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Overview of Recent Developments of Indole Derivatives as An Antimicrobial Agent

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ABSTRACT

The global difficulty of microbial resistance has attracted researchers due to the lack of availability of potent antimicrobial agents against the evolving various new antimicrobial resistant microbial strains. The indole moiety fascinated the interest of researchers because of its diverse biological and pharmacological activities *viz.* antifungal, antibacterial, antiviral, antidiabetic, anticancer, antitubercular, anti-inflammatory, antipsychotic, and antioxidant activities. This review focuses on the antimicrobial activities of the various indole derivatives in detail and the information presented in this review may help in the drug design and development of the more effective antimicrobial agents bearing indole moiety.

INTRODUCTION

Antimicrobial agents are very important in minimizing the effect of infectious diseases all over the globe. It is becoming a health threat because of the exposure and spreading of multidrug-resistant (MDR) strains of pathogenic bacteria as there are very few antimicrobial agents are present for the infection caused by this bacterial strain **Luitel *et al.* (2019).** In recent years researchers have been highly triumphant in the improvement of the scaffolds of the previously available antibiotics**.**

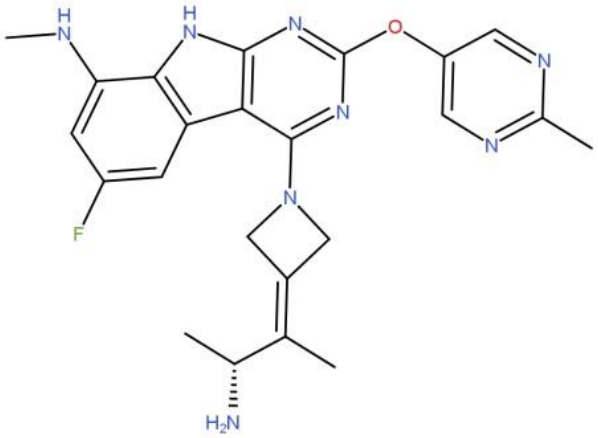
The heterocyclic compounds are the cyclic ring compounds composed of elements other than carbon, where the most frequent substituents are Oxygen (O), Nitrogen (N), and Sulfur (S). Indole accommodates the benzenoid nucleus and has 10 π-electrons which results in its aromatic nature. Indole derivatives comprise several therapeutic activities, some of these therapeutic activities include antiviral, anti-inflammatory, antimicrobial, anticancer, anti-HIV, antitubercular, antioxidant, antidiabetic, antimalarial, anticholinesterase activities, etc. **Kumar*et al.* (2020).**

[1]

Antimicrobial Activities

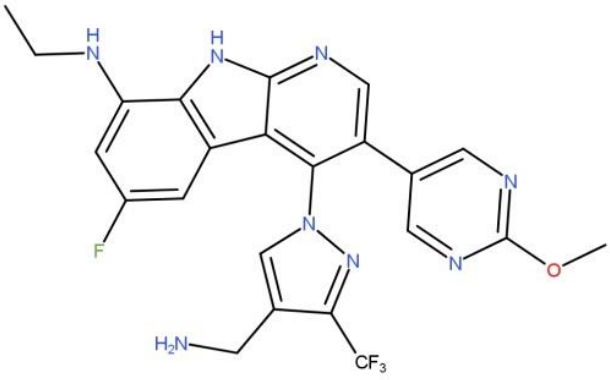
Indole derivatives are important and broadly knowns chemical compounds that contain a basic indole heterocyclic nucleus. A slight change in the substitution pattern in the indole nucleus shows the recognizable difference in their pharmacological activities. Literature survey of recent studies done on indole derivatives indicates that they have antimicrobial activities like antibacterial, antifungal, anticancer, and antitubercular activities which have been briefly epitomized as below.

Kong *et al.* (2021) Novel pyrimido[4,5-b]indole derivatives based on the tricyclic scaffold were prepared and shows the potent antibacterial against both gram-positive and gram-negative bacterial strain but were limited by hERG inhibition and shows poor pharmacokinetics profile.



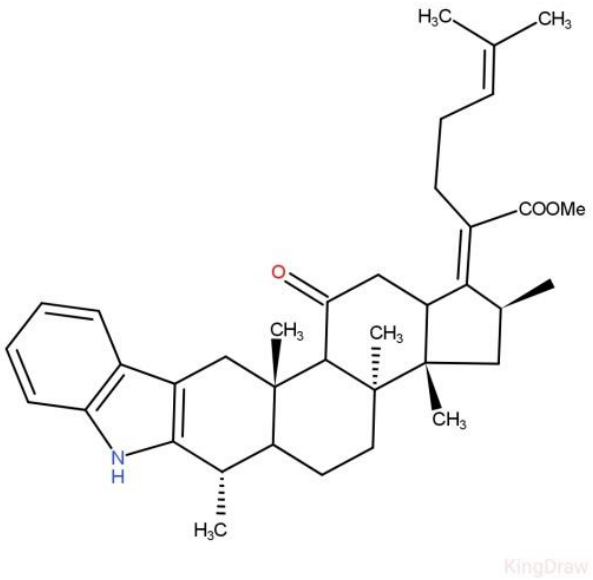
[2]

Hu Yimin *et al.* (2020) 4-[4-(aminomethyl)-3-(trifluoromethyl)-1H-pyrazol-1yl]-N-ethyl-6-fluoro-3-(2-methoxypyrimidin-5-yl)-9H-ptrido[2,3-b]indol-8-amine was prepared and its antibacterial activity was evaluated gram-negative bacterial strain which shows the highly potent activity, high aqueous solubility, and desirable PK features. The bactericidal efficacy was shown on the neutropenic mouse thigh injection model.



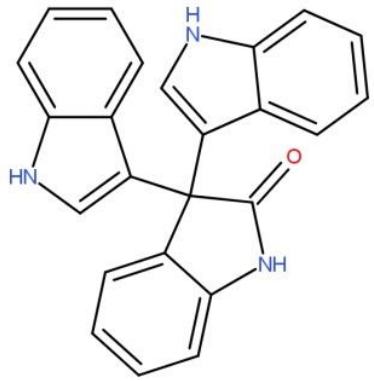
[3]

Salimova *et al.* (2020) New indole derivatives of fusidic acid were synthesized through Fischer reaction and they were further evaluated for their antibacterial activity against *S. aureus*(MRSA) and the result showed the potent antibacterial activity.



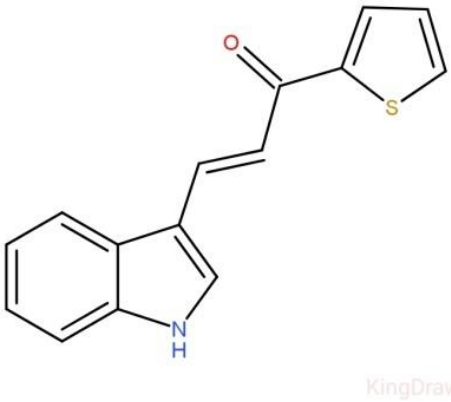
[4]

Lavrenov*et al.* (2020) Novel 3,3-bis(indol-3-yl)-1,3-dihydroindol-2-one derivatives were synthesized and they were further studied for their biological activity. The result exhibited high in vitro cytotoxic activity on human tumor cell lines and lower cytotoxic activity on donor human fibroblasts.



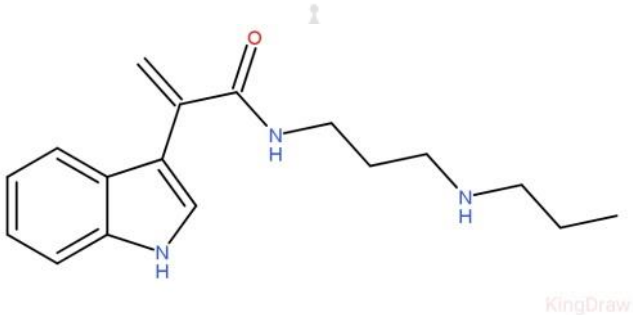
[5]

Ramesh *et al.* (2020) A series of novel indole chalcones were synthesized and evaluated against $H_{37}Rv$ strain of *Mycobacterium tuberculosis.* The test result showed high antitubercular activity and cytotoxic screening depicted that, the synthesized compounds were non-cytotoxic to human megakaryocytes and murine B cells.



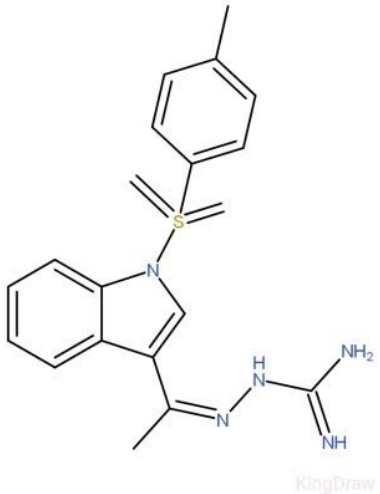
[6]

Cadelis *et al.* (2019) A series of substituted di-indolglyoxyamido- spermine derivatives were synthesized and screened for their antimicrobial activity against gram-positive bacteria and gram-negative bacteria (*P. aeruginous* and *E. coli*) and antifungal activity against *Cryptococcus neoformans.* The result showed modest activity towards the gram-negative bacterial strain.



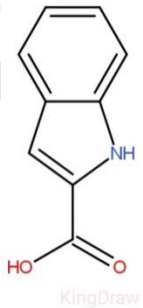
[7]

Song *et al.* (2019) Thirty-six N-arylsulfonyl-3-substituted indole derivatives were synthesized by putting together, N-aryl sulfonyl indoles with aminoguanidine, semicarbazide, and thiosemicarbazide, respectively. The synthesized compounds were further evaluated for their antibacterial and cytotoxic activities. The test results exhibit that, the aminoguanidines showed much better antibacterial activity than semicarbazides and thiosemicarbazides.



[8]

Cury *et al.* (2019) A series of novel 3-substituted and 3,6-disubstituted-2-carboalkoxy indoles were synthesized and further evaluated for their mechanism of action and in vivo antileukemia efficacy. 3-substituted-2-carboalkoxyindoles were synthesized by two Heck arylations of methyl acrylate and methyl cinnamates. One of the synthesized compounds showed good activity and selective cytotoxicity against leukemia cells.

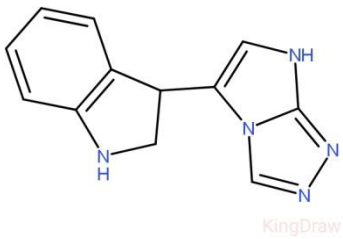


[9]

Li Zhen *et al.* (2019) Novel enone-bridged indole nitroimidazole scaffold was prepared and the antibacterial activity was observed on MRSA membrane (MIC= 1µg/mL). The bioassay of **10**compound shows that it permeates the MRSA membrane and bind with penicillin-binding protein. The introduction of metal ions in the synthesized compound results in the improvement of supramolecular transport behavior and the hybrid of the compound shows low cytotoxicity towards the normal lung epithelial cell line.

[10]

El-Mekabaty *et al.* (2018) 13 novel 3-substituted indole derivatives were synthesized and screened for their in vitro antimicrobial activity. 3-H(7H-imidazo[2,1-c][1,2,4]triazol-5-yl)-1H-indol showed equipotent activity to that of ampicillin against *E. faecalis* and 50% higher activity than ampicillin against *S. aureus* and *B. subtilis.* It also showed potent activity against antifungal strains.

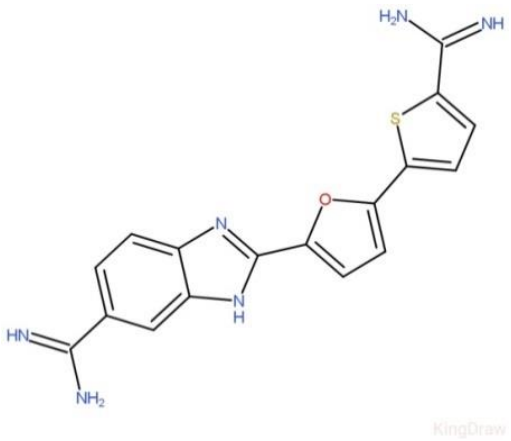


[11]

Abo-Ashour*et al.* (2018) Two different sets of indole- thiazolidinone conjugates were evaluated for their in vitro antibacterial and antifungal activities against gram-positive, gram-negative, acid-fast bacteria and fungi. The novel compound **12** shows the most potent antibacterial and antifungal activity having MIC values between 0.39- 0.98 µg/mL and 0.49-0.98 µg/mL respectively.

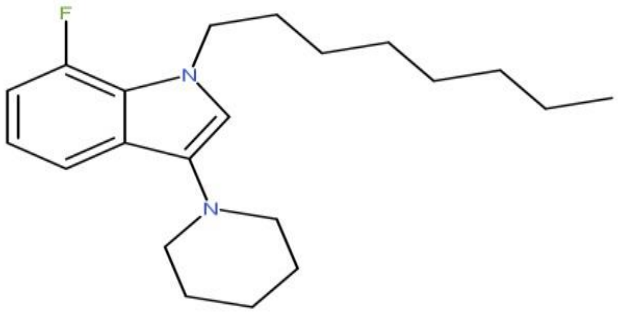
[12]

Farahat *et al.* (2018) A novel series of indole and benzimidazole derivatives were synthesized and evaluated for their antimicrobial activity against the tropical parasites causing African sleeping sickness and malaria. The test result showed that diamidino-indole derivatives were highly active while benzimidazole derivatives were less active.



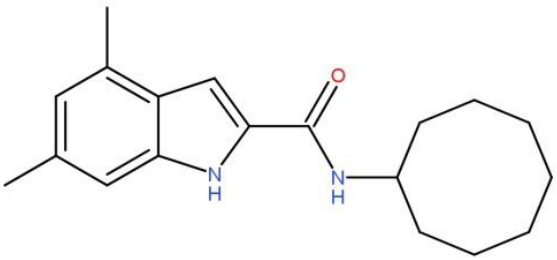
[13]

Yang *et al.* (2017) 4-fluoro and 6-methoxyindoles having a cationic amphiphilic pattern illustrated by a n-octyl side chain at position 1 and a positively Azapanyl or 1,4-dioxa-8-azaspirodecane moiety at position 3 were reported for antimycobacterial activities. The antibacterial activity was observed against both growing and non-growing mycobacterial cultures.



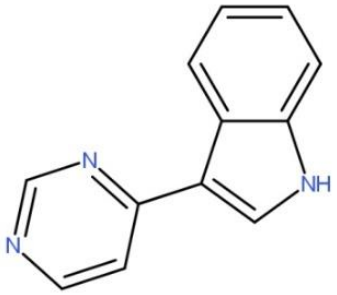
[14]

Kozikowski *et al.* (2017) A series of indolecarboxamides were evaluated and its *in-vitro* antimycobacterial activity was tested against the *M. abscessus*isolates and infected mirophges. The lead compound shows strong activity and biochemical analysis illustrates that while de novo mycolic acid synthesis remains unaltered.



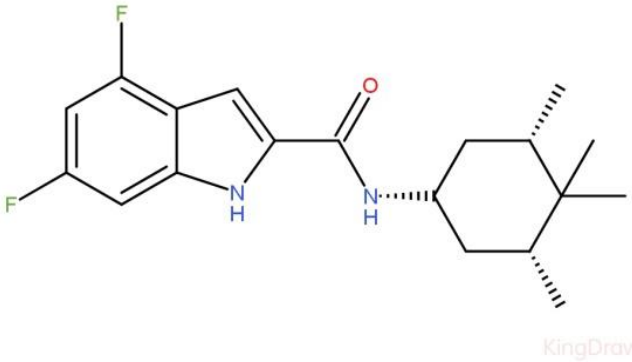
[15]

El-Sayed *et al.* (2016) New 3-(pyrimidin-4-yl)-1H-indol thioglycoside and N-glycoside derivatives were synthesized by 1-(1-ethyl-1H-indol-3-yl)-3-pyridin-4-yl-prop-2-en-1-one. The structural analysis was confirmed by IR, (^{1}H and ^{13}C) NMR. The synthesized compound showed high potent activity.



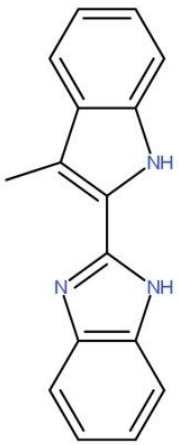
[16]

Stec *et al.*(2016)New analog, 4,6-difluoro-N-((1R,2R,3R,5S)-2,6,6-trimethylbicycloheptane-3-yl)-1H-indole-2-carboxamide was evaluated and shows potent activity against drug-sensitive, multidrug-resistant (MDR), and extensively drug-resistant (XDR) *Mycobacterium tuberculosis* strains. The result shows its brilliant activity in the TB aerosol lung infection model and also shown to work in coaction with Rifampin.



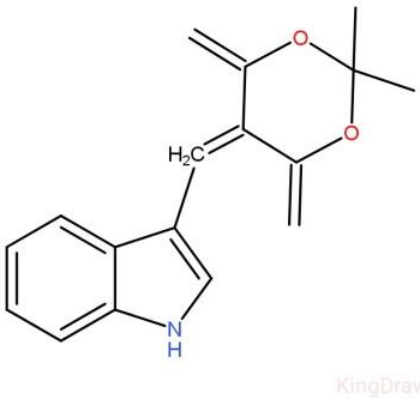
[17]

Babu *et al.* (2014) A new series of N-alkyl-2-(3-methyl-indolyl)benzimidazoles were synthesized through the condensation of N-alkyl-2-propylbenzimidazole-phenylhydrazone derivatives in polyphosphoric acid (PPA) by cyclization through Fischer indole synthesis. It was further evaluated for their antimicrobial and anticancer activity and was found that it was active only against gram-positive bacterial strain.



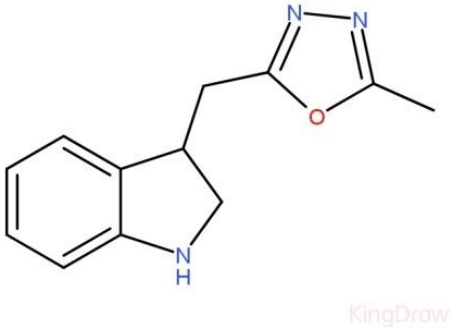
[18]

Tirupathi *et al.* (2014) A series of substituted-5-((1H-indol-3-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives were synthesized by using L-tyrosine as a catalyst. The synthesized compounds were further evaluated for their antimicrobial activity.



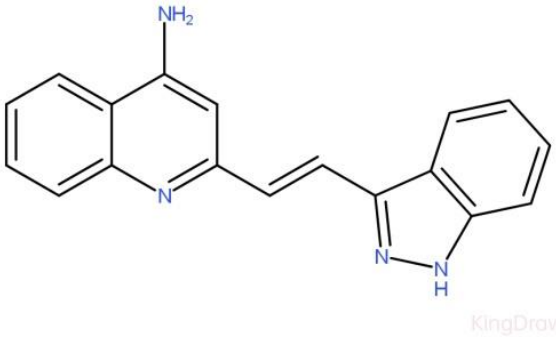
[19]

Zhang *et al.* (2013) Novel indole-based 1,3,4-oxadiazoles were synthesized by pimprinine which is a natural product. The testing of the antifungal activity of the compound shows the potent antifungal activity.



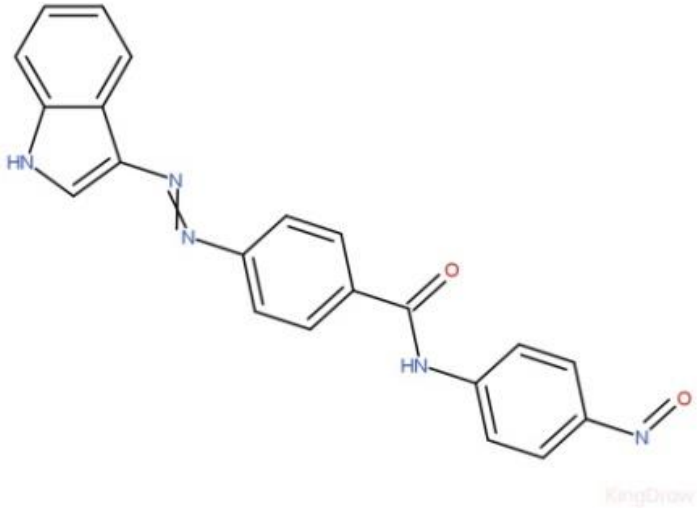
[20]

Teguh *et al.* (2013) Novel indol-3-yl linked to the 2- position of a 4-aminoquinoline moiety exhibit excellent activity against the malarial parasite, *Plasmodium falciparum*. The non-quaternerized 4-aminoquinoline shows weak activity against the K_1 strain and quinoline indoles impart weak activity as inhibitors of β-hematin formation.



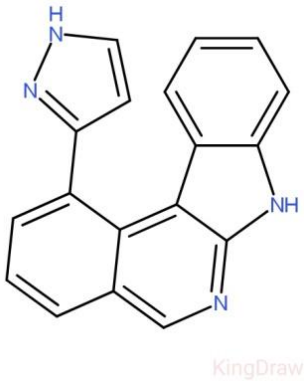
[21]

Kumar *et al.* (2013) 4-(1H-indol-3-ylazo)-N-(4-nitro-phenyl)benzamide was synthesized and the antibacterial and antifungal was screened against gram-negative bacteria and *C. albicans*respectively, the screened result showed the potent activity. It was also screened for its antiproliferative activity against human colon cancer, murine leukemia, and breast cancer cell lines which resulted as the novel antiproliferative agent.



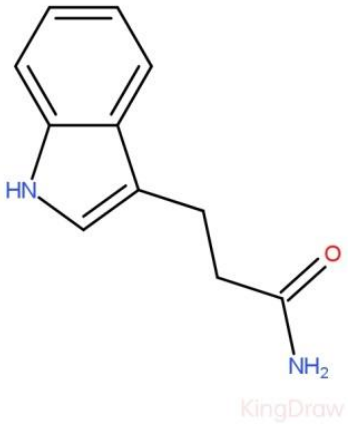
[22]

Saundane *et al.* (2013) Novel indolo[2,3-c]isoquinolinyl pyrazole derivatives were synthesized through a formyl bridge formation and the structural analysis was confirmed by MS and elemental analysis. The synthesized compounds were evaluated for their antimicrobial activity and the result showed promising activity.



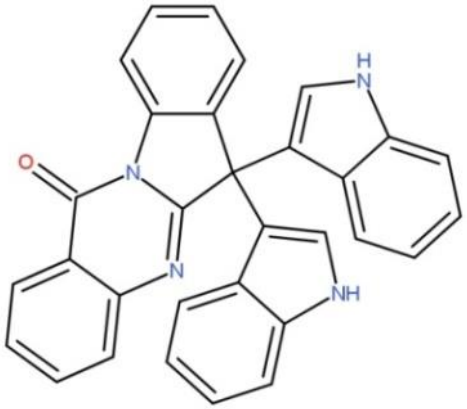
[23]

Karuvalam *et al.* (2013) (1H-indol-3-yl) alkyl-3-(1H-indol-3-yl) propanamide was synthesized and screened for its antibacterial, antifungal, and antitubercular activity. The synthesized showed high potent antimicrobial activity.



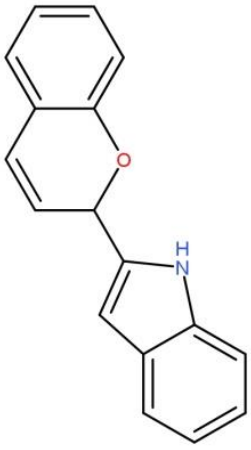
[24]

Moskovkina *et al.* (2013) 6,6-di(indol-3-yl)-indolo[2,1-b]quinazolin-12(6H)-one and its 2,8-dimethyl and 2,8-dibromo derivatives have been synthesized and they were further evaluated for their antifungal activity against *Candida albicans* and exhibit potent activity.



[25]

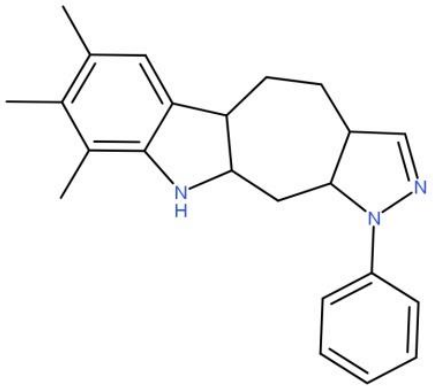
Kathrotiya *et al.* (2012) A new series of indole basrdchromene derivatives were synthesized by a one-pot cyclo condensation reaction with 2-phenyl-1H-indol-3-carbaldehyde, malononitrile and 1,3-cyclohexanedione under microwave irradiation method, and 4-(N, N-dimethylamino)pyridine was used as the catalyst. Antibacterial and antifungal activity screening showed that some of the synthesized compounds were equipotent or more potent than that of the reference drug used.



[26]

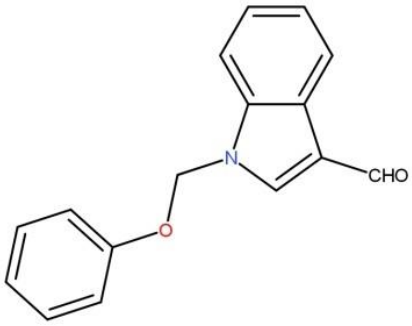
Yamuna *et al.* (2012) Three novel series of pyrazolo-, isoxazolo- and pyrimidocycloheptaindoles were prepared through condensation of substituted 7-(hydroxymethylene)-7,8,9,10-tetrahydrocycloheptaindol-6(5H)-one in the presence of hydrazine hydrate, hydroxlyame hydrochloride, phenylhydrazine, urea, and thiourea. The compounds were screened for in vitro antimicrobial and antimycobacterial activity against

Mycobacterium tuberculosis. The structural analyses of the compounds are confirmed by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral analysis, and X-ray diffraction.



[27]

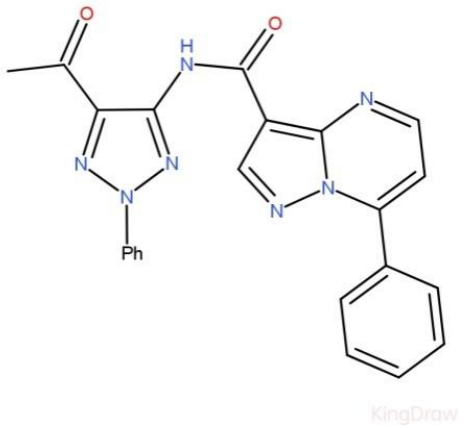
Laxmi *et al.* (2012) Under microwave irradiation procedure a series of 1-((2-oxo-2-phenyl-ethyl)-2-phenyl-1H-indol-3-yl)methylene semicarbazone derivatives were prepared through the condensation of derivatives of 1-(2-oxo-2-phenyl-ethyl)-2-phenyl-1H-indol-3-carbaldehyde and semicarbazide in ethanol-water. Using borth dilution method the antimicrobial activity of the compounds was evaluated and shows moderate antibacterial activity and good antifungal activity.



[28]

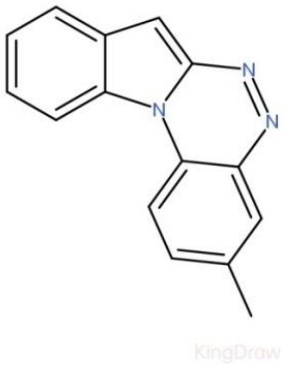
Shah *et al.* (2011) Novel spiro-[azetidine-2,3'-indol]-2',4(1'H)-dione was synthesized by reacting 3-(phenylimino)-1,3-dihydro-2H-indol-2-one derivatives with choracetyl chloride in the presence of triethylamine (TEA). The structural analysis was confirmed by ^{1}H NMR, MS, and elemental analysis, the antimicrobial screening of the synthesized compound exhibit very good antimicrobial activity.

Behbehani *et al.* (2011) A new uniquely substituted heterocyclic compound has been prepared and screened for its antimicrobial activity against gram-positive bacteria, gram-negative bacteria, and yeast. The result shows very potent activity against all the tested organisms.



[29]

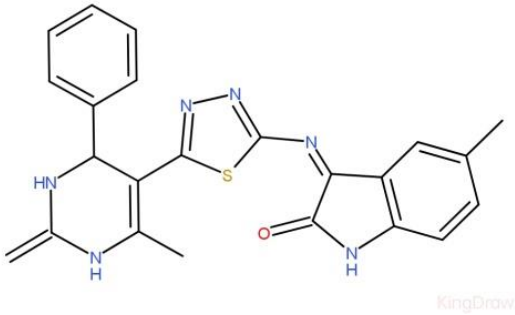
Xu Hui *et al.* (2011) A series of novel indole[1,2-c]-1,2,4-benzotriazine derivatives were prepared through Sandmeyer reaction in the presence of tert-butylnitrite. The compound was further screened for its antifungal activity against phytopathogenic fungi which, results show the high antifungal activity.



[30]

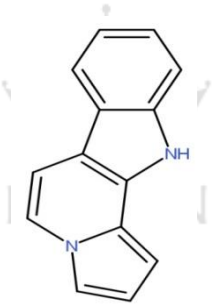
Akhaja *et al.* (2011) 5-substituted-3-[{5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl}imino]-1,3-dihydro-2Hindol-2-one derivatives were prepared by using one pot multicomponent Biginelli reaction where $CaCl^2$ was used as catalyst. The structural analysis was confirmed by IR, (^1H and ^{13}C) NMR, and

MS. The synthesized compound shows good antitubercular, antibacterial, and antifungal activity against certain and selected strains.



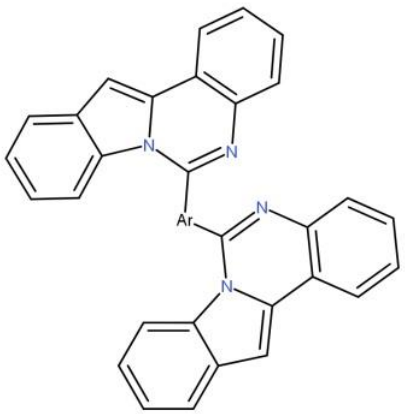
[31]

Nurmaganbetov *et al.* (2011) Novel indolizino[8,7-b]indole derivatives were synthesized by reacting harmine with phenacyl bromides or ethyl bromoacetate which leads to the formation of phenacylharminium, it's salt further yields the corresponding derivatives. The synthesized compounds were further evaluated for their biological activity.



[32]

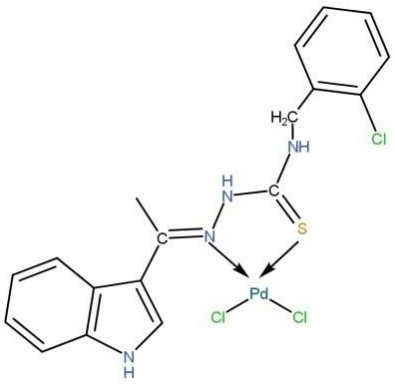
Rohini *et al.* (2010) Novel series of indolo[1,2-c]quinazoline derivatives were synthesized by reacting 2-(o-aminophenyl)indole with various arylaldehydes. The confirmed structures of the compounds were stated through IR, ^{1}H NMR, ^{13}C NMR, Mass spectral analysis, and elemental analysis. The prepared compounds were tested for their antimicrobial activity against gram-positive bacteria, gram-negative bacteria, and a pathogenic fungus which shows the positive result as compared with Ampicillin and Ketoconazole as these were used as reference compounds.



[33]

Sharma *et al.* (2009) A new series of spiro-2-[3'-(2'-phenyl)-3H-indolyl]-1-aryl-3-phenylaziridines were synthesized. The structural analysis was confirmed by IR, ^{1}H NMR, MS, and elemental analysis. The synthesized compound showed excellent antimicrobial activity.

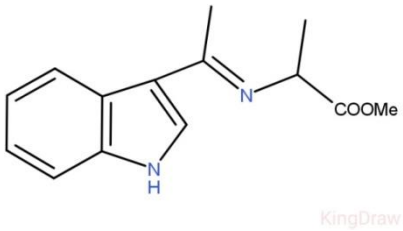
Husain *et al.* (2008) 3-indole carboxaldehyde thiosemicarbazones were synthesized by reacting 3-indole carboxaldehyde with aminothiocarbonyl hydrazines. Hence, the semicarbazone which was synthesized was used as a ligand for the formation of $[PD(TSC)Cl_2]$ complex. The structure of complexes was confirmed by FABMS and DTA. The antiamoebic activity screening against the protozoan parasite *Entamoeba hystolytica* shows that it is less potent.



[34]

Sinha *et al.* (2008) Novel heterocyclic Schiff base derivatives of indol-3-carboxaldehyde were synthesized by reacting indol-3-carboxaldehyde with different L-amino acids as well as

aminophenols. The structural characterization was confirmed by IR, ^{1}H NMR, and MS. The synthesized compounds were also evaluated for their anticancer and antimicrobial activity.



[35]

Ambrogi *et al.* (1993) Indolo[2,3-b]-1,5-benzothiazepine was prepared by Fischer indolization through phenylhydrazone. The antimicrobial and cytostatic activity against gram-positive and *Cryptococci* showed good activity.

[36]

CONCLUSION

This manuscript has been made up and shows remarkable information about antimicrobial activities of various derivatives based on indole heterocyclic nucleus. It has been concluded by this article that the indole nucleus is a multifaceted and medicinally vital nuclei having the reassuring antimicrobial activity which leads to the drug design and development of the lead compound of strong antimicrobial agents for future to provide effective antimicrobial activity to the patients suffering from microbial infection.

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