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Review Article

Nanocatalyzed Synthetic Approach for the Quinazolinone and Quinazoline Derivatives: A Review (2015 – Present)

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Abstract

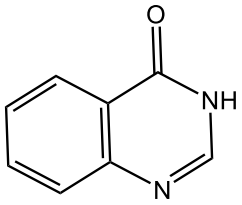
Due to their diverse chemical reactivities and essential range of biological action, quinazolines and their derivatives rank among the most significant heterocyclic compounds. Quinazoline and quinazolinone scaffolds pharmacological properties have sparked medicinal chemists' interest in creating original medications or drug candidates. The growth of quinazoline hybrid lead compounds and the related heterocycles is summarised in the current review of medicinal chemistry. Additionally, by shedding light on the potential significance of these hybridised pharmacophoric characteristics in the demonstrating a range of pharmacological activities, the review contributes to the acceleration of the drug development process.

Keywords: Fused Heterocycles, Quinazolinone and Quinazoline Derivatives, Drug Development

INTRODUCTION

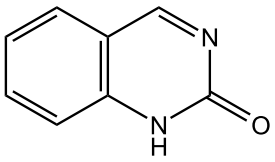
The among a wide variety of the nitrogen heterocycles that have explored for pharmaceutically important roles, quinazolinone are one of the category of fused heterocycles that are of considerable interest[1].

Manufacture the of small molecule mimics of biological structures is a key contribution of organic chemistry to the invention of the new pharmaceuticals with the wide range of biological activities. There are two structural isomers, quinazolin-4-one (a) and quinazolin-2- one (b) with the 4-isomer being the more common[2].



quinazolin-4-one

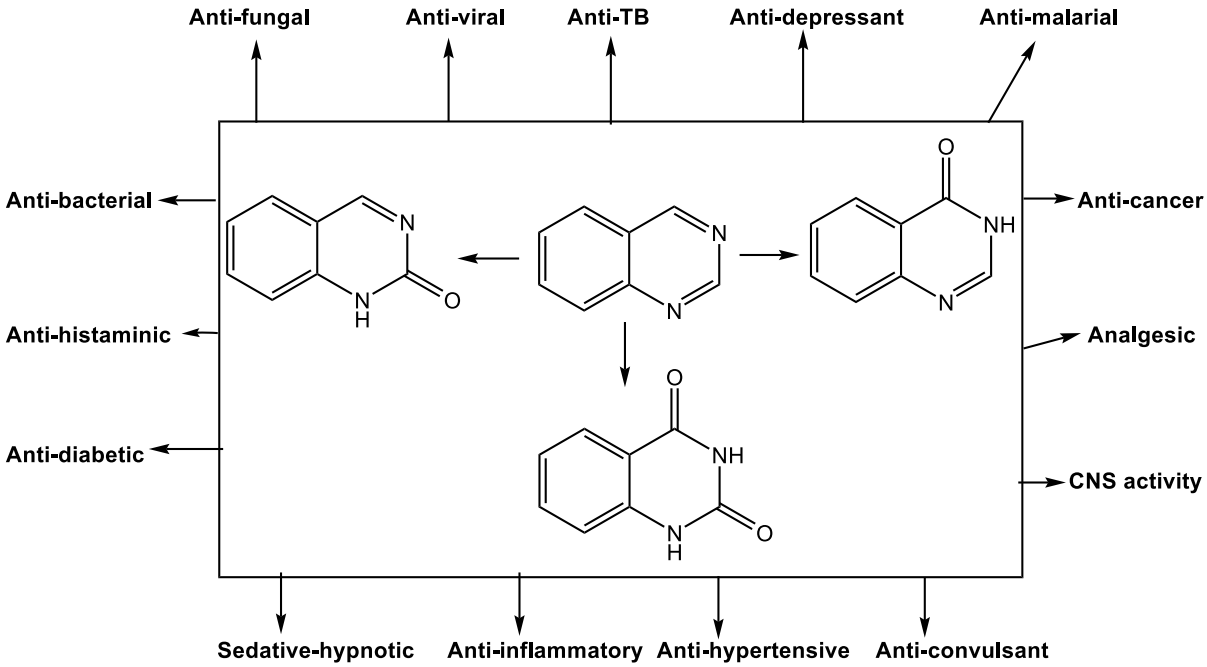
(a)



quinazolin-2-one

(b)

Heterocyclic rings containing nitrogen and sulfur are of much intention as they are therapeutically and pharmacologically more active. These substances serve as the foundation for numerous pharmacological products. For this review, quinazoline has been chosen among all heterocyclic moieties since it has a very wide range of the pharmacological activity and little negative side effects[3].



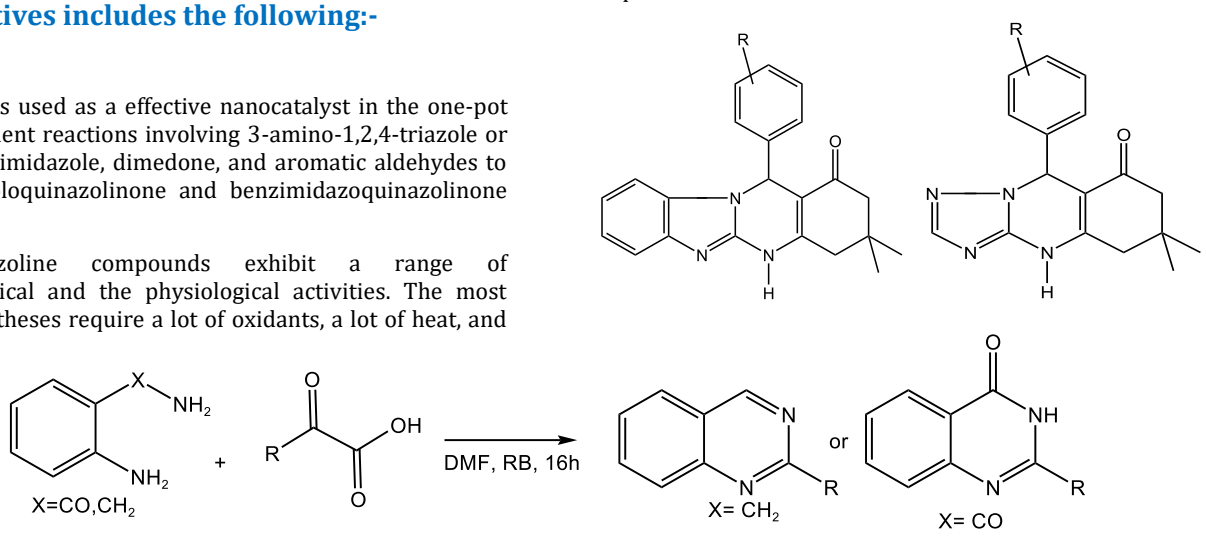
Due to the wide diversity of their biological or organic properties, the classes of fused heterocycles quinazolines and quinazolinones are of the great interest[4].

Biological significance of the quinazoline and its derivatives includes the following:-

In 2022

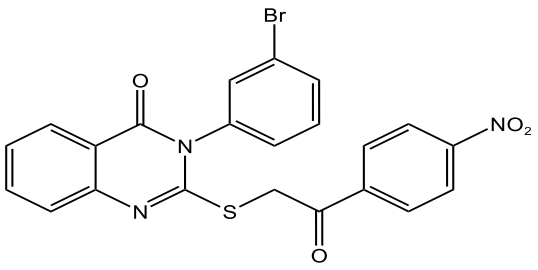
The TiO2 was used as a effective nanocatalyst in the one-pot multicomponent reactions involving 3-amino-1,2,4-triazole or 2-aminobenzimidazole, dimedone, and aromatic aldehydes to create triazoloquinazolinone and benzimidazoquinazolinone derivatives[5].

The quinazoline compounds exhibit a range of pharmacological and the physiological activities. The most frequent syntheses require a lot of oxidants, a lot of heat, and other harsh conditions. In this investigation, quinazoline compounds were produced without the use of transition metal catalysts or additives by condensation of keto acid and 2-aminobenzylamine followed by decarboxylation at room temperature[6].

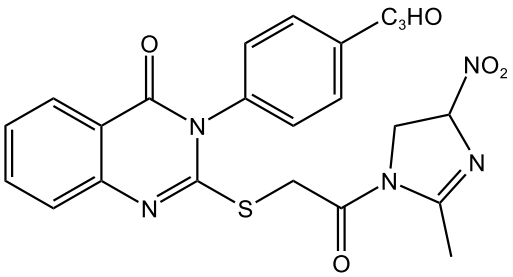


In 2021

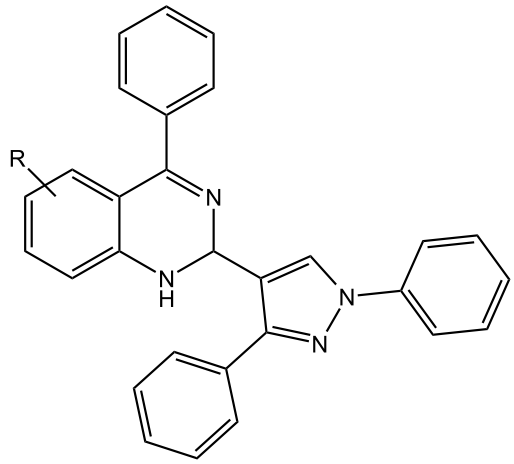
The effects of the quinazolinone analogues on alpha-glucosidase inhibition were developed and evaluated. Results revealed that the most tested members were powerful and significantly inhibited the alpha-glucosidase enzyme when compared to conventional acarbose[7].



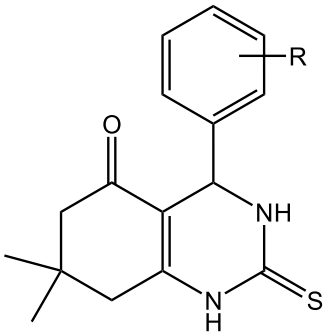
Quinazolinone-2-thio-metronidazole derivatives were created, produced, and tested for their efficacy against the enzyme glucosidase. The results indicated that all the synthesized compounds exhibited excellent inhibitory activities against mentioned enzyme as compared with standard inhibitor. Biological testing prove that mainly α-glucosidase inhibitor was compound with 4-methoxyphenyl moiety. It was 5-times more active that acarbose as the standard inhibitor[8].



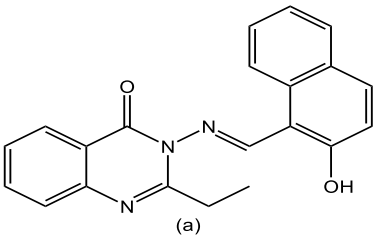
Mahesh reported an environmentally friendly method for producing zinc oxide nanoparticles (ZnO-NPs) at the room temperature employing sunflower leaf aqueous extract. The produced nanocatalyst was shown to be an effective and useful catalyst separation of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-4-phenyl-1,2-di-hydroquinazoline derivatives through a one-pot reaction of 2-amino benzophenone,1,3-diphenyl-1H-pyrazole ammonium acetate and carbaldehydes, in green protocols[9].



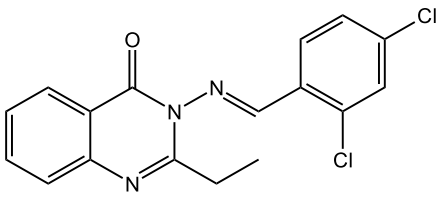
Recently, reported the zinc ferrite nanocatalyst (ZnFe2O4) as a new and efficient nanocatalyst and study of its efficacy designed for research of 7,7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazoline-5-one compounds from dimedone. In incidence of an produced nanocatalyst , the aryl aldehydes were substituted with thiourea, which increases the yield in reflux by condensation, then cyclization to provide the desired product[10].



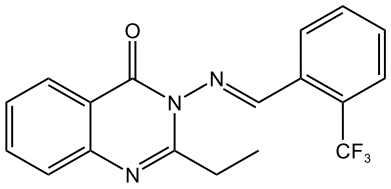
According to Tokal and Taslimi, certain quinazolinone derivatives were made using a variety of aldehydes and the compound 2-ethyl,3-aminoquinazolin4(3H)-one. A number of the metabolic enzymes, in particular alpha-glucosidase, were tested the compounds against[11].



(a)



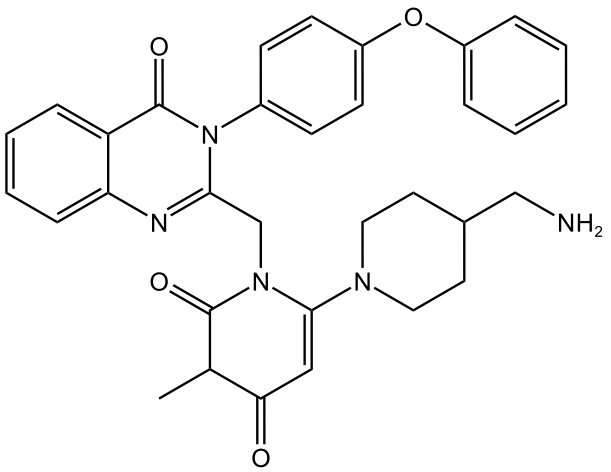
(b)



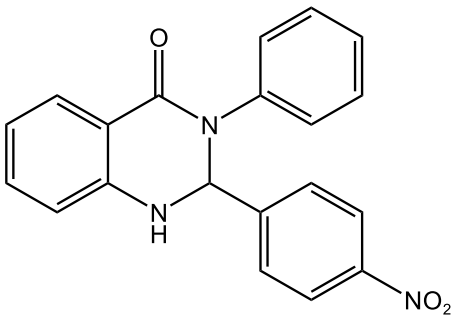
(c)

In 2020

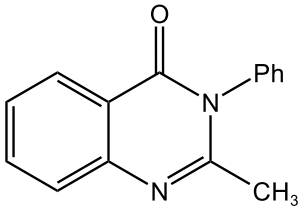
Emami and Faghih created the new quinazolinone pyrimidine and benzyl-pyrimidine hybrids and tested their ability to inhibit the dipeptidyl peptidase peptidase-4. Most effective agent was discovered to be compound, with an IC50 value of 34.3-3.3 μM[12].



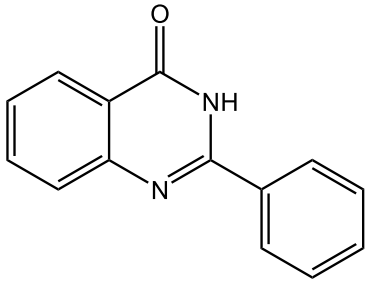
When isatoic anhydrides are combined with aryl aldehydes and 1-amines in ethanol, a green solvent, Azizi found that the KCC-1/Pr-SO3H nanocatalyst produces di-hydroquinazolinone derivatives with high-quality yields under reflux conditions[13].



The analysis of Grimmel, Guinther, and Morgan When phosphorus trichloride is present, the 2-acetamidobenzoic acid combines with an amine to the produce 2-methyl-3-phenylquinazolin-4(3H)-one[14].

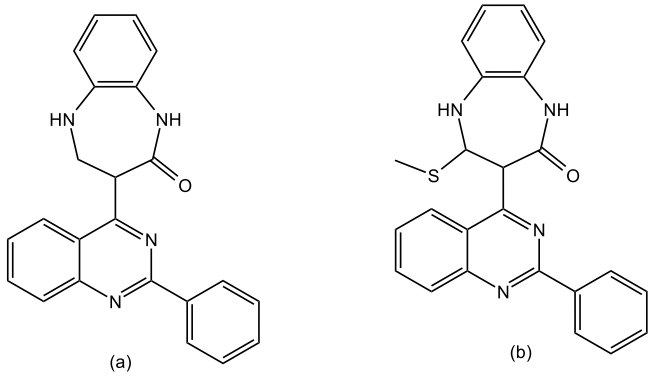


Di-tertiary-butyl peroxide (DTBP) and p-toluene sulfonic acid (p-TsOH) were used by Sharif to create 2-phenylquinazolin-4(3H)-one by reacting 2-aminobenzamide with styrene[15].

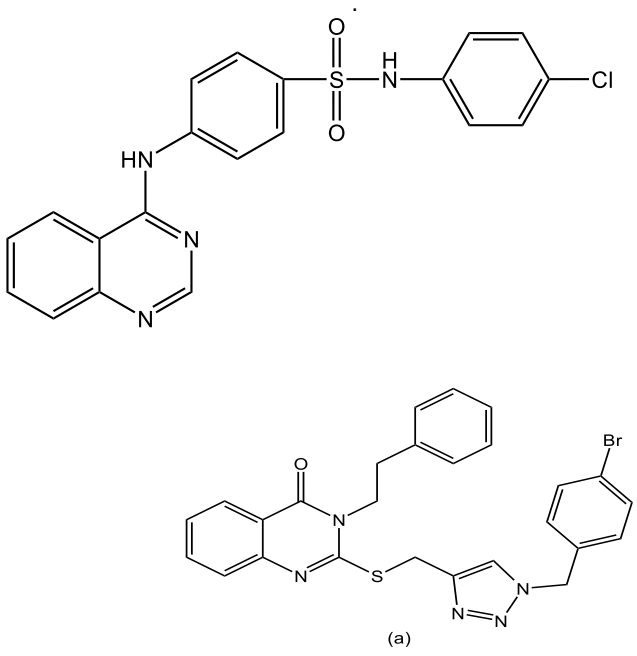


Quinazoline derivatives have antibacterial properties.

A fresh batch of 1,5-benzodiazepine analogues ornamented with quinazolines was synthesised by Misra, and their antibacterial efficacy was tested. fabricated substances (Z)-3-(2-phenylquinazolin-4-yl)-1H-benzo(b). The compounds diazepin-2(5H)-one and (E)-4-(methylthio)-3-(2-phenylquinazolin-4-yl)-1H-benzo(b). the compound1,4-diazepin-2(5H)-one Staphylococcus aureus and Escherichia coli were the two microbes that the compound was shown to be particularly efficient against (IC50 (g/mL) (a): I 200, (ii) 200, (b): I 200, (ii) 200)[16].

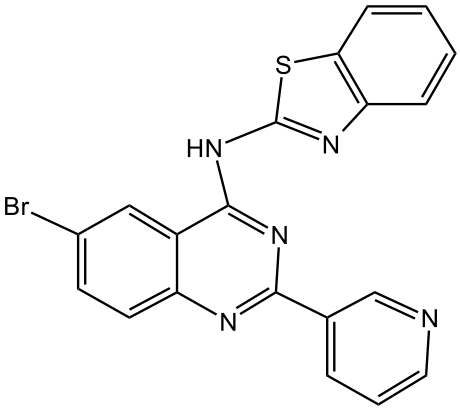


The antibacterial activity of a novel series of 4-amino-N-(phenyl)benzenesulfonamide derivatives was assessed by the Kumar. The most effective candidate against the gram-negative bacteria strain was discovered to be a chloro-derivative of the produced compound (Microbe Selected-(i)-Gram-positive Bacteria,(ii)-Gram-negative Bacteria and Activity-MIC in mg/mL, I 6.25, (ii) 3.12)[17].



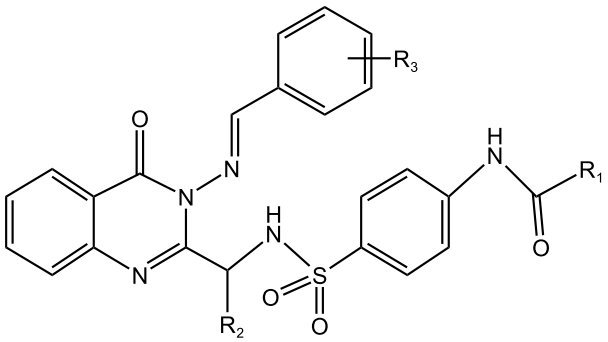
Using anti-tumor medicines based on quinazoline

HepG2, MCF-7, PC-3, HCT-116, and HeLa tumour cell lines were used to investigate the antitumor activity of produced substances. The ability of the compound to simulate cell cycle arrest in the G2/M phase and the results demonstrated substantial EGFR inhibitory activity. A good correlation between molecular modelling findings and biological outcomes was discovered while studying the interaction of active sites. 6-Bromo-2-(pyridin-3-yl) With the initial reagent, a series of 4-substituted quinazolines was created. derivatives of 4-chloro (Activity Tested Against Cells: I EGFR, (ii) A549, (iii) MCF7, (iv) WI38, (v) PC9, (vi) HCC827)[18].



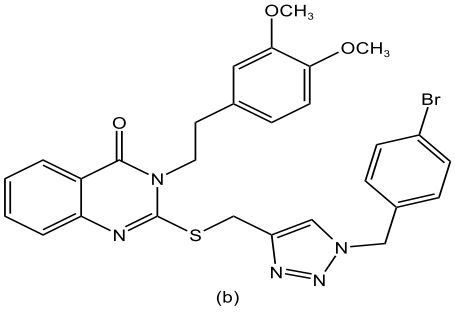
Quinazolinone's ability to the prevent malaria

Patel performed the *N*-heterocyclization of leucine-linked sulphonamides that synthesize quinazolinone- and sulphonamide-based hybrids *via* modified Grimmel's method (R1=CH3,R2= X=Cl,I and R3=4- Cl)[19].



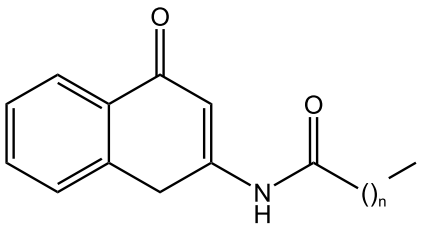
In 2019

Reported Saeedi M a series of quinazolinone-1,2,3-triazole hybrids 10a-p as potent α-glucosidase inhibitors for use as anti-diabetic agents that the exhibited more potent inhibitory activity against yeast α-glucosidase (IC50 181.0-474.5 μM) greater than the reference drug acarbose (IC50 = 750.0). These compounds' quinazolinone-1,2,3-triazoles with the 4-bromobenzyl moiety attached to the 1,2,3-triazole rings (a) and (b) showed the strongest-glucosidase inhibitor action[20].

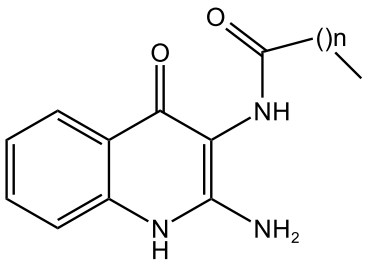


Anti- virulence activity

Espinosa-Valdes The production of biofilms was inhibited by 2-amino-4-quinolone long chain amide derivatives. The most important effective substances were those with an alkyl chain longer than 12 carbon atoms, and the generally speaking, they were more effective against P. aeruginosa biofilm progress than S. aureus. At a concentration of 20 M, the two most effective compounds (a) and (b) likewise condensed the creation of pyocyanin by between 62.6 and 68.2%. None of the investigated substances had an impact on bacterial growth, indicating that the derivatives' activity might have been modulated by QS[21].



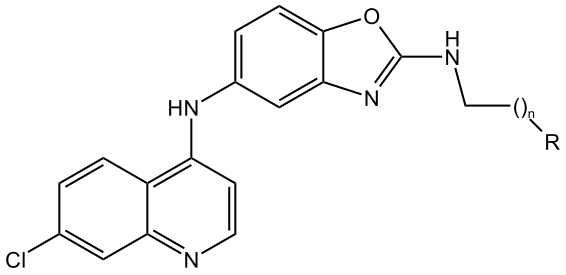
(a) n=10



(b) n=10

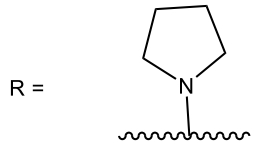
Anti-Malarial Activity

Leven provide the three compounds (a), (b), and (c) showed in vivo efficacies in a dose-dependent manner with 99.5% parasitemia reduction, with derivative (c) being the most successful. 8-Aminoquinolines Other well-known and effective the antimalarial medications include primaquine and tefenoquine. The biotransformation of terminal amino groups into hazardous aldehydes is a shared drawback of these molecules. The synthesis of novel compounds with aminoxy and oxime-groups was done to stop this change and to preserve good antimalarial activity[22].

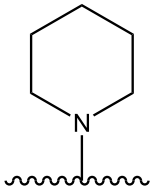


(a) n=1

R =

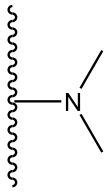


n= 2, R=



(b)

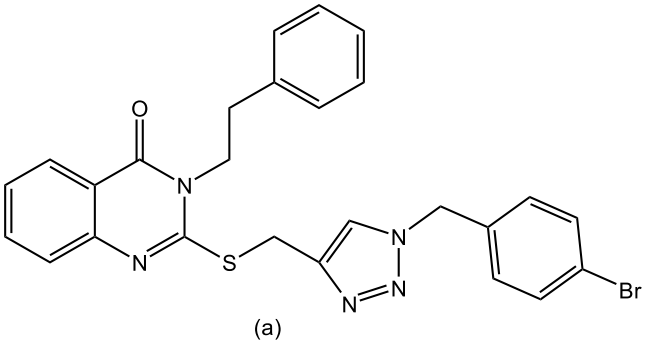
n= 1, R=



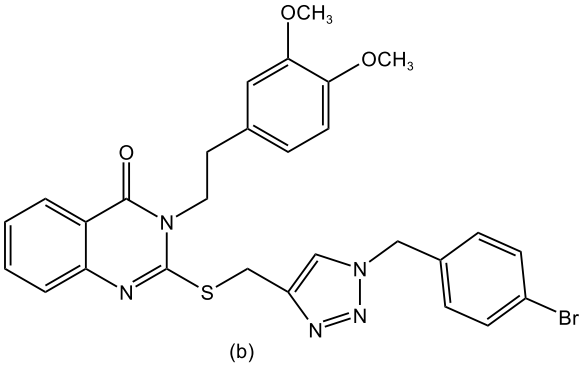
(c)

Inhibitory action of Alpha-glucosidase

As powerful -glucosidase inhibitors for use as anti-diabetic medications, Saeedi M. reported a series of quinazolinone-1,2,3-triazole hybrids 10a-p. These compounds displayed increased inhibitory action[23].



(a)

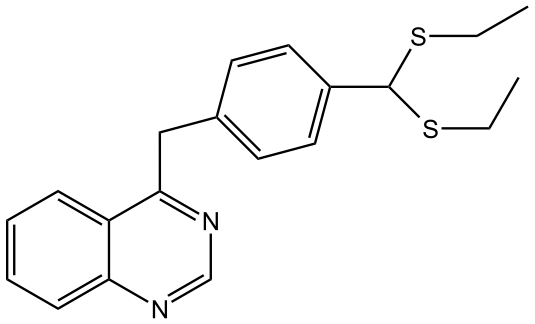


(b)

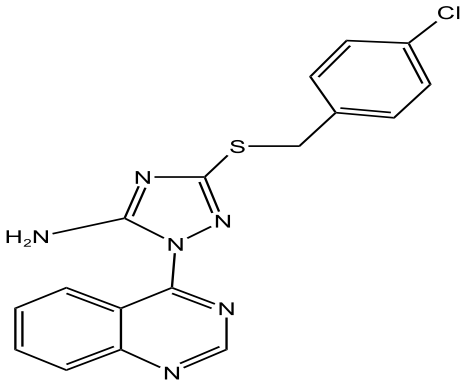
In 2018

Quinazoline derivative's antiviral properties

In relation to ningnanmycin, a dithioacetal moiety containing quinazoline derivatives was created as a potential antiviral drug. In the comparison to commercially available ningnanmycin quinazoline was found to have maximum therapeutic effectiveness against CMV (cucumber mosaic virus) with EC50 = 248.6 ug/mL and potatovirus Y (EC50 = 350.5 g/mL)[24].

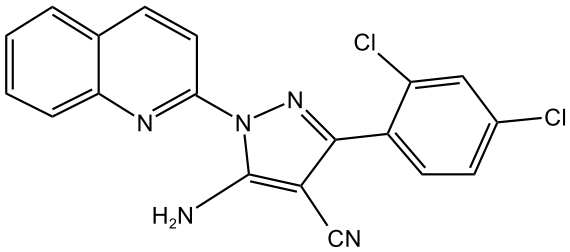


Ethyl 2-(5-amino-1-(quinazolin-4-yl)-1H-1,2,4-triazol-3-ylthio) acetate and its Compound have exhibited strong inhibitory effect the against phytopathogenic microorganisms. These substances had been EC50 values of the 93.1 ug/mL and 56.9 ug/mL, respectively, against the bacterium Xanthomonas axonopodis pv. Citri, outperforming the commercially available agrobactericide Bismerthiazol[25].



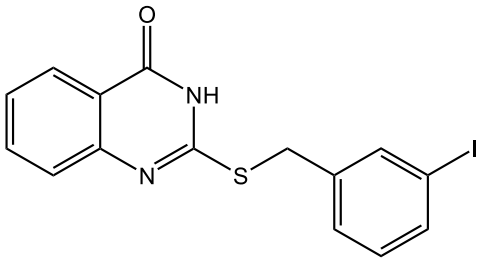
Anti-tuberculosis activity of quinazoline derivative

The various interaction between quinoline and pyrazole derivatives also known for their bioactivities against tuberculosis or TB, viruses, and inflammation and three different series of the antimicrobials was evaluated. Most derivatives showed pure antibacterial and antifungal properties, and compound emerged as the most promising one. Its MICs for Shigella flexneri, Klebsiella pneumonia, Staphylococcus epidermidis, and Proteus vulgaris were in the range of ampicillin and gentamycin MICs and varied from 0.12 to 0.98 g/ml[26].



Monoamine oxidase inhibitor activity (MAO)

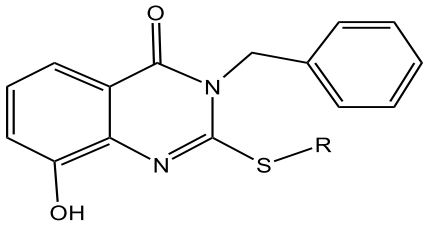
The seven quinazolinone compounds have been identified as the potent and specific MAO-B inhibitors by Qhobosheane, with the most effective inhibitor having an IC50 value of 0.142μM[27].



In 2017

Anti-tumor medications based on quinazoline

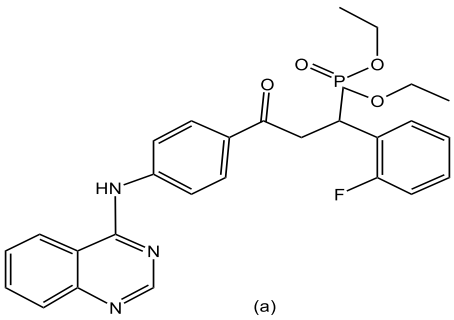
The intrinsic thioxo group of one more series of quinazoline derivatives has been hydrozinolyzed to produce matching thioethers. The mainly or most compounds are displayed demonstrated strong activity against the very tested cell-lines, with IC50 values for HeLa and MDA-MB231 cells ranging from 1.85 to 2.81 μM, respectively (Activity Tested against the Cells-HeLa, MDA-MB231 and Cytotoxicity- 1.85, 2.33 μM)[28].



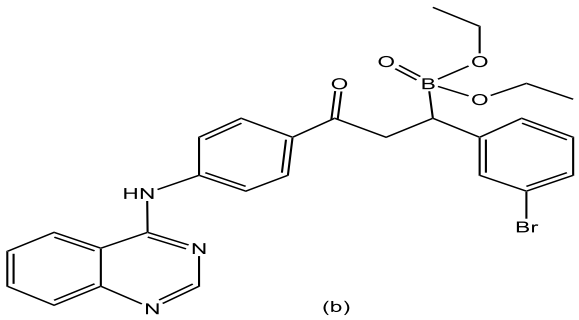
R=3-(Phthalimido-2-yl)propyl

Quinazoline derivatives' antiviral properties

The synthesis of chalone-like molecules, alpha, beta-unsaturated carbonyl compounds have been 1,4-hydrophosphinylated. The cucumber mosaic virus was used as a test subject for antiviral activity. a few compounds The protective activities of the compound are equivalent to those of the commercially available medicines ningnanmyin and dufulin at 55.1% and 56.8%, respectively[29].



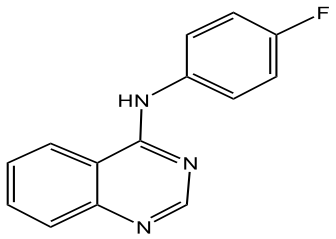
(a)



(b)

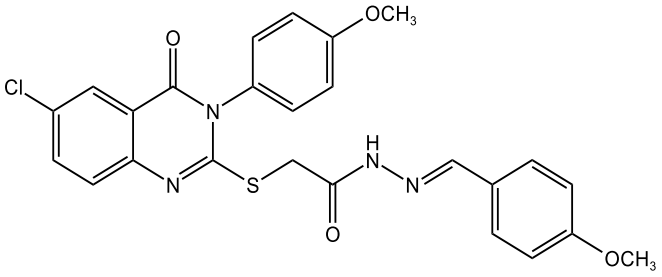
Anti-Inflammatory Effects of Quinazoline

In comparison to diclofenac, synthetic substituted pyrrolo-quinazoline derivatives were investigated for biological efficacy as anti-inflammatory agents. The created substance was discovered to be the most effective anti-inflammatory agent[30].



Active inhibition of thymidine synthase

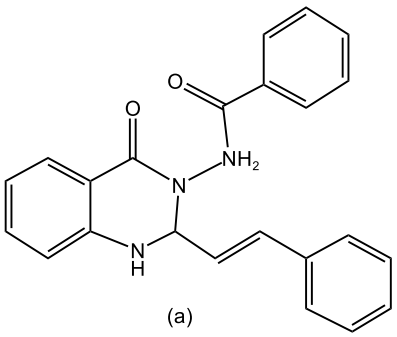
According to Gazzar, a derivative of 2-mercaptoquinazolin-4(3H) is a powerful inhibitor of the DHFR enzyme in the liver of cattle (IC50 = 0.01µM)[31].



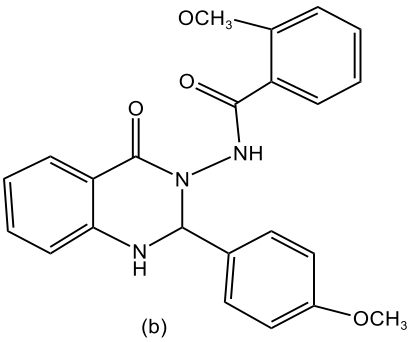
In 2016

Anti-fungal activity of quinazolinone

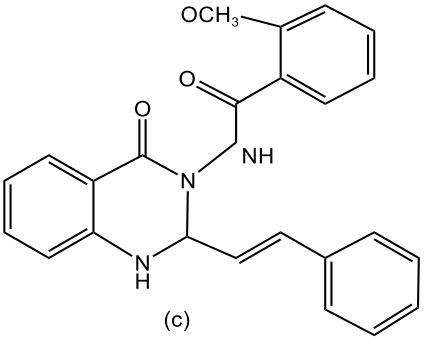
The quinazolinone derivatives containing 3-acrylamino motifs were screened for the antifungal activities against four phytopathogenic fungi by minimum inhibitory concentration (MIC) method. Compounds (a),(b) and (c)) exhibited side street the activity of antifungal and substituent's play essential position in activities[32].



(a)



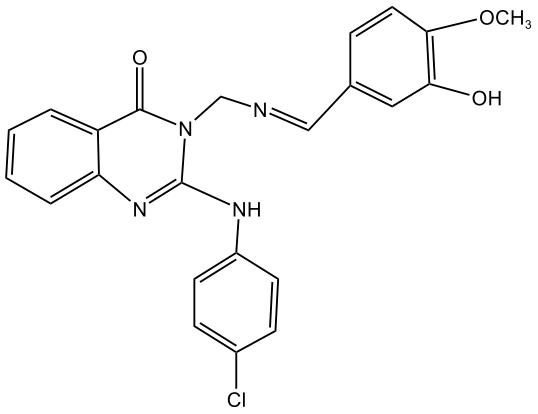
(b)



(c)

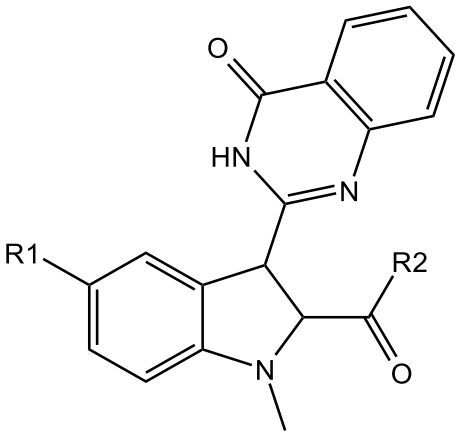
Quinazolinone's anti-bacterial properties

The appearance of antibiotic resistance have spawned a pressing medical need for the invention and creation of novel types of antibacterial medicines. The necessity for the creation of novel antibiotics to treat drug-resistant bacterial strains is increasing as a result of their appearance. Quinazolinones have a wide range of the biological actions[33].



Anti-cancer activity of quinazolinone

By taking into account the ability of various indole-based amides to induce apoptosis, Gokhale created indole and quinazolinone-based amides for anti-cancer activities. Additionally, the insertion of amide into the second position of the indole results in cytotoxicity via inhibiting histone deacetylase (HDAC). Based on these findings, quinazolinone-based indolyl amides were created and manufactured, and then their anti-cancer activity was tested.[34].

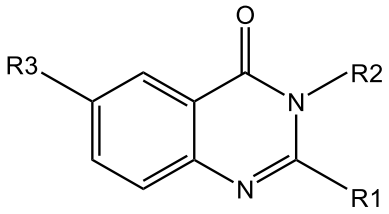


(a). R1= F, R2=3,4-difluorophenylamino

(b), R1=H, R2= cyclohexylmethylamino

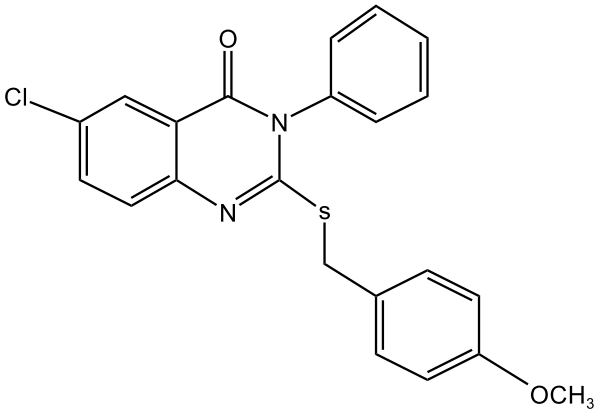
Quinazolinone's anticonvulsant properties

The structure-activity relationship of the 4(3H)-quinazolinones nucleus's anticonvulsant activity showed that a methyl group at position-2 and a substituted aromatic ring at position-3 are crucial for the anticonvulsant activity of substances like methaqualone (R1 = CH3, R2 = o-tolyl, R3 = H), etaqualone (R1 = CH3, R2 = 2-ethylpheny Methaqualone is 1.5 times more effective than phenytoin sodium at preventing electroshock-induced convulsions, and at lower dosages it inhibits convulsions by acting on GABA type-A receptors, while at higher levels it has sedative and muscle-relaxing properties[35].



Activity as a thymidine synthase inhibitor

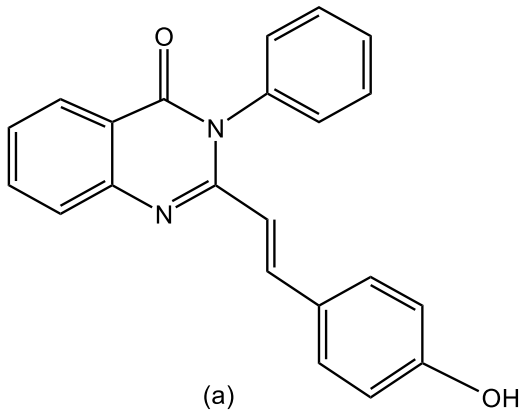
Several 2,3,6-substituted quinazolin-4(3H)-ones have been created. With an IC50 value of 0.02 μM, compound is the most effective inhibitor of bovine liver DHFR among these substances[36].



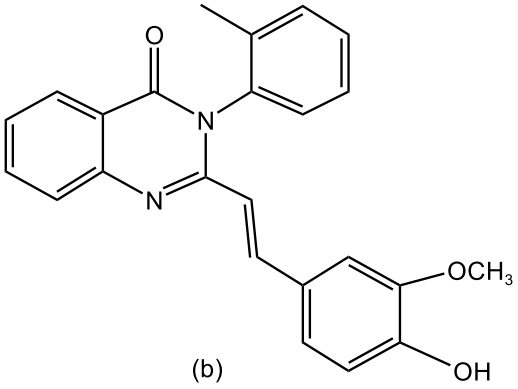
In 2015

Anti-malarial activity

Birhan have synthesized 3-aryl2-(substituted styryl)-4(3H)-quinazolinone derivatives (a) & (b) effective anti-malarial agents[37].



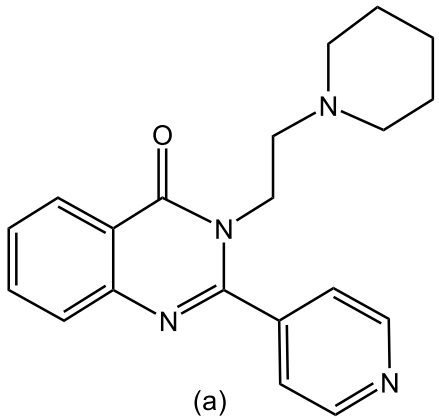
(a)



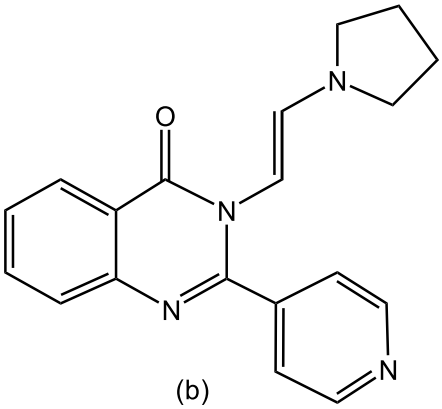
(b)

Anti-viral activity

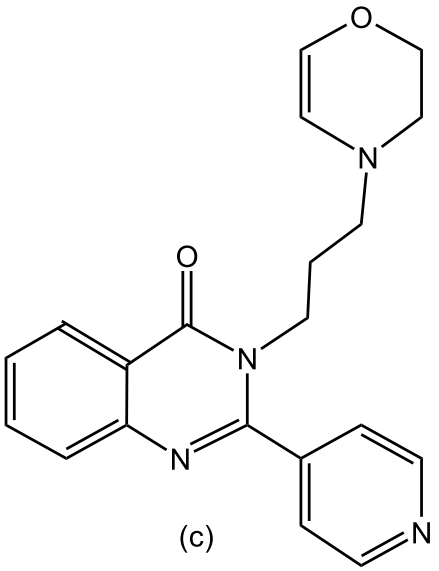
Liu reported a number of 2-pyridinyl-3-substituted-4(3H)-quinazolinones as influenza A virus antagonists. Of these derivatives, compounds (a,b,c, & d) shown robust action (IC50 = 51.6-93.0 μM) superior to that of the clinically used medication, ribavirin. furthermore, it was discovered that compound (d) might stop the spread of the influenza A virus by blocking the cellular NF-kB pathway, however it was not as efficient as ribvarin[38].



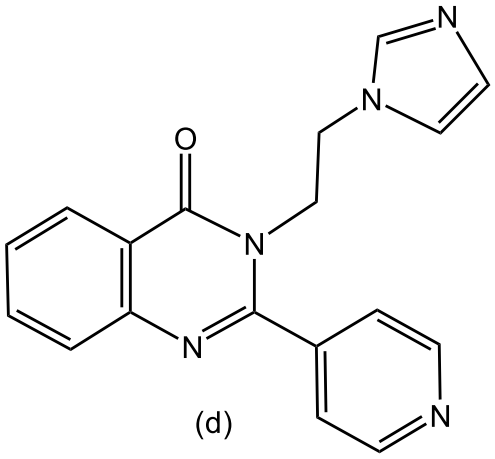
(a)



(b)



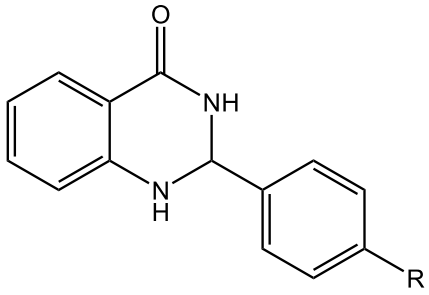
(c)



(d)

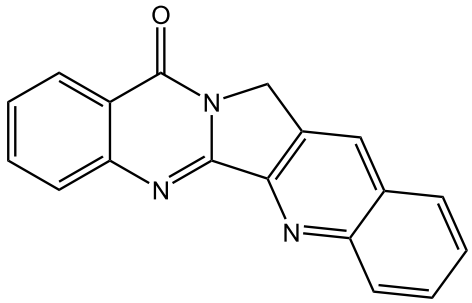
Activity that inhibits cathepsin

A series of 2,3-dihydroquinazolin-4(1H)-ones were synthesised and studied by Singh and Raghav as cathepsin inhibitors. The substances 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one) and 2- (4-chlorophenyl) The highest level of inhibition on cathepsin B was demonstrated by compounds containing 2,3-dihydro quinazolin-4(1H)-one (R = Cl). However, the most effective inhibitors of cathepsin H have been discovered to be 2,3-dihydro-2-(4-methylphenyl)quinazolin-4(1H)-one (R = Me) and 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (R = F)[39].



Quinazolinone's anti-cancer properties

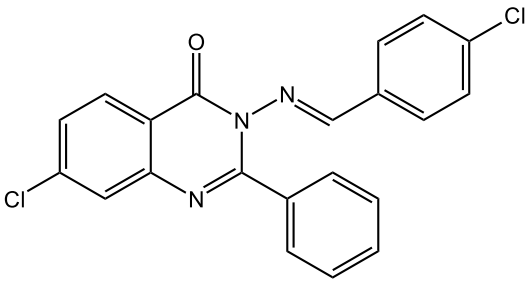
The structural chemical shows the naturally occurring cytotoxic quinazolinones. Luotonin, a Chinese herbal remedy A chemical is a cytotoxic natural alkaloid with a pentacyclic fused-quinazolinone moiety. It was first isolated from Peganum migellastrum in 1997, is used clinically as an anticancer drug, and exhibits poor human topoisomerase-I inhibitor efficacy[40].



Inhibitory activity of topoisomerase

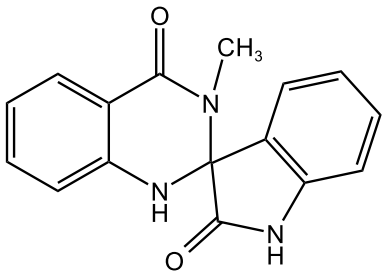
Khadka created derivatives of the 2-arylquinazolinone to test their potential as topoisomerase-targeting cytotoxic medicines that are efficient, secure, and selective (topos). However, they had no effect on topo IIa while having greater potency as topo I-inhibitors[44].

According to Malinowski, a 6-substituted quinazolinone molecule showed substantial action against the HT29 (IC50 = 50.90 µM) and HCT116 (IC50 = 46.00 µM) cell lines[41].



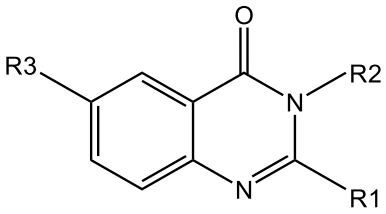
Quinazolinone's anti-inflammatory properties

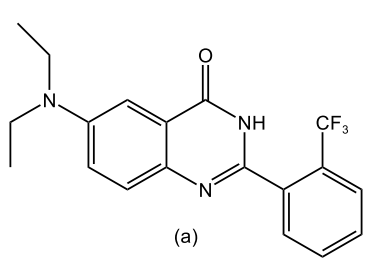
Additionally, Hemalath K created a 2,3-dihydroquinazolin-4(1H)- one that was more effective than the standard medicine diclofenac sodium at preventing denaturation of bovine serum albumin (BSA)[42].

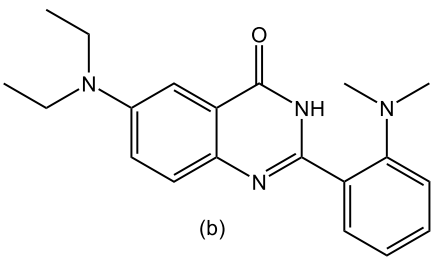


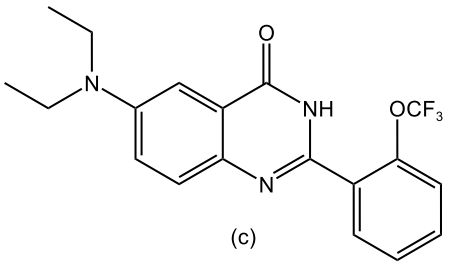
Quinazolinone's anticonvulsant properties

To prevent seizures caused by pentylenetetrazol, methaqualone is 10 times more effective than troxidone (R1 = CH3, R2 = 2,4 = dimethylphenyl, R3 = CH3). It is 1.5 times more effective than phenytoin sodium as an anticonvulsant[43].



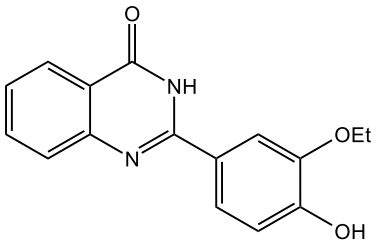






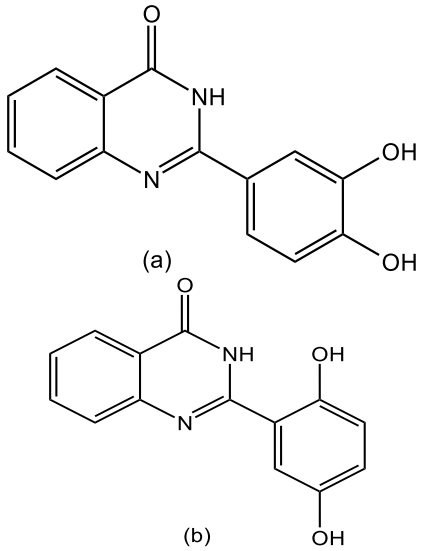
Activity as an inhibitor of Alpha-glucosidase

A quinazolinone derivative with an IC50 value of 0.3 0.01 μM that Javaid described is approximately 2800 times more powerful than the reference standard medication acarbose[45].



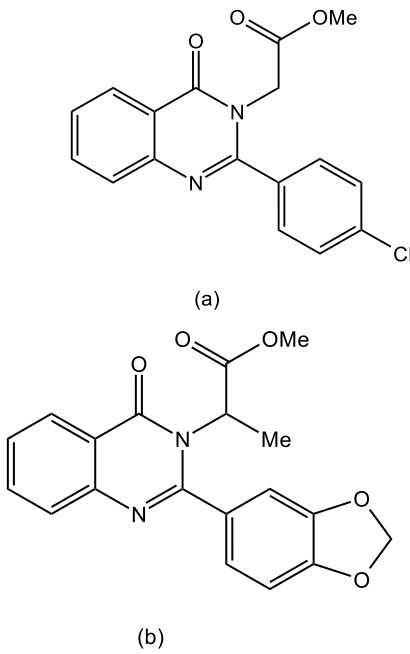
Active inhibition of thymidine synthase

Among these derivatives, compounds (a, b) were found to be the lead compounds (IC50 = 42.9, 1.0 and 59.5, 1.9 μM, respectively). Javaid and coworkers reported a series of 25 2-arylquinazolin-4(3H)-ones as strong thymidine phosphorylase inhibitors[46].



Inhibitory action of monoamine oxidase

A series of quinazolinones carrying amino acid ester or amino acid hydrazides were reported by Khattab, and they shown competitively stronger inhibitory activity towards MAO-A than MAO-B. Against-MAO-A activity[47].



CONCLUSION

The properties of quinazoline and quinazolinone derivatives with in particular activity have been examined and described in this review. The development of more effective quinazoline and quinazolinone-based activity druds may benefit from the medicinal chemist's understanding of this comprehensive and target-oriented knowledge.

Acknowledgement

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