DIFFERENT HETEROCYCLIC MOTIF AS PROSPECTIVE ANTIFUNGAL: A MINI-REVIEW

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Abstract: **Heterocyclic compounds constitute the largest and most diverse family of organic compounds. Due to extensive synthetic study and their usefulness in synthetic processes, there are already a large number of heterocyclic compounds that are known, and this number is steadily growing. Most scientific disciplines, including medicinal chemistry, agro-chemistry, and veterinary chemistry, depend on heterocyclic compounds that have recently been synthesized or extracted from plants for their use in a variety of pharmacological processes, including antifungal, antibacterial, antioxidant, anti-allergic, herbicidal, anticancer, antimalarial, antidepressant, and immunosuppressive ones. In this review, we mainly discussed the antifungal activity of four different heterocycles i.e. quinoxaline, pyrimidine, isatin, and coumarin showing activity moderate to good.**

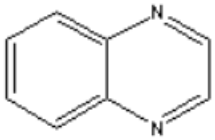
Keywords**: heterocyclic compounds; antifungal; medicinal chemistry**

INTRODUCTION:

Heterocyclic compounds are organic compounds comprised of at least one atom of carbon and atleast one element other than carbon, for example, sulfur, oxygen, or nitrogen within a ring structure. The study of heterocyclic molecule, which make up around 65% of the literature on organic chemistry, is the focus of heterocyclic chemistry [1]. Due to its broad spectrum of activity in a variety of diseases, heterocyclic compounds are recognized as one of the essential types of organic compounds that are used in many biological areas. Biological molecules like DNA and RNA, chlorophyll, hemoglobin, vitamins, and many more contain the heterocyclic ring in the major skeleton [2]. About 50% of all current research on organic chemistry comprises studies on heterocyclic chemicals. The main reason is that heterocyclic structures are somehow the basis of many developed or developing products in different fields including agrochemical, medicinal, and veterinary chemistry [3]. Researchers have considerably dragged their attention toward synthetic compounds that have necessary pharmacological properties and diverted way toward synthetic drugs obtained by making various structural modifications in natural compounds that have similar or superior activity [4].

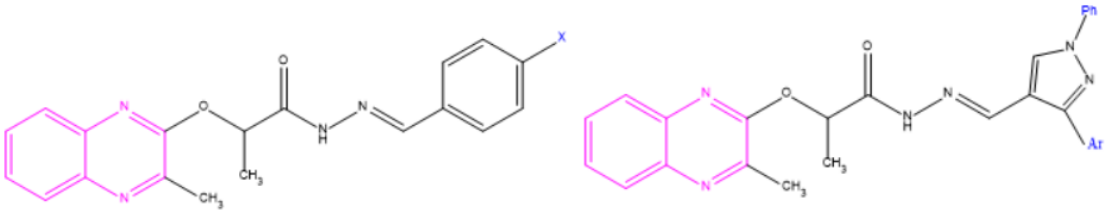
QUINOXALINE

Quinoxaline also known to be benzopyrazines are well-known and important nitrogen-containing heterocyclic compound containing a ring complex made of a benzene ring and a pyrazine ring[5]. Quinoxaline moiety is a bioisostere of the quinoline and naphthalene is one of the attractive candidates in medicinal chemistry[6]. They constitute the building blocks for many natural and synthetic pharmacologically active compounds quinoxaline derivatives [7] [8] possess antiviral, antihistaminic[9], anti-inflammatory[10], and antidiabetic activities[11], [12], antimalarial [13], antidepressant[14], antifungal[15], immunosuppressive activities[16] due to presence of the para-posed double nitrogen of condensed ring of quinoxaline.



A new series of quinoxaline derivatives incorporating N-propionic and O-propionic hydrazide moieties were created by El-shery *et.al.* (2018) and screened in vitro for their expected antibacterial and antifungal activities against sixteen test organisms. Compound 7c is four times more effectively inhibiting the growth of *A.fumigatus* than amphotericin B, twofold as effective as gentamycin in inhibiting the growth of *N. Gonorrhoeae*, equally as effective as ampicillin for inhibiting the growth of *S. pyogenes*, and equally as effective as gentamicin for inhibiting the growth of *P.vulgaris* and *S.flexner*, equipotent of amphotericin B in inhibiting the growth of *A.clavatus*, *G. candidum*, and *P. marnefei* [7].

S.NO.	GROUP	MICROBIAL STRAIN
1.	Gram positive	*Staphylococcus aureus* (RCMB 010027), *Staphylococcus epidermis* (RCMB 010024), *Staphylococcus pyogenes* (RCMB 010015), *Bacillus subtilis* (RCMB 010063), *Enterococcus feacalis* (RCMB 010068);
Reference drug		Ampicillin
2.	Gram negative	*Neisseria gonorrhoeae* (RCMB 010076) ,*Proteous vulgaris* (RCMB 010085), *Klebseilla pneumonia*(RCMB 010093), *Shigella flexneri*(RCMB 0100542), *Pseudomonas aeruginosa* (RCMB 010043)
Reference drug		Gentamicin
3.	Fungus	*Aspergillus fumiga*tes (RCMB 02564), *Aspergillus clavatus* (RCMB 02593) , *Candida albicans* (RCMB 05035) , *Geotrichum candidum* (RCMB05096), *Penicillium marneffei* (RCMB 01267), *Syncephalastrumr acemosum* (RCMB 05922)
Reference drug		Amphotericin B

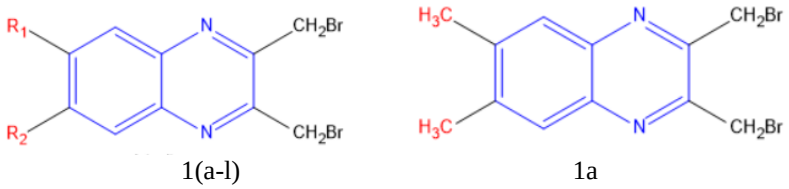


6a, X=H 6d, X=CH_3
6b, X=F 6e, X=NO_2
6c, X=Br

7a, Ar = Ph
7b, Ar = C_6H_4Cl-4
7c, Ar = $C_6H_4(CH3)$-4F

Fig 1: Quinoxaline derivatives incorporating N-propionic and O-propionic hydrazide moieties

Twelve derivatives of 2,3-bis (bromomethyl) quinoxaline was developed by H. Ishikawa *et.al.*(2012), nine of which showed antibacterial activity and eight demonstrated antifungal activity. The minimum inhibitory concentration assay was used for the screening of antibacterial activity against Gram-positive bacteria i.e. Bacillus subtilis (IFO 3513) and S. aureus (IFO 12732); Gram-negative bacteria i.e. *P.aeruginosa* (IFO 3080) and *Serratia marcescens* (IFO 3735); and Fungal strains i.e. *Aspergillus niger*(IFO6341), *Penicillium citrinum* (IFO 6352), *Aureobasidium pullelans*(IFO 6353),*Cladosporium cladosporiodes* (IFO 6348), *Mucor spinescens* (IFO 6071), *Alternaria sps*. and *Gliocladium virens* (IFO 6355), and *Rhodotorula rubra* (IFO 0907) and *Saccharomyces cerevisi*ae (IFO 0209). They laid out that the electron-withdrawing group and lipophilicity of the substituent at the 6-position are prerequisites for high antibacterial activity. They also discussed how the electronic effect of the substituent at the 6-position influences both the breadth of the antifungal spectrum and the degree of activity, and compounds with stronger electron-releasing or withdrawing substituents had better antifungal spectra and activity [17].



1(a-l) 1a

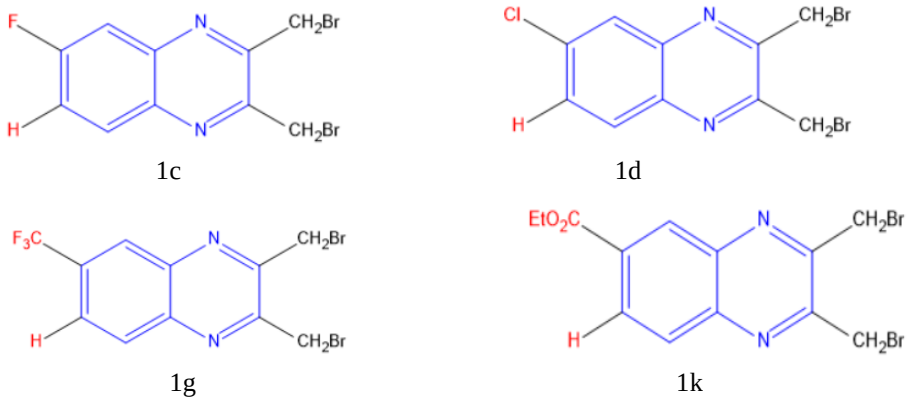
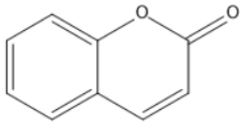


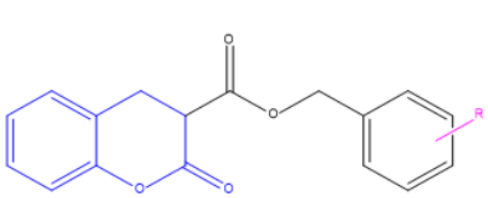
Fig 2: 2,3-bis (bromomethyl) quinoxaline derivatives

COUMARINS

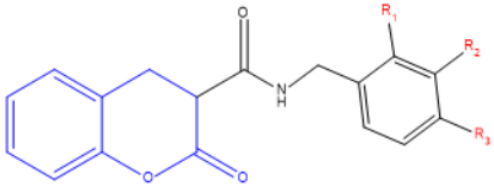
Coumarin compounds are a significant class of natural products and chemical synthesis. The skeleton of coumarin has the structure of a benzene ring and pyrone termed 1,2-benzopyrone, which is found in nature and has a variety of biological functions [18][19]. This moiety is found in nature and has a variety of biological actions; it is known that a wide variety of medicinal plants have significant quantities of coumarins. Coumarin derivatives, both natural and synthetic, have a wide range of biological actions, including inflammatory[20][21], anticancer[22], antioxidant[21][23], anticoagulant[24], antibacterial[25], antiviral [26][27], and antifungal activity[28].



In this study, compounds 1-24 against strains of candida: *C. Albicans* (ATCC 90028), *C. Albicans* (ATCC 60193), *C.tropicalis,C.krusei* (ATCC 13803), *C. krusei*, *C.parasilosis* (ATCC 22019), *C.glabrata* (ATCC 90030) were tested by Alana R ferrira *et.al*. (2022). The bioactivity of the compounds was determined from minimum inhibitory concentration (MIC) values. Compounds 1,3,5,6,8, 16,18, and 20-24 were bioactive against at least one of the tested strains of Candida. Derivative 8, obtained from 7-hydroxycoumarin, presented the best antifungal profile with a strong activity (MIC of 0.067 mol/mL) against *C. Albicans* (ATCC 90028) and *C. tropicalis* (ATCC 13809), moderate activity (MIC of 0.269 mol/mL) agains *C.krusei* (ATCC 6258), and a weak (MIC between 1.07 mol/ml and 2.15 mol/mL) against *C. albicans* (ATCC 60193), *C. parasilosis* (ATCC 22019) and *C. glabrata* (ATCC 90030). Further, according to its MFC values and the MFC/MIC ratio, derivative **8** also exhibited fungicidal capacity against *C. albicans* (ATCC 90028), *C. tropicalis* (ATCC13809) and *C. krusei* (ATCC 6258). In this review, we are showing some of the target compound coumarin derivatives showing antifungal properties[29].



[9] R=H
[10] R=p-OCH_3
[11] R=m-OCH_3
[12] R=p-CH_3



[13] R_1=R_2=R_3=H
[14] R_1=R_2=H, R_3=OCH_3
[15] R_1=OCH_3, R_2=H, R_3=OCH_3
[16] R_1=H, R_2=R_3=OCH_3

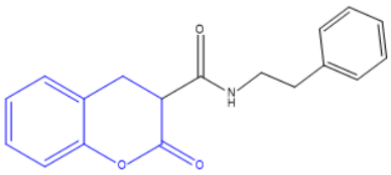


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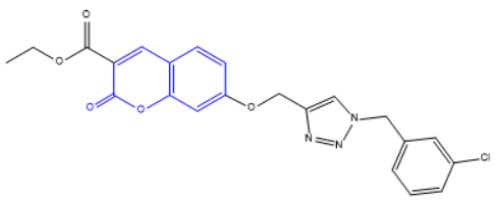
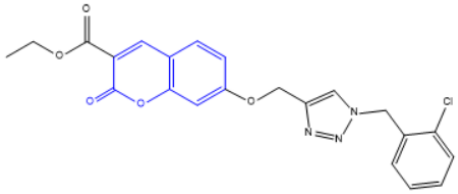
Fig 3: Different coumarin derivatives

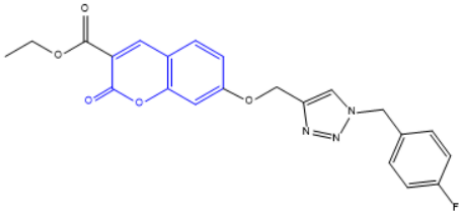
B.B. Shingate et.al produced eight derivatives 8a-h, of coumarins conjugated with 1,2,3-triazole moiety and proved that these compounds possess antifungal activity against five human pathogenic fungal strain *Candida albicans*(NCIM3471), *Fusarium oxysporum* (NCIM1332), *Aspergillus flavus* (NCIM539), *Aspergillus niger* (NCIM1196), and *Cryptococcus neoformans* (NCIM576), and compare evaluated results with fluconazole, miconazole and antioxidant activity, by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay and the results were compared with standard synthetic antioxidant BHT (Butylated Hydroxy Toulene). Compound 8a shows potential antioxidant activity (IC_{50} = 15.20 µg/Ml) when compared with standard BHT. Compound **8d, 8e,** and **8f** displayed significant antifungal activity as compared with the standard antifungal drug[30].



8d



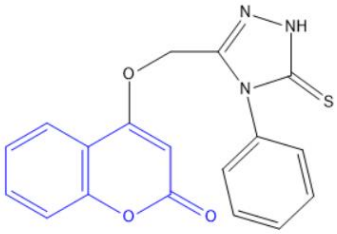
8e



8f

Fig 4: Derivative of Coumarin conjugated with triazole nucleus

In 2012 Al-Amiery *et. al.*synthesized new coumarins (2-7) and also performed in-vitro testing of the investigated compound 5 and 7 shoes good antifungal potency in comparison with the fluconazole i.e. reference drug[31].



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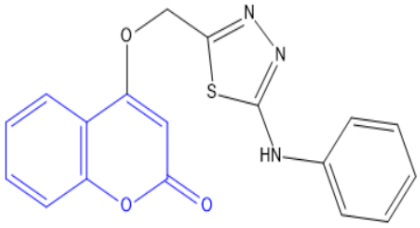

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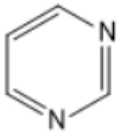
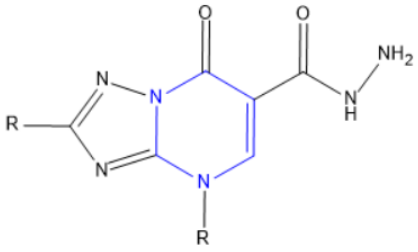
Fig 6: Coumarin derivative 5, 7 with antifungal potential

PYRIMIDINE

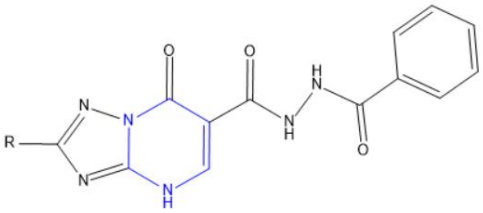
Pyrimidine which is an integral part of DNA and RNA, attracted attention as their derivative coincides with important biological activities[32], such as antifungal[33], antibacterial[34], insecticidal[35], and Herbicidal[36]. Many pyrimidine derivatives are known to exhibit antitumour[37], antimalarial[38], anti-oxidant[39], anti-mitotic[40] and anti-HIV activities[41] .



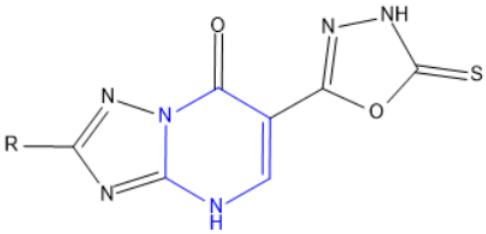
R.F. George *et.al.* (2019) designed twenty-six, 1,2,4-triazolo[1,5-a] pyrimidine derivatives and tested for the antibacterial activity against five bacterial strains *E. coli, K.pneumoniae, A. baumannii, P.aeruginosa* (Gram-negative) and Methicilin Resistant activity against two fungal isolates *C.albicans and C. neoformans* was performed using fluconazole as a positive control as well as their safety profile. They also revealed that many of the synthesized compounds were safe having no cytotoxicity against human embryonic kidney and red blood cells at concentrations up to 32 μg/mL[42].



6a, R=H, R1=$CH_2C_6H_5$
6b, R=CH_3, R1=$CH_2C_6H_5$
7a, R=R1=H
7b, R=CH_3, R1=H



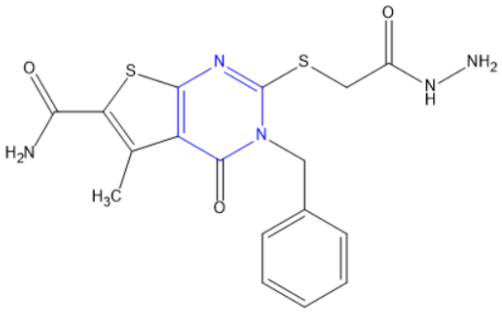
9a, b, R=H, CH_3



10a, b
R=H, CH_3

Fig 7: 1,2,4-triazolo[1,5-a] pyrimidine derivatives

A series of substituted 3,4-dihydrothieno [2,3-d] pyrimidines were synthesized by O.G. Shaaban *et.al.* in 2019. The preliminary test for their *in-vitro* activity against six bacterial and three fungal strains using the agar diffusion technique was done in the series of newly synthesized compound[43].



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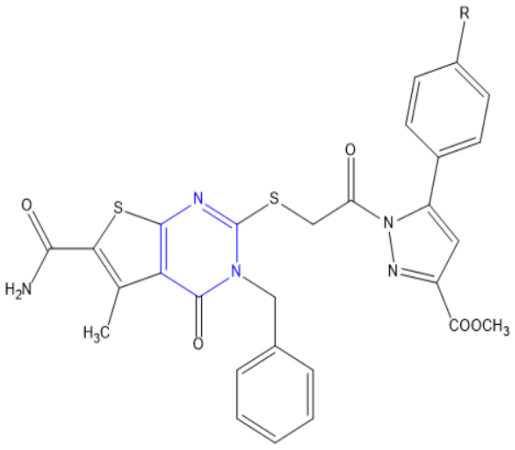
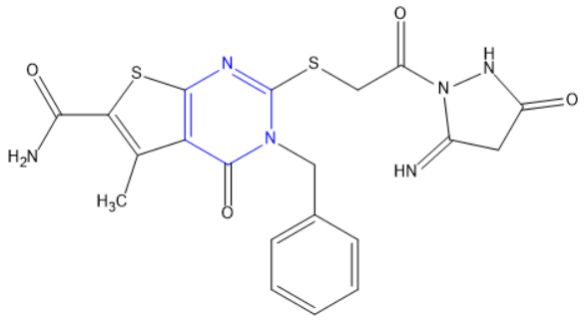


5a, b
a: R=H b: R=CH_3



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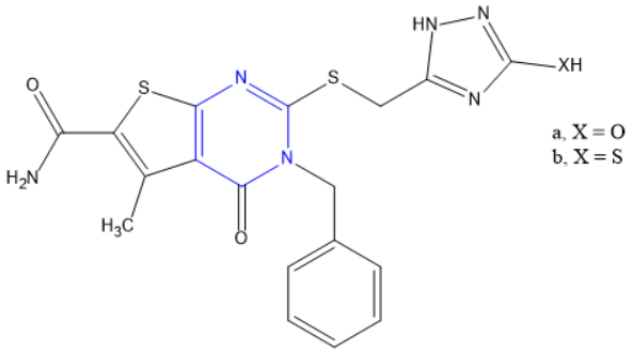
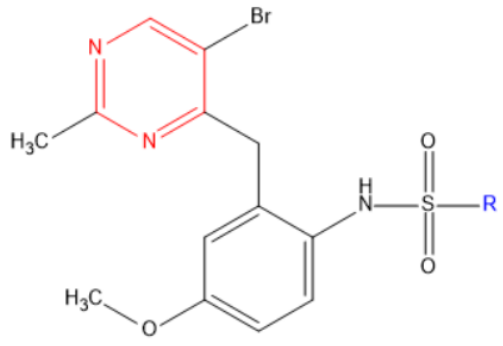


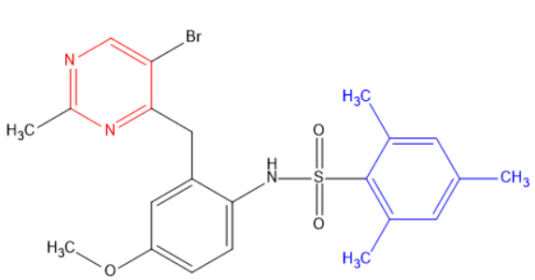
8a, b

Fig 8: Substituted 3,4-dihydrothieno [2,3-d] pyrimidine derivatives

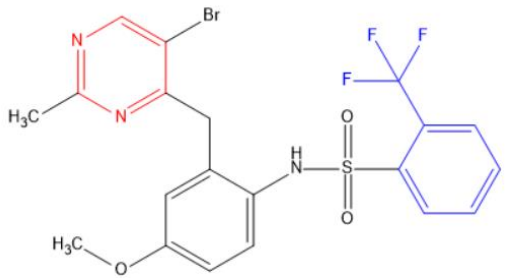
In 2017, C. Mallikarjunaswamy *et. al.* synthesized nine novel series of pyrimidine derivatives mainly novel 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine and screened their *in-vitro* antibacterial activity against four bacterial strain i.e. Gram-positive bacteria (*Bacillus substilis* MTCC 121, Staphylococcus aureus MTCC 7443) and Gram-negative bacteria (*Xanthomonas campestris* MTCC 7908) and *Escherichia coli* MTCC 7410) by comparing with the bacteriocin and gentamycin as reference standard drug and antifungal activity against *Fusarium oxysporum* MTCC 2480 by comparing with nystatin as reference standard drug[44].



4a-i



4a

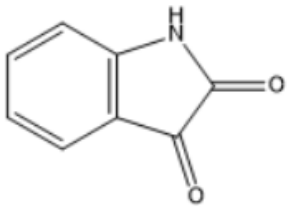


4e

Fig 9: Different pyrimidine derivatives with antifungal potential

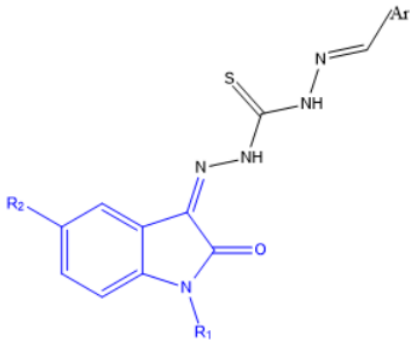
ISATIN

Isatin possesses an indole ring structure [45], common to many pharmaceuticals and heterocyclic natural products of biological interest. Its derivatives have shown important biological activities such as antimicrobial [46], anti-inflammatory [47], anti-viral[48], antihelminthic [49], and antiprotozoal activities[50]. It has wide spectrum activity due to its skeleton being widely used in drug discovery. Isatin moiety has been used by many researchers by taking advantage of - NH- at the position, C2 and C3 carbonyl position for the synthesis of various derivatives possessing different biological activity[51].



T.M Gabr *et.al* 2018 have synthesized a new series of isatin-β-thiocarbohydrazone hybrids possessing numbering from 4-17 which rely on isatin moieties showing antifungal activity, antibacterial activity against *Aspergillus fumigatus*, *Candida albicans* (fungal isolate), and S.aureus, B. cereus and E.coli compared with the standard drug Fluconazole and Ampicilin respectively. Referring to antifungal effectiveness, compound 14 exhibited the highest antifungal efficacy toward *A.fumigatus* and *C.albicans*. Furthermore, 5 and 12 demonstrated eminent activity against *A.fumigatus*, whereas 4,7,9,11,13,15, and 16 exhibited moderate efficacy over the same fungus.

In addition, 6 and 9 displayed moderate activity over *C.albicans*. All the analogues of the series having IC_{50} value > 50µM over the both cell lines used in the study, hence they are considered safe analogues. Taken together, 5,6,12,13, and 14 may be used as efficient antifungal agents with decreased hazard of antimicrobial resistance and decreased cytotoxicity[52].

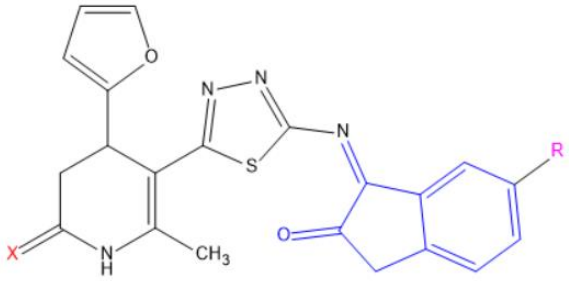


R_1=H Ar = varying
R_2=CH_3

Fig 10: Isatin-β-thiocarbohydrazone hybrids

In 2012, Akhaja *et.al.* modeled target compound 4a-I hybrid on the isatin, tetrahydro pyrimidines, and thiadiazole moieties in a single entity by using the concept of pharmacophore hybridization for the screening of antibacterial, antifungal, antitubercular activity. These target compounds were evaluated for their in vitro screening of antibacterial and antifungal using standard procedures against the representative gram-positive and gram-negative organisms. And also compared the MIC values of the target compound 4a-l with antibiotics, Griseofulvin, Nystatin for inhibitory action.

They confirmed that 4a, 4b, 4f, 4j, and 4l exhibited excellent activity against all tested microbial and fungal strains, while compounds 4d and 4 h displayed comparable activity against gram-positive strains, while compounds 4e and 4k were found to be moderate active against gram-negative as compared to standard antibiotics. In-vitro anti-tuberculostic activity was also determined by using lowenstein-jansen medium (conventional method) of all the newly synthesized target compounds against *M. tuberculosis* H37Rv strain was determined[53].

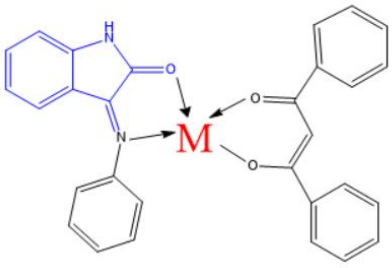


X= O/S R= H, Br, NO_2, F, I and Cl

Fig 11: Derivative of molecular hybrid (isatin, tetrahydro-pyrimidines, thiadiazole moieties)

O.A. Dar *et.al.*, 2019 produced a series of isatin-based mixed ligand complexes of [Cu (dbm) $LClH_2O$] (mlc1), Co (dbm) LCl2]-(mlc2) and [Ni(dbm)$LClH_2O$](mlc3) and evaluated their antifungal activity alone and in combination with fluconazole (FLC) against seven different Candida albicans strains. The order of potency of the compound (mlc3>mlc2>mlc1>L) based on MIC value obtained from standard procedure of CLSI of the invitro antifungal susceptibility testing of Candida species. They also evaluated fragmentation and visualized it with the help of TUNEL assay by labeling 3'OH ends of nicked DNA with fluorescent dUTP (TUNNEL-FITC) to investigate whether the series of newly synthesized compounds display features of the late stage of apoptosis as an insight of mechanism action in strains of candida albicans.

The MIC data values revealed that the transition of structural changes from ligand to its metal complexes produced a marked enhancement in their potency as antifungal agents and also concluded that mlc3, has more potential than the other two complexes to be used as an antifungal drug and significant potentiators in combination with known antifungal agent fluconazole in mediating fungal cell death by inducing apoptosis. Further investigations would result in a strategy that would lead to the development of novel antifungal agents that switch on endogenous cell suicide mechanisms and therefore pass the development of drug resistance[54].



M= Ni, Co, Cu

Fig 12: Isatin-based metal complexes

CONCLUSION

Heterocyclic compounds constitute the largest family of organic compounds. These are extremely important with a wide array of synthetic, pharmaceutical, and industrial applications. The increasing development of bacterial and fungal resistance to the already available traditional antibiotics has created an important need to elaborate new antimicrobial agents. The developed drugs should possess novel modes of action and/or different cellular targets. As a result, new classes of compounds, including quinoxaline, pyrimidine, isatin, coumarin, and heterocycles designed to avoid defined resistance mechanisms are undergoing pre-clinical and clinical studies.

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