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A brief review on heterocyclic compounds with promising antifungal activity against *Candida* species

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Abstract: The most common reason for fungal infections is the development of *Candida* yeasts. *Candida* naturally is occurs on the skin and on most mucosal surfaces. It is proven that 90% of infections are caused by five *Candida* species: *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis,* and *Candida krusei.* Herein we've reviewed isolated and fused heterocyclic compounds that exhibit antifungal activity against Candida strains. Over 200 potential fungicidal agents were described, and some of the particularities which affect the action values were determined. Thus, it was noted that the presence of nitro-, methoxy-, trifluoromethyl-, and/or halogeno-containing groups at the specific positions in the benzene ring could significantly increase the inhibition of yeasts growth. That's why using these patterns together with heterocycles while designing target compounds could speed up the search for new antifungal drugs.

Keywords: *Candida* sp.; heterocyclic compounds; fungicidal drugs; MIC; IC_{50}.

1. Introduction

The most common reason for fungal infections is the development of *Candida* yeasts.[1,2] *Candida* naturally is found on the skin[3,4] and on most mucosal surfaces.[5-7] It is proven that 90% of infections are caused by five *Candida* species: *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis,* and *Candida krusei.*[8] Patients with an impaired immune system are the most sensitive to fungal diseases. Thus, cancer,[9] HIV[10] and diabetes[11] promote the growth of fungus.

Unfortunately, it has been observed that *Candida* species are resistant to many of antifungal drugs.[12-16] Searching for new agents that could inhibit fungal growth is an important task for pharmacists and chemists.[17,18] Among well-known and freshly obtained substances with antifungal activity, heterocyclic compounds lead as the most efficient and easy-to-produce class.[19-21]

In our current review, we have summarized studies that include data on fungicidal action against *Candida* yeasts. The article is divided into sections according to the heterocyclic moiety, and more than

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200 significant compounds are described. The importance of this study might be explained by the observed particularities concerning substituents that raise antifungal activity. As a consequence, it will help to design and synthesize target fungicidal agents.

2. Literature Review

2.1. Thiophene Derivatives

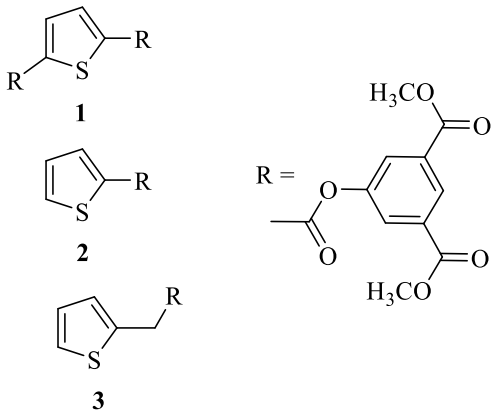


Figure 1. Chemical structure of thiophene derivatives **1-3**

All the described compounds[22] were found to be as active as ketoconazole against *Candida parapsilosis*, whereas they showed no significant anticandidal activity against *Candida krusei*. Especially compound **1** was the most effective against *Candida albicans* (MIC=50 μM/mL). Comparatively, thiophene **1** four-fold greater effect on *Candida albicans* than ketoconazole (Table 1). The testing was carried out by the standard microdilution method, and the results are presented by minimal inhibitory concentration in μM/mL.[23]

Table 1. Antifungal activity of thiophene derivatives **1-3** (MIC, μM/mL)

Microorganism	**1**	**2**	**3**	**Ketoconazole**
Candida albicans	5	100	100	200
Candida glabrata	100	200	100	200
Candida krusei	100	100	100	3.125
Candida parapsilosis	200	200	200	200

2.2. Pyrazole Derivatives

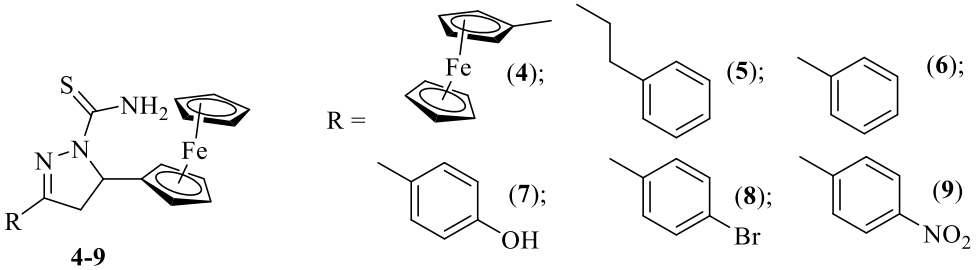


Figure 2. Chemical structure of pyrazole derivatives **4-9**

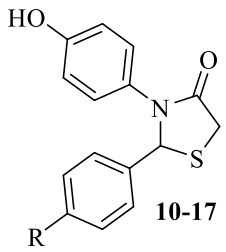
The results clearly depict that the compounds substituted at position 4 in the benzene ring, in the pyrazoline moiety with ferrocenyl, phenyl ethyl, phenyl, hydroxyl and bromo groups, gave average antimicrobial activity against the tested fungi strains.[24] All compounds **4-9** gave a range of MIC values between 32–64 μg/mL against *C. tropicalis*. Evaluation of fungicidal action was performed by broth

microdilution protocol,[25] and the comparing compound fluconazole was used. The results of antibacterial activity are summarized in Table 2.

Table 2. Antifungal activity of pyrazole derivatives **4-9** (MIC, μg/mL).

Microorganisms	4	5	6	7	8	9	Fluconazole
Candida albicans	128	128	128	128	128	128	64
Candida dubliniensis	256	256	256	256	128	128	64
Candida glabrata	128	64	64	64	64	64	64
Candida parapsilosis	128	64	128	64	128	64	64
Candida tropicalis	64	32	64	32	64	32	64
Candida kefyr	128	64	128	256	128	128	64
Candida krusei	128	128	128	128	128	128	64

2.3. Thiazole Derivatives



10-17

R = H (**10**); Br (**11**); Cl (**12**); CH_3 (**13**); OCH_3 (**14**); NO_2 (**15**); OH (**16**); C_2H_5 (**17**)

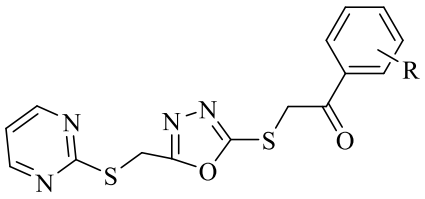
Figure 3. Chemical structure of pyrazole derivatives **10-17**

The antifungal activity of compounds **10-17** was determined against three commercially known fungicides (*C. albicans*, patient isolate *C. glabrata* and *C. krusei*) by measuring the minimum inhibitory concentration (MIC), expressed in μg/mL (Table 3).[26] It should be noted that the most significant result, according to the antifungal summary, showed compound **15** with the nitro group as the substituent at the 4th position of the benzene ring. The *in vitro* fungicidal action of the compounds **10-17** was tested by the tube dilution technique.[27] As standards, miconazole and fluconazole were used.

Table 3. Antifungal activity of thiazole derivatives **10-17** (MIC, μg/mL).

Compounds	*Candida albicans*	*Candida glabrata*	*Candida krusei*
10	22	23	10.5
11	25	22	11.75
12	21	22	11.55
13	20	25	12.45
14	25	23	11.5
15	12.5	25	6.25
16	22	23	12
17	20	21	11.85
Miconazole	6.25	3.125	1.56
Fluconazole	12.5	3.125	3.125

2.4. Oxadiazole Derivatives



18-23

R = H (**18**); *p*-Cl (**19**); *p*-NO_2 (**20**); *m*-NO_2 (**21**); *m*-Cl (**22**); 2,4-Cl (**23**)

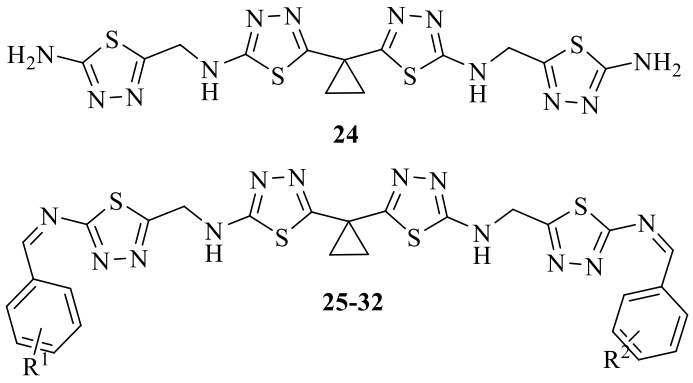
Figure 4. Chemical structure of oxadiazole derivatives **18-23**

The biological results indicate that *C. albicans* (clinical isolate) is the most susceptible fungus to compounds **18, 19,** and **22** (Table 4).[28] These compounds exhibit the strongest inhibitory activity against *C. albicans* (clinical isolate) with a MIC value of 0.015 mg/mL, when compared with the standard antifungal ketoconazole, which exhibits inhibitory activity with a MIC value of 0.007 mg/mL. This outcome confirms that phenyl and chlorophenyl groups may have a considerable influence on antifungal activity against the tested clinical *C. albicans* isolate. It can be attributed to the + π effect of phenyl and chlorophenyl groups. Compounds **20** and **21** exhibit lower inhibitory activity against *C. albicans* (clinical isolate) which may be due to -π effect of the nitro substituent. The standard strain *C. albicans* (ATCC 90028) showed an inhibition range with MIC values of 0.03–0.06 mg/mL of the tested compounds **18-23** suggesting moderate inhibitory activity compared to the clinical isolate versus ketoconazole. The other tested *C. albicans* strain (NRRL Y-12983) was less susceptible to the tested compounds, with a MIC = 0.03–0.125 mg/mL. The testing was done by microbroth dilution assay.

Table 4. Antifungal activity of oxadiazole derivatives **18-23** (MIC, μg/mL)

Microorganisms	**18**	**19**	**20**	**21**	**22**	**23**	**Ketoconazole**
C. albicans clinical isolate	0.015	0.015	0.06	0.125	0.015	0.03	0.007
C. albicans ATCC 90028	0.03	0.03	0.03	0.06	0.03	0.06	0.007
C. albicans NRRL Y-12983	0.03	0.125	0.06	0.06	0.125	0.06	0.003
C. glabrata clinical isolate	0.015	0.015	0.015	0.06	0.06	0.06	0.001
C. krusei NRRL Y-7179	0.06	0.06	0.03	0.06	0.06	0.06	0.001
C. parapsilosis NRRL Y-12696	0.06	0.06	0.06	0.125	0.06	0.06	0.001
C. tropicalis NRRL Y-12968	0.06	0.03	0.03	0.06	0.03	0.015	0.001

2.5. Thiadiazole Derivatives



24

25-32

R^1 = H (**25**); 2-Cl (**26**); 4-CH_3 (**27**); 4-Cl (**28**); 2-CH_3 (**29**); 3-Cl (**30**); 4-OH (**31**,**32**)

R^2 = H (**25**); 2-Cl (**26**); 4-CH_3 (**27**); 4-Cl (**28**); 2-CH_3 (**29**); 3-Cl (**30**); 4-OH (**31**); 3-OCH_3 (**32**)

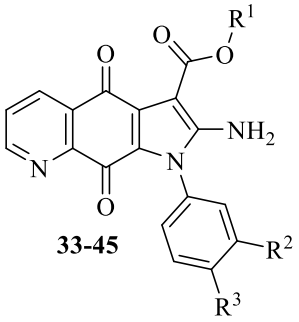
Figure 5. Chemical structure of oxadiazole derivatives **24-32**

Antimicrobial evaluation of compound **24** and 1,1-*bis*(2-phenyl-5-arylidine-1,3- thiadiazolidin-4-one)cyclopropanes **25-32** revealed that the conversion of compound **24** into Schiff bases **25-32** enhances biological potency.[29] Compounds **27, 31,** and **32** displayed the most potent antifungal spectra (Table 5). Thus, 4-methyl, 4-hydroxy and 3-methoxy phenyl substituents were found to be the most potent for raising the fungicidal action. For determination of the preliminary activity, the disk diffusion method was used.[30]

Table 5. Antifungal activity of thiadiazole derivatives **24-32** (inhibition zone, mm)

Compounds	*C. glabrata*	*C. albicans*	*C. krusei*
24	-	5	-
25	-	-	-
26	8	10	10
27	5	5	-
28	10	8	12
29	-	-	6
30	10	12	13
31	6	-	5
32	8	-	-
Fluconazole	15	16	15

2.6. Pyrroloquinoline Derivatives



33-45

R^1 = CH_3 (**33-35**); C_2H_5 (**36-45**)
R^2 = H (**33-44**); F (**45**)
R^3 = H (**33,36**); CH_3 (**34,37**); CH_3O (**35,38**); OH (**39**); F (**40,45**); Cl (**41**); Br (**42**); I (**43**); CF_3 (**44**)

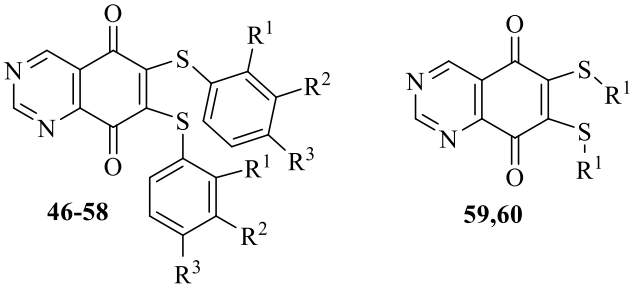
Figure 6. Chemical structure of pyrroloquinoline derivatives **33-45**

Among the tested compounds **33-45,** the most active against all three fungi species were **39** and **44** (Table 6).[31] It means that hydroxy and trifluoromethyl groups connected with and an aryl substituent could considerably increase the antifungal activity. Pyrroloquinoline derivatives were tested *in vitro* for their growth inhibitory activity against pathogenic fungi by the standard method.[32]

Table 6. Antifungal activity of pyrroloquinoline derivatives **33-45** (MIC, μg/mL)

Compounds	*C. albicans*	*C. tropicalis*	*C. krusei*
33	>100	>100	50
34	100	100	12.5
35	>100	>100	12.5
36	>100	6.3	>100
37	>100	3.2	12.5
38	>100	12.5	>100
39	3.2	0.6	12.5
40	>100	6.3	>100
41	>100	3.2	>100
42	50	3.2	>100
43	25	3.2	25
44	6.3	0.8	6.3
45	1.6	50	25
Fluconazole	12.5	6.3	25

2.7. Quinazoline Derivatives



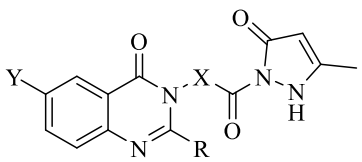
R^1 = H (**46-55,58**); F (**56,57**); C_2H_5 (**59**); C_2H_5OH (**60**)
R^2 = H (**46-50,54,56-58**); F (**52,55**); CH_3 (**51,53**)
R^3 = H (**52-54,57**); CH_3 (**50,51**); CH_3O (**47**);
OH (**58**); F (**46,55,56**); Cl (**48**); Br (**49**)

Figure 7. Chemical structure of quinazoline derivatives **46-60**

Fungicidal action with quinazoline derivatives is much more efficient than that above described pyrroloquinolines. The authors used the same standard method in their investigation.[32] Many of compounds **46-60** were comparable to those of 5-fluorocytosine against *Candida krusei*. The activities of compounds **46** or **53** were superior to those of 5-fluorocytosine against *C. neoformans* (Table 7).[33]

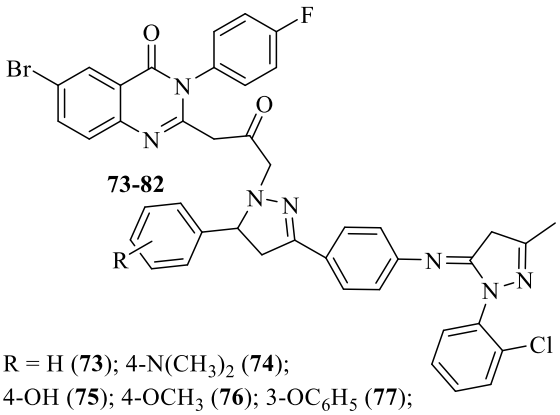
Table 7. Antifungal activity of quinazoline derivatives **46-60** (MIC, μg/mL)

Compounds	***C. albicans***	***C. tropicalis***	***C. krusei***	***C. neoformans***
46	1.6	6.3	12.5	1.6
47	25	25	3.2	6.3
48	6.3	12.5	3.2	6.3
49	6.3	50	6.3	12.5
50	12.5	6.3	6.3	50
51	12.5	12.5	12.5	3.2
52	6.3	25	12.5	1.6
53	3.2	12.5	25	0.8
54	6.3	6.3	6.3	25
55	12.5	6.3	12.5	6.3
56	6.3	6.3	12.5	1.6
57	6.3	6.3	12.5	1.6
58	3.2	3.2	25	12.5
59	12.5	12.5	6.3	6.3
60	25	>50	12.5	6.3
5-Fluorocytosine	50	6.3	25	6.3



61-72

Y = H (**62,64,66,68,70,72**); Br (**61,63,63,67,69,71**);
R = CH_3 (**61,62,65,66,69,70**); C_6H_5 (**63,64,67,68,71,72**);
X = 4-C_6H_4 (**61-64**); CH_2 (**62-68**); 4-C_6H_4 (**69-72**)



73-82

R = H (**73**); 4-$N(CH_3)_2$ (**74**);
4-OH (**75**); 4-OCH_3 (**76**); 3-OC_6H_5 (**77**);
3,4,5-$(OCH_3)_3$ (**78**); 3-OCH_3-4-OH (**79**);
2-Cl (**80**); 4-Cl (**81**); 4-NO_2 (**82**)

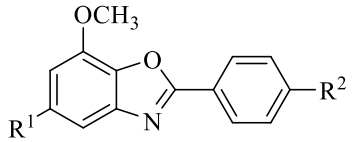
Figure 8. Chemical structure of quinazoline derivatives **61-82**

For the screening of fungal activity of quinazoline derivatives **61-82,** the cup-plate method was used.[34] Compounds **64, 67, 70, 71, 78,** and **82** exhibited moderate to good antifungal activity (Table 8).[35,36] Phenyl substituent, methoxy and nitro groups in aromatic rings promote the increase of quinazoline action.

Table 8. Antifungal activity of quinazoline derivatives **61-82** (MIC, μg/mL)

Compounds	***C. albicans***	***C. krusei***
61	11	10
62	21	22
63	20	18
64	8	5
65	20	22
66	18	24
67	7	9
68	10	11
69	17	20
70	5	8
71	7	9
72	15	18
73	-	20
74	12	0.8
75	17	9
76	-	12
77	20	-
78	0.9	20
79	10	17
80	17	8
81	10	0.7
82	7	0.8
Fluconazole	25	28

2.8. Benzoxazoles Derivatives



83-90

R^1 = allyl (**83**,**85**,**87**,**89**); propyl (**84**,**86**,**88**,**90**);
R^2 = H (**83**,**84**); Cl (**85**,**86**); OCH_3 (**87**,**88**); NO_2 (**89**,**90**)

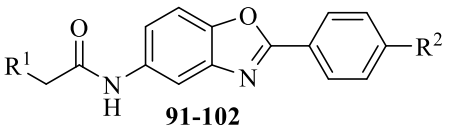
Figure 9. Chemical structure of benzoxazole derivatives **83-90**

Four benzoxazole derivatives (**83, 86, 87, 90**) showed activity against pathogenic and opportunistic species of *Candida* spp (Table 9).[37] The results were calculated using the inhibitory concentration of 50% microbial growth, and the interpretative criteria were those proposed by the document M27A3 from the Clinical and Laboratory Standards Institute.[38]

Table 9. Antifungal activity of benzoxazole derivatives **83-90** (IC_{50}, μM)

Compounds	*C. albicans*	*C. krusei*	*C. parapsilosis*	*C. glabrata*
83	380	-	-	-
84	-	-	-	-
85	-	-	-	-
87	331	-	-	338
88	-	-	-	-
89	-	-	-	-
90	321	321	-	-
Fluconazole	1.6	104.3	3.3	52.2

* "-" – not detected activity.



91-102

R^1 = morpholinyl (**91**,**94**,**97**,**100**); 4-methylpiperazine (**92**,**95**,**98**,**101**); piperazinyl (**93**,**96**,**99**,**102**);
R^2 = C_2H_5 (**91-93**); H (**94-96**); F (**97-99**); $C(CH_3)_3$ (**100-102**)

Figure 10. Chemical structure of benzoxazole derivatives **91-102**

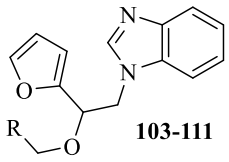
The antifungal investigation of benzoxazole derivatives **91-102** was performed by the standard method.[32] All compounds showed notable activity against *C. albicans*, *C. krusei*, and *C. glabrata* with MIC values of 3.12-50 μg/mL (Table 10). There were no significant results when the role of the substitution of the acetamido group on C-5 of benzoxazole for *C. albicans* was considered. Furthermore, compounds **92**, **101**, and **102** were found to be more active against *C. glabrata* than the others with a MIC value of 12.5 μg/mL. Moreover, compound **101** was also the most active among the compounds having a MIC value of 3.12 μg/mL against *C. krusei*. The compounds **93** and **100** were also very active ones in these series against *C. krusei* with a MIC value of 6.25 μg/mL. It is noted that those possessing a *p-tert*-butyl substituent of phenyl ring at the C-2 position of benzoxazole showed enhanced antifungal

activity against *C. krusei* and *C. glabrata*. Consequently, for developing new antifungal agents against *C. krusei*, compound **101** could be the lead for further studies.[39]

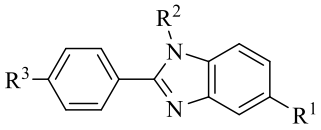
Table 10. Antifungal activity of benzoxazole derivatives **91-102** (MIC, μg/mL)

Compounds	*C. albicans*	*C. krusei*	*C. glabrata*
91	25	12.5	25
92	25	12.5	12.5
93	50	6.25	25
94	50	25	25
95	50	25	25
96	50	25	25
97	50	25	25
98	25	50	25
99	25	25	25
100	50	6.25	25
101	50	3.12	12.5
102	25	12.5	12.5
Oxiconazole	6.25	-	-
Haloprogin	3.125	-	-
Micanazole	3.125	1.56	3.125

2.9. Benzimidazole Derivatives



103-111



112-123

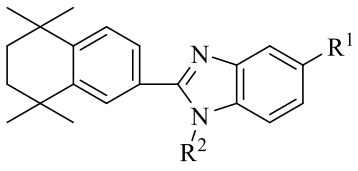
R = C_6H_5 (**103**); 4-F-C_6H_4 (**104**); 4-Cl-C_6H_4 (**105**); 4-Br-C_6H_4 (**106**); 4-CF_3-C_6H_4 (**107**); 2,4-Cl_2-C_6H_3 (**108**); 2,6-Cl_2-C_6H_3 (**109**); 2,5-Cl_2-C_6H_3 (**110**); 3,4-Cl_2-C_6H_3 (**111**)

R^1 = NO_2 (**112-114,118-120**); NH_2 (**115-117,121-123**);
R^2 = Et (**112,113,115,116**); Me (**118,119,121,122**); cyclopentyl (**114,117**); cyclopropyl (**120,123**);
R^3 = H (**112,115,118,121**); Br (**113,114,116,117,119,120,122,123**)

Figure 11. Chemical structure of benzimidazole derivatives **103-123**

All the benzimidazole derivatives **103-123**[40-43] were tested for their *in vitro* growth inhibitory activity against *C. albicans*, patient isolates *C. glabrata* and *C. krusei* (Table 11) according to the standard protocol[32] and the tube dilution technique.[27]

Thus, compounds **113-116, 118, 120, 121**, and **123** possessed comparable activity to fluconazole and cotrimoxazole against *C. albicans* with a MIC of 12.5 μg/ mL. However, none of the compounds was superior to the standards used against any fungi.



124-128

R^1 = H (**124**); CH_3 (**125**); NO_2 (**126**);
4' NO_2 (**127**); COOH (**128**);
R^2 = H (**124-127**); CH_3 (**128**)

Figure 12. Chemical structure of benzimidazole derivatives **124-128**

Table 11. Antifungal activity of benzimidazole derivatives **103-123** (MIC, μg/mL)

Compounds	*C. albicans*	*C. krusei*	*C. glabrata*	Reference
103	25	50	NT	40
104	50	50	NT	40
105	25	50	NT	40
106	25	50	NT	40
107	50	25	NT	40
108	12.5	25	NT	40
109	-	-	NT	40
110	50	25	NT	40
111	50	50	NT	40
112	25	12.5	25	41, 42
113	12.5	6.25	6.25	41, 42
114	25	12.5	12.5	41
	12.5	6.25	25	42
115	25	12.5	12.5	41
	12.5	12.5	25	42
116	12.5	6.25	6.25	41
	12.5	12.5	12.5	42
117	25	12.5	12.5	41
	25	6.25	25	42
118	12.5	6.25	6.25	43
119	25	12.5	25	43
120	12.5	6.25	25	43
121	12.5	12.5	25	43
122	25	6.25	25	43
123	12.5	12.5	12.5	43
Fluconazole	1.56[40]	25[40]	3.125[41-43]	
	12.5[41-43]	3.125[41-43]		
Miconazole	0.19[40]	0.78[40]	1.56[41]	
	6.25[41-43]	1.56[41-43]	3.125[42,43]	
Cotrimoxazole	12.5[42,43]	3.125[42,43]	3.125[42,43]	

* "**-**" – not detected activity; "NT" – not tested.

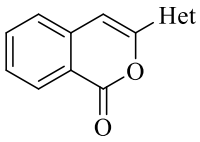
Among the benzimidazole derivatives **124-128** the compounds bearing a nitro group, located at the 5th and 4th positions of the benzimidazole phenyl ring (compounds **126** and **127**). The activity pattern was totally changed when the location of the nitro group switched to the 4th position. Compound **126** has a greater antibacterial efficacy because the nitro group is located at the 5th position, whereas the inactive compound (compound **127**) has the nitro group at the 4th position.[44]

Table 12. Antifungal activity of benzimidazole derivatives **124-128** (MIC, μg/mL).

Compounds	*C. albicans*	*C. krusei*
124	-	50
125	-	50
126	100	-
127	-	50
128	50	50
Fluconazole	0.78	50

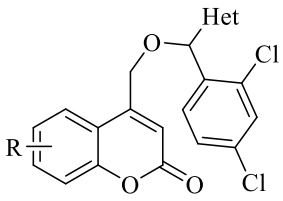
* "**-**" – not detected activity

2.10. Coumarin Derivatives



129-137

Het = imidazol-1-yl (**129**); pyrazol-1-yl (**130**); 1,2,4-triazol-1-yl (**131**); tetrazol-1-yl (**132**); 4-carbethoxyimidazol-1-yl (**133**); benzimidazol-1-yl (**134**); 2-trifluoromethylbenzimidazol-1-yl (**135**); benzotriazol-1-yl (**136**); 4-chloropyrazol-1-yl (**137**)



138-147

Het = imidazol-1-yl (**138-142**); benzimidazol-1-yl (**143-147**); R = 6-CH_3 (**138,143**); 7-CH_3 (**139,144**); 6-OCH_3 (**140,145**); 6-CCl (**141,146**); 7,8-Benzo (**142,147**)

Figure 13. Chemical structure of coumarin derivatives **129-147**

Among the coumarins the most active compound was derivative **132** (Table 13), possessing a tetrazole substituent. Other similar compounds **129-131**, with parent heterocycles, pyrazole, imidazole, and triazole as substituents, showed antifungal potential, with triazole derivative **131** being not just very active.[45]

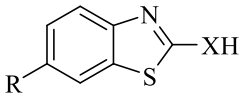
Compound **142** bearing 7,8-benzo substituted coumarin registered 4 μg/mL of MIC exhibited 200 to 400% improved efficiency against all three strains, viz., *Candida albicans*, *Candida utilis* and *Candida krusei*. The introduction of the benzimidazole moiety (i.e., compound **147**) in place of imidazole in **132** registered enhanced potency that is on par with the standard drugs against *Candida albicans*, and *Candida utilis*, whereas 50% diminished inhibitory activity is achieved against *Candida krusei*. From the overview of *in vitro* antifungal data for the tested compounds, it is very clear in general that benzimidazole substitution in place of imidazole and, in particular, aza-coumarin ethers in place of coumarin ethers demonstrated phenomenal inhibitory roles against all the tested yeast fungi.[46]

Table 13. Antifungal activity of coumarin derivatives **129-147** (MIC, μg/mL)

Compounds	***C. albicans***	***C. krusei***	***C. parapsilosis***	***C. utilis***
129	62.5	-	-	NT
130	31.2	>500	>500	NT
131	20	125	>500	NT
132	15.6	62.5	125	NT
133	62.5	>500	>500	NT
134	-	-	-	NT
135	150	-	-	NT
136	-	-	-	NT
137	5	125	>500	NT
138	16	62.5	NT	62.5
139	62.5	125	NT	125
140	31.25	16	NT	62.5
141	16	62.5	NT	31.25
142	4	4	NT	4
143	2	8	NT	4
144	4	2	NT	2
145	8	8	NT	16
146	8	31.25	NT	16
147	1	2	NT	1
Itraconazole	1	1	NT	1
Miconazole	1	1	NT	1
Voriconazole	7.8[45]	Resistant[45]	Resistant[45]	

* "-" – not detected activity; "NT" – not tested.

2.11. Benzothiazole Derivatives



148-170

X = NH (**148-162**); S (**163-170**);
R = H (**148,163**); OCH_3 (**149,170**); OC_2H_5 (**150**); OPh (**151,165**); OBn (**152,166**);
$O(CH_2)_2Ph$ (**153**); $O(CH_2)_3Ph$ (**154**); $O(CH_2)_4Ph$ (**155**); CH_2OPh (**156**);
F (**157,169**); Cl (**158,168**); CF_3 (**159,167**); OCF_3 (**160,164**); 4-ClBnO (**161**); 4-ClPhO (**162**)

Figure 14. Chemical structure of benzothiazole derivatives **148-170**

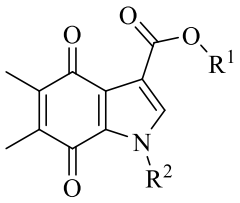
Derivative **161** showed the highest antifungal activity against *C. albicans* (MIC: 4 mg/mL), followed by compounds **152**, **153**, and **162** (MIC: 8 mg/mL). Compound **161** was also very active against *C. tropicalis*, showing the same MIC value as the reference (4 mg/mL), followed by compounds **161**, and **162** (MIC: 8 mg/mL). Compound **162** was the best of the series against *C. parapsilosis* (MIC: 4 mg/mL) followed by compounds **152,161** (MIC: 8 mg/mL). Both compounds **153** and **154** were indeed two-fold more potent than the reference compound fluconazole against *C. krusei*. The presence of the substitution at position 2 of the heterocyclic moiety is crucial for the benzothiazole derivatives activity: 2-amino derivatives were more potent against fungi. The study[47] suggests that 2-amino-1,3-benzothiazoles **161, 162** are promising scaffolds for the development of novel antifungal agents against *Candida* spp.

Table 14. Antifungal activity of benzothiazole derivatives **148-170** (MIC, μg/mL)

Compounds	*C. albicans*	*C. parapsilosis*	*C. tropicalis*	*C. krusei*
148	>512	>512	>512	>512
149	256	256	256	512
150	128	128	128	256
151	128	16	32	32
152	8	8	8	64
153	8	16	32	16
154	32	16	16	16
155	512	128	512	>512
156	32	16	16	64
157	256	128	256	256
158	64	64	64	128
159	16	64	64	64
160	64	64	128	128
161	4	8	4	64
162	8	4	8	32
163	32	32	32	32
164	32	32	16	32
165	>512	>512	>512	>512
166	>512	>512	>512	>512
167	16	64	16	32
168	4	32	8	16
169	32	64	64	32
170	32	64	64	64
Fluconazole	2	2	4	32

The compounds of series **163-170** showed high activity except for compounds **165**, and **166**, which were inactive.[48] Among the tested compounds, **168** was the most active, showing MIC values of 4 and 8 μg/mL against *C. albicans* and *C. tropicalis*, respectively. Position and electronic properties of the substituent on the aromatic moiety seems not to be crucial for determining any variation in activity (Table 14).

2.12. Indole Derivatives



171-183

R^1 = CH_3 (**171, 173-183**); C_2H_5 (**172**);
R^2 = CH_3 (**171,172**); C_6H_5 (**173**); 4-F-C_6H_4 (**174**); 4-Cl-C_6H_4 (**175**);
4-Br-C_6H_4 (**176**); 4-I-C_6H_4 (**177**); 4-CH_3-C_6H_4 (**178**); 4-CH_3O-C_6H_4 (**179**);
3,4-$(CH_3)_2$-C_6H_3 (**180**); 4-CF_3O-C_6H_4 (**181**); 4-C_2H_5-C_6H_4 (**182**); 4-*i*C_3H_7-C_6H_4 (**183**)

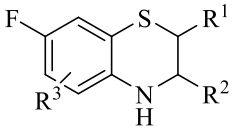
Figure 15. Chemical structure of indole derivatives **171-183**

The synthesized 1H-indole-4,7-diones **171-183**, were tested *in vitro* for their growth inhibitory activity against pathogenic fungi by the standard method.[32] The MIC values were determined by comparison with 5-fluorocytosine as a standard agent. As indicated in Table 15, most of the 1H-indole4,7-diones **171-183** generally showed potent antifungal activity against *Candida krusei*. In contrast, compounds **171-183** did not show significant antifungal activity against *C. albicans* and *C. tropicalis*, although compounds **173**, **175**, and **183** exhibited good activity. The activities of compounds **173**, **175** were superior or comparable to those of 5-fluorocytosine against all tested fungi. The compounds **173**, **175** completely inhibited the growth of all fungal species tested at the MIC level of 1.6–25 μg/mL.[49]

Table 15. Antifungal activity of indole derivatives **171-183** (MIC, μg/mL)

Compounds	*C. albicans*	*C. tropicalis*	*C. krusei*
171	>100	>100	3.2
172	>100	25	50
173	3.2	12.5	1.6
174	>100	>100	3.2
175	12.5	12.5	0.8
176	50	6.3	50
177	25	12.5	50
178	>100	>100	3.2
179	>100	50	3.2
180	12.5	>100	0.8
181	>100	>100	6.3
182	25	50	50
183	12.5	100	100
5-Fluorocytosine	6.3	12.5	6.3

2.13. Thiazine Derivatives



184-198

R^1 = H (**184-195**); C_6H_5 (**196-198**);
R^2 = H (**184-186**); C_6H_5 (**187-189**); CH_3 (**190-192**); O= (**193-198**);
R^3 = 5-Cl (**184,187,190,193,196**); 6-Cl (**185,188,191,194,197**);
8-Cl (**186,189,192,195,198**)

Figure 16. Chemical structure of thiazine derivatives **184-198**

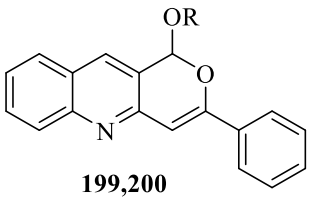
There are some facts concerning on the fungal data of thiazine compounds **184-198**: derivative **195**, which has a chlorine atom at the C8 position of the heterocycle, displayed moderate activity against the fungi *Candida parapsilosis* and *Candida tropicalis* with MIC values of 64 mg/mL. Interestingly, the introduction of a phenyl group at the C2 position of the 7-fluoro-2*H*-1,4-benzothiazin-3(4*H*)-one analogues (**196-198**) led to a decrease to the antimicrobial profile.[50]

Table 16. Antifungal activity of thiazine derivatives **184-198** (MIC, μg/mL)

Compounds	***C. albicans***	***C. parapsilosis***	***C. tropicalis***	***C. krusei***
184	32	8	32	32
185	R	500	500	-
186	500	500	500	-
187	R	R	R	-
188	128	64	256	256
189	128	32	128	256
191	-	-	-	-
193	500	500	500	-
194	512	512	512	512
195	250	64	64	-
196	250	250	250	-
197	250	250	250	-
198	R	R	R	-
Fluconazole	0.5	-	1	

* "-" – not detected activity; "R" – resistant.

2.14 Naphthyridine derivatives



199,200

R = CH_3 (**199**); C_2H_5 (**200**)

Figure 17. Chemical structure of naphthyridine derivatives **199, 200**.

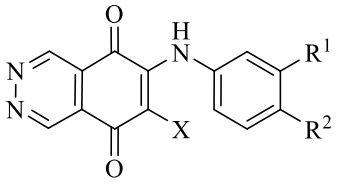
As was reported,[51] compound **199** isn't active against fungal strains. More interestingly, compound **200** was active against all microbial strains, with IC_{50} values in the range 4.5– 20 μM. The most sensitive to **200** was the fungus *C. krusei* (4.5 μM). It is noteworthy that the substitution of a methyl group (**199**) for an ethyl group (**200**) produces such a change in the activity profile.

Table 17. Antifungal activity of naphthyridine derivatives **199, 200** (IC_{50}, μM).

Microorganisms	199	200
C. albicans	>100	20 (±1.0)
C. glabrata	>100	18 (±1.3)
C. krusei	>100	4.5 (±1.6)
C. nivariensis	>100	16 (±1.1)
C. parapsilosis	>100	20 (±0.6)

* Values expressed as IC_{50} are given in μM and are means of three to six experiments, standard deviation is given in parentheses.

2.15. Phtalazine Derivatives



201-213

X = Cl (**201-208**); H (**209-213**);
R^1 = H (**201-203,205,206,209-212**); Cl (**204**);
F (**207**); CF_3 (**208**); CH_3 (**213**);
R^2 = H (**201,204,208**); F (**202,207,209**); Cl (**203**);
Br (**205,210**); I (**206**); CH_3O (**211**); CH_3 (**212,213**)

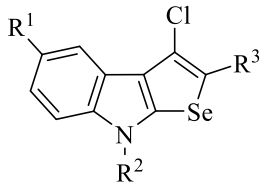
Figure 18. Chemical structure of phtalazine derivatives **201-213**

The activities of compounds **204, 205**, **211**, and **212** were superior or comparable to those 5-fluorocytosine against all tested fungi (Table 18). The compounds **204, 205**, **211**, and **212** completely inhibited the growth of all fungal species tested at the MIC level of 3.2–25 μg/mL.[52]

Table 18. Antifungal activity of phtalazine derivatives **201-213** (MIC, μg/mL)

Compounds	*C. albicans*	*C. tropicalis*	*C. krusei*
201	50	25	25
202	50	50	50
203	12.5	12.5	6.3
204	25	25	25
205	25	12.5	25
206	12.5	12.5	12.5
207	25	3.2	>100
208	25	12.5	100
209	50	25	25
210	12.5	3.2	12.5
211	12.5	6.3	12.5
212	6.3	12.5	12.5
213	3.2	100	50
5-fluorocytosine	25	12.5	50

2.15. Selenium Containing Compounds



214-218

R^1 = H (**214,216-218**); CN (**215**);
R^2 = H (**214-216**); Me (**217**); Ph (**218**);
R^3 = Ph (**214,215,218**); 3-MeC_6H_4 (**216**); 4-BrC_6H_4 (**217**)

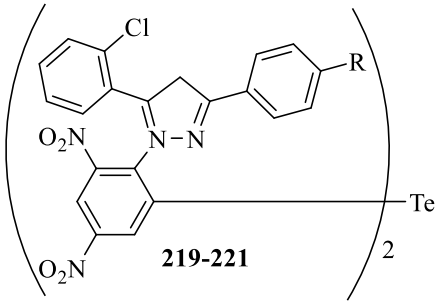
Figure 19. Chemical structure of compounds **214-218**

The antifungal activity of selected heterocycles (**214-218**) was studied, against several strains of *Candida*. The minimum inhibitory concentrations (MIC) are given in the Table 19; nystatin and fluconazole were used as comparators. It was observed that *Candida krusei* was among the most susceptible microorganisms and compound **216** was the most active against all the yeasts; this might be caused by the presence of a methyl group at the 3rd position of benzene ring.[53]

Table 19. Antifungal activity of compounds **214-218** (MIC, μg/mL)

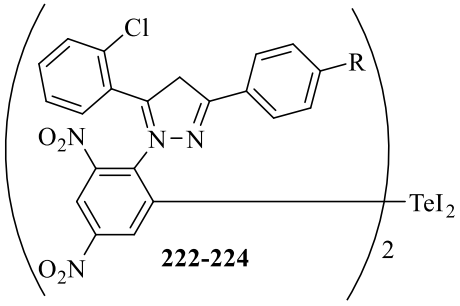
Microorganisms	214	215	216	217	218	Nystatin	Fluconazole
C. albicans	151.2	>562.3	290.1	472.1	411.8	1.7	81.7
C. tropicalis	151.2	>562.3	18.1	236.1	103.0	1.7	163.3
C. krusei	4.7	4.4	4.5	14.8	205.9	3.4	81.7
C. parapsilosis	151.2	281.2	290.1	472.1	205.9	1.7	5.1
C. dublienses	151.2	>562.3	72.5	118.0	103.0	1.7	10.2
C. glabrata	302.4	>562.3	290.1	472.1	3.2	3.4	10.2

2.16. Tellurium Containing Compounds



219-221

R = Br (**219**); CH_3 (**220**); OCH_3 (**221**)



222-224

R = Br (**222**); CH_3 (**223**); OCH_3 (**224**)

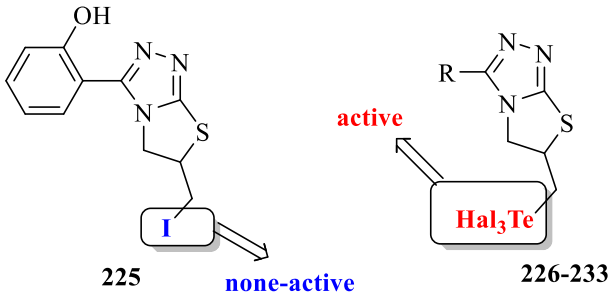
Figure 20. Chemical structure of compounds **219-224**

The antifungal activity for Tellurium-containing pyrazole derivatives **219-224** were assayed against *Candida albicans* ATCC2091.[54] Data of inhibition zones and MIC affirm that telluride compounds **219-221** were more active against the fungi than the other compounds and the control (amoxicillin) (Figure 20, Table 20).

Table 20. Antifungal activity of compounds **219-224** against *C. albicans*:MIC, μg/mL and inhibition zones, mm

Activity	219	220	221	222	223	224	Amoxicillin
MIC	50	200	50	120	110	110	100
Inhibition zones	41	30	33	27	18	22	30

It was reported[55] that iodo-substituted 5,6-dihydro[1,3]thiazolo[2,3-c][1,2,4]triazole **225** has weak antifugal activity, whereas the introducing trihalogenotellurium moiety leads to significant increasing of bioactivity of compounds **226-233** (Figure 21, Table 21).



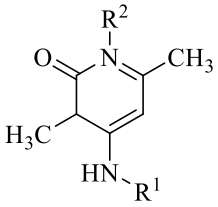
R = NH_2(**226**,**227**); AllylNH (**228**,**229**); Ph (**230**,**231**); 2-HOC_6H_4 (**232**,**233**)
Hal = Cl (**226**,**228**,**230**,**232**); Br (**227**,**229**,**231**,**233**)

Figure 21. Chemical structure of compounds **225-233**

Table 21. Antifungal activity of compounds **225-233** against *C. albicans* CCM 885.

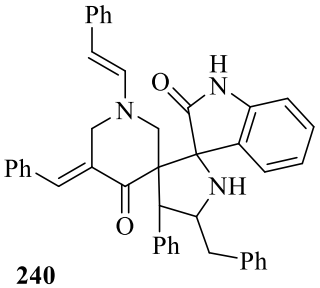
Activity	225	226	227	228	229	230	231	232	233	Ketoconazole
Inhibition zones, mm	-	14	14	12	14	11	10	22	27	14

2.17. Pyridine/Piperidine Derivatives

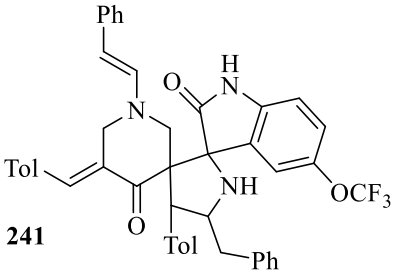


234-239

234: $R^1 = R^2 = 4\text{-}ClC_6H_4$; **235**: $R^1 = R^2 = 4\text{-}CH_3C_6H_4$ (Tol);
236: $R^1 = R^2 = C_6H_5$; **237**: $R^1 = R^2 = 4\text{-}CH_3OC_6H_4$;
238: $R^1 = R^2 = 3,4\text{-}(CH_3O)_2C_6H_3$; **239**: $R^1 = R^2$ = Het



240



241

Figure 22. Chemical structure of phtalazine derivatives **234-241**

The mean inhibitory concentration (MIC) assay was used to test the antifungal activity of compounds **234-241** (Figure 21, Table 21).[56,57] Fungal strain *Candida albicans* was acquired from ATCC resource after 48 h of incubation. It should be noted that the saturation of azine cycle leads to decreasing of antifungal activity as well as the introducing inductive or mesomeric electro-donating substituents such as methyl- or methoxy- on the aromatic rings led to a decrease in biological activity.

Table 21. Antifungal activity of compounds **234-241** against *C. albicans*: MIC, μg/mL

Activity	**234**	**235**	**236**	**237**	**238**	**239**	**240**	**241**	**Fluconazole**
MIC	12.5	25.0	45.0	50.0	50.0	45.0	2.0	8.0	0.5

3. Conclusion

Herein, we've reviewed isolated and fused heterocyclic compounds that exhibit antifungal activity against *Candida* strains. Over 200 potential fungicidal agents were described, and some of the particularities that affected the action values were determined; nystatin, 5-Fluorocytosine and fluconazole were mainly used as comparators. Thus, it was noted that the presence of nitro-, methoxy-, trifluoromethyl-, and/or halogen-containing groups at the specific positions in the benzene ring could significantly increase the inhibition of yeasts growth. That's why using these patterns together with heterocycles while designing target compounds could speed up the searching of new antifungal drugs.

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