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QUINAZOLINONE AS POTENTIAL NUCLEUS FOR BIOLOGICAL INTEREST

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Abstract: Heterocyclic compounds play a vital role in the search for new drug candidates and are essential to elucidating the Chemistry of living processes. Quinazoline and its derivatives have significant biological activities, drawn more and more attention in the synthesis and bioactivities research. Among Quinazolines, Quinazolinones is privileged class of nitrogen heterocyclic scaffolds that have been found to exhibit a broad spectrum of pharmacological activities, including anti-inflammatory, antitubercular, and antiviral activities. Quinazolinones continuing improvements in various aspects.This review summarizes the recent advances in the biological activities of quinazolinone and its derivatives.

Keywords: Quinazoline, Quinazolinone, antimicrobial, anti-inflammatory, anticancer, and anti-HIV activities.

1. INTRODUCTION

Today organic Chemistry and in particular organic synthesis,are enjoying an exciting period of intense and dynamic activity. A large part of research is carried out with a view tousing signal organic compounds in medicine, drug discovery and functional materials.

Quinazoline deserve special attention because it is also an important tool for the synthesis of new compounds. This unit features in many alkaloids and is also known to show a wide range of biological activity. Quinazoline is a frequently encountered unit in organic synthesis as well as in medicinal chemistry. The first quinazoline was synthesized in the late 1860s from anthranilic acid and cyanogen to obtain 2-cyano quinazolinone. Since then, a remarkable number of quinazoline synthesis have been reported.

Quinazoline is a heterocyclic moiety containing a benzene ring fused to a pyrimidine. There are other possible isomers that are identified by the positions of nitrogen in the ring, for e.g., Cinnoline(1,2-Benzodiazine; Benzo[*c*] pyridazine; 1,2-Diaza naphthalene, Phthalazine(2,3-Benzodiazine; Benzo[*d*] pyridazine) and Quinoxaline(1,4-

Benzodiazine; Benzo[*a*]pyrazine). They all have bicyclic aromatic ring comprising of a benzene ring linked to aromatic ring containing two nitrogen such as pyridazine, pyrimidine, pyrazine.

Quinazolinone a frequently encountered unit in organic synthesis as well as in medicinal chemistry. Quinazolinones constitute a class of fused heterocycles that are of considerable interest because of a wide range of biological properties, such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive activities [1].

The classification of Quinazolinones according to ring system substitution patterns into the five categories[2].

2-Substituted-4(3*H*)-quinazolinones

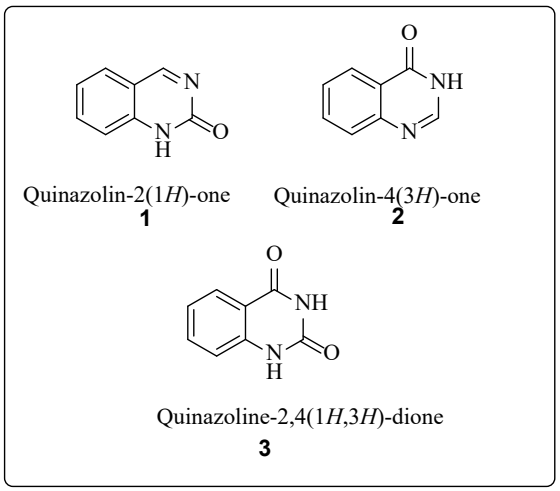
3-Substituted-4(3*H*)-quinazolinones

4-Substituted-quinazolines

2,3-Disubstituted-4(3*H*)-quinazolinones

2,4-Disubstituted-4(3*H*)-quinazolinones

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



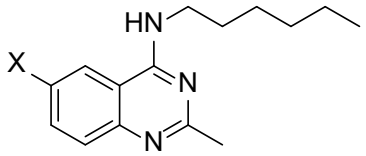
From these three quinazolinones, 4(3*H*)-quinazolinone is the most precursor, for many biosynthetic schemes. It is partly due to the structure being derived from the anthranilates (anthranilic acid or various esters, isatoicanhydride, anthranilamide and anthranilonitrile) while the 2(1*H*)-quinazolinone is predominantly a product of anthranilonitrile or benzamides with nitriles [3].

2. BIOLOGICAL IMPORTANCE

Quinazolinone have diversified biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities and other activities. Quinazolinones and their compounds with different substitutions make it as an important chemical for the various biological, physiological and pharmacological significance [4-6].

The multi-drug resistant microorganism is due to increasing incidence of infections caused by the microorganisms and their ability of developing antibiotic resistance to multiple antibiotics. Quinazolinone have attracted the special attention due to an important tool for the synthesis and shows a wide range of biological activity.

Chandrika et al. synthesized 2,4,6-trisubstituted quinazolines and evaluated for biologically various 2,4,6-trisubstituted quinazoline derivatives. The compound 4 showed antimicrobial activities against gram-positive bacterium and gram-negative bacterium [7].



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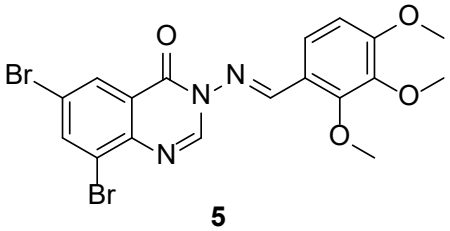
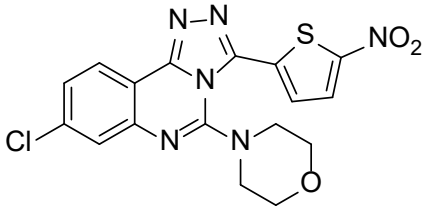
Panneerselvam et al. synthesized acylhydrazone quinazolines and on evaluation them the compound showed the most significant activity against various microbes S. aureus, S. epidermidi, M. luteus, B. cereus, E. coli, P. aeruginosa, K. pneumoniae, A. niger and A. fumigatus [8].



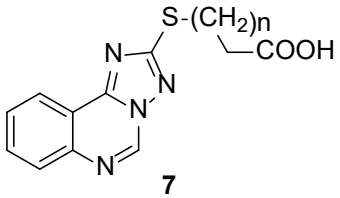
5

Jantova et al. were synthesized Fifteen [1,2,4] triazole [4,3-c] quinazoline derivates and evaluated for their antimicrobial activity by among which, compound 6 was found withthe highest potency against Bacillus subtilis, Staphylococcus aureus, Candida tropicalis and Rick-ettsia nigricans [9].



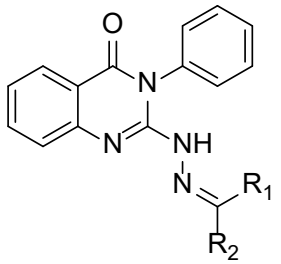
6

Antipenko et al. synthesized and investigated their bioactivities of novel 2-thio-[1,2,4]triazolo[1,5-c]quinazoline derivatives. The antimicrobial test have showed that compound 7 exhibited obvious suppression for Candida albicans, which was validated by further bioluminescence inhibition test and related to their lipophilicity [10].



7

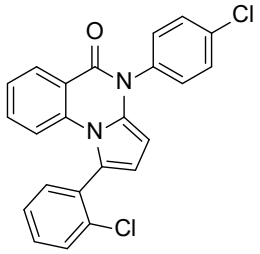
On the basis of these researches, they synthesized novel 3-phenyl -2-substituted-3H-quinazoline-4-ones in purpose of further reducing the ulceration side effects, analgesic, anti-inflammatory and ulcerogenic index activities of these compounds were tested. Among the synthesized derivates, compounds 8, 9 and 10 showed moderate analgesic activity. It is worth to mention that compound 10 exhibited higher anti-inflammatory potency, reference to standard drug of diclofenac sodium. In addition, the evaluated compounds all caused milder ulceration side effects, reference to aspirin. Indole-involved quinazolines Indole moiety involved heterocycles are proved to have a wide variety of pharmaceutical and medical profiles, such as anti-inflammation, anti-microbial, anti-cancer, anti-malarial, etc [11-17].



8 R1= CH3, R2=CH2CH3
9 R1= CH2CH3, R2=CH2CH3
10 R1= CH3, R2=CH2CH2CH3

Pandey et al. also conducted antimicrobial

researches on novel quinazolinones fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings. Compounds11 and 12 possessed excellent activities from all the quinazolinones derivates against Escherichia coli, pseudomonas aeruginosa, streptococcus pneumoniae, and bacillus subtilis [18].



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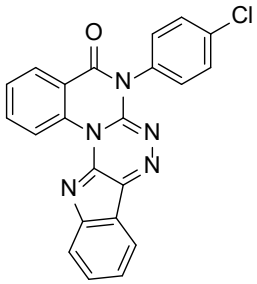
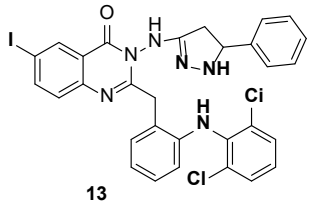


12

Patel et al. synthesized the series of new 2-[2-(2,6-dichlorophenyl)amino] phenylmethyl-3-[(5-substitutedphenyl)-1,5-dihydro-1*H*-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3*H*)onesand evaluated for antibacterial activity and compound 13 have shown good activity[19].



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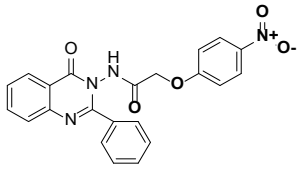
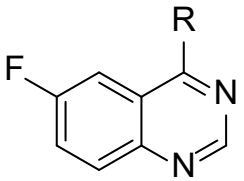
Cakici et al. were also synthesized and evaluated for antibacterial activity of quinazolinone derivatives and found compounds 14 more potent antibacterial activity [20].



14

We have summarized the potential antibacterial effects of quinazolinone in a review [21].

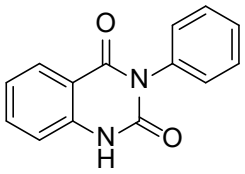
The antifungal activities had shown by a series of few novel S-substituted-6-fluoro-4-alkyl (aryl)thioquinazoline derivatives 15. From all, especially compound **c**, having a wide spectrum of bioactivity; it shows potent inhibitory activity on the growth of most of the fungi with EC50 values ranging from 8.3 to 64.2 □g/mL [22].



15

a. R= $SCH_2CH=CH_2$
b. R= $SCH_2CH_2CH_3$
c. R= SCH_2CH_3

3-Arylquinazoline-2,4(1*H*,3*H*)-diones16 were found as anti-TB agents along with a series of quinazoline derivatives 17 were exhibited for their pharmacological activity as anti-tuberculosis [23].



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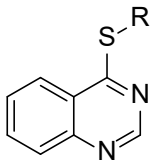
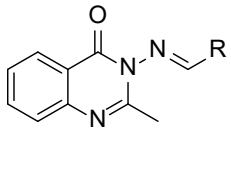


17

A series of Schiff bases of some 2-phenyl quinazoline-4(3)*H*-one derivatives are evaluated for their activity as antiviral agents [24].Compound 18 exhibited antiviral activity against herpes simplex virus-1 (KOS), herpes simplex virus-2(G), herpes simplex virus-1 (TK- KOS ACV), and vaccinia virus in HEL cell culture at selectivity index of 100, 100,

100, and 125, respectively, whereas cytotoxicity was observed at 100 □g/mL anddemonstrated good activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), and vaccinia virus. The protein kinase inhibitory activity and anticytomegaloviral activity showed few quinazolinecompounds 19 [25]. Quinazolinones act as anti-HIV activity whereas compounds 3-amino-2-methyl mercaptoquin-azolin-4(3H)-one 20 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 [26].



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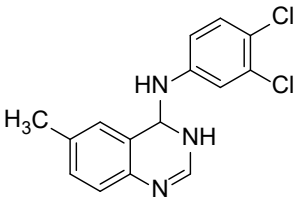

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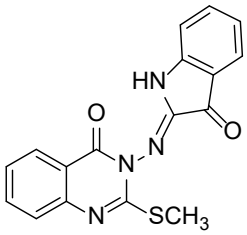
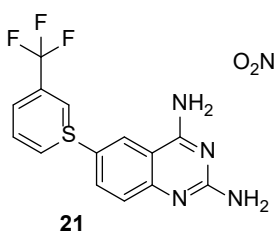


20

The 2,4-diamino-6-[(aryl)thio] quinazoline compounds were known to their antimalarial properties wherein the 4-amino group was replaced by hydrazine and hydroxyamino moieties and they found that such changes reduce markedly the antimalarial properties of this series. The compound 21 was tested against a normal drug-sensitive strain of *Plasmodium berghei*in mice by the parenteral route [27]. A series of quinazoline derivatives 22 were evaluated for their antiplasmodial activity [28] andshowed a high potential activity in comparison with chloroquine and doxycycline. A series of new 6-ureido-4-anilinoquinazolines 23 were evaluated for their potent activity as antimalarial agents [29].



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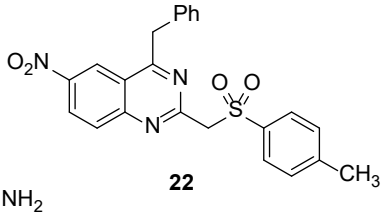

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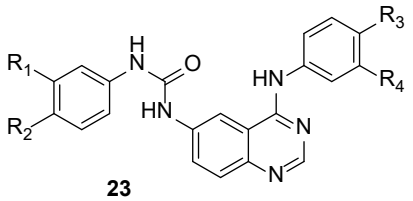
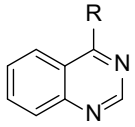


23

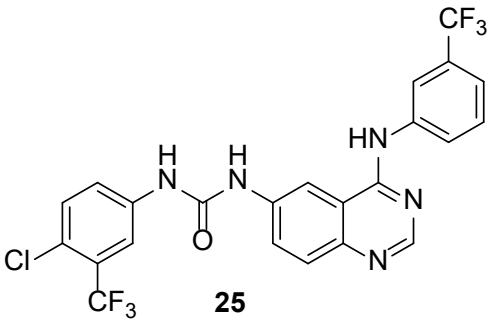
Quantitativestructureactivityrelationship (QSAR) model for antimalarial activity, developed from a set of 51 substituted quinazolines 24that exhibited remarkable *in vitro* activity against sensitive and multidrug-resistant *Plasmodium falciparum* malaria. 2D-QSAR was done using partial least squares method coupled with stepwise variable selection; subsequently, 3D-QSAR was carried out using stepwise variable selection k-nearest neighbor molecular field analysis (kNNMF) approach [30].



24

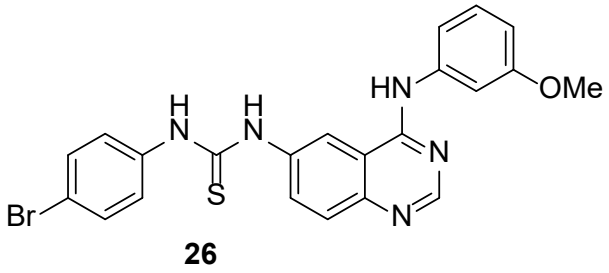
The synthesis and *in vitro* antimalarial evaluation of the series of new 6-ureido-4-anilinoquinazolines derivatives were reported activity against chloroquine-sensitive *P. falciparum*. Compound 25had IC50 value of 2.27 ng/mL which was equipotent to the standard drug

chloroquine used in the bioassay [31].



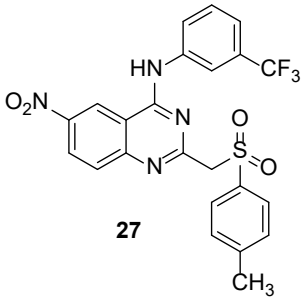
25

New series of 6-thioureido-4-anilinoquinazolines derivatives were synthesized and investigated those *in vitro* against multidrug resistant Plasmodium *yoeliinigeriensis*. Compound 26shows 50% curative effect in the mouse model at an oral dose of 100 mg/kg× 4 days [32].



26

The quinazoline derivatives were synthesized and screened for *invitro* antiplasmodial activity on the W2 chloroquino-resistant Plasmodium falciparum strain. The compounds 27&28have found both significant antiplasmodial activities and low toxicity, compared with two reference drugs: chloroquine and doxycycline [33].



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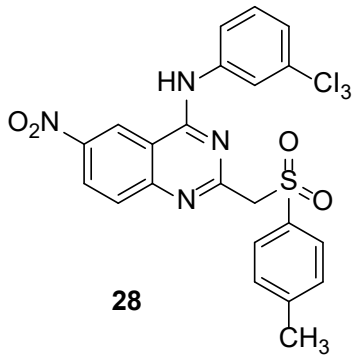
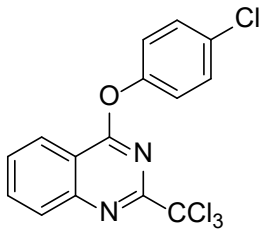


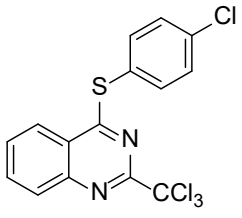
28

Theinvestigationofnewseries4-phenoxy-2-trichloromethylquinazoline was done and evaluation those *in vitro*antiplasmodial activity against multi resistant W2 *Plasmodium falciparum* strain. Compound 29shown significant specific activity against the Plasmodium genus in comparison with Toxoplasma [34].



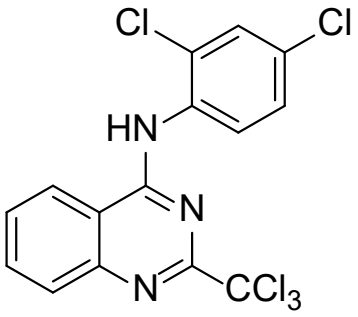
29

In vitro antiplasmodial activity against the human malaria parasite *Plasmodium falciparum* was studies of the series of new 4-thiophenoxy-2-trichloromethyquinazolines derivatives and compound 30in comparison with chloroquine and doxycycline chosen as reference- drugs [35].



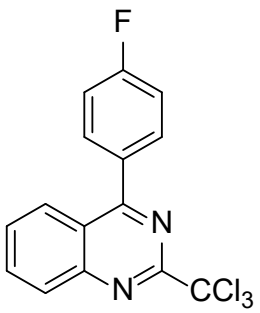
30

*In vitro*antiplasmodial activity evaluated of thesynthesized some new 4-anilino-2-trichloromethylquinazolines derivatives. The molecules substituted by a bromine, chlorine or CF3 group on the *meta* position of the aniline moiety were the most promising. Despite a non-negligible toxicity, compound 31, maintains good selectivity indexe because of its high antiplasmodial activity [36].



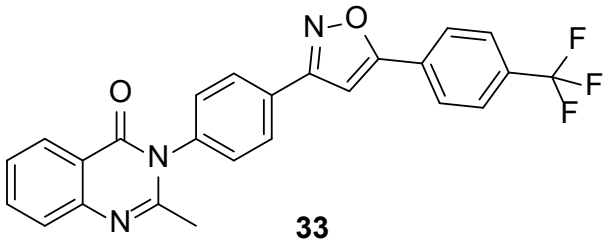
31

New 4-aryl-2-trichloromethylquinazo linesderivativesweresynthesized and they were evaluated for anti-plasmodial activity on both chloroquino-resistant and sensitive *Plasmodium falciparum* strains and the selectivity indexes for THP1 and HepG2 human cells were also calculated, revealing their anti-plasmodial potential. Compound 32, was found quite good selectivity index, similar to those of chloroquine, and so, despite superior IC50 values because of its safer profile toward human cells [37].



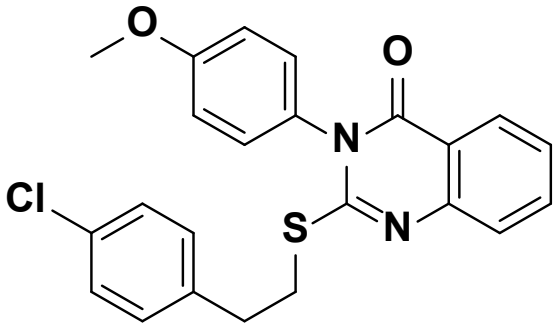
32

The antimicrobial evaluation of the synthesized series of novel isoxazole coupled quinazolin-4(3*H*)-one derivatives were done and all compounds shown mild to good antimicrobial activity. From all, compounds, 2-methyl-3-(4-(5-(4-(trifluoromethyl) phenyl) isoxazol-3-yl)phenyl)quinazolin-4(3*H*)-one 33was found to be the most active compound [38].



33

Gawad *et al*synthesized some new 3-substituted quinazolin-4(3*H*)-ones derivatives and screened these for their antitumor activity. Compound 2-(2-(4-chlorophenyl)-2-oxo-ethylthio)-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one 34 and 3-(4-chlorophenyl)-2-(2-(4-methoxyphenyl)-2-oxo-ethylthio) quinazolin-4(3*H*)-one 35 showed broad-spectrum antitumor activity toward numerous cell lines that belong to different tumor subpanels [39].



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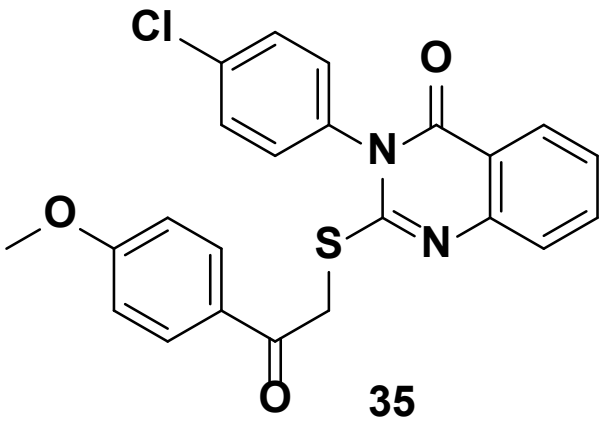
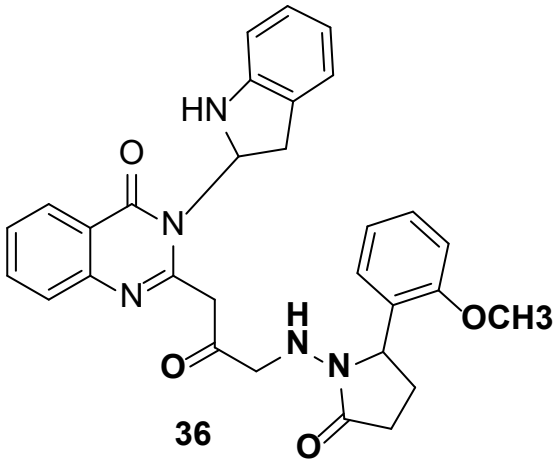


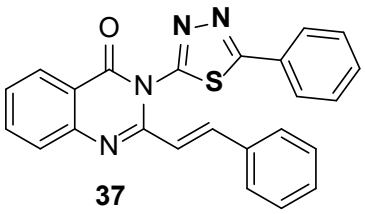
35

Kumar *et al* synthesized a series of quinazolinone derivatives and reported that compound 36exhibited good anti-inflammatory activity [40].



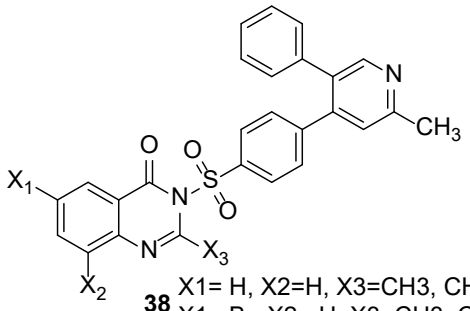
36

Jatav*et al* synthesized some novel 3-(5-substitutedphenyl-1, 3, 4 thiadia -zole-2-yl)-2-styrylquinazoline-4(3*H*)-one and screened for CNS depressant activities with the help of forced swim pool method and found that compound 37 were most active against CNS depressant activity [41].



37

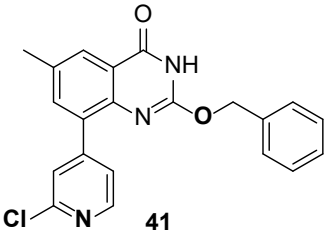
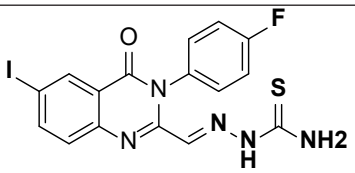
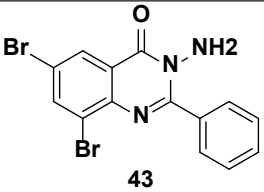
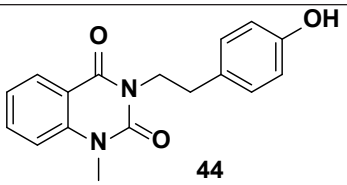
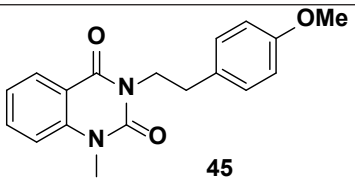
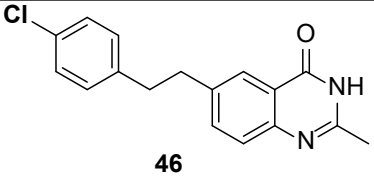
Venkataraman et al have formed various 2-substituted-3,1-benzoxazin-4-one derivatives and carried out for Anti inflammatory activity and Anti microbial activity. Some of quinazolinone compounds showed better anti-inflammatory activity and promising Anti microbial activity [42].

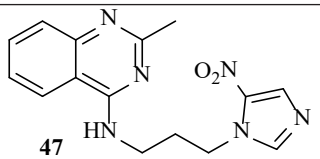
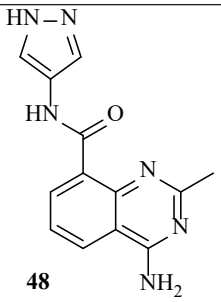
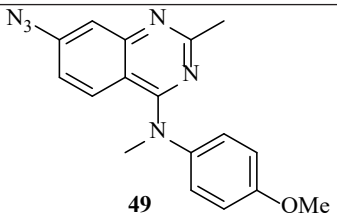
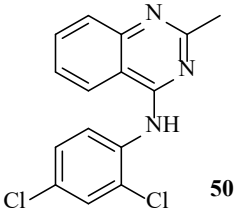
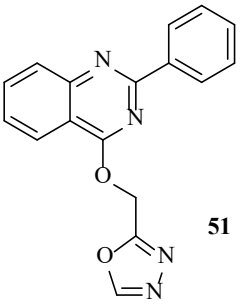


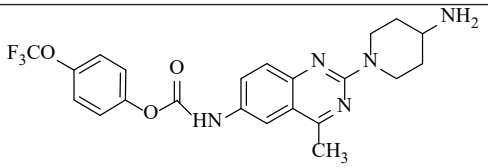
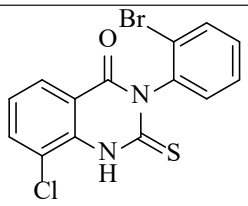
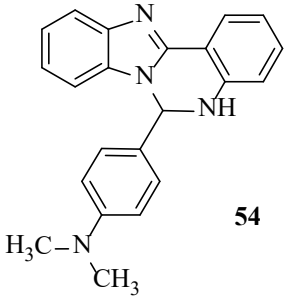
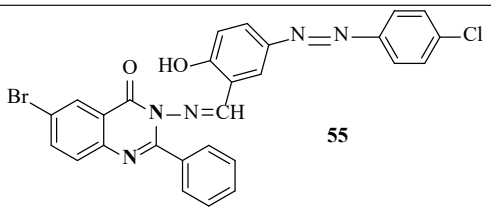
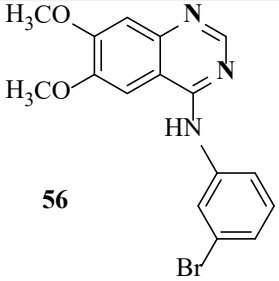
38 X1= H, X2=H, X3=CH3, CH2CH3, Ph
39 X1= Br, X2= H, X3=CH3, CH2CH3, Ph
40 X1= Br, X2= Br, X3=CH3, CH2CH3, Ph

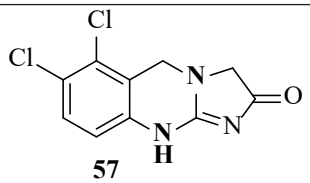
A number of synthetic quinazolines, have beenfound to possess a variety of biological activities suchas antifungal, antibacterial, anti-inflammatory, anticonvulsant or anticancer. Some are listed in **Table-I**.

Table-I

S.No.	Name of Compound	Structure	Activity
1.	2- and 8-disubstituted 6-methylquinazolin-4(3H)-one	 41	BRD9 binders [43]
2.	(*E*)-2-((3-(4-Fluoro phenyl)-4-oxo-3, 4 dihydroquinazolin-2yl) methylene) hydrazinecarbo thioamide	 42	Anticonvulsant [44]
4	3-Amino-6,8-dibromo-2-phenyl quinazolin-4(3*H*)-one	 43	Analgesic activity [45]
5	3-(4-Hydroxy phen ethyl)-1-methylquin azoline-2,4(1*H*,3*H*)-dione	 44	Potential antihypertensive agents [46]
6	3-(4-Methoxyphen ethyl)-1-methylquin azoline-2,4(1*H*,3*H*)-dione	 45	Potential antihypertensive agents [47]
7	6-(((4-Chlorophenyl) amino) methyl)-2-methylquinazolin-4(3*H*)-one	 46	Antitumor [48]

S.No.	Name of Compound	Structure	Activity
8.	2-Methyl-*N*-(3-(2-nitro-1*H*-imidazol-1-yl)propyl)-4-quinazolinamine	 **47**	Anticancer [49]
10.	4-Amino-2-methyl-*N*-1*H*-pyrazol-4-yl-8-quinazoline carboxamide	 **48**	PI3K/mTOR Dual inhibitors [50]
11.	7-Azido-*N*-(4-methoxyphenyl)-*N*,2-dimethyl-4-quinazolinamine	 **49**	Anticancer [51]
12.	*N*-(2,4-Dichlorophenyl)-2-methyl-4-quinazolinamine	 **50**	Antimalarial [29]
13.	4-(1,3,4-Oxadiazol-2-ylmethoxy)-2-phenyl quinazoline	 **51**	***DNA-Gyrase Inhibitors [52]***

S.No.	Name of Compound	Structure	Activity
14.	*N*-(2-(4-Amino-piperidin-1-yl)-4-methyl-quinazolin-6-yl)-2-(4-trifluoro methoxy-phenoxy)-acetamide	 **52**	MCHR1 antagonists [53]
15.	3-(2-Bromo phenyl)-8-chloro-4-oxo-2-thioxo-1,2,3,4-tetrahydro quinazoline	 **53**	Phosphodiesterase inhibitor [54]
16.	6-p-Dimethylamino phenyl-5,6 dihydro benzimidazo[1,2-c] quinazoline	 **54**	Anti-microbial [55]
17.	6-Bromo-3-((5-(4-chloro) diazenyl)-2-hydroxybenzyliden) amino-2-benzyl quinazolin-3*H*-4-one	 **55**	Anti-fungal [56]
18.	*N*-(3-Bromophenyl) -6,7-dimethoxy quinazolin-4-amine	 **56**	Anti-neoplastic agent [57]

S.No.	Name of Compound	Structure	Activity
19.	6,7-Dichloro-1,5-dihydroimidazo(2,1-b) quinazolin-2(3*H*)-one	 **57**	PDE-3 inhibitor [58]

CONCLUSIONS

Quinazolinone nucleus play a vitalrole as heterocyclic pharmacophores in the field of medicinal chemistry. The potential pharmacological profiles of quinazolinone have led the interest of many researchers to explore the utility of this moiety for better and varied pharmacological activities. Quinazolinone have shown biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities. This review will help to get an efficient way of understanding the biological profile of quinazolinone which can further aid the process of drug design developments.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interest regarding the publication of this paper.

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