IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Review on Quinazoline Possessing Heterocyclic Analogues: Exploration of Binding Sites of These Moieties and SAR Studies Against Pathogenic and Agricultural Fungal Strains

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ABSTRACT

The drug resistance problem is most acute in the case of fungal. There is always a need to develop novel antifungal drugs with better mechanisms of action. Most of the quinazoline-based antibiotics developed are potential antibacterial drug candidates. This review represents quinazoline/quinazolinone-based hybrids with antifungal activity and their structure–activity relationship (SAR). An attempt have been made to explore various binding sites of Quinazoline based heterocyclic analogues with various fungal strains. Structure activity relationship studies of the same analogues have been carried out, that provides better insight into the improvement of quinazoline/quinazolinone based antibiotics especially against multidrug-resistant fungal strains.

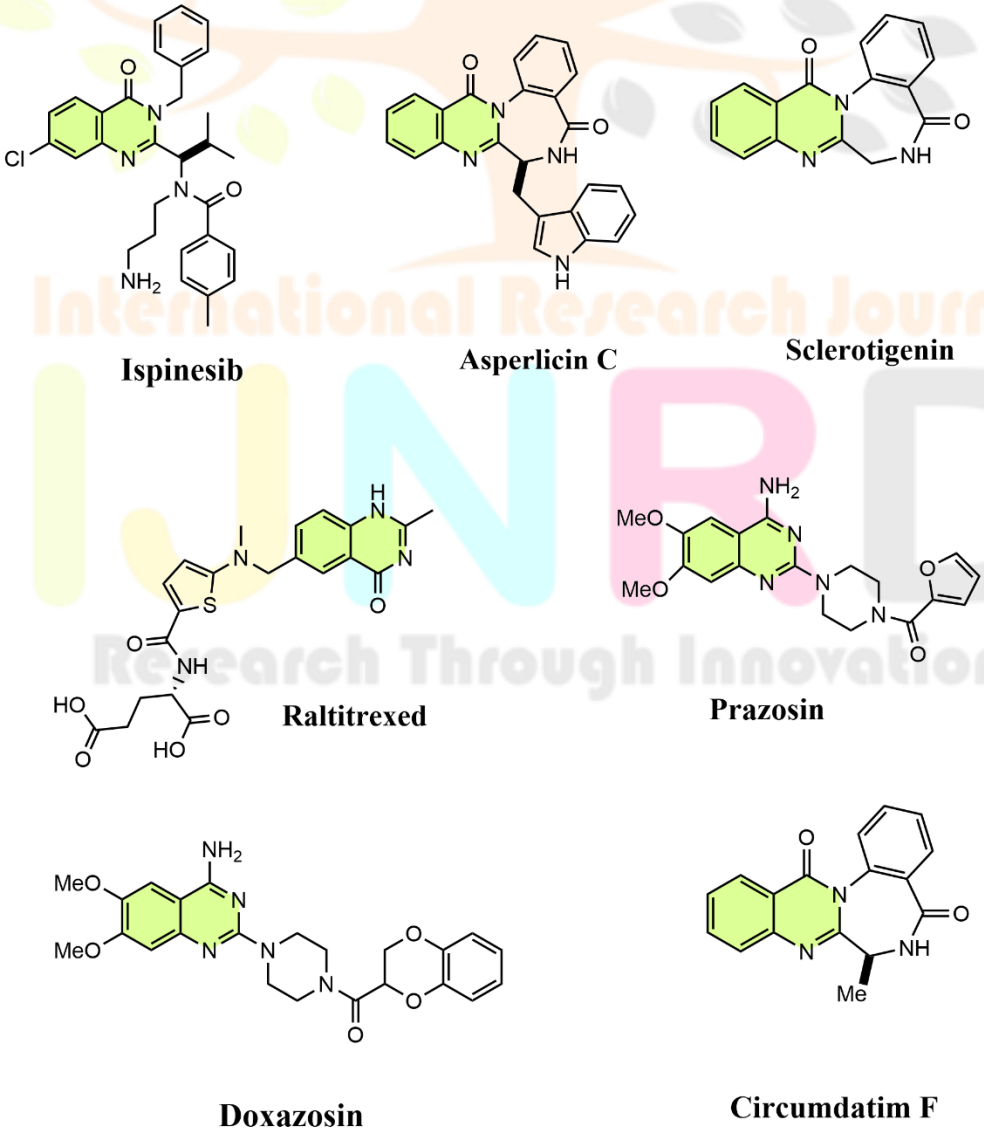
KEY WORDS: Quinazoline, Antifungal, SAR

1.0 INTRODUCTION

The number of life-threatening infectious diseases caused by multidrug-resistant fungal has reached an alarming level in many countries around the world [1-3]. The ever-growing demand for material protection from microbial contamination is a serious challenge. Despite great effort from the pharmaceutical industry to manage the resistance problem, the discovery and development of new mechanistic classes of antimicrobial has found very little success [4-5]. Currently, term “Black Fungus” has been widely applied to human pathogenic Mucorales in India [6]. subsequent contagion caused by black fungal infection, has threatened the whole of India and affected patients who are still recovering from COVID-19 [7-8]. black fungus infection caused by fungi Mucorales genera commonly found in our surrounding environments (for instance, soils, plants, manure, and rotting fruits, and so on), has recently grown a buzzword globally, mainly in South Asian countries. Though the exact epidemiological data of this infection is unknown, the prevalence of this black fungus infection in India is eighty (80) times higher than in developed countries. Due to this fungal infection,

the mortality rate might be up to 96% depending on the severity of the invasion and underlying patients' health situations. Black fungus (Auricularia auricula) is one of the four most important cultivated edible fungi in the world [9-11].

Nitrogen-containing heterocycles are ubiquitous scaffolds of many natural products and are being widely used in the field of pharmaceuticals [12]. Among them, quinazoline derivatives are of utmost interest for a wide cross-section of chemists due to their remarkable bioactivities. Quinazoline and quinazolinone derivatives represent one of the most active classes of compounds possessing a wide spread and diverse pharmacological activities [13-16]. Quinazoline and quinazolinone derivatives are reported to possess antibacterial [17,18], antifungal [19-21], antitumor [22], anti-inflammatory [23], anti-tubercular [24], antimalarials [25], anticancer [26,27], antiproliferative [28], Hepatitis B virus [29], antileishmanial [30], urease inhibitors [31], pancreatic lipase inhibitors [32], oxidase-A inhibitors [33], α-glucosidase inhibitors [34], α-amylase inhibition [35], PARP-1 inhibitors [36], tyrosinase inhibitors [37]. Some quinazoline and quinazolinone derivatives are already available in the medicinal world as an antimicrobial agent such as gefitinib, canertinib, afatinib, asperlicin C, doxazosin, etc [38]. This review represents the detailed SAR of potential antifungal activity counter to pathogens of quinazoline based analogoues to get insight into the development of potent antifungal agent.



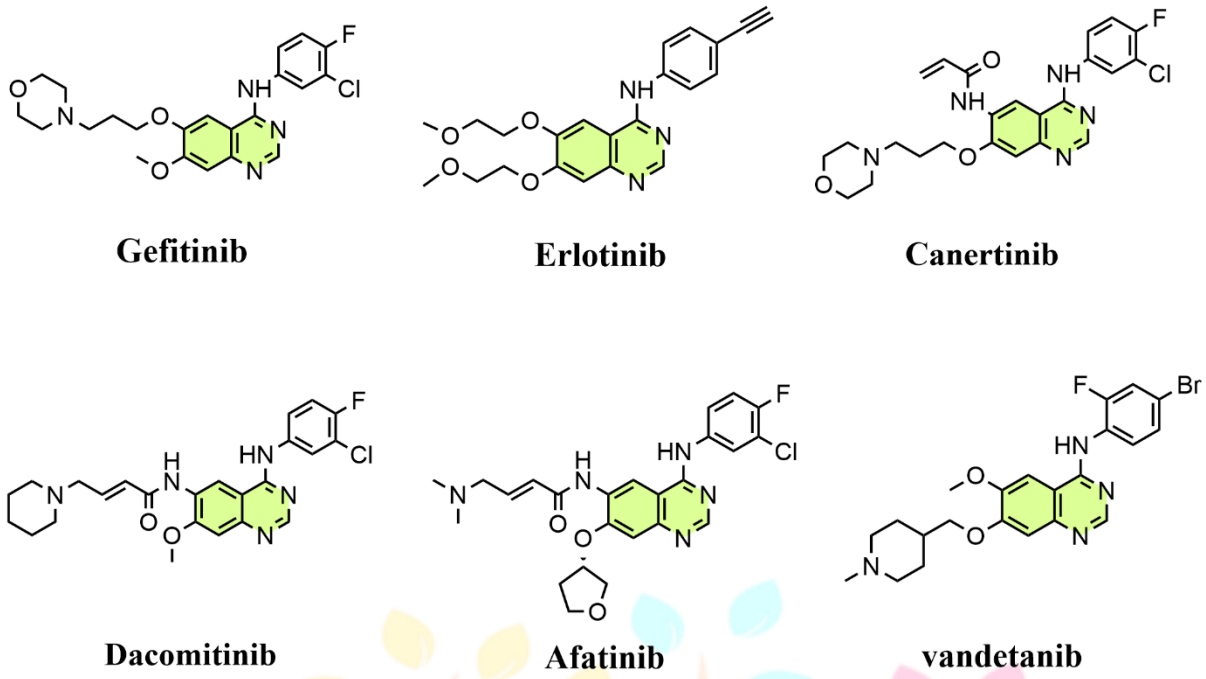


Figure:1 *Selected examples illustrating the importance of quinazolines and quinazolinones [39].*

2. Quinazoline and Quinazolinone based derivatives showed potential antifungal activities.

There is always a need for novel antifungal since many fungal strains have already generated resistance against antibiotics.

2.1 Urea and thiourea-based quinazoline derivatives

Urea based series of quinazoline derivatives were synthesized by Aniruddhasinh M. Rana and co-workers and screened for their antifungal activity against *C. albicans* fungal strain using fluconazole as a standard. As mentioned in table 1, figure 2 all tested compound showed moderate to good antifungal activity as compared to fluconazole with 10-40 µg/ml MIC value. SAR study revealed that compound with 4-Me-Cyclohexyl substituent **1c** in the place of R_1 was found to be the most active [40] As shown in table 1, figure 2.

Table:1 Potent antifungal urea based quinazolinone derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml)
		C. albicans
1a	Ph	20
1b	Cyclohexyl	20
1c	4-Me-Cyclohexyl	10
1d	2-Cl-Ph	20
1e	2-Me-Ph	20
1f	4-Me-Ph	20
1g	3,5-bis (CF3)-Ph	20
1h	4-SCH3-Ph	20
1i	2-Cl-5-CF3-Ph	20
Flucanazole	-	5

Another, urea and thiourea-based quinazoline derivatives were synthesized by Amit B. Patel and co-workers for their antifungal activity against *A. niger* and *C. albicans*. Fluoro-substituted thiourea analogue **2e** showed 50% more potent than the standard fluconazole against *C. albicans*. The SAR study revealed that R_1 is replace by bromo **2d** and methoxy **2f** substituent and compound with -F substituted urea analogue **2b** display similar antifungal activity against *C. albicans* with MIC value 12.5 µg/ml. as per table 2, figure 2 substitution of -Cl and -CH_3 on both urea and thiourea analogue lead to decrease the activity. substitution on phenyl ring favour the activity, unsubstituted compound display relatively weak antifungal activity [41].

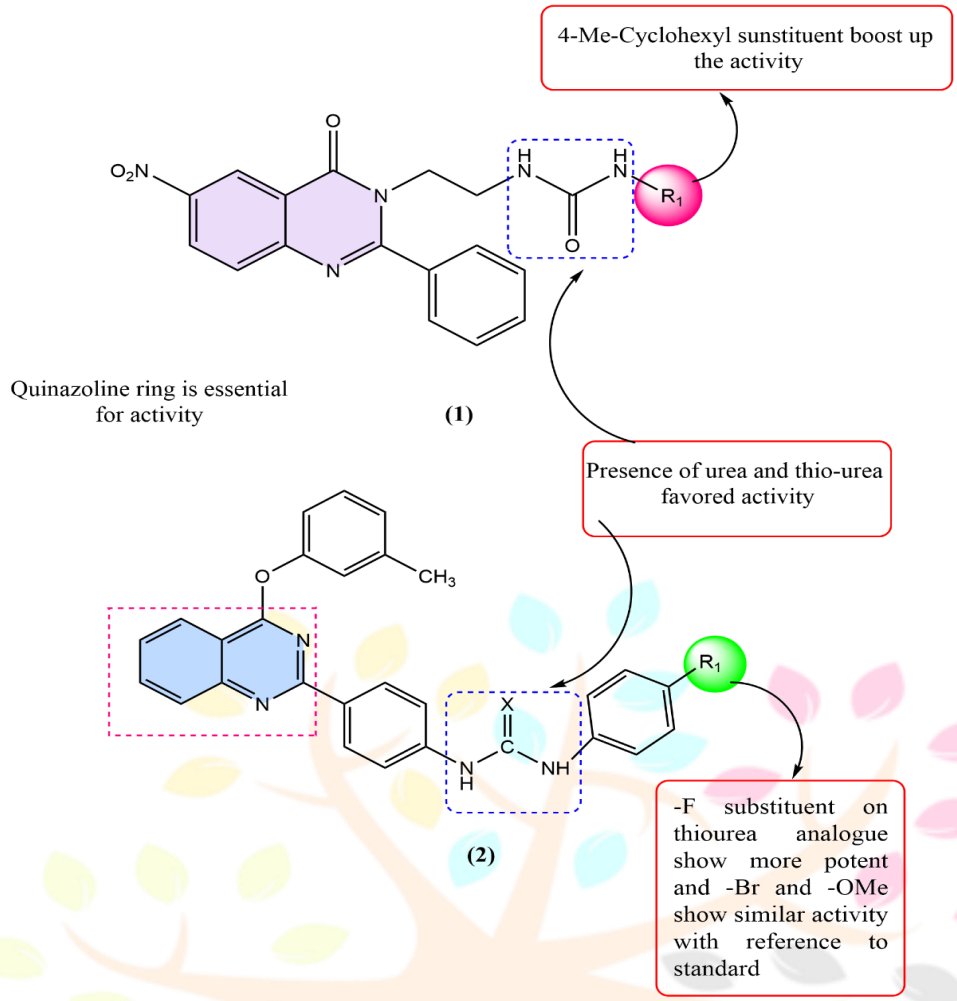


Figure:2 *Graphical SAR of urea and thiourea-based quinazoline as an anti-fungal agent.*

Table:2 Potent antifungal urea and thiourea-based quinazoline derivatives.

Compound	x	R_1	Antifungal activity (MIC: µg/ml)	
			A. niger	*C. albicans*
2a	O	H	200	250
2b	O	F	25	12.5
2c	S	H	50	200
2d	S	Br	25	12.5
2e	S	F	50	6.25
2f	S	OCH_3	50	12.5
Fluconazole	-	-	6.25	12.5

2.2 Benzimidazo-quinazoline derivatives

N. K. Nandwana and co-workers synthesized a new benzimidazo-quinazoline derivatives and screened for their antifungal activity. Some of them were most powerful then the reference drug amphotericin B (MIC 30 µg/ml). SAR study revealed that benzimidazole substrate fused with indole and azoles exhibit excellent antifungal activity. As shown in table 3 and figure 3, compound containing 1,2,4-triazole **4** and unsubstituted

indole ring **6a** showed most potent antifungal activity against both the strain. Substitution on indole ring slightly decrease the activity [42].

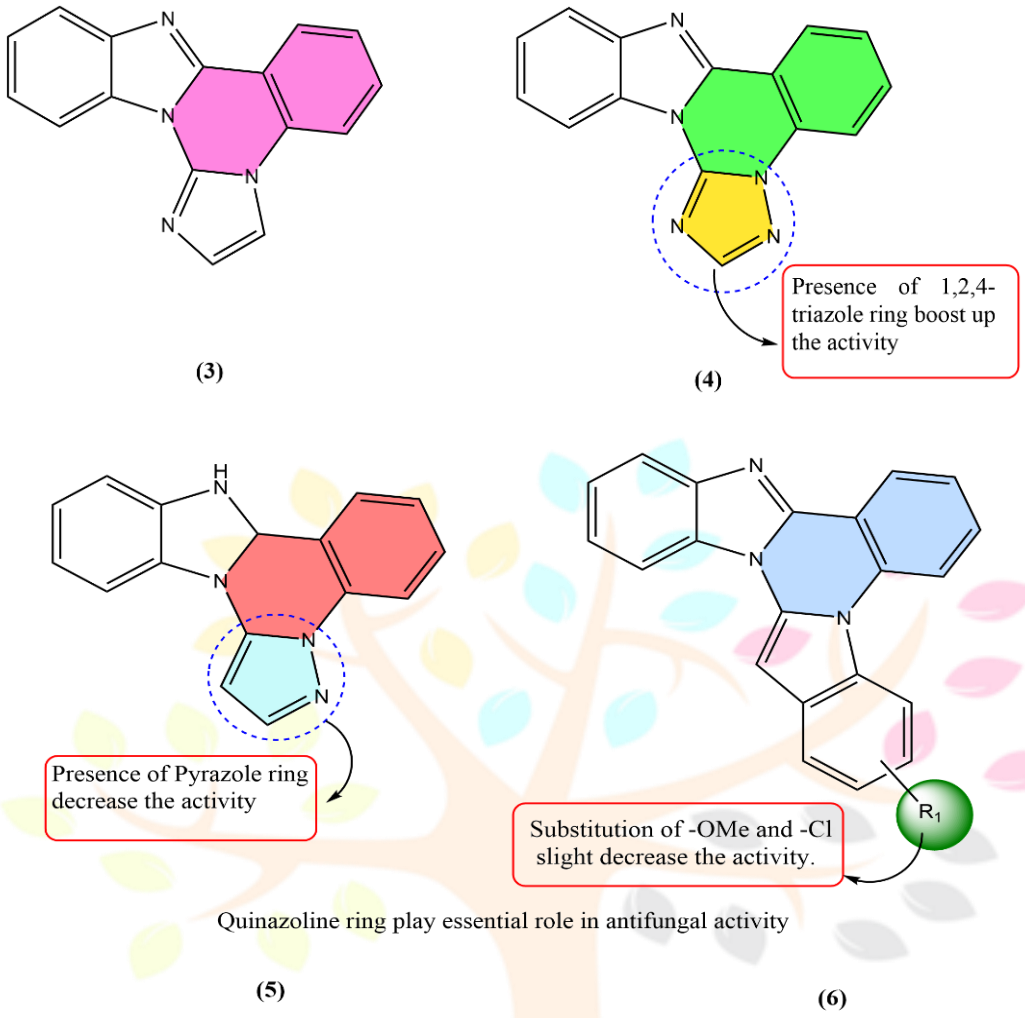


Figure: 3 *Graphical SAR of Azole/benzimidazo-quinazoline derivatives as an anti-fungal agent.*

Table:3 Potent antifungal Azole/benzimidazo-quinazoline derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)	
		A. niger	*C. albicans*
3	-	16	16
4	-	>8	8
5	-	32	32
6a	-H	8	8
6b	6-OMe	>16	>16
6c	5-Cl	16	16
Amphotericine-B		30	30

2.3 1,2,4-triazole containing quinazoline derivatives

1,2,4-triazole containing quinazoline derivatives were synthesized by Lan Yang and co-workers and screened for their antifungal activity with inhibition rate (%) at 50 µg/ml against *Fusarium oxysporum*, *Sclerotinia*

sclerotiorum and *Verticillium dahlia*. All quinazoline derivatives were less active than commercial agricultural fungicide Hymexazol used as a reference. As mentioned in table 4 and figure 4, SAR study demonstrate that R_1 is replace by methyl, propyl, phenyl and 4-fluoro phenyl substituent it shows moderate antifungal activity. Compounds **7a**, **7b**, **7c** and **7d** having an inhibition rate of >40% against *S. sclerotiorum* [43].

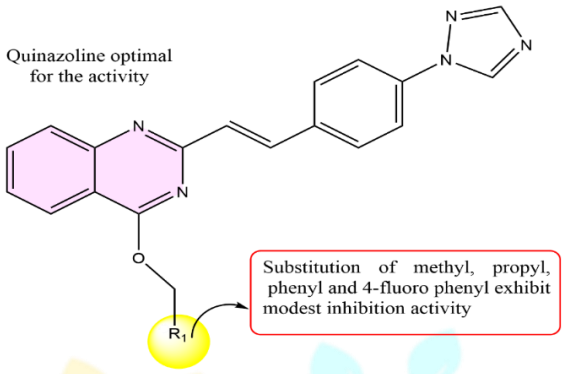


Figure:4 *Graphical SAR of 1,2,4-triazole containing quinazoline derivatives as an anti-fungal agent.*

Table:4 Antifungal 1,2,4-triazole containing quinazoline derivatives.

Compound	R_1	Antifungal activity (inhibition rate %)	
		F. oxysporum	***S. sclerotiorum***
7a	$-CH_3$	25.7	45.7
7b	$-(CH_2)_2CH_3$	17.6	40.7
7c	$4\text{-F-}C_6H_4$	21.7	43.6
7d	C_6H_5	21.7	43.1
Hymexazol	-	66.0	80.5

2.4 Benzotriazolo-Quinazoline derivatives

H. A. Abuelizz and co-workers have designed and synthesized a series of Benzotriazolo-Quinazoline derivatives and evaluated for their antifungal activity against ten different fungal strains using amphotericin B as a reference. Compounds showed moderate activity against *Candida tropicalis, Penicillium expansum, Microsporum canis, Trichophyton mentagrophytes* and no activity against *Cryptococcus neoformans*. As shown in table 5 figure 5, Compound **8c** show the equal activity against *A. fumigatus*, compound **10** showed stronger inhibition than the reference drug against *S. racemosum* and compound **8a**, **8b**, **8c**, **8d**, **9** and **10** showed stronger inhibition then the reference drug against *G. candidum*. Compound **8c** showed the equal inhibition activity against both *C. albicans* and *A. niger* [44].

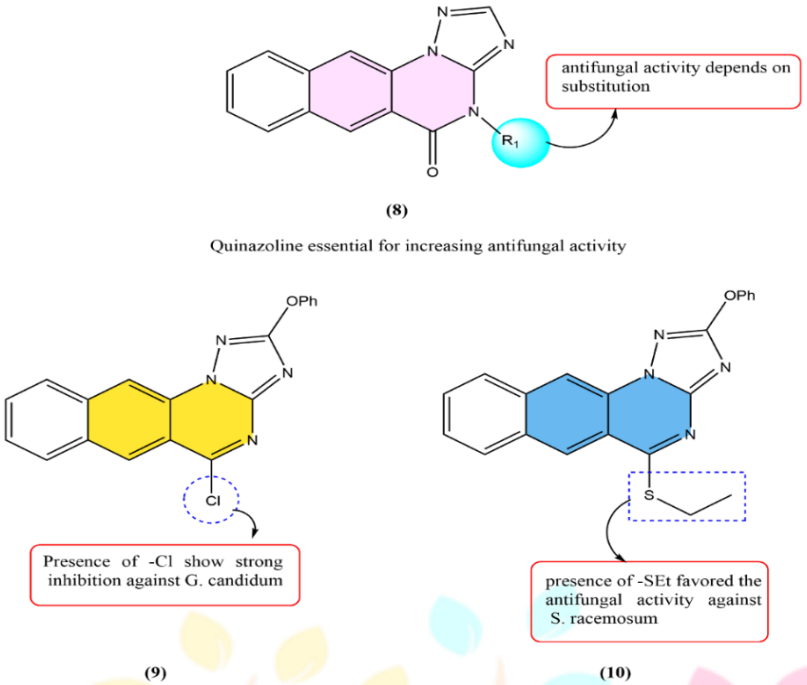


Figure:5 *Graphical SAR of benzotriazolo-Quinazoline derivatives as an anti-fungal agent.*

Table:5 Antifungal Benzotriazolo-Quinazoline derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)				
		A. fumigatus	***S. racemosum***	***G. candidum***	***C. albicans***	***A. niger***
8a	3-CN-benzyl	1.95	1.95	0.98	15.63	15.63
8b	4-CN-benzyl	0.98	3.9	0.98	3.9	31.25
8c	4-Cl-benzyl	0.49	1.95	0.49	1.95	3.9
8d	2-morpholinoethyl	0.98	0.98	0.98	7.81	31.25
8e	2-(phtalimido-2-yl) propyl	1.95	1.95	1.95	15.63	31.25
9	-	1.95	1.95	0.98	7.81	3.9
10	-	0.98	0.49	0.98	3.9	7.81
Amphotericine-B	-	0.49	0.98	1.95	1.95	3.9

2.5 1,2,4-triazole-thioether quinazoline derivatives

A series of triazole-thioether substituted quinazoline derivatives were constructed by zhijiang Fan et al. and their antifungal activity with inhibition rate (%) against *Pellicularia sasakii, Cytospora mandshurica, Gloeosporium fructigenum, Gibberella zeae, Verticillium dahlia, Phytophthora infestans* at 50 µg/ml. From the data of table 6 and figure 6, SAR study demonstrated that some compounds showed moderate antifungal activities against certain fungi such as compound **11a** containing -$COOC_2H_5$ against *G. zeae*. Substitution of 3-F-Ph in the place of R_1 showed moderate antifungal activity against *V. dahlia* while substitution of 2/4-F-

Ph lead to decrease the activity and substitution of 2-Cl-Ph showed moderate antifungal activity against *G. fructigenum* [45].

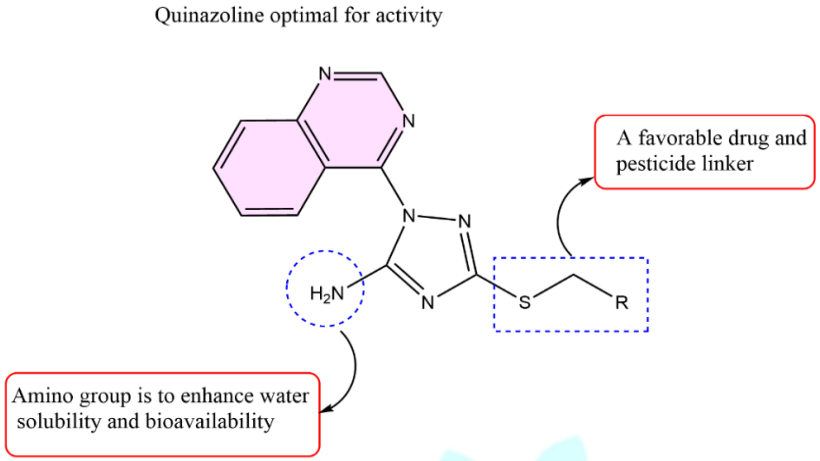


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Figure:6 *Graphical SAR of 1,2,4-triazol-ethioether quinazoline derivatives as an anti-fungal agent.*

Table:6 Antifungal 1,2,4-triazol-ethioether quinazoline derivatives.

Compound	R_1	Antifungal activity (inhibition rate %)		
		G. zeae	***V. dahlia***	***G. fructigenum***
11a	$COOC_2H_5$	32.2	23.1	25.6
11b	3-F-Ph	22.1	36.9	32.6
11c	2-Cl-Ph	24.3	23.9	37.8
11d	2,6-di-Cl-Ph	17.7	21.3	38.7
Hymexazol	-	47.0	86.3	43.1

2.6 Amino-quinazoline sulphonamide derivatives

A few amino quinazoline sulphonamide derivatives were evaluated for their antifungal activity against *A. niger* strain by A. S. kumar and co-workers. Compounds persuaded moderate to excellent antifungal activity. As mentioned in table 7 and figure 7, compound **12b** seen as intensely active against *A. niger*, which is more than reference fluconazole with MIC 8.0 µg/ml. SAR study signifies that sulfisoxazole derivative **12b** is more potent than sulfamethoxazole **12a** derivative. Quinazoline with sulfamethoxazole derivative shown moderate antifungal activity [46].

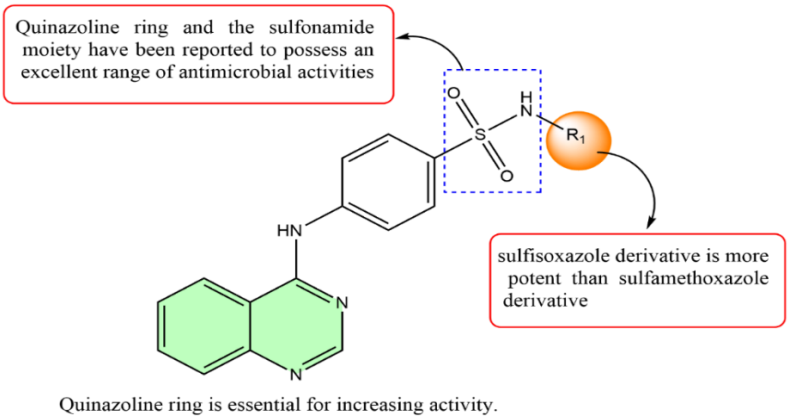
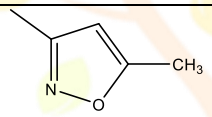
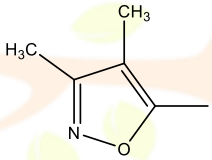


Figure:7 *Graphical SAR of amino-quinazoline sulphonamide derivatives as an anti-fungal agent.*

Table:7 Antifungal amino-quinazoline sulphonamide derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)
		A. niger
12a		25
12b		6.25
Fluconazole	-	8.0

2.7 Quinazolin-N-phenylacetamide derivatives

A series of quinazolin-N-phenylacetamide derivatives were structured by Zhijiang Fan and his research team and antifungal activity with inhibition rate (%) of these compounds against six phytopathogenic fungi were tested *in vitro*. As shown in table 8 and figure 8, SAR study revealed that compounds with presence of 3-nitro **13c** and 2,6-di-fluoro **13d** substituents display comparable antifungal activity against *Gloeosporium fructigenum* at 50 µg/mL with inhibition rate of 44.4% and 44.0% respectively, closer to hymexazol (49.8). Compounds with substitution of -F, -Cl, -CF_3, -CH_3 and -Br groups display moderate antifungal activity [47].

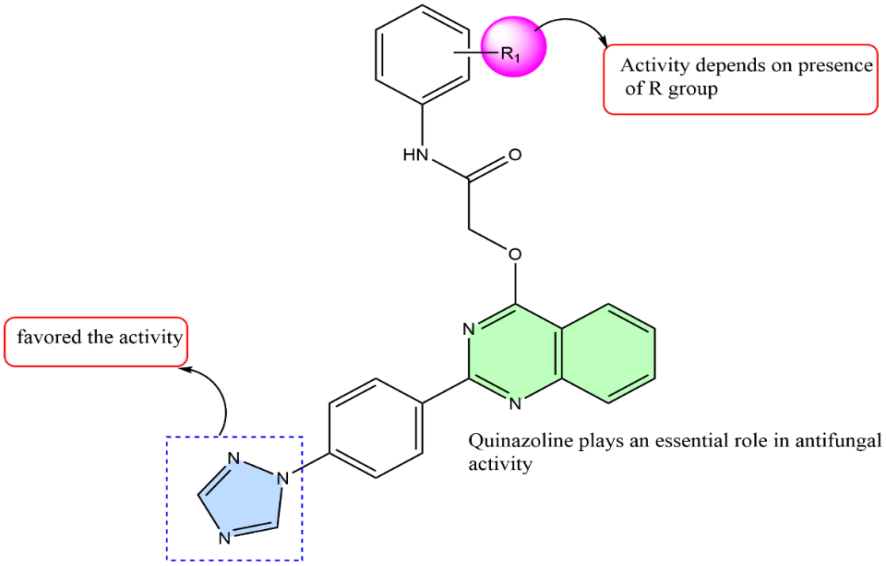


Figure:8 *Graphical SAR of Quinazolin-N-phenylacetamide derivatives as an anti-fungal agent.*

Table:8 Antifungal Quinazolin-N-phenylacetamide derivatives.

Compound	R_1	Antifungal activity inhibition rate (%)
		G. fructigenum
13a	-H	39.4
13b	2-NO_2	41.9
13c	3-NO_2	44.4
13d	2,6-di-F	44.0
Fluconazole	-	49.8

2.8 Quinazoline Thioether Derivatives

A series of 22 quinazoline thioether derivatives incorporating a 1,2,4-triazolo[4,3-a] pyridine moiety were synthesized and evaluated for *in vitro* antifungal activities. As per table 9, figure 9, SAR study demonstrated that substitution of 2-Cl-phenyl ring **14b** in the place of R_1 exhibit antifungal activity against the fungi *F. oxysporum* and *V. dahliae* having the inhibition rates of 52.5 and 65.4%, respectively and compound containing carboxylic acid ethyl ester group**14a** exhibit antifungal activity against *V. dahliae* with inhibition rate of 46.8 %. Substitution of phenyl, methyl phenyl, methoxy phenyl, fluoro phenyl, bromo phenyl and tri-fluoro methyl phenyl reduce the activity [48].

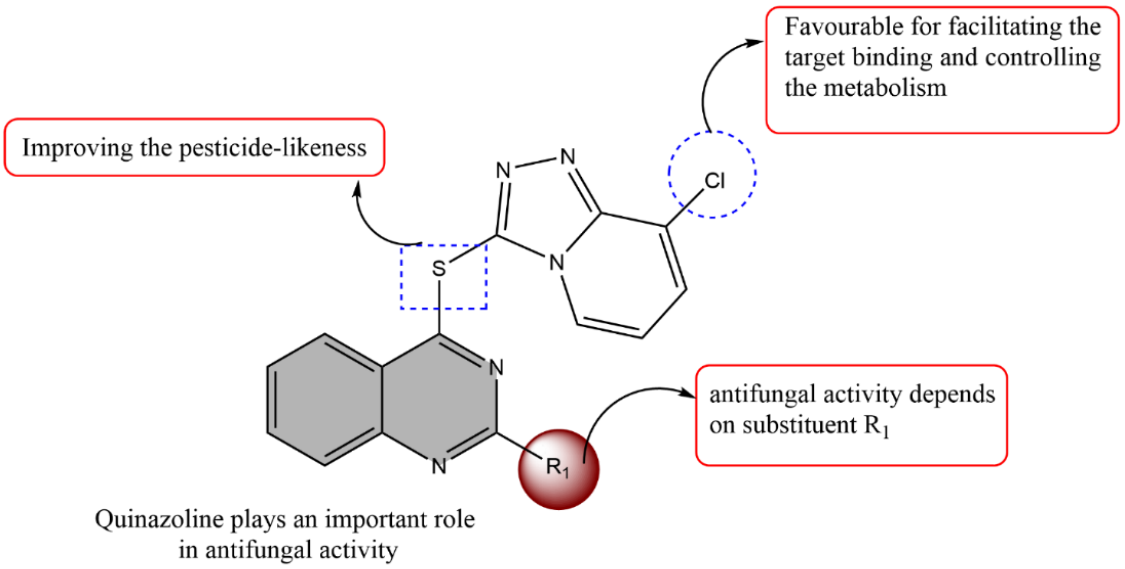


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Figure:9 *Graphical SAR of quinazoline Thioether Derivatives as an anti-fungal agent.*

Table:9 Antifungal quinazoline Thioether Derivatives.

Compound	R_1	Antifungal activity (inhibition rate %)	
		F. oxysporum	***V. dahliae***
14a	$COOC_2H_5$	21.3	46.8
14b	2-Cl-Ph	52.5	65.4
Hymexazol	-	51.2	86.3

2.9 Benzo-imidazo-quinazoline derivatives

J. c. Li, et al. designed and synthesized a series of benzo-imidazo-quinazoline derivatives and evaluated for their antifungal activity against six plant fungi in vitro. All derivatives show significant antifungal activity against different fungal *strain P. zeae, B. cinerea, S. sclerotiorum, M. oryzae, R. solani, F. oxysporum f. sp. Vasinfectum.* SAR study revealed that R_2 replace by H atom or methyl substituent were enhanced the antifungal activity. Amino substitution also show better inhibitory activity. As mentioned in table 10 and figure 10, compound **15a** which is substituted by H-atom exhibit 100% inhibition against *P. zeae* at both concentration of 100 µg/ml and 50 µg/ml which is more than the reference azoxystrobin and showed 90% inhibition against *M. oryzae* at concentration of 100 µg/ml. Compound with methyl substituent at R_2 position also exhibit excellent antifungal activity against all fungal strain [49].

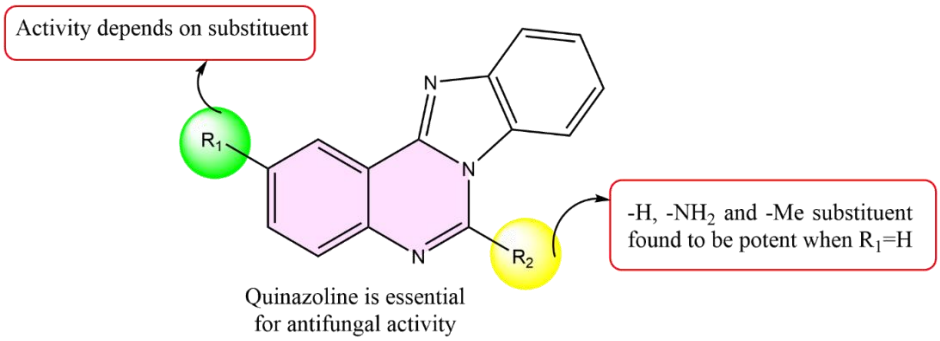

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Figure:10 *Graphical SAR of benzo-imidazo-quinazoline derivatives as an anti-fungal agent.*

Table:10 Antifungal benzo-imidazo-quinazoline Derivatives.

Compound	R_1	R_2	Conc.	Antifungal activity (MIC: µg/ml)					
				P. zeae	***B. cinerea***	***S. sclerotiorum***	***M. oryzae***	***R. solani***	***F. oxysporum***
15a	H	H	100	100.00	87.13	77.64	90.85	86.01	89.51
			50	100.00	85.46	77.35	87.69	78.58	90.51
15b	H	NH_2	100	94.60	38.13	85.01	76.50	86.60	74.81
			50	92.63	39.38	85.56	77.83	86.66	74.57
15c	H	Me	100	99.31	98.48	98.81	83.98	78.47	67.94
			50	99.15	88.00	61.36	86.54	73.01	67.02
15d	-F	Me	100	98.16	74.65	61.68	73.80	65.75	64.91
			50	86.00	58.94	41.90	78.84	61.13	63.52
Azoxystrobin	-	-	100	68.17	29.64	55.70	43.36	59.09	55.95
			50	83.3	42.08	74.58	28.75	48.33	52.50±

2.10 Amino-quinazoline N-phenyl benzene-sulfonamide derivatives

Quinazolin-4-ylamino derivatives containing phenylbenzenesulfonamides were synthesized by A. S. kumar and his research group and screened them for their antifungal activity against A. niger. From the data of table 11 and figure 11, all tested compound exhibited moderate antifungal activity. SAR study revealed that compound with -Cl, -F and $-CH_3$ substituent showed antifungal activity against A. niger at MIC value of 50 µg/ml [50].

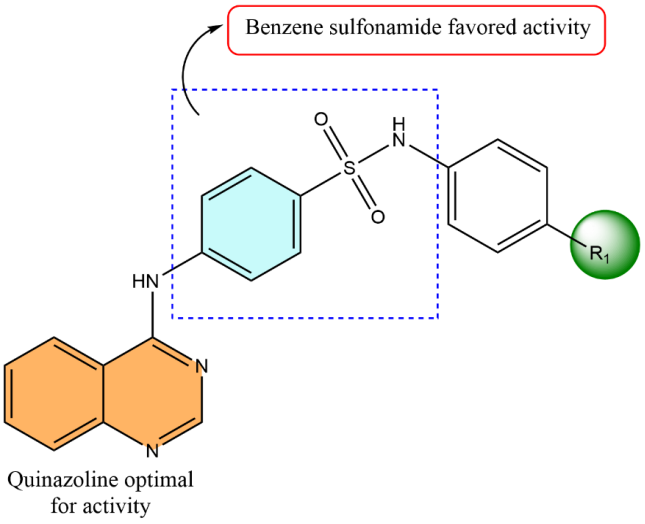

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Figure:11 *Graphical SAR of Amino-quinazoline N-phenyl benzene-sulfonamide derivatives as an anti-fungal agent.*

Table:11 Antifungal Amino-quinazoline N-phenyl benzene-sulfonamide Derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml)
		A.niger
16a	-Cl	50
16b	-F	50
16c	$-CH_3$	50
Fluconazole	-	4.0

2.11 Thiazolo-triazole bearing fluoroquinazolinyl derivatives

A novel series of fluoro-quinazoline derivatives with thiazolo-triazole ring synthesized by Muhan Ding and evaluate in vitro antifungal activity against six phytopathogenic fungi, including *Verticillium dahlia, Colletotrichum gloeosporioides, Gibberella zeae, Fusarium oxysporum, Cytospora mandshurica*, and *R. solani*. As mentioned in table 12 and figure 12 SAR study revealed that Compound with 2-CH_3-Ph substituent **17a** exhibited the same potency as control chlorothalonil for inhibiting *G. zeae* at 65.1 % of inhibition rate and compound with 3,4-di-Cl-Ph substituent **17b** displayed the inhibition potency of 80.8%, comparable to the commercialized chlorothalonil (85.9%) against *R. solani* [51].

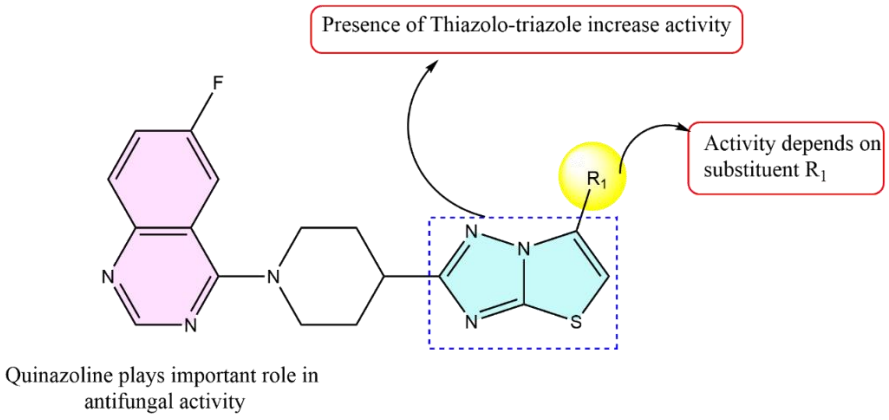

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Figure:12 *Graphical SAR of thiazolo-triazole bearing fluoroquinazolinyl derivatives as an anti-fungal agent.*

Table:12 Antifungal thiazolo-triazole bearing fluoroquinazolinyl Derivatives

Compound	R1	Antifungal activity inhibition rate (%) At 50 µg/ml					
		V. dahlia	***C. gloeosporioides***	***G. zeae***	***F. oxysporum***	***C. mandshurica***	***R. solani***
17a	2-CH_3-Ph	74.7	54.4	65.1	71.4	48.3	71.8
17b	3,4-di-Cl-Ph	28.3	36.0	42.1	53.9	28.2	80.8
chlorothalonil	-	82.6	74.9	63.0	72.8	70.1	85.9

2.12 Thiadiazole containing styryl quinazolinone derivatives

2-styryl substituted quinazolinone derivatives were synthesized by varsha jatav and co-workers and surveyed for their antifungal activity against *Aspergillus niger, Candida albicans* and *Fusarium oxysporum*. All quinazolinone derivatives revealed less antifungal activity than the reference clotrimazole against all tested fungal strain. From table 13, figure 13 SAR study prompted that p-methoxyphenyl substitution at Ar **18a** has moderate antifungal activity against *A. niger*. In the case of any other substituent Results indicated that higher concentrations of the compounds were required in order to inhibit fungal growth. The order of sensitivity was *A. niger*, then *F. oxysporum*, then *C. albicans*, from the most to the least sensitive [52].

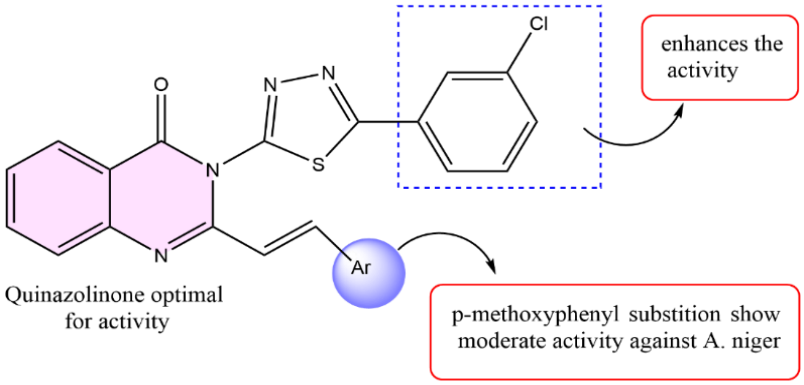

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Figure:13 *Graphical SAR of thiadiazole containing styryl quinazolinone derivatives as an anti-fungal agent.*

Table:13 Antifungal thiadiazole containing styryl quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)		
		A. nigers	***C. albicans***	***F. oxysporum***
18a	p-$OCH_3C_6H_4$	13.86	22.68	15.90
18b	p-$CH_3C_6H_4$	13.70	17.07	16.62
Clotrimazole	-	12.98	6.21	10.78

2.13 Triazole/triazine bearing quinazolinone derivatives

Triazole/triazine bearing quinazolinone derivatives were designed and synthesized by S.K. Pandey et al. and tested for their antifungal activity against *C. albicans, A. fumigatus, A. flavus* and *A. niger*. The screening data of antifungal activity of these series of compounds shows moderate to good antifungal activity. As mentioned in table 14, figure 14, SAR study revealed that High activity was demonstrated by **19e** against *A. fumigatus*, which is even more than standard drug Fluconazole (MIC: 6.25 µg/ml) for same pathogenic fungus which also shows equipotent against *C. albicans*, while the compounds **19b**, **19e** and **20b** found euqually active against *A. niger*. The compounds having a fused 1,2,4-triazole ring at N-1 and C-2 of parent compound quinazolinone, and were found more potent than other compounds, which having triazine and tetrazine ring fused at N-1 and C-2 of parent quinazolinone [53].

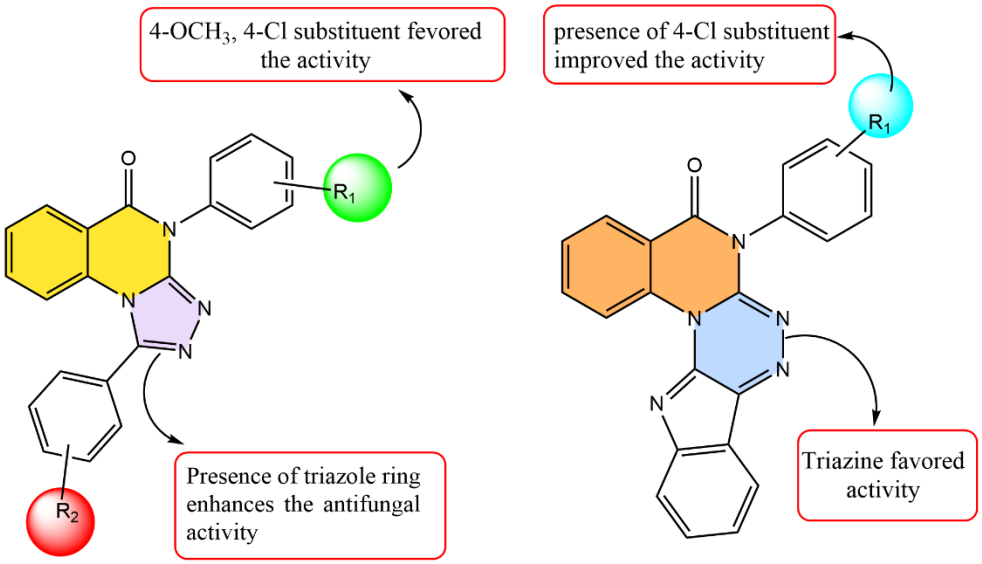


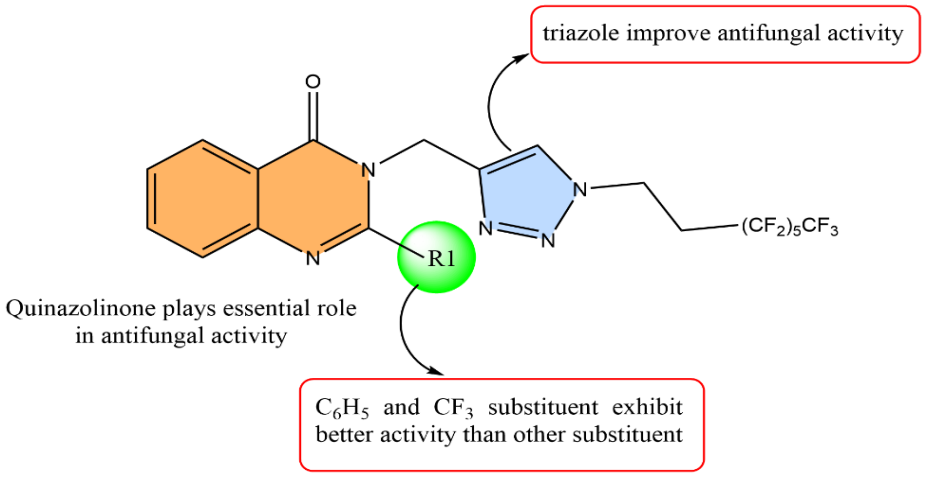
Figure:14 *Graphical SAR of triazole/triazine bearing quinazolinone derivatives as an anti-fungal agent.*

Table:14 Antifungal triazole/triazine bearing quinazolinone derivatives.

Compound	R_1	R_2	Antifungal activity (MIC: µg/ml)			
			C. albicans	*A. fumigatus*	*A. flavus*	*A. niger*
19a	H	2-CH_3	12.5	6.25	25	6.25
19b	4-OCH3	2-Cl	6.25	3.12	3.12	1.56
19c	4-Cl	H	12.5	6.25	12.5	25
19d	4-Cl	2-CH3	6.25	12.5	3.12	12.5
19e	4-Cl	2-Cl	1.56	3.12	6.25	1.56
20a	4-OCH3	-	6.25	6.25	3.12	12.5
20b	4-Cl	-	3.12	6.25	3.12	1.56
Fluconazole	-	-	1.56	6.25	3.12	1.56

2.14 Triazol-4-yl substituted quinazolinone derivatives

P. Mani Chandrika et al. synthesized triazol-4-yl substituted quinazolinone derivatives and screened for their antifungal activity against the fungal strain *Candida albicans, Saccharomyces cerevisiae* and *filamentous* fungal cultures like *Rhizopus oryzae, Aspergillus niger, Aspergillus flavus, Candida rugosa*. SAR study demonstrated that R_1 replace by phenyl ring and trifluoro methyl substituent showed promising activity against most of the fungi. From table 15, figure 15, It is found that the inhibition diameter increases with concentration. The inhibitory zone diameters of the compounds are compared with those obtained from standard amphotericin. Compound with trifluoro methyl substituent **21b** identified as most active compound against various fungal cultures [54].



(21)

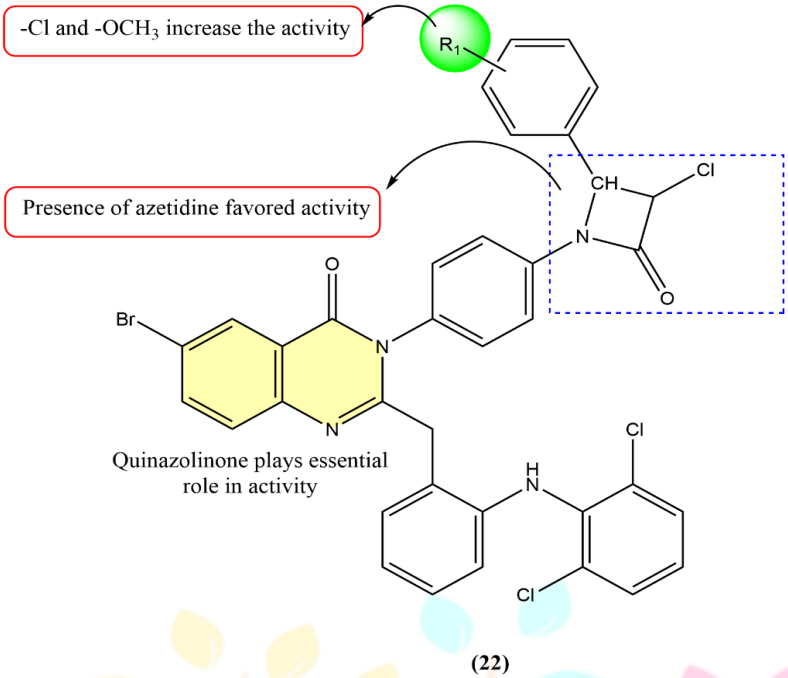
Figure:15 *Graphical SAR of Triazol-4-yl substituted quinazolinone derivatives as an anti-fungal agent.*

Table:15 Antifungal Triazol-4-yl substituted quinazolinone derivatives

Compound	R_1	Antifungal activity (ZOI:mm) At 100 µg/ml					
		C. albicans	***S. cerevisiae***	***R. oryzae***	***A. niger***	***A. flavus***	***C. rugosa***
21a	C_6H_5	12	12	10	12	12	10
21b	CF_3	9	12	13	9	12	13
Amphotericine-B (50 µg/ml)	-	22	25	22	-	-	-

2.15 Azetidinyl quinazolinone derivatives

N. B. Patel and J. C. Patel design and synthesized a new series of 2-azetidinyl-4-quinazolinones derivatives and screened for their anti-fungal effect with inhibition zone against *c. albicans* at two different MIC value of 50 and 100 µg/ml. all compounds showed less antifungal activity as compared to amphotericine-B, which is used as a standard. As mentioned in table 16 and figure 16, SAR study revealed that compounds with -Cl **22a** and -OCH_3 **22b** substituent in the place of R_1 showed good antifungal activity against *C. albicans*. 2-Azetidinone derivatives were found more active than that of Schiff base derivatives [55].



(22)

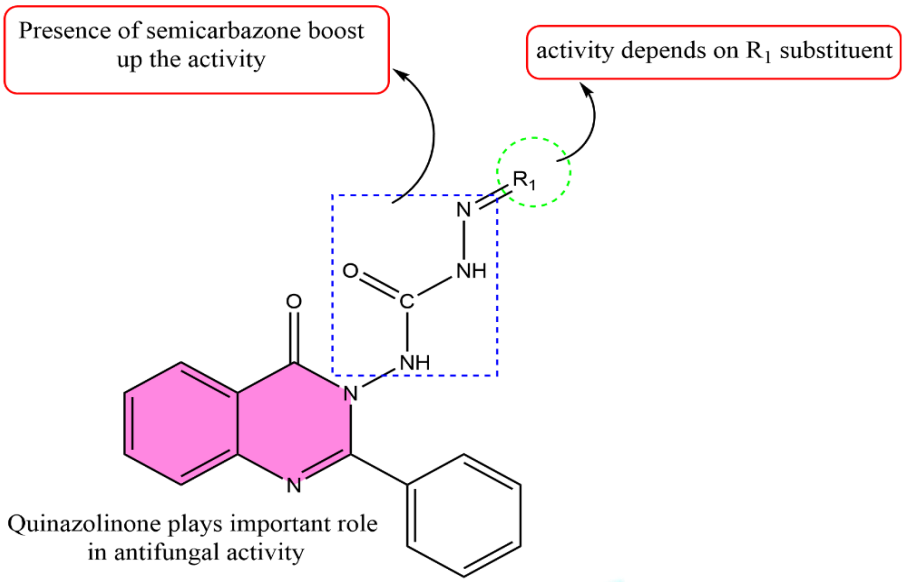
Figure:16 *Graphical SAR of Azetidinyl quinazolinone derivatives as an anti-fungal agent.*

Table:16 Antifungal Azetidinyl quinazolinone derivatives

Compound	R_1	Antifungal activity (ZOI=mm) (MIC: µg/ml)	
		A.niger	
		50 MIC	100MIC
22a	4-Cl	2	5
22b	4-OCH_3	2	4
Amphotericine-B	-	4	9

2.16 Quinazolinone semicarbazone derivatives

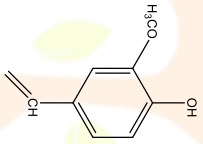
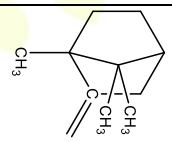
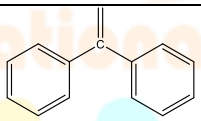
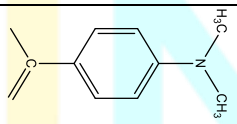
A series of quinazolinone semicarbazone derivatives were synthesized by M. Veerapandian and his research group and tested them for their antifungal activity against *candida albicans* with zone of inhibition. As shown in table 17, figure 17 all synthesized derivatives exhibited stronger activity than the standard clotrimidazole [56].



(23)

Figure:17 *Graphical SAR of quinazolinone semicarbazone derivatives as an anti-fungal agent.*

Table:17 Antifungal quinazolinone semicarbazone derivatives

Compound	R_1	Antifungal activity (ZOI = mm)
		C. albicans
23a		21
23b		20
23c		25
23d		21
clotrimidazole	-	14

2.17 Dibromoquinazolinone derivatives

M.S. Mohamed et al. have developed dibromoquinazolinone derivatives and assessed them for their in vitro antifungal activity against *Candida albicans* and *Aspergillus flavus*. The anti-fungal data revealed that all tested compounds of this investigation are exhibit moderate to good activity against all the tested pathogenic fungus. From table 18, figure 18, SAR study revealed that compound **25** was found to exhibit the most potent in vitro anti-fungal activity against *C. albicans* and *A. flavus*. Compound **24** from Schiff base series containing naphthalene and compound **26** showed better antifungal activity against *A. flavus* than the reference

fluconazole (MIC:0.78 µg/ml). Other quinazolinone derivatives containing oxadiazole, pyrazoles, pyrroles and other synthesized compounds showed moderate antifungal activity [57].

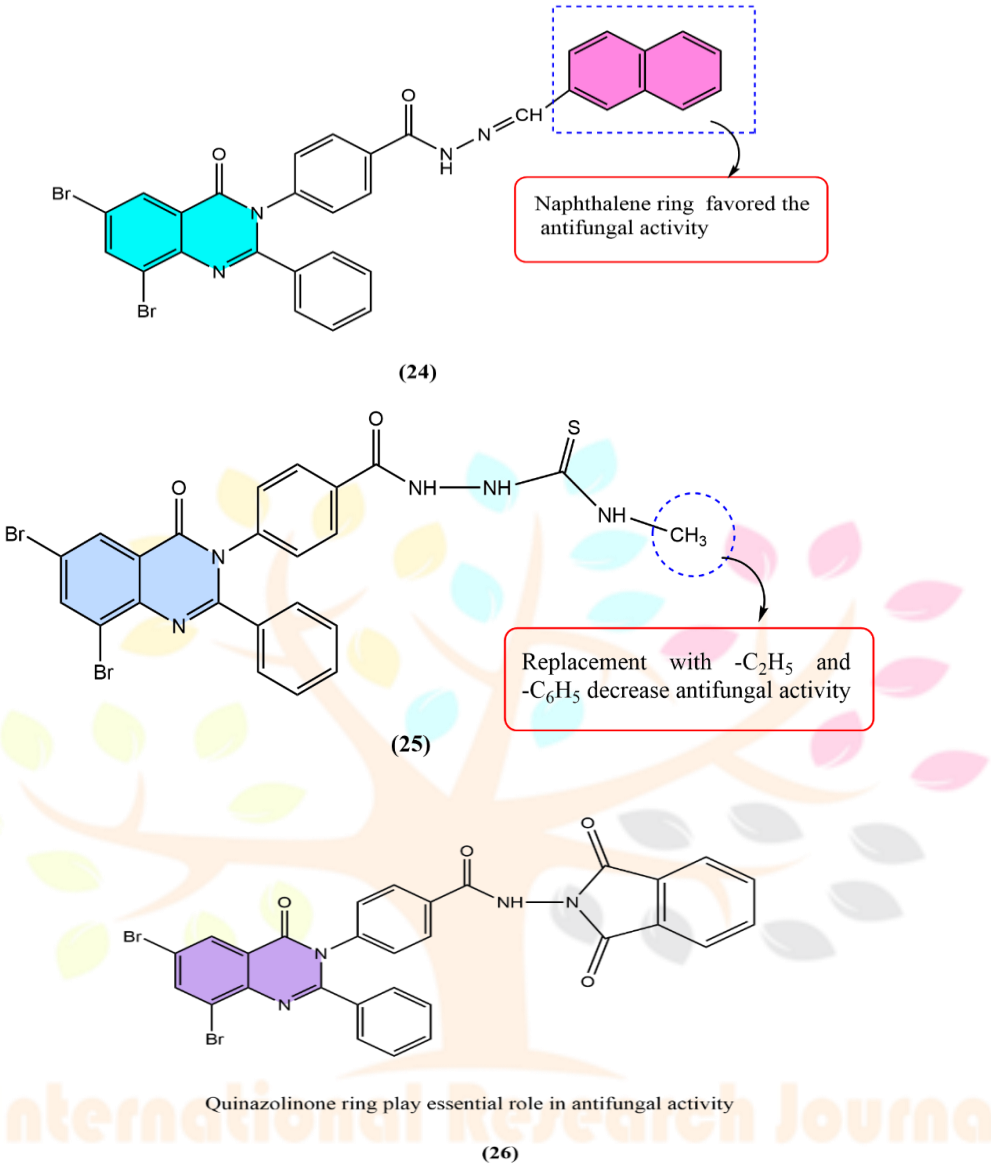


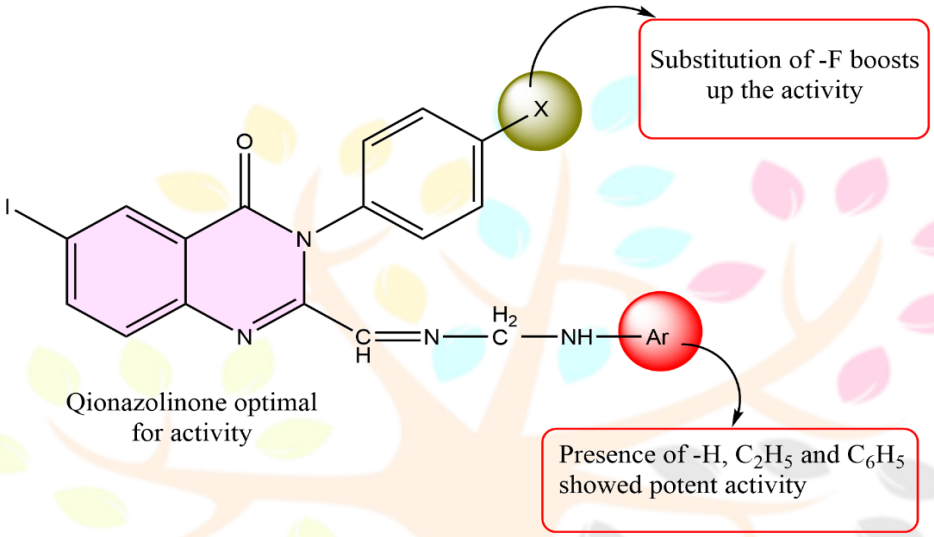
Figure:18 *Graphical SAR of dibromoquinazolinone derivatives as an anti-fungal agent.*

Table:18 Antifungal dibromoquinazolinone derivatives

Compound	Antifungal activity (MIC: µg/ml)	
	C. albicans	***A. flavus***
24	25	0.39
25	0.78	0.097
26	50	0.39
Fluconazole	1.56	0.78

2.18 Quinazolinone carboxaldehyde-thiosemicarbazones derivatives

Quinazolinone carboxaldehyde-thiosemicarbazones derivatives were synthesized by M.M. Aly et al. and evaluated for their antifungal activity against *Fusarium sp.* and *Aspergillus sp*. all the compounds exhibit moderate to high activity against tested fungal pathogens. As mentioned in table 19, figure 19, SAR study revealed that thiosemicarbazone derivatives containing H atom, ethane and phenyl ring in the place of Ar exhibit best activity against *fusarium*, these derivatives are inactive against *aspergillus* fungal strain. Compound **27c** with -F substituent in the place of x and phenyl substitution in the place of Ar found most potent antifungal activity against *Fusarium*, which is more active than nystatin reference [58].



(27)

Figure:19 *Graphical SAR of Quinazolinone carboxaldehyde-thiosemicarbazones derivatives as an anti-fungal agent.*

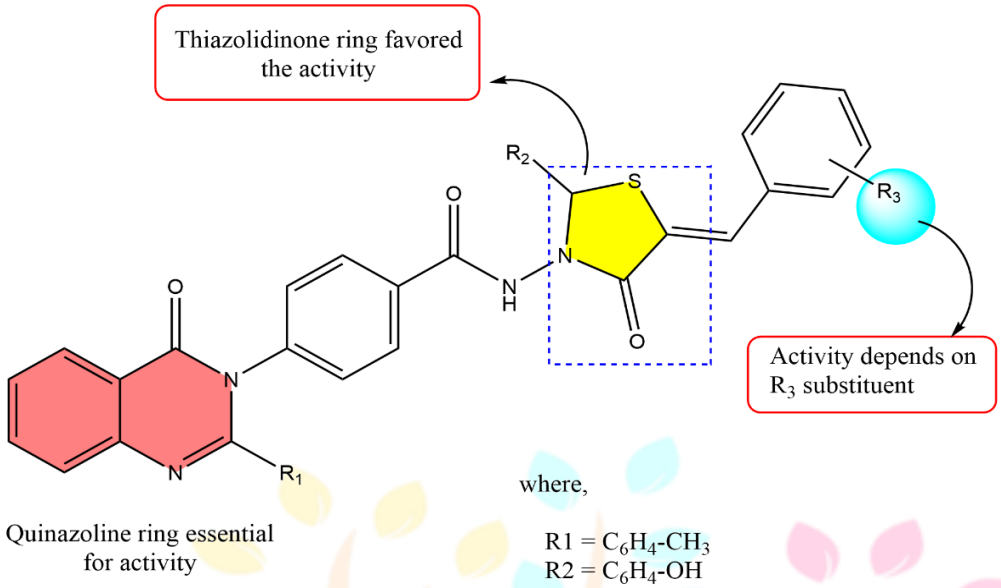
Table:19 Antifungal quinazolinone carboxaldehyde-thiosemicarbazones derivatives.

Compound	X	Ar	Antifungal activity ZOI (mm)(MIC)	
			Aspergillus	***Fusarium***
27a	H	H	0	23(12.5)
27b	H	$-C_2H_5$	0	15(12.5)
27c	-F	$-C_6H_5$	0	25(6)
Nystatin	-	-	12	20

2.19 Thiazolidinone-quinazolinone derivatives

A novel series of thiazolidinone-quinazolinone derivatives design and synthesized by N. C. desai et al. and screened for their antifungal activity against three different fungal strain *Candida albicans, Aspergillus niger*, and *Aspergillus clavatus*. From table 20 and figure 20 SAR study revealed that compounds with 4–F, 3–NO_2 and 4-Cl substituent are considered as a good active against *C. albicans*, while R_3 is replace by $-N(CH_3)_2$, 3–

NO_2, 4–OCH_3 and 2,6-$(Cl)_2$ substituent exhibit equally active against *A. niger* with reference griseofulvin [59].



(28)

Figure:20 *Graphical SAR of thiazolidinone-quinazolinone derivatives as an anti-fungal agent.*

Table:20 Antifungal thiazolidinone-quinazolinone derivatives

Compound	R_3	Antifungal activity (MIC: µg/ml)		
		C. albicans	*A. niger*	*A. clavatus*
28a	3,4,5-$(OCH_3)_3$	1000	100	1000
28b	-$N(CH_3)_2$	1000	100	1000
28c	2–OH–naphthyl	100	1000	500
28d	4–F	100	500	100
28e	4–OH	1000	1000	1000
28f	3–NO_2	100	100	100
28g	4–OCH_3	1000	100	100
28h	2–OCH_3	500	500	500
28i	2–OH–5–Br	500	1000	100
28j	2,6-$(Cl)_2$	500	100	1000
28k	4–Cl	100	1000	1000
Griseofulvin	-	500	100	100

2.20 Quinoline based quinazolinone derivatives

Quinoline based quinazolinone derivatives design and developed by N. C. Desai and A. M. Dodiya and assessed them for their antifungal activity against *C. albicans, A. niger, A. clavatus*. All tested derivatives

showed moderate to good antifungal activity against all three strains. SAR study revealed that compound with 3-Cl, 2-NO_2, 4-NO_2, and 3-OH substituent exhibit highest antifungal activity against *C. albicans*, which is more than reference griseofulvin. As shown in table 21, figure 21, When R_1 substituent is replace by 4-Cl and 2/4-OH exhibit equal antifungal activity against *A. niger* with reference. Only 4-methyl substitution on R_1 showed weak antifungal activity against all tested strain [60].

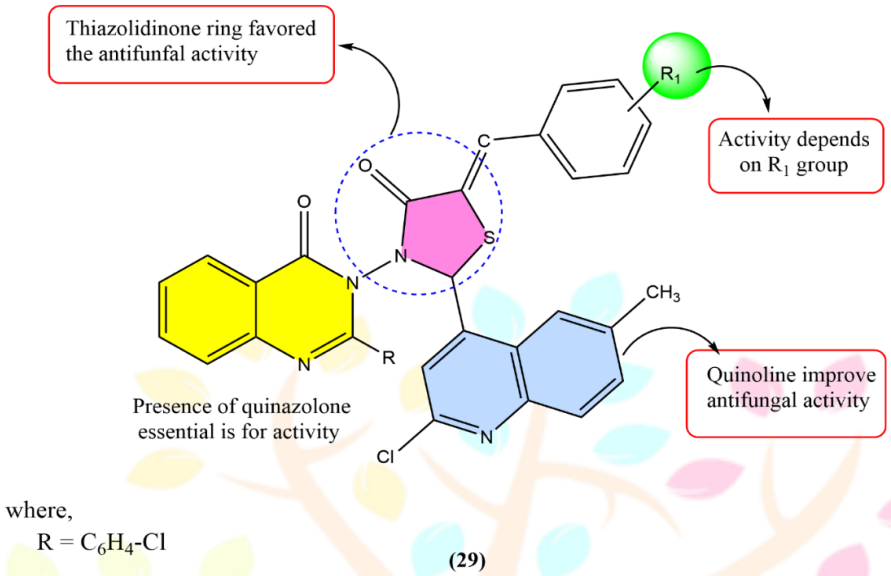


Figure:21 *Graphical SAR of quinoline based quinazolinone derivatives as an anti-fungal agent.*

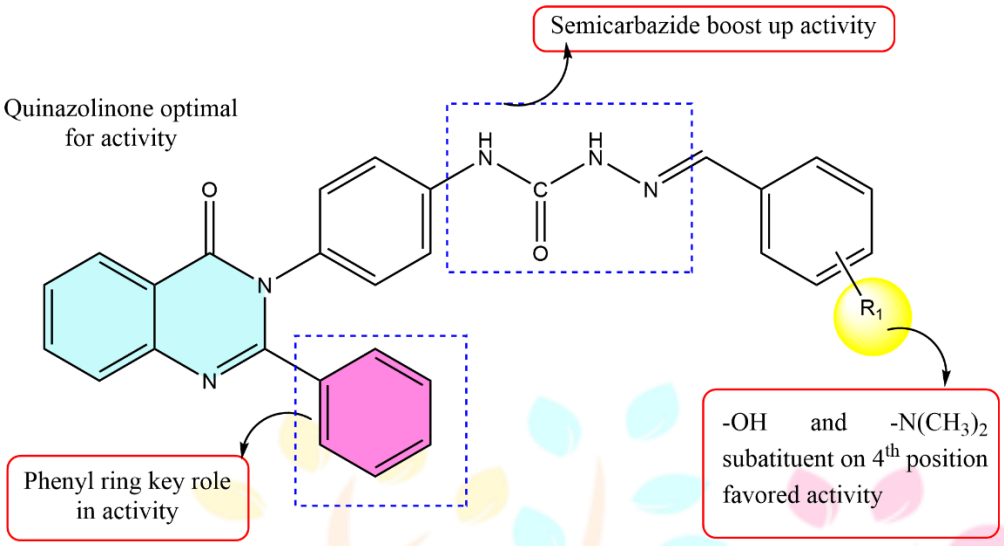
Table:21 Antifungal quinoline based quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)		
		C. albicans	***A. niger***	***A. clavatus***
29a	2-Cl	500	500	100
29b	3-Cl	100	1000	1000
29c	4-Cl	500	100	500
29d	2-NO_2	100	500	500
29e	3-NO_2	500	200	100
29f	4-NO_2	100	1000	500
29g	2-OH	500	100	100
29h	3-OH	100	500	200
29i	4-OH	500	100	500
Griseofulvin	-	500	100	100

2.21 Semicarbazide quinazolinone derivaties

Govindaraj and his research group design and developed semicarbazide bearing quinazolinone derivatives and screened for their antifungal activity against *A. niger* and *A. fumigatus*.from table 22, figure 22, SAR study prompted that the compound having -OH group at 4th position of phenyl ring in place of R_1 showed

equal antifungal activity against A. fumigatus with reference Ketoconazole al MIC 7.81 µg/ml and compound with dimethylamine substituent at 4th position exhibit equal activity against A. niger with reference. Other substituent like -OH, -Cl or unsubstituted phenyl ring led to decrease antifungal activity [61].



(30)

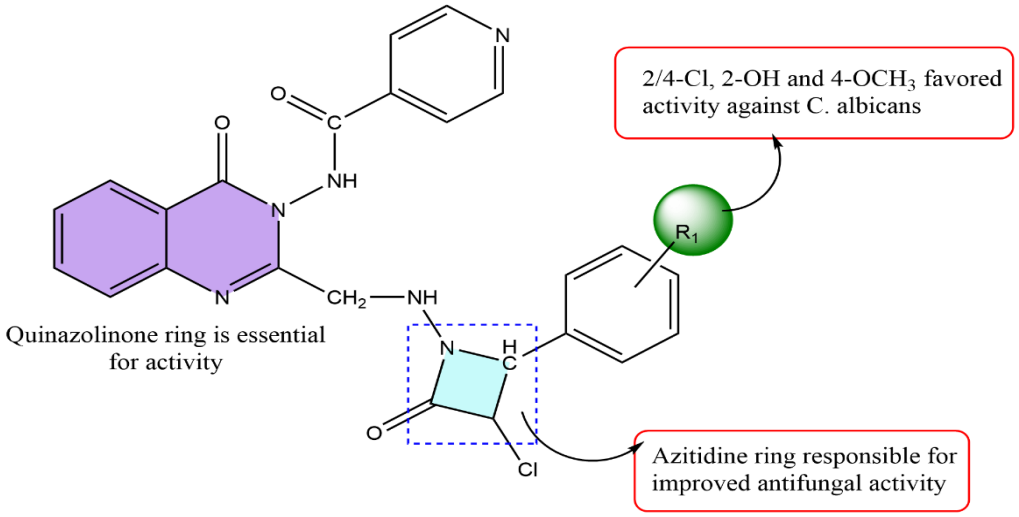
Figure:22 *Graphical SAR of Semicarbazide quinazolinone derivatives as an anti-fungal agent.*

Table:22 Antifungal Semicarbazide quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)	
		A. niger	***A. fumigatus***
30a	4-OH	31.25	7.81
30b	4-$N(CH_3)_2$	15.62	15.62
Ketoconazole	-	15.62	7.81

2.22 Azetidinyl and pyridine containing quinazolinone derivatives

Azetidinyl quinazolinone derivatives were design and synthesized by K. N. Myangar and J. P. Raval and tested foe their antifungal activity against *A. niger, C. albicans* and *A. clavatus* fungal strain. As mentioned in table 23, figure 23, all synthesized compounds exhibit moderate to good antifungal activity. SAR study revealed that substitution of 2/4-Cl, 2-OH and 4-OCH_3 in place of R_1 exhibit better activity against *C. albicans* as compared reference greseofulvin, while compound with -NO_2, -OH and -Br substituted sowed equal activity against *C. albicans*. Among the tested compounds, all compound found less active against *A. niger* and *A. clavatus* with respect to reference Nystatin and greseofulvin [62].



(31)

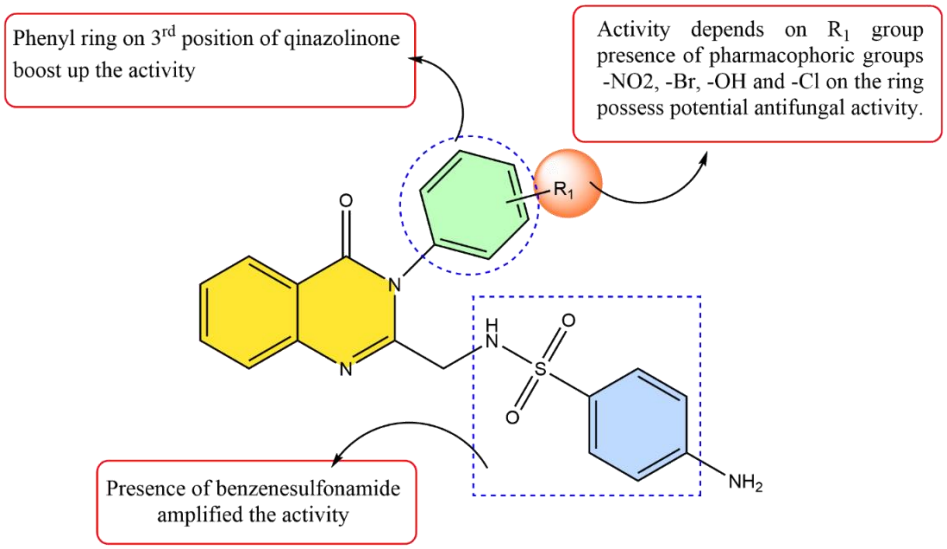
Figure:23 *Graphical SAR of Azetidinyl and pyridine containing quinazolinone derivatives as an anti-fungal agent.*

Table:23 Antifungal azetidinyl and pyridine containing quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)		
		C. albicans	*A. niger*	*A. clavatus*
31a	4-NO_2	500	>1000	>1000
31b	2-Cl	200	200	250
31c	2-Cl	250	1000	1000
31d	2-OH	250	1000	1000
31e	2-OH	500	>1000	>1000
31f	4-OCH_3	200	250	200
Nystatin	-	100	100	100
Greseofulvin	-	500	100	100

2.23 Sulfonamide linked quinazolinone derivatives

A new series of dihydroquinazolinone benzenesulfonamide derivatives were design and synthesized by S. F. Vanparia and his research group and screened for their in vitro antifungal activity against two different fungal strain *A. niger* and *C. albicans*. All compound exhibite moderate to good activity against both fungal strains as compared to reference ketoconazole. SAR study revealed that presence of cyclic ring substituent at 3rd position of quinazolinone ring is necessary requirement for its medicinal properties. furthermore, from table 24 and figure 24 it is conclude that the presence of pharmacophoric groups -NO_2, -Br, -OH and -Cl on the ring possess potential antimicrobial activity. Compounds with halogen substituent like 4-Cl and 3-Br in place of R_1 exhibit equal antifungal activity against *A. niger* as compared to reference with MIC 40 and compounds with 3/4-OMe substituent exhibit equal activity against *c. albicans* with MIC 50. Compounds with 3-Cl, 4-NO_2 and 4-F substitution showed moderate anti-fungal activity against both strains [63].



(32)

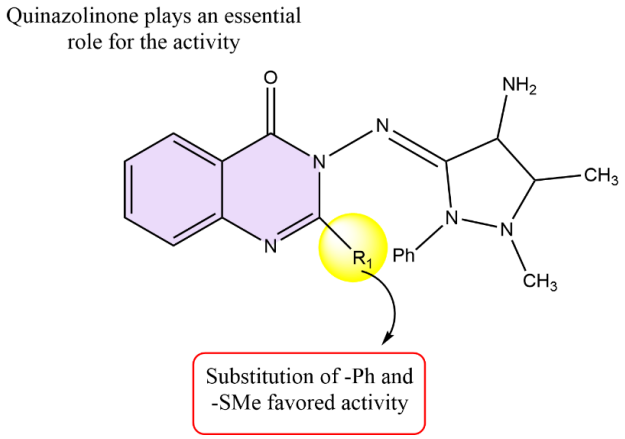
Figure:24 *Graphical SAR of sulfonamide linked quinazolinone derivatives as an anti-fungal agent.*

Table:24 Antifungal sulfonamide linked quinazolinone derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml)	
		A. niger	***C. albicans***
32a	3-OMe	50	50
32b	4-OMe	45	55
32c	4-NO_2	45	55
32d	3-Cl	50	55
32e	4-Cl	40	45
32f	2-Br	45	55
32g	3-Br	40	45
32h	4-Br	45	55
32i	4-f	45	60
Ketoconazole	-	40	50

2.24 Aminoantipyrine linked quinazolinone derivatives

Ahmed A. Al-Amiery and co-workers synthesized a novel quinazolinone derivatives linked with quinazolinone and inspected for their *in vitro* antifungal activity against *C. albicans* and *A. niger*. From table 25, figure25, SAR study revealed that compound containing methyl substituent in place of R_1 exhibit antifungal activity against both strains as compared with the reference fluconazole, while the compound with -S-Me substituent display potential antifungal activity against *C. albicans* [64].



(33)

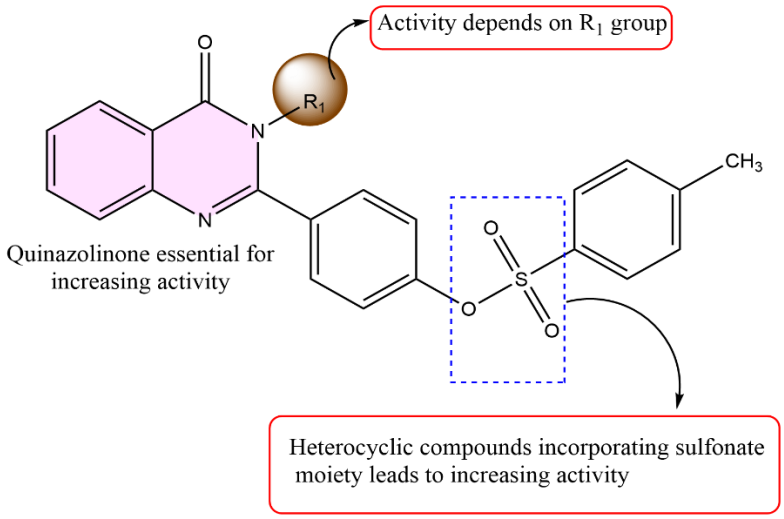
Figure:25 *Graphical SAR of aminoantipyrine linked quinazolinone derivatives as an anti-fungal agent.*

Table:25 Antifungal aminoantipyrine linked quinazolinone derivatives

Compound	R_1	(MIC: µg/ml)	Antifungal activity (ZOI:mm)	
			A. niger	*C. albicans*
33a	-Ph	0.125	7	7
		0.25	12	14
		0.50	16	20
33b	-SMe	0.125	5	4
		0.25	9	8
		0.50	12	11
Fluconazole	-	0.1	26	27

2.25 Quinazolinone with sulfonates

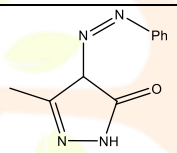
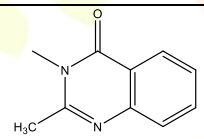
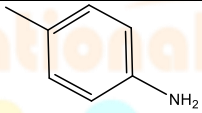
Another series of quinazolinone derivatives were synthesized by Osman Habib and his research group and assessed them for their antifungal activity against *F. oxysporum* and *A. fumigatus* fungal strain. As shown in table 26, figure 26, compounds **34a** and **34c** exhibit moderate activity against *F. oxysporum*, while compound **34b** found moderately active against *F. fumigatus* [65].



(34)

Figure:26 *Graphical SAR of quinazolinone with sulfonates derivatives as an anti-fungal agent.*

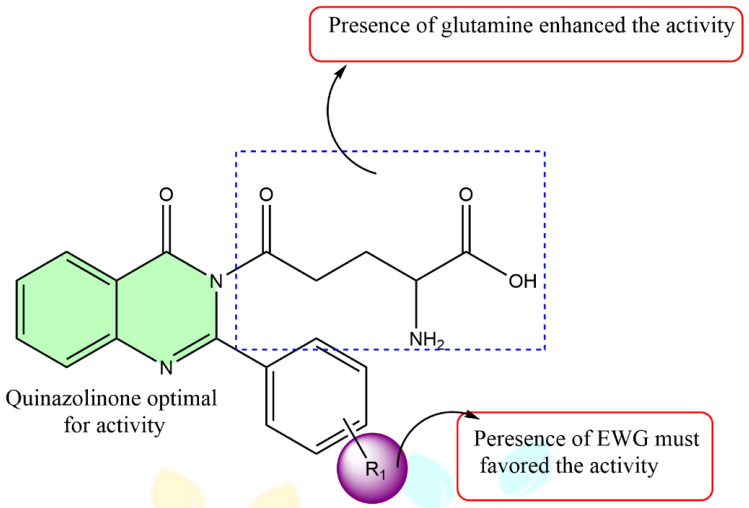
Table:26 Antifungal quinazolinone with sulfonates derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml) ZOI (mm)	
		F. oxysporum	***A. fumigatus***
34a		12.5(31)	100(16)
34b		100(15)	6.25(38)
34c		6.26(37)	25(26)
Ketoconazole	-	3.125(43)	3.125(42)

2.26 Glutamine linked quinazolinone derivatives

A series of novel glutamine linked 2,3-disubstituted quinazolinone conjugates was synthesized by M. K. Prashanth and H. D. Revanasiddappa. All compounds were screened for their in vitro antifungal activity against *Candida albicans* and *Aspergillus flavus*. From table 27 and figure 27, SAR study revealed that compounds with tri-fluoro substituent **35b** and nitro substituent at para position **35d** exhibit good antifungal activity *C. albicans* and *A. flavus* compared to the standard drug fluconazole. In the whole series, compound **35d** showed the highest percentage inhibition against both fungal strains, whereas none of the tested compounds restricted the fungal growth. compounds **35a** and **35c** displayed differences in activity due to the presence of fluoro group at different positions. Instead of methyl or methoxy groups, halogen substituted

compounds **35a**, **35b**, and **35c** seemed better in displaying pronounced inhibitory power against *C. albicans* and *A. flavus* [66].



(35)

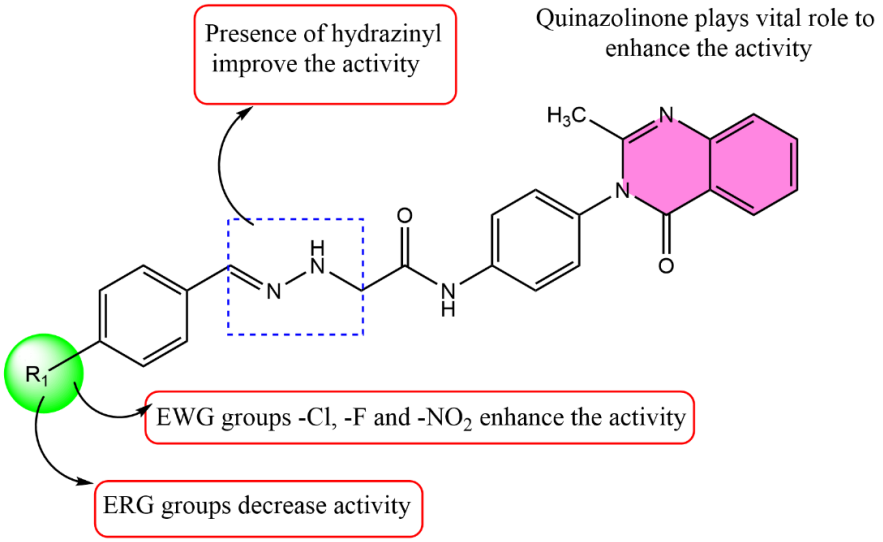
Figure:27 *Graphical SAR of glutamine linked quinazolinone derivatives as an anti-fungal agent.*

Table:27 Antifungal glutamine linked quinazolinone derivatives

Compound	R_1	Antifungal activity ZOI (mm) (MIC: µg/ml)	
		C. albicans	***A. flavus***
35a	m-di-F	11(15)	10.4(25)
35b	2,3,4-tri-F	13.6(10)	14.4(15)
35c	o,m-di-F	11.4(10)	10.9(15)
35d	p-NO_2	14.1(10)	13.6(12.5)
Flucanazole	-	16(05)	19(05)

2.27 Hydrazinyl quinazolinone derivatives

A series of hydrazinyl quinazolinone derivatives were designed and synthesized by G. Saravanan and his research team and evaluated them for their antifungal activity against *A. niger* and *A. fumigatus* using ketoconazole as a reference. All compound displayed moderate to good antifungal activity against both fungal pathogens. As mentioned in table 28, figure 28 SAR study demonstrated that compounds with presence of electron withdrawing substituent like fluoro, chloro, trifluoromethyl, and nitro group exhibit good antifungal activity While, other compounds, though they contain electron donating substituents like methyl, methoxy, and hydroxyl groups exhibited less in vitro antifungal activity. Compound with trifluoromethyl substituent **36b** exhibit highest antifungal activity against *A. niger* which is more than the reference ketoconazole and compound with -Cl substituent **36a** showed equal antifungal activity against *A. fumigatus* [67].



(36)

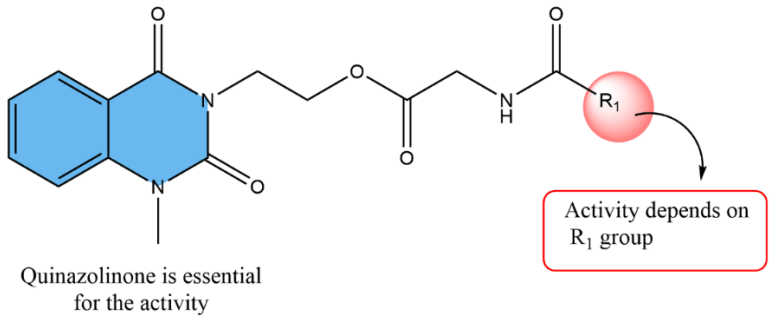
Figure:28 *Graphical SAR of hydrazinyl quinazolinone derivatives as an anti-fungal agent.*

Table:28 Antifungal hydrazinyl quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)	
		A. niger	***A. fumigatus***
36a	-Cl	15.62	7.81
36b	CF_3	7.81	15.62
36c	$-NO_2$	15.62	15.62
Flucanazole	-	15.62	7.81

2.28 Methyl substituted quinazolinone derivatives

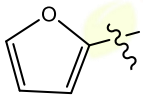
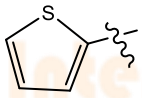
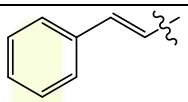
A series of 1-methyl-3-substituted quinazoline-2,4-dione derivatives was designed, synthesized, and evaluated for their *in vitro* antifungal activities against five fungal strains *Candida mycoderma, Candida albicans, Saccharomyces cerevisiae, Aspergillus flavus* and *Cryptococcus neoformans*. SAR study showed that compounds with m-F, p-F, o-Cl, p-OCH_3 and p-CH_3 substituent showed excellent activity against *C. albicans*. The MIC values of compounds with substituent p-F, o-Cl and m-NO_2 were equivalency with the positive control drug polyoxin D whose MIC was 32 µg/ml, compound with m-F substituent **37a** showed excellent activity against *C. albicans*. For the *A. flavus*, all the compounds except compounds **37c** and **37d** have shown good antifungal activity that are comparable to fluconazole. The most active compound **37j** showed activity against *C. Neoformans* [68], as shown in table 29, figure 29.



(37)

Figure:29 *Graphical SAR of Methyl substituted quinazolinone derivatives as an anti-fungal agent.*

Table:29 Antifungal Methyl substituted quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)			
		C. mycoderma	*C. albicans*	*A. flavus*	*C. neoformans*
37a	3-F-Ph	512	16	64	256
37b	4-F-Ph	64	32	64	16
37c	2-Cl-Ph	64	32	128	128
37d	4-OCH_3-Ph	512	32	128	32
37e	4-Ch_3-Ph	512	32	64	16
37f	3-NO_2-Ph	16	64	64	128
37g	4-Cl-Ph	512	64	32	32
37h		64	32	64	128
37i		512	512	64	256
37j		512	512	32	8
Polyoxine D	-	8	32	32	0.03125
Fluconazole	-	8	16	64	0.03125

2.29 Imidazolyl/benzimidazolyl-quinazolinone derivatives

D. A. patil have developed a series of disubstituted-quinazolinone derivatives containing inidazole and benzimidazole nucleus and assessed them for their antifungal activity against *C. albicans, A. niger, C. gullerimondii* and *A. flavus*. All tested derivatives showed moderate to good antifungal activity against all tested fungal strains. From table 30, figure 30, SAR study demonstrated that compound with 2-methyl at C-2 and the 6-nitro function on the quinazolinone nucleus, along with the benzimidazole heterocycle **39c** was found to have the best results in antifungal activity against A. flavus. The 3-imidazolyl derivative with no substitutions at the 6,8-positions and 2-phenyl on the quinazolinone ring **38c** was observed to be more potent

than amphotericin B against *A. flavus, A. niger* and *C. gullerimondii*. Compound **38a** was found to be potent against *C. albicans* and *A. flavus* probably due to 6,8-dibromo substitution. Compound **38b** was potent against *C. albicans* probably due to 6,8-dichloro substitution [69].

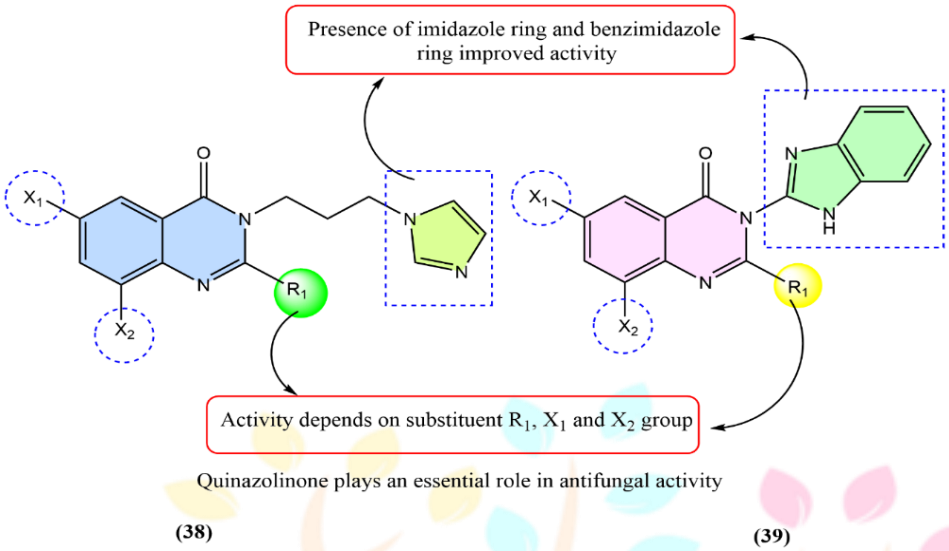


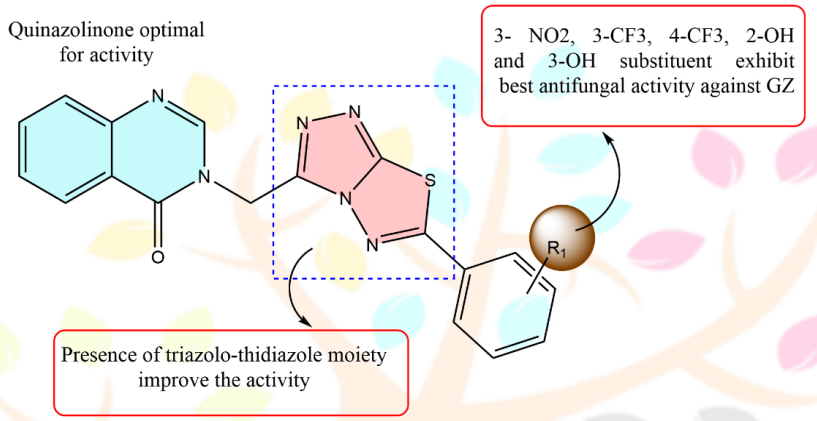
Figure:30 *Graphical SAR of imidazolyl/benzimidazolyl-quinazolinone derivatives as an anti-fungal agent.*

Table:30 Antifungal imidazolyl/benzimidazolyl-quinazolinone derivatives

Compound	X_1	X_2	R_1	Antifungal activity ZOI in mm (MIC: µg/ml)			
				C. albicans	*A. niger*	*C.gullerimondii*	*A. flavus*
38a	Br	Br	CH_3	21.40 (32)	19.37	-	22.12 (8)
38b	Cl	Cl	CH_3	19.59 (16)	-	16.66	14.11
38c	H	H	Ph	14.07	24.71 (8)	19.0 (64)	21.90 (8)
38d	Cl	Cl	Ph	18.88 (8)	18.02	17.14	21.26 (16)
39a	Cl	Cl	CH_3	17.41 (8)	-	12.58	13.0
39b	H	H	Ph	13.91	24.42 (32)	-	15.36
39c	NO_2	H	CH_3	13.83	16.1	-	23.59
amphotericin B	-	-	-	17.71	25.13	20.82	20.77

2.30 Triazolo-thiadiazole quinazolinone derivatives

A series of novel quinazolin-4(3H)-one derivatives containing a 1,2,4-triazolo[3,4-b] [1,3,4] thiadiazole moiety were designed and synthesized Xinyang Lv and co-workers and examined for their antifungal activity. From table 31, figure 31, SAR study revealed that compound with 3- NO_2, 3-CF_3, 4-CF_3, 2-OH and 3-OH substituent exhibit best antifungal activity against *Gibberella zeae* which is more than the reference commercial agrofungicide Hymexazol and compound with 2-F substituent found to be more potent against *Cytospora mandshurica* with 51.3% inhibition rate which is more than the hymexazol [70].



(40)

Figure:31 *Graphical SAR of triazolo-thiadiazole-quinazolinone derivatives as an anti-fungal agent.*

Table:31 Antifungal Triazolo-thiadiazole-quinazolinone derivatives

Compound	R_1	Antifungal activity (inhibition rate %) At 50 µg/ml					
		B. cinerea Pers	***P. infestans***	***V. dahliae***	***C. mandshurica***	***G. zeae***	***G. fructigenum***
40a	2-F	58.5	37.4	42.5	51.3	30.5	17.2
40b	3-NO2	7.1	19.4	21.9	31.4	79.5	2.5
40c	3-CH3	15.2	40.6	23.2	33.4	82.4	16.5
40d	4-CH3	15.5	30.9	15.0	33.1	78.1	18.3
40e	2-OH	24.6	24.8	21.8	23.7	83.9	17.0
40f	3-OH	23.3	13.3	10.1	29.9	85.3	8.1
Hymexazol	-	66.5	68.4	82.5	49.6	55.5	58.2

2.31 N_3 substituted quinazolinone derivatives

Quinazolinone derivatives with N_3 substitution were synthesized via an efficient three-component condensation reaction by Masoumeh Divar and his research team and their antifungal activity were evaluated. From table 32, figure 32, SAR study revealed that compound with methyl substuion on 2nd position and chloro substitution on 5th position **42b** exhibited considerable antifungal activities against most of the tested *Candida* species, when the substitution replaces by -Cl on 4th position **42a** it exhibited desirable antifungal activities against *C. albicans, C. dubliniensis* and *C. neoformans* and the compound with 2,4 di-F and compound with 2-OMe-5-Cl substituent **41c** and **41b** displayed desired antifungal activities against *C. neoformans* and *C. tropicalis*, respectively [71].

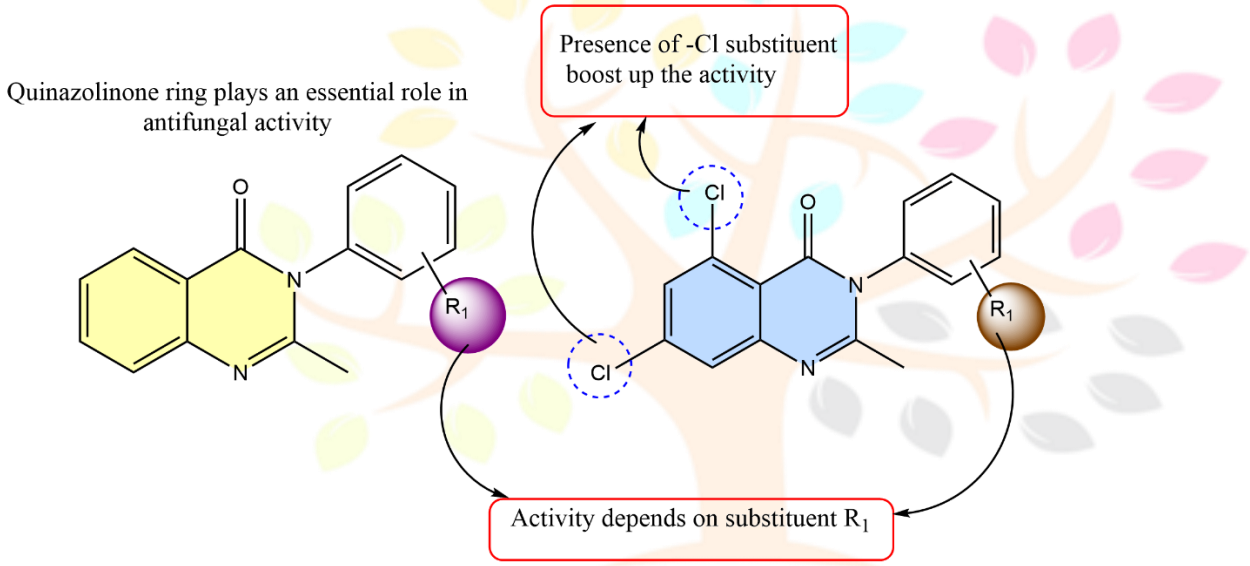


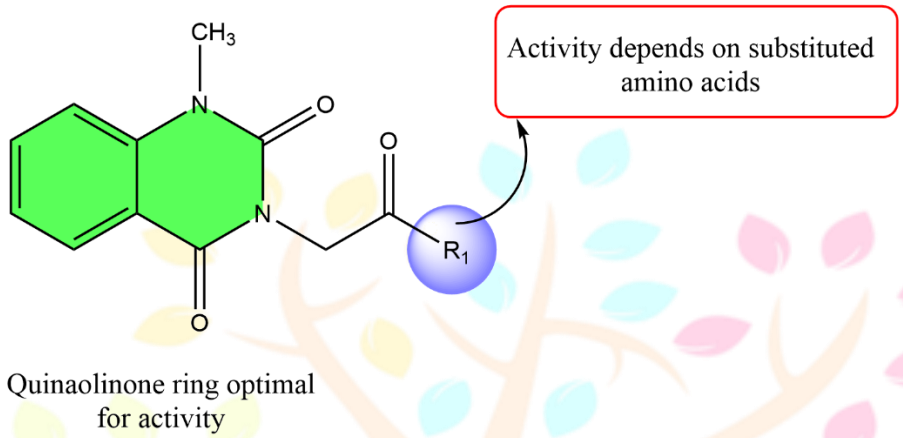
Figure:32 *Graphical SAR of N_3 substituted quinazolinone derivatives as an anti-fungal agent.*

Table 32 Antifungal N_3 substituted quinazolinone derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml)						
		C. albicans	*C. dubliniensis*	*C. glabrata*	*C. krusei*	*C. parapsilosis*	*C. tropicalis*	*C. neoformans*
41a	4-Cl	256	256	-	-	-	-	256
41b	2-OMe-5-Cl	-	-	-	-	-	-	256
41c	2,5-di-F	-	-	-	-	-	256	-
41d	2-Me-5-Cl	256	-	-	-	-	128	128
42a	4-Cl	256	-	-	-	-	-	256
42b	2-Me-5-Cl	256	64	64	128	256	64	128
fluconazole	-	4	1	4	16	-	-	-

2.32 Amino acids containing quinazolinone derivatives

N. A. Noureldin and co-workers design and synthesized a series of new quinazolinnone derivatives containing different amino acids. These synthesised compounds were evaluated for their *in vitro* antifungal activity using *Aspergillus fumigates, Aspergillus flavus, Crytococcus neoformans* and *Candida albicans*. Unfortunately, the 14 synthesized compounds showed lower in vitro activity as compared to fluconazole and polyoxin B. However, compound with proline amino acid **43b** and Fluconazole have synergistic effect on *aspergillus flavus* as mentioned in table 33, figure 33 [72].



(43)

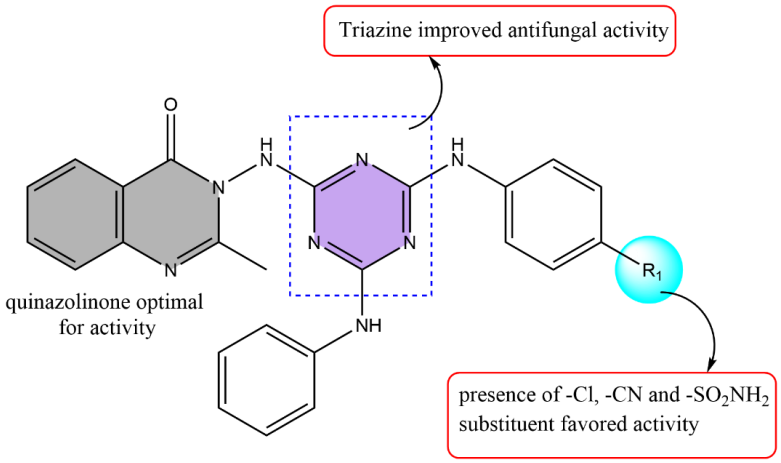
Figure:33 *Graphical SAR of Amino acids containing quinazolinone derivatives as an anti-fungal agent.*

Table:33 Antifungal Amino acids containing quinazolinone derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml)			
		A. fumigates	***A. flavus***	***C. neoformans***	***C. albicans***
43a	Tryptophane	>1.21	0.60	0.60	>1.21
43b	Proline	0.77	1.54	0.77	>1.54
Fluconazole	-	0.05	0.10	0.10	0.20
Polyoxin B	-	0.12	0.12	0.06	0.12

2.33 Triazine-quinazolinone derivatives

M. Dinari et al. design and synthesized a new series of 1,3,5-triazine incorporating aromatic quinazolinone moiety and screened for their antifungal activity against *candida albicans*. From table 34 and figure 34, SAR study revealed that compound with -Cl, -CN and $-SO_2NH_2$ substituent were found to be most potent members. Unsubstituted phenyl ring and substitution of $-OCH_3$ and $-NO_2$ group leads to decrease the activity [73].



(44)

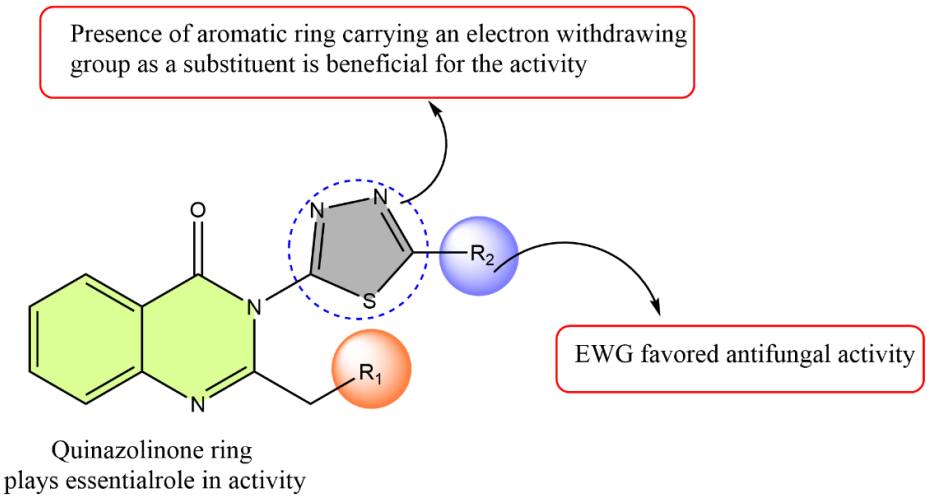
Figure:34 *Graphical SAR of Triazine-quinazolinone derivatives as an anti-fungal agent.*

Table:34 Antifungal triazine quinazolinone derivatives.

Compound	R_1	Antifungal activity (MIC: µg/ml)
		C. albicans
44a	-Cl	128
44b	-CN	128
44c	$-SO_2NH_2$	128
Fluconazole	-	8

2.34 Thidiazole-quinazolinone derivatives

A new series of novel quinazolino-thiadiazoles as fused pharmacophore were designed and constructed by H. Patel et al. The result of SAR study shown in table 35 and Figure 35, revealed that the presence of aromatic ring carrying an electron withdrawing group as a substituent is beneficial for antifungal activity. Compound **45a** and **45b** with a 4-chloro phenyl and 4-nitro phenyl at C-2 of thiadiazolyl of quinazolino-thiadiazoles, displayed the highest antifungal activities. Series of compounds where 2-ethyl group is present on the quinazoline ring, compounds **45c**, **45d** and **45e** all bearing electron withdrawing groups, Cl, Br and NO2 respectively- displayed the significant MIC value of 62.5 µg/ ml against A. Niger [74].



(45)

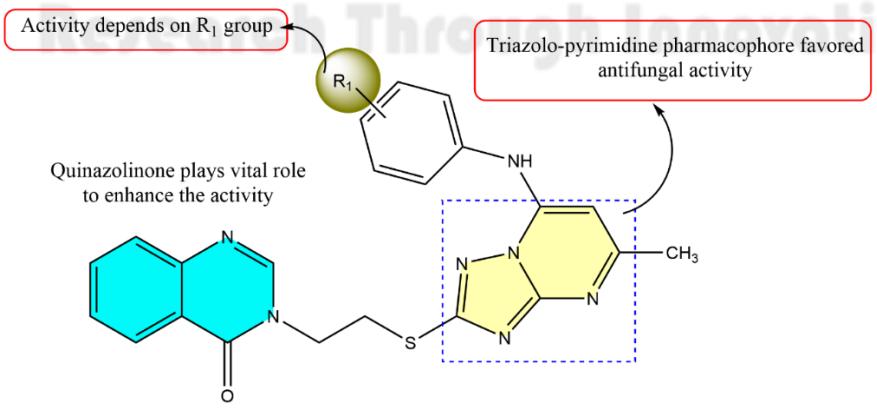
Figure:35 *Graphical SAR of thidiazole -quinazolinone derivatives as an anti-fungal agent.*

Table:35 Antifungal triazine quinazolinone derivatives

Compound	R_1	R_2	Antifungal activity (MIC: µg/ml)	
			C. albicans	*A. niger*
45a	-Cl	-Cl	62.5	62.5
45b	-Cl	$-NO_2$	62.5	62.5
45c	-H	-Cl	250	62.5
45d	-H	-Br	250	62.5
45e	-H	$-NO_2$	250	62.5
Fluconazole	-	-	0.98	1.80

2.35 Triazolo-pyrimidine containing quinazolinone derivatives

A series of novel 1,2,4-triazolo[1,5-a] pyrimidine-containing quinazolin-4(3H)-one derivatives were designed, synthesized and assessed for their in vitro antifungal activity. From table 36, figure 36, SAR study revealed that compounds with 2,4-di-F and 2,5-di-OCH_3 substituent had the inhibition rates of 34.0% and 23.4% against *V. dahliae* which is highest from all the tested derivatives [75].



(46)

Figure:36 *Graphical SAR of Triazolo-pyrimidine-quinazolinone derivatives as an anti-fungal agent.*

Table:36 Antifungal Triazolo-pyrimidine quinazolinone derivatives

Compound	R_1	Antifungal activity (inhibition rate %)		
		G. zeae	***V. dahliae***	***S. sclerotiorum***
46a	4-CF_3	15.1	17.2	21.9
46b	4-OCH_3	0	0	21.8
46c	2,4-di-F	10.8	34.0	10.2
46d	2,5-di-OCH_3	12.2	23.4	0
Greseofulvin	-	49.8	86.1	87.8

2.36 Quinazolinones with C_2 and N_3 substitution

Quinazolinones with C_2 and N_3 substitution synthesized by R. A. Haggam and his research group and screened for their antifungal activity against *candida albicans* and *aspergillus niger*. As shown in table 37, figure 37, SAR study revealed that compounds **48, 49** and **50** have exhibited excellent antifungal activity which is more than standard drug nystatin. Compound **48** found the most active compound on both the strain *C. albicans* and *A. niger* [76].

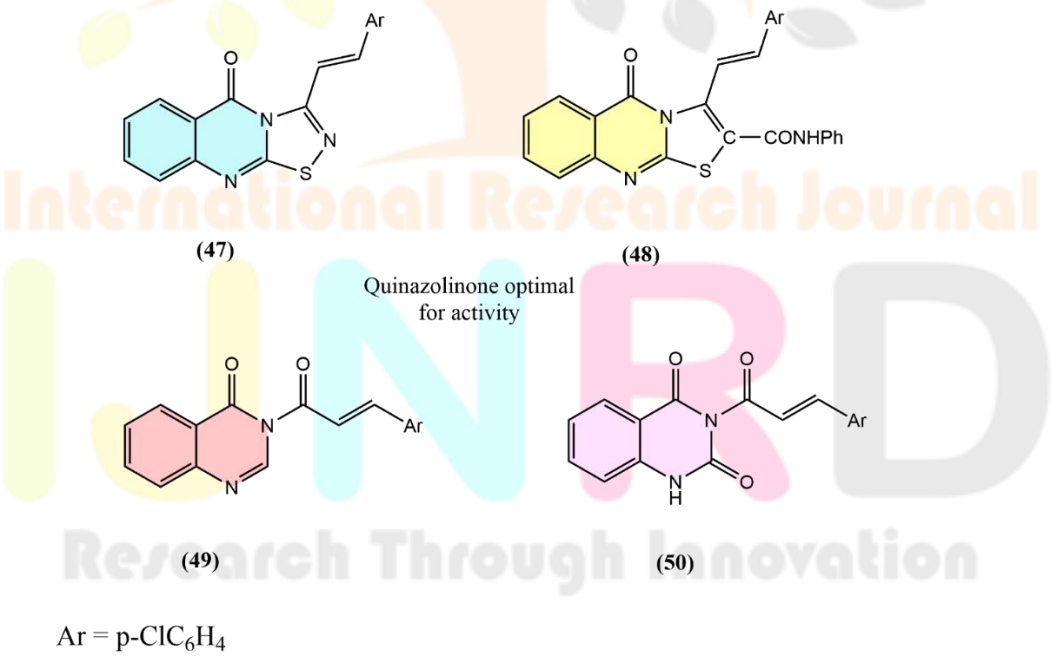


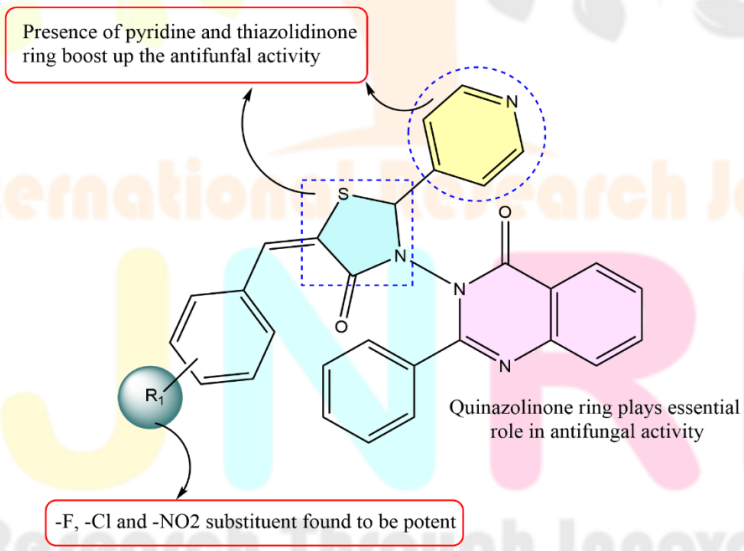
Figure:37 *Graphical SAR of novel quinazolinone derivatives as an anti-fungal agent.*

Table:37 Antifungal novel quinazolinone derivatives

Compound	Antifungal activity	
	C. albicans	*A. niger*
47	7.0	9.0
48	14.0	10.0
49	12.0	10.0
50	13.0	11.0
Nystatin (5 mg/mL)	12.5	8.5

2.37 Thiazolidinone pyridine containing quinazolinone derivatives

N. C. Desai and co-workers have developed a new series of thiazolidinone pyridine containing quinazolinone derivatives and assessed them for their antifungal activity. All the tested compounds exhibit moderate to excellent antifungal activity against both the tested strain. From table 38, figure 38, SAR study revealed that compounds with -F, -Cl and -NO_2 substituent at 4th position of phenyl ring exhibited excellent potency against *A. niger* compared to both standard drugs nystatin and griseofulvin, when -Cl substituent replace on 3rd position **51b** exhibited excellent antifungal activity against *C. albicans* compared to both standard drugs, remaining compounds exhibited moderate potency as compared to standard [77].



(51)

Figure:38 *Graphical SAR of thiazolidinone pyridine containing quinazolinone derivatives as an anti-fungal agent.*

Table:38 Antifungal thiazolidinone pyridine containing quinazolinone derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml)	
		A. niger	*A. fumigatus*
51a	4-F	250	100
51b	3-Cl	100	250
51c	4-Cl	250	100
51d	4-NO_2	250	100
Nystatin	-	100	100
Griseofulvin	-	500	100

2.38 Thioacetamide benzenesulfonamides quinazolinone derivatives

A series of thioacetamide and benzenesulfonamide substituent containing novel quinazolinone derivatives were design and synthesized by M. M. Ghorab and screen for their antifungal activity against candida albicans. As mentioned in table 39 and figure 39, all the tested derivatives displayed potent antifungal activity. SAR study revealed that compound **52l** with 2-CH_3-4-NO_2 substituent found most potent in this series with MIC value of 1.25 µg/ml against *C. albicans* which is excellent as compared to amphotericin B with MIC 15.63 µg/ml. R_1 is replace by 3-methyl and 4-ethyl substituent slightly decrease the activity and substituent 2-CH_3, 4-CH_3, 3,4,5-tri-OCH_3 and 2-4-di-NO_2 substituent also showed best activity [78].

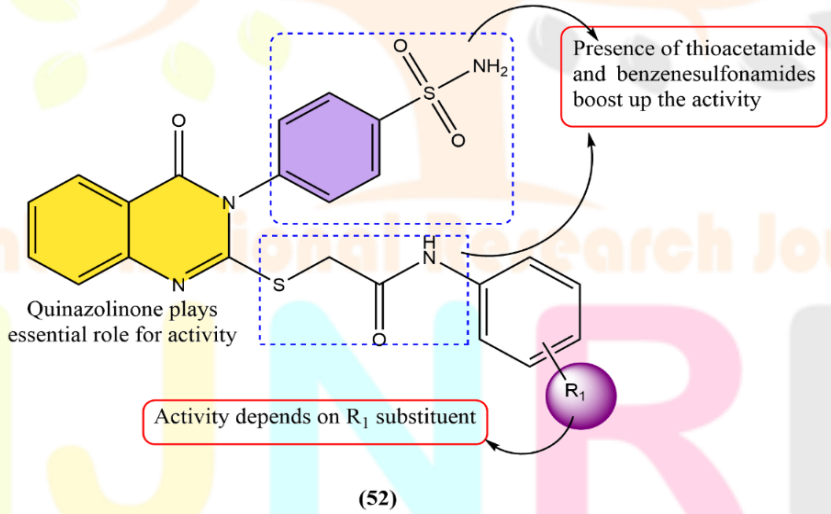


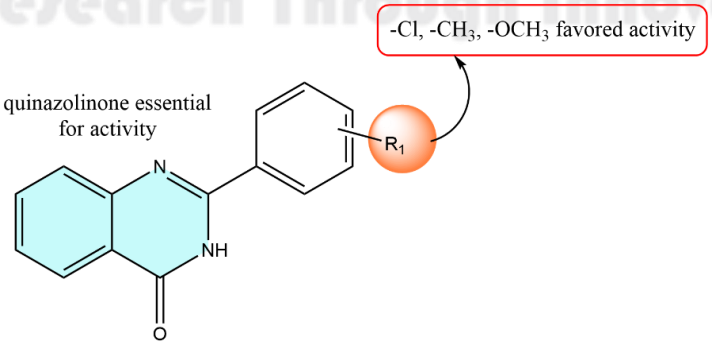
Figure:39 *Graphical SAR of Thioacetamide-benzenesulfonamides quinazolinone derivatives as an anti-fungal agent.*

Table:39 Antifungal Thioacetamide-benzenesulfonamides quinazolinone derivatives

Compound	R_1	Antifungal activity (MIC: µg/ml) *C. albicans*	
		ZOI (mm)	MIC
52a	-	19±0.05	5.00
52b	2-Me	20±0.25	3.91
52c	3-Me	22±0.08	10.00
52d	4-Me	24±0.16	6.31
52e	2-Et	21±0.14	5.00
52f	3-Et	-	-
52g	4-Et	18±0.19	10.00
52h	4-OMe	21±0.05	7.81
52i	4-OEt	26±0.30	5.00
52j	3,5-di-OMe	20±0.21	6.31
52k	3,4,5-tri-OMe	14±0.11	3.80
52l	2-Me-4-NO_2	27±0.12	1.25
52m	2-NO_2-6-Me	22±0.20	10.00
52n	2,4-di-NO_2	24±0.27	3.13
Amphotericin B	-	22±0.11	15.63

2.39 Substituted quinazolinone

A facile, one-pot greener route has been employed to synthesize 2-substituted quinazolin-4(3H)-one derivatives by V. K. Singh and team and screened for their antifungal activity against *candida albicans* and *aspergillus clavatus* with zone of inhibition. As per table 40 and figure 40, SAR study revealed that Compounds with -Cl, -CH_3, -OCH_3 subatituent at 4th position of phenyl ring have shown reasonably good antifungal activities against *Candida albicans* and *Aspergillus clavatus* compared to standard drug and compound with -OCH_3 at 3rd position also showed reasonable activity [79].



(53)

Figure:40 *Graphical SAR of substituted quinazolinone derivatives as an anti-fungal agent.*

Table:40 Antifungal substituted quinazolinone derivatives

Compound	R_1	Antifungal activity ZOI (mm) (MIC:25 µg/ml)	
		C. albicans	*A. clavatus*
53a	4-Cl	20	21
53b	4-CH_3	20	22
53c	3-OCH_3	20	21
53d	4-OCH_3	19	20
53e	-H	20	20
Griseofulvin	-	47	43

2.40 Quinazolinone schiff's bases

Two series of quinazolinone derived Schiff's bases were synthesized and characterized by B.J. Ullas et al in 2020. All the compounds were screened for their in vitro antifungal activity. SAR study revealed that electron donating and electron withdrawing factor could boost up the antifungal activity. Table 41, 42 and figure 41 showed that the presence of both electron donating groups like -OH and -OMe and electron withdrawing group -Cl, -Br, -F and -NO_2 in combination makes the Schiff's bases as potent antifungal agent. Compound with presence of heterocyclic ring as a part of Schiff's bases makes more potent antifungal agent. Compounds with imidazole ring and indole moiety were nearly about twice active as compared to standard [80].

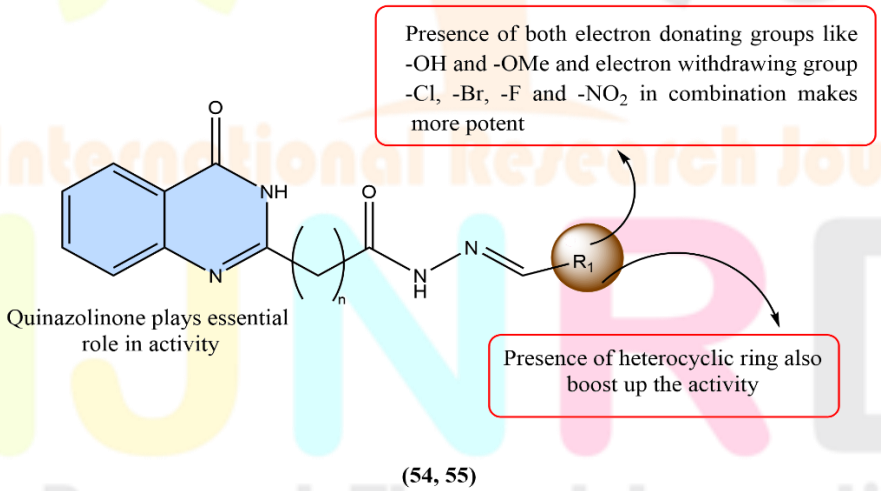


Figure:41 *Graphical SAR of quinazolinone Schiff's bases as an anti-fungal agent.*

Table:41 Antifungal quinazolinone Schiff's bases

Compound	R_1 (n=2)	Antifungal-activity ZOI(mm) (MIC:50 µg/ml)	
		F. moniliforme	*A. niger*
54a	3,5-di-Br-4-OH-Ph	12	12
54b	3-Br-4-OH-Ph	13	14
54c	3-Br-4-OMe-Ph	15	14
54d	3-Br-4-OH-5-OMe-Ph	19	17

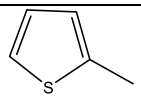
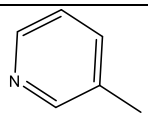
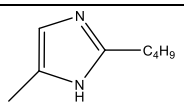
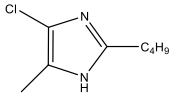
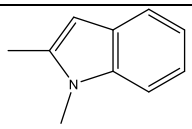
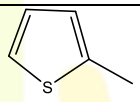
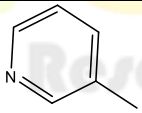
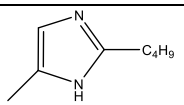
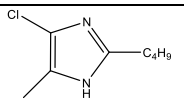
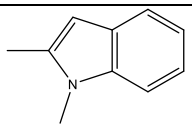
54e		13	15
54f		17	15
54g		19	21
54h		11	13
54i		20 ± 0.11	22 ± 0.14
Bavistin	-	11 ± 0.11	10 ± 0.11

Table:42 Antifungal quinazolinone Schiff's bases

Compound	**R_1 (n=3)**	**Antifungal-activity ZOI(mm) (MIC:50 µg/ml)**	
		F. moniliforme	***A. niger***
55a	3,5-di-Br-4-OH-Ph	12	13
55b	3-Br-4-OH-Ph	11	12
55c	3-Br-4-OMe-Ph	11	13
55d	3-Br-4-OH-5-OMe-Ph	11	13
55e		19	18
55f		20	21
55g		21	18
55h		12	11

55i		19	23
Bavistin	-	11	10

2.41 Bisquinazolinone derivatives

A novel series of bisquinazolinone derivatives were synthesized by M.M. Ayoob and F.E. Hawaiz and tested their anti-fungal activity. From table 43, figure 42, SAR study revealed that compound with 3-Cl-4-CH3 substituent **56c** exhibit the antifungal activity comparable with reference fluconazole [81].

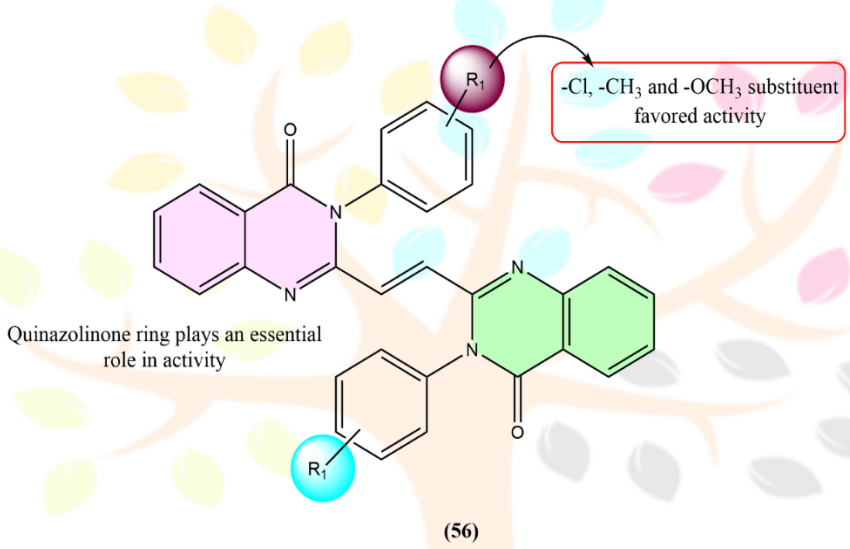


Figure:42 *Graphical SAR of bisquinazolinone derivatives as an anti-fungal agent.*

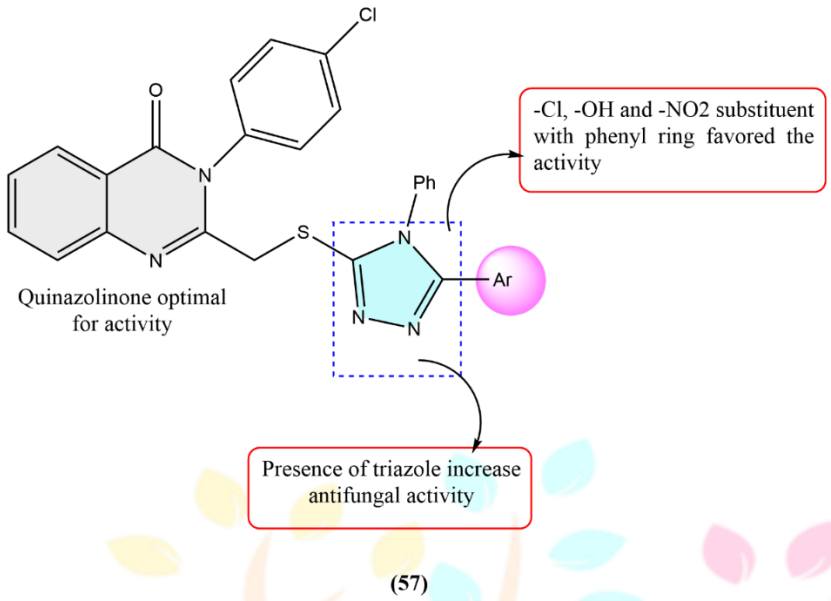
Table:43 Antifungal bisquinazolinone derivatives

Compound	R_1	Antifungal activity (ZOI mm) (MIC:200µg/ml)
		C. albicans
56a	2-CH_3	30
56b	3-OCH_3	30
56c	3-Cl-4-CH_3	34
56d	4-OCH2CH_3	30
Fluconazole	-	33

2.42 Azole bearing quinazolinone derivatives

Azole bearing quinazolinone derivatives were synthesized by M. Mohammadi and co-workers and screened for their antifungal activity. As mentioned in table 44 and figure 43 result of SAR study revealed that type and position of the functional group have some substantial impact on activity. Compounds with phenyl functional

groups along with triazole derivatives showed comparatively good antifungal activity. Compound with 2-chlorophenyl substituent **57b** found the most active against *C. albicans* among all tested compound [82].



(57)

Figure:43 *Graphical SAR of Azole bearing quinazolinone derivatives as an anti-fungal agent.*

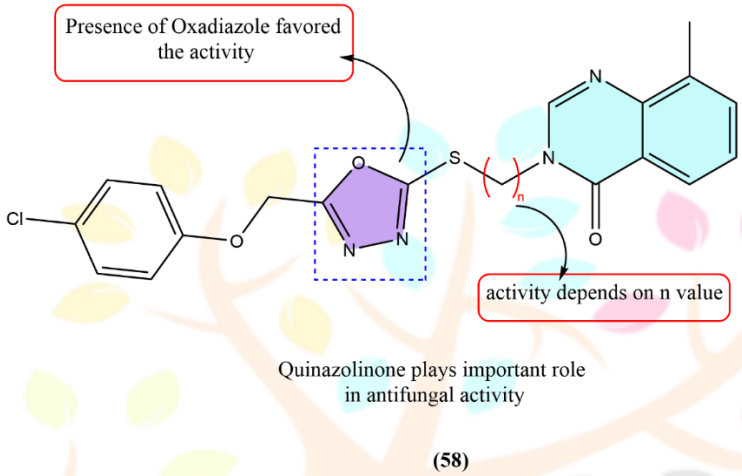
Table:44 Antifungal Azole bearing quinazolinone derivatives.

Compound	Ar	Antifungal activity ZOI (mm) (MIC: µg/ml)			
		C. albicans	*C. glabrata*	*A. fumigatus*	*A. niger*
57a	Phenyl	24 (≤250)	19 (≤500)	24 (≤250)	22 (≤250)
57b	2-chlorophenyl	28 (≤125)	21 (≤250)	27 (≤125)	29 (≤125)
57c	2-hydroxyphenyl	25 (≤250)	14 (≤1000)	26 (≤125)	26 (≤125)
57d	3-nitrophenyl	24 (≤250)	12 (≤1000)	24 (≤250)	24 (≤250)
Amphotericin B	-	30 (≤62.50)	38 (≤31.25)	40 (≤31.26)	44 (≤15.62)

2.43 Oxadiazole bearing quinazolinone derivatives

Some novel series of quinazolinone derivatives containing oxadiazole moiety were design and synthesized by X. Wang et al. and evaluate their inhibition effect against phytopathogenic fungi. All tested compounds exhibit good to moderate antifungal activity against all three fungal strain as compared with two hymexazol and boscalid as a standard.

In the first series Different alkyl chains were introduced into the position between quinazolin-4(3H)-one and 1,3,4-oxadiazole fragments to investigate their effects on antifungal activities. From table 45 and figure 44, SAR study revealed that antifungal effect against three tested fungi firstly increased and then decrease with increase in the length of alkyl chains. The antifungal effects of the title compound **58a** at 50 μg/mL reached the highest against *R. solani* and *F. graminearum* with the corresponding inhibition rates of 62.08% and 52.53%, which were better than that of hymexazol (37.29% and 49.20%) and compound containing a C4-chain **58c** showed the highest antifungal effects against B. cinerea at 50 μg/mL, with the inhibition rate (83.32%) exceeded that of boscalid (82.86%) [83].



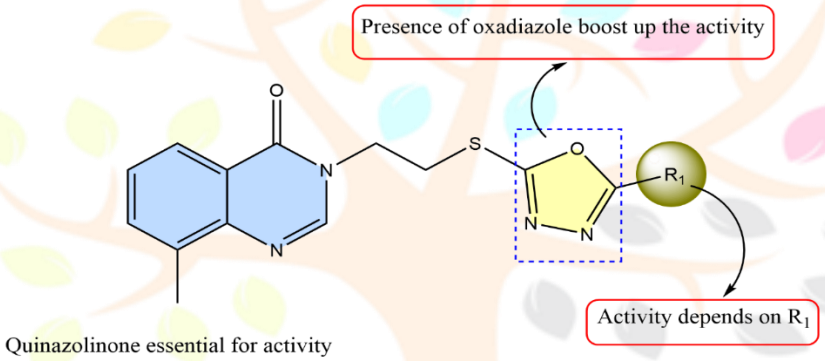
(58)

Figure:44 *Graphical SAR of Oxadiazole bearing quinazolinone derivatives as an anti-fungal agent.*

Table:45 Antifungal Oxadiazole bearing quinazolinone derivatives.

Compound	n	Antifungal activity (inhibition rate %)		
		R. solani	*F. graminearum*	*B. cinerea*
58a	2	62.08	52.53	41.43
58b	3	54.24	31.48	46.31
58c	4	50.37	18.21	83.32
58d	5	44.40	14.26	39.75
Hymexazol	-	37.29	49.20	61.04
Boscalid	-	89.64	29.82	82.86

Another series of compounds were rationally constructed investigate the effects of the substituents at the 5-position of 1,3,4-oxadiazole fragments on the antifungal activities. From table 46 and figure 45, SAR study revealed that compounds with 4-ClPhSCH$_2$, 4-ClPhSO$_2$CH$_2$ and 4-ClBn substituent would have better activity against *R. solani* as compared to hymexazole [83].



(59)

Figure:45 *Graphical SAR of Oxadiazole bearing quinazolinone derivatives as an anti-fungal agent.*

Table:46 Antifungal Oxadiazole bearing quinazolinone derivatives.

Compound	R_1	Antifungal activity (inhibition rate %)		
		R. solani	*F. graminearum*	*B. cinerea*
59a	4-ClPhSCH$_2$	58.56	42.64	34.78
59b	4-ClPhSO$_2$CH$_2$	42.49	36.34	27.81
59c	4-ClPh	37.26	15.75	17.35
59d	4-ClBn	72.86	55.91	52.21
Hymexazol	-	37.29	49.20	61.04
Boscalid	-	89.64	29.82	82.86

Substituted benzyl fragment at the 5-position of 1,3,4-oxadiazole scaffolds were synthesized. The antifungal effects of

compounds against R. solani were better than the corresponding antifungal effects against F. graminearum and B. cinerea. As mentioned in table 47 and figure 46, SAR study revealed that the antifungal effects of constructed molecules against R. solani dropped sharply after replacing a Bn fragment with a 3-ClBn moiety and with the introduction of a chlorine atom into the 2- or 4-position of benzene rings would greatly improve their antifungal effects against R. solani but decrease the antifungal activity after introducing the methyl group at 2nd position of benzene ring [83].

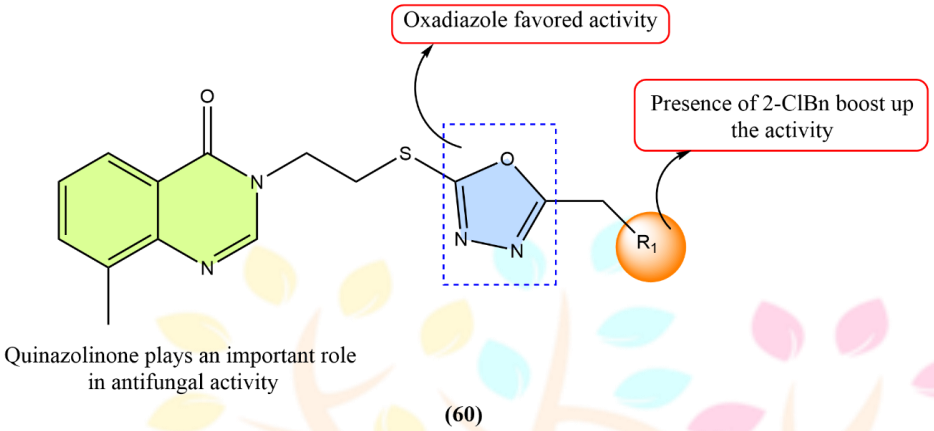


Figure:46 *Graphical SAR of Oxadiazole bearing quinazolinone derivatives as an anti-fungal agent.*

Table:47 Antifungal Oxadiazole bearing quinazolinone derivatives

3.

Compound	R_1	Antifungal activity (inhibition rate %)		
		R. solani	*F. graminearum*	*B. cinerea*
60a	Bn	73.06	35.47	49.31
60b	2-ClBn	84.98	31.24	50.47
60c	3-ClBn	75.88	32.80	37.10
60d	4-FBn	71.65	47.47	52.21
60e	2-MeBn	75.18	37.24	48.15
Hymexazol	-	37.29	49.20	61.04
Boscalid	-	89.64	29.82	82.86

Conclusive Remarks

Quinazoline-based hybrids have a broad range of pharmacological and biological properties. Quinazoline plays a crucial role development of new antibiotics. Some quinazoline and quinazolinone hybrids are even currently used in the treatment of bacterial infections. In this review, we have discussed quinazoline-based hybrids which were designed, synthesized, and evaluated for their antifungal activity against various types of fungal strain and multidrug-resistant microorganisms. The SAR studies revealed that the antimicrobial activity in heterocyclic class of quinazoline molecule depends on the nature of the peripheral substituents and their spatial relationship. Further, the type of moiety and EWG or EDG substitution on different moieties, plays an essential role in their efficacy against fungal infections. The SAR provides a better perspective for

synthesizing better bioactive quinazoline analogues. This review anticipates that quinazoline hybrids will play leading roles in designing of new analogues with better antifungal potency.

4. Acknowledgements

The authors wish to thank Sajjan Institute of Science, Ankleshwar managed by Ankleshwar Environmental Preservation Society (AEPS), affiliated to Veer Narmad South Gujarat University (VNSGU), Surat.

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