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Review Article **OPEN ACCESS**

Recent Advances in Quinazoline Derivatives: Synthesis, Biological Activities, and Therapeutic Potential

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A B S T R A C T

Among heterocyclic compounds, quinoline is an advantage that appears as a significant assembly motive for the development of new drug entities. Quinoline and its derivatives tested with diverse biological activity constitute an important class of compounds for new drug development. Therefore, many scientific communities have developed these compounds as intent structure and evaluated their biological activities. The present, review provides brief natural sources of quinoline and including a new extent of quinoline-based marketed drugs. This review also confers information about the biological activities of quinoline derivatives such as antibacterial, antifungal, antimycobacterial, antiviral, anti-protozoal, antimalarial, anticancer, cardiovascular, CNS effects, antioxidant, anticonvulsant, analgesic, anti-inflammatory, anthelmintic and miscellaneous activities.

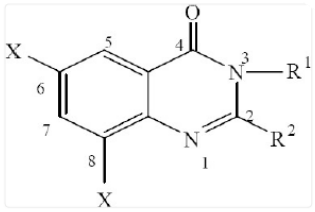
Keywords: heterocyclic compound, quinazoline.

INTRODUCTION

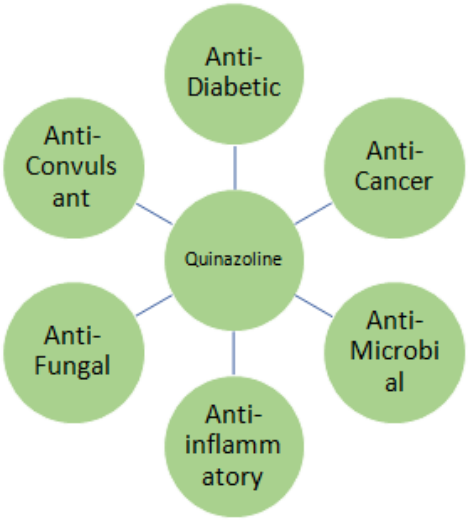
Heterocycles containing nitrogen atom are an important category of the favourable structures in the field of medicinal chemistry [1]. quinazoline hasbeen taken for this review, as quinazoline has a very broad spectrum of pharmacological activitieswith minimum side effects.[2]S

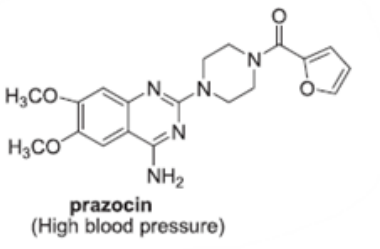
Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [3-6], anti-inflammation [7,8], anti-bacterial [8-10], analgesia [7,9], anti-virus [11], anti-cytotoxin [12], anti-spasm [9,13], anti-tuberculosis [14], anti-oxidation [15], antimalarial [16], anti-hypertension [17], anti-obesity [18], anti-psychotic [19], anti-diabetes [20], etc.

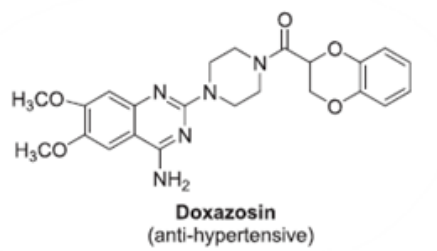
Structure activity relationship studies of quinazolinone derivatives in various literatures have revealed that substitution at positions 2 and 3, existence of halogen atom at 6 and 8 positions and substitution (mainly amine or substituted amine) at 4th position of the quinazolinone ring can improve their antimicrobial activities.[21],[22],[23],[24]

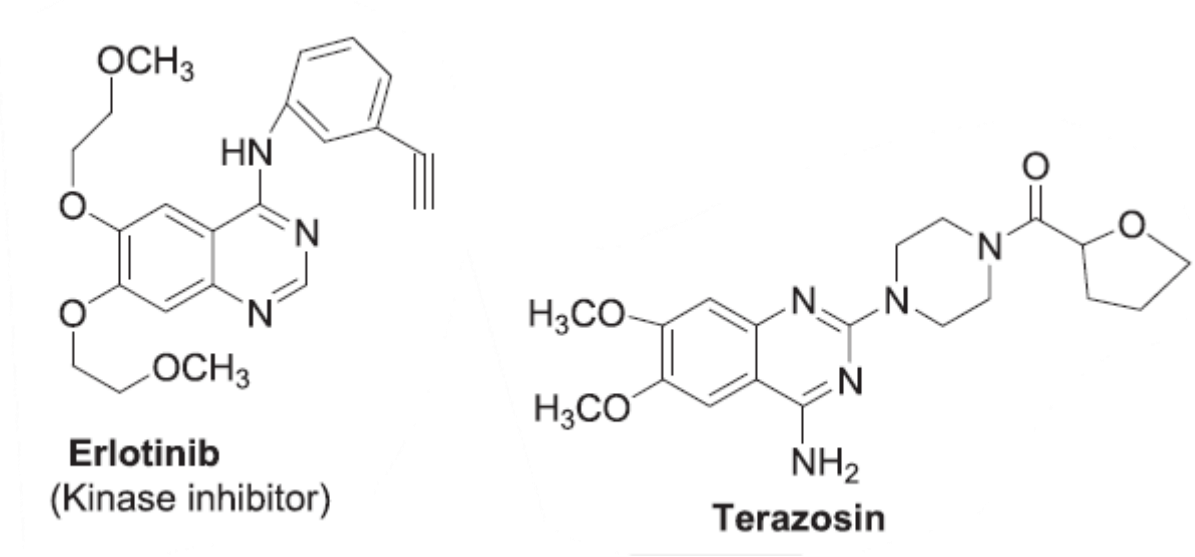


Several quinazoline derivatives are approved drugs, such as Terazosin hydrochloride, Prazosin hydrochloride and Doxazosin mesylate [25] (Fig. 1). Moreover, due to the promising therapeutic efficacy against human cancers, various quinazoline derivatives like Erlotinib [26]



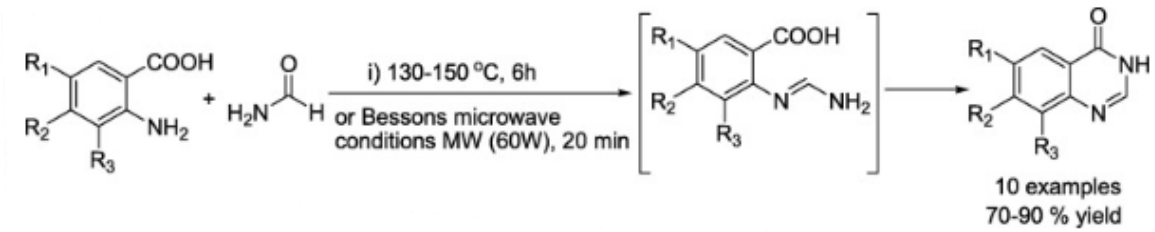




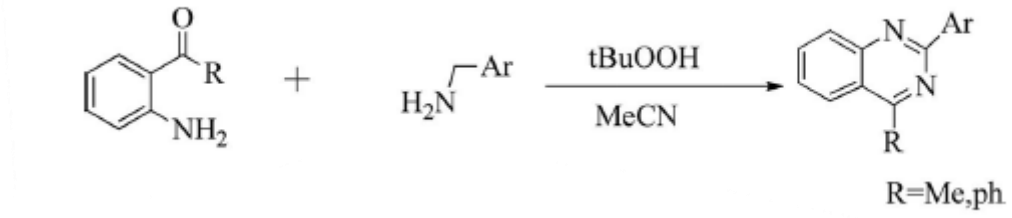


Approved marketed drugs with quinazoline structure.

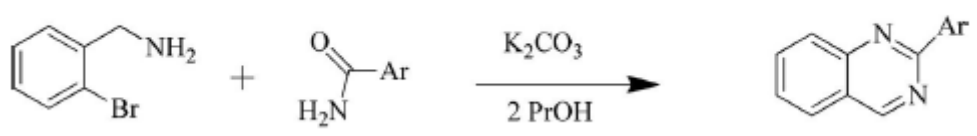
Most of these approaches use the Niementowski reaction, which fuses the analogues of anthranilic acid with amides (Scheme 1) at temperatures between 130 and 150 °C *via* the formation of an *o*-amidobenzamide intermediate [27].



Scheme 1. Synthesis of quinazoline by Niementowski reaction or by Besson's microwave conditions.
Hydroperoxide in acetonitrile 2-aminobenzophenones and benzylic amines yields quinazoline derivatives. [28]

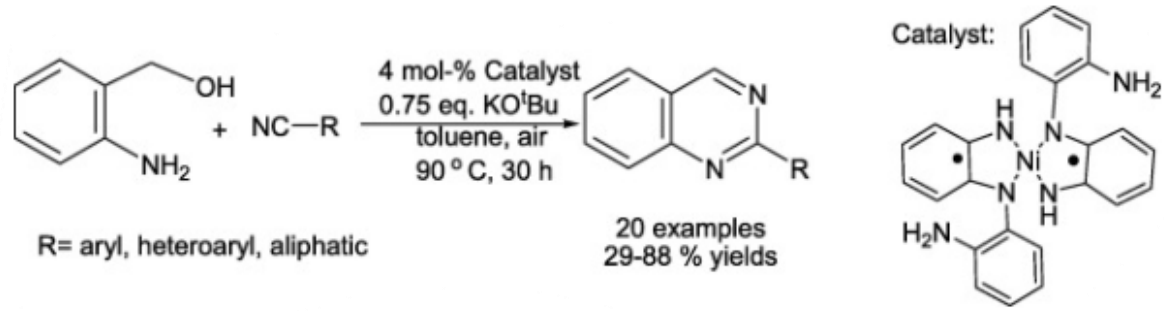


Scheme 2. Synthesis of 2-phenyl quinazoline
Quinazoline derivatives are prepared by reaction of 2-bromophenyl methyl amines andamindescatalyzed by ligand free copper (Scheme 3) [29]



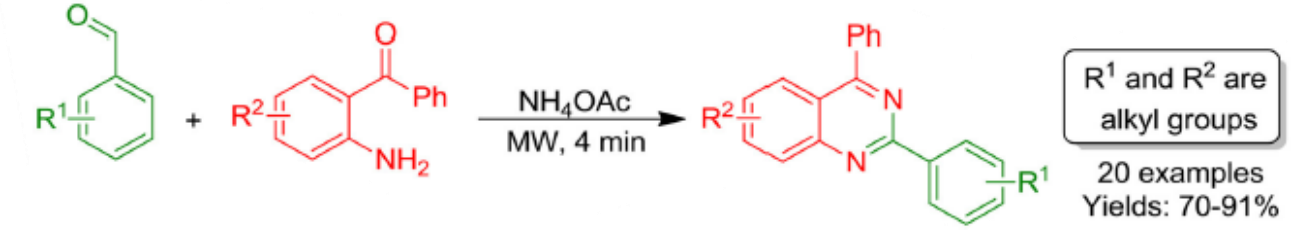
Scheme 3. Synthesis of 2-aryl quinazoline.

Paul and coworkers [30] recently reported reaction of nitriles with 2-aminobenzyl alcoholfor the preparation of quinazolines in good yields, by means of a biomimetic dehydrogenative condensation/couplingprocess Scheme 4.



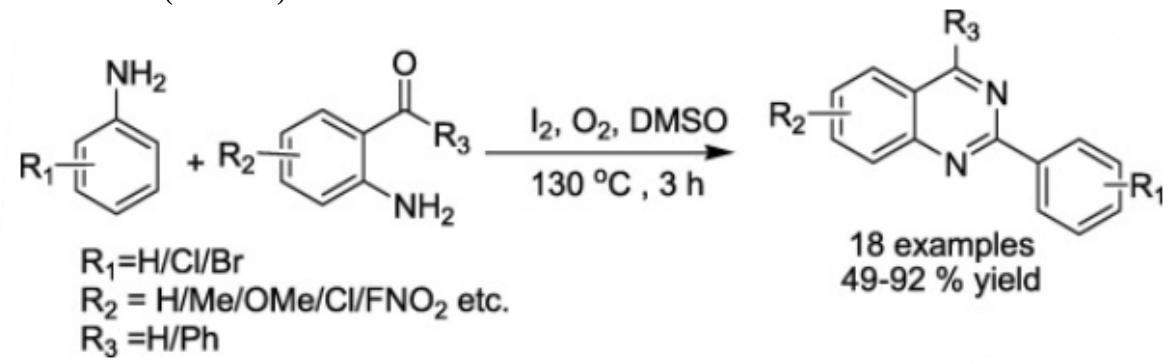
Scheme 4. Singlet diradical diamine Ni (II) catalysed the synthesis of arylquinazolines.

Sarma and Prajapati reported a catalyst- and solvent-freesynthesis of quinazoline derivatives **20** from aldehydes **18**,2-aminobenzophenones **19,** and ammonium acetate undermicrowave heating conditions (**Scheme 5**)



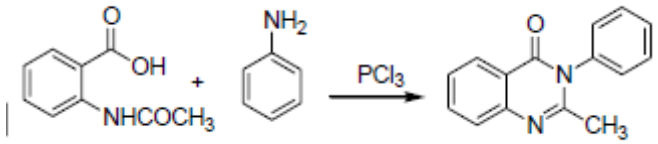
SCHEME 5 | Reaction of aldehydes and 2-aminobenzophenones under microwave heating conditions..

The synthesis of quinazoline derivatives by the 2-aminobenzaldehydes or 2-aminobenzophenones with benzyl- amines was recently published by Bhanageetet al. (32) Using a set of samples of functionalized 2-aminobenzaldehydes or 2-aminobenzophenones, numerous functionalized hetero- aryl or aryl amines were studied to produce quinazolines in yields of 49–92% (Scheme 6).



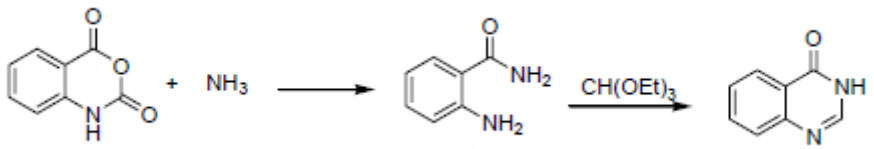
Scheme 6. Molecular iodine catalysed reaction of benzyl-amines with 2-amino benzophenones or 2-aminobenzaldehydes.

Morgan's method for the synthesis of quinazoline (Scheme 2) involve the reaction between2acetamido benzoic acid and an amine in the presence of phosphorous trichlorideto produce 2-methyl-3-phenylquinazolin-4(3H)one(Scheme7) [33,34]



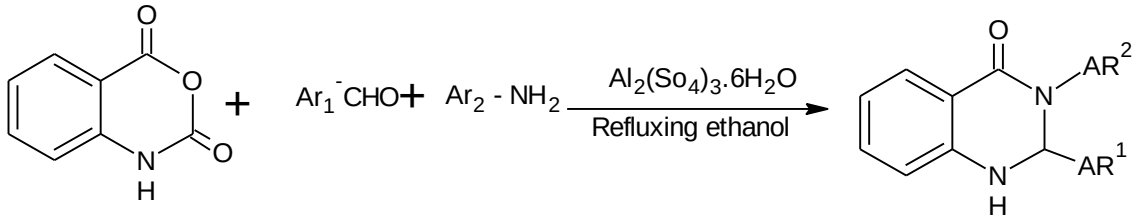
Scheme 7 4-quinazolineone by Morgan's method.

The reaction between isotopic anhydride and an amine, followed by refluxing withethyl orthoformate (Scheme 3) produces 4-(3H)-quinazolinone [35]



Scheme 8. Synthesis of 4-quinazolinone.

Alireza Barmak et. al [36] synthesized 2,3-dihydroquinazolinones by thereaction between aromatic aldehydes (2) and isatoic anhydridewith aniline derivatives (3)and investigated under optimizedconditions.



Scheme 9

Biological Activities

Antioxidant Activity

Recently, antioxidants been extensively discussedin relation to oxidative stress and radicals, cancerprophylaxis and therapy.[37] To study the freeradical scavenging ability of the synthesized compounds (4g–4l), the DPPH [diphenyl-(2,4,6-trinitrophenyl) iminoazanium]assay was used.The majority of compounds presented a goodradical scavenging activity, though the compound 4j exhibited the strongest activity, even to the standard of ascorbic acid.Further studies are required to determine whether these main compounds could be a potential treatment for diabetes andhyperlipidaemia diseases.

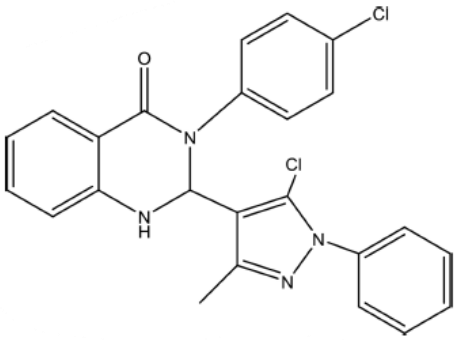


Figure 4j 2-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-(ptolyl)-2,3-dihydroquinazolin-4(1H)-one

Thetested compounds, in particular, compounds 4j and 4l, were found to be uniquely reducing blood sugar levels.[38]

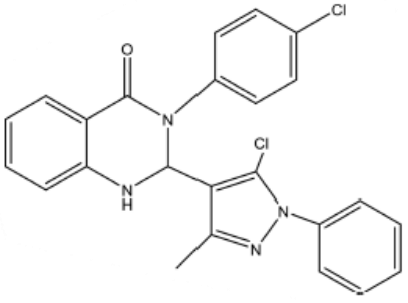


FIG 4J

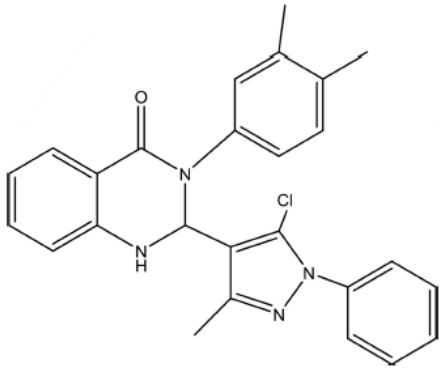
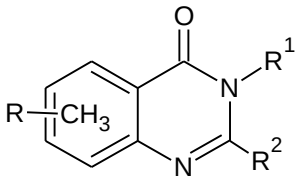


FIG 4I

Hatem A. Abuelizz et. al[39]prepareda new series of quinazoline-4(3H)-ones and are evaluated for anticonvulsant activity.Out of twenty-four, compound**FIG1**proved to be the most active with a remarkable protection (100%) against PTZ induced convulsionsand four times more potent activity than ethosuximide.benzyl substitution at position 3 has showna strong anticonvulsant activity but with less seizure prevention compared to the butyl substitution.



R=CH_3,OCH_3 R^1=BUTYL, BENZYL

FIGURE1. The structures of anticonvulsant and designed quinazolines

Analgesic Activity

Many quinazolines have been synthesized and evaluated for their analgesic and anti-inflammatory activities. 2-Phenyl quinazolinone FIG **1**was synthesized byAlagarsamy et al. in 2002 [40]. It was biologically evaluated as an analgesic agent.

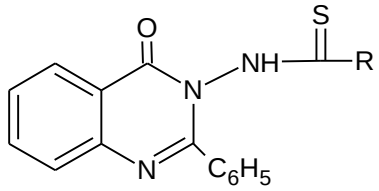


FIG **1**

Themodification of compound **1**to thiourea-substituted 2-methyl quinazolinone derivatives FIG **2** produced more active compounds. The most active one was the compound which had thepyrrolidine ring at C-3 [41].

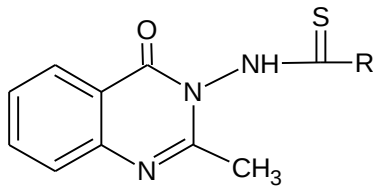


FIG2

Alafeefy Ahmed M. et .al (42) were Synthesized some novel quinazoline derivatives and evaluated analgesic and anti-inflammatory All the new compounds were screened to evaluate their analgesic and anti-inflammatory activities and acute toxicity. Indomethacin was used as a reference standard. The analgesic activity was performed by the heat-induced nociception and the anti-inflammatory activity was evaluated by the formaldehyde-induced oedema techniques. It is worth to mention that the potent analgesic effect of compound FIG 1 without any significant inhibition of inflammation and induction of S-shaped tail suggests that this compound seemed to be an opioid analgesic (43).

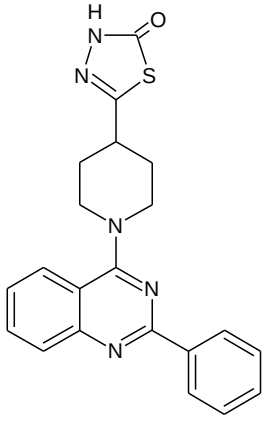


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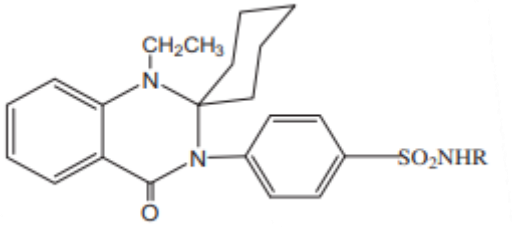
Fig1

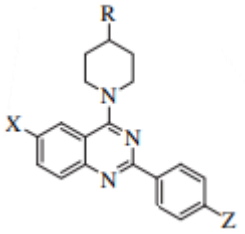
Anti-inflammatory activity

K.M. Amin et.al (41) Synthesized, biologically evaluate and molecular docking of novel series of spiro [(2H,3H) quinazoline-2,10 - cyclohexan]-4(1H)- one derivatives as anti-inflammatory and analgesic agents. Three series of Spiro [(2H,3H) quinazoline-2,10 -cyclohexan]-4(1H)-one derivatives have been synthesized. Some of the novel quinazolinone derivatives II showed considerable potent anti-inflammatory and analgesic activity of in comparing to indomethacin and tramadol as reference drugs. Docking study into COX-2 has been made for derivatives of highest anti-inflammatory activity.



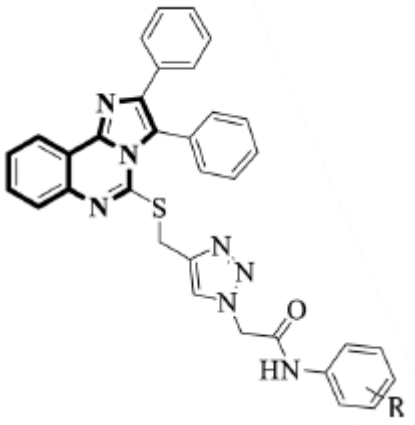
II

Alafeefy Ahmed M. et .al (42) were tested against formaldehyde induced inflammation, 6 compounds were considered devoid of activity, and 8 compounds showed weak anti-inflammatory activity. However, 13 compounds (6aej, 7b, 10, 12) showed significant inhibition, of which 6b and 6f were more potent than the reference drug and compound 7b was almost as active as indomethacin



6b: X=H. Z=H. R= Ph.
6f: X=I. Z=H. R= Ph.

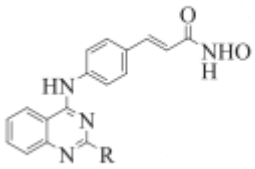
Fariba Peytam et. al. (43) was Designed, synthesized, and evaluate of novel substituted imidazole[1,2-*c*] quinazoline derivatives as potential *α*-glucosidase inhibitors with bioactivity and molecular docking insights.Among them, 2-(4-(((2,3-diphenylimidazo [1,2-c] quinazolin-5-yl) thio) methyl)-1H-1,2,3-triazol-1-yl)-N-(2-methoxyphenyl) acetamide (19e) showed good antidiabetic activity.



R' = H, 4-Cl, 4-OCH_3
R = H, 4-CH_3, 4-OCH_3, 3-OCH_3, 2-OCH_3, 4-Cl, 3-Cl, 2-Cl

Anticancer agent

Shweta Mishra et.al (44) was Designed, synthesized, molecular docking, and biological evaluationof quinazoline-tethered hydroxamic acid derivatives as HDAC inhibitors for anticancer activity. All three cancer cell lines were most sensitive to the N-hydroxyacrylamide derivatives as compared to Nhydroxybenzamides derivatives. In particular, compound 5a (0.39, 0.26, 0.41 µM respectively) and 5b (0.27, 0.57, 0.32 µM respectively) were found to be the most potent derivatives among all tested cell lines.



5a H
5b Cl

Alonso et al. (45) describes the synthesis of 1,2,3,4-tetrahydroquinolinyl phosphine oxides, phosphanes and phosphine sulphides as well as that of quinolinyl phosphine oxides and phosphine sulfides. Among themmost of the compounds showed excellent activity as topoisomerase I inhibitors. Human lungadenocarcinoma(A549), human embryonic kidney (HEK293), human ovarian carcinoma (SKOVO3) was also screened for the cytotoxic effect on cell lines. Against the lung cancer cell line compound figure 16 showed potent activity with IC50 value of 0.25±0.23 µm whereas compounds figure 17 and figure 18 showed better activity against lung cancer cell line with IC50 value of 0.08±0.01 µm and 0.03± 0.04 µm.

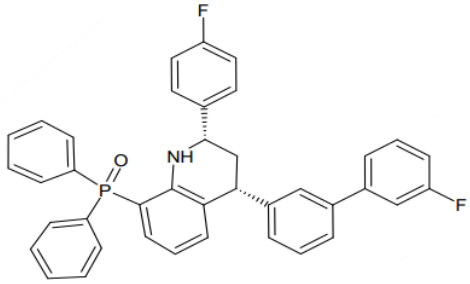


Fig16

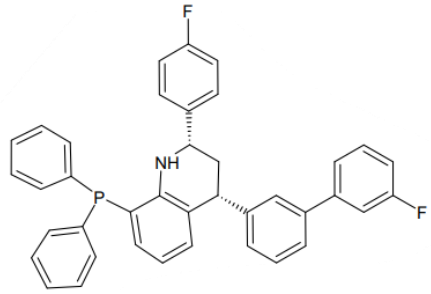


Figure 17

Yong-Feng Guan et.al (46) was Designed,Synthesized, and evaluated their Anticancer Activity of Novel Quinoline-Chalcone Derivatives.Quinoline-chalcone derivatives were designed and synthesized, and explored their antiproliferative activity against MGC-803, HCT-116, and MCF-7 cells. Among these compounds, compound 12e exhibited a most excellent inhibitory potency against MGC-803, HCT-116, and MCF-7 cells with IC50 values of 1.38, 5.34, and 5.21 µM, respectively.

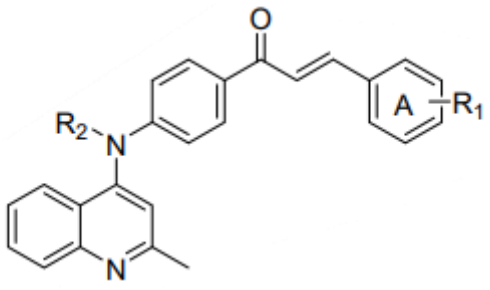
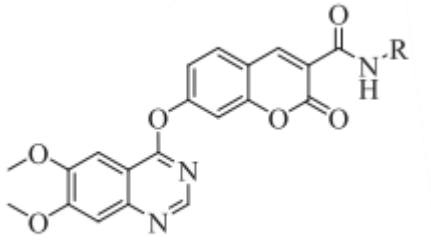


FIGURE 12e
R1=3, 4,5-triOCH3

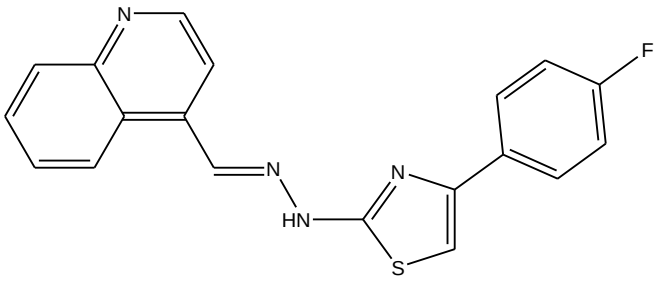
R2= H

Zahra Emamgholipour et. al(47) Synthesizedand biologicallyevaluate in silico study of novel coumarin-quinazoline analogs as potential Anti-Angiogenesis agents. In cytotoxic tests conducted using the MTT assay, compound 13f exhibited significant anti-proliferative potency against HUVECs, with an IC50 value of 20.2 μM, compared to that of sorafenib (12.8 μM)



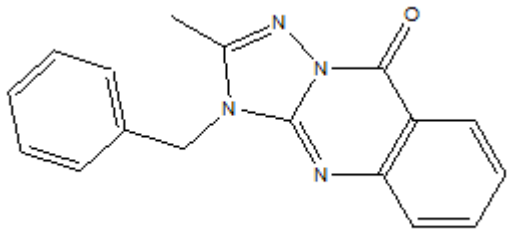
13 f – R= CYCLOPROPANE

Antifugal agent
Mehlika Dilek Altintop et.al (48) was synthesize new quinoline-based thiazolyl hydrazone derivatives and evaluate their anticandidal and anticancer effects.New thiazolyl hydrazone derivatives were evaluated for their anticandidal effects using disc diffusion method.4-(4-Fluorophenyl)-2-(2-((quinolin-4-yl) methylene) hydrazinyl) thiazole (1) showed antifungal activity against Candida albicans and Candida krusei in the concentration of 1 mg/mL.



4-(4-Fluorophenyl)-2-(2-((quinolin-4-yl) methylene) hydrazinyl) thiazole

Figure 1
Antihypertensive Agent
Veerachamy Alagarsamy et. al. (49) Synthesized and evaluate antihypertensive activity of novel 3-benzyl-2-substituted-3H- [1,2,4] triazolo[5,1-b] quinazolin-9-ones. A series of 3-benzyl-2-substituted-3H-[1,2,4] triazolo[5,1-b] quinazolin-9-ones have been synthesized by the cyclocondensation of 3-amino-2-benzylamino-3H-quinazolin-4-one with a variety of one-carbon donors.Among the series, 3-benzyl-2-methyl-3H-[1,2,4] triazolo[5,1-b]quinazolin-9-one (7b) was found to be the most active antihypertensive agent which is more potent than the reference standard prazocin.

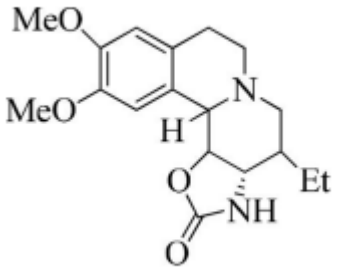


, 3-benzyl-2-methyl-3H-[1,2,4]triazolo[5,1-b] quinazolin-9-one

7b

Caroon et al. [50] synthesized the 2R*,llbS* and ZS*, llbS* diastereoisomers of the spiro [1,3,4,6,7,1 lb-hexahydro-2H-benzo[a]quinolizine-2,50 -oxazolidin-20 -one] system and evaluated for antihypertensive activity. Compound 54 was

found to be most potent at 25 mg/kg. Percentage fall in blood pressure in 1 and 2 h was found to be 44 and 30% respectively.



CONCLUSION

This review focuses on potent and diverse pharmacological activities of the derivatives of quinazoline moiety reported in the past years. It also delivers an outlook on recent developments of quinazoline derivatives having various biological activities like anticancer, antimalarial, antimicrobial, anticonvulsant and antidiabetic with lesser toxicity. Quinazoline is a structure of countless interest in the area of pharmaceutical chemistry, featuring various drugs, clinical candidates and bioactive molecules. The focus of thisreview was on the synthesis and potential biological activity of quinazoline derivatives. This review will provide significant benefit to scientists for the design andsynthesis of quinazoline moiety-based drugs for the safe treatment of various fatal diseasesin future.

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