Research Article

In silico Investigations, Design and Synthesis of Some Novel Quinazolinone Derivatives

Dr. Mayura A Kale[*1], Dr. Gajanan Sonwane[2], Tirupati Panchal[1], Arpita Wangujare[3], Pooja Bargire[3]
[1] Government College of Pharmacy, Vidyanagar, Karad-415124, Satara, Maharashtra, India.
[2] Rajesh Bhaiyya Tope College of B Pharmacy, Aurangabad-431007, Maharashtra, India.
[3] Government College of Pharmacy, Osmanpura, Aurangabad-431005, Maharashtra, India.
***Corresponding author's E-mail:** kale19mayura@gmail.com

Received: 03-04-2024; **Revised:** 25-05-2024; **Accepted:** 06-06-2024; **Published on:** 15-06-2024.

ABSTRACT

The present research has been focused on designing and synthesizing new derivatives of quinazolinone heterocycle. The designed derivatives were subjected to in silico investigations by conducting PASS studies in which novel predicted antiviral activity of this heterocycle against picornavirus was explored. These designed derivatives were also subjected to in silico toxicity risk assessment studies using Osiris property explorer in which toxicities viz., mutagenicity, tumorigenicity, carcinogenicity and irritability were predicted and prediction of properties viz., c logP, solubility, mol weight and drug score was also done. All the compounds were found to be devoid of any predicted toxicities with predicted properties in acceptable range. Hence, they were further subjected to docking studies where interaction with protein 4CTG identified as target for the antiviral (Picornavirus) activity was studied. The docking results were found to be comparable to that of the parent quinazolinone molecule. Hence, the designed quinazolinone derivatives were further subjected to wet-lab synthesis. The compounds were recrystallized and subjected to structure elucidation studies by IR spectroscopy. As these derivatives of quinazolinone have shown promising results in docking, with compounds 2a, 2b and 2c showing optimum binding affinity of -8.0 kcal/mol, -8.1 kcal/mol and -8.2 kcal/mol; respectively which is better than that shown by parent compound showing binding affinity of -7.1 kcal/mol to the target protein 4CTG. Conclusively, it can be surmised that these synthesized compounds can be further subjected to in vitro and in vivo biological screening against Picornavirus.

Keywords: *In silico*, quinazolinones, Docking, PASS studies, Toxicity studies, Synthesis.

INTRODUCTION

Quinazoline heterocycle is considered to be an important class of six-membered fused heterocycles in which quinazolin-4(3H)-one and its derivatives have gained structural importance because of their biological significance viz., quinazolinone alkaloids form a basic core of febrifugine and isofebrifugine, which has been found to possess significant antimalarial activity and have been extracted from the traditional Chinese medicine [1]. The chemistry of quinazolinone has been well-explored during the conduct of its synthetic studies, although still many novel and multifaceted variants of quinazolinone structures are needed to be discovered.

After extensive research on quinazolinones, an exact understanding of the complex behavior of quinazolinone ring with different targets in the body has been understood with definite conclusions. The majority of substitutions found at 2nd and 3rd positions of the quinazolinone system have been found to be influencing their biological activities viz., antimalarial, antitubercular, anticancer activities[2], antiparkinsonian properties[3]. For antimalarial and antitubercular activities, the groups substituted at 2nd and 3rd positions of the ring can be phenyl, ketone, ether, amide or carboxamide and in case of anticancer activity, thioether and aryl ketone have been observed as beneficial substitutions on the same positions. Likewise for anticonvulsant activity, substitutions of phenyl or benzyl groups as well as short and long simple alkyl group thio-ethers and carboxamides have been found to be good for the said biological activity [4].

Quinazolinone derivatives have been found to be elevated melting crystalline products, which are generally insoluble in water and organic solvents but found to be soluble in aqueous alkali and sometimes in concentrated acids viz., 6N hydrochloric acid. They have been found to form stable salts of mono-hydrochlorides, chloro-platinate, chloro-aurates and picrates including their metal salts such as silver and mercury [5,6]. Overall, the quinazoline and quinazolinone skeleton has been frequently encountered in medicinal chemistry. Besides the above mentioned biological activities, this skeleton has also been explored for antitumor[7], antihypertensive[8], analgesic [9], antibacterial and antimicrobial [10], anti-inflammatory [11], antineoplastic, antidepressant, antipsychotic, antiarrhythmic, sedative-hypnotics, antifungal, anticoccidial and many other activities [12-16].

MATERIALS AND METHODS

PASS studies

PASS studies were performed on the designed compounds. It is a web tool that has the ability to predict nearly 3678 pharmacological effects; mechanisms and special toxicities of the molecule including mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity. The predicted activity spectrum includes 65 of 374 pharmacological effects, 176 of 2755 molecular mechanisms, 7 of 50 toxic effects, 11 of 121 metabolism terms at default Pa > Pi cutting points. The

web tool can freely display the predicted activity of a molecule at various threshold levels. The PASS training set has been compiled from various sources including publications, patents, chemical databases, and "gray" literatures and consists of over 26000 biological compounds which include drugs, lead compounds, drug-candidates, and toxic substances.

The result of prediction is presented as the list of activities with appropriate Pa values which gives the estimation of probability for the compound to be active for each type of activity from the biological activity spectrum with the values ranging from 0.000 to 1.000. It is reasonably that only those types of activities may be revealed by the compound, which Pa > Pi and so they are put into the biological activity spectrum. Usual interpretation of prediction results from PASS is based on the Pa values. If Pa> 0.7, the chance to find the activity in experiment is high, but in many cases the compound may occur to be the close analogue of known pharmaceutical agents. If 0.5<Pa 0.7, the chance to find the activity in experiment is less, but the compound is not so similar to known pharmaceutical agents and if Pa<0.5, the chance to find the activity in experiment is even more less, but if it will be confirmed the compound might occur to be a NCE (New Chemical Entity)[17].

Toxicity and property determination studies

These studies have been carried out by using Osiris property Explorer in which toxicity risk predictor searches for potential toxicity risks by working on toxicity alerts. The prediction process relies on a precomputed set of structural fragments that give rise to toxicity alerts in case they are encountered in the structure currently drawn. These fragment lists were created in the software by rigorously shreddering all compounds of the RTECS database known to be active in a certain toxicity class. During the shreddering, any molecule was first cut at every rotatable bond leading to a set of core fragments. These in turn were used to reconstruct all possible bigger fragments being a substructure of the original molecule. Afterwards, a substructure search process determined the occurrence frequency of any fragment (core and constructed fragments) within all compounds of that toxicity class. It also determined these fragments' frequencies within the structures of more than 3000 traded drugs. Based on the assumption that traded drugs are largely free of toxic effects, any fragment was considered a risk factor if it occurred often as substructure of harmful compounds but never or rarely in traded drugs. The toxicities that were predicted by the software are mutagenicity, tumorigenicity, reproductive affective effects and irritability [18,19,20].

In the current *in silico* studies of derivatives of quinazolinones, it was found the all the predicted toxicities viz., mutagenicity, carcinogenicity, teratogenicity and irritability were absent and the compounds exhibited good drug likeness and drug score with acceptable clogP values which are crucial during actual development of drug molecule.

Molecular docking

Docking in conjunction with a score function enables rapid screening of vast databases of possible medications *in silico* in order to find compounds that are capable of binding to a particular target of interest. Docking can be used to anticipate the location and relative position of a ligand's interaction to a protein (also referred to as the binding mode or pose). This data can be utilized to develop more powerful and selective analogues. The docking studies were carried out using Autodock 4.2 version software which involved preparation of protein 4CTG which was identified as target for the selected antiviral (Picornavirus) activity. Later, ligand (viz., the designed molecules) preparation was done. The AutoDock calculations were performed in several steps such as preparation of coordinate files using AutoDock tools, pre-calculation of atomic affinities using Auto Grid, docking of ligands using AutoDock and analysis of results using AutoDock tools [21,22,23].

Synthesis

The chemicals used in the synthesis of intermediates and final compounds were of synthesis grade and were procured from the BLD Pharma Chemicals, Malkajgiri, Hyderabad-501401. All the synthesized quinazoline-4-one derivatives were characterized by melting point determination using digital melting point apparatus in open capillary tubes and are uncorrected. The IR spectra were recorded using Shimadzu spectrophotometer IRPrestige-21 using potassium bromide pellet technique. TLC was performed using pre-coated silica gel plates of 0.25 mm thickness, using ethyl acetate and chloroform in 2:8 proportion, respectively as mobile phase.

Synthesis of quinazolinone and its derivatives

A] Synthesis of 2-phenyl quinazolin-4(3H)-one (Compound 1) [24-26]

To the pre-heated mixture of 2-amino benzamide (1 mol) and acetophenone (1 mol) in DMSO in a round-bottom flask, iodine (10 mol%) was added as oxidising agent with addition of 20 ml of dimethyl sulphoxide as solvent. The reaction mixture was heated at 110oC for 16 hrs. The product was extracted three times with ethyl acetate (3×10 ml) to get pure quinazolinone.

B] Synthesis of quinazolinone derivatives (Compounds 2a-2e) [27]

After the successful drying of 2-benzyl-quinazolin-4(3H)-one,)1 gm equivalent) was reacted independently with respective aromatic amines viz., aniline (0.40 gm equivalent, o-/p-/m-Nitro Anilines (o-nitro aniline taken as 0.58 gm equivalent, m-/p-nitro anilines (taken as 0.4 gm equivalent) and anisidine (taken as 0.35 gm equivalent) in presence of catalytic quantity (1-2 ml) of glacial acetic acid

as oxidising agent, so as to afford respective derivatives of benzyl quinazolinones.

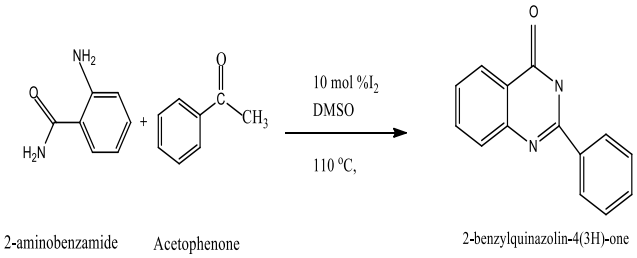

Figure 1: Synthesis scheme of Compound 1

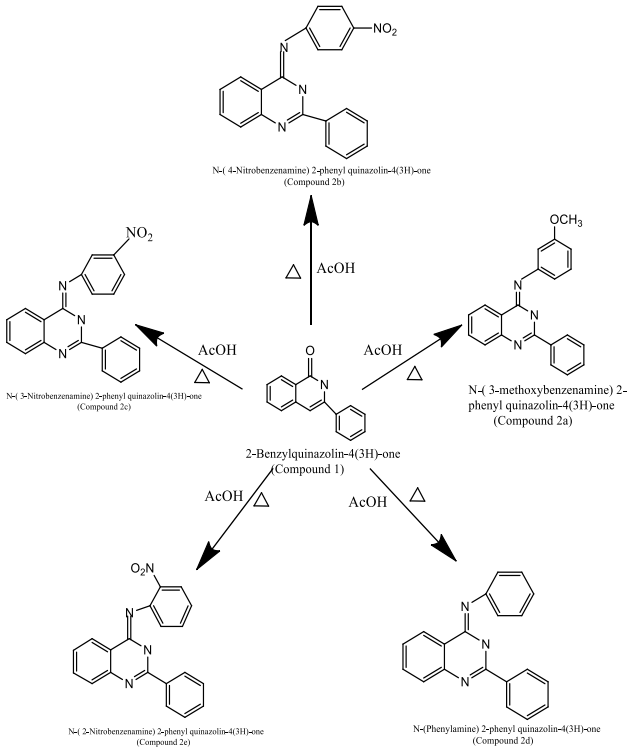

Figure 2: Synthesis scheme of Compounds (2a-2e)

Structural elucidation by IR spectroscopic studies

Compound (1) –2-Benzyl-quinazolin-4(3H)-one: IR (v cm-1): 2379 (C-N str in Ar); 1662 (C=O str), 1129 (str in quinazolinone ring)

Compound (2a) - N-(2-Methoxybenzenamine)-2-phenyl quinazolin-4-(3H)-one: IR (v cm-1): 2349 (C-N str in Ar); 1041(str in quinazolinone ring); 1529 (-NO2, Ar-N)

Compound (2b) - N-(4-Methoxybenzenamine)-2-phenyl quinazolin-4-(3H)-one: IR (v cm-1): 1354 (C-N str in Ar);1120 (str in quinazolinone ring); 1354 (-NO2, Ar-N)

Compound (2c) - N-(3-Nitrobenzenamine)-2-phenyl quinazolin-4-(3H)-one: IR (v cm-1): 2349 (C-N str in Ar); 1344 (str in quinazolinone ring); 1500(-NO2, Ar-N)

Compound (2d) - N-(Phenylamine)-2-phenyl quinazolin-4-(3H)-one: IR (v cm-1):2351 (C-N str in Ar); 1029 (str in quinazolinone ring)

Compound (2e) - N-(3-Methoxybenzenamine)-2-phenyl quinazolin-4-(3H)-one: IR (v cm-1): 2295 (C-N str in Ar);1043 (str in quinazolinone ring); 1219(C-O str in Ar); 1504(C-H str in aliphatic)

RESULTS AND DISCUSSION

In the present research project, quinazolinone derivatives have been designed and synthesized. The designed derivatives were subjected to *in silico* PASS studies in which novel predicted biological activity (antiviral activity against picornavirus) was found out. Also, in toxicity risk assessment studies, the compounds were found to be devoid of any predicted toxicities. Hence, they were further subjected to docking studies where interaction with protein 4CTG which has been identified as target for the antiviral (Picornavirus) activity. The docking results were found to be comparable to that of the parent quinazolinone molecule. Hence, the designed quinazolinone derivatives were further subjected to wet-lab synthesis. The compounds were recrystallized and subjected to structure elucidation studies by IR spectroscopy in which the functional groups present in the structures of these compounds were confirmed. As these derivatives of quinazolinone have shown promising results in docking, these can be considered as eligible compounds to be subjected further to in vitro and *in vivo* biological screening of this new antiviral activity.

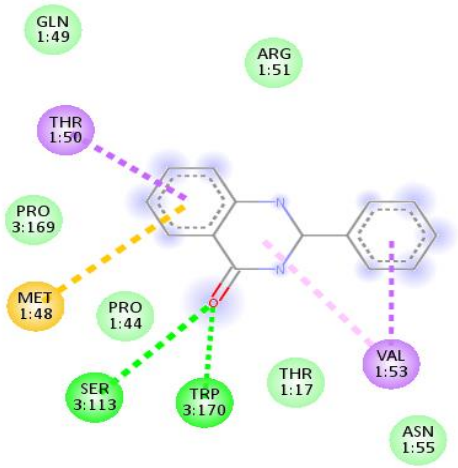

Figure 3: Docking analysis of Compound 1

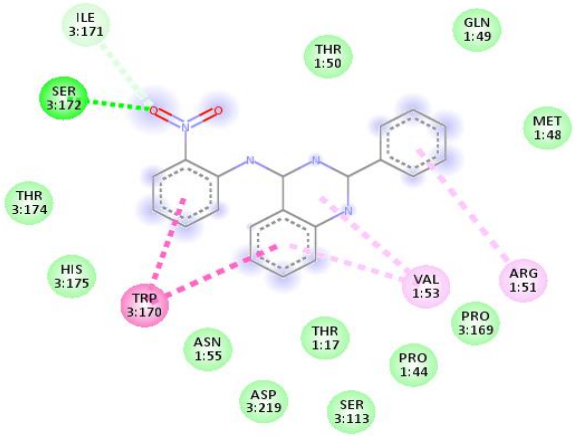

Figure 4: Docking analysis of Compound 2a

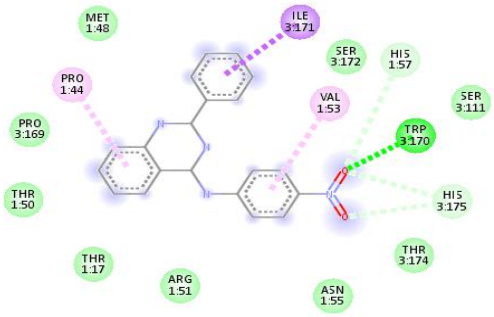

Figure 5: Docking analysis of Compound 2b

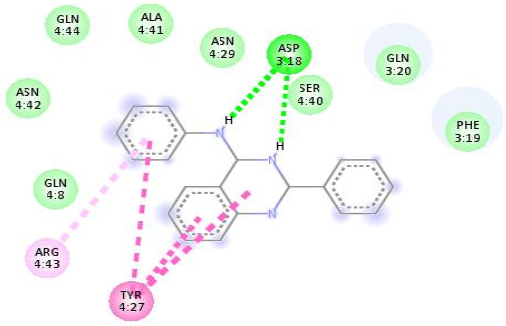

Figure 7: Docking analysis of Compound 2d

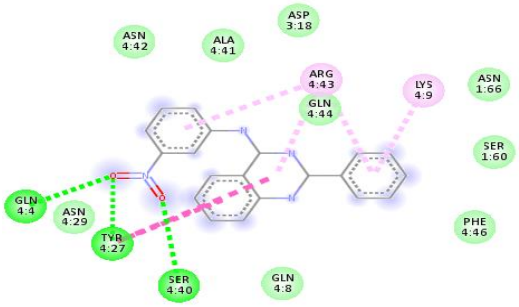

Figure 6: Docking analysis of Compound 2c

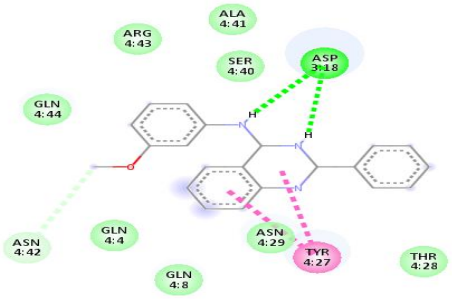

Figure 8: Docking analysis of Compound 2e

Table 1: Predicted biological activities of novel derivatives of quinazolinones by PASS studies

Name of compound (IUPAC)	Name of predicted biological activity	Pa
2-benzyl Quinazolin-4(3H)-one (Compound 1)	Antiviral (Picornavirus)	0.546
N-(2-methoxybenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2a)	Antiviral (Picornavirus)	0.543
N-(4-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2b)	Antiviral (Picornavirus)	0.587
N-(3-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2c)	Antiviral (Picornavirus)	0.572
N-(Phenylamine) 2-phenyl quinazolin-4(3H)-one (Compound 2d)	Antiviral (Picornavirus)	0.515
N-(3-methoxybenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2e)	Antiviral (Picornavirus)	0.504

Table 2: Predicted toxicities of novel derivatives of quinazolinones by toxicity risk assessment studies

Name of compound (IUPAC)	Name of predicted toxicity	Present/Absent
2-benzyl Quinazolin-4(3H)-one (Compound 1)	Mutagenicity	Absent
	Carcinogenicity	
	Teratogenicity	
	Irritability	
N-(2-methoxybenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2a)	Mutagenicity	Absent
	Carcinogenicity	
	Teratogenicity	
	Irritability	
N-(4-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2b)	Mutagenicity	Absent
	Carcinogenicity	
	Teratogenicity	
	Irritability	
N-(3-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2c)	Mutagenicity	Absent
	Carcinogenicity	
	Teratogenicity	
	Irritability	

N-(Phenylamine) 2-phenyl quinazolin-4(3H)-one (Compound 2d)	Mutagenicity	Absent
	Carcinogenicity	
	Teratogenicity	
	Irritability	
N-(3-methoxybenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2e)	Mutagenicity	Absent
	Carcinogenicity	
	Teratogenicity	
	Irritability	

Table 3: Predicted properties of novel derivatives of quinazolinones by toxicity risk assessment studies

Name of compound (IUPAC)	Predicted property			
	c log P	Solubility	Mol weight	Drug score
2-benzyl Quinazolin-4(3H)-one (Compound 1)	2.21	-3.2	222.0	0.87
N-(2-methoxybenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2a)	1.81	-2.38	221.0	0.9
N-(4-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2b)	1.81	-2.38	221.0	0.9
N-(3-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2c)	1.81	-2.38	221.0	0.9
N-(Phenylamine) 2-phenyl quinazolin-4(3H)-one (Compound 2d)	1.81	-2.38	221.0	0.9
N-(3-methoxy benzenamine)-2-phenyl quinazolin-4(3H)-one (Compound 2e)	1.81	-2.38	221.0	0.9

Table 4: Docking analysis of synthesized derivatives of quinazolinones

Compound no	Ligand	Binding Affinity (kcal/mol)	rmsd/ub	rmsd/lb
Compound 1	3jd7_Untitled_Document-1_mmff94_E=50.36	-7.1	2.611	1.726
Compound 2a	3jd7_1_mmff94_E=89.28	-8	2.856	2.107
Compound 2b	3jd7_2_mmff94_E=83.15	-8.1	2.072	1.663
Compound 2c	3jd7_3_mmff94_E=81.12	-7.6	2.611	1.726
Compound 2d	3jd7_4_mmff94_E=90.66	-7.8	34.521	30.655
Compound 2e	3jd7_5_mmff94_E=85.26	-8.2	2.425	1.574

Table 5: Synthesis parameters of quinazolinone and its derivatives

Compound	Practical Yield (g)	Melting point (°C)
2-benzyl Quinazolin-4(3H)-one (Compound 1)	5.2	205
N-(2-methoxybenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2a)	1.02	210
N-(4-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2b)	0.77	235
N-(3-Nitrobenzenamine) 2-phenyl quinazolin-4(3H)-one (Compound 2c)	1.0	260
N-(Phenylamine) 2-phenyl quinazolin-4(3H)-one (Compound 2d)	0.20	340

CONCLUSION

In the present research, the designed derivatives of quinazolinone were subjected to *in silico* investigations through PASS studies which predicted novel antiviral activity of this heterocycle against picornavirus. These designed derivatives when subjected to *in silico* toxicity risk assessment studies using Osiris property explorer, revealed that toxicities viz., mutagenicity, tumorigenicity, carcinogenicity and irritability were absent and property prediction viz., c logP, solubility, mol weight and drug score revealed that these were within acceptable limits. Further, docking studies involving interaction with protein 4CTG identified as target for the antiviral (Picornavirus) activity showed that the compounds 2a, 2b and 2c exhibited optimum binding affinity of -8.0 kcal/mol, -8.1 kcal/mol and -8.2 kcal/mol; respectively which is better than that shown by parent compound showing binding affinity of -7.1 kcal/mol to the target protein. Finally, the designed quinazolinone derivatives were further subjected to wet-lab synthesis. As these derivatives of quinazolinone have shown promising results in docking, with 4CTG, it can be concluded that these synthesized compounds may show promising results when subjected to *in vitro* and *in vivo* biological screening against Picornavirus.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Zhu S, Wang J, Chandrashekar G, Smith E, Liu X, Zhang Y, Synthesis and Evaluation of 4-Quinazolinone Compounds as Potential Antimalarial Agents, European Journal of Medicinal Chemistry, 2010; 45:3864-3869. DOI: 10.1016/j.ejmech.2010.05.040, PMID: 20538379
2. Alsibaee M, Hanan M, Huda S, Quinazolinones, the Winning Horse in Drug Discovery. Multidisciplinary Digital Publishing, 2023; 28:978. DOI: 10.3390/molecules28030978, PMID: 36770645
3. Kumar S, Kaur H, Kuma A, Synthesis of New Azetidinonyl/Thiazolidinonyl Quinazolinone Derivatives as Antiparkinsonian Agents, Arab. J. Chem., 2012; 5:475-484. DOI:10.1016/j.arabjc.2010.09.014
4. Jiang S, Zeng Q, Gettayacamin M, Tungtaeng A, Wannaying S, Lim A, Hansukjariya P, Okunji C, Zhu S, Fang D, Antimalarial Activities and Therapeutic Properties of Febrifugine Analogs, Antimicrobial Agents Chemother., 2005; 49:1169-1176. DOI: 10.1128/AAC.49.3.1169-1176.2005, PMID: 15728920
5. Singh J, Negi A, Singh B, Sharma D K, Chemistry and activity of quinazoline moiety: A systematic review study, International journal of pharmaceutical chemistry and analysis, 2020; 7(2):61-65. DOI:10.18231/j.ijpca.2020.009
6. Abdelaal A, Mohamed H, An efficient synthesis and evaluation of some novel quinazolinone-pyrazole hybrids as potential antiproliferative agents, Synthetic Communications, 2021; 51(16):2498-2509. DOI:10.1080/00397911.2021.1939058
7. Hekal M, Fatma S, New potential antitumor quinazolinones derived from dynamic 2-undecyl benzoxazinone: Synthesis and cytotoxic evaluation, Synthetic Communications, 2018; 48:2391-2402. DOI:10.1080/00397911.2018.1490433
8. Pathak S, Malhotra V, Nath R, Shanker K, Synthesis and Antihypertensive Activity of Novel Quinazolin-4(3H)-One Derivatives, Cent. Nerv. Syst. Agents Med. Chem., 2014; 14:34-38. DOI: 10.2174/1871524914666140825144729, PMID: 25174978
9. Pawar P, Khandave P, Gokhale S, Microwave assisted synthesis and analgesic screening of some thiazolyl quinazolinones, Int J Sci Dev Res., 2019; 4(9):174-198.
10. Assy M, Abdalha, A, Abdel A, Synthesis and Antimicrobial Evaluation of Some New Benzoxazinone and Quinazolinone Derivatives, JAC, 2016; 8:1491-1499. DOI:10.24297/jac.v8i1.4030
11. Azab M, Synthesis, antimicrobial and anti-inflammatory activity of some new benzoxazinone and quinazolinone candidates, Chem Pharm Bull., 2016;64(3):263-271. DOI: 10.1248/cpb.c15-00904, PMID: 26699093
12. Asif M, Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives, Hindawi Publishing Corporation International Journal of Medicinal Chemistry, 2014; 11:2-27. doi: 10.1155/2014/395637, PMID: 25692041
13. Rajput, Mishra, A review on biological activity of quinazolinones, International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(2):66-70
14. Vijayakumar, Prasanthi, Teja, Quinazoline derivatives and pharmacological activities: a review, International Journal of Medicinal Chemistry & Analysis, 2013; 3(1):10-21, DOI:10.22159/ijcpr.2023v15i1.2074
15. Kumar S, Ganguly S, Veerasamy R, E. De Clercq, Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3)H-ones, European Journal of Medicinal Chemistry, 2010; 45:5474-5479. DOI: 10.1016/j.ejmech.2010.07.058; PMID: 20724039
16. Lu W, Baig, I, Sun HJ, Cui CJ, Guo R, Jung IP, Wang D, Dong M, Yoon MY, Wang JG, Synthesis, Crystal Structure and Biological Evaluation of Substituted Quinazolinone Benzoates as Novel Antituberculosis Agents Targeting Acetohydroxyacid Synthase, European Journal Medicinal Chemistry, 2015; 94:298–305. DOI: 10.1016/j.ejmech.2015.03.014; PMID: 25771108
17. Filimonov D, Poroikov V, Bioactive compound design: possibilities for industrial use-PASS: Computerized prediction of biological activity spectra for chemical substances, BIOS Scientific Publishers. 1996:47–56, DOI: 10.18097/BMCRM00004
18. Kumar A, Senthamarikannan K, Parthasarathy V, Screening and Toxicity Risk Assessment of Selected Compounds to Target Cancer using QSAR and Pharmacophore Modelling, International Journal of Pharm Tech., 2017; 10(4):219-224, DOI:10.20902/IJPTR.2017.10428
19. Ajay Kumar T V, Kabilan S, Parthasarathy V, Screening and Toxicity Risk Assessment of Selected Compounds to Target Cancer using QSAR and Pharmacophore Modelling, International Journal of PharmTech Research, 2017;10(.4): 219-224. DOI:10.20902/IJPTR.2017.10428
20. Khan T, Lawrence A, Azad I, Raza S, Joshi S, Khan A R, Computational Drug Designing and Prediction Of Important Parameters Using in silico Methods- A Review, 2019;15(5):384-397. DOI: 10.2174/1573399815666190326120006, PMID: 30914032
21. Mohamadzadeh M, Zarei M, Vessal M, Synthesis, in vitro biological evaluation and in silico molecular docking studies of novel β-lactam-anthraquinone hybrids, Bioorganic Chemistry,2020; 95:103515 . doi: 10.1016/j.bioorg.2019.103515. Epub 2019 Dec 17, PMID: 31884134
22. Raval K, Ganatra T, Basics, types and applications of molecular docking: A review, Int J Comprehensive Adv Pharmacol., 2022; 7(1):12-16. doi.org/10.18231/j.ijcaap.2022.003
23. Forli S, Huey R 1, Pique M E, Sanner M, Goodsell D S, Olson A J, Computational protein-ligand docking and virtual drug screening with the AutoDock suite, Nature protocols,2015; 11(5):905-19. DOI: 10.1038/nprot.2016.051, PMID: 27077332
24. Alsibaee AM, Yousef HM, Huda S, Al-Salem, Quinazolinones, the Winning Horse in Drug Discovery, Molecules. 2023; 28(3): 978-984. doi: 10.3390/molecules28030978, PMID: 36770645.
25. Feldman JR, Wagner E, Some reactions of methylene-bis-amines as ammono-aldehydes, J Org Chem., 1942; 7:31–47. doi.org/10.1021/jo01195a006.
26. Endicott M M, Wick E, Mercury M L, Sherrill M L, Quinazoline Derivatives-the synthesis of 4-(4'-Diethylamino-1'-methyl butyl-amino)-quinazoline (SN 11,534) and the Corresponding 2-Phenylquinazoline, J Am Chem Soc., 1946; 68:1299– 1301, DOI: 10.1021/ja01211a055, PMID: 20990986.
27. Ram A V, Mohammed S, Sandip BB, Iodine catalysed oxidative synthesis of quinazolin-4(3H)-ones and pyrazolo[4,3-d] pyrimidin7(6H)-ones via amination of sp3 C-H bond, Journal of medical chemistry, 2015; 80(13):6915–6921. DOI:10.1021/acs.joc.5b00989, PMID: 26067767.