CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2566371

Available online at: http://www.iajps.com *Research Article*

SYNTHESIS AND MOLECUAR DOCKING STUDY OF NOVEL 2- PHENYL QUINAZOLINE -4(-3H-)-ONE DERIVATIVE AS COX-2 INHIBITOR

Kavitha K[*1], [2]Srinivasan N, [3]Hari Babu Y, [4]Suresh R
(E.mail:kavithakrocks@gmail.com)
[1]Department of pharmaceutical chemistry, Grace College of pharmacy, Kodunthirapully, Athalur, Palakkad, Kerala. [2]Department of pharmacy, faculty of engineering and technology, Annamalai University, Annamalai nagar, Tamil nadu.

Abstract:
A new class of cox-2 inhibitors of novel 2 phenyl 3 substituted aniline derivatives were synthesized using anthranillic acid as starting material in three step reaction. The purity of the newly synthesized compounds were tested by TLC and melting point and recrystalisation by ethanol, structures were confirmed by using UV, IR, 1H-NMR spectra. Assortment of literature cancer is one of the leading cause of death worldwide ,also one of the mechanism of action ,cancer drugs has to inhibit COX-2.furthermore quinazolinone class of drugs or compounds have anticancer activity which possess epidermal growth factor receptor(EGFR inhibitors).in this research virtual screening were carried out by docking the design of compounds in to binding site of COX-2 enzyme (PDB 5f19) to predict if these compounds had analogous binding mode to the COX-2 inhibitor. Results were produced in the form of bond energy, indicated by the value of RS.the small RS small RS value indicated a molecular bond that was stable and predictable had high activity. The smallest RS value was -372.26 kcal/mol and synthesized ranged between 70-85%.

Key words: *phenyl quinazolinone, COX-2, molecular docking, cancer, aniline derivatives.*

Corresponding author:
Kavitha K,
Assistant professor, Department of pharmaceutical chemistry,
Grace College of pharmacy, Kodunthirapully.
Palakkad, Kerala, E.mail:kavithakrocks@gmail.com
Ph.no:7868008884.

QR code

Please cite this article in press Kavitha K et al., ***Synthesis And Molecuar Docking Study Of Novel 2- Phenyl Quinazoline -4(-3h-)-One Derivative As Cox-2 Inhibitor.,*** *Indo Am. J. P. Sci, 2019; 06(02).*

INTRODUCTION:

Cancer is one of the important major causes of death in the world, also the second after cardiovascular disease. This fact makes the many researchers in world try to design new effective anticancer drug. Cancer is a multifactorial disease which caused by epigenetic changes ,genetic mutations that occur in genes which directly involved in the process of cell division, programmed cell death [1].Nonsteroidal anti inflammatory drugs (NSAIDS) which appear to decrease the risk of developing cancer. One mechanism via NSIADS which act to reduce carcinogenesis is to inhibit the activity of cyclooxygnase-2 (COX-2), an enzyme that is over expressed in various cancer tissues. Over expression of COX-2 enhances cell proliferation, inhibits apoptosis. Several attempts have been made to produce the anticancer drug molecule. Modification of molecules against cancer drugs which have been done so they became more effective, efficient. One mechanism of action of cancer agents has to inhibit COX-2. Quinazolinone derivatives molecules has anticancer activity and also which is one of the epidermal growth factor receptor (EGFR) inhibitor. Moreover compounds containing the 4(3H) Quinazolinone ring system having different biological activities [2].the majority of COX-2 inhibitors are diaryl Heterocycles part could be the six or five membered ring, a quinazoline ring or as a cyclic form. So that the present study ,we synthesized some 2 phenyl 3 substituted benzyleneamine quinazoline-4(3H)-ones(fig.1) followed by molecular docking ,Insilco studies which were carried out in an attempt to evaluate the drug molecule as a COX-2 inhibitor[4].moreover assortment of literature quinazolinone compounds exhibits anti inflammatory [5,6,7,8] ,cyto toxic activity [9] ,anti leishmanial activity [10], etc ,.. Quinazoline is one of the most widespread scaffolds among natural and synthetic bioactive compounds, although the first natural quinazoline –based alkaloid, peganine, was discovered in 1888, the literature about quinazoline chemistry effectively began only in 1940 [11] furthermore quinazolinone derivatives have attracted strong interest in organic and medicinal chemistry due to their potent biological and pharmacological activities. The present research provides a brief overview on the recent advances and future perspectives on pharmacological aspects of quinazolinone and its derivatives reported in the last decade.

EXPERIMENTAL:

General procedures [3]:

The melting points of synthesized molecules were determined in open capillaries and therefore the values reported are uncorrected. The homogeneity and purity of newly synthesized compounds were routinely checked by thin layer chromatography on silica Gel-G plates, benzene: chloroform as mobile phase and iodine vapour as the detection method. The IR spectra of molecules were recorded in the region ,4000-400 cm-1 using KBr discs on JASCO 4100 FTIR and the NMR spectral study was done by using DMSO as the solvent on JOEL FX90Q, FOURIER transform NMR spectrometer.

Synthesis of 2 phenyl benzoxacine -4 –one:

A mixture of ortho or (2)-amino benzoic acid (O.O1mol) and benzoyl chloride (O.O2mol) in the presence ethanol and added a drop of pyridine were taken in RBF was refluxed at 4-6 hrs, after completion of reaction, the content was poured into a ice cold water to get corresponding solid state produced which was filtered, washed with water followed by recrystalisation with hot water.

Synthesis of 2 phenyl 3- amino quinazoline -4-one:

A mixture of 2 phenyl benzoxacine 4 one and hydrazine hydrate were taken if RBF was dissolved in ethanol and the mixture was stirred for 5 minutes followed by reflex at 4 hrs.the progress of reaction monitored, later completion of reaction, content of the flask then it was poured in to the cruced ice the corresponding solid mass produced filtered, washed with water, dried and recrystallized by methanol.

Synthesis of 3-(benzylideneamino)-2-(phenyl) quinazolin-4-(3H)-one derivatives: (4a-h)

Equimolr amount of 2 phenyl 3 amino quinazoline 4 one and formaldehyde, various derivatives of substituted aniline were mixed together and dissolved in ethanol were taken in RBF.the mixture was stirred for 5-10 minutes and reflux for 5-7hrs.

The progress of the reaction was monitored by TLC .after completion of reaction, the content of flask was poured into a 100ml of cold water to get corresponding 2, 3 di substituted quinazolinone in the solid state. The product was further filtered, by Buchner funnel, washed with 10percent Na_2CO_3 Solution .the separated solid product filtered, washed with water and recrystallized by hot water or ethanol.

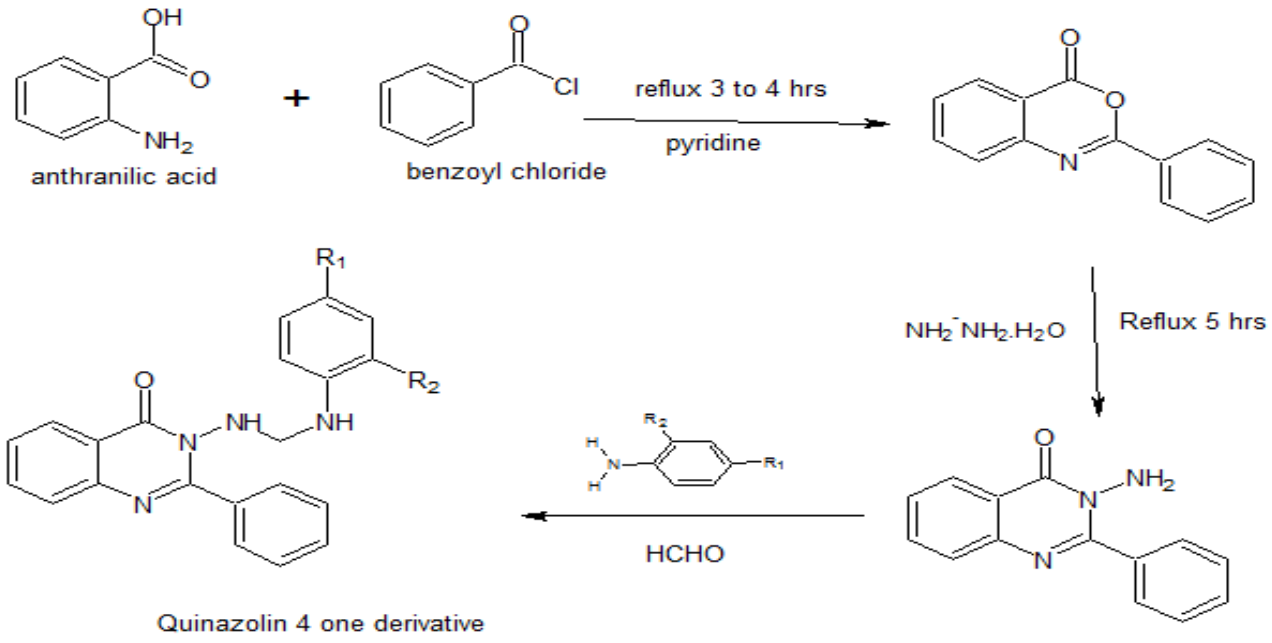
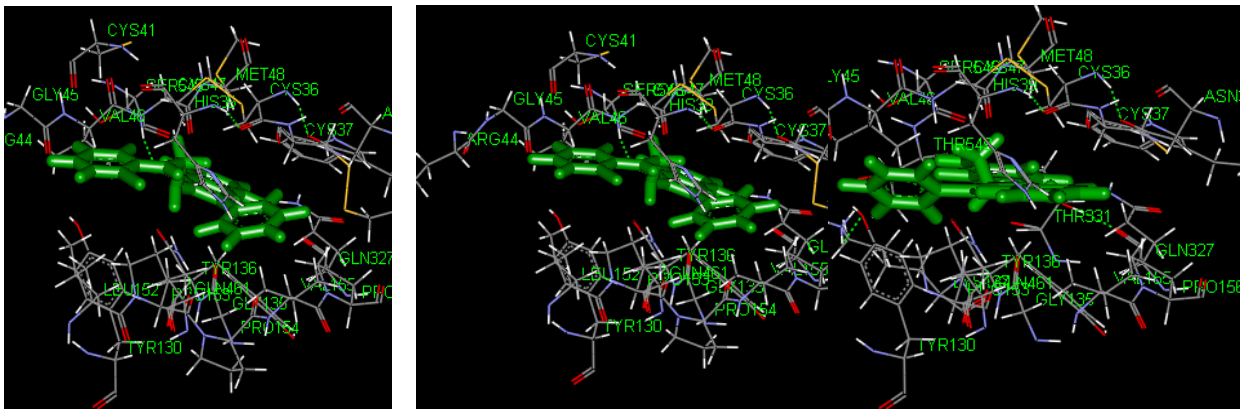


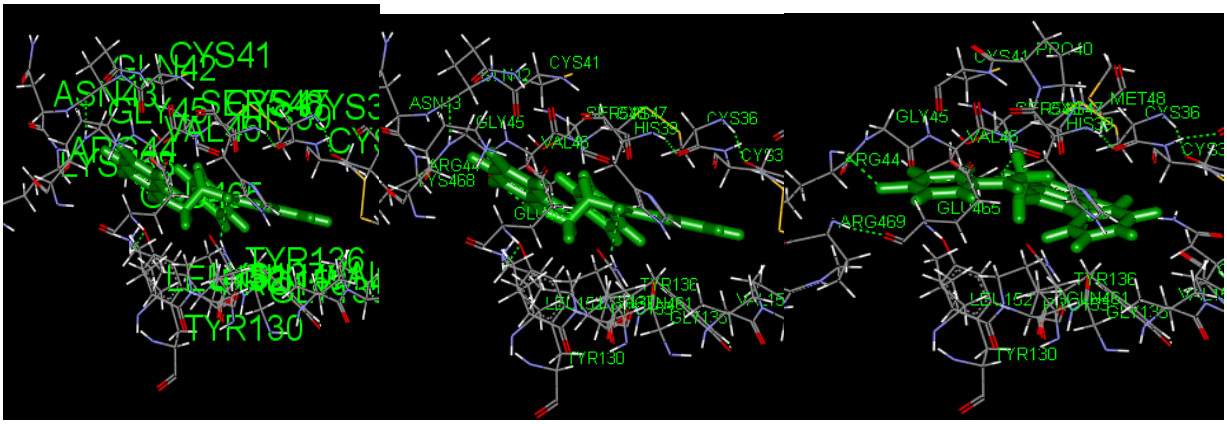
Fig:1

Scheme: 1, Synthesis of 2 phenyl 3 substituted (amino) quinazolin-4-(3H) one derivatives

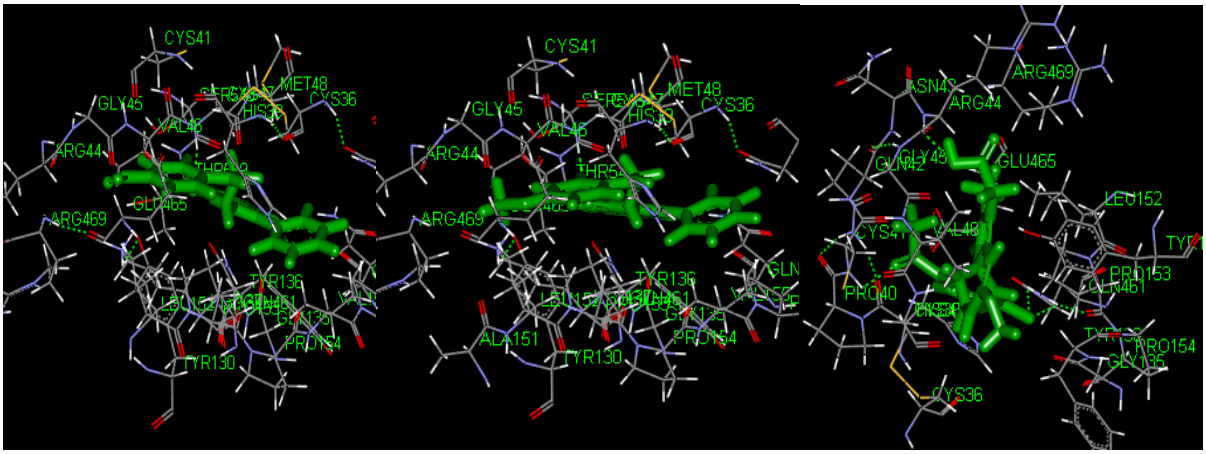
4a=R_1=R_2=H & 4b= R_1=R_2=CH_3, CH3 4c= R_1=R_2=Cl, OH & 4d= R_1=R_2=Cl, H 4e=R_1=R_2=H, Cl & 4f= R_1=R_2=F, Hs 4g= R_1=R_2=NO_2, H&4h= R_1=R_2=O-CH_3,H



4a 4b 4c



4d 4e 4f



4g 4h STD

Figure: 2. Molecular docking of indomethacin and compound (4a-4h) in interaction with 5f19.

Molecular docking study [4]:

To estimate the anticancer activity of derivatives of some 2phenyl 3 substituted amino quinazoline-4(3H)-ones, molecular docking study was evaluated by using paach dock and we used receptor COX-2 or cyclo oxygenase (PDB: 5f19) as the target protein. The most stable chemical conformation of the target compounds was determined. The active conformation of 5f19 was selected for the preparation step. Cavity was detected to select the pocket binding site (active site of the enzyme). The target compounds (4a-h) and indomethacin were then docked on to the protein, on the same cavity. The results, concluded which conformation produced the lowest energy state when bound to the target protein, were shown as rerank score (RS).

RESULS AND DISCUSSION:

Table No: 1

Compound name	Molecular formula	Rank score	Elemental analysis (%)					
			C	H	N	O	Halogen group	Log p
4a	$C_{21}H_{18}N_4O$	-418.68	74	5.30	16.7	4.7	----	4.42
4b	$C_{23}H_{22}N_4O$	-424.68	74.6	6.0	15.12	4.32	-----	5.4
4c	$C_{21}H_{17}ClN_4O_2$	-421.84	64.21	4.4	14.3	8.2	9.02	4.59
4d	$C_{21}H_{17}ClN_4O$	-428.07	67	4.6	14.9	4.25	9.41	4.98
4e	$C_{21}H_{17}ClN_4O$	-428.07	66.93	4.55	14.87	4.25	9.41	4.98
4f 4g	$C_{21}H_{17}FN_4O$ $C_{21}H_{17}N_5O_3$	-385.10 -416.40	70 65.11	4.8 4.42	15.6 18.08	4.44 12.4	5.27 ----	4.58 4.5
4h	$C_{22}H_{20}N_4O_2$	-372.26	71	5.41	15.04	9.0	-----	4.3
Indomethacin		-326.70						

4a: 2-phenyl- 3- ((phenyl amino)methyl amino) quinazolin-4(3H)-one: Mol.wt-342, IR (KBr, vmax, cm-1):3058(Ar-H) 1720(C=O):1655(C=N) 1530(C-N),H NMR,(δppm):7.4(CH,Ar), 7.9(Ar-C=O(N),7.62 (benzylideneamino),2.0(amine),4.0(Ar-C-NH),4.42 (CH2),6.58 (Ar-N-C).1.71(methyl),2.2(CH_2),MS m/z:342.

4b.3-((2,4-dimethylphenylamino)methylamino)-2-phenylquinazoline-4(3H)-one;Mol.wt-350,IR(KBr,vmax,cm-1):3068(Ar-H) 1727(C=O):1625(N=C)1425(C-N).CH_3(2936).H NMR,(δppm):7.3-7.6(CH,Ar), 1.71(methyl),2.2(CH_2),MS m/z:350.

4c.3-((4-chloro-2-hydroxyphenylamino) methyl amino)-2-phenylquinazoline-4(3H)--one: Mol.wt-393,IR(KBr,vmax,cm-1):3080(Ar-H) 1726(C=O):1626(C=N)1547(C-N).C-Cl(691)..H NMR,(δppm):7.4-7.9(CH,Ar)7.62(benzylideneamino,),,2.0(AMINE),4.0(Ar,C-NH) ,6.61(Cl),4.42(CH_2),5.0 (Ar-C-OH).MS m/z:392.

4d.3-((4-chlorophenylamino)methylamino)-2-phenylquinazoline-4(3H)-one;Mol.wt-377,IR(KBr,vmax,cm-1):3061(Ar-H)1721(C=O):1655(C=N)1556(C-N).HNMR,(δppm):7.4-7.5(CH,Ar), 7.62(benzylideneamino,),2.0(AMINE),4.0(Ar,C-NH) ,7.1(Cl),4.42(CH_2),MS m/z:376.

4e.3-((2-chlorophenylamino)methylamino)-2-phenylquinazoline-4(3H)-one;Mol.wt-377,IR(KBr,vmax,cm-1):3048(Ar-H) 1720(C=O):1625(C=N)1225(C-N).C-Cl(704).H NMR,(δppm):7.4-7.9(CH,Ar),7.62(benzylideneamino,)2.0(NH),4.0(Ar,C-NH) ,6.92(Cl),4.42(CH_2),MS m/z:376.

4f.3-((4-fluorophenylamino)methylamino)-2-phenylquinazoline-4(3H)-one:Mol.wt-360,IR(KBr,vmax,cm-1):3296(Ar-H) 1723(C=O):1662(C=N)1570(C-N),C-F(410)..H NMR,(δppm):7.4-

7.9(CH,Ar),7.62(benzylideneamino,)2.0(NH),4.0(Ar,C-NH) ,6.75(Cl),4.42(CH_2),MS m/z:360.

4g.3-((4-nitrophenylamino)methylamino)-2-phenylquinazoline-4(3H)-one:Mol.wt-367,IR(KBr,vmax,cm-1):3058(Ar-H) 1708(C=O):1626(C=N)1567(C-N).N=O(1421).H NMR,(δppm):7.3-7.9 (CH,Ar),7.50(benzylideneamino,) 6.95(NO_2),2.0(CH_2),MS m/z:367.

4h.3-((4-methoxyphenylamino)methylamino)-2-phenylquinazoline-4(3H)-one: Mol.wt-372, IR (KBr, vmax, cm-1):3056(Ar-H) 1710(C=O):1655(C=N) 1568(C-N), C-OCH_3 (2723).H NMR,(δppm):7.4-7.9 (CH,Ar),7.29(benzylideneamino,) 4.0(Ar-C-NH)2.0(Amine)6.55 (Ar-N-C),4.42(CH2)3.72(CH_3),MS m/z:372.

CONCLUSION:

In the present study, we have discussed and synthesized some derivatives of 2 phenyl 3 substituted amino quinazolinone with the yield of 70% to 85% and in silico study data the smallest RS value was -372.26.the molecular docking study signified that the compounds act as the COX-2 inhibitor. The generated pharmacophores can further to be used for the design and development of new drugs.

ACKNOWLEGEMENT:

The authors are grateful thanks to the principal and management of Grace College of pharmacy, athalur, Kodunthirapully, Palakkad, Kerala, India for their assistance.

REFERENCES:

1. Rakesh K.P., Manukumar H.M., Channe Gowda D., Schiff Bases Of Quinazolinone Derivatives: Synthesis And SAR Studies Of Novel Series Of Potential Anti Inflammatory And Anti Oxidants.Bio Organic And Medicinal Letters.2015: 25:1072-1077.
2. Kitazawa M.Sy., Medeiros M., Whitman R., Cheng L., Lane D.Inflammation Induced By Infection Potentiates The Pathological Features In Transgenic Mice.Am.J.Pathol.2011: 178: 2811-2822.
3. Kavitha K*, Nehla Yahoob, Vijayakumar B, Reshma Fathima K. Synthesis and Evaluation of Quinazolinone Derivatives. Asian Journal of Research in Chemistry 10(4):577-581:2017.
4. Tutuk Budati, Suko Hardjono, Melanny Lka Sulistyowaty. Synthesis and Molecular Docking Study Of 4 Chlorophenylquinazoline-4-(3h)-One Derivatives As Cox-2 Inhibitor .International Jornal Of Pharmaceutical And Clinical Research.2016:8(12):1605-1609.
5. Gounon P., Huerre R.M., And Inflammation: Patterns and New Concepts.Res .Immunol.1996:147:417-434.
6. Bot M.,Carney M.R., Freeland E.K.,Rubin H.E., Rich W.M.,Steimmeyer C.B.,Mann L.D.,Inflammation And Treatment Response To Sertraline In Patients With Coronary Heart Disease And Co Morbid Major Depression.J.Psychosom. Res.2011:71:13-17.
7. Kalsi R., Pande K., Bhalla TN., Barthwal JP., Gupta GP., Parmar SS., Anti Inflammatory Activity Of Quinazolinoformazans.J Pharma Sci.1990:4:((79):317-320.
   Redha I., Al-Bayati., I., Ahmed A.H., Al-Amiery & Yasmien K., Al-Majedy. Novel Quinazolinone Derivatives: Synthesis And Anti Inflammatory Activity.14thinternational Electronic Conference On Synthetic Organic Chemistry.2010:1-30.
8. Selvam C., Pannecouque E., De Clercq. Synthesis, Anti- HIV Activity and Cytotoxicity of 2 Phenyl, 3-Sulphonamido Quinazoline-4-(3H)-Ones. International Journal of Pharmacy and Analytical Research.2012:1 :(1):18-22.
9. Yihenew Simegniew Birhan, Adnan Ahmed Bekhit And Ariaya Hymete, Synthesis And Anti Leishmanial Evaluation Of Some 2, 3-Disubstituted 4-(3H)-Quinazolinone Derivatives. Organic and Medicinal Chemistry Letters. 2014:4:1
10. Kavitha K* Srinivasan N, Hari Babu Y. Review of Quinazolinone Scaffold As Anti Cancer Agents. World Journal of Pharmaceutical Research.2018: 7 (9), 434 – 454.