


Review

Recent Advances on Quinazoline Derivatives: A Potential Bioactive Scaffold in Medicinal Chemistry

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Abstract: This paper intended to explore and discover recent therapeutic agents in the area of medicinal chemistry for the treatment of various diseases. Heterocyclic compounds represent an important group of biologically active compounds. In the last few years, heterocyclic compounds having quinazoline moiety have drawn immense attention owing to their significant biological activities. A diverse range of molecules having quinazoline moiety are reported to show a broad range of medicinal activities like antifungal, antiviral, antidiabetic, anticancer, anti-inflammatory, antibacterial, antioxidant and other activities. This study accelerates the designing process to generate a greater number of biologically active candidates.

Keywords: quinazoline; antifungal; anticancer; anti-inflammatory; antibacterial; antioxidant



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1. Introduction

Heterocyclic rings containing nitrogen and sulfur are of much intention as they are therapeutically and pharmacologically more active. These compounds are the building blocks of many pharmaceutical products. Among all heterocyclic moieties, quinazoline has been taken for this review, as quinazoline has a very broad spectrum of pharmacological activities with minimum side effects [1]. Quinazoline is a well known heterocyclic compound having the chemical formula $C_8H_6N_2$. Quinazoline is a light yellow crystalline solid and is also known as 1,3-diazanaphthalene, which comprises one benzene and one pyrimidine ring. Synthesis of quinazoline was first reported through decarboxylation of 2-carboxy derivative by August Bischler and Lang in 1895 [2]. Anthranilic acid on treatment with amide resulted in 4-oxo-3,4-dihydroquinazolines by Niementowski synthesis [3]. Other isomers of quinazoline are quinoxaline, cinnoline and phthalazine [4]. Quinazolines are also the building blocks of more than 200 natural alkaloids isolated from plants, microorganisms and animals [5,6]. Vasicine (\pm) (peganine) was the first known quinazoline alkaloid which was isolated from *Adhatoda vasica* in 1888. It is highly effective against bronchodilator activity [7].

Quinazolinone is one of the derivatives of quinazoline which is active like quinazoline [8]. Based on the substitution pattern, quinazolinones are further divided into subcategories such as 2-quinazolinone (a) and 4-quinazolinone (b) as shown in Figure 1 [9].

Thus, quinazoline is a structure of great interest in the area of pharmaceutical chemistry, featuring in various drugs, clinical candidates and bioactive molecules. The focus of this review is on potential biological activity of quinazoline derivatives. This review article will be advantageous in providing information regarding the latest developments on quinazoline analogs having completely different pharmacological activities like antitumor, antimicrobial, antimalarial, antiviral and antidiabetic, etc. This review will also be

stimulating for the researchers to design, synthesize and enhance the potentiality of vital medicine having quinazoline moieties for the treatment of assorted diseases in the future.

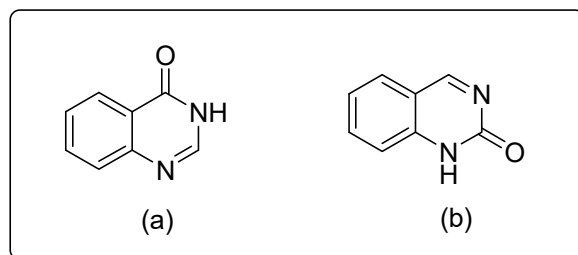


Figure 1. 2-quinazolinone (a) and 4-quinazolinone (b).

2. Synthesis Routes of Quinazoline

There are several reported methods to synthesize quinazoline moiety.

- (i) Niementowski quinazoline synthesis: Anthranilic acid when treated with formamide at higher temperature resulted 3,4 dihydro-4-oxaquinazoline (Figure 2) [10].
- (ii) Grimmel, Guinther and Morgan's synthesis: The 2-acetamidobenzoic acid reacts with an amine in the presence of phosphorous trichloride gave 2-methyl-3-phenylquinazolin-4(3H)-one (Figure 3) [10].
- (iii) Synthesis of quinazolin-4(3H)-one from Isoitic anhydride: The Isoitic acid anhydride reacts with amine followed by refluxing with ethyl orthoformate resulted in dihydro-4-oxaquinazolines (Figure 4) [1].
- (iv) Synthesis of 2-methyl-5-nitroquinazolin-4(3H)-one from 2-methyl-5-nitro-4H-benzo[d]oxazin-4-one: Amines reacted with 2-methyl-5-nitro-4H-benzo[d][1,3]oxazin-4-one to give respective quinazoline (Figure 5) [5].
- (v) Synthesis of quinazoline-2,4(1H,3H)-dione: Anthranilic acid and potassium cyanate reacted to get o-ureidobenzoic acid followed by cyclization by heating with acid or base to result in respective quinazoline-2,4(1H,3H)-dione (Figure 6) [10].
- (vi) Synthesis of 2-phenylquinazolin-4(3H)-one: 2-aminobenzamide reacted with styrene using Di-tertiary-butyl peroxide (DTBP) and p-Toluene sulfonic acid (p-TsOH) to get 2-phenylquinazolin-4(3H)-one (Figure 7) [11].

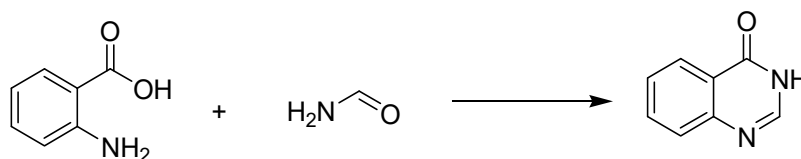


Figure 2. Synthesis of 3,4 dihydro-4-oxaquinazoline.

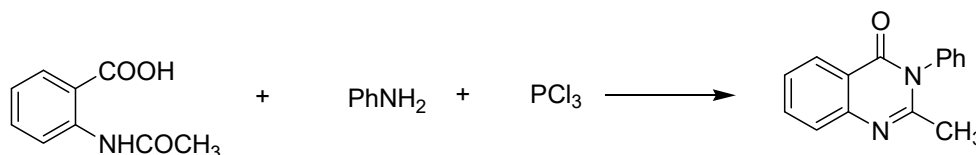


Figure 3. Synthesis of 2-methyl-3-phenylquinazolin-4(3H)-one.

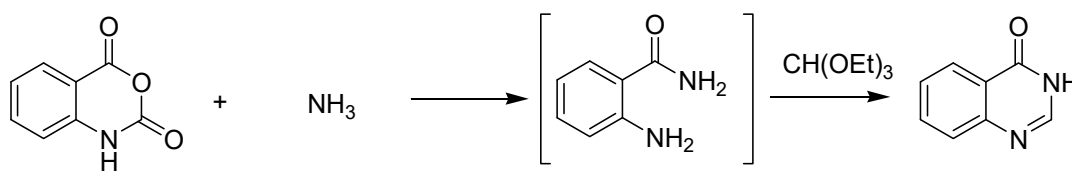


Figure 4. Synthesis of quinazolin-4(3H)-one.

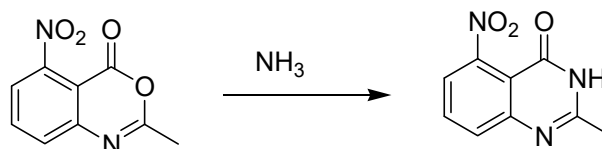


Figure 5. Synthesis of 2-methyl-5-nitroquinazolin-4(3H)-one.

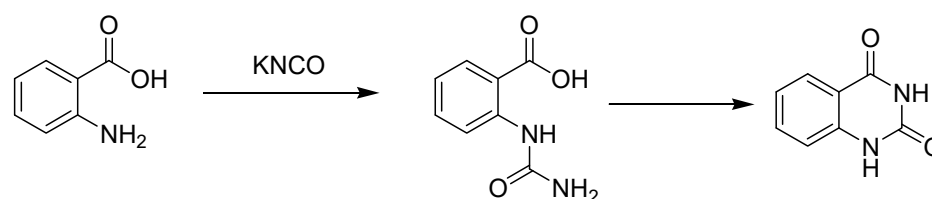


Figure 6. Synthesis of quinazoline-2,4(1H,3H)-dione.

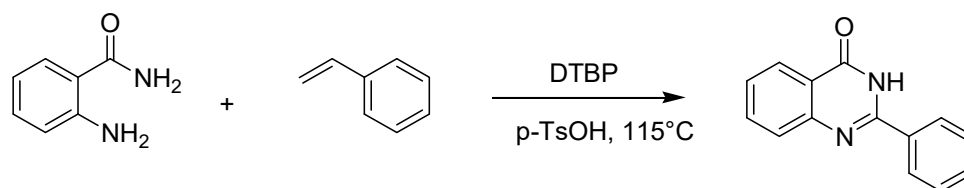


Figure 7. Synthesis of 2-phenylquinazolin-4(3H)-one.

3. Pharmacological Significance of Quinazoline Derivatives

Quinazoline and quinazolinone based molecules are significant in pharmaceutical chemistry because of their broad range of medicinal and therapeutic activities, such as anti-tumor, antifungal, anti-inflammatory, antibacterial, antioxidant and other activities. Certain synthesized molecules having quinazoline moieties exhibited anticancer activity, such as epidermal growth factor receptor (EGFR) inhibitory activity with half maximal inhibitory concentration (IC_{50}) values equal to known drugs.

There are several approved drugs in the market with quinazoline moiety, as shown in Table 1.

Table 1. Quinazoline based commercial drugs.

S. no.	Commercial Name	Structure	Usage	Ref.
1.	Gifitinib		For treatment of non-small cell lung cancer	[12]

Table 1. Cont.

S. no.	Commercial Name	Structure	Usage	Ref.
2.	Prazocin		For high blood pressure	[13]
3.	Erlotinib		For non-small cell lung cancer, pancreatic cancer and several other types of cancer	[14]
4.	Letemovir		Antiviral drug	[15]
5.	Vandetanib		Antagonist of the vascular endothelial growth factor receptor	[16]
6.	Dacomitinib		Non small cell lung carcinoma	[17]
7.	Afatinib		For treatment of cancers resistant to gefinitib and erlotinib	[18]

Table 1. Cont.

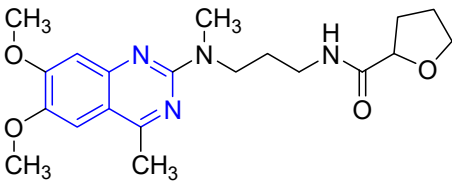
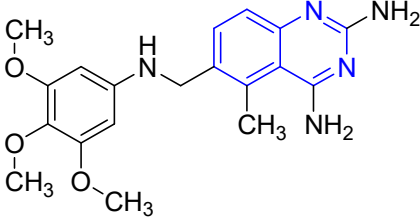
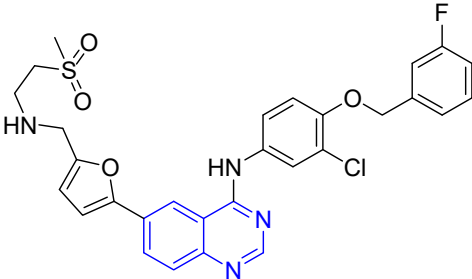
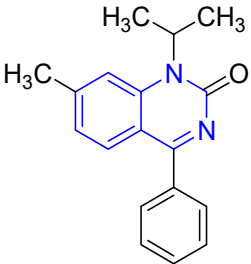
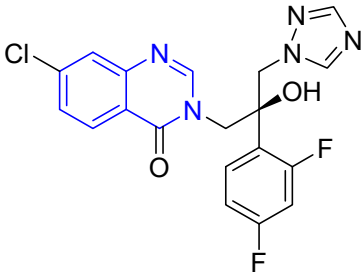
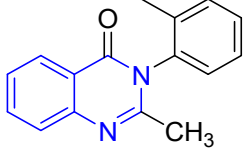
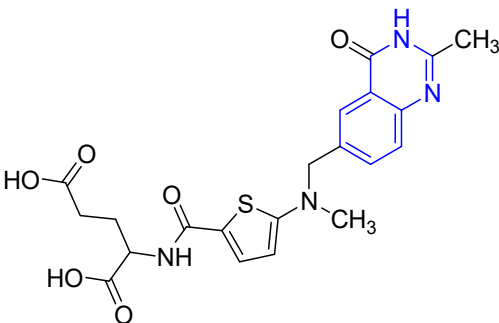
S. no.	Commercial Name	Structure	Usage	Ref.
8.	Alfuzosin		Prostatic hyperplasia	[19]
9.	Trimetrexate		Antineoplastic agent, and as an antiparasitic agent against pneumocystis	[20]
10.	Lapatinib		For treatment of advanced-stage or metastatic breast cancer	[21]
11.	Proquazone		Non-steroidal anti-inflammatory drug	[22]
12.	Albaconazole		Anti-fungal agent	[23]
13.	Methaqualone		Sedative effects	[24]

Table 1. Cont.

S. no.	Commercial Name	Structure	Usage	Ref.
14.	Raltitrexed		Cancer of large intestine	[25]

4. Quinazoline as Anti-Tumor Agents

Quinazoline and its numerous derivatives can be extracted from plants. The substituted quinazoline has been widely used as an anti-tumor agent due to its structure–activity relationship. Many studies reported several synthesis derivatives of quinazoline and elucidated their promising characteristics as anticancer agents against various tumors. Recent developments in quinazoline derivatives are highlighted in this study.

A series of triazolo[4,3-*c*]quinazolines were prepared by Eves et al. [26]. Antitumor activity of synthesized compounds was tested against HepG2, MCF-7, PC-3, HCT-116 and HeLa cancer cell lines. Results showed strong EGFR inhibitory activity and the competence of the simulating cell cycle can arrest at the G2/M phase (Table 2, Compound 1). Molecular modelling was performed to study active site interaction and found a good relation with biological results. 6-Bromo-2-(pyridin-3-yl)-4-substituted quinazolines series were synthesised with the starting reagent 4-chloro derivative [27]. Human cancer cell lines MCF7 (breast) and A549 (lung) were used to evaluate the *in vitro* cytotoxicity. Synthesized compound *N*-(benzo[d]thiazol-2-yl)-6-bromo-2-(pyridin-3-yl) quinazolin-4-amine (Table 2, Compound 2) was found to be extremely selective and potent against EGFR inhibition ($IC_{50} = 0.096 \mu M$) and as showing anticancer activity against the MCF-7 cell line ($IC_{50} = 2.49 \mu M$). Binding mode was found to be constant with the EGFR inhibitory activity in molecular docking studies of the shown compound. 6- and 7-substituted amino-4-anilinequinazoline derivatives were prepared by Das et al. [28] and tested for anticancer activity as irreversible dual EGFR/HER2 inhibitors. Synthesized compounds (Table 2, Compound 3) were found to be the most potent with reference to afatinib and osimertinib with the ($IC_{50} = 0.23 \text{ nM}$) and ($IC_{50} = 1.28 \text{ nM}$), which is better than AZD9291 ($IC_{50} = 0.44 \text{ nM}$), afatinib ($IC_{50} = 1.39 \text{ nM}$) and gefitinib ($IC_{50} = 0.42 \text{ nM}$).

A series of quinazoline derivatives was prepared by the structural modification at the 6- and 7-position of quinazoline core. The most potent derivative (Table 2, Compound 4) obtained in this series was observed as a multi-kinase inhibitor and also shows effective cellular anti-proliferative activity against several cancer cell lines [29].

Quinazoline derivatives bearing benzene sulfonamides moieties were prepared and tested for antitumor activity by El-Azab et al. [30]. Synthesized compounds (Table 2, Compound 5) were found most potent against carbonic anhydrase (CA) inhibitory activity. Activity was compared with the reference drug acetazolamide, a typical sulphonamide inhibitor.

Rahmannejadi et al. [31] synthesized a very new series of bis-quinazolin-4(3*H*)-ones derivatives and evaluated them for their antitumor activity. Bromo derivatives of this compound were found to have the maximum potential of cytotoxic activity over dibromo or dimethyl compounds. Most competent derivatives are shown in Table 2, Compound 6.

Quinazoline derivatives having 3-substituted 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one moiety were synthesized by Khodiar et al. [32]. Antitumor activity was evaluated

against MCF-7 and HepG2 cell lines and found to be potent as a cell inhibitor with IC_{50} values of 2.09 and 2.08 μM against MCF-7 and HepG2, respectively (Table 2, Compound 7).

A series of 3-methyl-quinazolinone derivatives was designed and prepared by Le et al. [33]. Antitumor activity of synthesized compounds was tested in three human cancer cell lines including A549, PC-3 and SMMC-7721. Selected compounds as in Table 2, Compound 8, 2-f4-[(3-Fluoro-phenylimino)-methyl]-phenoxyethyl-3-methyl-3H-quinazolin-4-one, 2-f4-[(3,4-Difluoro-phenylimino)-methyl]-phenoxyethyl-3-methyl-3H-quinazolin-4-one and 2-f4-[(3,5-Difluoro-phenylimino)-methyl]-phenoxyethyl-3-methyl-3H-quinazolin-4-one, were found to be the most potent inhibitor of EGFR with an IC_{50} value of 10 nM.

Quinazoline derivatives containing piperazine moiety were prepared via substitution reactions with 6,7-disubstituted 4-chloroquinazoline and benzyl piperazine. Antitumor activity of the synthesized compound was evaluated against A549, HepG2, K562 and PC-3 cell lines. Out of all the synthesized compounds, *N*-(3-chlorophenyl)-2-(4-(7-methoxy-6-(3-morpholino-propoxy)quinazolin-4-yl)piperazine-1-yl)acetamide (Table 2, Compound 9) was found to have outstanding activity [34].

A series of 2-[(3-(4-sulfamoylphenethyl)-4(3H)-quinazolinon-2-yl)thio]anilide derivatives was prepared by Alkhtani et al. [35]. The cytotoxic activity of the derivatives was assessed against breast adenocarcinoma (MCF-7), colorectal adenocarcinoma (HT-29) and acute myeloid leukaemia (HL-60 and K562) cells along with human fibroblast cell line, MRC-5. Selected compounds exhibited (Table 2, Compound 10) excellent activity with the IC_{50} values of 0.34, 0.28 and 0.39 mM, respectively. The activity of these compounds was compared to sorafenib having an IC_{50} value of 0.11 μM .

One more series of quinazoline derivatives has been synthesised by alkylation, and hydrazinolysis of the inherent thioxo group gives corresponding thioethers [36]. Compounds shown (Table 2, Compound 11) had great activity against the used cell-lines with IC_{50} values ranging from 1.85 to 2.81 μM against HeLa and MDA-MB231 cells, respectively.

Vu et al. [37] synthesized quinazoline derivatives and evaluated their anticancer activity against SKLU-1 (Lung cancer), MCF-7 (breast cancer) and HepG-2 (liver cancer) cell lines inhibition. The synthesized compound 3-benzyl-2-methylquinazolin-4(3H)-one, as shown in Table 2, Compound 12, shows maximum cytotoxicity inhibition against cancer cell lines with IC_{50} values of 9.48, 20.39 and 18.04 $\mu\text{g}/\text{mL}$.

4-Arylamino-6-(5-substituted furan-2-yl)quinazoline derivatives were prepared by Zhang et al. [38]. Biological activities of synthesized compounds were assessed against SW480, A549, A431 and NCI-H1975 cells. The selected compounds shown in Table 2, Compound 13, had the maximum inhibitor activity toward wild type EGFR with $IC_{50} = 5.06$ nM. Activity of these compounds was compared to commercially available Lapatinib and found to be significant.

Srinivas et al. [39] prepared a series of novel derivatives of quinazoline and tested their anticancer activity. Synthesized compounds 5-((3,4-dihydro-2-phenylquinazolin-4-yl)oxy)methyl-*N*-phenyl-1,3,4-thiadiazol-2-amine and 5-((3,4-dihydro-2-phenylquinazolin-4-yl)oxy)methyl-*N*-(2-nitrophenyl)-1,3,4-thiadiazol-2-amine as in Table 2, Compound 14, are the most potent glycogen synthase kinase (GSK-3) inhibitors and showed high hypoglycemic activity.

Quinazoline analogs, such as 1-(4-(4-((thiazol-2-yl)methoxy)-3-chlorophenylamino)quinazolin-6-yl)-3-(1-hydroxypropan-2-yl)thiourea (a) and their derivatives as shown in Table 2, Compound 15, were designed and synthesized by Wallace et al. [40]. These synthesized analogs exhibited activity as receptor tyrosine kinase inhibitors.

R.A. Vishwakarma [41] synthesized 6-aryl-4-phenylamino-quinazoline analogs. Synthesized compounds (Table 2, Compound 16) 2-(4-(6-phenylquinazolin-4-ylamino)phenyl)acetonitrile (a), 2-(4-(6-(2,4-difluorophenyl)quinazolin-4-ylamino)phenyl)acetonitrile (b), 2-(4-(6-(3-nitrophenyl)quinazolin-4-ylamino)phenyl)acetonitrile (c) and 2-(4-(6-*o*-tolylquinazolin-4-ylamino)phenyl)acetonitrile (d) were found as phosphoinositide-3-kinase inhibitors against various cancers such as pancreatic, prostate, breast and melanoma.

Table 2. Quinazoline based anti-tumor agents.

Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
1				
	(a)		IC ₅₀ (uM)	
		(i) HepG2, (ii) MCF-7 (iii) PC-3 (iv) HCT-116 (v) HeLa	(a) (i) 15.02 ± 1.4 (ii) 9.73 ± 1.1 (iii) 21.65 ± 1.8 (iv) 14.76 ± 1.4 (v) 18.93 ± 1.6 (b) (i) 15.30 ± 1.4 (ii) 8.58 ± 1.3 (iii) 10.58 ± 1.5 (iv) 13.47 ± 1.7 (v) 9.47 ± 0.9 (c) (i) 10.30 ± 1.7 (ii) 8.90 ± 1.9 (iii) 10.54 ± 1.2 (iv) 11.47 ± 1.6 (v) 13.41 ± 0.9	[26]
2	(b)			
3	(c)			
		(i) EGFR (ii) A549 (iii) MCF7 (iv) WI38 (v) PC9 (vi) HCC827	IC ₅₀ (uM) (i) 0.096 ± 0.00278 μM (ii) 178.34 ± 8.9 (iii) 2.49 ± 0.12 (iv) 82.8 ± 4.14 (v) 1.05 ± 0.02 (vi) 3.43 ± 0.066	[27]
3				
	(a)	(i) EGFR (ii) NCIH1975 (iii) HCC827 (iv) A431	IC ₅₀ (nM) (a) (i) 0.6 (ii) 107.0/12.2 (iii) 0.2/0.3 (iv) 20.0/1.52 (b) (i) 1.01 (ii) 60.6 (iii) 1.2 (iv) 288.3	[28]
	(b)			

Table 2. Cont.

Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
4		(i) HCT-116 (ii) MESSA (iii) MKN45 (iv) H1975 (v) H446 (vi) MOLM-13 (vii) MV4-11	(IC ₅₀ = 30.5 nM) (i) 16 (ii) 506 (iii) 128 (iv) 491 (v) 102 (vi) 76 (vii) 73	[29]
5		(i) hCA I (ii) hCA II (iii) hCA IX (iv) hCA XII	KI (nM) (a) (i) 2672 (ii) 519.4 (iii) 100.4 (iv) 16.9 (b) (i) 3628 (ii) 75.4 (iii) 18.6 (iv) 66.7	[30]
6		(i) A549 (ii) MCF-7 (iii) SKOV3	IC ₅₀ (μM) (a) (i) 25.00 ± 0.85 (ii) 22.83 ± 12.85 (iii) 403.00 ± 17.68 (b) (i) 15.00 ± 1.77 (ii) 10.70 ± 0.42 (iii) 64.23 ± 12.12 (c) (i) 2.51 ± 0.18 (ii) 4.48 ± 0.94 (iii) 58.53 ± 13.58	[31]
7		(i) MCF-7 (ii) HepG2	IC ₅₀ (μM) (i) 2.09 (ii) 2.08	[32]

Table 2. Cont.

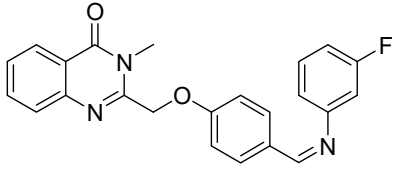
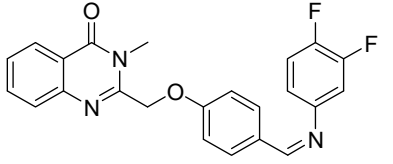
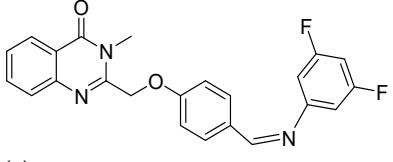
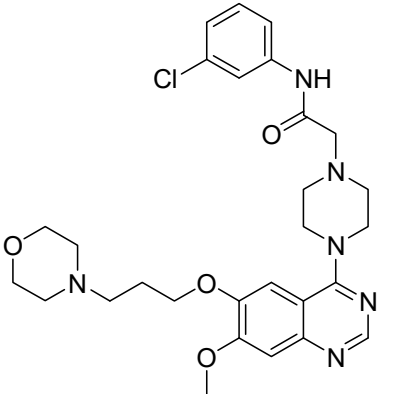
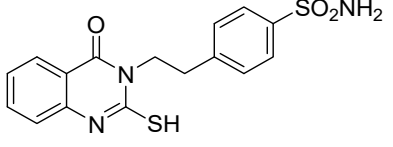
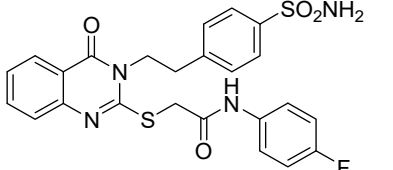
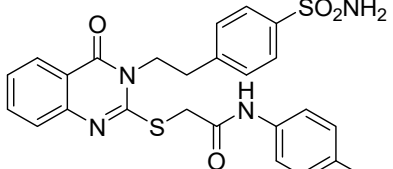
Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
8			(a)	[33]
			(i) 0.047 ± 0.004	
			(ii) 19.73 ± 2.34	
		(iii) 30.06 ± 1.86		
		(iv) 35.92 ± 5.85		
		(i) EGFRwt-TK (ii) A549, (iii) PC-3, and (iv) SMMC-7721	(b)	
			(i) 0.010 ± 0.001	
			(ii) 12.30 ± 4.12	
			(iii) 17.08 ± 3.61	
			(iv) 15.68 ± 1.64	
			(c)	
			(i) 0.54 ± 0.031	
			(ii) 7.22 ± 3.51	
			(iii) 13.29 ± 1.12	
			(iv) 6.04 ± 0.55	
9		(i) A549, (ii) PC-3 (iii) HepG2 (iv) K562	IC ₅₀ (μM)	[34]
			(i) 8.24 ± 1.40	
			(ii) 7.66 ± 1.27	
			(iii) 38.62 ± 2.41	
			(iv) 21.96 ± 3.51	
10			IC ₅₀ (mM)	[35]
			(a)	
			(i) 0.65 ± 0.15	
		(ii) 4.60 ± 1.08		
		(iii) 1.71 ± 0.01		
		(iv) 3.67 ± 0.43		
		(v) 13.46 ± 2.19		
		(i) MCF-7 (ii) HT-29 (iii) HL-60 (iv) K562 (v) MRC-5	(b)	
			(i) 3.86 ± 0.78	
			(ii) 3.56 ± 1.09	
			(iii) 1.50 ± 0.14	
			(iv) 0.42 ± 0.10	
			(v) 7.07 ± 0.41	
			(c)	
			(i) 1.04 ± 0.07	
			(ii) 1.43 ± 0.45	
			(iii) 0.41 ± 0.02	
			(iv) 2.03 ± 0.40	
			(v) 3.77 ± 1.21	

Table 2. Cont.

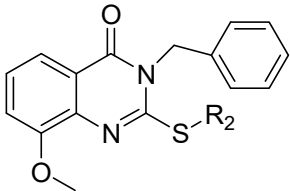
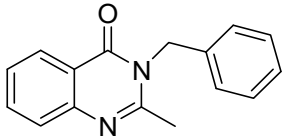
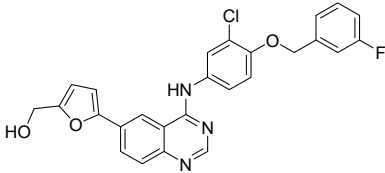
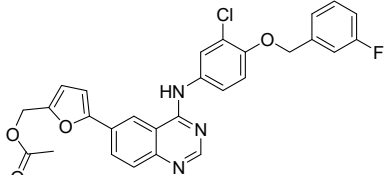
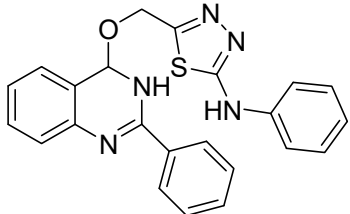
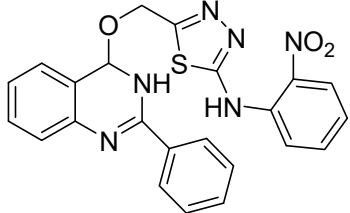
Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
11	 <p>(a) R₂= 3-(Phthalimido-2-yl)propyl</p>	(i) HeLa (ii) MDA-MB231	IC ₅₀ (mM) (a) (i) 1.85 (ii) 2.33	[36]
12		(i) SKLU (ii) MCF (iii) HepG-2	IC ₅₀ (i) 9.48 (ii) 20.39 (iii) 18.04 µg/mL.	[37]
13	 <p>(a)</p>  <p>(b)</p>	(i) SW480, (ii) A549 (iii) NCI-H1975 (iv) A431	IG ₅₀ (µM) (a) (i) 5.58 ± 1.43 (ii) 7.35 ± 1.42 (iii) 3.01 ± 1.07 (iv) 3.64 ± 0.51 (b) (i) 5.18 ± 0.99 (ii) 5.49 ± 1.54 (iii) 6.78 ± 1.98 (iv) 8.33 ± 1.29	[38]
14	 <p>(a)</p>  <p>(b)</p>	Glycogen synthase kinase (GSK-3) inhibitors	Docking score (a) -6.11 (b) -7.55	[39]

Table 2. Cont.

Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
15	<p>(a)</p>	Type-I receptor tyrosine kinase inhibitors	Effective for the treatment of hyperpro-liferative diseases, e.g., cancer	[45]
	<p>(b)</p>			
	<p>(c)</p>			
	<p>(d)</p>			

Table 2. Cont.

Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
16			(a) (i) 32 (ii) 24 (iii) 23 (iv) 40 (v) 27 (vi) 16.4	[41]
		(i) HL-60 (ii) A375 (iii) MCF-7 (iv) Panc-1 (v) PC-3 (vi) PI3K-a at 0.5 uM	(b) (i) 7 (ii) 9 (iii) 10 (iv) 21 (v) 28 (vi) 17	
			(c) (i) 15 (ii) 23 (iii) 12 (iv) 7 (v) 29 (vi) 38.1	
			(d) (i) 36 (ii) 32 (iii) 100 (iv) 68 (v) 38 (vi) 4.1	
17		vascular endothelial cell growth (VEGF)	–	[42]
18		HER2 positive or HER2 amplified	–	[43]

Table 2. Cont.

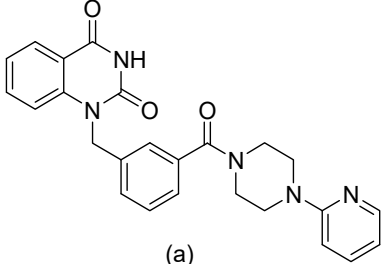
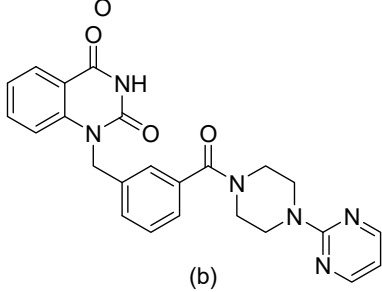
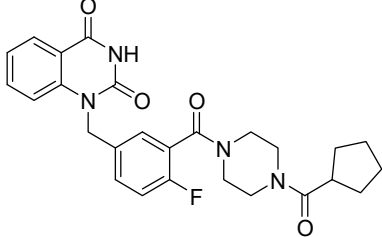
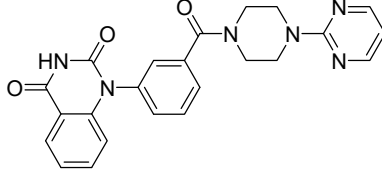
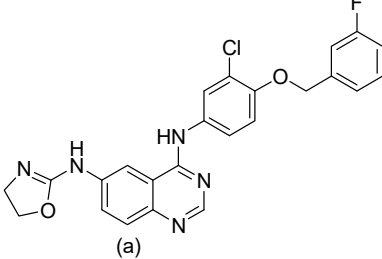
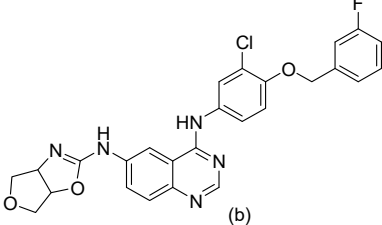
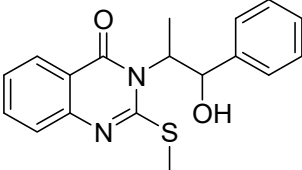
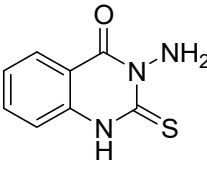
Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
19	 <p>(a)</p>	ADP ribose polymerase (PARP) inhibitors	effective for breast cancer treatment	[44]
	 <p>(b)</p>			
				
				
20	 <p>(a)</p>	Type 1 receptor tyrosine kinase inhibitors.	Effective for the treatment of hyperproliferative diseases such as cancer	[45]
	 <p>(b)</p>			

Table 2. Cont.

Compound no.	Structure	Activity Tested against the Cells	Cytotoxicity	Ref.
21	(a) 	(i) MDA-MB-231 (ii) MCF-7 (iii) HCT-116 (iv) HepG-2 (v) EGFR (vi) breast cancer cell line	(a) (i) 1.53 ± 0.01 (ii) 5.43 ± 0.14 (iii) 5.76 ± 0.11 (iv) 4.14 ± 0.03 (v) 0.76 ± 0.10	[46]
	(b) 	(i) 1.60 ± 0.01 (ii) 7.23 ± 0.07 (iii) 10.6 ± 0.19 (iv) 17.6 ± 0.15 (v) 2.13 ± 0.21		

Synthesis of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline analogs was performed by Golden et al. [42]. Synthesized compound 4-(4-bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-ol as in Table 2, Compound 17, is a potent inhibitor of vascular endothelial cell growth (VEGF) RTK, and also exhibits activity against epidermal growth factor.

Lindmark et al. [43] published a patent for synthesized quinazoline analog and used as anticancer agents. Synthesized compound N4-(4-((thiazol-2-yl)methoxy)-3-chlorophenyl)-N6-((R)-4,5-dihydro-4-methyloxazol-2-yl)quinazoline-4,6-diamine as in Table 2, Compound 18, shows remarkable anti-cancer activity.

Ci et al. [44] have also synthesized and patented novel 1-(aryl methyl) quinazoline-2,4-(1H,3H)-ones analogs. Synthesized compounds as shown in Table 2, Compound 19, were used as poly ADP ribose polymerase (PARP) inhibitors, which is effective for the breast cancer treatment.

Wallace et al. [45] have synthesized quinazoline analogs. Synthesized compounds N4-(4-(3-fluorobenzyloxy)-3-chlorophenyl)-N6-(4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine, and N4-(4-(3-fluorobenzyloxy)-3-chlorophenyl)-N6-(3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-2-yl)quinazoline-4,6-diamine as in Table 2, Compound 20, were used as type 1 receptor tyrosine kinase inhibitors.

A new set of quinazolinone analogs were synthesized by using *L-norephedrinewas* as a basic unit by Ghorab et al. [46]. The cytotoxicity of synthesized compounds was evaluated against the MDA-MB-231, MCF-7, HepG-2, HCT-116 cancer cell lines along with the EGFR activity. Synthesized compounds 3-(1-hydroxy-1-phenylpropan-2-yl)-2-(methylthio)quinazolin-4(3H)-one and its analog, as shown in Table 2, Compound 21, were reported as potent molecules against breast cancer cell line.

5. Quinazoline as Anti-Viral

Antiviral activity of a molecule is entirely related to the compounds that either kill the virus or reduce its growth rate without displaying any toxicity to the host and nearby tissues. The various derivatives of quinazoline have been explored to show significant antiviral activities as discussed.

A series of 2,4 disubstituted quinazoline derivatives with many amide groups were synthesized and tested for antiviral activity as a drug for anti-influenza [47]. The SAR studies exhibited that synthesized compounds 2-(2-(dimethylamino)quinazolin-4-yloxy)-N-phenylacetamide and *N*-(2-(2-(3,4-dihydroisoquinolin-2(1H)-yl)quinazolin-4-yloxy)ethyl)benzamide as shown in Table 3, Compound 1, are the most active compounds having highest anti-influenza virus activity with IC_{50} of less than 10 μ M.

To eliminate the side effects and disadvantages of HCV, Rothan et al. [48] designed a new series of quinazoline derivatives and evaluated their biological activity as antiviral agents. Synthesized compounds as in Table 3, Compound 2, show remarkable activity against HCV NS3-4Apro with a considerable reduction in *Renilla luciferase* (Rluc) activities at 40 μM .

Based on the pharmacophore hybrid approach, quinazoline derivatives were synthesized having 1,2,4-triazole thioether moiety and tested for their antibacterial and antifungal activities. Synthesized compounds have shown potent inhibition activity against the Gram-negative bacteria, e.g., bacterium *Xanthomonas axonopodis* pv. *citri* (*Xac*), *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Ralstonia solanacearum* (*Rs*). Synthesized compounds ethyl 2-(5-amino-1-(quinazolin-4-yl)-1H-1,2,4-triazol-3-ylthio) acetate and their derivatives as in Table 3, Compound 3, have shown prominent inhibition activity against phytopathogenic bacteria. These compounds exhibited EC_{50} values of 46.9, 47.8 and 43.2 $\mu\text{g}/\text{mL}$, respectively, against the bacterium *Xanthomonas axonopodis* pv. *Citri* which were more effective than marketed drug agrobactericide Bismethiazol (56.9 $\mu\text{g}/\text{mL}$) [49].

Table 3. Antiviral activity of quinazoline derivatives.

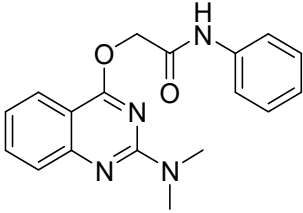
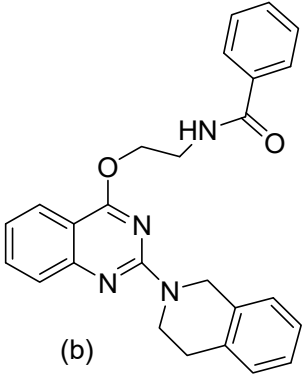
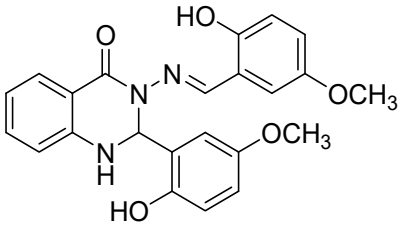
Compound no.	Structure	Microbe Selected	Activity	Ref.
1	 <p>(a)</p>	Anti-IAV A/WSN/33 (H1N1)	IC_{50} (μM)	[47]
	 <p>(b)</p>		(a) 3.70 ± 0.82 (b) 8.64 ± 1.76	
2		(i) HCV NS3-4Apro	IC_{50} (μM) (i) 42	[48]

Table 3. Cont.

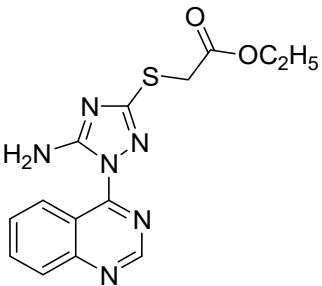
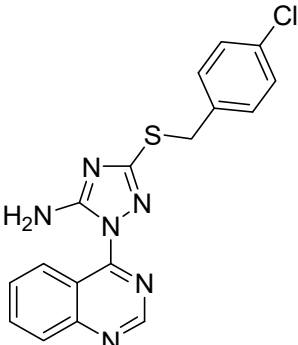
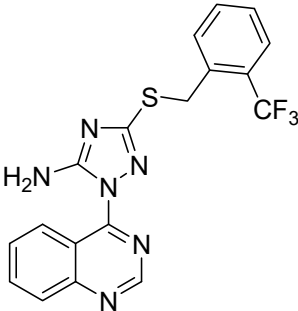
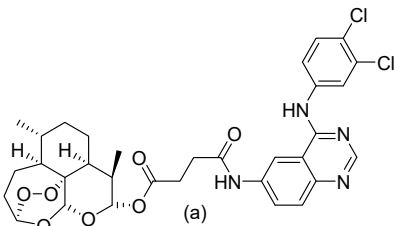
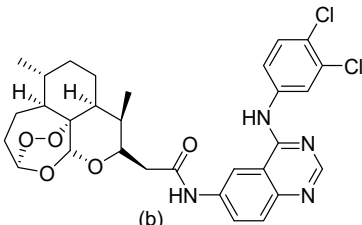
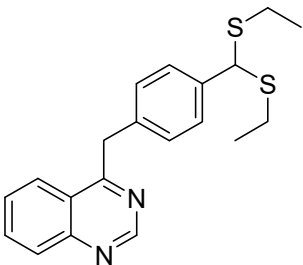
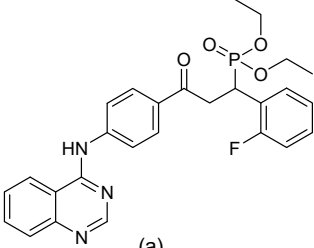
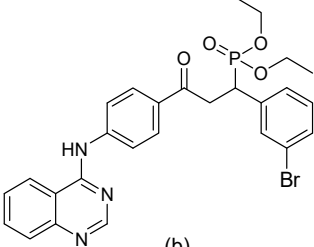
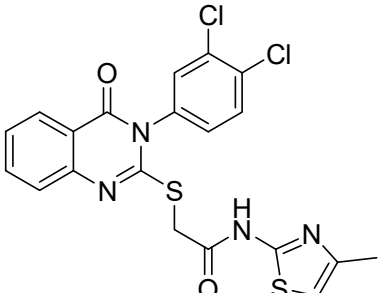
Compound no.	Structure	Microbe Selected	Activity	Ref.
	 <p>(a)</p>			
3	 <p>(b)</p>	(i) Bacterium <i>Ralstonia solanacearum</i> (Rs)	EC ₅₀ (µg/mL) (a) 81.6 (b) 93.1 (c) 43.2	[49]
	 <p>(c)</p>			
4	 <p>(a)</p>	(i) Cytomegalovirus 3D7	EC ₅₀ (µg/mL) (i) 3.8 ± 1 (ii) 5.89 ± 1.07	[50]
	 <p>(b)</p>	(ii) HCMV EC50	(b) 39.9 ± 0.8 (ii) 0.15 ± 0.05	

Table 3. Cont.

Compound no.	Structure	Microbe Selected	Activity	Ref.
5		(i) Anti-CMV (ii) Anti-PVY	(i) 248.6 ± 2.9 (ii) 350.5 ± 3.6	[51]
6	(a)  (b) 	CMV (i) Curative effect (%) (ii) Protective effect (%) (iii) Inactive effect (%)	(a) (i) 40.5 ± 1.5 (ii) 55.1 ± 2.3 (iii) 21.0 ± 0.9 (b) (i) 14.7 ± 0.9 (ii) 56.8 ± 2.6 (iii) 35.9 ± 3.5	[52]
7		(i) Hepatitis C Virus (ii) Japanese Encephalitis Virus	–	[53]

Quinazoline artemisinin hybrids were synthesized and evaluated for their in vitro biological activity. Novel quinazoline artemisinin hybrids were synthesized and evaluated for their antiviral activity [50]. Synthesized hybrids as in Table 3, Compounds 4(a) and (b), were found to have most potent activity against cytomegalovirus having $EC_{50} = 0.15\text{--}0.21\ \mu\text{M}$. These compounds were compared with ganciclovir having $EC_{50} = 2.6\ \mu\text{M}$ and found to be superior by a factor of 12–17.

Dithioacetal moiety containing quinazoline derivatives were synthesized as an antiviral agent with reference to ningnanmycin. The prepared compound 4-(4-(bis(ethylthio)methyl)benzyl)quinazoline as in Table 3, Compound 5, found to have maximum therapeutic effectiveness against CMV (cucumber mosaic virus) with $EC_{50} = 248.6\ \mu\text{g}/\text{mL}$ and potato virus Y ($EC_{50} = 350.5\ \mu\text{g}/\text{mL}$), which is better than commercially available ningnanmycin ($357.7\ \mu\text{g}/\text{mL}$ and $493.7\ \mu\text{g}/\text{mL}$, respectively) [51].

1,4-hydrophosphinylation of α,β -unsaturated carbonyl compounds have been applied for the synthesis of chalone-like compounds. Antiviral activity was tested against the cucumber mosaic virus. Selected compounds in Table 3, Compound 6, reveal protective

activities at 55.1% and 56.8%, respectively, which is comparable to the marketed drugs ningnanmyin (49.3%) and dufulin (53.1%) [52].

Quinazoline analogs have been used for treating or preventing certain viral infection, specifically, Hepatitis C virus and Japanese Encephalitis virus [53]. Synthesized compounds 2-(3-(3,4-dichlorophenyl)-3,4-dihydro-4-oxoquinazolin-2-ylthio)-N-(4-methylthiazol-2-yl)acetamide, as in Table 3, Compound 7, were found to be potent antivirals and these quinazoline analogs were used.

6. Quinazoline as Anti-Bacterial

Various researches have confirmed the antibacterial activity of quinazolinone derivatives higher than of standard drugs. This is due to the structural features of these analogs which is the main reason of the interest for research in this area.

Misra et al. [54] have synthesized a new series of quinazoline embellished analogues of 1,5-benzodiazepine and evaluated their antibacterial activity. Synthesized compounds (Z)-3-(2-phenylquinazolin-4-yl)-1H-benzo[b][1,4]diazepin-2(5H)-one and (E)-4-(methylthio)-3-(2-phenylquinazolin-4-yl)-1H-benzo[b][1,4]diazepin-2(5H)-one as shown in Table 4, Compound 1, were observed to be highly potent, which showed to be highly effective against *Staphylococcus aureus* and *Escherichia coli*.

Table 4. Antibacterial activity of quinazoline derivatives.

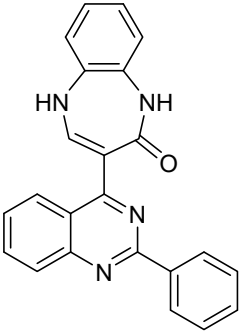
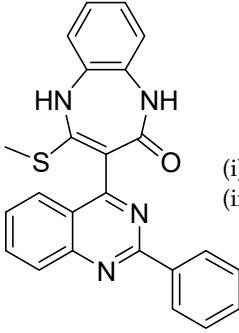
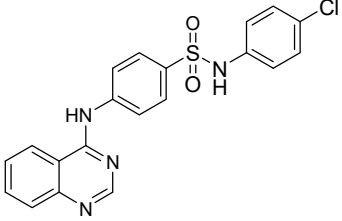
Compound no.	Structure	Microbe Selected	Activity	Ref.
1	 <p>(a)</p>	(i) <i>S. aureus</i> (ii) <i>E. coli</i>	IC ₅₀ (µg/mL)(a) (i) 200 (ii) 200 (b) (i) 200 (ii) 200	[54]
	 <p>(b)</p>			
2	 <p>(a)</p>	(i) Gram-positive Bacteria (ii) Gram-negative Bacteria	MIC in mg/mL (i) 6.25 (ii) 3.12	[55]

Table 4. Cont.

Compound no.	Structure	Microbe Selected	Activity	Ref.
3	<p>(a)</p> <p>(b)</p> <p>(c)</p> <p>(d)</p>	<i>A. baumannii</i> bacteria	–	[56]
4		<i>Staphylococcus aureus</i> M (RSA) (gram positive bacteria)	–	[57]

Kumar et al. [55] synthesized novel series of 4-amino-*N*-(phenyl)benzenesulfonamides derivative and evaluated their antimicrobial activity. Chloro-derivative of synthesized compounds as in Table 4, Compound 2, were found to be most potent candidate against the gram-negative bacteria strain.

Peter et al. [56] have synthesized disubstituted quinazoline-2,4 diamines analogs. Synthesized compounds *N*2-benzyl-*N*4-methyl-6-((*E*)-pent-1-enyl)quinazoline-2,4-diamine and its analogs as shown in Table 4, Compound 3, are effective to kill and to prevent *Acinetobacter baumannii* bacteria.

A new class of compounds was synthesized by Chang et. al. [57]. The synthesized compound 3-(2-(4-ethynylstyryl)-4-oxoquinazolin-3(4H)-yl) benzoic acid as in Table 4, Compound 4, is a highly effective antibiotic against gram positive bacteria, viz., *S. aureus* M (RSA).

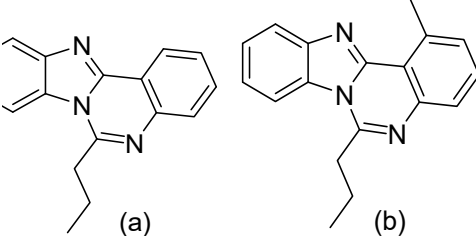
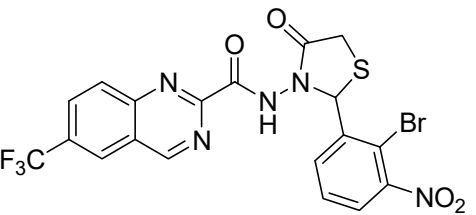
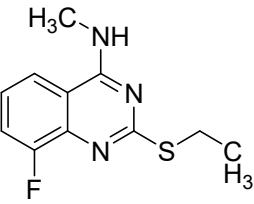
7. Quinazoline as Anti-Tubercular Activity

TB is one of the most prevalent and contagious diseases. Quinazoline molecules have been explored as a potent scaffold for anti-tubercular activity. The following studies explored the strong approach of quinazoline derivatives as biologically active antitubercular agents.

Thirty two compounds were prepared using benzimidazo quinazoline as scaffold [58] and tested for biological activity as anti-tubercular activity. Prepared compounds 6-Propylbenzo[4,5]imidazo[1,2-*c*]quinazoline (a) and 2-Methyl-6-propylbenzo[4,5]imidazo[1,2-*c*]quinazoline (b) as shown in Table 5, Compound 1, were found to be the most potent

compounds against *M. tuberculosis* with MIC values in the range of 12.5 and 0.78 $\mu\text{g/mL}$, respectively.

Table 5. Antitubercular activity of quinazoline derivatives.

Compound no.	Structure	Activity	Observed Values	Ref.
1	 <p>(a) (b)</p>	As anti-TB agents <i>M. tuberculosis</i>	MIC values in the range of 12.5 and 0.78 $\mu\text{g/mL}$	[58]
2		(i) Antitubercular activity MIC (μM) on H37RV (ii) DprE1 IC ₅₀ (μM)	(i) 1.12 (ii) 11.6 \pm 1.3	[59]
3		(i) Antitubercular activity MIC on <i>Mycobacterium tuberculosis</i> (<i>M. tb</i>) (ii) Ex vivo activity	MIC $\mu\text{g/mL}$ (i) 0.02 IC ₅₀ $\mu\text{g/mL}$ (ii) 0.011	[60]

6-(trifluoromethyl)-N-(4-oxothiazolidin-3-yl)quinazoline-2-carboxamide derivatives (Table 5, Compound 2) have been designed as an antitubercular agent for the inhibition of DprE1 [59]. Compounds with nitro and hydroxyl groups have maximum antitubercular activity against *Mycobacterium tuberculosis* H37RV.

Lupien et al. have synthesized new derivatives of 2-Ethylthio-4-methylaminoquinazoline and evaluated for their biological activity against *Mycobacterium tuberculosis* (*M. tb*) [60]. It was concluded that quinazoline based derivatives are a potent moiety for the tuberculosis drug targeting (Table 5, Compound 3).

8. Quinazoline as Anti-Oxidant Activity

Excessive formation of free radicals due to oxidative stress need to be suppressed in the human body. Developments of antioxidative agents are the one major necessity in the area of drug designing, as the antioxidant can defend the body due to the damage by free radicals. Antioxidative properties of quinazolines derivative is a recent and emerging concern.

Synthesis of novel 2-thioxobenzo quinazoline with their analogs was performed by Salahi et al. [61] and tested as anti-oxidant. Synthesized benzoquinazolines as shown in Table 6, Compound 1, were found to have high DPPH and free radical scavenging activities along with the reduction competence. Butylated hydroxyl toluene (BHT) was taken as the reference compound.

Table 6. Antioxidant activity of quinazoline derivatives.

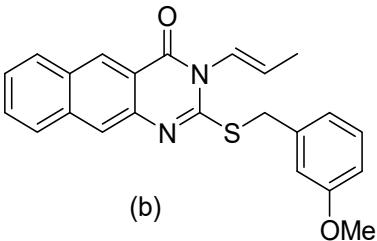
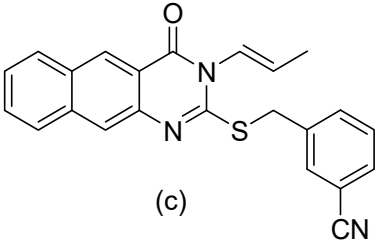
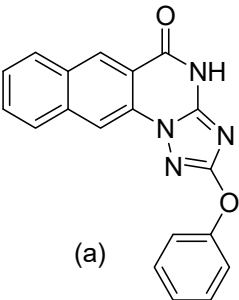
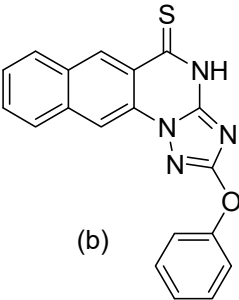
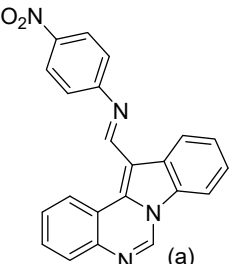
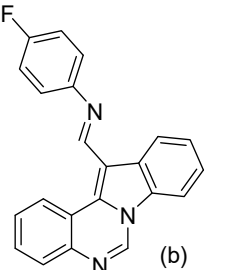
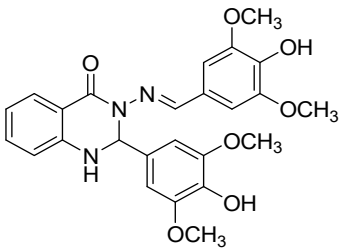
Compound no.	Structure	Activity	Observed Values	Ref.
1	 <p>(b)</p>	Anti-Oxidant activity DPPH and free radical scavenging activities were evaluated	Dock score kcal/mol (a) −8.76 (b) −7.88	[61]
	 <p>(c)</p>			
2	 <p>(a)</p>	(i) DPPH scavenging activity (ii) FRAP of benzotriazolo- quinazolines	(a) (i) 50.88 ± 0.15 (ii) 36.01 ± 0.13 (b) (i) 1376 ± 12.53 (ii) 813 ± 5.86	[62]
	 <p>(b)</p>			
3	 <p>(a)</p>	(i) DPPH free radical scavenging activity (ii) H ₂ O ₂ free radical scavenging activity	IC ₅₀ µg/mL (a) (i) 18.78 ± 1.86 (ii) 16.84 ± 2.60 (b) (i) 18.83 ± 2.89 (ii) 16.61 ± 3.00	[63]
	 <p>(b)</p>			

Table 6. Cont.

Compound no.	Structure	Activity	Observed Values	Ref.
4		(i) DPPH-radical-scavenging (ii) Fe ³⁺ /Fe ²⁺ Reducing Power (Absorbance)	(i) 20.234 ± 0.094 (ii) 0.071 ± 0.036	[64]

Novel analogs of 2-phenoxy benzo triazoloquinazoline were prepared by Almezahia et al. [62]. These compounds were tested for their biological activity as anti-oxidant by using three different assays. The results showed that benzotriazoloquinazoline derivative has good antioxidant activities with the capability of scavenging the free radicals. The synthesized compounds as shown in Table 6, Compound 2, were found to exhibit the highest antioxidant activity. BHT was taken as the reference agent.

Dixit et al. [63] synthesized a series of quinazoline analogs and tested them for their biological activity as antioxidant activity. Analog synthesized (14E)-N-((H-indolo[1,2-c]quinazolin-12-yl)methylene)-4-nitrobenzenamine (a) and its fluoro (b) derivatives as shown in Table 6, Compound 3, were found to have maximum activity as antioxidants with an IC₅₀ value of 18.78 ± 1.86 µg/mL, 16.84 ± 2.60 µg/mL and 18.64 ± 2.40 µg/mL, respectively.

A new series of 2, 3 substituted quinazolinones analogs were synthesized and tested for their biological activity [64]. Antioxidant activity was tested by DPPH-radical-scavenging, reducing power and total antioxidant status (TAS) assay. Synthesized compounds as shown in Table 6, Compound 4, possess antioxidant activity.

9. Quinazoline as Anti-Convulsant

Novel 2,3-disubstituted-4-(3H) quinazolinone derivatives were prepared and evaluated for their anti-convulsant activity [65]. The synthesized drug was used against electroshock-induced seizures and PTZ-induced clonic seizures. Compounds as in Table 7, Compound 1, were screened for anticonvulsant activity and found to be the most potent anti-convulsant and carbamazepine.

Table 7. Miscellaneous activities of quinazoline derivatives.

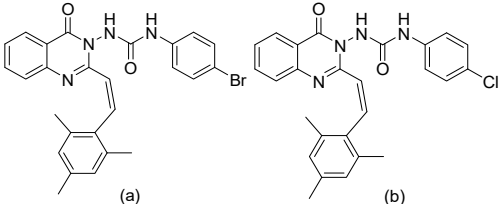
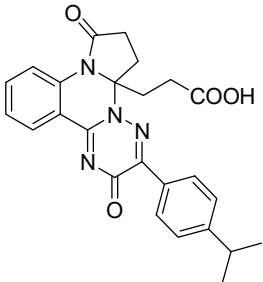
Compound no.	Structure	Activity	Results	Ref.
1		Evaluated as anti-convulsant activity	Synthesized compounds were performed against maximal electroshock-induced seizures and PTZ-induced clonic seizures	[65]
2		Evaluated as anti-inflammatory agent	Synthesized compounds showed high anti-inflammatory activity. Fluorine atom has crucial role in the anti-inflammatory activity of the synthesized compounds	[66]

Table 7. Cont.

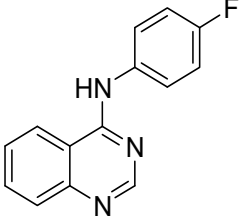
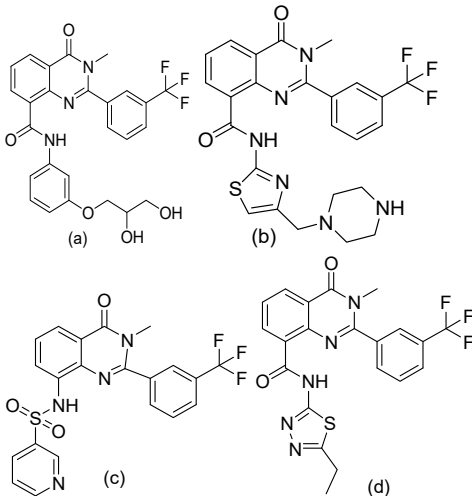
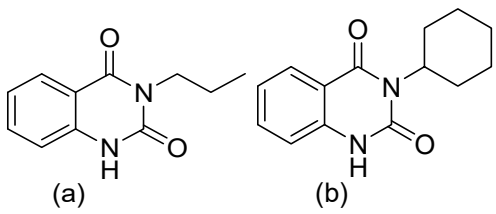
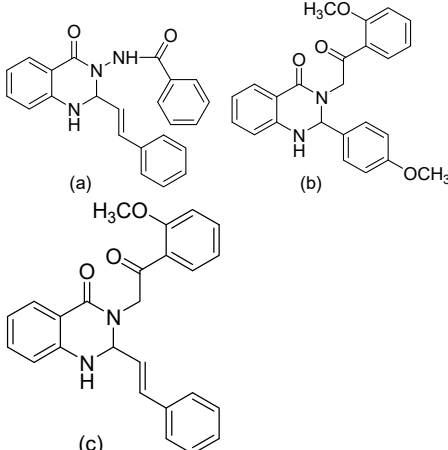
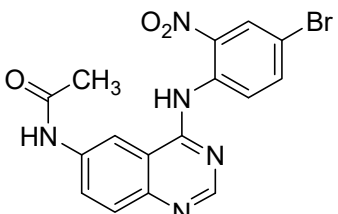
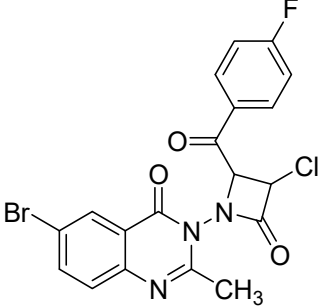
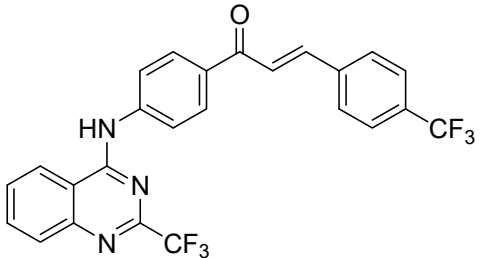
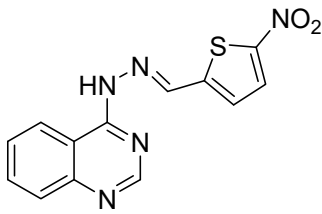
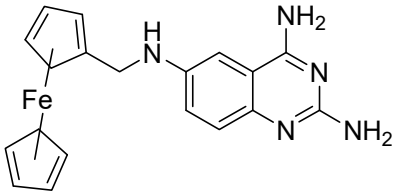
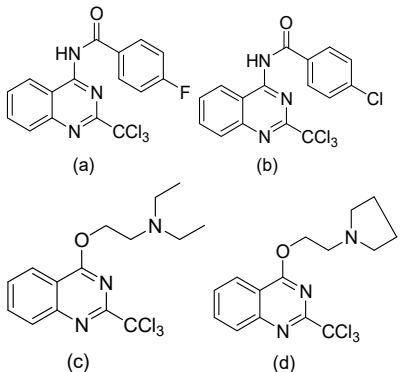
Compound no.	Structure	Activity	Results	Ref.
3		Evaluated as anti-inflammatory agent	Introduction of Fluorine atom on the phenyl ring leads to strengthening anti-inflammatory activity	[67]
4		Evaluated as Sirtuin Modulating agents	Increases the mitochondrial activity and lifespan of a cell; uses for various diseases and disorders.	[68]
5		Evaluated as Antidiabetic agents	Alpha-amylase and alpha-glucosidase inhibitors	[69]
6		Evaluated as antifungal		[70]
7		Evaluated as antifungal	Antifungal activity against <i>Fusarium moniliforme</i>	[71]

Table 7. Cont.

Compound no.	Structure	Activity	Results	Ref.
8		Evaluated as antifungal	Antifungal activity against <i>Candida albicans</i> and <i>Aspergillus flavus</i>	[72]
9		Evaluated as Antiparasite agents	B-hematin formation inhibitors	[73]
10		Evaluated as Antiparasite agents	Most effective derivatives against <i>P. falciparum</i> 3D7 and K1 strains	[74]
11		Evaluated as Antiparasite agents	Showed activity on promastigotes and intracellular amastigotes	[75]
12		Evaluated as Antiplasmodium agents	IC ₅₀ <i>P. falci</i> . K1 = 0.94 μM IC ₅₀ <i>P. falci</i> . K1 = 0.9 μM	[76]

10. Quinazoline as Anti-Inflammatory Agents

Stavytskyi et al. [66] synthesized substituted pyrrolo-quinazoline derivatives and tested their biological activity as an anti-inflammatory activity with reference to diclofenac. The synthesized compound as in Table 7, Compound 2, was found to be the most potent anti-inflammatory agent. Bansal et al. [67] designed and synthesized a novel class of 4-amino quinazoline derivatives and tested them for their anti-inflammatory activity. The

synthesized compound *N*-(4-fluorophenyl)quinazolin-4-amine as shown in Table 7, Compound 3, was found to be the most potent compound which showed high anti-inflammatory activity. The synthesized compound was compared to standard drug indomethacin.

11. Quinazoline as Sirtuin Modulating Agents

Sirtuin modulating compounds were designed by Oalman et al. [68] to increase the life of cells. Synthesized compounds *N*-(3-(2,3-dihydroxypropoxy)phenyl)-2-(3-(trifluoromethyl)phenyl)-3,4-dihydro-3-methyl-4-oxoquinazoline-8-carboxamide (a) and their derivatives as in Table 7, Compound 4, were used for increasing the mitochondrial activity and preventing wide varieties of diseases and disorders.

12. Quinazoline as Antidiabetic Agents

A series with 3-substituted quinazoline-2,4 diones scaffolds was synthesized and evaluated for their biological activity as antidiabetic agents [69]. Synthesized compounds 3-propylquinazoline-2,4(1H,3H)-dione (a) and 3-cyclohexylquinazoline-2,4(1H,3H)-dione (b) as shown in Table 7, Compound 5, were found to have highly alpha-amylase and alpha-glucosidase inhibitory activity in molecular docking studies artemia salina assay. These active compounds have shown unusual intermolecular interaction in the pocked site of the studied enzymes. Results showed that the synthesised compound is an inhibitor of the enzymes responsible for diabetic conditions like alpha-amylase and/or alpha-glucosidase.

13. Quinazoline as Antifungal Agents

Zhang et al. [70] synthesized a series of quinazolinone derivatives and evaluated them for their biological activity as antifungal agents. Synthesized compounds as shown in Table 7, Compound 6, were found to be highly potent as antifungal agents.

Nangare et al. [71] synthesized 4-(substituted aniline) quinazoline derivatives and evaluated them for their biological activity. Synthesized compound *N*-(4-(4-bromo-2-nitrophenylamino)quinazolin-6-yl)acetamide as shown in Table 7, Compounds 7, had shown the strong antifungal activity against *Fusarium moniliforme* compared to the standard drug griseofulvin.

Agarwal et al. synthesized a series of quinazoline derivatives and evaluated them for their biological activity. The synthesized compound as shown in Table 7, Compounds 8, had shown strong antifungal activity compared to standard drug fluconazole [72].

14. Quinazoline as Antiparasite Agents

Mishra et al. prepared a series of quinazoline-chalcone hybrids and synthesized molecules were evaluated for their biological activity. The synthesized molecule (E)-1-(4-(2-(trifluoromethyl)quinazoline-4-ylamino)phenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one as shown in Table 7, Compound 9, was found to be a considerable inhibition of beta-hematin formation [73].

Tahghighi et al. prepared new synthetic derivatives of 1-(heteroaryl)-2-((5-nitroheteroaryl)methylene) hydrazine and evaluated their biological activity. The synthesized molecule as shown in Table 7, Compound 10, was most effective and had considerable inhibition of beta-hematin formation [74].

Martinez et al. synthesized a series of quinazoline 2,4,6-triamine derivatives and evaluated their biological activity. N6-(ferrocenemethyl)quinazoline-2,4,6-triamine as shown in Table 7, Compound 11, showed high activity on promastigotes and intracellular amastigotes with low cytotoxicity in mammalian cell [75]. Amrane et al. synthesized and evaluated antiplasmodial activity of 4-carboxamido and 4-alkoxy-2-trichloromethyl quinazoline derivatives. Synthesized compounds *N*-(2-(trichloromethyl)quinazoline-4-yl)-4-fluorobenzamide (a), 4-chloro-*N*-(2-(trichloromethyl)-quinazoline-4-yl)benzamide (b), 2-(2-(trichloromethyl)quinazoline-4-yloxy)-*N,N*-diethylethanamine (c) and 4-(2-(pyrrolidin-1-yl)ethoxy)-2-(trichloromethyl)quinazoline (d) as shown in Table 7, Compound 12, were

found to be highly effective as antiplasmodium agents against the multiresistant K1 P.falciparum strain, using doxorubicin and chloroquine as references [76].

15. Conclusions

Quinazoline is a structure of great interest in the area of pharmaceutical chemistry, featuring various drugs, clinical candidates and bioactive molecules. The focus of this review was on the potential biological activity of quinazoline derivatives. This review is additionally useful in providing information regarding the latest developments in quinazoline analogs having completely different pharmacological activity like antitumor, antimicrobial, antimalarial, antiviral and antidiabetic, etc. Diversified biological activities of quinazoline-based drugs comprise the role of substituents along with the position at quinazoline moiety, which gives an insight to understanding the drug and target relation. Therefore, critical and deep research for the various substituents of quinazoline is crucial for potential drug development. This review will provide substantial benefit to scientists for the design and synthesis of quinazoline moiety-based drugs for the safe treatment of various fetal diseases in future.

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