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Review Article

A REVIEW ON BIOLOGICAL ACTIVITY OF QUINAZOLINONES

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ABSTRACT

Quinazolinones is considered as an important chemical synthesis of various physiological significance and pharmacological utility. Quinazolinones are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans. Literature studies on quinazolinones have shown that these derivatives possess a wide variety of biological activities such as anti HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, CNS depressant, antimalarial, antioxidant, antileukemic activity, antileishmanial activity. This review focused on the various biological activities of quinazolinones.

Keywords: Quinazolinones,

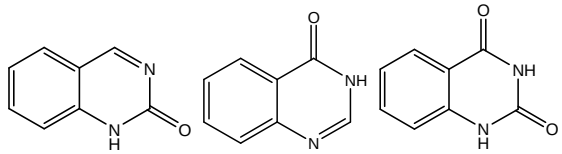
INTRODUCTION

Quinazolines are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities.[1]

Quinazolinones will be classified into the following five categories, based on the substitution patterns of the ring system.[2]

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

Depending upon the position of the keto or oxo group, these compounds may be classified into three types[3].



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, isatoicanhydride, anthranilamide and anthranilonitrile) while the 2(1H)-quinazolinone is predominantly a product of anthranilonitrile or benzamides with nitriles[3]

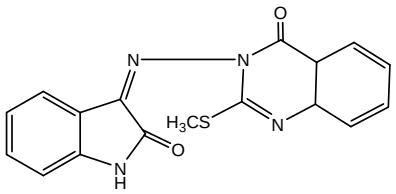
Biological importance of Quinazolinones

The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, CNS depressant, anticonvulsant, anticoccidial, anti-parkinsonism, and cancer activities. Little number of quinazolinones was reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example 3-aryl-6, 8-dichloro-2H-1, 3-benzoxazine-2, 4(3H)-diones and 3-arylquinazoline-2, 4(1H, 3H)-diones as antimycobacterial agents, quinazolinone derivatives as antitubercular agents.[3]

Compounds of both synthetic and natural origin comprising a diverse group of chemical structure have been reported as antileishmial agents. These include mostly nitrogen heterocyclic such as quinolines, purine, pyrimidine, acidine, phenothiazines, bis-benzamides, pyrazolol, pyridine, benzothiazole, imidazolines.[4]

Quinazolinones as anti HIV activity

Pandeya *et al* (1999) synthesized 3-amino-2-methyl mercapto-quinazolin-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 secondary amines and evaluated for anti-HIV activity against HIV-1 III B. in MT-4 cells.[5]

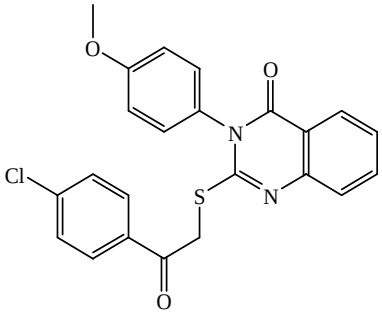


3-(2-oxoindolin-3-ylideneamino)-2-(methylthio) quinazolin-4(3H, 4aH, 8aH)-one

Fig. 1

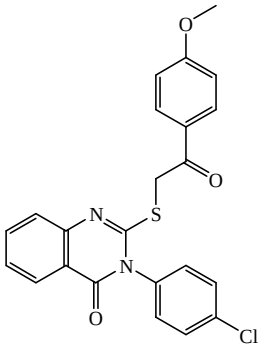
Quinazolinones as anticancer activity

Gawad *et al* (2010) synthesized some new 3-substituted quinazolin-4(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 (Fig.3), and 3-(4-chlorophenyl)-2-[2-(4- methoxyphenyl)-2-oxo-ethylthio] quinazolin 4(3H)-one (Fig.4) as broad-spectrum antitumors showing effectiveness toward numerous cell lines that belong to different tumor subpanels.[6]



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

Fig. 3

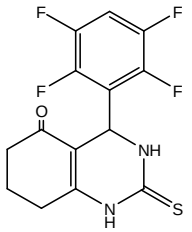


3-(4-chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio] quinazolin-4(3H)-one

Fig. 4

Quinazolinones as antifungal activity

Ghorab *et al* (2000) synthesized key intermediate octahydroquinazoline obtained in one pot synthesis by a modification of the Biginelli reaction with phenacyl bromide and bromo malono 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 pyrimidino thiazolo [2, 3-*b*] quinazolines and evaluated for their antifungal activity against *Candida albicans.*[7]

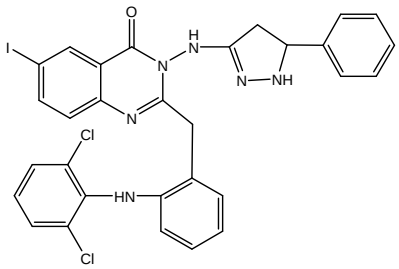


4-(2, 3, 5, 6-tetrafluorophenyl)-1, 2, 3, 4, 7, 8-hexahydro-2-thioxoquinazolin-5(6H)-one

Fig. 5

Quinazolinones as antibacterial activity

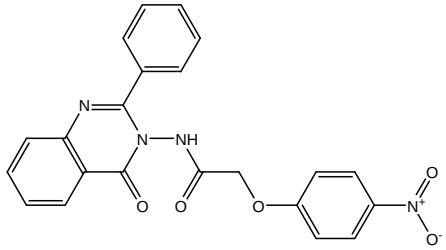
Patel *et al* (2011) synthesized a series of new 2-[2-(2,6-dichlorophenyl) amino] phenyl methyl-3-[(5-substitutedphenyl)-1,5-dihydro-[1]H-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3H) ones by the reaction of 2-[2-(2,6-dichlorophenyl)amino]phenyl methyl-3-substituted phenyl acryl amido-6- iodoquinazolin-4(3H) ones with hydrazine hydrate in the presence of glacial acetic acid. The synthesized compounds (Fig.6) were tested for their antibacterial activity *in vitro* by measuring zone of inhibition in mm by cup-plate method against different strains like two Gram positive bacteria viz. *Staphylcoccus aureus, Bacillus subtilis* and two Gram negative bacteria viz. *Escherichia coli, Certium* at two different concentration 100 µg/mL and 50 µg /mL.[8]



2-(2-(2,6-dichlorophenylamino)benzyl)-3-(4,5-dihydro-5-phenyl-1H-pyrazol-3-ylamino)-6-iodoquinazolin-4(3H)-one

Fig. 6

Kohli et al (2009) synthesized quinazolinone derivatives (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6 & DK-7) by treating 2-Chloro-N-(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 and chemical structures of the synthesized compounds were confirmed by means of their m.p., TLC, IR and [1]HNMR data and they reported that the synthesized compounds were evaluated for antibacterial activity by cup plate method by measuring inhibition zone. The compound DK-2 (Fig.7) showed more potent antibacterial activity than the standard drug ampicillin.[9]

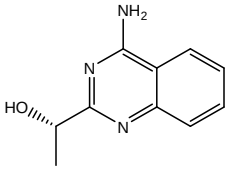


2-(4-nitrophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide

Fig. 7

Quinazolinones as animutagenic 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)-4-aminoquinazoline alcohols were investigated by using *Salmonella typhimurium* TA1535, and *Escherichia coli* WP2uvrA tester strains at 0.01, 0.1, and 1 lg/plate concentrations. (S)-4-aminoquinazoline alcohols were found to be genotoxically safe at the tested concentrations. Among the tested (S)-4-aminoquinazoline alcohols, the best antimutagenic activity was obtained with a methyl derivative at 0.1 µg/plate dose.[10]

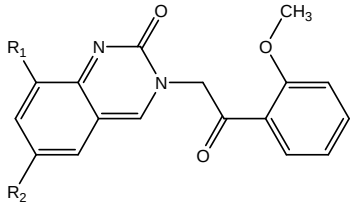


(S)-1-(4-Aminoquinazolin-2-yl) ethanol

Fig. 8

Quinazolinones as anticoccidial activity

Changwen *et al* (2010) synthesized a series of 3-(2-(2-methoxyphenyl)-2-oxoethyl) quinazolinone derivatives as anticoccidial agents by modifying the quinazoline ring of febrifugine against *Eimeria tenella* in the chicken at a dose of 9 mg/kg. 3-(2-(2-methoxyphenyl) 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.[11]

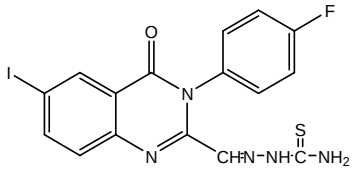


3-(2-(2-methoxyphenyl)-2-oxoethyl) quinazolinone derivetives

Fig. 9

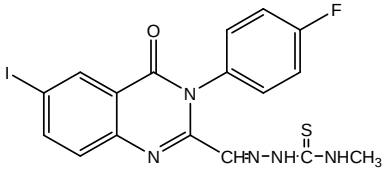
Quinazolinones as anticonvulsant activity

Aly *et al* (2010) synthesized novel 3-aryl-4(3H)-quinazolinone-2 carboxaldehydes, their corresponding Schiff's base and thio-semicarbazone derivatives and reported Compounds (Fig. 10, 11, 12) as anticonvulsants.[12]



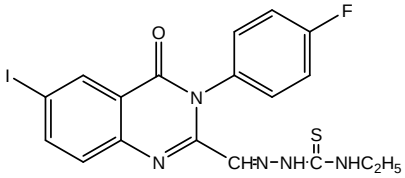
1-((3-(4-fluorophenyl)-3, 4-dihydro-6-iodo-4-oxoquinazolin-2-yl) methylene) thiosemicarbazides

Fig. 10



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

Fig. 11



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

Fig. 12

Quinazolinones as anti-inflammatory activity

Kumar *et al* (2003) synthesized various 2-(substituted phenyl methylene imino) amino acetyl methylene-3-(2'-substitutedindol-3'-yl)-halosubstituted-4(3H) quinazolinone and 2-(substituted phenyl amino methylene acetyl-4'-oxo-1'-thiazolidinyl-3-(2"-substituted indol-3"-yl) 4 (3H)-quinazolinones and reported that compound (Fig.13) exhibited good anti-inflammatory activity.[13]

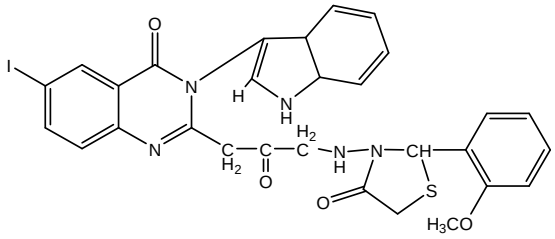
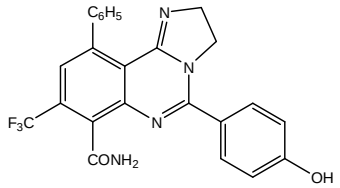


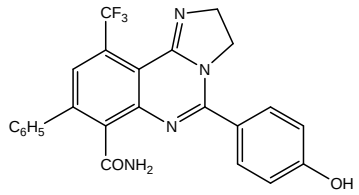
Fig. 13

Balakumar *et al* (2010) synthesized a series of novel 8/10-trifluoromethyl-substituted-imidazo [1, 2-c] quinazolines and evaluated *in vivo* (rat paw edema) for their anti-inflammatory activity and in silico (docking studies) to recognize the hypothetical binding motif with the cyclooxygenase isoenzymes (COX-1 and COX-2) employing GOLD (CCDC, 4.0.1 version) software and found that compounds (Fig.14 and Fig.15) shows good anti-inflammatory activity against standard: indomethacin.[14]



8-(trifluoromethyl)-2, 3-dihydro-5-(4-hydroxyphenyl)-10-phenylimidazo [1, 2-c] quinazoline-7-carboxamide

Fig. 14

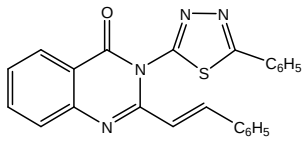


10-(trifluoromethyl)-2, 3-dihydro-5-(4-hydroxyphenyl)-8-phenylimidazo [1, 2-c] quinazoline-7-carboxamide

Fig. 15

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 (**Fig.16**) were most active against CNS depressant activity.[15]



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

Fig. 16

Kashawa *et al* (2009) synthesized several new 1-(4-substituted-phenyl)-3-(4-oxo-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 and they found that compounds 1, 2, 3, 4, 5, 6 and 7 were active in the MES screen whereas 1, 6, 7 and 8 were found to be active in the scPTZ screen.[16]

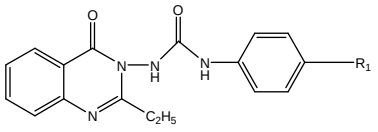


Fig. 17

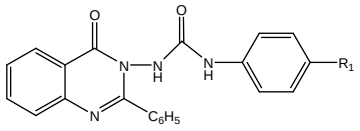
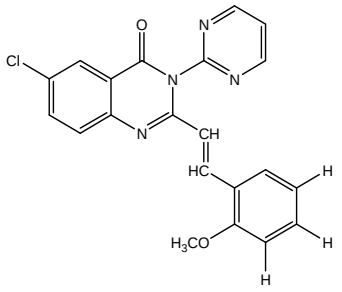


Fig. 18

1. -H
2. $-NO_2$
3. $p(CH_3)$
4. $-OCH_2-CH_3$
5. -Cl
6. -Br
7. -I
8. $-OCH_3$

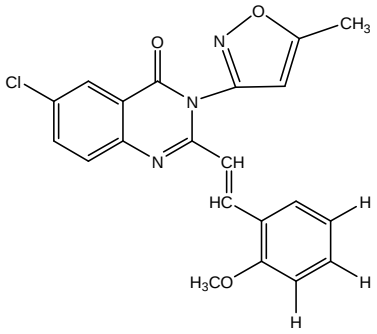
Quinazolinones as antileukemic activity

Raffa *et al* (2004) synthesized 3-(3-Methylisoxazol-5-yl) and 3-(pyrimidin-2-yl)-2 styrylquinazolin-4(3H)-ones (Fig. 19 and 20) by refluxing in acetic acid the corresponding 2-methylquinazolinones with the benzoic aldehyde for 12 h and tested for their *in vitro* antileukemic 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.[17]



2-(2-methoxystyryl)-6-chloro-3-(pyrimidin-2-yl) quinazolin-4(3H)-one

Fig. 19

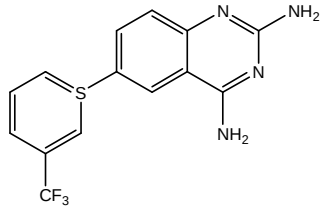


2-(2-methoxystyryl)-6-chloro-3-(5-methylisoxazol-3-yl) quinazolin-4(3H)-one

Fig. 20

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 hydrazino and hydroxyamino moieties and they found that such changes reduce markedly the antimalarial properties of this series. The compound Fig.21 was tested against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route.[18]

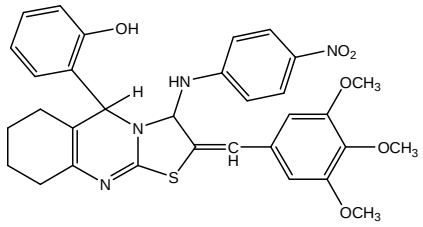


6-(3-(trifluoromethyl) thiopyran-1-yl) quinazoline-2, 4-diamine

Fig. 21

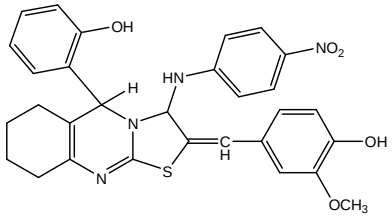
Quinazolinones as antioxidant activity

Selvam *et al* (2010) synthesized a series of novel thiazolo quinazoline derivatives by condensation of different aromatic aldehydes with 4-nitro aniline and chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, mass spectroscopy and elemental analyses and screened for anti-oxidant activity by DPPH radical assay, nitric oxide scavenging activity and Hydrogen Peroxide scavenging activity and reported that synthesized compounds (Fig.22, 23 and 24) was found to be the most potent anti-oxidant activity.[19]



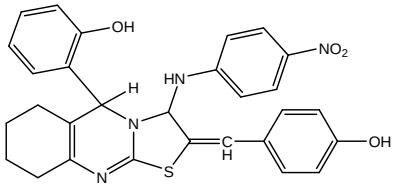
2-(2-(3,4,5-trimethoxybenzylidene)-3-(4-nitrophenylamino)-3, 5, 6, 7, 8, 9-hexahydro-2H-thiazolo[2,3-b]quinazolin-5-yl)phenol

Fig.22



2-(2-(4-hydroxy-3-methoxybenzylidene)-3-(4-nitrophenylamino)-3, 5, 6, 7, 8, 9-hexahydro-2H-thiazolo [2, 3-b] quinazolin-5-yl) phenol

Fig. 23

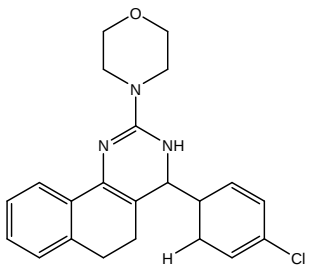


2-(2-(4-hydroxybenzylidene)-3-(4-nitrophenylamino)-3, 5, 6, 7, 8, 9-hexahydro-2H-thiazolo [2, 3-b] quinazolin-5-yl) phenol

Fig. 24

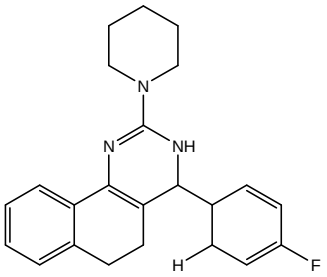
Quinazolinones as antileishmanial activity

Agarwal *et al* (2009) synthesized 4-(Substituted-benzylidine)-2-substituted-5, 6 dihydrobenzo[h]quinazoline and 4-(substitutedbenzylidine) - 2-substituted-3, 4, 5, 6 tetrahydrobenzo[h]quinazoline from 2-(substituted-benzylidine) tetralone-1 and several substituted guanidine sulfates and evaluated for their in vitro antileishmanial activity and they reported that compounds (Fig.25, 26 and 27) show promising antileishmanial activity against Leishmania donovani.[20]



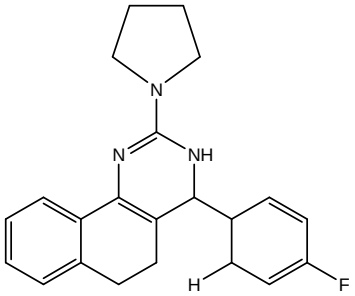
4-(4-chlorocyclohexa-2,4-dienyl)-3,4,5,6-tetrahydro-2-morpholinobenzo[h]quinazoline

Fig. 25



4-(4-fluorocyclohexa-2,4-dienyl)-3,4,5,6-tetrahydro-2-(piperidin-1-yl)benzo[h]quinazoline

Fig. 26



4-(4-fluorocyclohexa-2,4-dienyl)-3,4,5,6-tetrahydro-2-(pyrrolidin-1-yl)benzo[h]quinazoline

Fig. 27

Quinazolinones as analgesic activity

Hemlatha *et al* (2011) synthesized a series of some novel 2, 3-disubstituted quinazolinone derivatives by condensing 2-methyl/ 2-phenyl/6-bromo-2-methyl/6-bromo-2-phenyl/6, 8-dibromo-2-methyl/ 6, 8-dibromo-2-phenyl benzoxazines with compounds containing amino group were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data and evaluated for their analgesic activity and they reported that compound (Fig.28) show promising analgesic activity compared to standard drug Diclofenac sodium.[21]

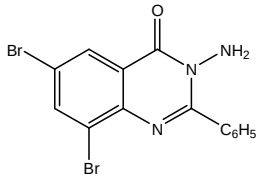


Fig. 28

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