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Heterocyclic Compounds as Antifungal Agents: A Comprehensive Review

Mukhtyar S. Saini

Department of Chemistry, Govt. Degree College, Thathri, Doda, 182203, (J&K) India
Email: *mukhtyarsaini1969[at]gmail.com*

Abstract: ***Fungal infections have emerged as a key universal health concern due to the rising prevalence of immune compromised patients, extensive use of broad-spectrum antibiotics, and the quick appearance of antifungal resistance. Although several classes of antifungal agent are accessible, their clinical efficacy is frequently limited by toxicity, drug combating, poor bioavailability, and a thin spectrum of activity. as a result, the development of novel antifungal agents with enhanced efficacy and protection has become a priority in medicinal chemistry. Among various heterocyclic compounds have involved important awareness because of their diverse biological activities, including antifungal, antibacterial, antiviral, anticancer, anti-inflammatory, and antiparasitic properties. The combination of triazole, oxadizole, thiadiazole and triazolo pyrimidine rings provides only one of its kind physicochemical sorts that make possible strong exchanges with fungal molecular targets, leading to improved biological activity. Many triazolopyrimidine and other heterocyclic derivatives have confirmed compelling inhibitory effects against clinically important fungal pathogens such as* **Candida albicans, Candida glabrata, Aspergillus fumigatus, Cryptococcus neoformans,** ***and a number of plant pathogenic fungi. This review discusses the chemistry, synthesis, structural modification, mechanism of antifungal action, structure–activity relationships, and recent advances in the expansion of heterocyclic-based antifungal agents.***

Keywords: Heterocyclic Compounds; Pyrimidine derivatives, 1,2,4-Triazole; 1,3,4-Oxadiazole; Synthesis; Antifungal Activity; Biological Evaluation; Structure–Activity Relationship (SAR); Medicinal Chemistry; Drug Design

1. Introduction

Fungal infections characterize a growing threat to global public health. Opportunistic fungal pathogens have become increasingly common among patients by way of undermined immune systems, including individuals with HIV/AIDS, cancer, diabetes mellitus, organ transplantation, and those receiving immunosuppressive treatment. Common pathogenic fungi include species of Candida, Aspergillus, Cryptococcus, and a number of dermatophytes that cause superficial and systemic infections, in spite of advances in antifungal chemotherapy, the surfacing of multidrug-resistant fungal strains has drastically reduced the effectiveness of active antifungal drugs.

Currently available antifungal agents belong primarily to four major classes: polyenes, azoles, echinocandins, and allylamines, even though these drugs have improved the management of fungal infections, each class has distinguished restrictions such as nephrotoxicity, hepatotoxicity, drug–drug interactions, fungistatic activity, and increasing divergence. Therefore, there is a continuous need for original chemical entities possessing broad-spectrum antifungal activity, enhanced selectivity, and condensed toxicity.

Nitrogen-containing fused heterocyclic compounds have wide renowned as valuable pharmacophores in medicinal chemistry. Among them, triazolopyrimidines occupy a prominent position because they combine the pharmacological advantages of both triazole and pyrimidine rings into a single molecular framework. This fused heterocyclic system exhibits remarkable chemical stability, favourable pharmacokinetic properties, and the ability to interact effectively with biological macromolecules through hydrogen bonding, π–π stacking, and hydrophobic interactions.

latest studies have confirmed that structural adaptation of the triazolopyrimidine nucleus can extensively improve antifungal potency and selectivity. Introduction of electron-withdrawing substituent's, aromatic rings, heterocyclic moieties, and lipophilic functional groups has formed derivatives with improved activity against a wide range of fungal pathogens. In addition, computational approaches such as molecular docking and quantitative structure–activity relationship (QSAR) studies have facilitated the rational design of more potent triazolopyrimidine-based antifungal agents.

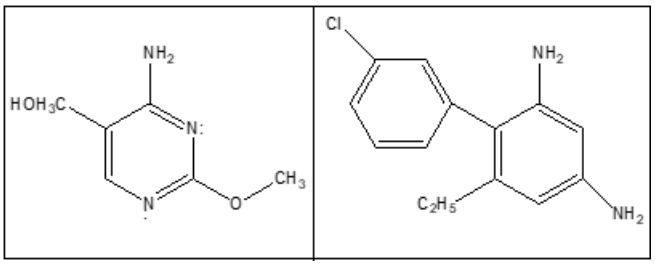
This review summarizes the chemistry, synthesis, biological evaluation, and structure–activity relationships of triazolopyrimidine derivatives reported as antifungal agents. It also places of interest in recent challenges and future information for the development of this talented class of compounds.

Chemistry of heterocyclic compounds:

Triazolopyrimidines are fused bicyclic heterocyclic compounds consisting of a triazole ring condensed with a pyrimidine ring. Depending on the site of ring fusion, a number of structural isomers be there, including [1, 2, 4] triazolo [1, 5-a] pyrimidines, [1, 2, 4] triazolo [4, 3-a] pyrimidines, and [4, 3-c] triazolopyrimidines. These isomers differ in their electronic sharing, molecular geometry, and biological property. The existence of multiple nitrogen atoms imparts large electron deficiency to the heterocyclic system, allow strong exchanges with biological target. The aromatic fused-ring structure contribute to chemical stability, even as the accessibility of multiple substitution sites enable extensive structural diversification for medicinal chemistry applications.

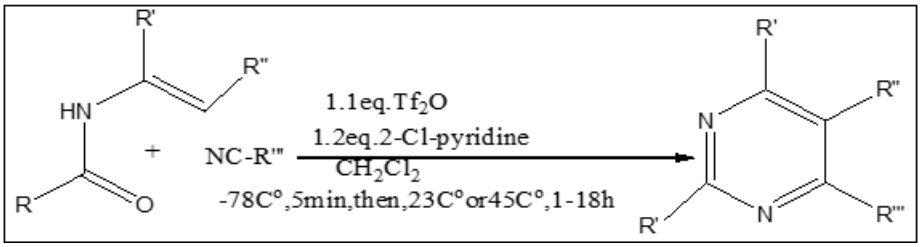
Synthetic Approaches:

Several synthetic strategies have been reported for the preparation of triazolopyrimidine derivatives. The most common methods includes Cyclocondensation of aminotriazoles with β-dicarbonyl compounds, Condensation of aminotriazoles with aldehydes followed by cyclization, Multicomponent one-pot synthesis using suitable aldehydes, ketones, and aminotriazoles, Microwave-assisted synthesis for rapid and high-yield production, Metal-catalyzed cyclization reactions, Green synthetic methods employing environmentally friendly catalysts and solvents. Some pyrimidines of physiologically as well as pharmacologically importance are as under: e.g., cytosine, bedmethrin (1) and trimethoprim (2).



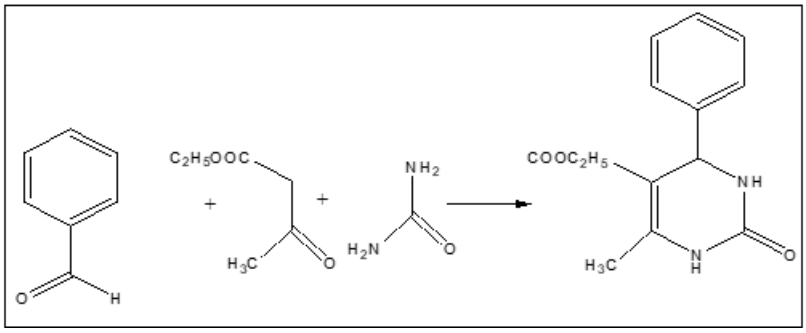
1 2

M. Movassaghi etal [1] have synthesised (3).as below.



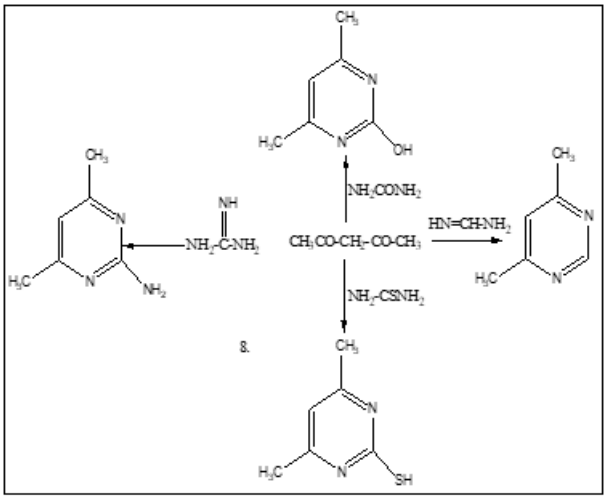
3

Biginelli et al [2] have synthesised (7). Biginelli reaction involves the reaction between an aldehyde (4), a 1,3-dicarbonyl (5) and urea (6) under acidic conditions, which proceeds through a sequence of reactions. The product of this novel one-pot, three-component synthesis is that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1H)-one (7).

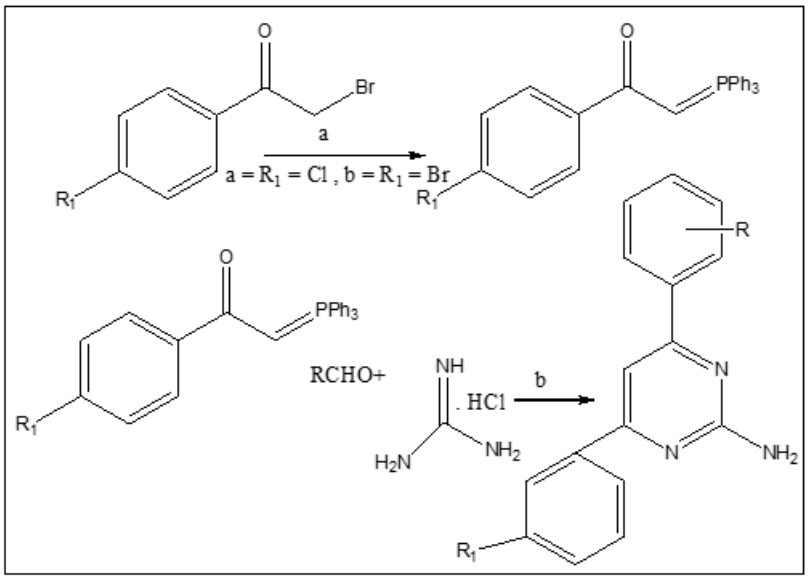


4 5 6 7

The nitrogen containing fragment may be an amidine, urea, thiourea or guanidine and acetyl acetone serves as an excellent illustrative example, it readily under goes reaction with formamidine [3], Guaidine [4], urea [5] or thiourea [6] to produce 4, 6 dimethyl pyrimidines (8).

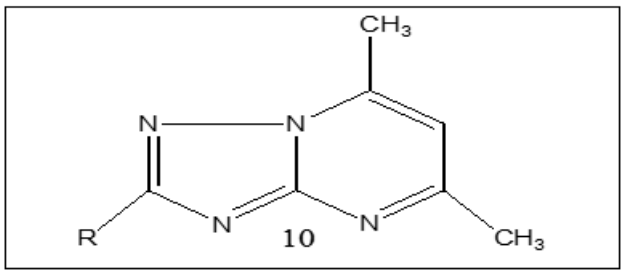


Nguyen DT etal [7-8] have synthesised a series of 4-(4-bromophenyl)-6-phenylpyrimidin-2-amine, 4-(4-bromophenyl) -6 - (4-methoxyphenyl) pyrimidin-2-amine, and 4-(4-bromophenyl)-6-(2, 4-dimethoxyphenyl) pyrimidin-2- amine (9a-c).



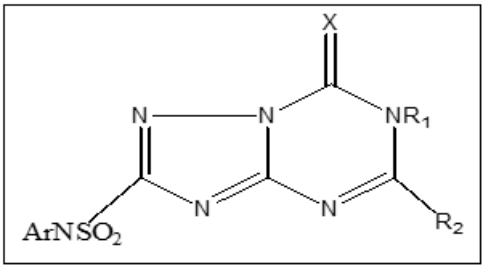
9a R=H, R_1=4-Br 9b R=4-OCH_3, R1=4-Br 9c R=2, 4-OCH_3, R_1=4-Br

V. Ram et al [9] have synthesised triazole substituted triazolo-pyrimidine derivatives. In compound (10), R= pyridyl.



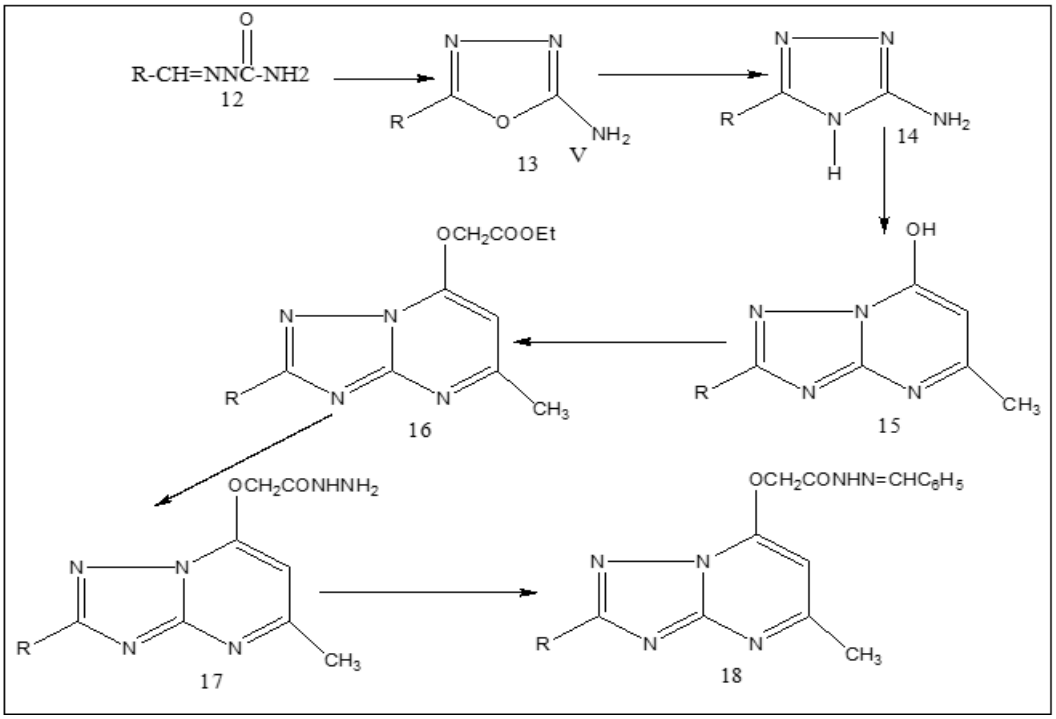
10

Westerman et al [10] have prepared 6,7-dihydro-1,3,4-triazolo-pyrimidine [1, 5-a]-1,3,5-triazin-2-Sulfonamides (11) and found them as agents with herbicidal and plant growth regulting activity. In compound 2. Ar=(un) / substituted Ph, naphthyl, pyridyl; R=H, acyl, alkyl, phenyl-alkyl, (un) substituted carbonyl etc. R_1, R_2= phenyl; X=O, S.



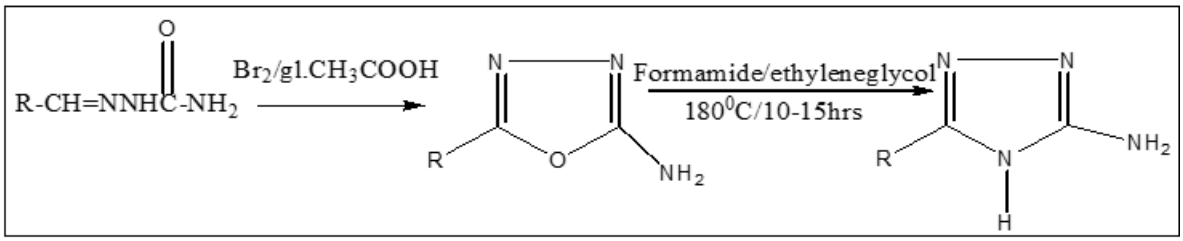
11

A series triazolo-pyrimidine derivatives [11]-[15]. have been prepared (15-18)



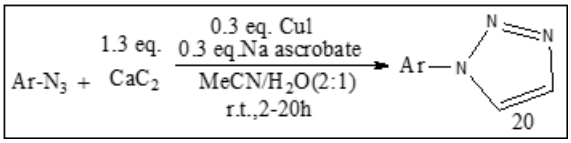
R = Phenyl
R=3, 4, Dimethoxy Phenyl
R=3-Methoxy phenyl
R=4-Hydroxy-3-methoxy phenyl, R=Furfuryl

V. Ram et al [16] have synthesised (19) triazole derivatives as below

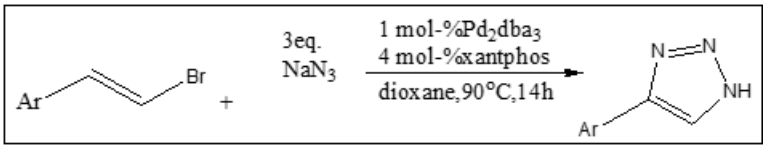


19.

Y. Jiang et al,have synthesised, [17] 1-monosubstituted aryl 1,2,3-triazoles (15) was prepared in good yields using calcium carbide as a source of acetylene. The copper-catalyzed 1,3-dipolar cycloaddition reactions were carried out without nitrogen protection and in a MeCN-H_2O mixture.

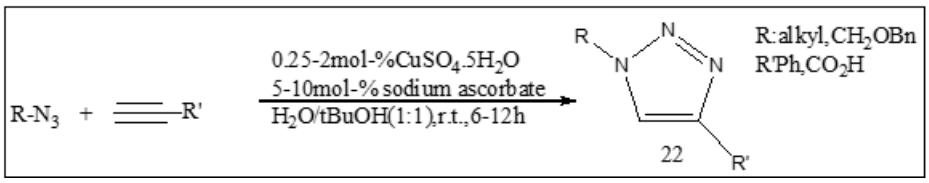


J. Barluenga et al, [18] have synthesised (21). a Pd-catalyzed synthesis of 1*H*-triazoles from alkenyl halides and sodium azide represents a completely new reactivity pattern in the context of Pd chemistry.

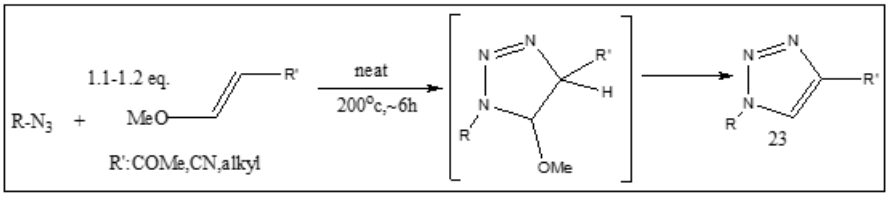


21

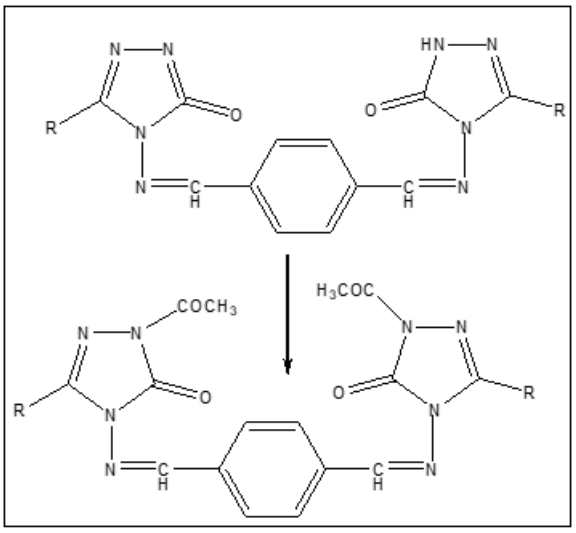
F. Himo et al [19], have synthesised, Cycloadditions of copper(I) acetylides to azides and nitrile oxides provide ready access to (22) 1,4-disubstituted 1, 2, 3- triazoles and 3,4-disubstituted isoxazoles, respectively.

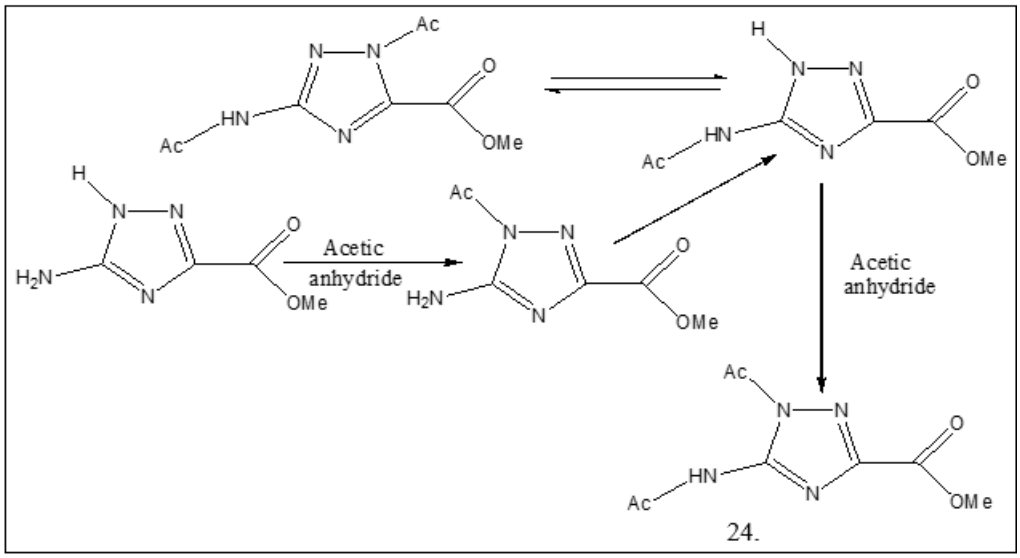


D. R. Rogue et al [20], have synthesised 1,2,3-Triazoles (23), were prepared in good to modest yields by cycloaddition of alkyl azides onto enol ethers under solventless conditions. The reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions and is easily scalable. The 1, 2, 3-triazole products bear functionality that may be readily derivatized.



Rebecca Hluhanich et al[21] ,Ilkay kucukguzel et al [22] summersied acetylation reactions**:** N, N'- bis(3-alkyl-4,5-dihydro-1, 2, 4- triazol-5-on-4-yl)-1,4-xylenediimines undergoes acetylation reaction in presence of acetic anhydride to form N, N'- bis(1-acetyl-3-alkyl-4,5-dihydro-1, 2, 4- triazol-5-on-4-yl)-1,4-xylenediimines **[23],** methyl 5-amino-1H-[1,2,4] triazole-3-carboxylate undergoes acetylation in presence of acetic anhydride (AC_2O) to form two isomeric diacetylated products **[24]**



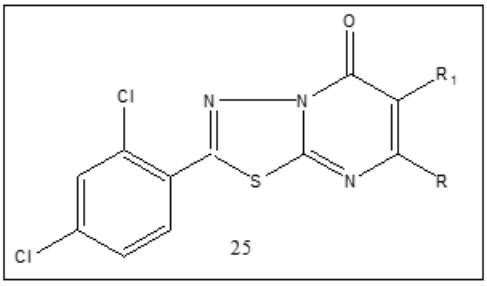


24.

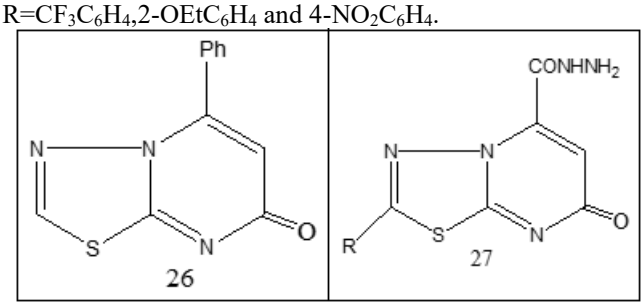
Biological activities:
In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in cytosine, thymine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one of the possible reasons for their activities [25]. eg. Cytosine, Thymine, Uraciland we have concentrated upon antifungal characterization.

Antifungal: Antifungals are the class of drugs that are used to eradicate fungal infections from the human body. Fungi are heterotropic microorganisms that are distinguished from algae by lack of photosynthetic ability. Fungi includes both yeast and moulds.The former are spherical,oval and mucosid colonies in agar medium and the latter consists of elgonated cells that usually reproduce by budding and forming branches of cells.

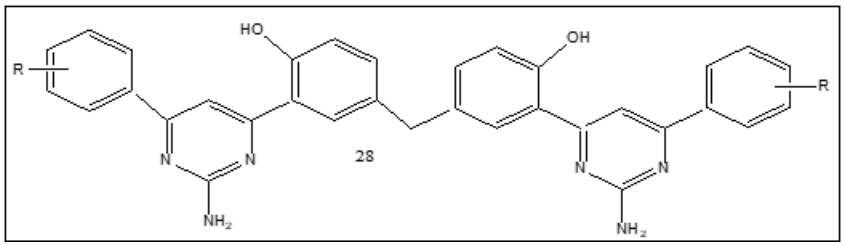
Gogia et al [26] have synthesized 1,3,4- thiadiazolo –(3,2-a) pyrimidin-5-one (25) which shows antifungal activity.



F. Russo et al [27] have synthesized thiadiazolo pyrimidines (26) and their hydrazines (27)
R=$CF_3C_6H_4$,2-$OEtC_6H_4$ and 4-$NO_2C_6H_4$.



Nagaraj A. et al [28]. have prepared compounds (28-29) and found antifungal activity.



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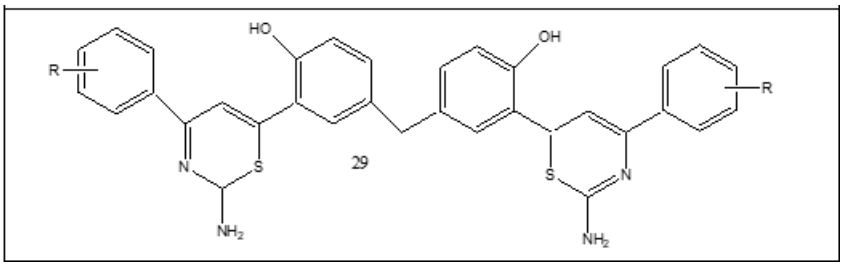
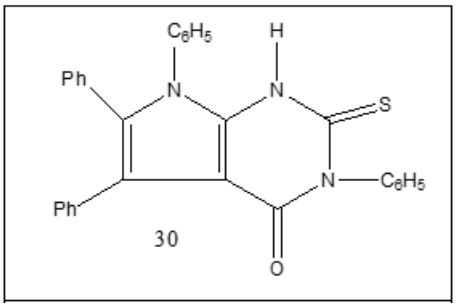


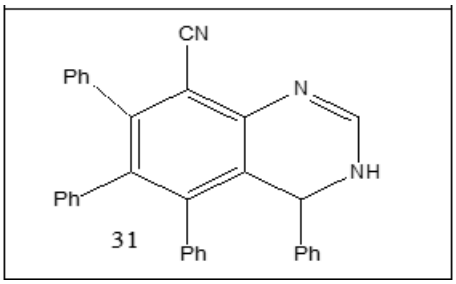
29

Mishra A. D etal [29]. have prepared compounds (30) and found antifungal active agent.



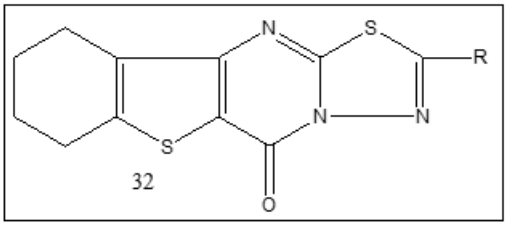
30

Mazaahir Kidwai etal [30]. have prepared compounds (31) and found antifungal active agent.



31

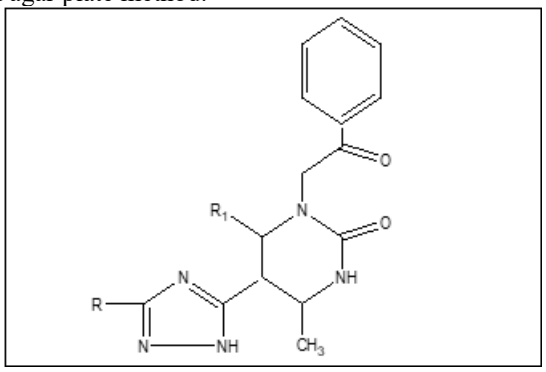
V. Alagarsamy *et al.,* [31] have synthesized some 2 substituted (1, 3, 4) thiadiazole(2, 3-b) tetrahydro-benzothieno [3, 2-e] pyrimidines (32) and then screened for antifungal activities.



32

R= H, CH_3, $NHCH_3$, $(CH_2)_2CH_3$

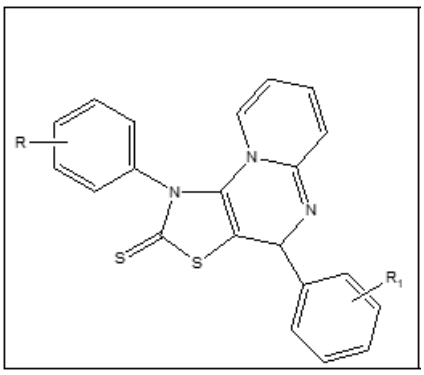
Mishra *et al.,* [32] have synthesized various derivatives of pyrimidines (33). The fungicidal activities of the compound were evaluated against *P. infestans* and *C. falcatum* by the usual agar plate method.



33

R= C_6H_5, p-ClC_6H_4, m-NO2C_6H_4, p-$OCH_3C_6H_4$; R'= m- $NO_2C_6H_4$, p- $OCH_3C_6H_4$

Singh JS *et al*.,[33] synthesized a number of 3,10-diaryl-2-thiothiazolo[4,5-*d*] pyrido [2,1-*b*] pyrimidines and 3,6,9-triaryl-2-thiothiazolo[4,5-*d*][1,3,4] thiadiazolo [2,3-*b*] pyrimidines from the Michael adducts which in turn have been prepared by the reaction of arylidenorhodanines with 2-aminopyridine and 2-amino-5-aryl-1,3,4-thiadiazoles. The antifungal activity of the title compounds (34-35) has been screened and found postive.



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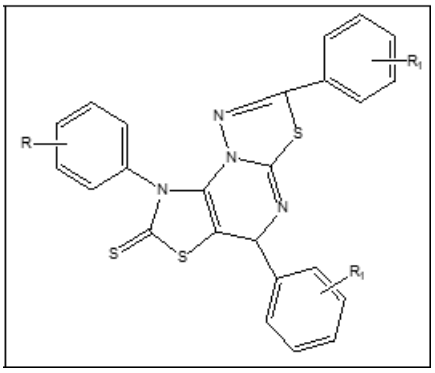


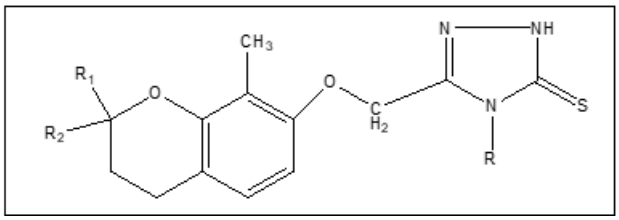
35

Triazolopyrimidine derivatives generally have high aromatic stability, good hydrogen-bonding ability due to multiple nitrogen atoms, moderate lipophilicity depending on substituents and favourable drug-like description that can be optimized during structural modification.

The physicochemical properties of these compounds manipulate their absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, making them prepossessing scaffolds for antifungal drug expansion.

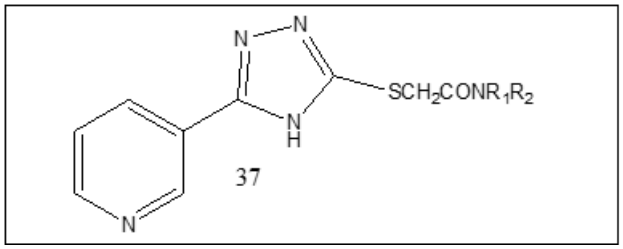
Antifungal activity in case triazoles derivatives: Antifungals are the class of drugs that are used to eradicate fungal infections from the human body. Fungi are heterotropic microorganisms that are distinguished from algae by lack of photosynthetic ability.Fungi includes both yeast and moulds.The former are spherical,oval and mucosid colonies in agar medium and the latter consists of elgonated cells that usually reproduce by budding and forming branches of cells.

Ahluwalia et al,[34] have synthesized (36). 5-(3',4'-dihydro-2',2',8'-trimethyl-2'H-1'-benzopyran-7-yloxymethyl)-4-phenyl-1,3,4-triazole-3(4H)-thiol (III)which shows significant antifungal activity.R=C_6H_5, mcl-C_6H_4, pcl-C_6H_4, m-or pCH_3- C_6H_4, pCH_3O- C_6H_4.R_1=CH_3, C_6H_5, R_2=H, CH_3.



36

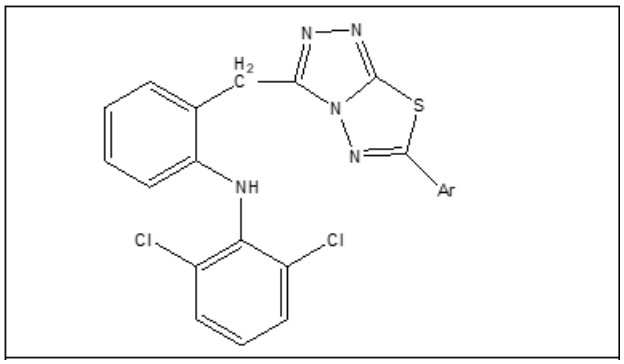
R.K. Mali et al [35] synthesized 5-(N-substituted carboxamidomethylthio)–3-(3'-pyridyl) - 1, 2, 4-triazole (90) derivatives. (37) Anti-fungal activity was carried out against C. albicans and A. niger at the concentrations of 50 and 100 µg/mL using Fluconazole as the standard.



37

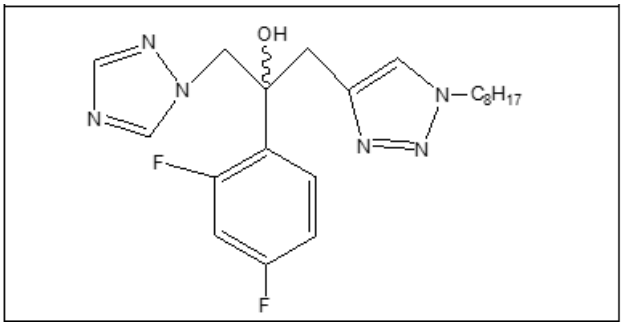
37

K. Ilango et al [36] synthesized a new series of 3, 6-disubstituted-1, 2, 4-triazolo-[3, 4-b]-1, 3, 4- thiadiazoles. The compounds (38) were screened for antifungal activity against Candida albicans and Aspergillus niger using Ketoconazole as standard.



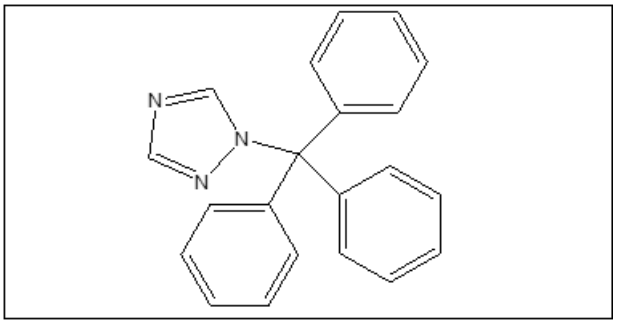
38

Nilkanth G. Aher et al [37] Candida fungal pathogens were impinged by the new triazole derivatives **(39),** analogous to the fluconazole both by in vivo and in vitro. The easily accessible molecules, 1, 4-disubstituted-1, 2, 3-triazole compounds with long alkyl chains displayed a good antifungal activity. It was more potent than the standard drugs namely ketoconazole, amphoterecin B and fluconazole. The enantiomers are still under process as they are supposed to have more potent activity than the racemic compounds.



39

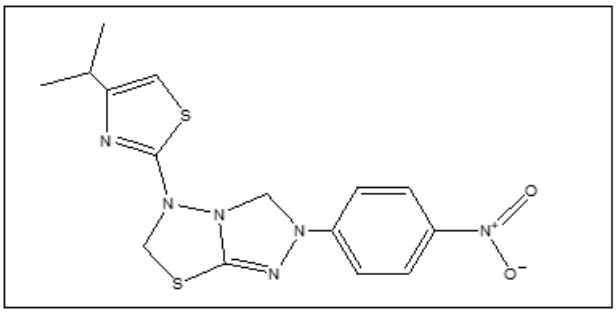
Xiaoyun Chai, et al [38] *fumigatus* was impinged by nearly all type of synthesized compounds and showed broad spectrum activity. The compound **(40)** showed 128 times more activity against *Candida albicans*.



40

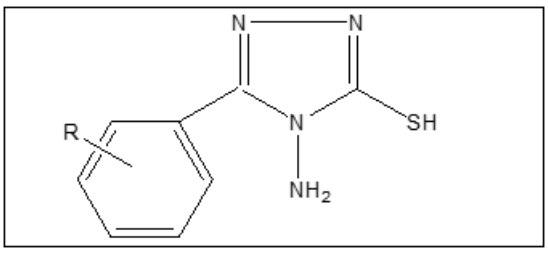
Mitscher LA et al [39], Novel 2- substituted-5-[isopropylthiazole] clubbed 1, 2, 4-triazole were synthesized as potent antifungal agent. The activity was

shown by the compound **(41),** named 3-(4-Isopropylthiazol-2-yl)- 6-(4-nitrophenyl)- [1,2,4] triazolo [3, 4-b] [1, 3, 4] thiadiazole.

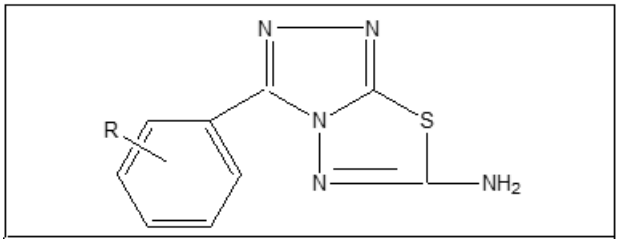


41

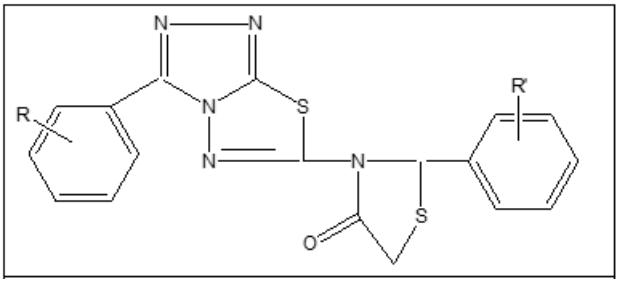
Todoulou O.G et al [40] have evaluated the compounds (42-45). as below and found antifungal.



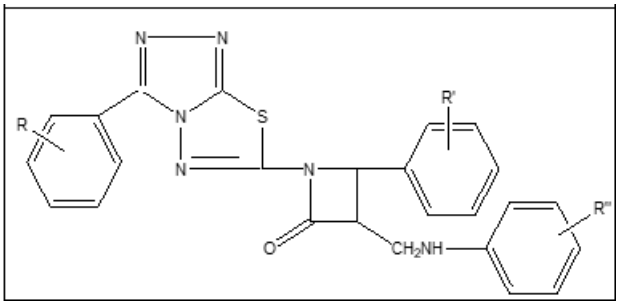
42



43

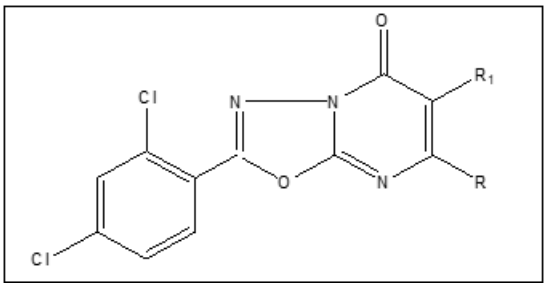


44



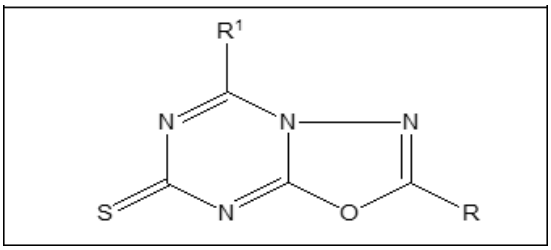
45

Antifungal activity in case of oxadiazole derivatives:
Fungi are heterotropic microorganisms that are distinguished from algae by lack of photosynthetic ability.Fungi includes both yeast and moulds. The former are spherical, oval and mucosid colonies in agar medium and the latter consists of elgonated cells that usually reproduce by budding and forming branches of cells.
Gogia et al[41] have synthesized 1,3,4-oxadiazolo –(3, 2-a) pyrimidin-5-one (46) which shows antifungal activity.



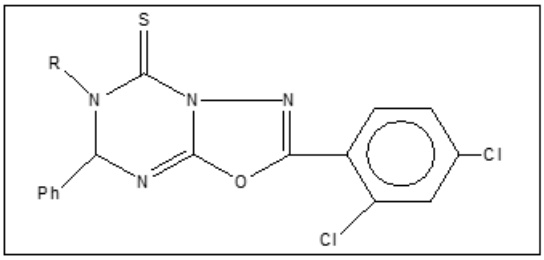
(46)

Singh et al [42] have synthesized 1,3,4-oxadiazolo-(3,2-a)-s-triazin-7-thione (47).and found antifungal.In compound (2), R= C_6H_5 CH_2-, C_6H_5, O-ClC_6H_4, m-MeC_6H_4, p-Mec_6H_4; R^1=C_6H_5, O- ClC_6H_4



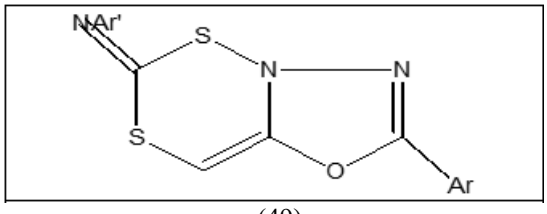
(47)

Dutta et al [43] have synthesized 2-substituted1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazin-5-(6H,7H)-thione derivatives (3) and found antifungal. In compound (48), R= C_6H_5 ,4-BrC_6H_4,4-ClC_6H_4,2-ClC_6H_4,3- ClC_6H_4,2-$No_2C_6H_4$; 3-$No_2C_6H_4$.



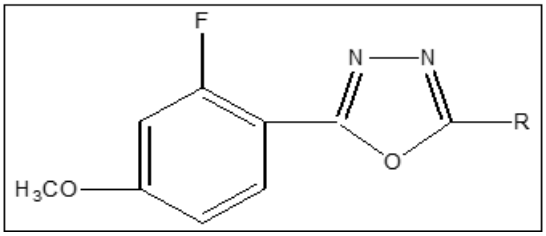
(48)

Dhar et al[44] have synthesized 1,3,4-oxadiazolo-[3,2-a]-1,3,4-dithiazines (49). and found antifungal. In compound (4) Ar=2- ClC_6H_4, Ar'=2- $ClC_6H_4OCH_2$.



(49)

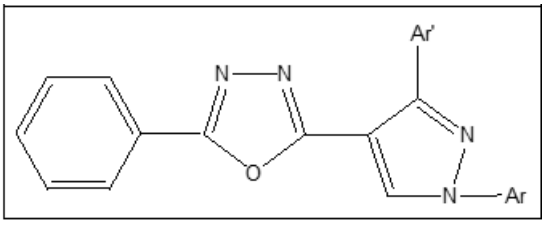
Chandrakantha et. al. **[45]** have synthesised some novel 1,3,4-Oxadiazole bearing 2-flouro-4-methoxy phenyl moiety (50a-50b) and tested for antifungal activity against Candida albicans. Compounds tested for antibacterial activity was compared with standard drug Furacin and for antifungal activity standard drug was Flucanazol.



50

5a: R= 2-Br_5-ClC_6H_5
5b: R= 5-methylisoxazole

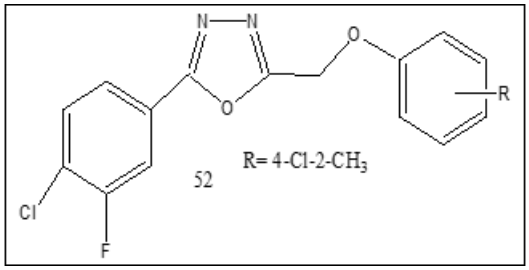
Prakash et. al. [46] have synthesised a series of novel unsymmetrical 2,5-disubstituted 1,3,4- Oxadiazoles (51a-51b) and then tested for their antifungal activities.



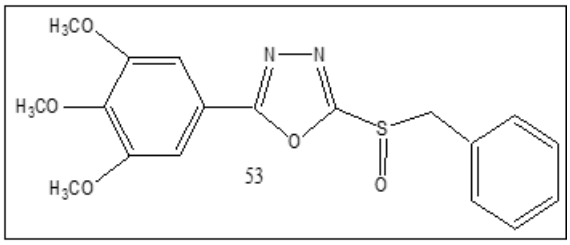
51.

51a: Ar = 4-$NO_2C_6H_5$ Ar'= C_6H_5
51b: Ar = 4-$NO_2C_6H_5$ Ar'= 4-$OCH_3C_6H_5$

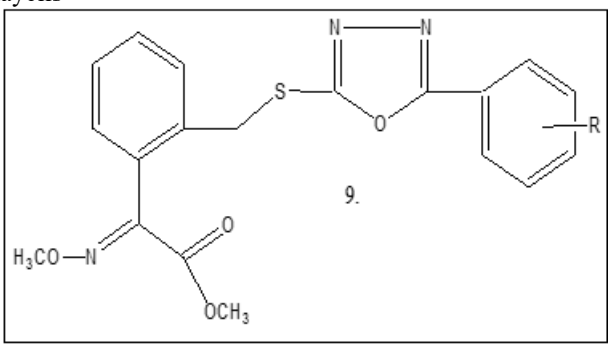
Karthikeyan et. al.[47] synthesized 2,4-dichloro-5-flourophenyl containing Oxadiazoles
(52) and was tested for its and showed good fungicidal activity against Candida albicans, Aspergillus fumigatus and Penicillium marneffei fungal strains and compared with standard drug Greseofluvin.



Liu et. al. [48] have synthesized sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-Oxadiazole moiety (53) and tested for their antifungal activity. Compound 8. was found to be more active against Gibberella zeae, F. oxysporum and C. mandshurica than other ones. Hymexazol was used as standard drug.



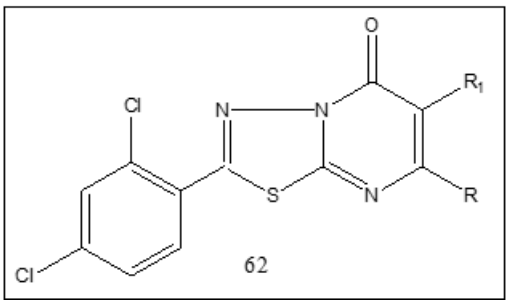
Li et. al. [49] have synthesized (E)-α-(methoxyimino)-benzeneacetate derivatives containig 1,3,4- Oxadiazole ring (54-61) and tested fortheir fungicidal activities. All the compounds(9a-9h) showed potent fungicidal activities against Rhizoctonia solani, Botrytis cinereapers, Gibbereapers zeae, Physalospora piricola and Bipolaris mayclis



54: R= H, 59: R= 2,4-Cl_2
55: R= 4-OCH_3, 60: R= 2,5-Cl_2
56: R= 4-C_6H_5-CH_2O, 61: R= 2,4-Cl_2-5-F
57: R= 3-Cl
58: R=2,3-Cl_2

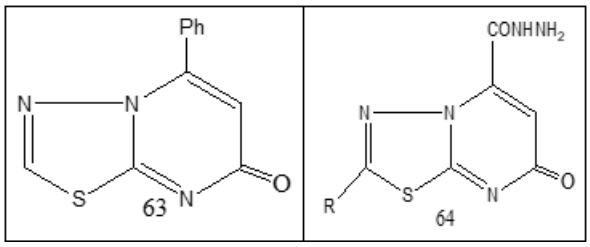
Antifungal in case of thiadiazoles derivatives: Antifungals are the class of drugs that are used to eradicate fungal infections from the human body. Fungi are heterotropic microorganisms that are distinguished from algae by lack of photosynthetic ability.Fungi includes both yeast and moulds.The former are spherical,oval and mucosid colonies in agar medium and the latter consists of elgonated cells that usually reproduce by budding and forming branches of cells.

Gogia et al [34] have synthesized 1,3,4- thiadiazolo – (3, 2-a) pyrimidin-5-one (62) which shows antifungal activity.

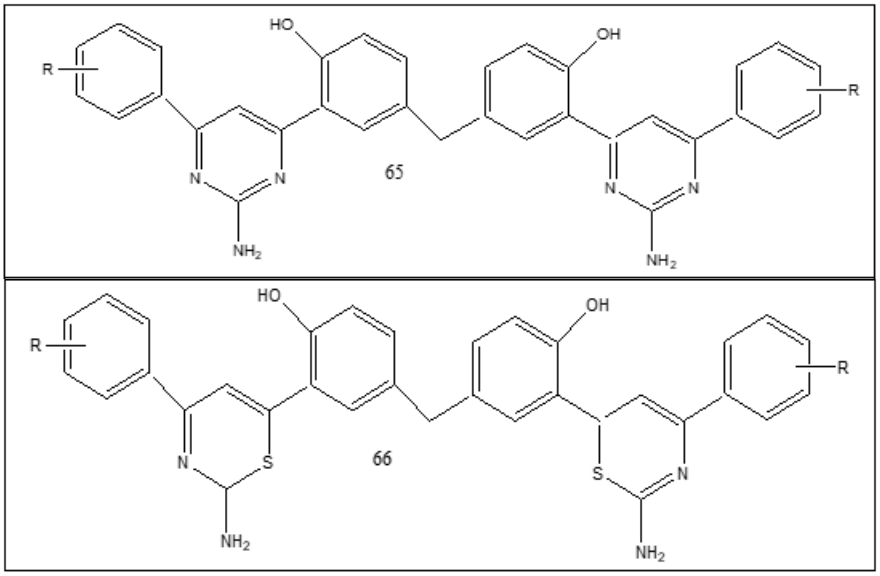


F. Russo et al [50] have synthesized thiadiazolo pyrimidines (63) and their hydrazines (64)

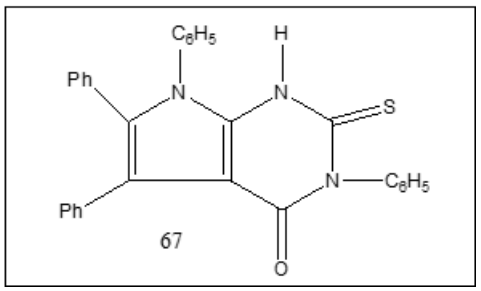
R=$CF_3C_6H_4$,2-$OEtC_6H_4$ and 4-$NO_2C_6H_4$.



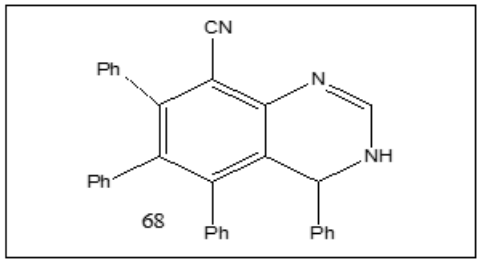
Nagaraj A. etal [51]. have prepared compounds (65-66) and found antifungal activity



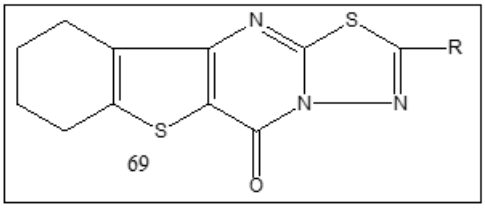
Mishra A. D et al [52]. have prepared compounds (67) and found antifungal active agent.



Mazaahir Kidwai etal [53]. have prepared compounds (68) and found antifungal active agent.

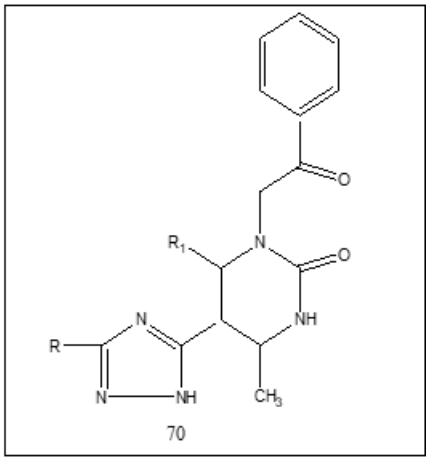


V. Alagarsamy *et al.,* [54] have synthesized some 2 substituted (1, 3, 4) thiadiazole(2, 3-b) tetrahydro-benzothieno [3, 2-e] pyrimidines (69) and then screened for antifungal activities.



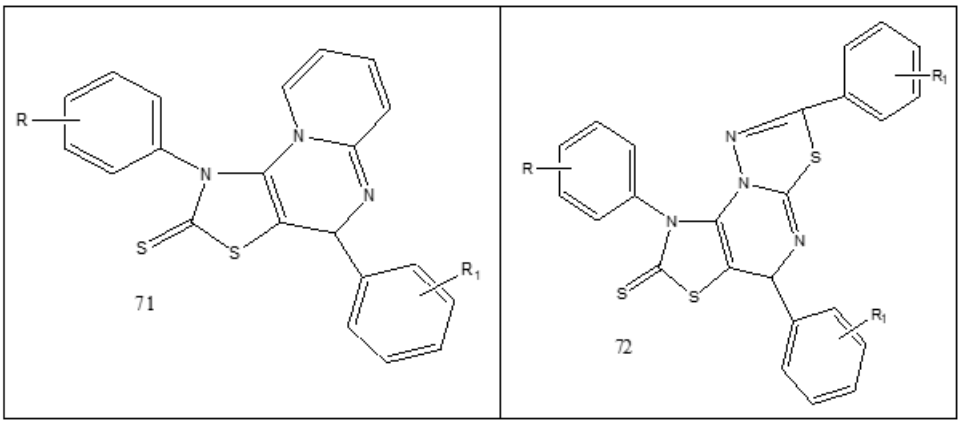
R= H, CH_3, $NHCH_3$, $(CH_2)_2CH_3$

Mishra *et al.,* [55] have synthesized various derivatives of pyrimidines (70). The fungicidal activities of the compound were evaluated against *P. infestans* and *C. falcatum* by the usual agar plate method.



R= C_6H_5, p-ClC_6H_4, m-$NO2C_6H_4$, p-$OCH_3C_6H_4$; R'= m- $NO_2C_6H_4$, p- $OCH_3C_6H_4$

Singh JS *et al*.,[56] synthesized a number of 3,10-diaryl-2-thiothiazolo [4, 5-*d*] pyrido [2,1-*b*] pyrimidines and 3,6,9-triaryl-2-thiothiazolo [4,5-*d*] [1, 3, 4] thiadiazolo [2,3-*b*] pyrimidines from the Michael adducts which in turn have been prepared by the reaction of arylidenorhodanines with 2-aminopyridine and 2-amino-5-aryl-1,3,4-thiadiazoles. The antifungal activity of the title compounds (71-72) has been screened and found positive.



2. Conclusion

Heterocyclic compounds containing pyrimidine, 1,2,4-triazole, and 1,3,4-oxadiazole moieties have attracted considerable attention because of their broad spectrum of pharmacological activities and their importance in modern medicinal chemistry. Numerous studies have demonstrated that pyrimidine derivatives exhibit significant antibacterial, antifungal, anti-inflammatory, and anticancer properties, making them valuable scaffolds for the development of novel therapeutic agents. Similarly, 1,2,4-triazole derivatives have emerged as an important class of heterocyclic compounds with diverse biological activities, including antifungal, antibacterial, antitubercular, anticancer, antioxidant, anti-inflammatory, analgesic, and anticonvulsant effects. Their structural versatility has enabled the synthesis of many novel derivatives with improved pharmacological potential. In addition, 1,3,4-oxadiazole derivatives possess favorable physicochemical properties and have demonstrated promising biological activities such as antibacterial, antifungal, antitubercular, anticancer, anti-inflammatory, and anticonvulsant effects.

Overall, the extensive research conducted on these heterocyclic nuclei highlights their immense potential as lead structures for drug discovery. Continued exploration and structural modification of pyrimidine, 1,2,4-triazole, and 1,3,4-oxadiazole derivatives are expected to facilitate the development of safer, more effective, and highly selective therapeutic agents for the treatment of a wide range of pathological conditions.

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