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Biological value of the heterocyclic compound quinazoline

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Abstract

The present review reveals the various biological activities of the heterocyclic compound, indazole including anti-inflammatory, antimicrobial, antitubercular, anticancer, antidepressant, anticonvulsant, antihistaminic, antihypertensive and other activities. From the observed biological activities of the heterocyclic moiety, indazole, we conclude that medicinal properties of quinazolines have to be explored in near future for treatment of various pathological conditions.

Keywords: quinazoline, anticonvulsant, antimicrobial, anticancer.

Introduction

Quinazolines are of wide interest because of their diverse biological and clinical applications. This created interest in researchers who have synthesized variety of quinazoline derivatives and screened them for their various biological activities. In the present study, we have made an attempt to collect biological properties of quinazoline derivatives. Various quinazoline derivatives have been synthesized and their anti-inflammatory and analgesic activities have been investigated. A variety of novel 3-(4-methoxyphenyl)-2-substituted-aminoquinazolin-4-(3*H*)-ones **(1-7)** were synthesized by reacting the amino group of 2-hydrazino-3-(4-methoxyphenyl)-quinazolin-4-(3*H*)-one with a variety of alkyl and aryl ketones. These were investigated for analgesic, anti-inflammatory and ulcerogenic index activities. The compounds 2-(1-methyl propylidene) hydrazino-3-(4-methoxyphenyl) quinazolin-4-(3*H*)-one **(1)**, 2-(1-ethyl propylidene) hydrazino-3-(4-methoxyphenyl) quinazolin-4-(3*H*)-one **(2)** and 2-(1-methylbutylidene) hydrazino-3-(4-methoxy phenyl) quinazolin-4-(3*H*)-one **(3)** showed moderately more potent analgesic activity, while the compound 2 showed moderately more potent anti-inflammatory activity than the reference standard diclofenac sodium (Alagarsamy and Murugesan 2007a).

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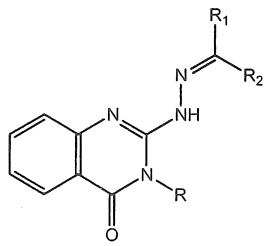
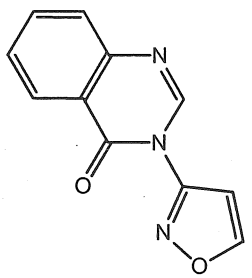


(1) R = *p*-$OCH_3C_6H_4$ $R_1 = CH_3$ $R_2 = C_2H_5$
(2) R = *p*-$OCH_3C_6H_4$ $R_1 = C_2H_5$ $R_2 = C_2H_5$
(3) R = *p*-$OCH_3C_6H_4$ $R_1 = CH_3$ $R_2 = CH_2CH_2CH_3$
(4) R = C_6H_5 $R_1 = CH_3$ $R_2 = C_2H_5$
(5) R = C_6H_5 $R_1 = C_2H_5$ $R_2 = C_2H_5$
(6) R = C_6H_5 $R_1 = CH_3$ $R_2 = CH_2CH_2CH_3$
(7) R = C_6H_4N $R_1 = CH_3$ $R_2 = CH_2CH_2CH_3$

Similarly, compounds, 2-(N'-2-butylidenehydrazino)-3-phenyl-3*H*-quinazolin-4-one (54), 2-(N'-3-pentylidenehydrazino)-3-phenyl-3*H*-quinazolin-4-one **(5),** 2-(N'-2-pentylidene-hydrazino)-3-phenyl-3*H*-quinazolin-4-one **(6)** and 2-(1-methyl butylidene)hydrazino-3-(2-pyridyl)quinazolin-4-(3*H*)-one **(7)** have been reported to have better analgesic, anti-inflammatory potential than the Diclofenac sodium (Alagarsamy et al. 2007b and 2008).

Daidone et al. (1999), *s*ynthesized several new 3-(isoxazol-3-yl)-quinazolin-4-(3*H*)-one **(8)** derivatives and tested them for their analgesic and anti-inflammatory activities, as well as for their acute toxicity and ulcerogenic effect. Few compounds were as active as phenylbutatzone in the writhing and acetic acid peritonitis tests and they possessed very low ulcerogenic effect.



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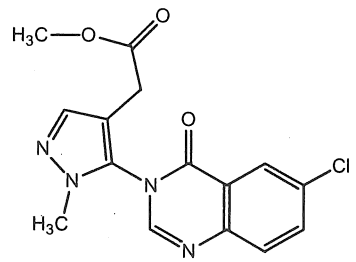

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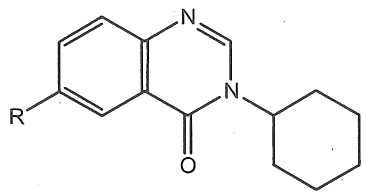
Several new ethyl-1-methyl-5-(substituted 3,4-dihydro-4-oxoquinazolin-3-yl)-1*H*-pyrazole-4-acetates substituted at 2 and, alternatively at 6, 7 or 8 positions of the quinazolinone nucleus were synthesized and screened for their analgesic and anti-inflammatory activities, acute toxicity and ulcerogenic effect. Compound, **(9)** showed potent anti-inflammatory and analgesic activity when compared to Indomethacin. It was seen that the substitution in the benzene moiety of the quinazolinone ring did not show any advantage for the analgesic activity, whereas it improved in some cases the anti-inflammatory activity. Some compounds showed appreciable anti-inflammatory activity and, at the same time, very low ulcerogenic index (Maggio et al. 2001)

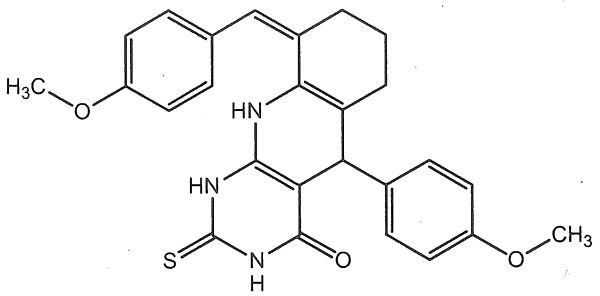
Santagati et al. (1999) synthesized and evaluated the anti-inflammatory activity of a series of 4-quinazolinone derivatives. The pharmacological results revealed that the synthesized derivatives

exhibited a significant anti-inflammatory effect in an experimental ocular inflammation model and significantly lower protein concentration and polymorphonuclear leukocytes number compared to the control group. All the tested compounds lowered the prostaglandin E_2 (PGE_2) production than reference drug Tolmetin. Out of these 3-cyclohexyl-6-chloro-quinazolin-4-(3*H*)-one **(10)** and 3-cyclohexyl-quinazolin-4-(3*H*)-one **(11)** were the most active compounds.



10) R = Cl
11) R = H

Baraka reported the synthesis of novel 2,4-(1*H*, 3*H*)-quinazolinedione derivatives as potential analgesic and anti-inflammatory agents (Baraka 2001). Another category quinazolinones were synthesized and tested for their anti-inflammatory activity. The compound, 5-(4-methoxy phenyl)-9-(4-methoxyphenylmethylene)-5,10-dihydro-2-thioxo-6,7,8,9-tetrahydro pyrimido-[4,5-b]-quinazolin-4-one **(12)** exhibited a potent anti-inflammatory activity in carrageenan-induced paw edema test in rats (El-Gazzar et al. 2009).



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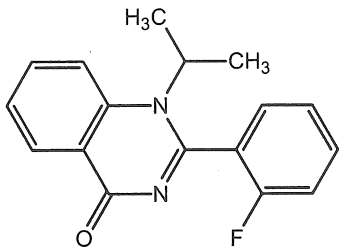
A number of new 4-(1*H*)-quinazolinones were synthesized and evaluated in the carrageenan-induced paw edema test. Structure activity relationship studies were carried out which suggested that 2-isopropyl-1-phenyl, 2-cyclopropyl-1-phenyl and 1-isopropyl-2-phenyl-4-(1*H*)-quinazolinones afford optimal potency and the presence of a halogen atom is preferred for activity. The best result taking into account better efficacy was displayed by 1-isopropyl-(2-fluorophenyl)-4-(1*H*)-quinazolinone **(13)** (Ozaki et al. 1985).



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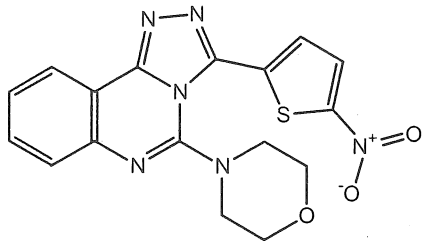
Quinazolines as antimicrobial agents

The antimicrobial activity of some substituted triazoloquinazolines has been studied and it was noted that the broadest antimicrobial activity resides with 5-morpholin-4-yl-3-(5-nitrothien-2-yl)-[1,2,4]-triazolo-[4,3-*c*]-quinazoline **(14)** in concentration of 10 mg/L for *B. subtilis*, 50 mg/L for *S. aureus* and 100 mg/L for *C. tropicalis*. The highest tested concentration of derivative caused 83% growth inhibition of *R. nigricans* (Jantova et al. 2005).



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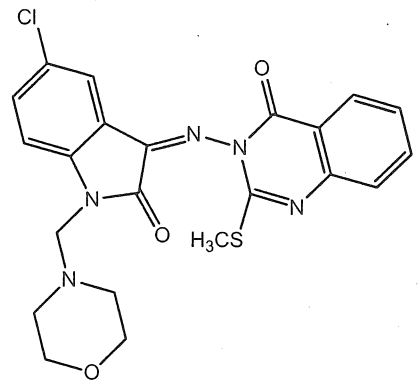
Bekhit et al. (2001) their investigation on antimicrobial evaluation of chalcone and syndrome derivatives of 4-(3*H*)-quinazolinone found that the nitroso derivative exhibited interesting antimicrobial activities against *Escherichia, Staphylococcus aureus*, and *Candida albicans*. In the study of synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4-(3*H*)-ones, Pandeya et al. (1999) reported that 5-chloro-3-(3',4'-dihydro-2'-methylmercapto-4'-oxoquinazolin-3'-yl)-l-morpholino methyl imino isatin **(15)** was the most active antimicrobial agent.



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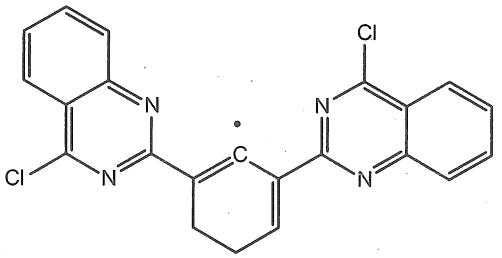
Shiba et al. (1997) studied the antimicrobial potential of bis-[4-chloroquinazolin-2-yl]*m*-phenylene **(16)** against different microorganisms. A series of new copper (II) complexes with 2-methyl-3-amino-(3*H*)-quinazolin-4-one (MAQ) and various anions (Cl^-, Br^-, ClO_4^-, NO_3^-, SCN^- and SO_4^{2-}), which had both antibacterial and antifungal activities against the organisms were tested. Both the free ligand and its Cu (II) complexes were found to be active and in most cases, the complexes were found to be more active than the free ligand, but in some cases, an equal activity was displayed (Ramadan 1997).



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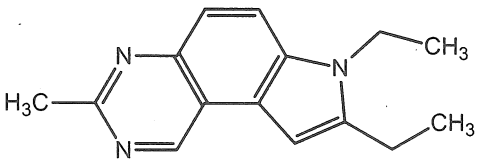
Kuyper et al. (1996) studied a series of 7,8-diethyl-3-methyl-7*H*-pyrrolo-[3,2-f]-quinazoline **(17)** which were prepared as inhibitors of bacterial and fungal dihydrofolate reductase (DHFR). The compounds displayed *in vivo* activity against *Pneumocystis carinii* and *Candida albicans*.



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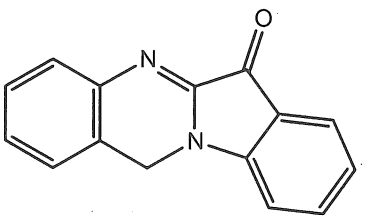
Baiocchi et al. (1993) reported antimicrobial potential of a series of indolo-[2,1-b]-quinazolin-6-(12*H*)-one **(18)**. El-Zohry et al. (1992) in their study on synthesis and antibacterial activity of certain quinoline and quinazoline derivatives containing sulfide and sulfone moieties reported that some of these compounds possess potent antibacterial activity in comparison with Tetracycline.



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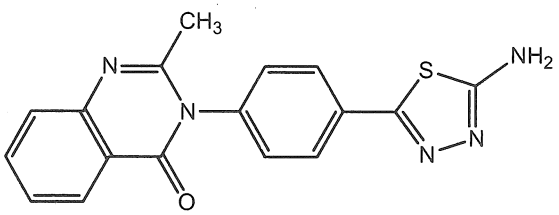

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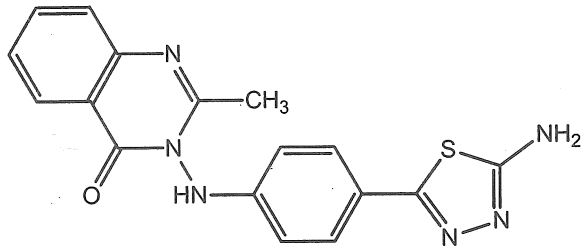
Khalil and Habib (1987) synthesized various quinazolinone derivatives, 3-[4-(2-amino-1,3,4-thiadiazol-5-yl)-phenyl]-2-methyl-4-(3*H*)-quinazolinone **(19),** 3-[4-(2- amino-1,3,4-thiadiazol-5-yl)anilino]-2-methyl-4-(3*H*)-quinazolinone **(20)** and 3-[(2-methyl amino-1,3,4-thiadiazol-5-yl)-methyl]-2-methyl-4-(3*H*)-quinazolinone **(21).** These derivatives were found to possess antimicrobial activity.



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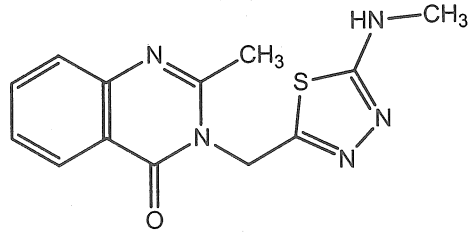
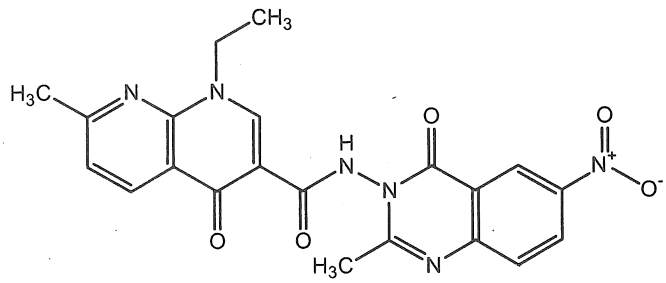


(21)

A series of new nalidixic acid derivatives having quinazolines moiety were synthesized and studied for their *in vitro* antimicrobial activity by Grover and Kini (2006).

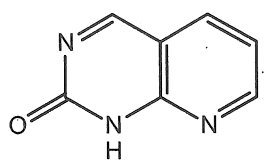
The derivative, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid-(2-methyl-6-nitro-4-oxo-4*H*-quinazolin-3-yl)amide **(22)** showed marked inhibitory activity against enteric pathogen *Aeromonas hydrophila,* a causative agent of diarrhoea,



(22)

respiratory pathogen *Streptococcus pyogenes, Candida* colonies and *Candida albicans,* when compared to standard Ampicillin and Fluconazole respectively. The derivatives showed decreased inhibitory activity against *Proteus vulgaris* and no significant inhibitory activity against *Coagulase negative Staphylococcus* (Grover and Kini 2006).

Hamad and Azab (2001) reported the antimicrobial activity of 8-azaquinazolone **(23)** and 2-thiono-[1*H*]-5-spirocyclohexyl imidazo-[4,3-b]-quinazolone derivatives against different pathogenic microorganisms.



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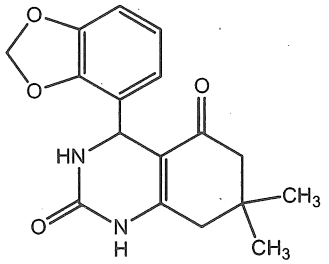
A series of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-ones were synthesized and screened for their *in vitro* antibacterial against standard strains of *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Compound, 4-benzo-[1,3]-dioxol-4-yl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione **(24)**, showed potent antibacterial activity in comparison with Norfloxacin (Kidwai et al. 2005).



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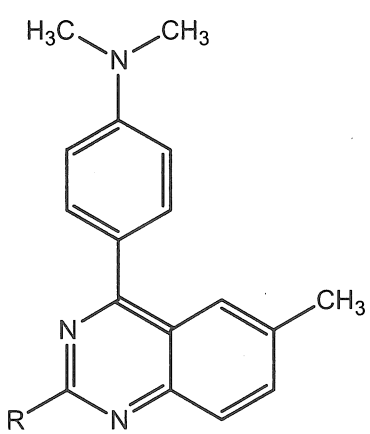
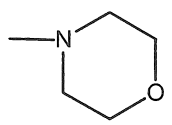
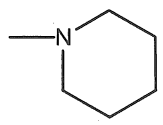
A novel series of 6-methyl-2-aryl/secondary amino-4-aryl-quinazolines were prepared by the microwave condensation reactions of N-imidoyl iminophosphorane with aldehydes (Bedi et al. 2004). These were evaluated for their antibacterial activity against a panel of microorganisms. The compound, dimethyl-[4-(6-methyl-2-morpholin-4-yl-quinazolin-4-yl) phenyl]-amine **(25)**, was superior in action against *S. aureus, E. faecalis* and *K. pneumoniae* over the Ciprofloxacin and dimethyl-[4-(6-methyl-2-piperidin-1-yl-quinazolin-4-yl) phenyl]-amine **(26)** was found to possess the maximum activity against *K. pneumoniae*. It also indicated that compound, **(27)** showed maximum activity against *S. sonnei* and exhibited significant activity against *E. faecalis* and *P. aeruginosa* as compared to Ciprofloxacin (Sharma and Kaur 1989, Bedi et al. 2004).



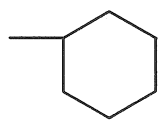
(25) R =



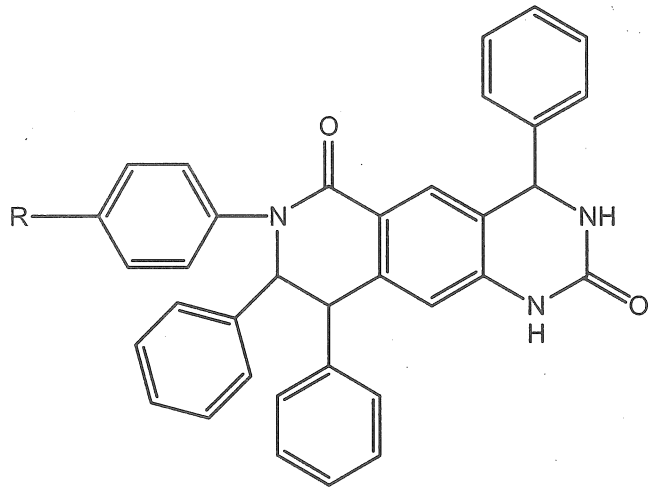
(26) R =



(27) R =



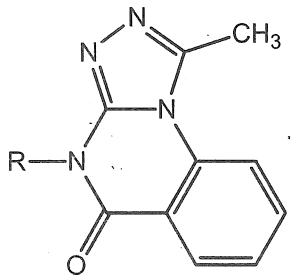
Tiwari et al. (2006) reported simple, high yielding synthesis and *in vitro* study of novel pyrido-quinazolone analogues as anti-fungal and antibacterial agents. The compounds, 4,6,7-triphenyl-8-(1-vinyl propenyl)-4,6,7,8-tetrahydro-1*H*,3*H*-1,3,6-triaza anthracene-2,5-dione **(28)** and 6-(4-chlorophenyl)-4,7,8-triphenyl-4,6,7,8-tetrahydro-1*H*,3*H*-1,3,6-triazaanthracene-2,5-dione **(29)**, showed good antimicrobial activity against *Staphylococcus aureus, Aspergillus flavus* and *Aspergillus niger*.



(28) R = H
(29) R = Cl

Quinazolines as antihistaminic agents

Alagarsamy et al. (2006a) in their search for novel 1-alkyl-4-(4-substituted aryl/heteroaryl)-1,2,4-triazolo-[4,3-*a*]-quinazolin-5-(4*H*)-ones as a new class of H_1-antihistaminic agents, noted that compound 1-methyl-4-(2-pyridyl)-1,2,4-triazolo-[4,3-*a*]-quinazolin-5-(4*H*)-one **(30)** was more potent (71.43% protection) when compared to the reference standard, Chlorpheniramine maleate (71% protection) and also showed negligible sedation (8%) when compared to Chlorpheniramine maleate (25 %).



(30) R = C_6H_5N
(31) R = *p*-ClC_6H_4
(32) R = *p*-$OCH_3C_6H_4$
(33) R = $CH_2C_6H_5$
(34) R = C_6H_5CH

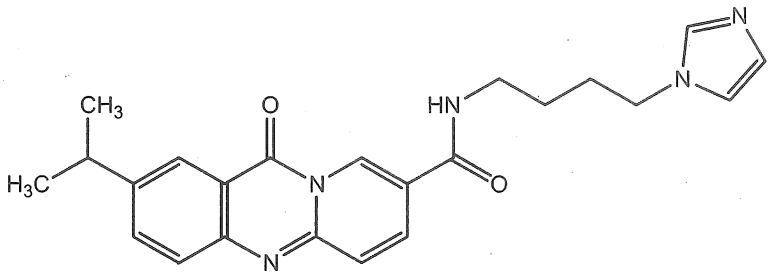
Further, in their study of pharmacological investigation of novel 1-substituted-4-(4-substituted phenyl)-4*H*-[1,2,4]-triazolo-[4,3-*a*]-quinazolin-5-ones as anti-histaminic agents, the compound 1-methyl-4-(4-chlorophenyl)-4*H*-[1,2,4]-triazolo-[4,3-*a*]-quinazolin-5-one **(31)** was more potent (72.71% protection), and 1-methyl-4-(4-methoxy phenyl)-4*H*-[1,2,4]-triazolo-[4,3-*a*]-quinazolin-5-one **(32)** was equipotent (71% protection), when compared with the reference standard, Chlorpheniramine maleate (71% protection) (Alagarsamy et al. 2006b).

A series of novel 1-substituted-4-benzyl-4*H*-[1,2,4]-triazolo-[4,3-*a*]- quinazolin-5-ones were synthesized by the cyclization of 2-hydrazino-3-benzyl-3*H*-quinazolin-4-one with various one carbon donors. When tested for their *in vivo* H_1-antihistaminic activity on guinea pigs, all the test compounds protected the animals from histamine induced bronchospasm significantly.

The compound 1-methyl-4-benzyl-4*H*-[1,2,4]-triazolo[4,3-*a*]-quinazolin-5-one (**33**) emerged as the most active compound of the series and it is more potent (76% protection) when compared to the reference standard Chlorpheniramine maleate (71 protection %) (Alagarsamy et al 2007b).

Another derivative, 1-methyl-4-phenyl-1,2,4-triazolo-[4,3-*a*]-quinazolin-5-(4*H*)-one (**34**) was found to be equipotent with the reference standard Chlorpheniramine maleate and showed negligible sedation (Alagarsamy et al. 2005).

Tilley et al. (1987) synthesized a series of N-(heterocyclic alkyl)-pyrido-[2,1-b]-quinazoline-8-carboxamides and these were studied for their antiallergic activity. It was noted that the compound, 2-(1-methyl ethyl)-N-(1*H*-imidazol-1-ylbutyl)-11-oxo-11*H*-pyrido-[2,1-*b*]-quinazoline-8-carboxamide (**35**) was the most effective one.



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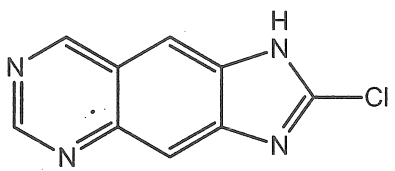
Quinazolines as anticancer agents

Interest in quinazoline chemistry has further increased because of their association with anticancer property. Tiwari *et al.,* undertook the synthesis of quinazolone derivatives that have some resemblance to folic acid. These compounds were mainly evaluated for inhibiton of enzyme dihydrofolate reductase, which they inhibited in human leukaemia cells.

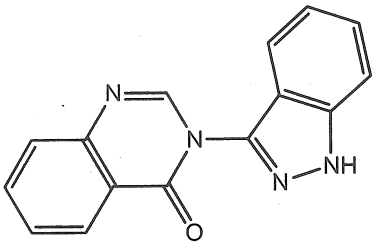
They synthesized various pyrido-quinazolone analogues as anticancer agents. Radiolabeling and biodistribution studies of these compounds have confirmed the respective receptor binding and showed promising results for future application. The compounds, (**28**) and (**29**), exhibited positive cytotoxic activity (Tiwari et al. 2006).

The anti-tumor activity of 2-chloro-1*H*-imidazo[4,5-*H*]-quinazoline (**36**) was investigated *in vitro* and *in vivo* with a human tumour model by Dupuy *et al.* After LD_{50} determination using Swiss mice, they determined the *in vivo* activity with A2780 ovarian carcinoma using xenografted Swiss nude mice, which indicated that the compound, **36** intercalates into DNA and thereby it has proved to be an effective new anti-tumor agent (Dupuy et al. 2002).

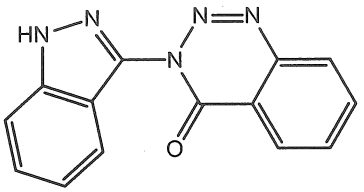


(36)

Raffa et al. (1999) reported synthesis and antiproliferative activity of novel 3-(indazol-3-yl)-quinazolin-4-(3*H*)-one (**37**) and 3-(indazol-3-yl)-benzotriazin-4-(3*H*)-one (**38**) derivatives.

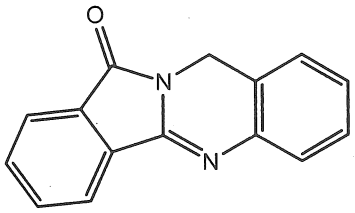


(**37**)

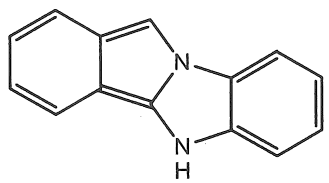


(**38**)

The synthesis and pharmacological activity of isoindolo-[1,2-*b*]-quinazolin-12-(10*H*)-one (**39**) and isoindolo-[2,1-*a*]-benzimidazole (**40**) related to Batracylin has been reported. They found that the acute toxicity of Batracyclin has been associated with the formation of its N-acetyl metabolite which is a potent inducer of unscheduled DNA synthesis in rat hepatocytes. The desamino derivative and the 8-aza analog of Batracylin retained the ability to inhibit topoisomerase II but did not induce unscheduled DNA synthesis. While less active than Batracylin, these analogs were cytotoxic to CCRF CEM leukemia cells (*Meggalla* et al. 1994).

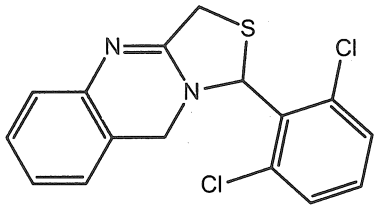


(**39**)



(**40**)

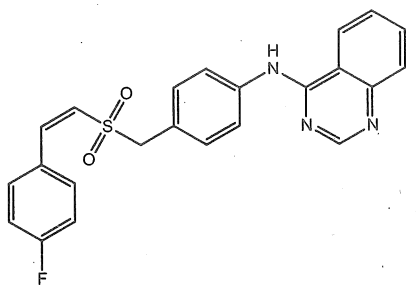
Grasso et al. (2000) synthesized a series of 1*H*, 3*H*-thiazolo-[4,3-*b*]-quinazolines and evaluated for their *in vitro* antitumour activity against ca. 60 human tumour cell lines. Only 1-(2,6-dichlorophenyl)-1*H*, 3*H*-thiazolo-[4,3-*b*]-quinazoline (**41**) possessed significant growth inhibitory activity on 22 cell lines at a concentration of 10^{-5} M.



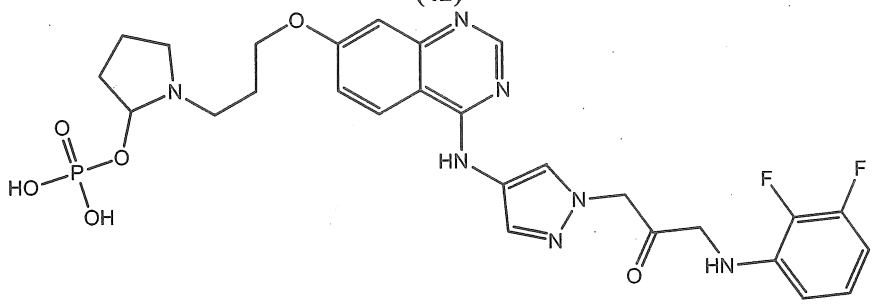
(**41**)

Another series, [4-(2-phenylethenesulfonylmethyl)phenyl]quinazolin-4-yl-amines was prepared and tested for its *in vitro* cytotoxic activity against a panel of human cancer cell lines. Among the synthesized compounds, {4-[2-(4-fluoro phenyl) ethenesulfonylmethyl]-phenyl}quinazolin-4-yl-amine (**42**), exhibited promising activity when tested for its *in vivo* efficacy in the HT-29 human colon adeno carcinoma xenograft model (Sharma et al. 2004). Foote et al. (2008) studied a new series of aminopyrazole-substituted quinazoline as aurora kinase inhibitors which led to the discovery of phosphoric acid mono-{1-[3-(4-{1-[3-(2,3-difluoro phenylamino)-2-oxopropyl]-1H-pyrazol-4-ylamino}quinazolin-7-yloxy)-propyl]pyrrolidin-2-yl}ester (43), which, in pre-

clinical *in vivo* models has shown activity at lower doses compared with other series synthesized.



(42)

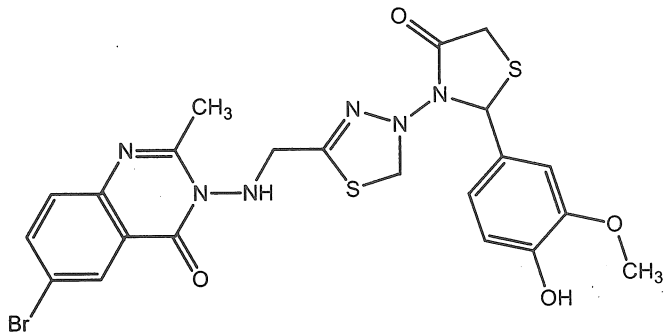


(43)

Quinazolines as anticonvulsant agents

Quinazolinone derivatives prepared by substituting different heterocyclic moieties at 3rd position of this heterocyclic system have been reported to exhibit anticonvulsant property. Several of these 3-heterocyclic substituted quinazolinones show a high level of protection against maximal electroshock (MES) induced convulsions in animal models. Incorporating thiadiazole moieties in 3rd position of quinazolinone nucleus might yield more potent anticonvulsant compound, as substituted moieties are themselves anticonvulsant and substitution at 3rd position further results in protection against convulsions.

A series of 3-({4-[2-(alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazo-l-2-yl}methyl amino)-2-methyl-6-monosubstitutedquinazolin-4-(3*H*)-ones were synthesized and screened for their anticonvulsant activity which was compared with the standard drugs, Phenytoin sodium, Lamotrigine and Sodium valproate.

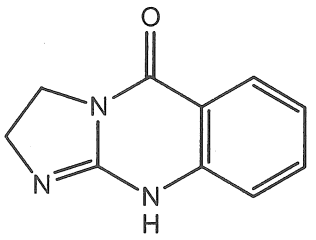


(44)

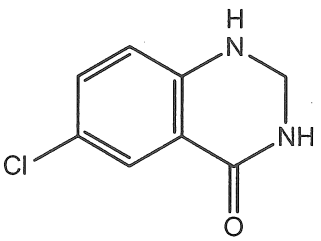
Out of the 30 compounds tested, the most active compound was 3-({4-[2-(*m*-methoxy-*p*-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-bromoquinazolin-4-(3*H*)-one **(44)** (Archana et al. 2002). El-Feky and Abd el-Samii (1991) have reported the anticonvulsant potential of some quinazolone-thiosemicarbazone derivatives.

Miscellaneous activities of Quinazoline

The study on synthesis and biological evaluation of 10-substituted 2,3-dihydroimidazo-[2,1-*b*]-quinazolin-5-(10*H*)-one **(45)**, a new class of bronchodilators found that these group of compounds produced bronchodilator effects without having central nervous system or cardiovascular side effects (Hardtmann et al. 1975).



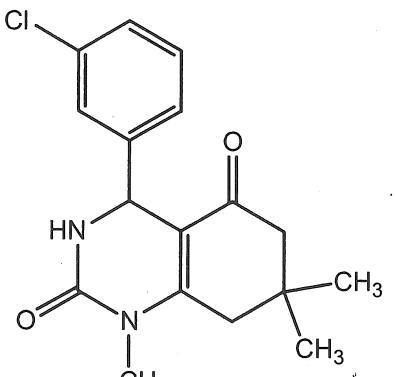
(45)



(46)

A series of 6-chloro-2,3-dihydro-4-(1*H*)-quinazolinone derivatives **(46)** as antiemetic and gastrointestinal motility enhancing agents have been reported (Baldazzi et al. 1996).

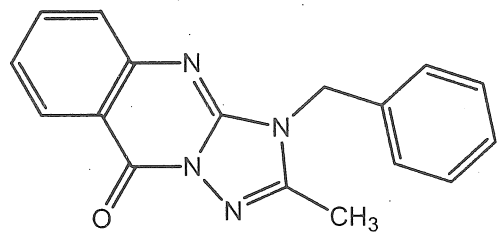
Quinazoline derivatives have also been reported to possess calcium antagonist activity. A series of 4-aryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones, 4-aryl-7,7-dimethyl and 1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydro quinazoline-2,5-diones were synthesized by condensing urea or N-methylurea with 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione and appropriate aromatic aldehydes according to the Biginelli reaction (Sarac et al. 1998).



(47)

The synthesized compounds were tested for their *in vitro* calcium antagonist activity on isolated rat ileum. Compound, 4-(3-chlorophenyl)-1,7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione **(47)** was the most active compared with standard Nicardipine (Yarim et al. 2003).

Alagarsamy and Pathak (2007d) synthesized a novel series of 3-benzyl-2-substituted-3*H*-[1,2,4]-triazolo-[5,1-*b*]-quinazolin-9-ones and evaluated them for their *in vivo* antihypertensive activity using spontaneously hypertensive rats (SHR).



(48)

They found that all the test compounds exhibited significant antihypertensive activity, especially 3-benzyl-2-methyl-3*H*-[1,2,4]-triazolo-[5,1-*b*]-quinazolin-9-one (48) exhibited anti-hypertensive activity more than the reference standard Prazocin (Alagarsamy and Pathak 2007d).

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