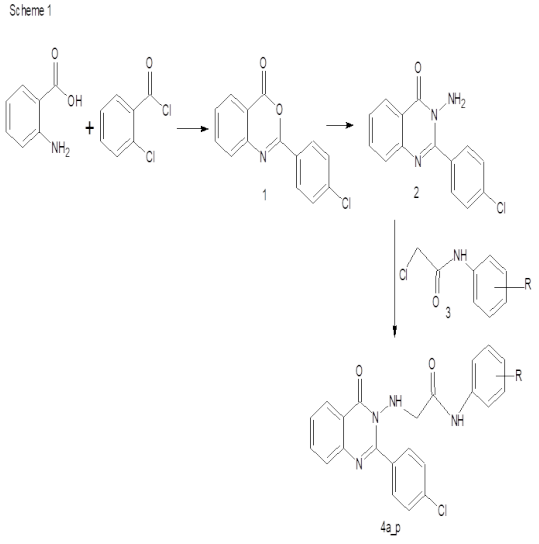

Figure 1: 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) Acetamides

Molinspiration software

Molinspiration software was used to obtain parameter such as MiLogP, TPSA, and drug likeness. Log P measure molecular hydrophobicity that affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity. Molecular Polar Surface Area (TPSA) are calculated based as a sum of fragment contributions of O- and N- centered polar fragments and related to the hydrogen bonding potential of a molecule. TPSA is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood brain barrier penetration etc. The molecular properties and structure features of a drug can be checked by drug likeness data of a molecule. The calculated value for the drug likeness score and the various parameters of the all the acetamide derivatives were given in **Table 1** and the bioactivity scores in **Table 2**.

Table 1: Drug likeness score for the compounds.

Comp code	R	miLogP	TPSA	N-atoms	N-ON	NO-HNH	N viol	N rotb	Volume	MW
4a	H	4.78	76.02	29	6	2	0	5	345.17	404.86
4b	2-CH3	5.18	76.02	30	6	2	1	5	361.73	418.88
4c	3-CH3	5.2	76.02	30	6	2	1	5	361.73	418.88
4d	4-CH3	5.22	76.02	30	6	2	1	5	361.73	418.88
4e	2-Cl	5.41	76.02	30	6	2	1	5	358.71	439.3
4f	3-Cl	5.43	76.02	30	6	2	1	5	358.71	439.3
4g	4-Cl	5.45	76.02	30	6	2	1	5	358.71	439.3
4h	2-NO2	4.69	121.85	32	9	2	0	6	368.51	449.85
4i	3-NO2	4.71	121.85	32	9	2	0	6	368.51	449.85
4j	4-NO2	4.74	121.85	32	9	2	0	6	368.51	449.85
4k	2-Br	5.54	76.02	30	6	2	1	5	363.06	483.75
4l	3-Br	5.56	76.02	30	6	2	1	5	363.06	483.75
4m	4-Br	5.59	76.02	30	6	2	1	5	363.06	483.75
4n	2-OCH3	4.79	85.26	31	7	2	0	6	370.72	434.88
4o	3-OCH3	4.81	85.26	31	7	2	0	6	370.72	434.88
4p	4-OCH3	4.86	85.26	31	7	2	0	6	370.72	434.88

Table 2: Bioactivity score of the compounds.

Comp code	R	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
4a	H	-0.19	-0.5	-0.11	-0.53	-0.37	-0.17
4b	2-CH3	-0.24	-0.54	-0.14	-0.52	-0.43	-0.22
4c	3-CH3	-0.23	-0.56	-0.14	-0.54	-0.42	-0.23
4d	4-CH3	-0.22	-0.55	-0.15	-0.54	-0.41	-0.21
4e	2-Cl	-0.21	-0.49	-0.09	-0.55	-0.41	-0.19
4f	3-Cl	-0.2	-0.49	-0.1	-0.52	-0.39	-0.18
4g	4-Cl	-0.19	-0.48	-0.1	-0.51	-0.36	-0.16
4h	2-NO2	-0.3	-0.54	-0.25	-0.68	-0.49	-0.23
4i	3-NO2	-0.6	-0.51	-0.21	-0.6	-0.46	-0.24
4j	4-NO2	-0.29	-0.49	-0.22	-0.56	-0.45	-0.23
4k	2-Br	-0.28	-0.58	-0.2	-0.7	-0.49	-0.23
4l	3-Br	-0.29	-0.55	-0.12	-0.65	-0.47	-0.24
4m	4-Br	-0.27	-0.55	-0.14	-0.61	-0.46	-0.22
4n	2-OCH3	-0.23	-0.56	-0.13	-0.55	-0.45	-0.22
4o	3-OCH3	-0.23	-0.54	-0.13	-0.53	-0.41	-0.21

4p	4-OCH3	-0.22	-0.53	-0.13	-0.51	-0.4	-0.2

Results and Discussion

The 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides (4a-p) obeyed the Lipinski's rule and showed good drug likeness score (Table 1). MiLog P values were found to be below 5 in most of the compounds, however it was higher in the methyl and chloro analogs which indicated good permeability of these compounds. All the derivatives were found to have TPSA in the range of 76.02 to 121.85 (well below 160) and their molecular weights less than 500. Number of hydrogen bond donors (<5) and hydrogen bond acceptors (<7) were found to be within Lipinski's limit i.e., less than 5 and 10 respectively. All the above compounds were flexible (< 7 rotatable bonds) and found to have n violations =0-1.

Bioactivity score of the compounds

The bioactivity scores of the sixteen acetamide derivatives selected for the calculation on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor given in Table 2 showed the following observations as per the rule. These scores for organic molecules can be interpreted as active (bioactivity score > 0), moderately active (bioactivity score: -5.0-0.0) and inactive (bioactivity score < -5.0) [8]. All the 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl)acetamide derivatives were found to be moderately bioactive (<0) towards all the enzymes considered for the study. However, all the molecules exhibited better activity towards kinase inhibitor compared to other enzymes.

Conclusion

Among the sixteen derivatives though few of them showed higher miLop value all other derivatives obeyed Lipinski rule and the compounds have been found to possess moderate activity towards all the enzymes considered for study, hence the parameters evaluated in this study shall provide an interesting value for the design of novel quinazolinone molecules as enzyme inhibitors.

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