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THE ANTIFUNGAL PROPERTIES OF 1,2,3-TRİAZOLES

[1]Bakhtiyar BABAZADE, [1]Gulnar ATAKISHIYEVA, [1]Aliyar BABAZADE, [2]Peri HUSEYNOVA, [1,3]Qemze YAHYAYEVA, [1]Muskunaz AXUNDOVA, [1]Khatira GARAZADE, [4]Narmin MURSHUDLU, [5]Namiq Q. SHIKHALIYEV

[1] Organic Chemistry Department, Baku State University, Z. Khalilov str. 23, AZ 1148, Baku, Azerbaijan,

[2] Chemistry Department, Nakhchivan State University, University Campus, AZ7012, Nakhchivan, Azerbaijan.,

[3] Chemistry and physics Department, Azerbaijan University of Architecture and Construction, Ayna Sultanova str, Baku, Azerbaijan,

[4]Chemistry Department, Sumgait State University, 1 Baku Street, 5008, Sumqayit Azerbaijan,

[5] Department of Chemical Engineering, Baku Engineering University, Hasan Aliyev str, AZ0101, Baku, Azerbaijan,

*Corresponding author.

E-mail addresses: namiqst@gmail.com (Namiq Q. Shikhaliyev).

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ABSTRACT

Fungicides are very important for agriculture, animal husbandry and medicine, as the various infections induced by certain fungi cause harm to plants and animals which are used as a source of food, as well as directly to humans themselves. More than 1,5 million deaths are caused by fungi each year, both the incidence of fungal infections and the resistance against already existing antifungal drugs are on the rise, which renders the search for inexpensive and new effective fungicides very urgent. On the other hand, some compounds containing 1,2,3-triazole moieties (for example, Radezolid and Cefatrizine) display strong antifungal activity and are used as fungicides. Azoles prevent lanosterol 14-alpha-demethylase enzyme from converting to ergosterol, and therefore inhibit growth of fungi. Today many scientists all across the world synthesize new compounds containing 1,2,3-triazole moieties and research their antifungal properties by applying them against various pathogenic fungal strains. This article is a review of recent scientific literature describing antifungal activity of compounds containing 1,2,3-triazole moieties.

1. Introduction

Antifungal drugs are utilized widely in agriculture, animal husbandry, medicine, because the infections caused by fungi are harmful to plants and animals important for agriculture and even directly to humans themselves. [1] Fungi-induced infections cause deaths of 1,5 million people per year. Moreover, both the the incidence of fungal infections and the resistance against already existing antifungal drugs are on the rise, therefore new efficient antifungals are needed. [2]

Generally speaking, the antifungal properties of azole derivatives were first discovered in 1944, and nowadays there are several antifungal drugs based on 1,2,3-triazoles, for example Cefatrizine, Tazobactam, Carboxyamidotriazole, Radezolid, Tertbutyldimethylsilylspiroaminooxathioledioxide. The antifungal properties of azoles are explained by the fact that these

compounds prevent lanosterol 14-alpha-demethylase enzyme from converting to ergosterol, which is used to create cell walls. [3]

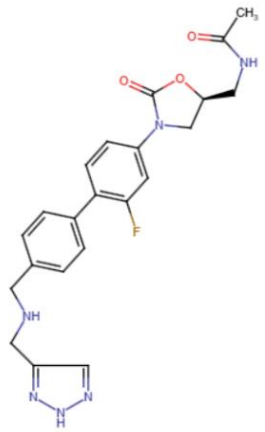


Figure 1. The structure of the radezolid compound.

This article is a review of scientific articles concerning antifungal properties of 1,2,3-triazoles.

2. Result and discussion

Konda and their team [4] synthesized a series of new benzoxazine-6-sulfonamides with excellent yields. Most compounds have shown promising activity against *Candida albicans*. Some compounds have demonstrated activity similar to the reference drug fluconazole. For fluconazole, minimum inhibition concentration (MIC) is equal to 32 μg/mL, the values for these compounds are as follows: 1 (MIC=62,5 μg/mL), 2 (MIC=31,25 μg/mL), 3 (MIC=31,25 μg/mL), 4 (MIC=62,5 μg/mL), 5 (MIC=62,5 μg/mL) and 6 (MIC=31,25 μg/mL).

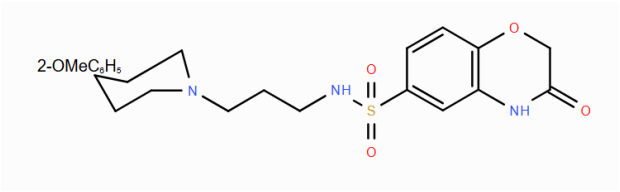


Figure 2. Compound №1.

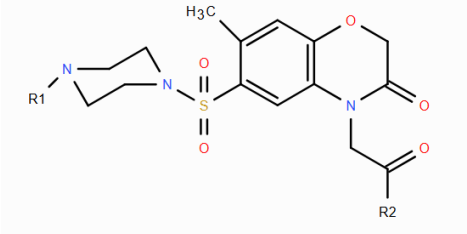
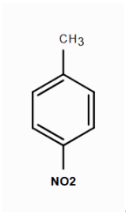


Figure 3. The general scheme of compounds № 2-6. For compounds №2 and 3 R1=4-(trifluoromethyl)phenyl; for compounds № 4-6 R1=2-methoxyphenyl. R2 substituents are: for 2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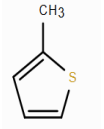
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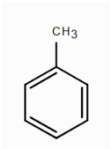
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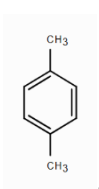
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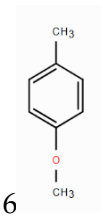


García-Monroy and their colleagues [5] obtained several benzylic 1,2,3-triazole-4-carboxamides via a one-pot procedure and tested their activity *in vitro* against eight fungal strains (*Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae*, *Mucor hiemalis*, *Candida krusei*, *Candida albicans*, *Candida utilis* and *Candida glabrata*). The best results were shown by compounds № 7, 8 and 9 against *R. Oryzae* fungi (MIC values, respectively, 0,017 μmol/mL, 0,017 μmol/mL and 0,07 μmol/mL). Itraconazol was used as a reference drug, its MIC against *R. Oryzae* is 0,14 μmol/L. This means that these compounds are stronger fungicides against *R. Oryzae* than itraconazole.

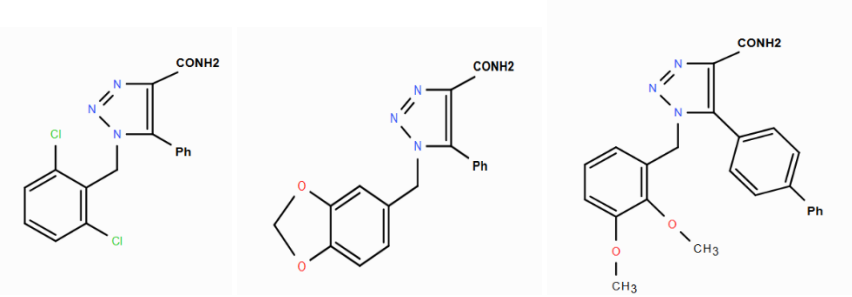


Figure 4. Compounds № 7, 8, 9.

Two other compounds (10 and 11) showed MIC = 0,14 μmol/L against this same fungal strain, which means their antifungal activity is equal to that of itraconazole. The authors expressed a hypothesis that stronger fungicides can be obtained in the future by modifying the compounds №7 and 8.

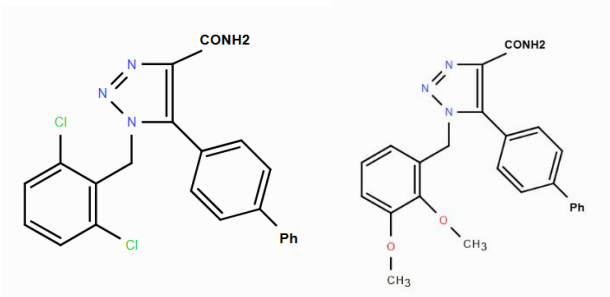


Figure 5. Compounds №10 and 11.

Guiqing Xu and their team [6] synthesized 1,4-disubstituted 1,2,3-triazoles containing indole ring via $CuCl_2$/Zn catalyzed Huisgen cycloaddition and tested their antifungal activities against *Colletotrichum Capsici* and *Cotton Physalospora*. The research has demonstrated that these compounds, especially 12 and 13, show significant inhibitory activity.

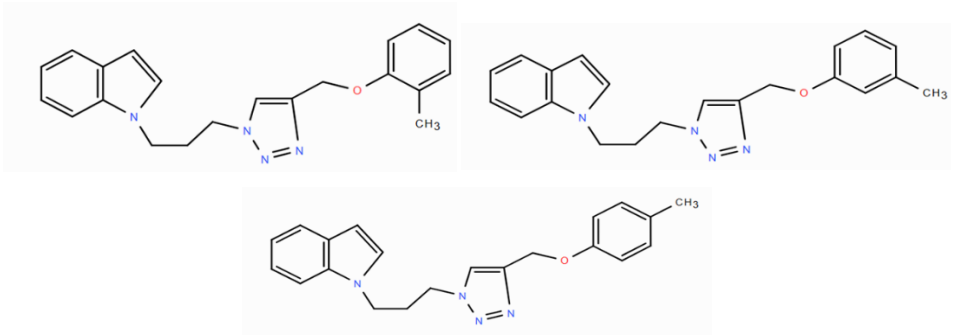


Figure 6. Compounds №12, 13, 14.

Flutriafol was used for a comparison. The best inhibitors of *Colletotrichum Capsici* were 12 (inhibition rate 100%) and 13 (inhibition rate 87,4%), the best inhibitors of *Cotton Physalospora* were 14 (inhibition rate 71,4%) and 13 (inhibition rate 56,2%).

Pertino and their team [7] synthesized twenty four new triazole derivatives starting from carnosic acid and carnosol and tested their antifungal properties against *Candida albicans ATCC 10231* and *Cryptococcus neoformans ATCC 32264* fungi, and used amphotericin B for comparison. All of these compounds fully inhibited the growth of pathogenic fungi with minimum inhibition concentrations (MIC_{100}) >250 μg·mL^{-1}. The strongest fungicide against *C. Albicans* was compound №15 at concentration 250 μg·mL^{-1} (inhibition percentage 57,9 ± 1.0%), but against *Cryptococcus neoformans* the strongest fungicide was the compound №16 at concentration 250 μg·mL^{-1} (inhibition percentage 91,3 ± 3.0%).

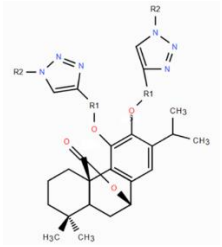
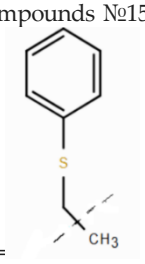
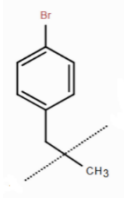


Figure 7. The general scheme of compounds №15 and 16. For both compounds R1 = $CO(CH_2)_3$, but for the compound №15 R2=  and for compound №16 R2 = 

It bears mentioning that six compounds at concentrations lower than 250 μg·mL^{-1} inhibited 50% growth of *C. Albicans*.

Mallikanti and their colleagues [8] synthesized new benzimidazole-based 1,2,3-triazoles via Suzuki coupling, cyclization and microwave-supported Cu-catalyzed chemical reaction. The impact of all the compounds on *Candida albicans* and *Aspergillus niger* fungi has been tested. Three compounds (with R substituent being 3-fluorobenzyl; 4-fluorobenzyl; R=3-cyanobenzyl) have proven themselves to be strong antifungals.

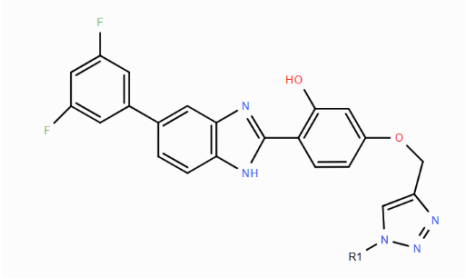


Figure 8. The general scheme of the compounds described in Mallikanti's article.

Dhawan and their colleagues [9] synthesized coumarine-tethered 1,2,3-triazoles via the 1,3-dipolar cycloaddition reaction of coumarine with various substituted azides and tested their

antifungal properties. The triazoles at the concentration of 32 μg/mL were applied against two fungal strains (*Candida albicans* and *Cryptococci neoformans*), and fluconazole's percentage inhibition was also mentioned (0,41 against *Candida albicans*; 26,1 against *Cryptococcus neoformans*). Neither of the synthesized triazoles was active against *Cryptococci neoformans*, but some activity was observed against *Candida albicans*, and the structures of the three most active compounds (17 (percentage inhibition 10,43%), 18 (percentage inhibition 6,08%) and 19 (percentage inhibition 6,04%)) are presented below (figures 9,10,11).

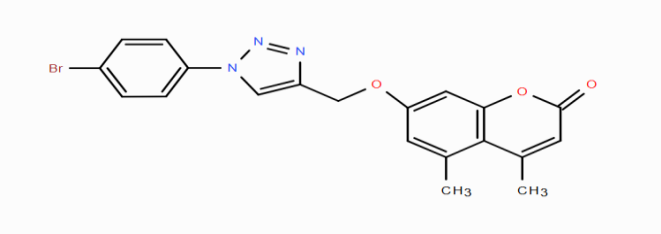


Figure 9. Compound №17

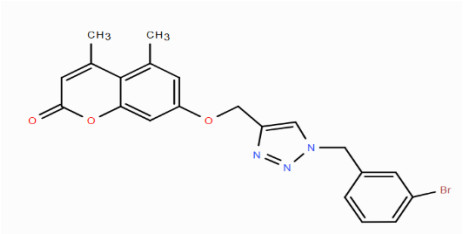


Figure 10. Compound №18.

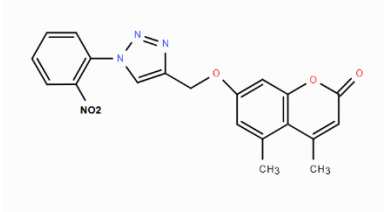


Figure 11. Compound №19.

Akolkar and their team [10] synthesized 1,4-disubstituted-1,2,3-triazoles via ultrasonic radiation and applied them against various fungal strains (*Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, and *Cryptococcus neoformans*) in order to test their antifungal activity. Miconazole was used as a reference drug. Two compounds were inactive against all fungal strains, but some others have proven themselves to be very good antifungals. The compounds №20, 21, 22 had MIC = 12 μg mL^{-1} against *Candida Albicans*, while compounds №23, 24, 25 have shown MIC = 25 μg mL^{-1} (for comparison: the reference drug miconazole's MIC against the same fungal strain is 25 μg mL^{-1}). The strongest antifungal against another fungal strain (*Fusarium oxysporum*) was compound № 22, which was even stronger than miconazole (MIC=12,5 μg mL^{-1} and MIC=25 μg mL^{-1} respectively), and five other compounds (20, 21, 24, 26, and 25) have demonstrated activity equal to that of miconazole. The most active compounds against *Aspergillus flavus* were 26 and 25 (both have shown MIC=12,5 μg mL^{-1}, which is equal to that of miconazole). The best result against *Aspergillus niger* was shown by compound №22 (MIC=12,5 μg mL^{-1}), which is better than that of miconazole (MIC=25 μg mL^{-1}), and four compounds (20, 24, 26 and 25) were as active as miconazole. Finally, compounds №22, 25, 26 have demonstrated

MIC=12,5 μg mL^{-1} against *Cryptococcus neoformans*, which is better that the results of miconazole (MIC=25 μg mL^{-1}), and 21 was equal in activity to miconazole.

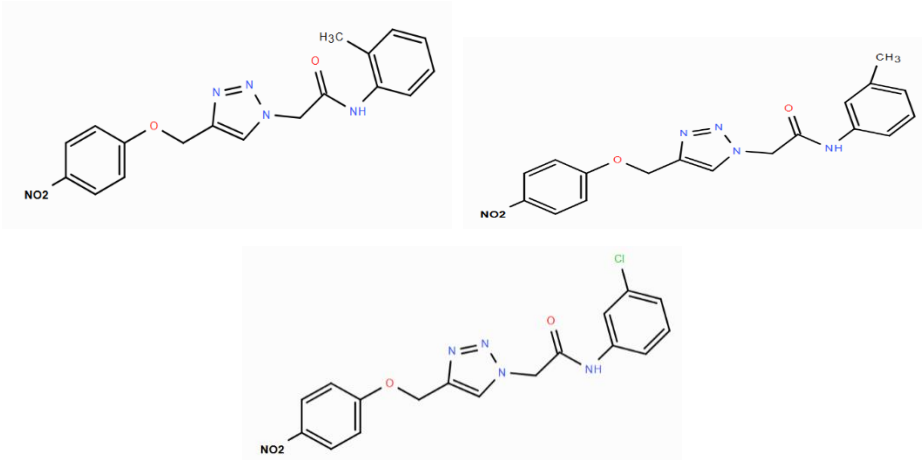


Figure 12. Compounds №20, 21, 22.

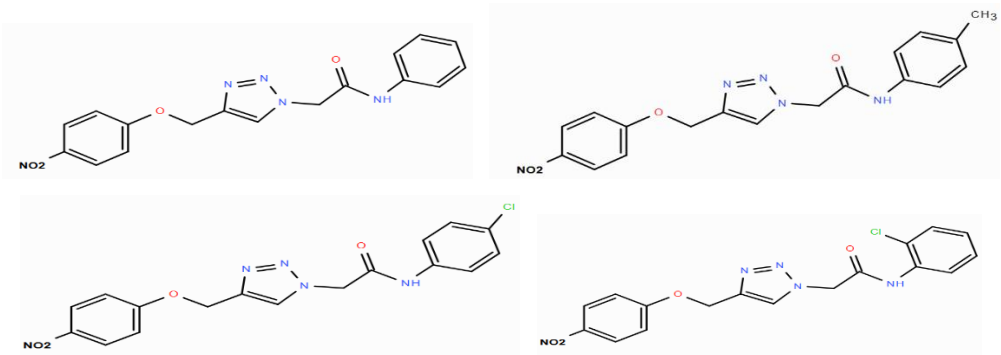


Figure 13. Compounds №23, 24, 25, 26.

P.A.R. Gazolla and their colleagues [11] synthesized twenty two vaniline derivatives with 1,2,3-triazole fragment via click reaction copper-catalyzed alkyne-azide cycloaddition with good yields and tested their antifungal activity against *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans*, *Cryptococcus gattii*, *Trichophyton rubrum*, and *Trichophyton interdigitale* fungi. The minimum inhibition concentrations of these compounds varied between 32 μg mL^{-1} and 512 μg mL^{-1}. With the exception of 3-methoxy-4-((1-(4-nitrobenzyl)-1H-1,2,3-triazole-4-yl)methoxy)benzaldehyde against *C. gattii* R265, all vaniline derivatives have shown themselves to be fungicides. Molecular docking calculations have demonstrated that all compounds bind to the active site of lanosterol 14*α*-demethylase enzyme (binding energies being in the range between –9,1 and –12,2 kcal/mol). Based on the analysis and the calculations, researchers claim that the synthesized compounds have a potential of becoming drugs in the future.

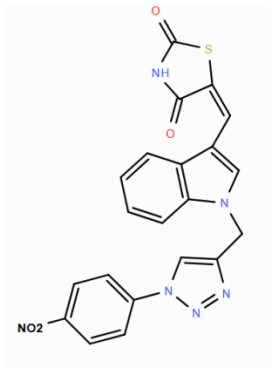


Figure 14. According to Gazolla's article [11], this compound shows minimum inhibition concentration 56 μM against *Ca. Albicans*.

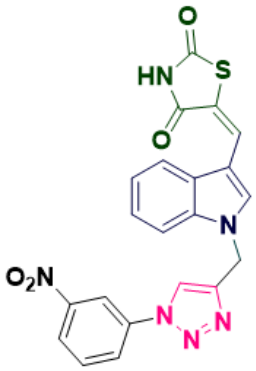


Figure 15. According to Gazolla's article [11], this compound shows MIC=56 μM against *As.niger*.

L. S. de Magalhães and their colleagues [12] synthesized eighteen new glucosyl-1,2,3-triazoles and tested their anti-*Candida* properties. Nine compounds have shown anti-*Candida* potential, and among them the strongest fungicides were 27 (2-[1-(2,3,4,6-tetra-O-acetyl-β-D-glikopyranosyl)-1,2,3-triazole-4-(methyl)oxy]-4-allyl-2-methoxy-benzene) and 28 (2-[1-(2,3,4,6-tetra-O-acetyl-β-D-glycopyranosyl)-1,2,3-triazole-4-(methyl)oxy]-2-methoxy-4-propyl-benzene). The compound № 27, which is the derivative of eugenol, has shown remarkable activity against the three *Candida* strains (26,1–52,1 μM) and was specifically very active against *Candida krusei* (four times stronger than fluconasole). The compound №28, which is dihydroeugenol derivative, has shown activity similar to the compound № 27, and it was four times stronger and less toxic against *C. Krusei* than fluconasole. Respective deacetylated glucosydes and non-glucosylated derivatives didn't demonstrate significant activity, which proves the critical role that acetyl groups play in the anti-*Candida* properties. Molecular docking and molecular dynamics studies, 14*α*-lanosterol enzyme is a valid molecular target for the compounds №27 and 28, because they can be deacetylated and bind to this enzyme. Furthermore, the article emphasizes the importance of hydrophobic substituents in the phenyl ring.

V.K.R. Tangadanchu and their colleagues [13] synthesized isomannide monoundecenoate-based 1,2,3-triazoles via click chemistry method with good yields and tested their activity against *Candida* fungi. Phenyl-substituted №29 and hydroxyphenyl-substituted №30 compounds have shown excellent antifungal properties (MIC=3,9 μg/mL).

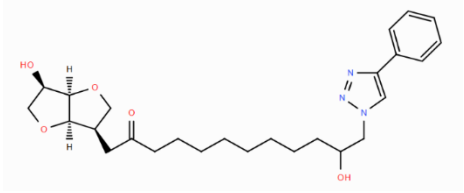


Figure 16. Compound №29

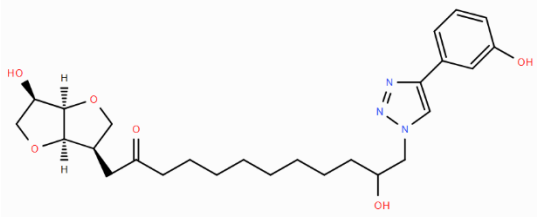


Figure 17. Compound №30

Danne and their team [14] synthesized new 1,2,3-triazole-appended bis-pyrazoles via molecular hybridization and tested their activity against *Candida albicans*, *Cryptococcus neoformans*, *Candida glabrata*, *Candida tropicalis*, *Aspergillus niger*, and *Aspergillus fumigatus* fungi. The best antifungal properties were demonstrated by compound № 31 against *Candida glabrata* (minimum inhibition concentration was 2 μg/mL). Except from the aforementioned compound, the highest antifungal properties were shown against *Candida albicans1* by compounds №32, 33, 34, 35 (MIC=4 μg/mL). Compounds №31 and 36 have shown MIC=8 μg/mL, which is also a good value. Besides these, the MIC=8 μg/mL was demonstrated by compounds № 33 and 36 *C. albicans2*, compound №33 against *C. Neoformans*, compound №34 against *C. Glabrata*. Authors conducted molecular docking study and concluded that the molecules can behave like inhibitors of sterol 14*α*-demethylase. The authors also expressed their conviction that these compounds can be used as antifungal agents in medical research.

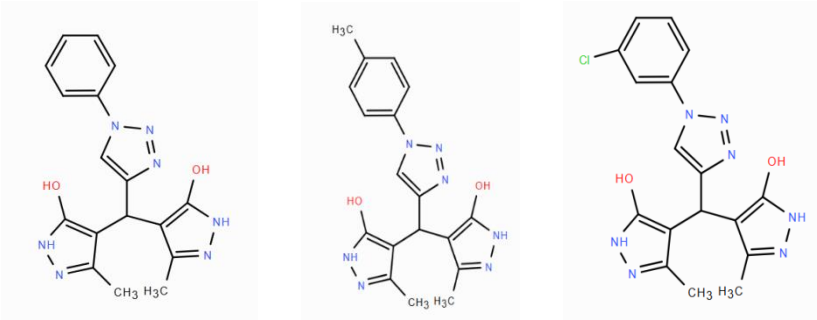


Figure 18. Compounds № 31, 32, 33.

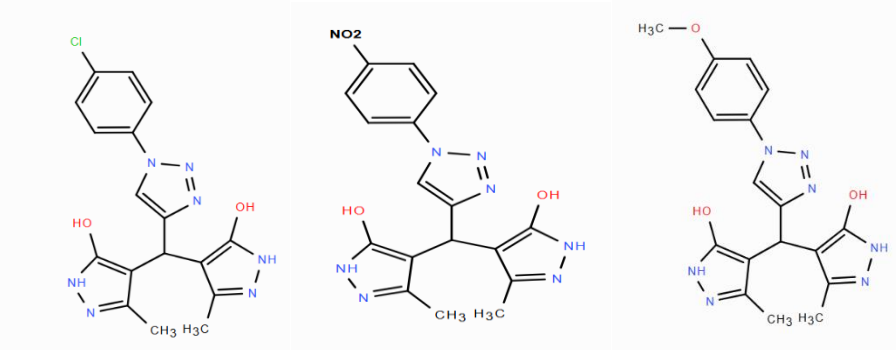


Figure 19. Compounds №34, 35, 36.

Considering all this, 4-azido-2,5-diphenyl-2H-1,2,3-triazole derivatives have been synthesized [15-16]. The presence of a triazole group would lead to antifungal activity in the compounds.

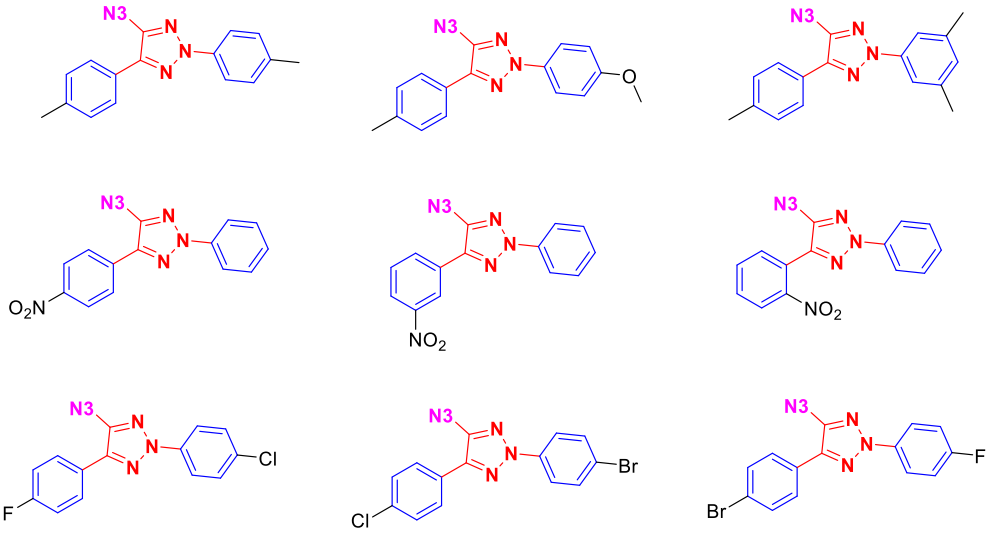


Figure 20. 4-azido-2,5-diphenyl-2H-1,2,3-triazole derivatives

3. Conclusion

In this article, we presented a review of several scientific articles about antifungal properties of compounds containing 1,2,3-triazoles. The MIC values and/or percentage inhibitions for most active antifungals were provided. This review will aid specialists in organic chemistry and mycology who are working on developing new fungicides containing 1,2,3-triazoles.

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