



REVIEW ARTICLE

MEDICINAL CHEMISTRY

**MEDICINAL AND BIOLOGICAL SIGNIFICANCE OF QUINAZOLINE: A  
HIGHLY IMPORTANT SCAFFOLD FOR DRUG DISCOVERY: A REVIEW**



*Corresponding Author*

**Vijaychand.A**

Department of pharmacology, Jss college of pharmacy,  
JSS university, mysore-15 , India

*Co Authors*

**S.N.Manjula, Bharath .E. N and Divya.B**

Department of pharmacology, jss college of pharmacy, JSS university, mysore-15 ,India

**ABSTRACT**

This article outlines the medicinal and biological significance of one of the most important heterocycles, the quinazoline. Quinazoline is a highly active scaffold exhibiting wide variety of medicinal and biological activities. An attempt is made in this article to cover the medicinally active compounds, along with the recent discoveries, which were reported to possess various biological activities. This might be helpful in the development of these novel lead molecules to potential drug candidates.

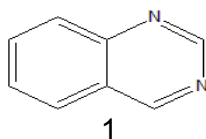
## KEY WORDS

Heterocycles, Quinazolines, Scaffold, Medicinal significance, biological significance

## INTRODUCTION

The chemistry of quinazoline compounds has more than centuries old history; however the intense search for biologically active substances in this series began only in the last few decades. Evolution of quinazolines began only with discovery of febrifugine, a quinazolinone alkaloid, possessing anti-malarial potential from the Chinese plant aseru (*Dichroa febrifuga* Lour), which served as an impetus for initiation of the research on quinazolines.

Quinazoline (1) is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. It is also called benzopyrimidine. It has the molecular formula  $C_8H_6N_2$  and molecular mass 130.15 g/mol. It is isomeric with quinoxaline, phthalazine and cinnoline.



Earlier research in nineteen fifties and sixties revealed effectiveness of quinazolines not only as anti-malarial but also against various diseases caused by bacteria, protozoa and virus. But the research was restricted mostly to anti microbials.

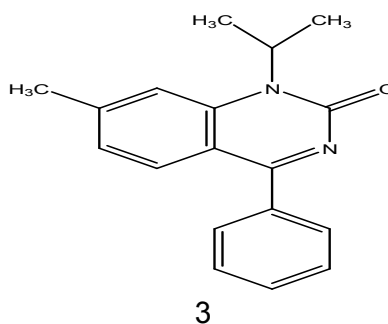
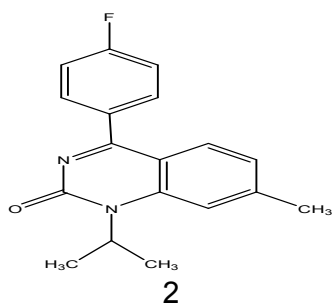
An important stage in the development of research on the biological activity of quinazoline compounds was the discovery of considerable soporific and sedative action of 2-methyl-3 aryl-4 quinazolone derivatives. Synthesis of these compounds with general concepts stimulated an extensive search for various pharmacologically active compounds.

In the last 10-15years the search for quinazoline compounds has been characterized by significant advances. They have been reported to possess wide spectrum of biological activities like analgesic and anti-inflammatory<sup>1,2,3,4,5,6</sup>, antimicrobial<sup>16,17,18,19,20,21,22,23,24</sup>, anti-tubercular<sup>34</sup>, antihistaminic<sup>35,36,37</sup>, anti-tussive and bronchodilator<sup>38</sup>, anti diabetic<sup>40</sup>, antidiuretic<sup>41,42,43</sup>, anti-hypertensive<sup>47,48,49,50,51,52</sup>, sedative-hypnotic activity<sup>57,58,59,60</sup>, antidepressant<sup>69</sup>, antiparkinsonian<sup>70</sup>, Phosphodiesterase inhibition<sup>71</sup>, anticancer<sup>72,73,74,75</sup>.

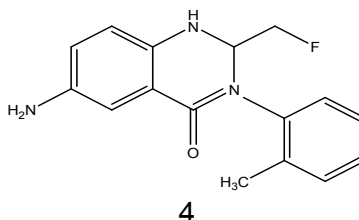
### ***Analgesic and anti-inflammatory agents:***

Efforts towards the development and identification of new molecules for analgesic and anti-inflammatory activities with minimal gastrointestinal ulceration side effects have gained significance in the recent past during which the quinazolines came into the scenario. There are no promising quinazolines which are in the market in these NSAIDs criteria except few drugs like Proquazone, Afloqualone and Diproqualone etc. The novel derivatives of quinazolines mentioned might be beneficial in terms of biological activity for which further studies can be done to confirm it as a potential drug candidate.

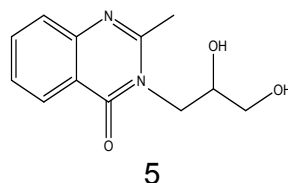
Proquazone (2) - a derivative of quinazoline-2-one exhibits potential NSAID potential which has been used in the disease conditions like rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, musculoskeletal disorders, acute inflammatory conditions and acute pain states such as dysmenorrhoea, postoperative pain and headache<sup>1</sup>. Its derivative fluproquazone (3) has potent analgesic and anti inflammatory actions with less gastric ulceration.



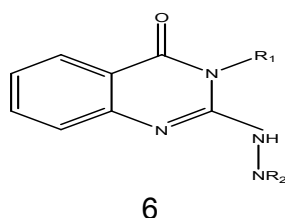
Afloqualone (4) -a derivative quinazoline-4-one is being used as successful anti-inflammatory agent in the management of lower back pain<sup>2</sup>as well as a centrally acting muscle relaxant<sup>3</sup>.

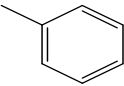
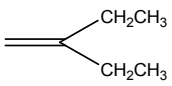
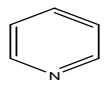
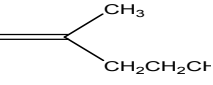
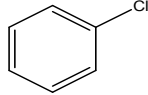
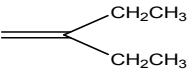
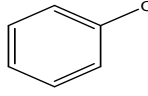
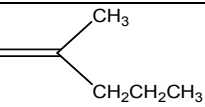
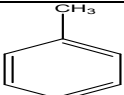
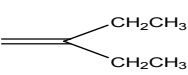
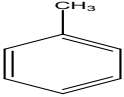
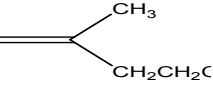
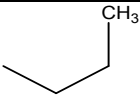
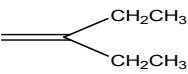
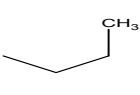
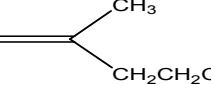
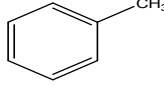
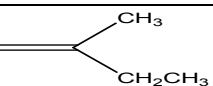
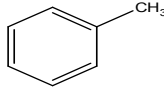
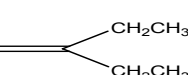
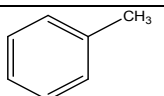
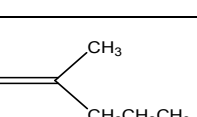
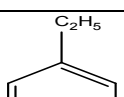
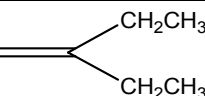
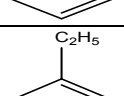
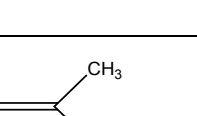


Diproqualone (5) - a derivative quinazoline-4-one which has been used primarily for the treatment of inflammatory pain associated with osteoarthritis and rheumatoid arthritis<sup>4</sup>.

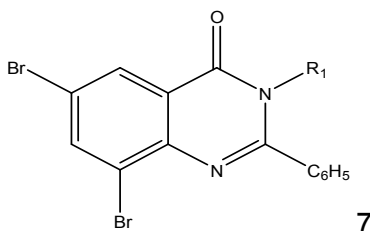


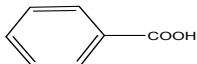
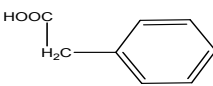
Alagarswamy et.al worked on several 3(H)-quinazoline-4-ones(6) and came up with some compounds which showed different ranges of potency from mild to moderate in both analgesic and anti-inflammatory activity when compared with diclofenac sodium and showed mild ulcerogenic potential when compared with aspirin<sup>5, 6, 7, 8, 9, 10, 11</sup>.



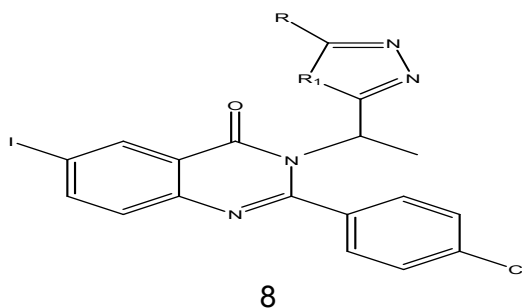
S.no	Substitution (R1)	Substitution(R2)	IUPAC name	Activity reported
6a			3-benzyl-2-[N'-(1-ethyl-propylidene)-hydrazino]-3H-quinazolin-4-one <sup>5</sup>	Analgesic and anti-inflammatory activity
6b			2-(1-methylbutylidene)-hydrazino-3-(2-pyridyl)-quinazolin-4(3H)-one <sup>6</sup>	Analgesic and anti-inflammatory activity
6c			(2-(1-ethylpropylidene-hydrazino)-3-(4-chlorophenyl)-3H-quinazolin-4-one) <sup>7</sup>	Analgesic activity
6d			(2-(1-methylbutylidene-hydrazino)-3-(4-chlorophenyl)-3H-quinazolin-4-one) <sup>7</sup>	Anti-inflammatory activity
6e			2-(1-ethylpropylidene-hydrazino)-3-(3-methylphenyl)-3H-quinazolin-4-one <sup>8</sup>	Analgesic activity
6f			2-(1-methylbutylidene-hydrazino)-3-(3-methylphenyl)-3H-quinazolin-4-one <sup>8</sup>	Anti-inflammatory activity
6g			3-butyl-2-(1-methylbutylidene-hydrazino)-3H-quinazolin-4-one <sup>9</sup>	Anti-inflammatory activity
6h			3-butyl-2-(1-ethylpropylidene-hydrazino)-3H-quinazolin-4-one <sup>9</sup>	Analgesic activity
6i			2-(N <sup>1</sup> -2-Butylidene-hydrazino)-3-(4-methylphenyl)-3H-quinazolin-4-one <sup>10</sup>	Analgesic activity
6j			2-(N <sup>1</sup> -3-pentylidene-hydrazino)-3-(4-methylphenyl)-3H-quinazolin-4-one <sup>10</sup>	Analgesic activity
6k			2-(N <sup>1</sup> -2-pentylidene-hydrazino)-3-(4-methylphenyl)-3H-quinazolin-4-one <sup>10</sup>	Analgesic and anti-inflammatory activity
6l			2-(N <sup>1</sup> -3-pentylidene-hydrazino)-3-(3-ethylphenyl)-3H-quinazolin-4-one <sup>11</sup>	Analgesic activity
6m			2-(N <sup>1</sup> -2-pentylidene-hydrazino)-3-(3-ethylphenyl)-3H-quinazolin-4-one <sup>11</sup>	Anti-inflammatory activity

B.A. Rather et al. also worked on quinazolin-4(3H)-ones (7) to produce different compounds of varied potency when compared with the standard aspirin and indomethacin<sup>12</sup>.

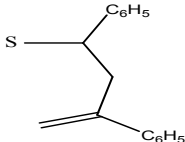


S.no	Substitution(R1)	IUPAC name	Activity reported
7a		6,8-dibromo-2-phenyl-3-(49-carboxyl phenyl)quinazolin-4(3H)-one <sup>12</sup>	Analgesic and anti-inflammatory activity
7b		6,8-dibromo-2-phenyl-3-(29-phenylethanoic acid)quinazolin-4(3H)-one <sup>12</sup>	Analgesic and anti-inflammatory activity

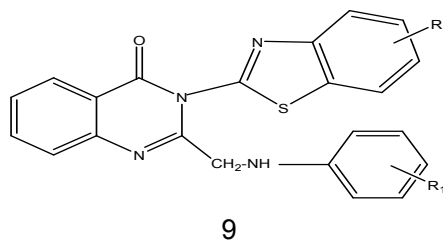
A.M. Alafeefy et al. also worked on 3(H) quinazolin-4-ones (8) to produce different compounds of varied potency<sup>13</sup>.



S.no	Substitution(R)	Substitution(R1)	IUPAC name	Activity reported
8a	SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	O	2-(4-Chlorophenyl)-6-iodo-3-[1-(5-substituted thio-1,3,4-oxadiazol-2-yl)-ethyl]-3H-quinazolin-4-one <sup>13</sup>	Analgesic and anti-inflammatory activity
8b	C <sub>6</sub> H <sub>5</sub>	O	2-(4-Chlorophenyl)-6-iodo-3-[1-(5-phenyl-1,3,4-oxadiazol-2-yl)-ethyl]-3H-quinazolin-4-one <sup>13</sup>	Analgesic and anti-inflammatory activity
8c	NH C <sub>6</sub> H <sub>5</sub>	O	2-(4-Chlorophenyl)-6-iodo-3-[1-(5-phenyl amino-1,3,4-oxadiazol-2-yl)ethyl]-3H-quinazolin-4-one <sup>13</sup>	Analgesic and anti-inflammatory activity
8d	NH C <sub>6</sub> H <sub>5</sub>	S	2-(4-Chlorophenyl)-6-iodo-3-[1-(5-phenyl amino-1,3,4-thiadiazol-2-yl)-ethyl]-3H-quinazolin-4-one <sup>13</sup>	Analgesic and anti-inflammatory activity

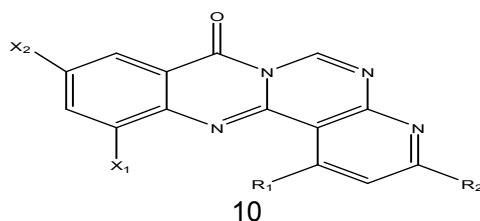
8e		N	7-[1-[2-(4-Chlorophenyl)-6-iodo-4-oxo-3H-quinazolin-3-yl]ethyl]-2,4-diphenyl-7,8-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine <sup>13</sup>	Analgesic and anti-inflammatory activity
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M. D. Salahuddin et al worked on novel quinazolinones to produce different compounds of varied potency when compared with standard indomethacin<sup>14</sup>.



S.no	Substitution(R)	Substitution(R1)	IUPAC name	Activity reported
9a	CH <sub>3</sub>	Cl	2-[[4-(4-Chlorophenyl) amino] methyl]-3-(6-methyl-1,3-benzothiazol-2-yl)quinazolin-4(3H)-one <sup>14</sup>	Anti-inflammatory activity
9b	OCH <sub>3</sub>	Cl	2-[[4-(4-Chlorophenyl) amino] methyl]-3-(6-methoxy-1,3-benzothiazol-2-yl)quinazolin-4(3H)-one <sup>14</sup>	Anti-inflammatory activity
9c	Cl	OCH <sub>3</sub>	3-(6-Chloro-1,3-benzothiazol-2-yl)-2-[[4-(4-methoxyphenyl) amino] methyl]quinazolin-4(3H)-one <sup>14</sup>	Anti-inflammatory activity
9d	F	OCH <sub>3</sub>	3-(6-Fluoro-1,3-benzothiazol-2-yl)-2-[[4-(4-methoxyphenyl) amino] methyl]quinazolin-4(3H)-one <sup>14</sup>	Anti-inflammatory activity
9e	F	Cl	2-[[4-(4-Chlorophenyl) amino] methyl]-3-(6-fluoro-1,3-benzothiazol-2-yl)quinazolin-4(3H)-one <sup>14</sup>	Anti-inflammatory activity

S. S. Laddha et al worked on various quinazolinones(10) to produce different compounds of varied potency<sup>15</sup>.



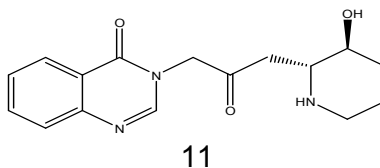
S.no	Substitution (R <sub>1</sub> )	Substitution (R <sub>2</sub> )	Substitution (X <sub>1</sub> )	Substitution (X <sub>2</sub> )	IUPAC name	Activity reported
10a	2-furfuryl	4-tolyl	Br	Br	9,11-dibromo-1-(2-furfuryl)-3-(4-tolyl)-8H-pyrido[2,3-b]pyrimido[6,1-b]quinazolin-8-one <sup>15</sup>	Anti-inflammatory activity

10b	p-methoxy - Phenyl	Phenyl	Br	Br	9,11-dibromo-1-(4-methoxyphenyl)-3-phenyl-8H-pyrido[20,30:4,5]pyrimido[6,1-b]quinazolin-8-one <sup>15</sup>	Anti-inflammatory activity
10c	4-chloro phenyl	4-tolyl	Br	Br	9,11-dibromo-1-(4-chlorophenyl)-3-(4-tolyl)-8H-pyrido[20,30:4,5]pyrimido[6,1-b]quinazolin-8-one <sup>15</sup>	Anti-inflammatory activity
10d	4-chloro phenyl	4-tolyl	H	Br	9-bromo-1-(4-chlorophenyl)-3-(4-tolyl)-8H-pyrido[20,30:4,5]pyrimido[6,1-b]quinazolin-8-one <sup>15</sup>	Anti-inflammatory activity

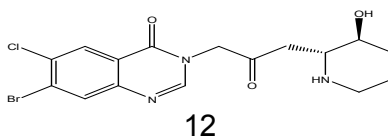
### Anti-microbial agents:

Anti-microbials cover large spectrum biological activities like anti bacterial, anti fungal, anti viral, anti leishmanial, antiprotozoal, antiplasmodial etc. With time several derivatives of quinazolines possessing potential anti-microbial activities have evolved but still they do not occupy a prominent position in this section of market.

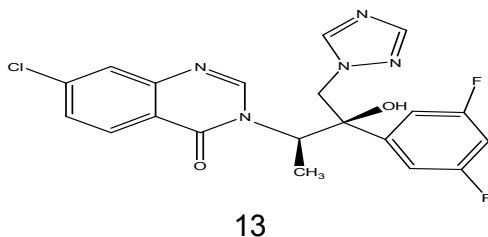
Febrifugine (11)-It was found to possess anti malarial activity and used as coccidiostat in veterinary medicine<sup>16</sup>.



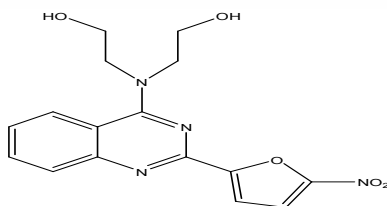
Halofuginone (12) - It is a halogenated derivative of febrifugine, used as coccidiostat in veterinary medicine. It has received FDA approval for use in scleroderma. It has been used potentially for treatment of auto immune disorders<sup>17</sup>.



Albaconazole (13)-It is a tirazole class antifungal agent having broad spectrum of anti fungal activity<sup>18</sup>.

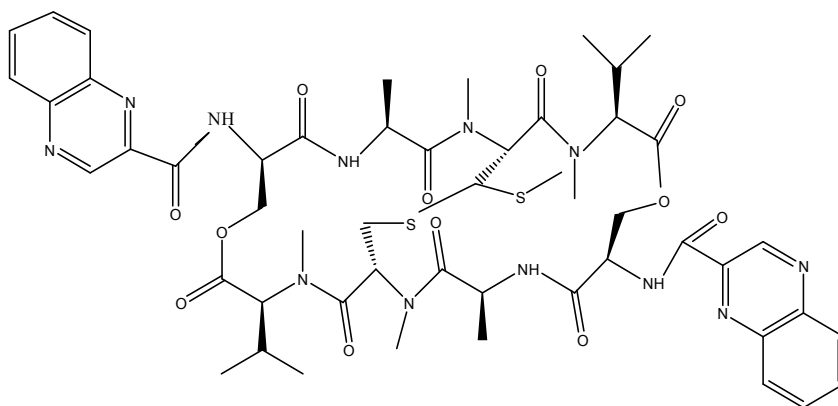


Nifurquinazol (14)-It is a nitro furan class anti bacterial agent which was never marketed<sup>19</sup>.



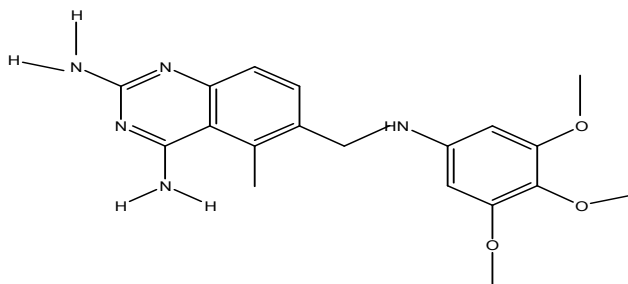
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Echinomycin (15) - It is a peptide antibiotic used as antibacterial agent which is effective against gram positive bacteria. Its derivatives Levomycin and actinoleutin also possess the same action<sup>20</sup>.



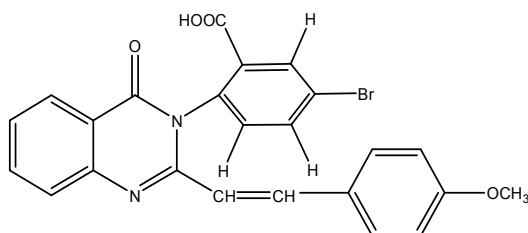
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Trimetrexate (16) - It is a dihydrofolate reductase inhibitor used along with leucovorin in the treatment of pneumocystis pneumonia<sup>21</sup>.



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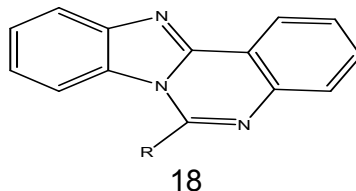
Jessy et.al worked on several 2, 3-disubstituted-3, 1-quinazolin-4-(3H) ones(17) which were evaluated for antibacterial activity against various strains of bacteria which were comparable to ciprofloxacin among which following compounds were found to be potent<sup>22</sup>.



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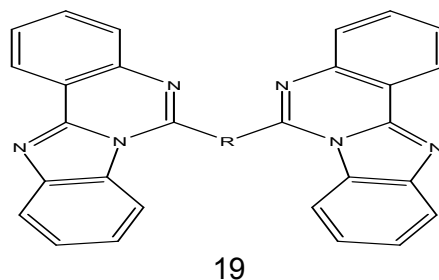


Rohini et.al worked on several 6-Arylbenzimidazo [1, 2-c] quinazolines which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to ampicillin and ketoconazole respectively among which following compounds were found to be potent<sup>23</sup>.



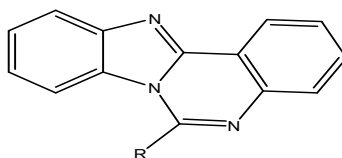
S.no	Substitution(R1)	IUPAC name
18a	2-hydroxy-5-nitro-benzaldehyde	2-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-4-nitrophenol <sup>23</sup>
18b	Quinoline-2-carbaldehyde	6-(1-Isoquinolyl)benzo[4,5]imidazo[1,2-c]quinazoline <sup>23</sup>
18c	Pyridine-3-carbaldehyde	6-(3-Pyridyl)benzo[4,5]imidazo[1,2-c]quinazoline <sup>23</sup>

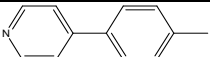
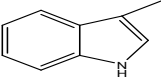
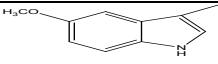
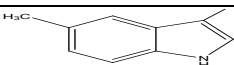
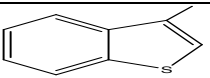
Rohini et.al worked on several Bis- 6-Arylbenzimidazo [1, 2-c] quinazolines(18) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to ampicillin and ketoconazole respectively among which following compounds were found to be potent<sup>24</sup>.



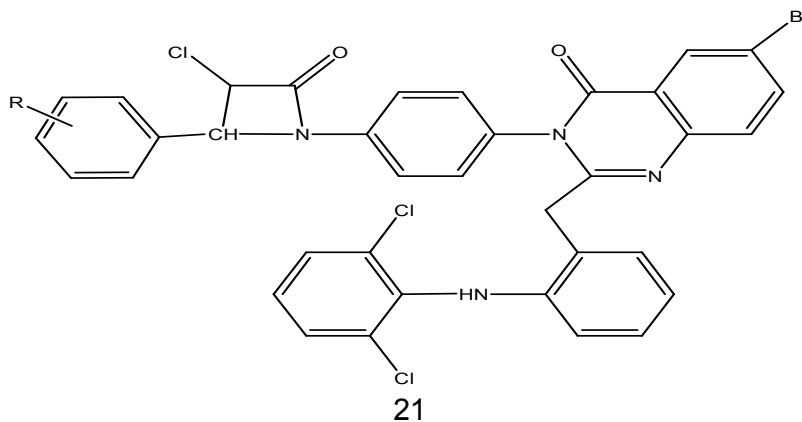
S.no	Substitution(R1)	IUPAC name
19a	2,6 pyridyl	6-(6-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-2-pyridyl)benzo[4,5]imidazo[1,2-c]quinazoline <sup>24</sup>
19b	2,5 thienyl	6-(5-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-2-thienyl)benzo[4,5]imidazo[1,2-c]quinazoline <sup>24</sup>

Rohini et.al worked on several 6-substituted indolo [1, 2-c] quinazolines(20) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to ampicillin and ketoconazole respectively among which following compounds were found potent<sup>25, 26</sup>.



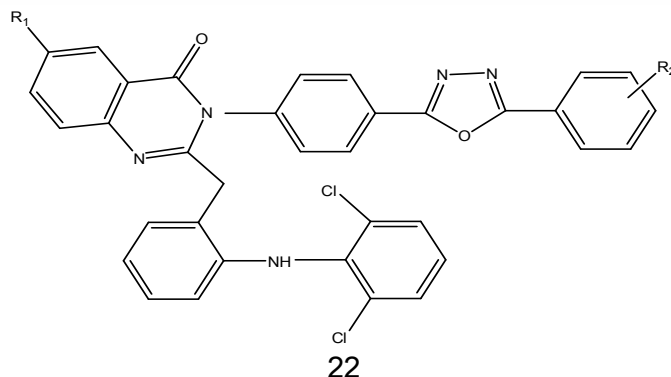
S.no	Substitution(R1)	IUPAC name
20a		6-[4-(4-pyridyl)phenyl]indolo[1,2-c]quinazoline <sup>25</sup>
20b		6-(1H-3-indolyl)indolo[1,2-c]quinazoline <sup>25</sup>
20c		6-(5-Methoxy-1H-3-indolyl)indolo[1,2-c]quinazoline <sup>25</sup>
20d		6-(5-Methyl-1H-3-indolyl)indolo[1,2-c]quinazoline <sup>25</sup>
20e		6-benzo[b]thiophen-3-ylindolo[1,2-c]quinazoline <sup>25</sup>
20f	Quinoline-2-carbaldehyde	6-(1-Isoquinolyl)indolo[1,2-c]quinazoline <sup>26</sup>
20g	Pyridine-3-carbaldehyde	6-(3-Pyridyl)indolo[1,2-c]quinazoline <sup>26</sup>

Navin et.al worked on several 2-azetidiny-4-Quinazolines(21) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to Penicillin-G and Amphotericin-B respectively among which the following compound were potent<sup>27</sup>.



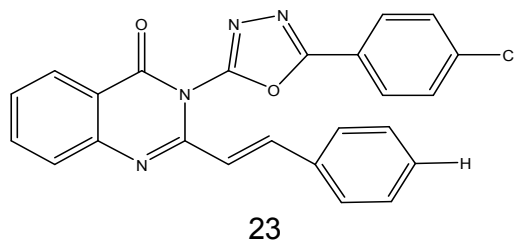
S.no	Substitution(R1)	IUPAC name
21a	4-Cl	2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(4-chlorophenyl)-3-chloro-2-oxoazetidiny]aryl}-6-bromoquinazolin-4(3H)one <sup>27</sup>
21b	4-OCH <sub>3</sub>	2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[4-(4-methoxyphenyl)-3-chloro-2-oxo-azetidiny]aryl}-6-bromoquinazolin-4(3H)one <sup>27</sup>

Navin et.al worked on several 1, 3, 4-Oxadiazolylquinazolin-4(3H) ones(22) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to Ampicillin and Griseofulvin respectively among whom the following compound was potent<sup>28</sup>.

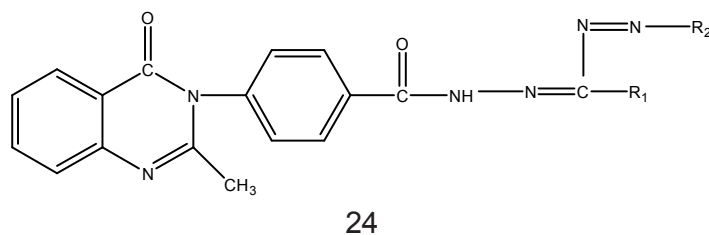


S.no	Substitution(R1)	Substitution(R2)	IUPAC name
22	I	3-NO <sub>2</sub>	2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-iodoquinazolin-4(3H)one <sup>28</sup>

Vivek et.al worked on several 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-Styryl quinazoline-4(3H)-ones(23) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to Norfloxacin and clotrimazole respectively. Among all the compounds the following compound was promising<sup>29</sup>.



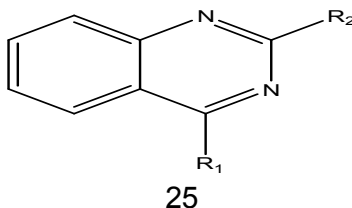
Ramarao et.al worked on several new quinazolinone formazans(24) which were evaluated for their anti microbial and antihelminthic property which were comparable to ciprofloxacin, fluconazole, albendazole and piperazine citrate respectively, among whom the following were found to be potent<sup>30</sup>.



S.no	Substitution(R1)	Substitution(R2)	IUPAC name
24a	C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub>	C <sub>6</sub> H <sub>3</sub> FCI	1-(3-Fluoro-4-chlorophenyl)-3-(4-nitrophenyl) - 4-[benzamido(2 - methyl - 3- quinazoline) - 4-one]formazan <sup>30</sup>

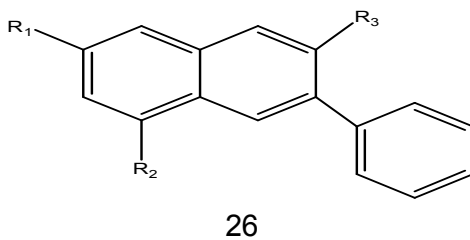
24b	C <sub>6</sub> H <sub>6</sub> N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> Cl	1-(4-Chlorophenyl)-3-(4-dimethylaminophenyl)-4-[benzamido(2-methyl-3-quinazoline)-4-one]formazan <sup>30</sup>
24c	C <sub>6</sub> H <sub>3</sub> (OH)(OCH <sub>3</sub> )	C <sub>6</sub> H <sub>3</sub> FCI	1-(3-Fluoro-4-chlorophenyl)-3-(2-hydroxy-4-methoxyphenyl)-4-[benzamido(2-methyl-3-quinazoline)-4-one]formazan <sup>30</sup>

S. Kumar et. al , worked on several new quinazolinone formazans which were evaluated for their anti leishmanial property which were comparable to sodium stilboglucanate and pentamidine respectively, among whom the following were found to be potent<sup>31</sup>.



S.no	Substitution(R1)	Substitution(R2)	IUPAC name
25a	2,4,6-triOCH <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>		2-(4-methyl-piperazin-1-yl)-4-(2,4,6-trimethoxy phenyl)-quinazoline <sup>31</sup>
25b	2,4-DiOCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>		4-(2,4-dimethoxy-phenyl)-2-(4-methyl-piperazin -1-yl)-quinazoline <sup>31</sup>

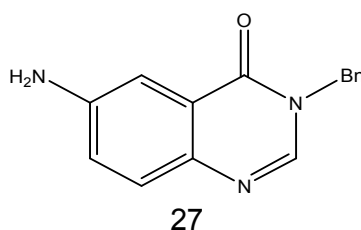
Selvam et. al , worked on several 2-Phenyl-3-Disubstituted Quinazolin-4(3H)-ones which were evaluated for their anti viral property which were comparable to Brivudin, Ribavirin, Acyclovir, ganciclovir and DHPA respectively, among whom the following were found to be potent<sup>32</sup>.



S.no	Substitution(R1)	Substitution(R2)	Substitution(R3)	IUPAC Name
26a	H	H		2-(o-phenyl carboxylic acid)-3-phenyl quinazolin-4(3H)-one <sup>32</sup>
26b	H	H		2-(o-aminophenyl)-3-phenyl quinazolin-4(3H)-one <sup>32</sup>
26c	H	H		2-(o nitrophenyl)-3-phenyl quinazolin-4(3H) -one <sup>32</sup>

F. A. M. Al-Omary et al, worked on several 2,6-substituted-quinazolin-4-ones(27) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were

comparable to Gentamicin and Sulfacetamide respectively. Among all the compounds the following compound was promising<sup>33</sup>.

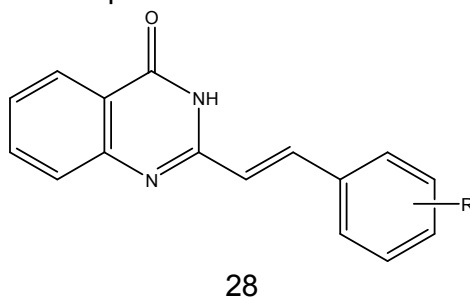


6-Amino-3-benzyl-quinazolin-4(3H)-one (27)

### **Anti-tubercular agents:**

There are no promising quinazolines marketed presently in the category of tuberculosis. But several novel molecules have been synthesized in the past which showed promising results but unfortunately could not make it up to the marketing stage.

Josef et al. Synthesized novel 2-styrylquinazolin-4(3H)-one and 4-chloro-2-styrylquinazolin-4(3H)-one derivatives. It was found that the electronic withdrawing properties of the R substituent, and not the total lipophilicity of the compound, were decisive for the compounds to exhibit potent anti-tubercular activity when compared with isoniazid by invitro method. Among all the synthesized compounds following were found to be potent<sup>34</sup>.



S.no	Substitution(R1)	IUPAC name
28a	2,4-OCH <sub>3</sub>	2-[(E)-2-(2,4-dimethoxyphenyl)vinyl]quinazolin-4(3H)-One <sup>34</sup>
28b	2- OCH <sub>3</sub>	4-chloro-2-[(E)-2-(2-methoxyphenyl)vinyl]quinazolin-4(3H)-One <sup>34</sup>

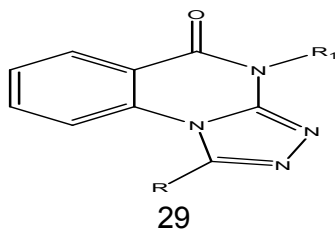
### **Anti-Histaminic agents:**

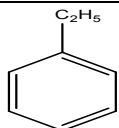
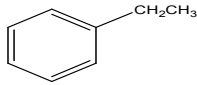

In the recent days lot of research is being done in the category of histaminic antagonists with relatively less sedation effect than existing drugs. Though few drugs possessing this activity are presently in the market novel drugs are still being synthesized.

Diproqualone (4) - Diproqualone was found to poses potent anti-histaminic activity though it was never marketed under this category.

Alagaraswamy et al. synthesized several 4-(3-ethylphenyl)-1-substituted-4H [1,2,4] triazolo [4,3-a]quinazolin-5-ones<sup>35</sup>, 4-(4-ethylphenyl)-1-substituted-4H [1,2,4] triazolo [4,3-a]quinazolin-5-ones<sup>36</sup> and 1-substituted-4-cyclohexyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-ones<sup>37</sup>. It was found that by varying substitution over the first position of the triazolo quinazoline ring there was variation in the biological activity. The presence of methyl group showed better activity than the unsubstituted compound. With increased lipophilicity the activity remained but further increase

in lipophilicity led to a decrease in activity. Replacement of the methyl group by other groups decreased the activity. The anti-histaminic potential was tested in vivo by comparing with chlorpheniramine maleate in which the following compound showed promising anti histaminic activity with less sedation<sup>35, 36, 37</sup>.

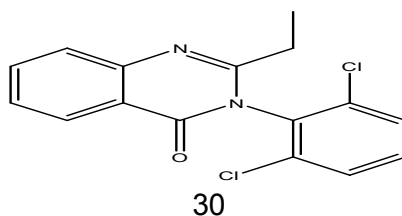


S.no	Substitution(R)	Substitution(R1)	IUPAC name
29a	CH <sub>3</sub>		4-(3-ethylphenyl)-1-methyl-4H [1,2,4] triazolo [4,3-a]quinazoline-5-one <sup>35</sup>
29b	CH <sub>3</sub>		4-(4-ethylphenyl)-1-methyl-4H [1,2,4] triazolo [4,3-a]quinazolin-5-one <sup>36</sup>
29c	CH <sub>3</sub>		4-cyclohexyl-1-methyl-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one <sup>37</sup>

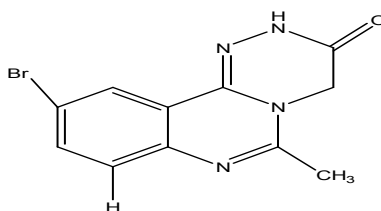
#### **Antitussive and bronchodilator agents:**

Several attempts were made in the past to synthesize quinazolines possessing antitussive and bronchodilator activities. Except chloroqualone none of the quinazolines were marketed in this category.

Chloroqualone (30) – It is used as anti-tussive agent in France and other European countries during 1980, which was sold either alone, or in combination with other ingredients as a cough medicine<sup>38</sup>.



Kombu et al. synthesized several 6-Alkyl/Aryl-1,2,4-Triazino[4,3c] Quinazolines<sup>39</sup>. It was found that incorporation of an aryl ring with halo substitution to the theophylline bioisostere increases its potency. The bronchodilator activity was assessed in vivo by comparing with aminophylline in which the following compound showed promising activity<sup>39</sup>.



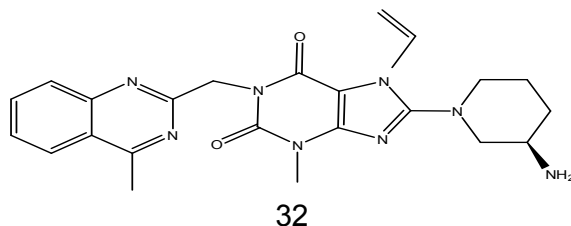
31

10-Bromo-6-methyl-3-oxo-3,4-dihydro-2H-[1,2,4]triazino[4,3-c]quinazoline(31)

**Anti-diabetic agent:**

Though several molecules of quinazolines were synthesized in the past targeting diabetes, none were promising except Linagliptin which got recently through phase-III clinical trials.

Linagliptin (32)- It is a DPP-4 inhibitor used for treating type-II diabetes<sup>40</sup> Which showed promising results in phase-III clinical trials and going to be launched into market with the brand name of ONDERO.

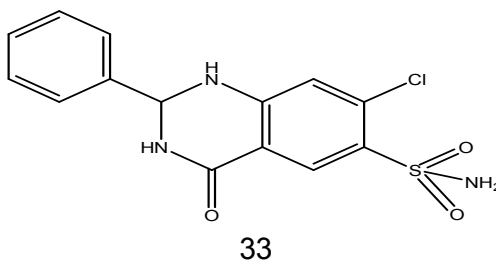


8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione(32)

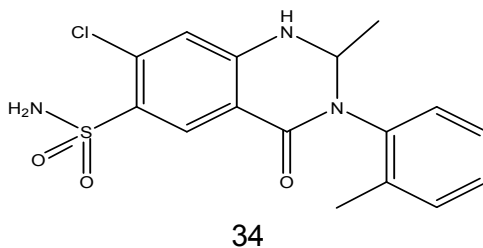
**Anti diuretic agents:**

There are very few promising anti diuretic drugs of quinazoline category, which are presently marketed. They are mostly used for the management of hypertension. To overcome its side effects novel drugs are still being synthesized.

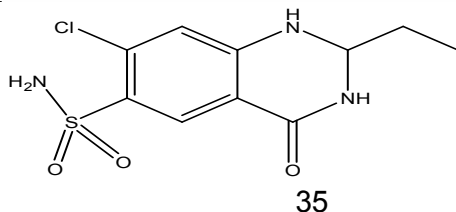
Fenquizone (33): It is a low ceiling sulfonamide diuretic used primarily in the treatment of oedema and hypertension<sup>41</sup>.



Metolazone (34): It is a thiazide like diuretic used primarily to treat congestive heart failure and high blood pressure. In severe conditions it is used along with loop diuretics like Furosemide, bumetanide etc. It was found to be effective in patients with renal insufficiency<sup>42, 43</sup>.



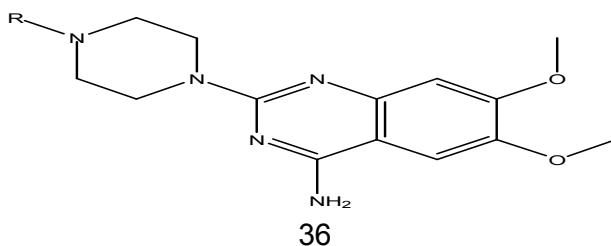
Quinethazone (35): It is a thiazide diuretic used in the treatment of hypertension<sup>44</sup>.

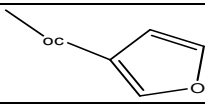
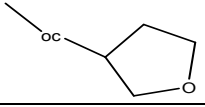


### Anti hypertensive activity:

Quinazolines enjoy a promising position in the anti-hypertensive's market. They are also the drugs of choice for renal impaired patients and effectively the drugs of second line choice for newly diagnosed patients.

Prazosin (36a): It is a selective alpha-1 receptor blocking agent used for the management of severe hypertension<sup>45</sup>, benign prostrate hyperplasia<sup>45</sup> and post traumatic stress disorders<sup>46</sup>.



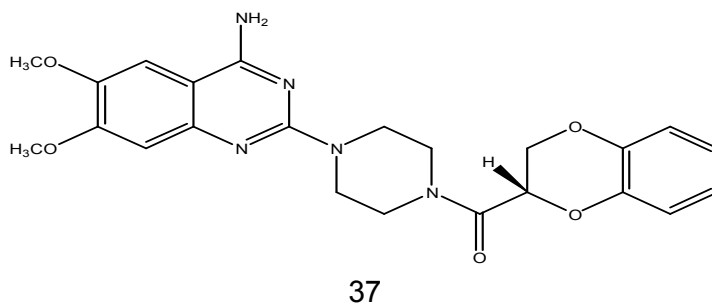
S.No	Substituent(R)
36a	
36b	
36c	-COCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
36d	-COCH <sub>2</sub> C(OH)-(CH <sub>3</sub> ) <sub>2</sub>

Terazosin (36b): It is a selective alpha-1 receptor blocking agent used for the management of benign prostrate hyperplasia<sup>47</sup>.

Bunazosin (36c): It is a selective alpha-1 receptor blocking agent used for the management of benign prostrate hyperplasia<sup>48</sup> which was recently approved in Japan for treatment of glaucoma<sup>49</sup>.

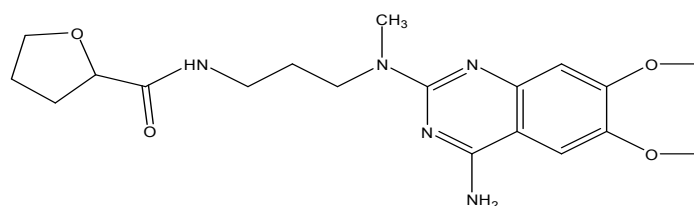
Trimazosin (36d): It is a selective alpha-1 receptor blocking agent used for the management of Hypertension<sup>50</sup>.

Doxazosin (37): It is a selective alpha-1 receptor blocking agent used for the management of benign prostrate hyperplasia<sup>51</sup>.



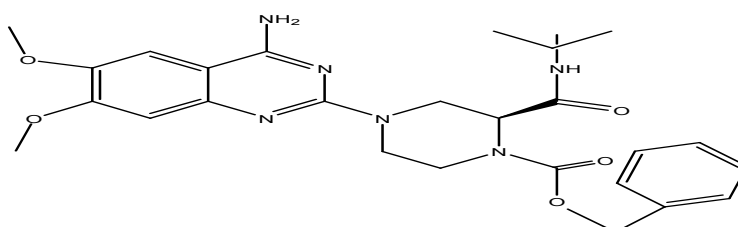


Afluzozin (38): It is a selective alpha-1 receptor blocking agent used for the management of benign prostrate hyperplasia<sup>52</sup>.



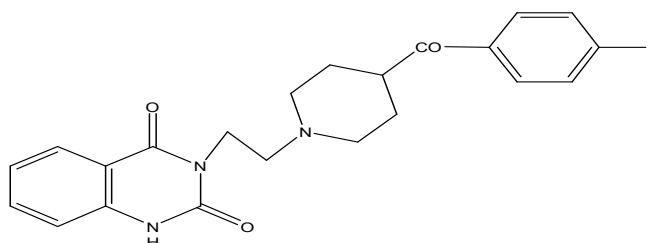
38

L-765,314(39): It is a selective alpha-1B<sup>52</sup> receptor blocking agent used for the management of Hypertension<sup>53</sup>.



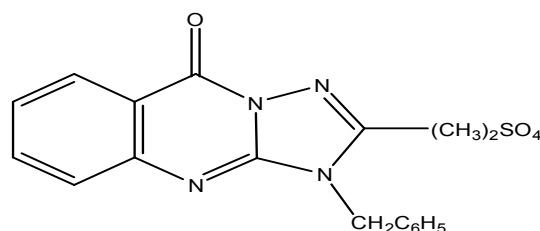
39

benzyl (2S)-4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-2-(tert-butylcarbonyl)piperazine-1-carboxylate(39)  
Ketansarin (40): It is a selective alpha-1 receptor and serotonin (5HT<sub>2A</sub>) receptor blocking agent used for the management of Hypertension<sup>54</sup>.



40

Alagaraswamy et al. synthesized several 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-ones<sup>55</sup>. It was found that different substitutions over the second position of triazoloquinazoline ring exerted varied biological activity. As lipophilicity is increased anti-hypertensive activity is retained when compared with the reference standard prazosin among which following compound was found to be potent.

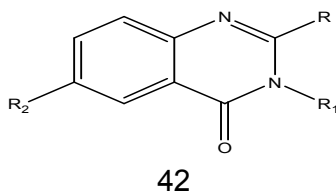


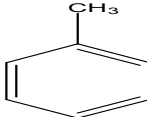
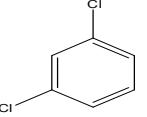
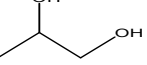
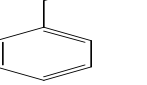
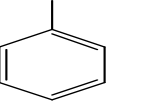
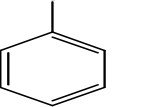
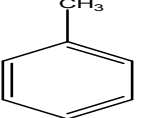
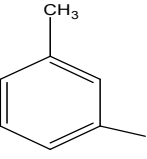
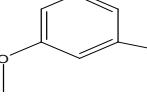
41

## 3-benzyl-2-methyl-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-one(41)

**Sedative –Hypnotic agents:**

Quinazolines have a greater share in the sedatives and hypnotics market. Quinazolinones were primarily used in surgical anaesthesia.

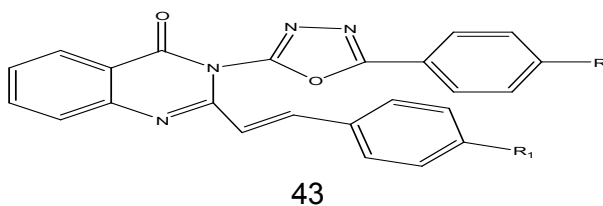


S.NO	Substitution(R)	Substitution(R1)	Substitution(R2)
42a	CH <sub>3</sub> F		NH <sub>2</sub>
42b	CH <sub>2</sub> CH <sub>3</sub>		----
42c	CH <sub>3</sub>		----
42d	CH <sub>3</sub>		----
42e	CH <sub>3</sub>		----
42f	CH <sub>3</sub>		----
42g	CH <sub>3</sub>		----
42h	CH <sub>3</sub>		----
42i	CH <sub>3</sub>		----

Afloqualone (42a): It is a quinazolinone analogue used as Sedative and centrally acting skeletal muscle relaxant<sup>57</sup>. Its analogues Chloroqualone (42b)<sup>58</sup>, Diproqualone (42c)<sup>59</sup>, Etaqualone (42d)<sup>60</sup>,

Mebroqualone (42e)<sup>61</sup>, Mecloqualone (42f)<sup>62</sup>, Methaqualone (42g)<sup>63</sup>, Methyl Methaqualone (42h)<sup>64</sup>, Nitromethaqualone (42i)<sup>65</sup> also possess sedative and hypnotic activity.

Sushil et al synthesized several novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-ones(42)<sup>66</sup> and stated that substitution of 4(3H)-quinazolinone at third position by 1,3,4-oxadiazole and second position by styryl moiety were essential for potent sedative and hypnotic activity. The following compounds were potent

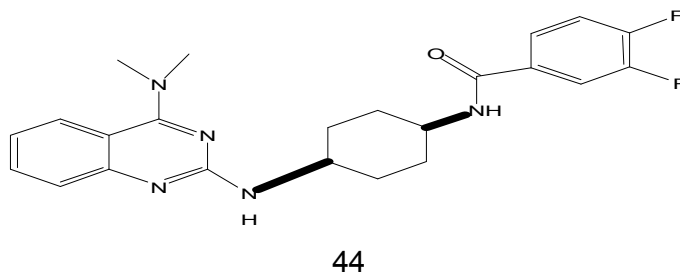


S.NO	Substitution(R)	Substitution(R1)
43a	Cl	H
43b	N(CH <sub>3</sub> ) <sub>2</sub>	H
43c	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>

#### **Anti-depressant agents:**

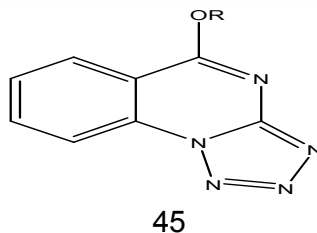
In the anti-depressant criteria still a promising molecule has yet to be launched. Except some drug candidates like ATC-0175 none of the other derivatives of quinazoline had come to the development phase.

ATC-0175(44): It is the drug in scientific research, which is a selective, non-peptide antagonist at the melanin concentrating hormone receptor MCH<sub>1</sub>. In animal studies it produced significant anti-depressant action without sedative and ataxic side effects<sup>67</sup>.



N-[cis-4-([4-(dimethylamino)quinazolin-2-yl]amino)cyclohexyl]-3,4-difluorobenzamide(44)

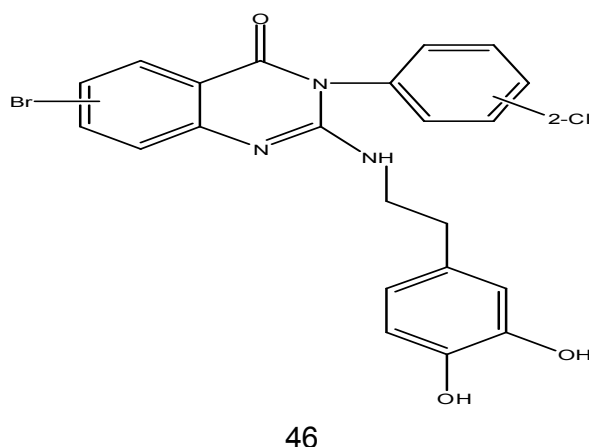
Wang et al. synthesized several 5-alkoxy-tetrazolo [1, 5-a] quinazoline(45) derivatives. They stated that length of the alkyl chain appears to have a direct impact on the antidepressant activity of the 5-alkoxyl derivatives. Among all the derivatives following were found to be potent when compared with reference standard fluoxetine<sup>68</sup>.



S.NO	Substituent(R)	IUPAC name
45a	n C <sub>6</sub> H <sub>13</sub>	5-(hexyloxy)tetrazolo[1,5-a]quinazoline
45b	C <sub>6</sub> H <sub>4</sub> (p-OCH <sub>3</sub> )	5-(4-methoxyphenoxy)tetrazolo[1,5-a]quinazoline

### **Anti-parkinsonian agent:**

Quinazolines were recently investigated for anti-parkinsonian potential and interestingly they were found to possess more biological activity when compared to standard drugs available in the market. Sunil et al. synthesized several 3-Substituted phenyl 2-(3,4-dihydroxyphenyl ethyl amino)-6-substituted quinazolin-4-(3H) ones (46)<sup>69</sup> and stated that dopamine was incorporated at 2 position with the hope to get better antiparkinsonian agents. Among them following derivative was found to be potent when compared with the standard drug Levo-dopa<sup>69</sup>.

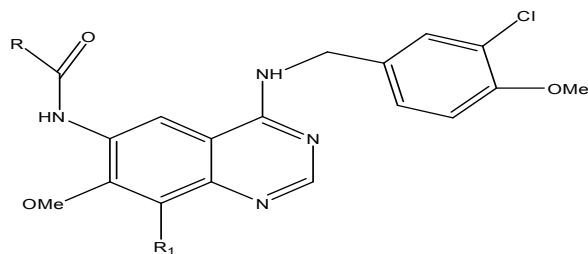


3-(2-Chloro phenyl)- 2-(3, 4-dihydroxyphenyl ethylamino)-6-bromo quinazolin-4-(3H) one(46)

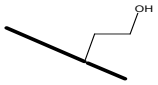
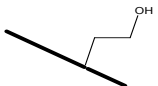
### **Phosphodiesterase inhibitory agents:**

Quinazolines were recently investigated for Phosphodiesterase inhibition potential and interestingly they were found to possess more biological activity and more specificity towards various Phosphodiesterase enzymes, which may be helpful in male erectile dysfunction.

Kim et al. synthesized various 4-(3-chloro-4-methoxy)-benzylamino-7-methoxy quinazoline derivatives<sup>70</sup> (47) and stated that by systematic variation of C6, C7, and C8 positions of quinazoline scaffold through unique and efficient, potent and highly selective analogues against PDE6 and PDE11 were obtained. Incorporation of polar functionality would lead to compounds that possess more preferable physicochemical properties such as solubility, membrane permeability and protein binding. The following derivatives were found to be potent than standard drug tadalafil<sup>70</sup>.

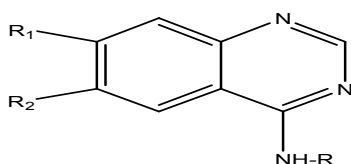


47

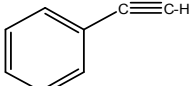
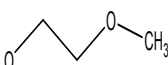
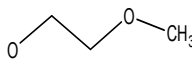
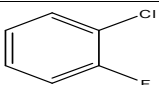
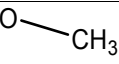
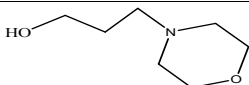
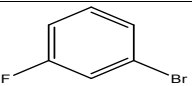
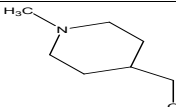
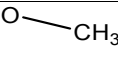
S.NO	Substituent(R)	Substituent(R1)
47a	CH <sub>3</sub>	
47b	Ethyl	

#### Anti-cancer agents:

Quinazolines occupy a promising section in the anti-cancer market because of their specificity. Most of the quinazolines are targeting protein tyrosine kinase. Even more selective compounds targeting EGFR, VEGFR and ERBB-2 are in the market. Receptors are being discovered and still in the developmental stages.



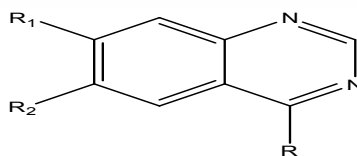
48

S.NO	Substitution(R)	Substitution(R1)	Substitution(R2)
48a			
48b			
48c			

Erlotinib (48a): It is a tyrosine kinase inhibitor targeting EGFR used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer<sup>71</sup>.

Gefatinib (48b): It is a tyrosine kinase inhibitor targeting EGFR used to treat non-small cell lung cancer, adenocarcinoma and several other types of cancer<sup>72</sup>.

Vandetanib (48c): It is a tyrosine kinase inhibitor targeting EGFR and VEGFR used for non-small cell lung cancer. It was not launched into the market as it showed no benefit when co administered alongside chemotherapy<sup>73</sup>.



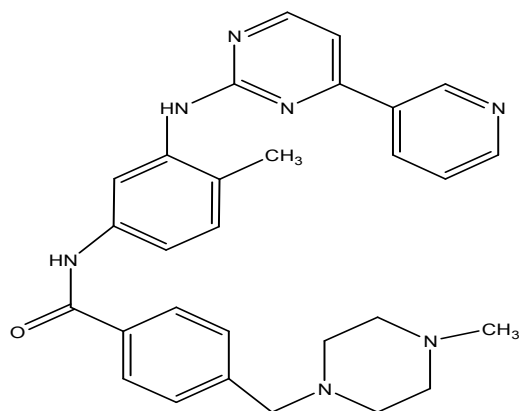
S.NO	Substitution(R)	Substitution(R1)	Substitution(R2)
49a		-----	
49b			
49c			

Lapatinib (49a): It is a dual tyrosine kinase inhibitor which interrupts the HER2 growth receptor pathway used for breast cancer and solid tumours<sup>74</sup>.

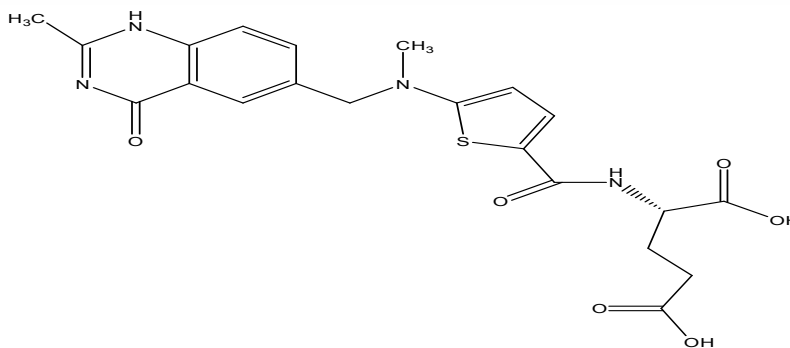
Afatinib( 49b): It is a next generation tyrosine kinase inhibitor (TKI) that irreversibly inhibits human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases. It is presently in phase-III clinical trials and yet to be launched in market<sup>75</sup>.

Cederanib (49c): It is a potent inhibitor of vascular endothelial growth factor (VEGFR) receptor tyrosine kinases. It was not launched into the market as it showed no benefit<sup>76</sup>.

Imatinib: It is a tyrosine kinase inhibitor used in treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs)<sup>77</sup>.

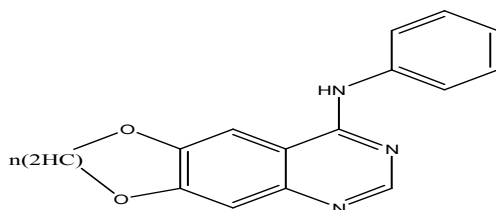


Raltitrexed (50): It is an inhibitor of thymidylate synthase. It is an antimetabolite drug used in cancer chemotherapy in colorectal cancer<sup>78</sup>.



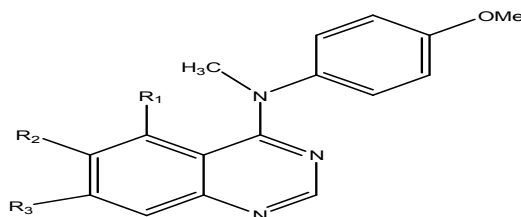
50

Conconi et al. Synthesized several dioxolane, dioxane(51), and dioxepine quinazoline derivatives and stated that size of the fused dioxxygenated ring was crucial for the biological activity, the dioxane derivatives being the most promising class of this series. Derivatives were able to counteract EGF-induced EGFR phosphorylation and showed better or at least comparable potency with respect to PD153035 of which the following compound was promising<sup>79</sup>.



HCl (51)

Sirisoma et al. synthesized several N-methyl-4-(4-methoxyanilino) quinazolines(52)<sup>80</sup> and stated that substitution at the 5-, 6-, 7-positions of the quinazoline and replacement of the quinazoline by other nitrogen-containing heterocycles. Replacement of the quinazoline ring with a quinoline, a benzo[d][1,2,3]triazine, or an isoquinoline ring showed that the nitrogen at the 1-position is important for activity, while the carbon at the 2-position can be replaced by a nitrogen and the nitrogen at the 3-position can be replaced by a carbon. The following compounds were found to be potent when compared with standard Azixa<sup>®</sup>.

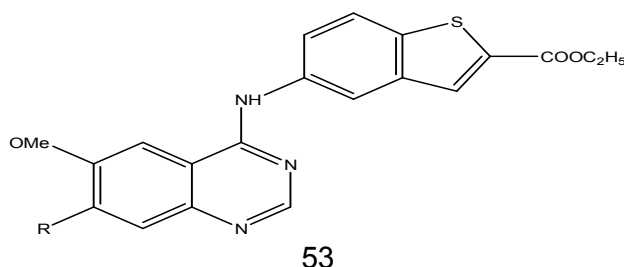


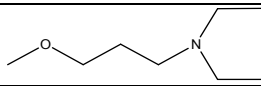
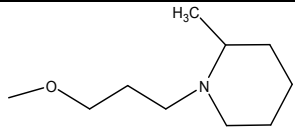
52

S.NO	Substitution(R1)	Substitution(R2)	Substitution(R3)
52a	H	NH <sub>2</sub>	H
52b	H	NO <sub>2</sub>	H

Wu et al. synthesized several 4-benzothieryl amino quinazolines in two series<sup>81</sup>. In series A, replacement of the benzene ring with benzothiophene, secondary amino-substituted propoxy side chain at position 6 and methoxy group at position 7 of the quinazoline nucleus; series B,

replacement of the benzene ring with benzothiophene, methoxy group at position 6 and secondary amino-substituted propoxyside chain at position 7 of the quinazoline nucleus. The following compounds were found to be potent when compared with standard Gefatinib.

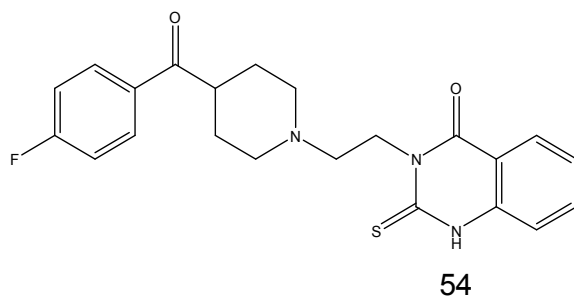


S.NO	Substitution(R1)	IUPAC name
53a		Ethyl 5-(7-(3-(diethylamino)propoxy)-6-methoxy quinazolin-4-ylamino)benzo[b] thiophene-2-carboxylate
53b		Ethyl 5-(6-methoxy-7-(3-(2-methylpiperidin-1-yl) propoxy) quinazolin-4-ylamino)benzo[b]thiophene-2-carboxylate

### Miscellaneous:

Quinazolines are effectively used in radio ligand binding studies. The drugs used in this category are

Altanserin (54): It binds to the 5-HT<sub>2A</sub> receptor (serotonin 2A receptor). Labeled with the isotope fluorine-18 it is used as a radio ligand in positron emission tomography (PET) studies of the brain, i.e., studies of the serotonin-2A neuro receptors. Besides human neuro imaging studies altanserin has also been used in the study of rats<sup>82</sup>.



Ketanserin (40): With tritium (<sup>3</sup>H) radioactively labeled ketanserin is used as a radioligand for the serotonin 5-HT<sub>2A</sub> receptor, This radio labeling enables the study of the serotonin-2A receptor distribution in the human brain<sup>83</sup>.

## CONCLUSION

Quinazolines occupy distinct and unique place in the medical field. This heterocyclic moiety has great medicinal and biological significance. A large array of quinazoline drugs possess a variety of





medicinal properties. Research on this scaffold over some novel targets of various diseases has increased significantly. In future we can expect novel drugs from this scaffold which would be more specific for various ailments.

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