Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **8(12),** 24-28, December **(2018)** *Res. J. Chem. Sci.*

Short Communication

Antimicrobial evaluations of propionic acid of quinazolines derivatives

Deepika Katariya and Ajit Joshi*
Synthesis Organic and Medicinal Chemistry lab, Department of Chemistry, Mewar University, Gangrar, Rajasthan-312901, India
ajitjoshi2k2@gmail.com

Available online at: www.isca.in, www.isca.me
Received 9th August 2018, revised 10th November 2018, accepted 12th December 2018

Abstract

The derivatives of Propionic Acid of Quinazoline were synthesized. It was prepped by reaction of distinct amino acids with 7-nitro-2-phenyl-4H-benzo [1,3]oxazin-4-one. Configurations of same compounds have been appraised by NMR, MASS and IR spectral analysis. Synthesized compounds were screened with against following pathogenic bacteria Staphylococcus aureus, Staphylococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumonia. We used 500ppm concentration in DMSO for their antibacterial activity by Kirby-Baur disk diffusion method.

Keywords: Quinazoline, *Pseudomonas aeruginosa, Klebsiella pneumonia.*

Introduction

In heterocyclic compounds, hetrocycles containing nitrogen are very important compounds for their significant organic chemistry. Applications of various heterocycles molecules not only in the pharmaceutical but also others chemistry branches. Now a days the synthesis of heterocyclic molecules has become a key challanges[1]. Quinazoline derivative has been applied in various biomedical field like an anti-oxidant[2], analgesic[3], anti-inflammatory[4], anti-cancer[5-7], anti-bacterial[8], anti-convulsant[9], anti-mycobacterial[10-11], anti-fungal[12], and malaria[13-14]. Quinazoline nucleus also available in many naturally occurring alkaloids. In natural products frequently encountered of Quinazolin nucleus is a unit such as L-vasicineone[15-16], Chrysogine[17] and medicine as methqualone[18] febrifungine, and isofebrifungine. Quinazoline and quinazolinone derivatives show a various kind biological activity[19] like anticonvulsant, antibacterial, and antidiabetic activity[20-21]. It impacts a lot of chemists and biologists, due to the important biological, chemical activities derivatives of quinazoline, show more attention for the continuing update research.

Materials and methods

All Synthesized compounds MP were taken in open capillaries, may be uncorrected. Perkin- Elmer 1300 FTIR spectrometer is used for the IR. Jeol ECS400 (400 MHz FT NMR) spectrometer determine our ^{1}H NMR. For internal standard we used TMS. WATERS XEVO-SQTOF with UPLC spectrometer recorded our Mass spectra. Purity was checked by elemental analysis. Silica gel-'G' (mfg by Mark) which is an absorbent used for TLC. Iodine and UV chamber visualization was accomplished.

Synthesis of 7-nitro-2-phenyl-4H-benzo [1,3] oxazin-4-one (I): Method-1: In the 100ml SNF charge the solution of 4-nitroanthranilic acid (0.01mol) in pyridine (50 ml), with the continue stirrer of the solution at the 5°C temperature added by drop by drop benzoyl chloride (0.01 mol) with maintains the same temperature. After the addition all, the Rxn solution was continue stirrer further 2hrs at RT, a solid product alienated out during stirring. Than reaction blend was neutralized by $NaHCO_3$ solution. For some time a pale yellow solid was set down. Than it filtered, washed with twice time water. By using ethanol the solid were recrystallized (m.p. 197-199°C; yield 81%).

Method-2: In excess of freshly distilled benzoyl chloride 4-Nitroanthranilic acid (0.1mol) was dissolved. For 4 hrs it heated under reflux. Under reduced pressure the excess of benzoyl chloride was distilled off. Than after cooling the compound was repeatedly washed with small portions of Pet Ether (60-80°C) to get a crystalline solid.

Synthesis of 2-(7-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl) propanoic acid [II-a]: In SNF with fitted condenser charge the solution of Molecule [1] (0.01mol) and Alanine (0.01mol) in pyridine as a solvent were refluxed for minimum 6-8hrs. Then the reaction mixture was quenched with ice, stirred the solution. Yellow solid were appear and after some time the yellow solid precipitate were settle down. The yellow Solid was passing through a filter, washed by water, dry and then crystallized from the ethanol.

Synthesis of 2-(7-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl)-3-sulfanylpropanoic acid [II-b]: In SNF with fitted condenser charge the mixture of Molecule [1] (0.01mol) and Cystein (0.01mol) in pyridine as a Solvent were refluxed for minimum 6-8 hrs. Then the reaction mixture was quenched with ice, stirred the solution. Solid were appear and after some time the solid precipitate were settle down. The Solid was passing through a filter, washed by water, dry and then crystallized from the ethanol.

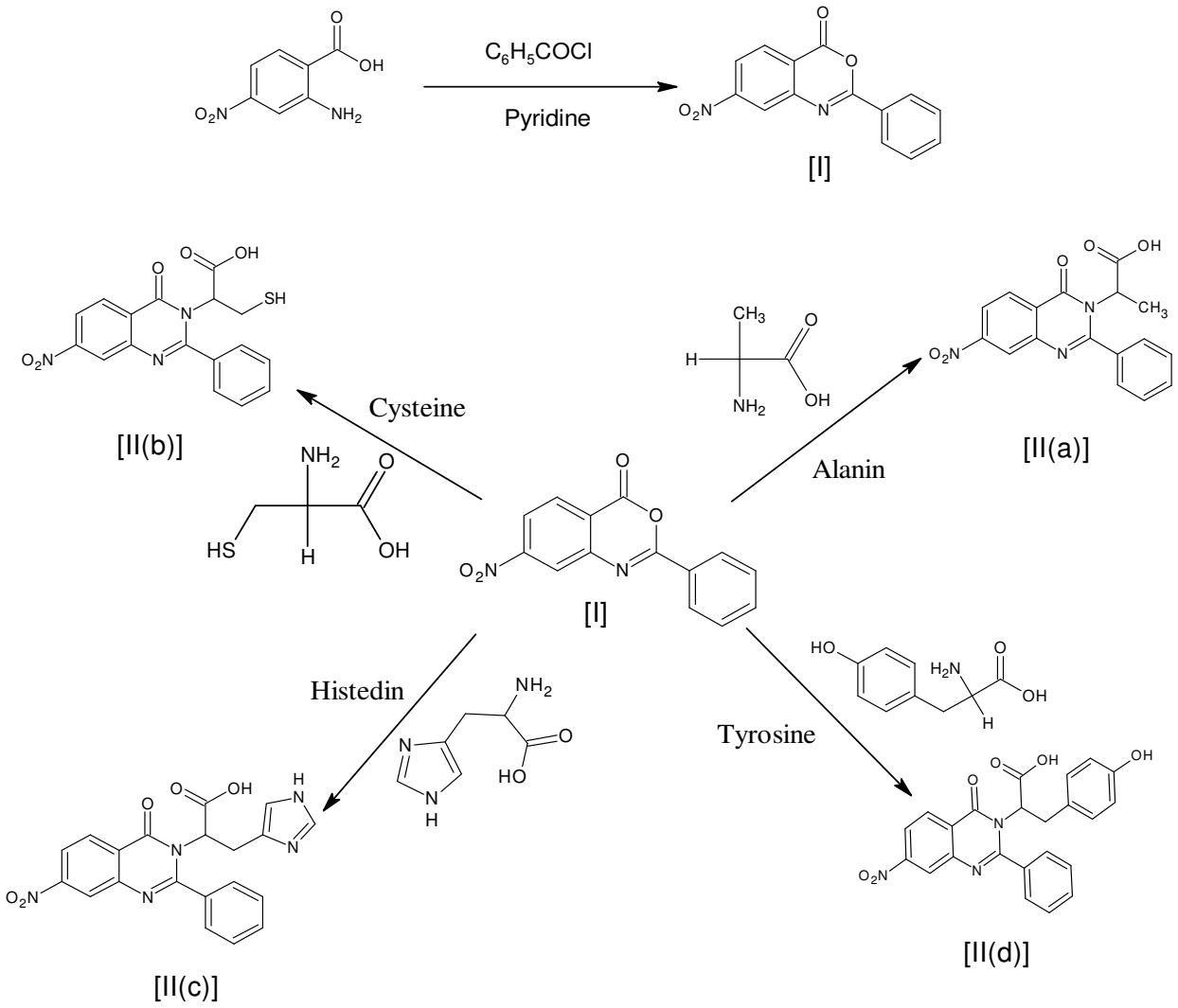
Synthesis of 3-(1*H*-imidazol-4-yl)-2-(7-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl) propanoic acid [II-c]: In SNF with fitted condenser charge the mixture of Molecule [1] (0.01mol) and Histedin (0.01mol) were refluxed in pyridine as a solvent for minimum 6-8 hrs. After cooling, the combination was decanted in crushed ice, stirred well and then leaves it to concede they obtained solid precipitate to get down. The solid was passing through filtered, washed by cold water, dry under the vacuum and then crystallized by the ethanol.

Synthesis of 3-(4-hydroxyphenyl)-2-(7-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl) propanoic acid [II-d]: In SNF with fitted condenser charge the mixture of Molecule [1] (0.01mol) and Tyrosine (0.01mol) were refluxed in pyridine as a Solvent for minimum 6-8 hrs. After cooling, the combination was decanted in crushed ice, stirred well and then leaves it to concede they obtained solid precipitate to get down. The Solid was passing through a filter, washed by water, dry under the vacuum and then crystallized by the ethanol.

Results and discussion

The Molecule [1] was acquired via ring closure, the interaction of benzoyl chloride with 4-Nitroanthranilic acid in basic solution, afforded the corresponding anthranil. The benzoxazinone derivative is uses as a starting raw material for the next step synthesis. The goal of the present work is to synthesis of Propionic Acid of Quinazolines Derivatives via interaction of Molecule [1] with nitrogen nucleophiles like Alanine, Cysteine, Histedine and Tyrosine in a pyridine and reflux for 6-8 hrs to resultant title derivatives [II(a-d)] in a good yield. Their structure was elucidated by MASS, NMR and IR spectra. Physical and an analytical data were shown in Table-1 and 2.

Antibacterial Screening: By use of Kirby-Baur technique to all the new synthesized molecules against five pathogenic bacteria and Ciprofloxacin as reference standard. All quinazoline derivatives showed Good activity (Table-3).



Scheme-1: Reaction Scheme.

Table-1: Physical and analytical data of synthesized new molecules.

Compounds	M.F.	MW	mp°C	Yield (%)	(%) of C Found/cal	(%) of H Found/cal.	(%) of N Found/cal.	(%) of O Found/cal	(%) of S Found/cal.
I	$C_{14}H_8N_2O_4$	268	197-199	81	62.65/62.63	1.14/ 1.11	2.96/ 2.98	23.88/ 23.86	–
[II(a)]	$C_{17}H_{13}N_3O_5$	339	179-180	60	60.14/60.12	3.81/ 3.83	12.37/ 12.35	23.58/ 23.57	--
[II(b)]	$C_{17}H_{13}N_3O_5S$	371	170-176	64	54.94/54.93	3.52/ 3.50	11.32/ 11.30	21.52/ 21.54	8.64/ 8.61
[II(c)]	$C_{20}H_{15}N_5O_5$	405	177-179	70	59.24/59.20	3.74/ 3.70	17.28/ 17.26	19.75/ 19.73	--
[II(d)]	$C_{23}H_{17}N_3O_6$	431	183-190	72	63.92/63.97	3.92/ 3.94	9.70/ 9.73	22.20/ 22.25	--

Table-2: IR, NMR and Mass spectra values of Synthesis New Molecules.

Compounds	IR (ν cm^{-1})	^{1}HNMR (δ)	Mass
I	3106.04 [Ar-H] 2887[C-H] 1746.7 [C=O] 1632.16 [C=N] 1531.82 [N=O]	7.6-8.3 [m,8H,Ar-H]	m/z 268 [M^+]
II-a	3264.5[OH str.Carboxylic] 3132.9 [Ar-H] 2924.5 [C-H] 1716.7 [C=O] 1675.1 [C=O] 1540.7 [N=O]	10.9[s, 1H, COOH] 7.3-8.5 [m 8H, Ar-H] 5.1 [q,1H] 1.8 [d, 3H]	m/z 339 [M^+]
II-b	3259.8[OHstr.Carboxylic] 3152.07 [Ar-H] 2965.3[C-H] 1726.4[C=O] 1654.5[C=O] 1567.6[N=O]	11.1 [s,1H, COOH] 7.1-8.3 (m, 8H, Ar-H) 5.0 (t,1H) 2.8-3.1 (dd, 2H) 1.7 (t-SH)	m/z 371 [M^+]
II(c)	3310.0 [OH str carboxylic] 3142.2 [Ar-H] 2986.5 [C-H], 1706.7 [C=O] 1675.1 [C=O] 1523.8 [N=O]	10.8 [s,1H,COOH] 9.2 [s, 1H, NH] 7.0-8.4 [m, 10H, Ar-H] 5.2[t,1H] 3.0-3.3 [dd,2H]	m/z 405 [M^+]
II(d)	3539.0 [Ar-OH] 3136.9 [Ar-H] 2914.4 [C-H] 1735.1[C=O] 1646.6[C=O] 1556.3[N=O]	11.0 [s, 1H, COOH] 7.2-8.5 [m,12H, Ar-H] 4.9 [t,1H] 4.4 [s, 1H] 2.8-3.4 [dd, 2H	m/z 431 [M^+]

Antimicrobial Activity: For antibacterial activity synthesized compounds were in vitro screened using 500 ppm concentrations in Dimethyl sulfoxide (DMSO) by Kirby-Baur disk diffusion method. 1ml of the broth suspension of *Staphylococcus aureus, Streptococcus pneumoniae, Pseudifllmas aeruginosa, Escherichia coli* and *Klebsiella pneumonia* was spread over different Muller-Hinton agar plates by using sterile cottons wab. The wells were cut with the help of 10mm sterile baurer. The different wells were filled with the different diluted synthesized compound with the help of sterile plastic droppers.

The plates were hatched for 24hrs at 37^{o}C. After incubation period plates were checked for the zone of inhibition and measured by the zone scale (Hi-Media) in mm. The activity is furnish has zone of inhibition in mm and collate with activity of

control C1 (Ciprofloxacin) to provide activity index value in Table-3 and Graphical. All the compounds showed modest to strong antibacterial action against these pathogenic bacteria. Activity index value against all these bacteria was more than one for all compounds. The most interesting thing was that all the compounds showed efficacy activity vise than the standard apply.

Conclusion

Synthesis and Characterized of all the Propionic Acid of Quinazoline derivatives have been appraised by different spectral analysis (MASS, IR, NMR) as well as antibacterial evaluation of all these molecules were assessed opposed to five microorganisms by Kirby-Baur disk diffusion method. The zone of inhibition was determined using ciprofloxacin as reference standard. All Propionic Acid of quninazoline derivatives showed stronger activity than the standard ciprofloxacin used.

Acknowledgement

Authors are thankful to the Director, DST-Inspire fellowship scheme, New Delhi Due to give financial help for research work. Head, Department of Chemistry, Mewar University, Gangrar, Chittorgarh for giving experimental facilities and the Director, MRC, MNIT, Jaipur, India for giving spectral and analytical data facilities. Special Thanks for Mr. Anirudh singh who were helping in evaluation of antibacterial activity of all my synthesis compounds.

Table-3: Antimicrobial activity of the new molecules (II a-d).

Antimicrobial activity					
Bacterial Strains	Standard	Synthesized compounds			
	C_1	II(a)	II(b)	II(c)	II(d)
Staphylococcus aureus	12	28(2.33)	25(2.08)	27(2.25)	29(2.41)
Streptococcus pneumonia	10	14(1.4)	11(1.1)	13(1.3)	13(1.3)
Pseudomonas aeruginosa	14	30(2.14)	26(1.85)	28(2.0)	29(2.07)
E.coli	13	30(2.30)	32(2.46)	31(2.38)	33(2.53)
Klebsiella pneumonia	16	21(1.3)	23(1.43)	24(1.5)	23(1.5)

Activity Index= [Inhibition zone of com./Inhibition zone of the STD drug for antibacterial activity], C_1 = Ciprofloxacin.

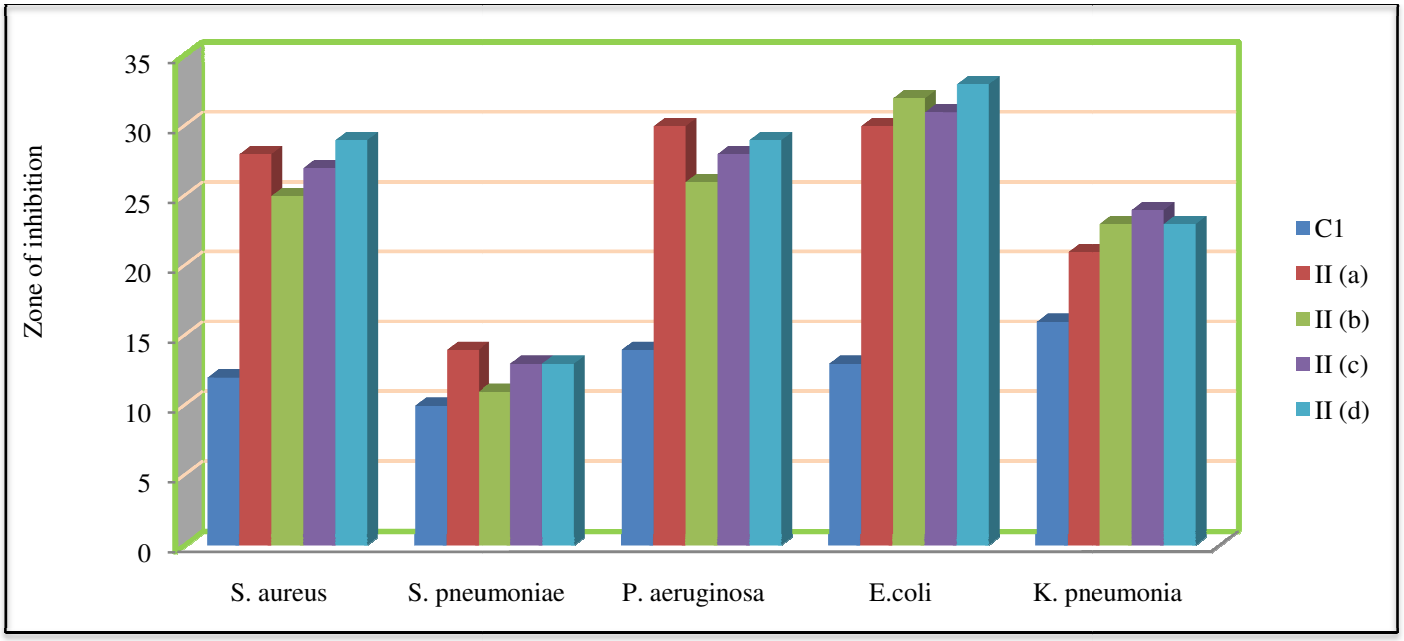


Figure-1: Result of the new molecule Antimicrobial Activity [II a-d] in Graphical.

References

1. Katritzky A.R. and Pozharskii A.F. (2003). Handbook of Heterocyclic Chemistry. Pergamon Press, Oxford.

2. Vijaynathappa J. and Bhojraj S. (2008). Efficient synthesis of 2-(2-hydroxyphenyl) quinazolin-4(3H)-one derivatives. *Journal of Health Sciences*, 54, 524-528.

3. Alagarsamy V., Solomon V.R. and Dhanabal K. (2007). Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3H-quinazolin-4-one as analgesic, anti-inflammatory agents. *Bioorganic and medicinal chemistry*, 15(1), 235-241.

4. Giri R.S., Thaker H.M., Giordano T., Williams J., Rogers D., Sudersanam V. and Vasu K. K. (2009). Design, synthesis and characterization of novel 2-(2, 4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF-κB and AP-1 mediated transcription activation and as potential anti-inflammatory agents. *European journal of medicinal chemistry*, 44(5), 2184-2189.

5. Al-Obaid A.M., Abdel-Hamide S.G., El-Kashef H.A., Alaa A.M., El-Azab A.S., Al-Khamees H.A. and El-Subbagh H.I. (2009). Synthesis, in vitro antitumor activity and molecular modeling study of certain 2-thieno-4(3H)-quinazolinone analogs. *Eur. J. Med. Chem.*, 44(6), 2379-2391.

6. Chandregowda V., Kush A.K. and Reddy G.C. (2009). Synthesis and in vitro antitumor activities of novel 4-anilinoquinazoline derivatives. *Eur. J. Med. Chem.*, 44(7), 3046-3055.

7. Giri R.S., Thaker H.M. and Giordano T. (2010). Design, synthesis and evaluation of novel 2-thiophen-5-yl-3H-quinazolin-4-one analogues as inhibitors of transcription factors NF-kappaB and AP-1 mediated transcriptional activation: Their possible utilization as anti-inflammatory and anti-cancer agents. *Bioorg. Med. Chem.*, 18(7), 2796-2808.

8. Vachala D. and Unnissa H. (2008). Synthesis, Characterization and Biological Screening of Tetrahydro-Quinazoline Analogues. *Indian J. Heterocycl. Chem.,* 17, 347-350.

9. Jatav V., Mishra P., Kashaw S. and Stables J.P. (2008). CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. *Eur. J. Med. Chem.*, 43(9), 1945-1954. DOI: 10.1016/j.ejmech.2007.12.003, PMID: 18222569.

10. Maddry J.A., Ananthan S., Goldman R.C., Hobrath J.V., Kwong C.D., Maddox C. and White E.L. (2009). Antituberculosis Activity of the Molecular Libraries Screening Center Network Library. *Tuberculosis,* 89(5), 354-363. DOI: 10.1016/j.tube.2009.07.006, PMID: 19783214.

11. Kabri Y., Azas N., Dumètre A., Hutter S., Laget M., Verhaeghe P. and Vanelle P. (2010). Original quinazoline derivatives displaying antiplasmodial properties. *Eur. J. Med. Chem.*, 45(2), 616-622.

12. Xu G.F., Song B.A., Bhadury P.S., Yang S., Zhang P.Q., Jin L.H. and Lu P. (2007). Synthesis and antifungal activity of novel s-substituted 6-fluoro-4-alkyl(aryl) thioquinazoline derivatives. *Bioorgan. Med. Chem.*, 15(11), 3768-3774. DOI: 10.1016/j.bmc.2007.03.037. PMID: 17412601.

13. Guan J., Zhang Q., O'Neil M., Obaldia N., Ager A., Gerena L. and Lin A.J. (2005). Antimalarial activities of new pyrrolo [3, 2-f] quinazoline-1, 3-diamine derivatives. *Antimicrobial agents and chemotherapy*, 49(12), 4928-4933. DOI: 10.1128/AAC.49.12.4928-4933.2005, PMID: 16304154.

14. Khalil A.A., Hamide S.G.A., Al-Obaid A.M. and El-Subbagh H.I. (2003). Synthesis and in-vitro anticancer evaluation of new 2-substituted mercapto-3H-quinazoline analogs. *Arch. Pharm. Med. Chem.*, 336(2), 95-103. DOI: 10.1002/ardp.200390011, PMID: 12761762.

15. Jone S. and Fujita E. (1984). Progress in the chemistry of organic natural products. *The quinazoline alkaloids*, Springer Publication Vienna, 159-229. ISBN-978-3-7091-8761-6.

16. Eguchi S., Suzuki T., Okawa T., Matsushita Y., Yashima E. and Okamoto Y. (1996). Synthesis of Optically Active Vasicinone Based on Intramolecular Aza-Wittig Reaction and Asymmetric Oxidation. *J. Org. Chem.,* 61(21), 7316-7319.

17. El-Hashash M.A. and Guirguis D.B. (2013). Synthesis and reactions of 2-(4-bromophenyl)-4H-3, 1-benzoxazine-4-one. *European Chemical Bulletin*, 2(9), 651-656.

18. Kacker I.K. and Zaheer S.H. (1951). Synthesis of Substituted 4-quinazolinones. *J. Indian Chem. Soc.*, 28, 344-346.

19. Sharma G.V.R. and Robert A.R. (2012). Synthetic Strategies to Quinazolinones. *Int. J. Adv.Pharm. Bio and Chem*., 1(3), 337-341.

20. Rafeeq M., Chittireddy V.R.R. and Dubey P.K. (2015). Alkylation of 2-substituted quinazolin-4(3H)-one with DMF-DMA. *Der pharma chemical*, 7(6), 335-357.

21. Samira I., Patel S., Hasmin M. and Patel S. (2012). Biological profile of Quinazoline. *Int. J. Pharm. and Chem. Sc.*, 1(4), 1863-1872.