REVIEW ARTICLE

Quinazolines: An Illustrated Review

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J. Adv. Pharm. Edu. & Res.

ABSTRACT

For the last few years, the heterocyclic fused nucleus quinazoline have drawn an immense attention owing to its diversified application in the field of medicinal chemistry research. Being considered as a privileged scaffold, the modification made with different substituents around the centroid paved the researchers a way to deal with at ease. This review is an attempt to magnify the immense potentiality of this ring system. This study may also accelerate the designing process to generate more number of therapeutically viable clinical candidates.

Key words: Quinazoline, Anti cancer activity, Anti-microbial activity, Anti HIV activity.

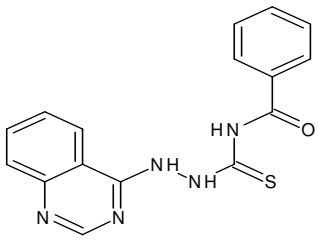
INTRODUCTION

Medicinally many substituted quinazoline derivatives are acknowledged to possess a wide range of bioactivities as anti-malarial, anti-cancer, anti-microbial, antifungal, antiviral, anti-protozoan, anti-inflammatory, diuretic, muscle relaxant, anti-tubercular, CNS depressant, anti-convulsant, acaricidal, weedicide, and many other functional materials. In the foregoing section, we preferentially wanted to frame our study categorically to get an efficient way of understanding about the target-pharmacophore relationship which can further aid the process of *de novo* drug design.

4-substituted Quinazoline

Quinazoline as anti-tumor agents

He et al[1] synthesized a series of novel quinazoline derivatives containing thiosemicarbazide moiety and evaluate their biological activity as antitumor agents. The therapeutically important candidates are as follows:



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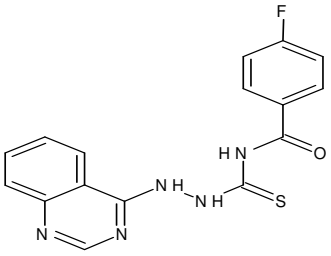

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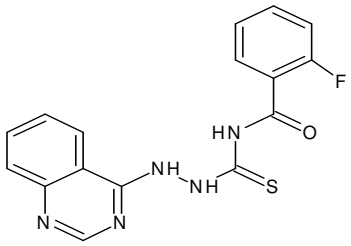

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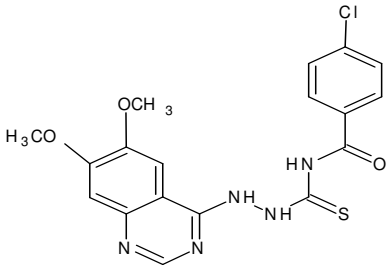

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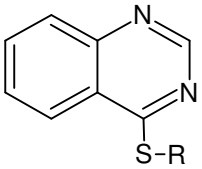
Quinazoline as anti-tubercular agents

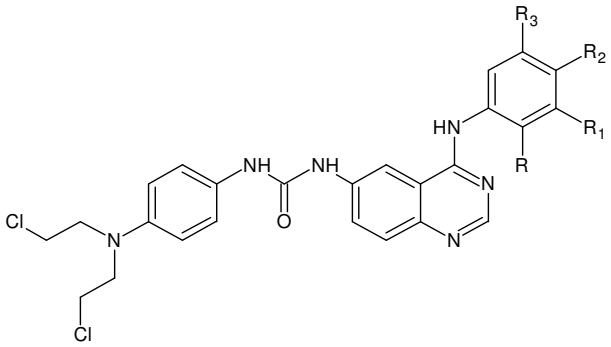
A series of quinazoline derivatives was synthesized by Kunes et al[2] and further evaluated for their pharmacological activity as antitubercular.



	R
5a	$-C_2H_5$
5b	$-C_3H_7$
5c	$-C_4H_9$
5d	$-CH(CH_3)_2$

(5)

Most of the synthesized compounds exhibited antimycobacterial activity against the strains of *Mycobacterium tuberculosis*, *Mycobacerium avium*, *Mycobacterium fortuitum*, *Mycobacterium kansasii* and *Mycobacterium intracellulare*. The modification process with various hydrophobic chain clearly suggests the existence of hydrophobic pocket in the active site of the target of various strains of *Mycobacterium spp*, which eventually raise the therapeutic efficacy.



(6)

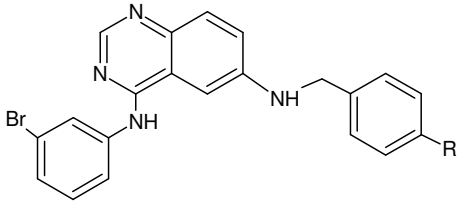
4, 6-disubstituted Quinazolines

Quinazoline as anticancer agents

Marvania et al[3] synthesized a series of phenyl N-mustard-quinazoline derivatives and subsequently evaluated their antitumor activity.

	R	R_1	R_2	R_3
6a	H	$-OCH_3$	$-OCH_3$	$-OCH_3$
6b	F	Cl	H	H
6c	H	Cl	F	H
6d	H	-C≡CH	H	H

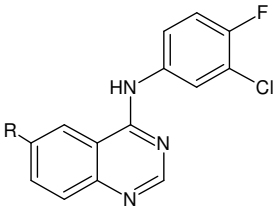
A series of few novel 4, 6 di substituted-(diphenylamino)quinazolines derivatives was synthesized by Li et al[4], which on evaluation for antitumor activity was considered as potent EGFR inhibitors.



	R
7a	-OH
7b	-Cl

(7)

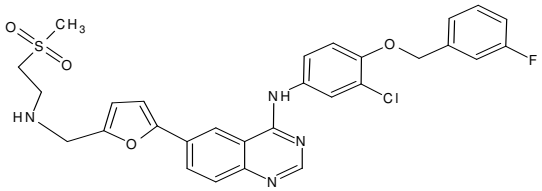
Fernandes et al[5] synthesized a series of quinazoline derivatives and evaluated their function as EGFR inhibitors by applying radioiodination. All the research compounds were further evaluated for potential SPECT activity for molecular imaging of breast cancer.



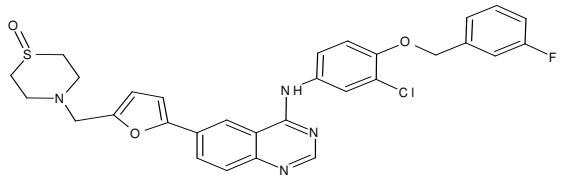
	R
8a	-NHCO$(CH_2)_2$Br
8b	-NHCO$(CH_2)_2$I
8c	-NH_2

(8)

A series of novel 6-furanylquinazoline derivatives were synthesized by Petrov et al[6] and subsequently evaluated for their biological activity as a potent ErbB-1/ErB-2 tyrosine kinase inhibitor.



[9]



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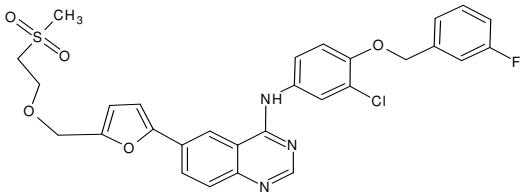

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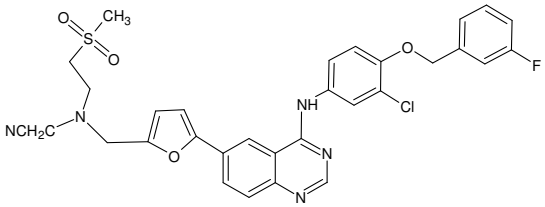
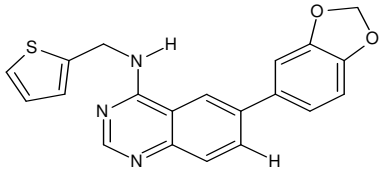


[12]

Rosenthal et al[7] synthesized a series of quinazoline derivatives and evaluated their activity as potent inhibitors of specific isoforms of Cdc2-like kinases (Clk) and dual specificity tyrosine-phosphorylation regulated kinases (Dyrk).



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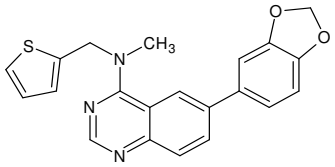

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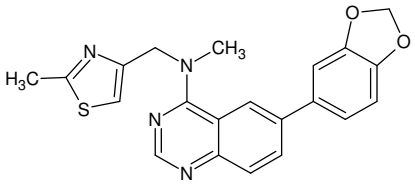

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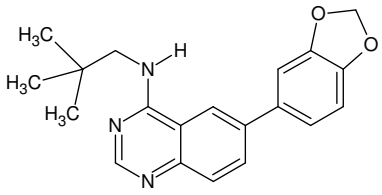
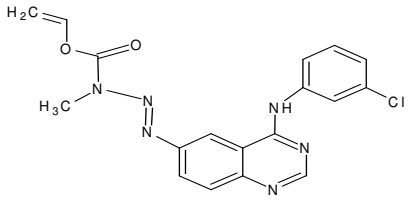


[16]

Rachid et al[8] designed and synthesized new stabilized combi-triazenes for targeting solid tumors expressing the epidermal growth factor receptor (EGFR) or its closest homologue HER2.



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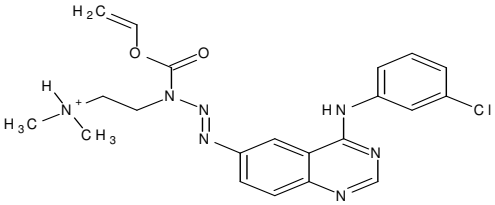
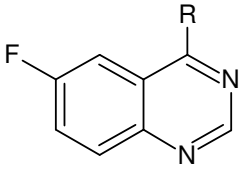


[18]

Quinazoline as antifungal agents

A series of few novel S-substituted-6-fluoro-4-alkyl (aryl) thioquinazoline derivatives were synthesized by Xu et al[9] and evaluated their pharmacological activity as antifungal.



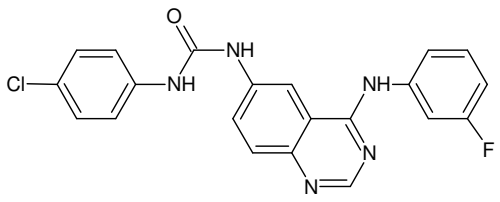
(19)

	R
19a	-$SCH_2CH{=}CH_2$
19b	-$SCH_2CH_2CH_3$
19c	-SCH_2CH_3

All of these compounds exhibited good antifungal activity, especially compound 19c, having a wide spectrum of bioactivity it shows potent inhibitory activity on the growth of most of the fungi with EC_{50} values ranging from 8.3 to 64.2 µg/mL.

Quinazoline as antimalarial agents

Madapa et al[10] synthesized a series of new 6-ureido-4-anilinoquinazolines and evaluated their potent activity as antimalarial agents.



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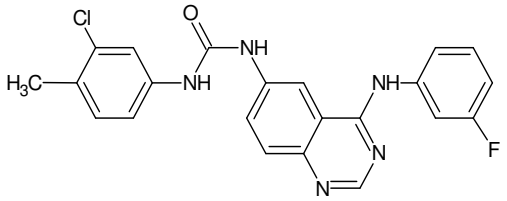

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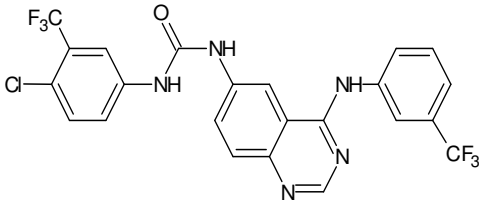

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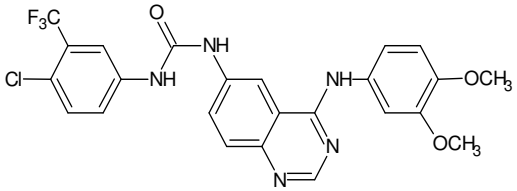
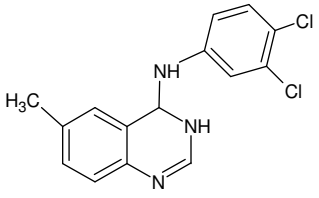


(23)

Quinazoline as antiviral agents.

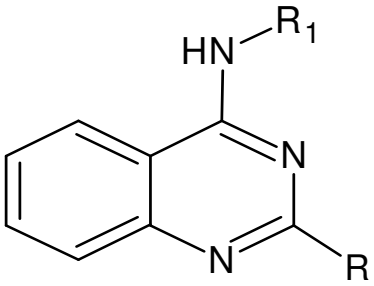
Schleiss et al[11] evaluated protein kinase inhibitory activity and anti-cytomegaloviral activity of the few quinazoline derivatives.



(24)

2, 4-disubstituted Quinazolines

Quinazoline as anticancer agents



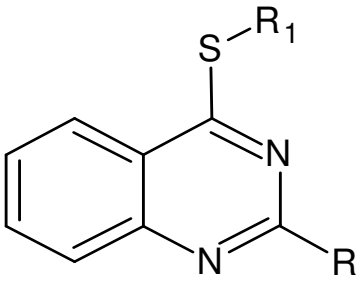
(25)

Gellibert et al[12] designed a series of novel quinazoline derivatives that showed potent ALK5 inhibitory activity.

	R	R_1
25a	6-methyl-2-pyridinyl	pyridine-4-yl
25b	6-methyl-2-pyridinyl	1H-indazol-5-yl
25c	6-methyl-2-pyridinyl	4-pyrimidnyl

Quinazoline as antimalarial agents

A series of 4-Thiophenoxy-2-trichloromethyquinazolines derivatives were synthesized by Verhaeghe et al[13] and their antiplasmodial activity against the human malarial parasite *Plasmodium falciparum* was determined.

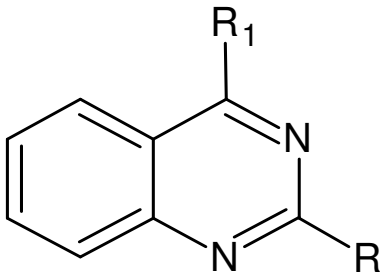


(26)

	R	R_1
26a	$-CCl_3$	$-S-C_6H_5$
26b	$-CCl_3$	$-S-C_6H_4-4Cl$

Compound 26a and 26b showed good activity against K1 *Plasmodium falciparum* (IC_{50} = 1.9µM and 0.9 µM respectively), whereas IC_{50} value of chloroquine is 0.5 µM.

Verhaeghe et al[14] Synthesized a new series of 4-aryl-2-trichloromethylquinazolines and subsequently evaluated their antiplasmodial activity.



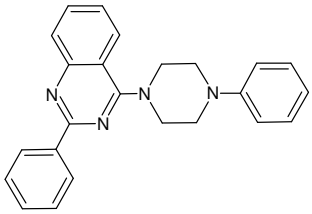
(27)

	R	R_1
27a	$-CCl_3$	$4-F-C_6H_4$
27b	$-CCl_3$	$4-Cl-C_6H_4$
27c	$-CCl_3$	$4-OCH_3-C_6H_5$
27d	$-CCl_3$	2-naphthyl

Compounds with the above substituents exhibited favourable antiplasmodial activity on THP1 and HepG2 human cell lines.

Quinazoline as anti inflammatory analgesics

Alafeefy et al[15] synthesized a series of quinazoline derivatives which showed potent analgesic and anti-inflammatory activity.



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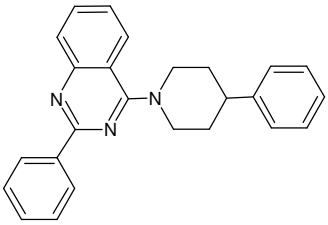


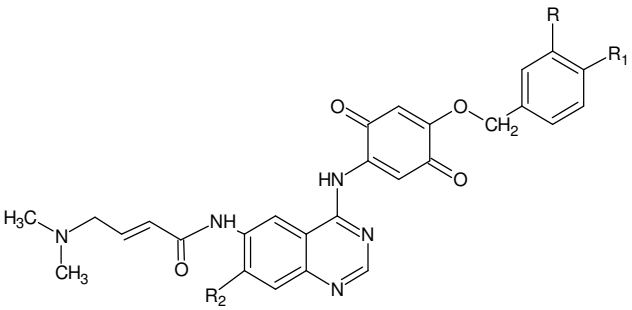
(29)

All the synthesized compounds demonstrated potent activity as anti inflammatory analgesic than the reference compound indomethacin.

Quinazoline as anticancer agents

Wissner et al[16] synthesized a Quinazoline-based novel anti cancer molecule, that are dual irreversible kinase inhibitors.

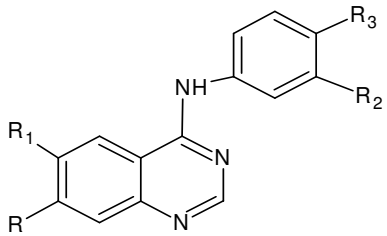
4, 6, 7-trisubstituted Quinazolines



(30)

A series of quinazoline derivatives were synthesized by Noolvi et al[17] and evaluated their biological activity against tyrosine kinase (EGFR).

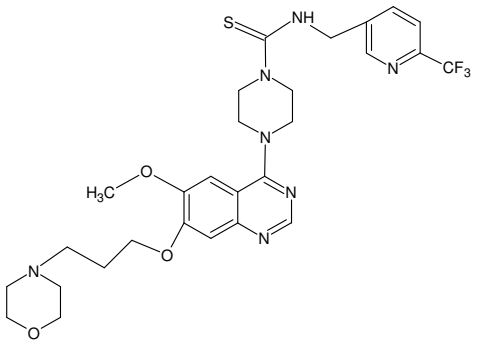
	R	R_1	R_2
30a	-F	H	$-OCH_3$
30b	-F	-F	$-OCH_3$



(31)

	R	R_1	R_2	R_3
31a	OCH_3	OCH_3	H	Br
31b	NO_2	H	F	H

Heath et al[18] synthesized a series of 4-piperazin-1-yl-quinazoline template based aryl and benzyl thiourea derivatives that showed potent, selective, and orally bioavailable antagonist of platelet-derived growth factor (PDGF) receptor.



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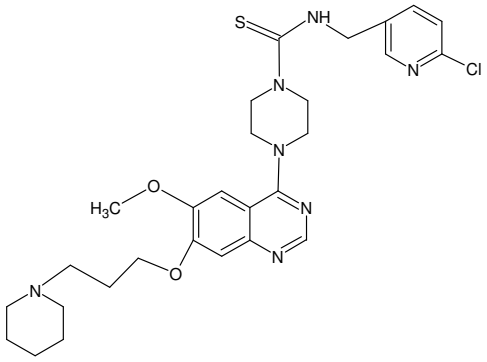

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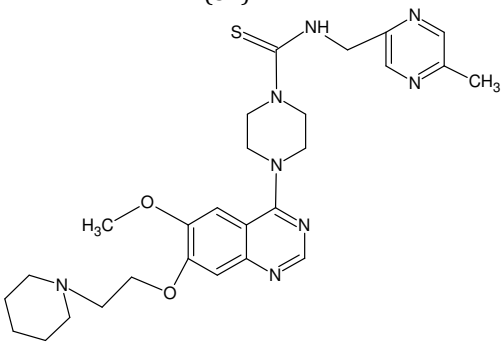

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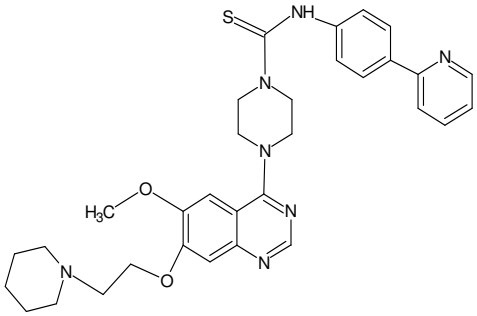
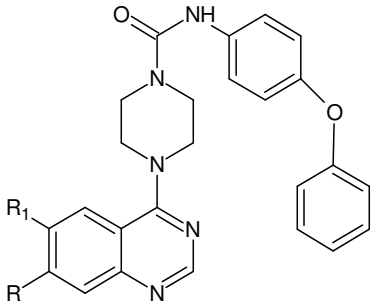


(35)

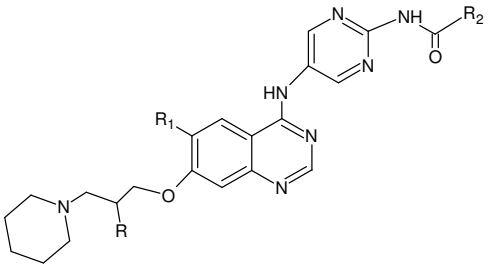
Matsuno et al[19] synthesized a series of 4-[4-(N-Substituted(thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives and evaluated their potential antagonizing activity against Platelet-Derived Growth Factor Receptor (PDGF).



(36)

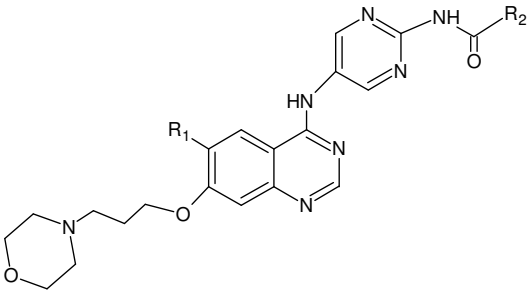
	R	R_1
36a	$-OC_2H_5$	$-OCH_3$
36b	$-COOCH_3$	H

Heron et al[20] synthesized a series of quinazoline derivatives which showed potent inhibitory activity against Aurora kinase.



(37)

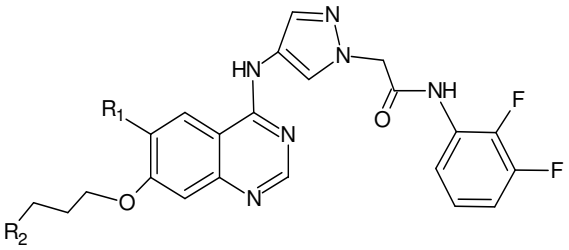
	R	R_1	R_2
37a	H	OCH_3	3-Cl-C_6H_4
37b	OH	OCH_3	C_6H_5



(38)

	R_1	R_2
38a	$-OCH_3$	3-Cl-4F-C_6H_3
38b	$-OCH_3$	3-Cl-C_6H_4

A series of 1-acetanilide-4-aminopyrazole substituted quinazoline derivatives were synthesized by Foote et al[21] and subsequently evaluated their inhibitory activity against Aurora B kinase as a potent anti-tumour agents.



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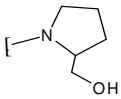
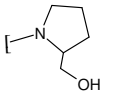
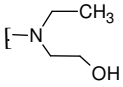
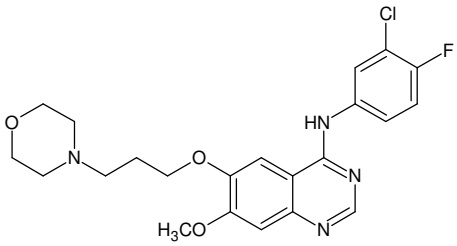
	R_1	R_2
39a	H	
39b	$-OCH_3$	
39c	$-OCH_3$	

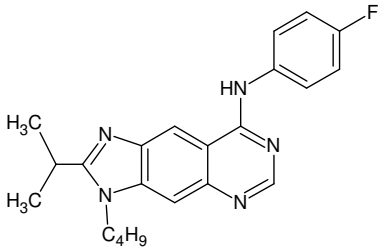
Quinazoline as anti tumor agents

Chen et al[22] evaluate the biological activity of some novel 2, 3-disubstituted 8-arylamino-3H-imidazo[4,5-g]quinazoline derivative as a potent anti-tumor agent.



(40)

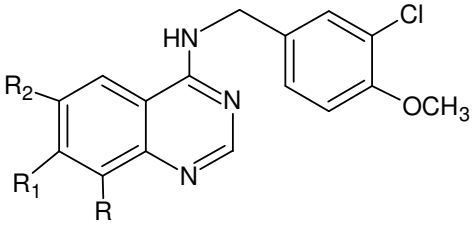
Compound 41 possessed the highest anti-NSCLC activity on the A549 cell line.



(41)

Quinazoline as neuroprotective agents

Kim et al[23] synthesized few quinazoline derivatives and evaluated their activity as potent and highly selective PDE5 inhibitors to be employed for male erectile dysfunction.



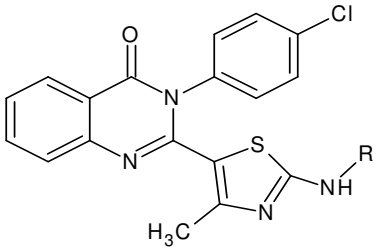
(42)

	R	R_1	R_2
42a	C_3H_7	OCH_3	$NHCOCF_3$
42b	CH_2CH_2OH	OCH_3	$NHCOCH_3$
42c	CH_2CH_2OH	OCH_3	$NHCOC_2H_5$

2, 3-disubstituted Quinazolin-4(3*H*)-one

Quinazoline as anti inflammatory analgesic

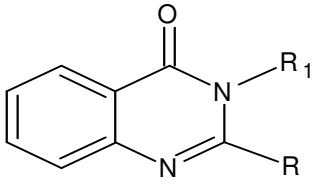
Giri et al[24] synthesized a series of novel 2-(2,4-disubstituted-thiazole-5- yl)-3-aryl-3H-quinazoline-4-one derivatives which became good inhibitors of NF-kB and AP-1 mediated transcription activation.



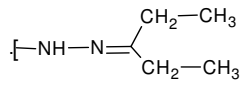
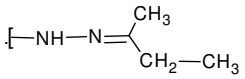
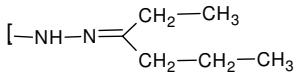
(43)

	R
43a	$-CH_3$
43b	$3Cl-C_6H_4$

A series of 3-phenyl-2-substituted-3H-quinazolin-4-one derivatives was synthesized by Alagarsamy et al[25] and subsequently evaluated their pharmacological activity as analgesic and anti-inflammatory agents.

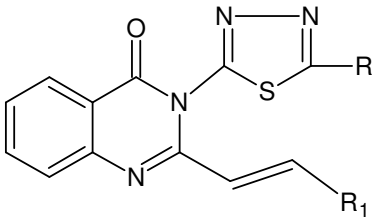


[44]

	R	R_1
44a	C_6H_5	
44b	C_6H_5	
44c	C_6H_5	

Quinazoline as CNS depressant and anticonvulsant

A series of novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones derivatives was synthesized by Jatav et al[26] and evaluated their activity as a CNS depressant agents.

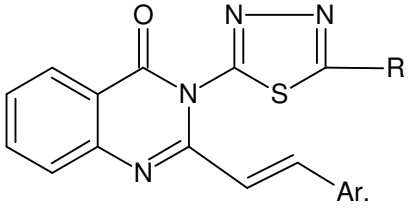


(45)

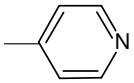
	R	R_1
45a	C_6H_5	C_6H_5
45b	$4-Cl-C_6H_4$	C_6H_5
45c	$4-Cl-C_6H_4$	$p-OCH_3C_6H_5$

All the compounds showed anticonvulsant activity in MES screen, however, compound 45a showed potency similar to standard drug (phenytoin, carbamazepine) without any neurotoxicity.

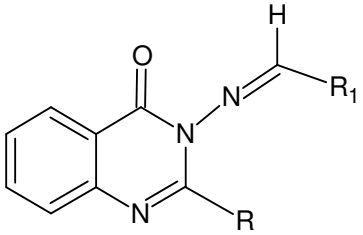
A series of some novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-one derivatives was synthesized by Jatav et al[27] and evaluated their activity as CNS depressant and anti convulsant agents.



(46)

	R	Ar
46a	C_6H_5	$p-ClC_6H_4$
46b	$p-OCH_3C_6H_4$	$p-ClC_6H_4$
46c	$p-ClC_6H_4$	

Compounds with the above substituents showed potent CNS depressant activity. Compound 46a showed anticonvulsant activity at 0.5 and 4 h in different test models, whereas 46c showed anticonvulsant activity at 4 h in MES screen and at 0.5 and 4 h in sub-cutaneous PTZ screen.



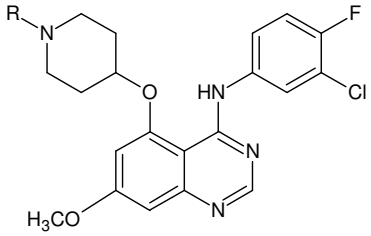
(47)

	R	R_1
47a	C_6H_5	2-OH-C_6H_4
47b	C_6H_5	4-OCH_3-C_6H_4
47c	C_6H_5	C_6H_5

Quinazoline as antiviral agents

Kumar et al[28] synthesized a series of Schiff bases of some 2-phenyl quinazoline-4(3)H-one derivatives and evaluated their activity as antiviral agents.

Compound 47a 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 µg/mL. Compounds 47b and 47c demonstrated good activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus.



(48)

	R
48a	-CH_3
48b	H

4, 5, 7-trisubstituted Quinazolines

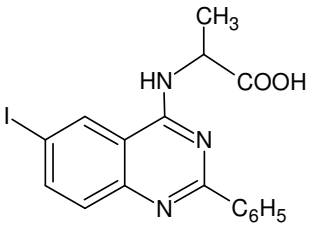
Quinazoline as anticancer agents

Ballard et al[29] synthesized a series of novel C-5 substituted anilinoquinazoline derivatives and evaluated their activity as an inhibitor of epidermal growth factor receptor tyrosine.

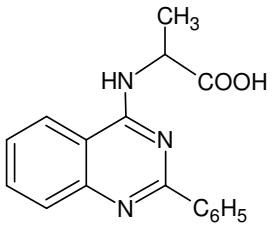
2, 4, 6-trisubstituted Quinazolines

Quinazoline as anticancer agents

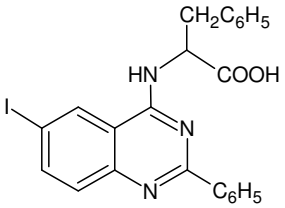
Chandrika et al[30] synthesized few novel 4, 6-disubstituted quinazoline derivatives, which showed good anti-inflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines.



[49]

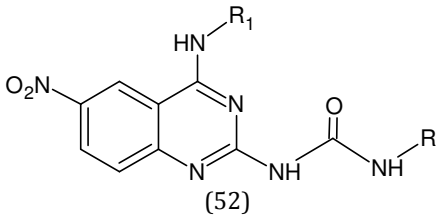


[50]



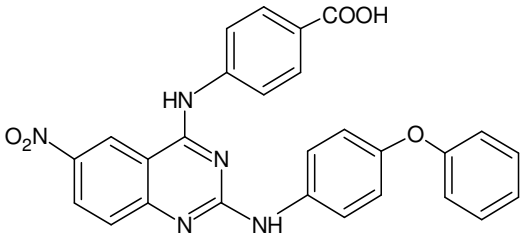
[51]

Zhu et al[31] synthesized a series of quinazoline derivatives with strong inhibition on human Pin1.



(52)

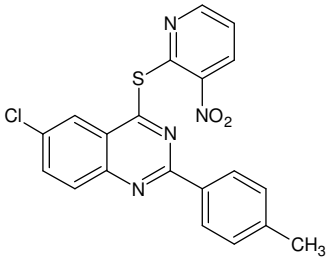
	R	R_1
52a	3, 4-Cl-C_6H_3	4-COOH-C_6H_4
52b	4-CF_3-C_6H_4	4-COOH-C_6H_4
52c	3-CF_3-C_6H_4	4-COOH-C_6H_4



(53)

Quinazoline as anti tumor agents

A series of quinazoline derivatives was designed, synthesiszed by El-Azab et al[32] and evaluated their biological activity as potential antitumor agents.



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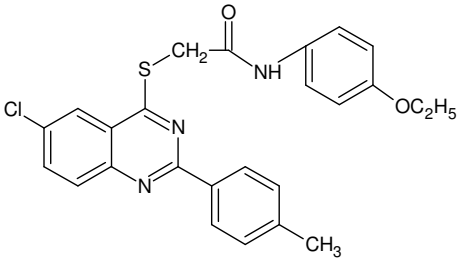

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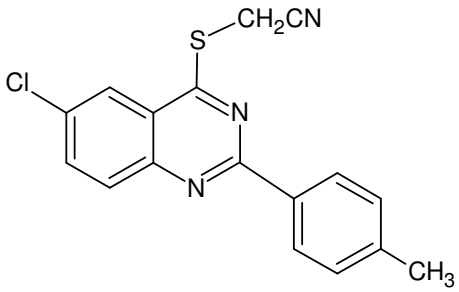
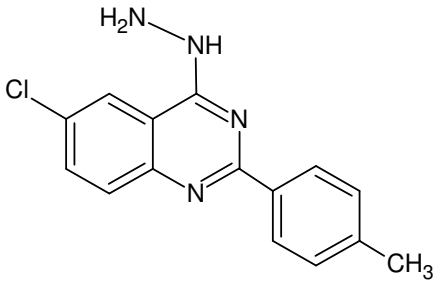


(56)

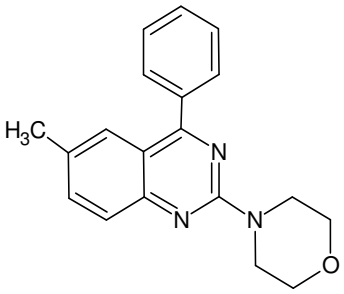


(57)

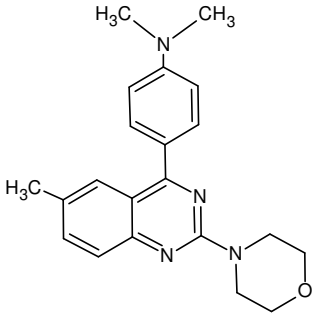
HEPG2 human liver cell line was proved to be sensitive toward compounds 56, 54 and 55 with IC_{50} concentration range of 4.17-5.99 µg/ml. Regarding HELA cervix cell line, higher sensitivity was observed with compounds 57, 56, 54 with IC_{50} concentration range of 3.56-5.39 µg/ml. With regard to broad-spectrum antitumor activity, compounds 57, 56 and 54 showed IC_{50} of 3.35-5.59 µg/ml against the three cell lines.

Quinazoline as antibacterial agents

Bedi et al[33] synthesized a series of quinazolines derivatives and evaluated their biological activity on various bacterial cultures.



(58)



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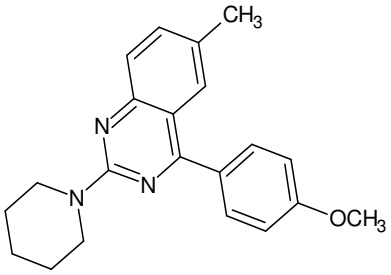
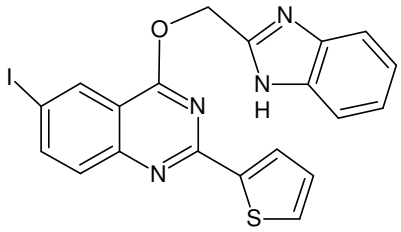


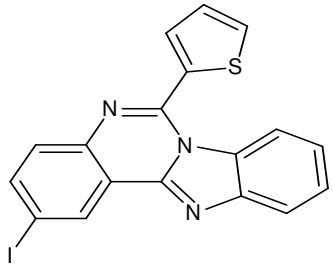
(60)

Compounds 59 and 60 showed comparative activity against *K. pneumoniae* as compared to ciprofloxacin. Compound 58 exhibited greater activity against *S. sonnei*, *E. faecalis* and *P. aeruginosa* as compared to ciprofloxacin.

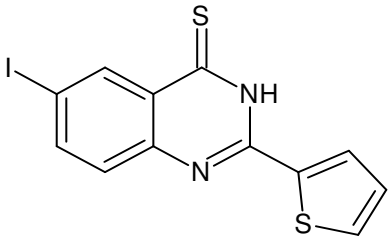
Alafeefy et al[34] synthesized a series of some novel substituted iodoquinazoline derivatives and evaluated their antimicrobial activity.



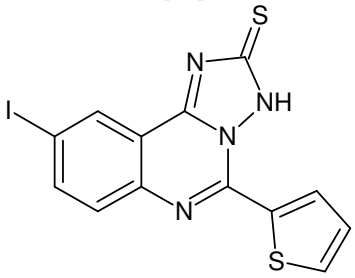
[61]



[62]



[63]

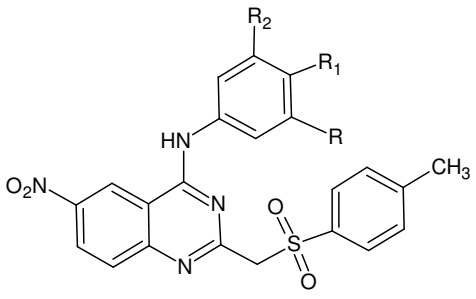


[64]

Compounds 62 and 63 showed remarkable activity towards the gram negative bacteria *E. coli*, whereas compounds 61 62 and 64 showed potent activity against *S. aureus*, *B. subitilis, S. Cerevsiae* and *C. albicans*.

Quinazoline as antimalarial agents

A series of quinazoline derivatives was synthesized by Kabri et al[35] and evaluated them for their antiplasmodial activity.



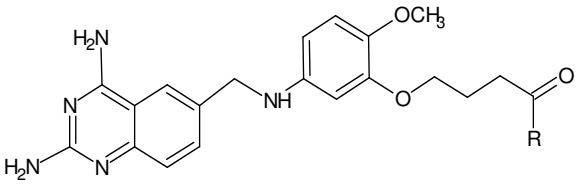
(65)

	R	R_1	R_2
65a	CF_3	H	H
65b	H	F	H
65c	Cl	H	H

Compound 65a and 65c shows a high potential activity (respective W2 IC_{50} values =0.95 and 1.3 µM) in comparison with chloroquine and doxycycline.

Schormann et al[36] synthesized a series of quinazoline derivatives and evaluated their pharmacological activity as a potent inhibitor of *Trypanosoma cruzi* dihydrofolate reductase.

Quinazoline as anti protozoan agents

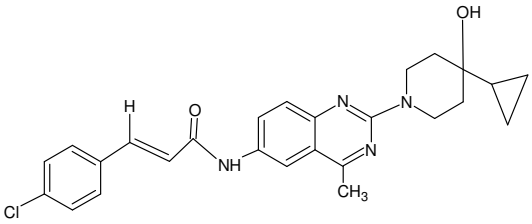


	R
66a	$-OC_2H_5$
66b	$-OCH_3$

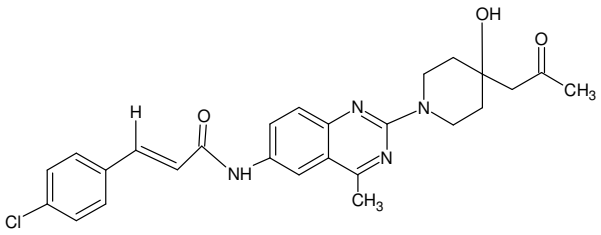
(66)

Quinazoline as anti obesity agents

Sasmal et al[37] synthesized a series of quinazoline derivatives to be considered as an antagonist for melanin concentrating hormone receptor 1 (MCHR1).



[67]



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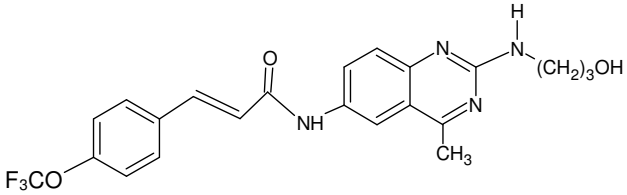

[69]

CONCLUSION

The above illustrations include various structural modifications around the fused ring, quinazoline and subsequently evaluate their usefulness in treating various disease conditions. Quinazoline, being the central body of the pharmacophore holds different types of substituent. Based on their various physicochemical properties, they exerted a diversified range of therapeutic efficacy. Thus we can conclude that this review will definitely provide the researchers a thorough understanding of the structure activity relationship study, which further help in designing good many number of quinazoline compounds with a strong impact in curing many fatal disorders.

ACKNOWLEDGEMENTS

Both the authors are very much thankful to their respective principals and management for the proper facilities provided to them in making the manuscript in a smooth manner.

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How to cite this article: Bibek Pati*, Subhasis Banerjee; Quinazolines: An Illustrated Review; J. Adv. Pharm. Edu. & Res. 2013: 3(3): 136-151.

Source of Support: Nil, **Conflict of Interest:** Nil