Research Article

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

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ABSTRACT

Purpose of the paper: Quinazolinone derivatives have been found to possess a wide range of biological activity, a series of 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]amino}-N-(substitutedphenyl) acetamides have been taken to study the molecular properties and bio-activity score that shall aid in designing newer compounds.

Design/methodology/approach: Molinspiration software was used for the calculation of Mi Log P values and all other biological data of the compounds.

Findings: It was found that the values were 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 hydrogenbond acceptor <7 (The sum of Os and Ns). These observation showed that the compounds can easily bind to receptor and weretaken further for the calculation of bioactivity score.

Research limitations/implications: The result of bioactivity score of GPCR ligand, ion channel modulator,nuclear receptor ligand, inhibitor activities towards enzymes, protease and kinase showed that the compounds exhibit moderate score towards all the receptors. Hence, these compounds shall be taken for further studies to evaluate their biological profile.

Practical implications: A series of similar analogs shall be considered for evaluating the bioactivity score and compared for designing newer compounds.

Social Implications: Designing of newer derivatives based on the bioactivity score of these reported compounds shall have profound biological activity.

What is original/value of paper: The article deals with evaluation of bioactivity score of a series of quinazolinone derivatives.

Keywords:{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]amino}-N-(substitutedphenyl) acetamides, molecular properties, bioactivity score

INTRODUCTION

The resistance to antibiotics with the existing compounds lead to continuous screening for new biologically effective compounds of either natural or synthetic origin. Quinazoline derivatives are extensively used biologically in medicine,pharmaceutical industry and agriculture.[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(4*H*)-yl]amino}-N-

(substitutedphenyl) acetamides (4a-p) that has been reportedearlier[7].

MATERIALS AND METHODS

The molecular structure of 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]amino}-N-(substitutedphenyl) acetamides(Fig.I**)**were drawn using online molinspirationsoftware (www.molinspiration.com) for calculation ofmolecular properties such as Log P, Total polar surface area,number of hydrogen bond donors and acceptors, molecularweight, number of atoms, number of rotatable bonds, moreover for the prediction of bioactivity score for drug targets like GPCRligands, kinase inhibitors, ion channel modulators, enzymesand nuclear receptors.

Molinspiration software

Molinspiration software was used to calculate various parameter suchas MiLogP, TPSA, and drug likeness. Log P measuremolecular hydrophobicity,that affects drug absorption,bioavailability, drug-receptor interactions, metabolism ofmolecules, as well as their toxicity. Molecular Polar SurfaceArea (TPSA) are calculated based as a sum of fragmentcontributions of O- and N- centered polar fragments andcorrelated with with the hydrogen bonding potential of a molecule.TPSA is a good contributor to predict drug transport propertiessuch as intestinal absorption, bioavailability, blood brainbarrier penetration etc. The molecular properties andstructure features of a drug can be analysed by drug likenessdata of a molecule. The calculated value for the druglikeness score and the various parameters of the all theacetamide derivatives were given in Table 1and the bioactivity scores in Table 2.

RESULTS AND DISCUSSION

The 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]amino}-N-(substitutedphenyl) acetamides (4a-p) obeyed the Lipinski's rule andshowed good drug likeness score (Table1). MiLog P valueswere found to be below 5 in most of the compounds, however it was higher in the methyl and chloro analogs which indicated good permeability ofthese compounds. All the derivatives were found to have TPSA inthe range of 76.02 to 121.85(well below 160) and theirmolecular weights less than 500. Number of hydrogen

Fig. 1: 2{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]amino}-N-(substitutedphenyl) acetamides

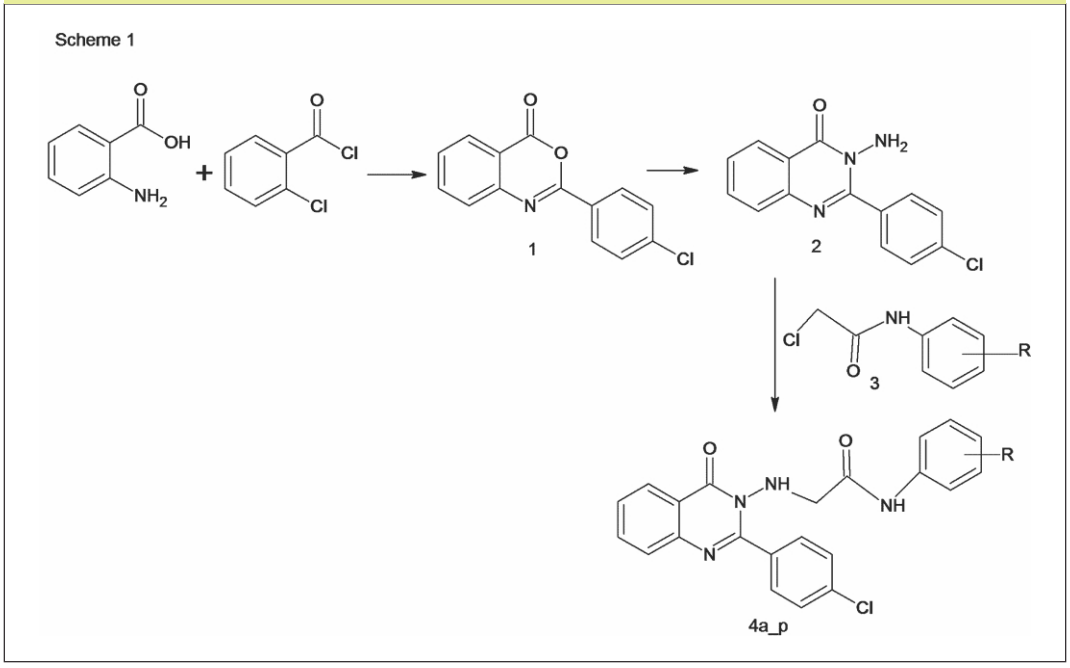

Table1: Drug likeness score for the compounds

Comp code	R	miLogP	TPSA	natoms	nON	nOHNH	nviol	nrotb	volume	MW
4a	H	4.78	76.02	29	6	2	0	5	345.17	404.86
4b	2-CH_3	5.18	76.02	30	6	2	1	5	361.73	418.88
4c	3-CH_3	5.20	76.02	30	6	2	1	5	361.73	418.88
4d	4-CH_3	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	439.30
4f	3-Cl	5.43	76.02	30	6	2	1	5	358.71	439.30
4g	4-Cl	5.45	76.02	30	6	2	1	5	358.71	439.30
4h	2-NO_2	4.69	121.85	32	9	2	0	6	368.51	449.85
4i	3-NO_2	4.71	121.85	32	9	2	0	6	368.51	449.85
4j	4-NO_2	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-OCH_3	4.79	85.26	31	7	2	0	6	370.72	434.88
4o	3-OCH_3	4.81	85.26	31	7	2	0	6	370.72	434.88
4p	4-OCH_3	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	-0.50	-0.11	-0.53	-0.37	-0.17
4b	2-CH_3	-0.24	-0.54	-0.14	-0.52	-0.43	-0.22
4c	3-CH_3	-0.23	-0.56	-0.14	-0.54	-0.42	-0.23
4d	4-CH_3	-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	-0.20	-0.49	-0.10	-0.52	-0.39	-0.18
4g	4-Cl	-0.19	-0.48	-0.10	-0.51	-0.36	-0.16
4h	2-NO_2	-0.30	-0.54	-0.25	-0.68	-0.49	-0.23
4i	3-NO_2	-0.60	-0.51	-0.21	-0.60	-0.46	-0.24
4j	4-NO_2	-0.29	-0.49	-0.22	-0.56	-0.45	-0.23
4k	2-Br	-0.28	-0.58	-0.20	-0.70	-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-OCH_3	-0.23	-0.56	-0.13	-0.55	-0.45	-0.22
4o	3-OCH_3	-0.23	-0.54	-0.13	-0.53	-0.41	-0.21
4p	4-OCH_3	-0.22	-0.53	-0.13	-0.51	-0.40	-0.20

bonddonors (< 5) and hydrogen bond acceptors (<7) were foundto be within the limits of Lipinski's rule i.e. less than 5 and10respectively.All the above compounds were flexible (< 7rotatable bonds) and found to have n violations =0-1.

Bioactivity score of the compounds

The bioactivity scores of the sixteen acetamide derivatives selected forthe calculation on the basis ofGPCR ligand, ion channel modulator, nuclear receptorligand , kinase inhibitor, protease inhibitor, enzymeinhibitor given in Table -2 showed the followingobservations 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(4*H*)-yl]amino}-N-(substitutedphenyl)acetamide derivatives werefound 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 theparameters evaluated in this study shall provide an interesting value for the design of novel quinazolinone molecules as enzyme inhibitors.

REFERENCE

1. P. Selvam, K. Babu, R. Padmaraj, L. Persoon, ED Clercq. *African J Pharm and Pharmacol.,* 2008, 2(6), 110-115.
2. B.Maggio, G.Daidone, D.Raffa, S.Plescia, L.Mantione, VMC.Cutuli, N.G.Mangano, A.Caruso, *Eur. J. Med. Chem*., 2001, 36, 737 - 42.
3. S.K.Sahu, A. Md. Afzal, M. Banerjee, S. Acharrya, C.C. Beheraa, S. Sic. *J. Braz. Chem. Soc.,* 2008,19(5), 963-70.
4. J.Y.Melvin, R.M. Jefferson, D.T. Richard, P.R. H. Peter, A.P. Lee, I. R. Kentteth. *Bioorg & Med Chem Lett*., 1992, 2(9), 1121-6.
5. K. Petr, R. Dirk, J. Ulrich. *Molecules*, 2006, 11, 286-297S.K. Pandey, S. Abhishek, S. Ashutosh, Nizamuddin. *Eur. J. Med. Chem*. xx, (2008), 01.
6. V.Alagarsamy, U.S.Pathak, *Bioorg & Med. Chem*., 2007, 15, 3457–62.
7. S.Rajasekaran, GopalKrishna Rao, Sanjay Pai P N, Qaseem Ahmad and Jasmine.A. *Ind J Het Chem*, (19), Nov-Dec, 2009, 191-2.
8. Singh S, Gupta AK, Verma A. Molecular properties and bioactivity score of Aloe vera antioxidant compounds-in order to lead finding. Res J Pharm Biol Chem Sci, 2013; 4(2): 876-81.