WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 3, 498-508. Review Article ISSN 2277– 7105

SIGNIFICANT PHARMACOLOGICAL / BIOLOGICAL ACTIVITIES OF NOVEL QUINAZOLINE DERIVATIVES IN MEDICINAL CHEMISTRY

Shirish P. Gavit* and Amol S. Jagdale

M.V.P Samaj's College of Pharmacy, Gangapur Road, District-Nashik-422 002 (M.S).

Article Received on
05 Jan. 2019,

Revised on 26 Jan. 2019,
Accepted on 17 Feb. 2019

DOI: 10.20959/wjpr20193-14290

***Corresponding Author**
Shirish P. Gavit
M.V.P Samaj's College of Pharmacy, Gangapur Road, District-Nashik-422 002 (M.S).

ABSTRACT

This review paper highlights biological and pharmacological utility of some quinazoline derivatives. Quinazolinones are large classes of bioactive chemical compounds exhibiting broad spectrum biological activities in animals as well as in humans. Literature studies on quinazolinones have shown that these derivatives possess a wide variety of pharmacological activities such as anti HIV, Anticancer, Antifungal, Antibacterial, Anti-mutagenic, Anti-coccidial, anticonvulsant, anti-inflammatory, CNS depressant, Anti-malarial, Antioxidant, Anti-leukemic activity, anti-leishmanial activity.

KEYWORD: Quinazoline, Quinazolinones, Bioactive.

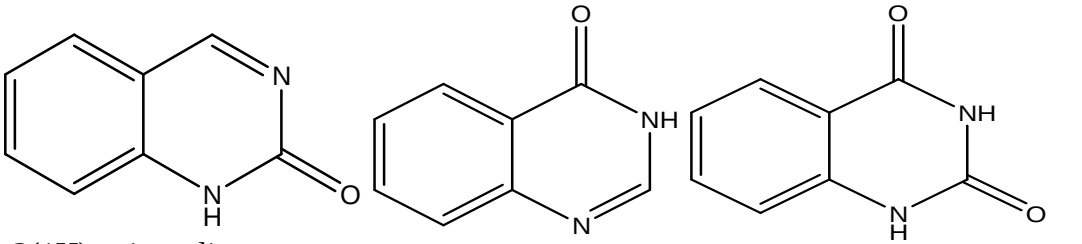
INTRODUCTION

Quinazoline is an organic heterocyclic compound having molecular formula $C_8H_6N_2$. Quinazoline is a yellow colour solid which is crystalline in nature and also has solubility in water. Quinazoline is made from fusion of benzene and pyrimidine ring. The presence of fused benzene ring affects the properties of pyrimidine ring. The presences of two nitrogen atoms in quinazoline are not equivalent. Scientists got attracted by quinazoline alkaloids since 1888 with the discovery of peganine. Now is being used for its bronchodilator activity. Preparation of quinazoline was first done by Gabriel in 1903 and isolation was done from aseru plant. Proposal of name was done by Widdege. Quinazoline is found to have biological activities, such as anticancer, antidiabetic, antiulcer, anticonvulsant, antihypertensive, anti-inflammatory, antibacterial, and antifungal and antimalarial.[1-4]

Quinazolinone will be classified into the following five categories, based on the substitution patterns of the ring system.[5]

1. 2-Substituted-4(3H)-quinazolinones
2. 3-Substituted-4(3H)-quinazolinones
3. 4-Substituted-quinazolines
4. 2, 3-Disubstituted-4(3H)-quinazolinones
5. 2, 4-Disubstituted-4(3H)-quinazolinones

Depending upon the position of the keto or oxo group, these compounds may be classified into three types



2(1H) quinazolinones 4(3H) quinazolinones 2,4(1H 3H) quinazolinedione

Out of the three quinazolinone structures, 4(3H)-quinazolinones are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways. This is partly due to the structure being derived from the anthranilates (anthranilic acid or various esters, Isatoic anhydride, anthranilamide and anthranilo nitrile) while the 2(1H)-quinazolinone is predominantly a product of anthranilo nitrile or benzamides with nitriles.[6]

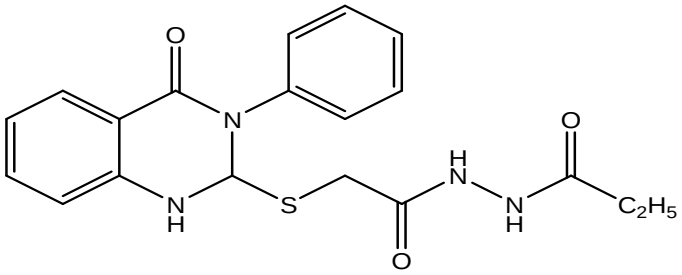
Pharmacological Application of Quinazoline Derivatives

The quinazolinone skeleton is a frequently encountered heterocycles in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, CNS, CNS depressant, anticonvulsant, anticoccidial, anti-parkinsonism, and cancer activities. Little number of quinazolinones was reported as potent chemotherapeutic agents in the treatment of tuberculosis. Compounds of both synthetic and natural origin comprising a diverse group of chemical structure have been reported as anti-leishmial agents. These include mostly nitrogen heterocyclic such as quinolines, purine, pyrimidine, acidine, phenothiazines, bisbenzamides, pyrazolol, pyridine, benzothiazole, and imidazolines.

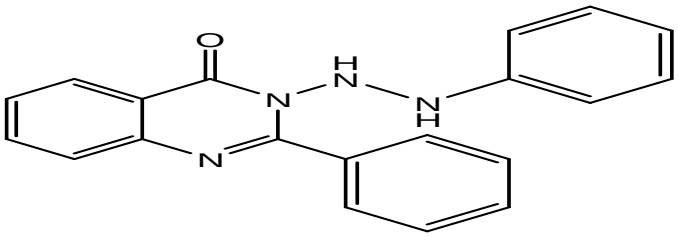
Pharmacological Activities of Quinazolines

Quinazolinones as anticonvulsant activity

Al-Salem *et al.* designed and synthesized new series of hydrazine carbothioamide, benzene sulfonohydrazide, and phenacyl acetohydrazide analogs of 4(3H)-quinazolinone analogues and were evaluated for their anticonvulsant activity using pentylenetetrazol (PTZ) and picrotoxin convulsive models.[7]

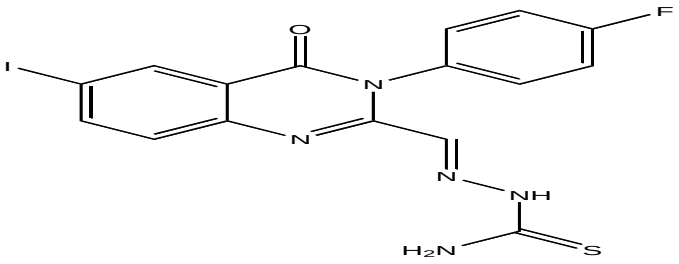


Kashaw *et al.* designed and synthesized a new series of bioactive 1-(4-substituted phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea and evaluated it for anticonvulsant, central nervous system (CNS) depressant and sedative activity.[8]



1-(4-substituted phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea

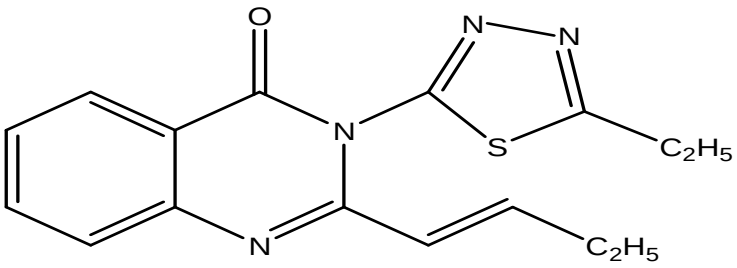
Aly *et al.* (2010) synthesized novel 3-aryl-4(3H)-quinazolinone-2 carboxaldehydes, their corresponding Schiff's base and thiosemicarbazone derivatives and reported Compounds as anticonvulsants.[9]



1-((3-(4-fluorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-yl)methylene) thiosemicarbazide

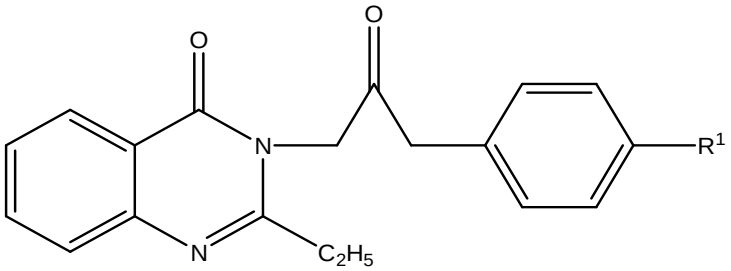
Quinazolinones as CNS depressant activity

Jatav *et al.* (2008) synthesized a series of novel 3-[5-substituted phenyl-1, 3, 4 thiadia -zole-2-yl]-2-styryl quinazoline-4(3H)-one and screened for CNS depressant activities with the help of the forced swim pool method and found that compound were most active against CNS depressant activity.[10]



3-(5-phenyl-1, 3, 4-thiadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

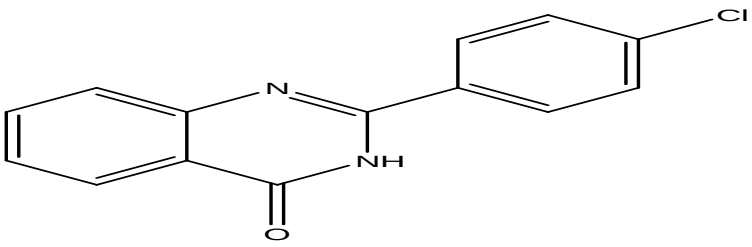
Kashawa *et al.* (2009) synthesized several new 1-(4-substitutedphenyl)-3-(4oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea and screened for CNS depressant activity by maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (ScPTZ) induced seizure models in mice.[11]



1-(4-substitutedphenyl)-3-(4oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea

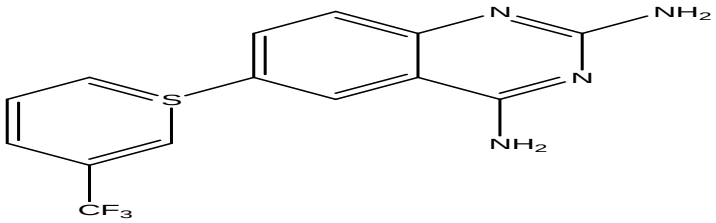
Quinazolinones as Antidiabetic activity

Wei *et al.* designed eight quinazolinone derivatives. They tested their inhibitory activities on alpha glucosidase in vitro.[12]



Quinazolinones as antimalarial activity

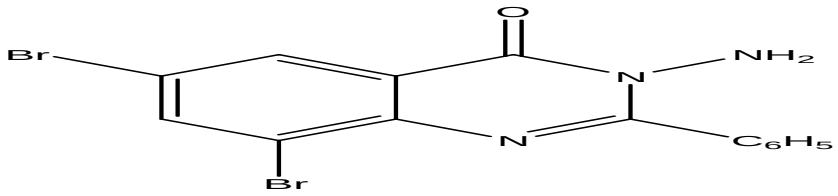
Werbel *et al.* (1987) synthesized a variety of analogues of 2, 4-diamino-6[(aryl) thio] quinazolines with known antimalarial properties wherein the 4-amino group was replaced by hydrazine and hydroxyamino moieties and they found that such changes reduce markedly the antimalarial properties of this series.[13]



2, 4-diamino-6[(aryl) thio] quinazolines

Quinazolinones as Analgesic activity

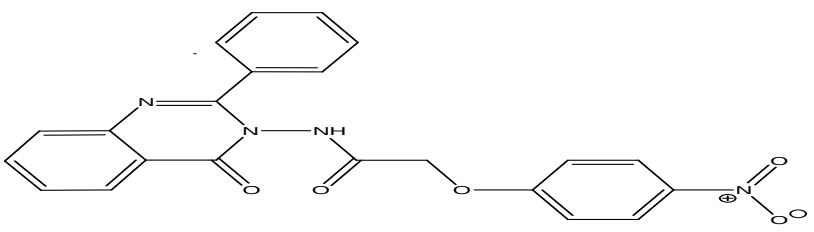
Hemlatha *et al.* (2011) synthesized a series of some novel 2,3-disubstituted quinazolinone derivatives by condensing 6, 8-dibromo-2-phenyl benzoxazine with Compounds containing amino group were confirmed by IR, 1H-NMR, 13C-NMR and Mass spectral data and evaluated for their analgesic activity and they reported that compound show promising analgesic activity compared to standard drug Diclofenacsodium.[14]



6, 8-dibromo-2-phenyl benzoxazine

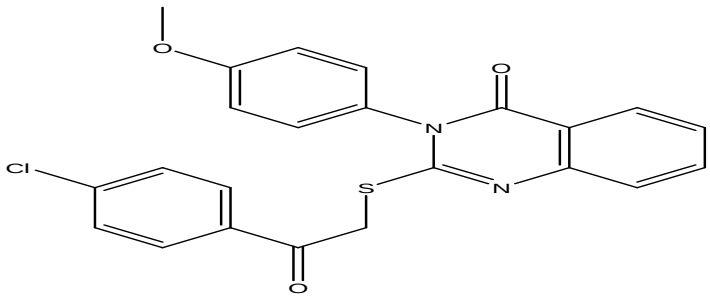
Quinazolinones as Antibacterial activity

Kohli *et al.* (2009) synthesized quinazolinone derivatives by treating 2-ChloroN-(4-oxo-2-phenylquinazolin-3(4H) - yl) acetamide with the different substituted phenols in presence of anhydrous potassium carbonate & catalytic amount of potassium iodide in dry acetone. The compound showed more potent antibacterial activity than the standard drug ampicillin.[15]



Quinazolinones as Anti-cancer activity

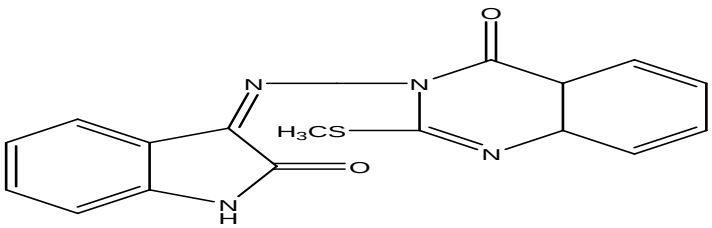
Gawad *et al.* (2010) synthesized some new 3-substituted quinazolin4(3H)-ones and 3, 4-dihydro-quinazolin-2(1H)-one derivatives and reported that compounds 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3(4-methoxyphenyl) quinazolin-4(3H) one, and 3-(4chlorophenyl)-2-[2-(4- methoxyphenyl)-2-oxo-ethylthio] quinazolin 4(3H)-one as broad-spectrum antitumors showing effectiveness toward numerous cell lines that belong to different tumor subpanels.[16]



2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3(4-methoxyphenyl) quinazolin-4(3H) one

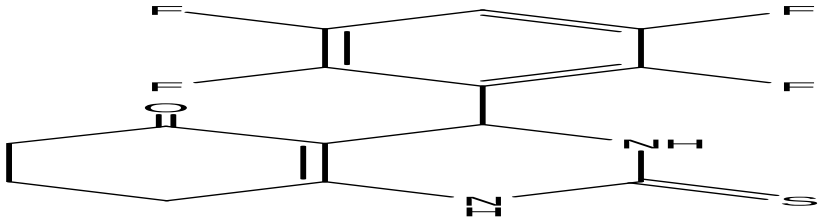
Quinazolinones as Anti-HIV activity

Pandeya *et al.* (1999) synthesized 3-amino-2-methyl mercaptoquinazolin-4(3H)-one from anthranilic acid. The N-Mannich bases of the above Schiff bases were synthesized by condensing the acidic imino group of isatin with formaldehyde and 2^{o} amines and evaluated for anti-HIV activity against HIV-1 III B. in MT-4 cells.[17]



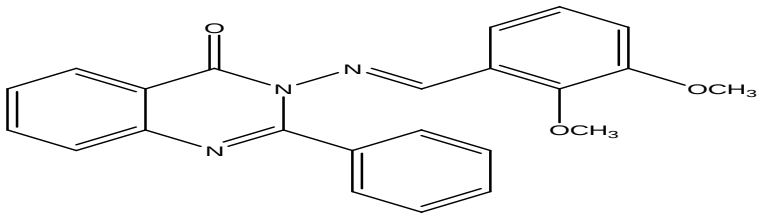
Quinazolinones as Anti-fungal activity

Ghorab *et al.*(2000) synthesized key intermediate octahydro quinazoline obtained in one pot synthesis by a modification of the Biginelli reaction with phenacyl bromide and bromo Malone nitrile to furnish thiazolo[2, 3-b] quinazoline and they found the interaction of compound with formamide, formic acid and phenyl isothiocyanate yielded the corresponding pyrimidinothiazolo[2, 3-b] quinazolines and evaluated for their antifungal activity against Candida albicans.Quinazolinones as antifungal activity.[18]



Quinazolinones as Cytotoxic activity

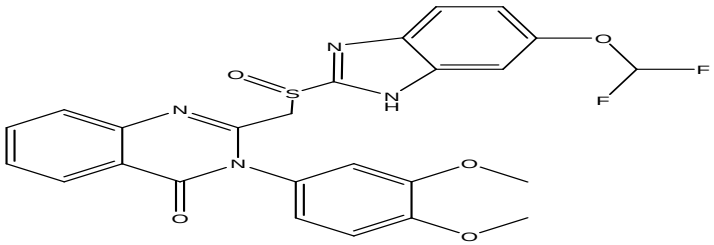
Krishnan *et al.* synthesized series of 3-(benzylideneamino)-2-phenyl quinazoline-4(3H)-ones was synthesized by reaction of 3-amino-2-phenyl-3H-quinazoline-4- one with various carbonyl compounds and investgated cytotoxic activity.[19]



3-(benzylideneamino)-2-phenyl quinazoline-4(3H)-ones

Quinazolinones as Anti-ulcer activity

Patil *et al.* synthesized 2-[5-substituted-10H-benzo(d)imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4(3H)-ones and evaluated for antiulcer activity. The Compounds was found to be most potent having 95 and 97% activity with reference to omeprazole having 100% activity.[20]

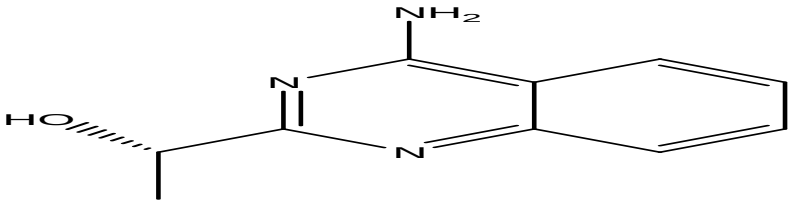


2-[5-substituted-10H-benzo(d)imidazol-2-ylsulfinyl]methyl-3-substitutedquinazoline-4(3H)-ones.

Quinazolinones as Anti-mutagenic activity

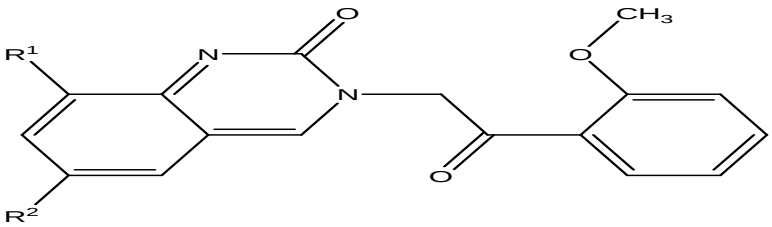
Cakici *et al.* (2010) synthesized (S)-4-aminoquinazoline alcohols a simple synthetic method for the preparation of enantiomerically pure from (S)-quinazolinone alcohols by key steps including chlorination, nucleophilic ipso substitution, and deacetylation is presented. Mutagenic and antimutagenic properties of the (S)-4aminoquinazoline alcohols were

investigated by using Salmonella typhimurium TA1535, and Escherichia coli WP2uvrA tester strains at 0.01, 0.1, and 1 lg/plate concentrations Among the tested (S)-4-aminoquinazoline alcohols, the best antimutagenic activity was obtained with a methyl derivative at 0.1 µg/plate dose.[21]



Quinazolinones as Anti-coccidial activity

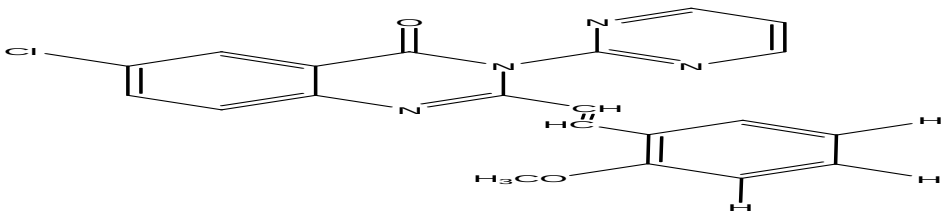
Changwen *et al.* (2010) synthesized a series of 3-(2-(2methoxyphenyl)-2-oxoethyl) quinazolinone derivatives as anti-coccidial agents by modifying the quinazoline ring of febrifugin against Eimeriatenella in the chicken at a dose of 9 mg/kg. 3-(2-(2methoxyphenyl) 2-oxoethyl) quinazolinone derivetives (Fig.9) possesses high anticoccidial activity and may serve as a lead compound for the development of anticoccidial drugs in the future.[22]



3-(2-(2methoxyphenyl)-2-oxoethyl) quinazolinone

Quinazolinones as Anti-leukemic activity

Raffa *et al.* (2004) synthesized 3-(3-Methylisoxazol-5-yl) and 3(pyrimidin-2-yl)-2 styrylquinazolin-4(3H)-ones by refluxing in acetic acid the corresponding 2-methylquinazolinones with the benzoic aldehyde for 12 h and tested for their in vitro anti-leukemic activity against L-1210 (murine leukemia), K-562 (human chronic myelogenous leukemia) and HL-60 (human leukemia) cell lines showing in some cases good activity.[23]



REFERENCES

1. Alam, J. A.; Alam, O.; Naim, J.; Alam, P. A Review: Recent Investigations on Quinazoline Scaffold. Int. j. adv. Res., 2015; 12: 1656–1664.
2. https://en.wikipedia.org/wiki/Quinazoline
3. Bandaru, M.; Sabbavarapu, N. M.; SantoshPavan, A. K. B.; Akula, A. K.; VenkataDurga, N. Y. Simple and Straight Forward Synthesis of 2,4-Disubstituted Quinazolines in Aqueous Medium. E. J. Med. Chem, 2012; 3: 252–257.
4. Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Synthesis of Quinazolinones and Quinazolines. Tetrahedron, 2005; 61: 10153–10202.
5. Mhaske, S. B.; Argade, N. P. Thechemistry of Recently Isolated Naturally Occurring Quinazolinone Alkaloids. Tetrahedron, 2006; 62: 9787–9826.
6. Mahato AK, Srivastava B, Nithya S. Chemistry Structure activity relationship and Biological activity of Quinazoline -4 (3H)-one derivatives. Inventi Rapid: Medicinal Chemistry, 2011; 2(1).
7. Al-Salem, H. S. A.; Hegazy, G. H.; EI-Taher, K. E. H.; EI-Messery, S. M.; AI-Obaid, A. M.; EI-Subbagh, H. I. Synthesis, Anticonvulsant Activity and Molecular Modeling Study of Some New Hydrazinecarbothioamide, Benzene sulfonohydrazide, and Phenacylacetohydrazide Analogues of 4(3H)-Quinazolinone. Bioorg. Med. Chem. Lett., 2015; 25: 1490–1499.
8. Kashaw, S. K.; Kashaw, V.; Mishra, P.; Jain, N. K.; Stables, J. P. Synthesis, Anticonvulsant and CNS Depressant Activity of Some New Bioactive,1-(4-Substituted-Phenyl)-3-(4-Oxo-2-Phenyl/ Ethyl-4H-Quinazolin-3-yl)-Urea. E. J. Med. Chem., 2009; 44: 4335–4343.
9. Aly, M. M.; Yahia, A. M. K.; EI-Byouki, A. M.; Basyouni, W. M.; Abbas, S. Y. Synthesis of Some New 4(3H)-Quinazolinone-2-Carboxaldehyde Thiosemicarbazones and their Metal Complexes and a Study on their Anticonvulsant, Analgesic, Cytotoxic and Antimicrobial Activities – Part-1. E. J. Med. Chem, 2010; 8: 3365–3373.
10. Jatav V, Mishra P, Kashaw S, Stables J P. Synthesis and CNS depressant activity of some novel 3-[5-substituted1,3,4thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. European Journal of Medicinal Chemistry, 2008; 43: 135-141.
11. Kashawa SK, Kashawa V, Mishra P, Jain NK, Stables JP. Synthesis, anticonvulsant and CNS depressant activity of some new bioactive 1-(4-substituted-phenyl)-3-(4-oxo-2phenyl/ethyl-4H-quinazolin-3-yl)-urea. European Journal of Medicinal Chemistry, 2009; 44: 4335–4343.

12. Wei, M.; Chai, W.-M.; Wang, R.; Yang, Q.; Deng, Z.; Peng, Y. Quinazolinone Derivatives: Synthesis and Comparison of Inhibitory Mechanisms on A-Glucosidase. Bioorg. Med. Chem., 2017; 25: 1303–1308. Werbel LM, Degnan MJ. Synthesis and Antimalarial and Antitumor Effects of 2-Amino-4-(hydrazino and hydroxyamino)-6-[(aryl) thio] quinazoline. Journal of Medicinal Chemistry, 1987; 30: 2151-2154.
13. Hemalatha K, Girija K. Synthesis of some novel 2, 3disubstituted quinazolinone derivatives as analgesic and antiinflammatory agents. International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(2): 103-106.
14. Kohli D, Hashim SR, Vishal S, Sharma M, Singh A. Synthesis and antibacterial activity of quinazolinone derivatives. International Journal of Pharmacy and Pharmaceutical Sciences, 2009; 1(1): 163-169.
15. Gawad, A. M. N.; Georgey, H. H.; Youssef, R. M.; EI Sayed, N. A. Design, Synthesis, and Anticonvulsant Activity of Novel Quinazolinone Analogues. Med. Chem. Res., 2011; 20: 1280–1286.
16. Pandeya SN, Sriram D, Nath G, Clercq E D. Synthesis antibacterial antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2 methylmercapto quinazolin-4(3H)-one. Pharmaceutica Acta Helvetiae, 1999; 74: 11–17.
17. GhorabM, Abdel-Gawad S M, M.S.A, El-Gaby M S A. Synthesis and evaluation of some new fluorinated hydroquinazoline derivatives as antifungal agents. IL Farmaco, 2000; 55: 249–255. 8. Patel NB, Patel JC. Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3H)-one. Arabian Journal of Chemistry, 2011; 4: 403-411.
18. Sinha N. K., Asnani A. J., Dravyakar B. R., A Novel Approach Towards Development of Quinazoline Derivatives in Pain Management Asain journal of pharmaceutical and clinical research, 2013; 6(3): ISSN - 0974-2441
19. Patil, A.; Ganguly2, S.; Surana, S. Synthesis and Antiulcer Activity of 2-[5-Substituted-1-H- Benzo(d)Imidazol-2-yl Sulfinyl]Methyl-3-Substituted Quinazoline-4-(3H) Ones. J. Chem. Sci., 2010; 122: 443–450.
20. Cakici M, Catir M, Karabuga S, Kilic H, Ulukanli S, Gulluce M, Orhan F. Synthesis and biological evaluation of (S)-4aminoquinazoline alcohols. Tetrahedron: Asymmetry, 2010; 21: 2027–2031.
21. Ye C, You J, Li XF, You R, Weng Y, Li J, Wang Y. Design, synthesis and anticoccidial activity of a series of 3-(2-(2methoxyphenyl)-2-oxoethyl) quinazolinone derivatives. Pesticide Biochemistry and Physiology, 2010; 97: 194-198.

22. Raffa D, Daidone G, Maggio B, Cascioferro S, Plescia F, Schillaci D. Synthesis and antileukemic activity of new 3-(5methylisoxazol-3-yl) and 3-(pyrimidin-2-yl)-2styrylquinazolin-4 (3H)-ones. IL Farmaco, 2004; 59: 451–455.
23. Agarwal KC, Sharma V, Shakya N, Gupta S, Design and synthesis of novel substituted quinazoline derivatives as antileishmanial agents. Bioorganic and Medicinal Chemistry Letters, 2009; 19: 5474–5477.