"Pyrazole Heterocyclic Nucleus: A Critical Overview of its Versatile Role in Antimicrobial Drug Design"

Mayank Yadav*,Meenakshi Tyagi

Department of Pharmaceutical Sciences, Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University, Gangoh, Saharanpur, UP

***Corresponding Author: Email id- mayankmp@gmail.com**

ABSTRACT

Increasing resistance of microorganisms to clinically used antimicrobial drugs is the major cause of morbidity and transience throughout the globe. Therefore, development of novel antimicrobial agents will always be in demand for medicinal chemists. Pyrazoles derivatives constitutes an important class of medicinal agents having widespread pharmacological activities such as antimicrobial, anti-inflammatory, antiviral, antitumour, anticonvulsant and antidepressant activities etc. Prompted by these observations, this review article is entitled to represent antimicrobial potential of novel pyrazole derivatives to curb the menace of microbial resistance towards antibiotics to treat microbial infections effectively.

Keywords: Pyrazole, Antibacterial, Antifungal activity

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INTRODUCTION

In the present era, there is a consistence reduction in the potency of antimicrobial agents due to microbial resistance making it difficult to treat the life threatening microbial infections effectively [1]. The extensive use of antimicrobial agents has resulted in the development of resistance to these drugs by pathogenic microorganisms, causing an increase in mortality rate globally [2]. Therefore, this worst situation demands intense effort in antimicrobial drug discovery to develop more promising and effective antimicrobial agents for their effective use in the clinical arena [3, 4].

Pyrazole derivatives have attracted the utmost interest of medicinal chemists due to their vast pharmacological importance especially potent antimicrobial activity by having different mode of action. Pyrazole is the parent compound for a large number of heterocyclic compounds with molecular formula $C_3H_3N_2H$. It is a heterocyclic ring system characterized by a 5- membered ring of three carbon atoms and two adjacent nitrogen centers. Pyrazole are also the class of compounds that have the ring C_3N_2 with adjacent nitrogen centres **(Fig. 1)** [5].

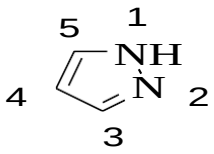
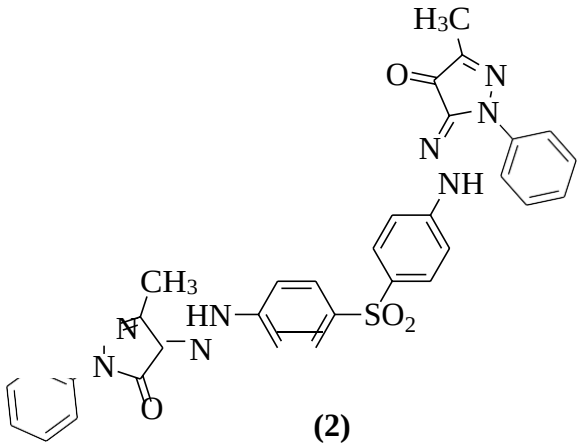


Fig. 1: Structure of pyrazole

ANTIMICROBIAL ACTIVITIES

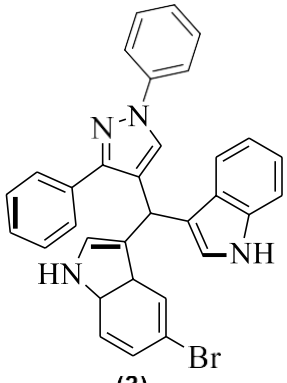
According to the recent literature survey, it may be observed that novel pyrazole derivatives are found to have potent antimicrobial activities and this information has been summarized in this section as given below:

Mehta *et al* synthesized the entitled bispyrazole and bispyrazolone derivatives **(2)**. All the synthesized compounds subjected for their antimicrobial (antibacterial and antifungal) activities. One compound showed potent anti-microbial activities against different bacterial species *Bacillus subtilis, Escherichia coli, Aspergillous flavus* and fungal spores *Aspergillous niger* at a concentration of 200 µg/mL. Benzylpenicillin and Iimidil were used as standard drugs [6].



(2)

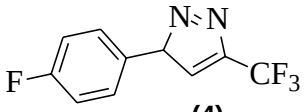
Sivaprasad *et al* synthesized a series of pyrazolylbisindole derivatives **(3)** and evaluated them for their antimicrobial and antifungal activities. One compound showed potent anti-microbial activities against three human pathogens such as *Candida albicans* (yeast), and *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* (bacteria) at a concentration of 20 µg/mL as compared to the standard drugs Ciprofloxacin and Fluconazole [7].



(3)

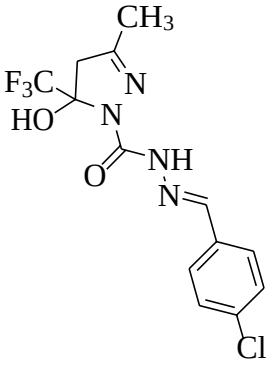
Wang *et al* prepared several new trifluoromethyl-1*H*-pyrazoles derivatives **(4)**. All the trifluoromethyl-1*H*-pyrazoles exhibited a certain degree of anti-bacterial and anti-fungal activities. The anti-microbial activities of the newly synthesized compounds were examined by disc diffusion method against *Escherichia coli, Staphylococcus aureus, Pyricularia oryzae* and *Rhizoctnia solani*. Although

some compounds showed potent anti-microbial activities as compared to their respective standard drugs as Triadimefon and Norfloxacin [8].



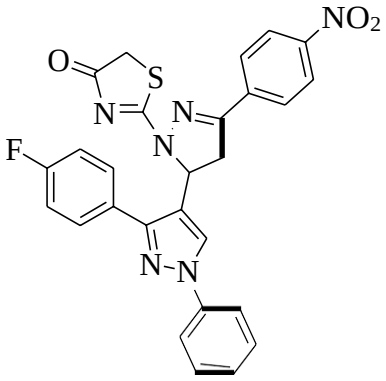
(4)

Bonacorso *et al* obtained a new series of trifluoromethyl-containing (E)-N0-arylidene-1*H*-pyrazole-1-carbohydrazides derivatives **(5)** and screened for their antimicrobial proprieties. Most of the compounds presented fungistatic and bacteriostatic activity and MIC levels ranging from 0.25 mg/mL to 0.5 mg/ml. One compound showed potent antimicrobial activity as compared to the respective standard drug Chloremphenicol and Nystatin for bacterial and fungal stains [9].



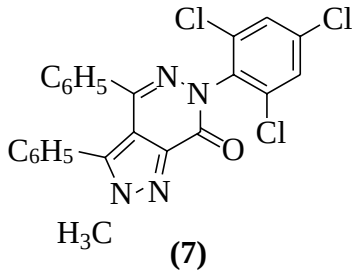
(5)

Desai *et al* synthesized a series of compounds 2,5-dihydro-1*H*pyrazolyl)thiazol-4(5*H*)-ones derivatives **(6)** and screened for *in vitro* antibacterial activity against the representative panel of Gram-positive *(Staphylococcus aureus, Streptococcus pyogenes) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa)* bacteria. These compounds were tested for their inhibitory action against stains of fungi (*Candida albicans, Aspergillus niger, Aspergillus clavatus*). One compound showed excellent activity against *S. aureus* having value of MIC 25 mg/mL as compared to standard Ampicillin [10].



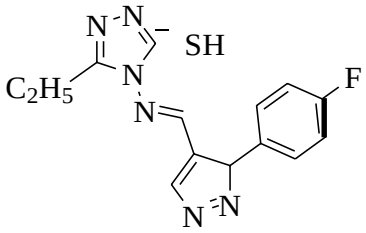
(6)

Akbas *et al* prepared several new pyrazolo pyridazin derivatives **(7)** and screened for their antimicrobial activities against Gram-negative, Gram-positive bacteria and fungi with minimum inhibitory concentrations in the range of 0.31 to < 0.0024 mg/ ml . Some compounds exhibited excellent activity against bacterias, such as *Bacillus cereus, S. aureus, Escherichia coli, Pseudomonas putida* and against the human pathogenic fungi, such as *Candida albicans* by using Ampicillin trihydrate and Fluconazole used as reference drugs for antibacterial & antifungal activities respectively [11].



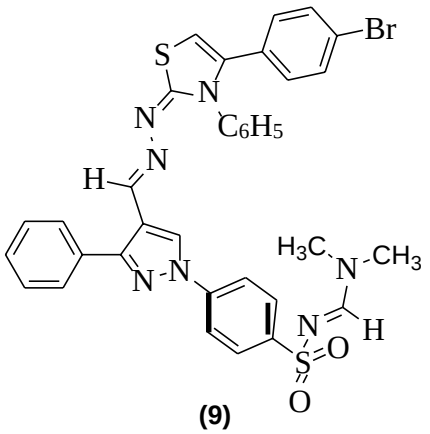
(7)

In the present study a series of new Schiff bases Pyrazole derivatives **(8)** were synthesized by **Malladi *et al*** and screened for their antibacterial against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa* activity. Antimicrobial results indicate that, most of the synthesized compounds showed good to moderate activity against various microorganisms. One compound exhibited excellent activity against *S. aureus* whereas it showed activity equal to that of standard drug Ceftriaxone [12].



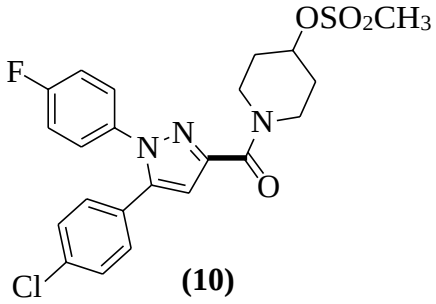
(8)

Bekhitt *et al* synthesized four series of pyrazolyl benzenesulfonamide derivatives **(9)** and evaluated their antimicrobial activities. Antimicrobial activity tests were expressed as minimal inhibitory concentrations (MIC). The results revealed that one compound showed comparable antibacterial activity as that of Ampicillin against *Escherichia coli,* possessed about half the activity of Ampicillin against *Staphylococcus aureus*. The resuting data showed that all the tested compounds had antifungal activity against *Candida albicans* as compared to standard drug Clotrimazole [13].



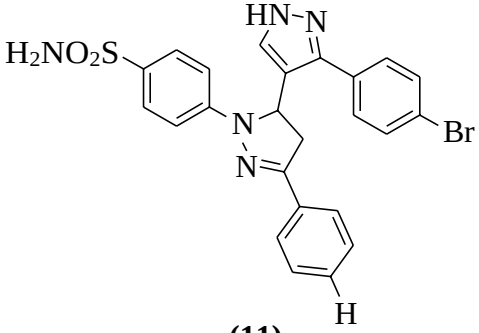
(9)

Ragavan *et al* synthesized a novel series of 1,5-diaryl pyrazole derivatives **(10)** and screened for their antibacterial activity against *Escherichia coli* , *Staphylococcus aureus* , *Pseudomonas aeruginosa* and *Klebsiella pneumonia.* All these compounds screened for their antifungal activity against *Aspergillus flavus, Aspergillus fumigates , Penicillium marneffei* and *Trichophyton mentagrophytes*. Interestingly one of the synthesized compounds exhibited good antibacterial and antifungal activity against bacterial and fungal stains as compared with the standard drugs Ciprofloxacin and Nystatin [14].



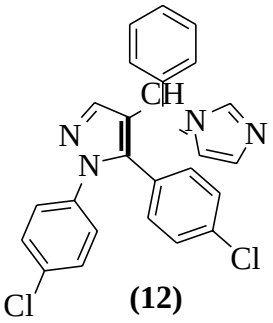
(10)

Sharma *et al* synthesized a new series of pyrazolylpyrazolines derivatives **(11)**. The synthesized compounds were evaluated for their *in vitro* antimicrobial activity against Gram-positive bacteria and Gram-negative bacteria. One compound was identified as the most biologically active member within this study with an interesting dual and *in vitro* antimicrobial activity against *Staphylococcus aureus ,Bacillus subtilis* representing Gram-positive bacteria, and *Pseudomonas aeruginosa , Escherichia coli* representing Gram-negative bacteria . One compound exhibited excellent activity as compared with the reference drug Ciprofloxacin [15].



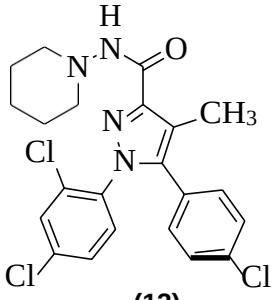
(11)

Menozzi *et al* synthesized a number of 1,5-disubstituted 4-[1*H*-imidazol- 1-yl(phenyl)methyl]-1*H*-pyrazoles analogues **(12)**. Some derivatives showed antimicrobial activities *in vitro* against *Candida albicans, Cryptococcus neoformans* and *Staphylococcus aureus.* Test compounds produced inhibitory effects against pathogens representatives of yeast (*C. albicans, C. neoformans*) and Gram positive bacteria *(S. aureus)* similar or superior to those of Bifonazole. In addition, their activity against bacterial stains were superior to that of standard drugs like Clotrimazole, Streptomycin, Miconazole and Amphotericin B [16].



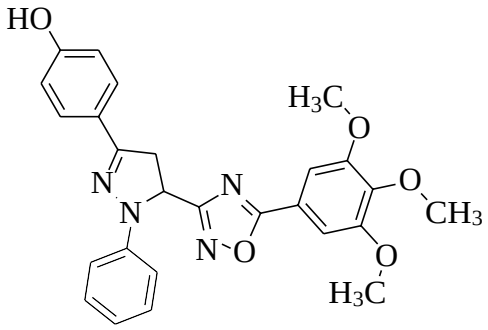
(12)

Alizadeh *et al* prepared a number of new dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylate derivatives **(13)** and investigated their antimicrobial activities. One compound containing trisubstituted pyrazole derivative showed potent antimicrobial activity against pathogens representatives of bacteria and fungal stains as compared to their respective standard drugs [17].



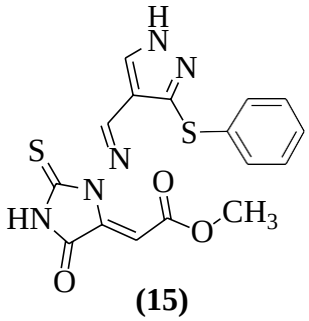
(13)

Ningaiah *et al* synthesized a novel series of pyrazoline amidoxime and pyrazoly-1,2,4-oxadiazole derivatives **(14)** of pharmacological significance. The synthesized compounds were evaluated for *in vitro* antimicrobial activity against gram-positive bacteria like *Bacillus cereus* (MTCC 8372), *Staphylococcus aureus* (MTCC 96) and gram-negative bacteria like *Escherichia coli* (MTCC 724), *Klebsiella pneumonia* (MTCC 3384), *Shigella flexneri* (MTCC 1457), MIC at 10-20µg/ml and two fungi *Aspergillus flavus* (MTCC 873), *Aspergillus niger* (MTCC 281).One compound showed excellent antimicrobial activity against all the tested stains of microbes exhibited good to potent antimicrobial activity as compared to the standard drugs Chloremphenicol and Fluconazole [18].



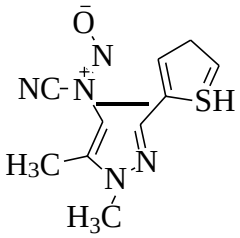
(14)

A novel series of a imidazole derivatives containing substituted pyrazole moiety **(15)** were synthesized by **Vijesh *et al***. All the compounds screened for their antibacterial activity and found to be exhibit good antimicrobial activities against *Pseudomonas aeruginosa* at concentrations of 1 and 0.5 mg/mL. The bacterial stains like *Escherichia coli, Bacillus subtilis, Salmonella typhimorium, Clostridium profingens* and *Pseudomonas aeruginosa* were used to investigate the antibacterial activity. The result indicated that one compound showed excellent activity against *P. aeruginosa* at concentrations of 1 and 0.5 mg/mL as compared to standard drug Streptomycin [19].



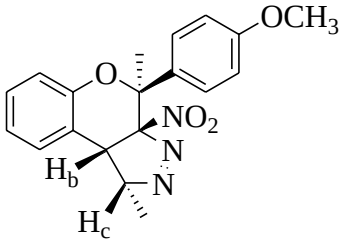
(15)

Boschi *et al* synthesized the 1,3-dimethyl-4-(cyano-NNO-azoxy)pyrazol-5-yl derivatives **(16)** and tested for their antimicrobial activities . Some compounds displayed excellent antimicrobial activity against *Staphylococcus aureus* stains, including the Methicillin resistant stain. All compounds displayed significant antifungal activity against *Candida krusei* and *Candida glabrata* at MIC of 0.25-0.5 µg/mL. *Candida parapsilosis* and *Candida tropicalis* isolates had higher MIC values than Erythromycim and Ciprofloxacin as reference drugs. One compound was particularly active against the stains of *Cryptococcus neoformans* which was susceptible to all the pyrazolylazoxycyanide derivatives [20].



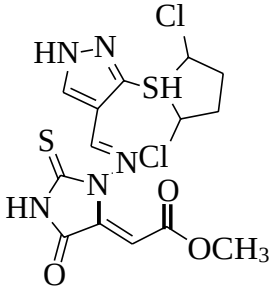
(16)

Kodukulla *et al* prepared a series of benzopyranopyrazoles and pyrazolines derivatives **(17)** and reported the antimicrobial activity of these compounds against the bacterial stains like *S. aureus. S. lutea. B. subtilis. E. coli. S. typhosa, S. cerevesciae md C. albicans.* The minimum inhibitory concentrations of these compounds were evaluated against the gram positive bacteria and fungi and the gram negative bacteria active against *S. typhosa*. One compound was found to exhibit the good to moderate potency than standard drug Ciprofloxacin [21].



(17)

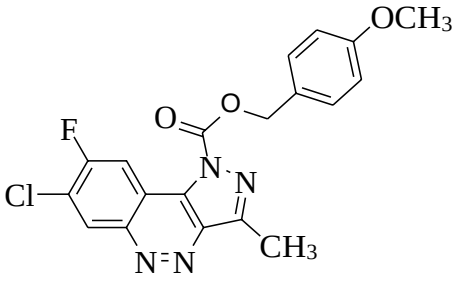
A novel series of imidazole derivatives containing substituted pyrazole moiety **(18)** synthesized by **Vijesh *et al***. New compounds were screened for antifungal and antibacterial activities. Among of the synthesized compounds, one compound found to be potent antimicrobial agent. In this work, *Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhimorium. Clostridium profingens and Pseudomonas aeruginosa* used to investigate the activity.The antibacterial screening revealed that some of the tested compound showed excellent activity against *P. aeruginosa* at minimum inhibitory concentrations of 1- 0.5 mg/mL compared to standard drug Streptomycin [22].



(18)

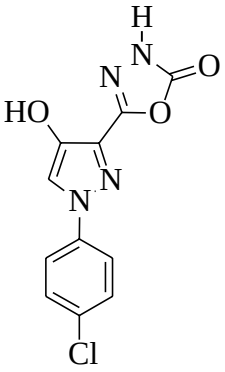
A series of pyrazolocinnoline derivatives **(19)** synthesized by **Tonk *et al*** and evaluated for antibacterial activity. All the compounds displayed significant antibacterial activity against gram-negative (*Escherichia coli and Pseudomonas aeruginosa*) and gram-positive (*Staphylococcus aureus*) bacteria. The antibacterial activity of each compound was compared against standard drug

Ciprofloxacin. Some compounds showed appreciable antimicrobial activities when compared with standard drugs [23].



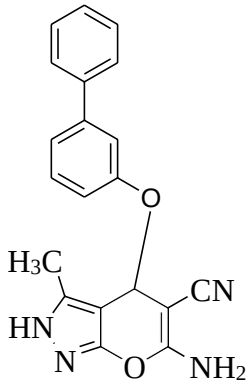
(19)

A novel series of 1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid hydrazide analogues **(20)** were synthesized by **Rostom *et al*** and tested for antimicrobial activities. One compound was proved to be the most active antimicrobial agent as compared to the Gentamicin as a standard drug at the variable minimum inhibitory concentrations [24].



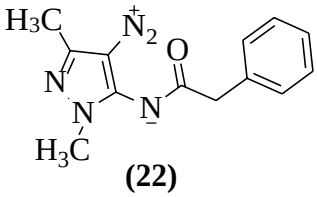
(20)

Mandha *et al* synthesized an ecofriendly green approach of substituted pyranopyrazoles derivatives **(21)** .These compounds were evaluated for their antibacterial activities. Investigation of antibacterial data at concentration of 100 µg/50 µL revealed that some compounds showed good activity against two bacterial stains like *Staphylococcus aureus* and *Escherichia coli* and their MICs ranged between 1.56 and 12.5 µg/mL. Some compounds showed potent antibacterial activity against both gram positive and gram negative standard stains. Ciprofloxacin drug was used as the standard protocol when compared to standard drug Ciprofloxacin [25].



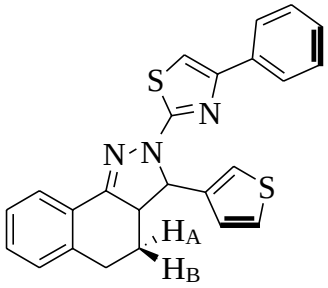
(21)

Several new 4-diazopyrazole derivatives **(22)** were obtained by **Raimondi *et al*** .The compounds were assayed for their activity against the *Staphylococcus aureus* reference stains. The best anti-staphylococcal profile was showed by [(R-substituted-phenyl)acetyl] (4-diazonio-1,3-dimethyl-1*H*-pyrazol-5-yl)azanides derivatives .One compound was showed an inhibition of 45.7% at sub-MIC concentration of 3.1 mg/ mL against *S. aureus*, ATCC 29213, ATCC 25923 and 708 respectively but resulted scarcely effective in preventing the biofilm formation of the other two tested stains as compared to the standerd drug Rifampicin [26].



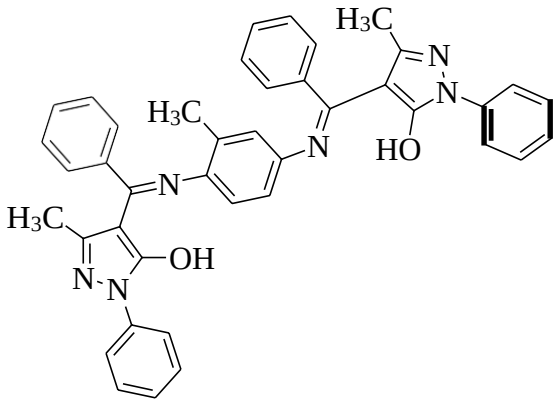
(22)

A series of novel 2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazoles derivatives **(23)** were prepared by **Sharifzadeh *et al***. The antibacterial activity of the selected products was examined. Some compounds exhibited promising antimicrobial activities against the *Escherichia coli* (E. coli) ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 as gram-negative models and *Staphylococcus aureus* (S. aureus) ATCC 29213 as a gram-positive model. One compound exhibited good antibacterial activity against *Pseudomonas aeruginosa* as compared to Gentamicin as standared drug [27].



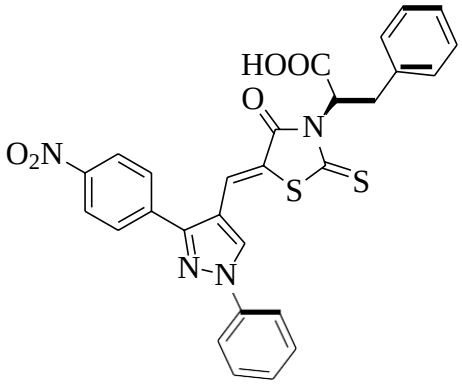
(23)

A series of nine new biologically active Schiff bases derivatives **(24)** were synthesized by **Parmar *et al*** . All the compounds were tested for their antibacterial activity against *Bacillus subtilis* and *Escherichia coli* and antifungal activity against *Phytophthora infestanse*, *Aspergillus niger*, *Aspergillus fumigates* in comparision to standard drug Griseofulvin. One compound exhibited excellent activity against *P. infestanse* in comparison to standard antibiotic Streptomycin [28].



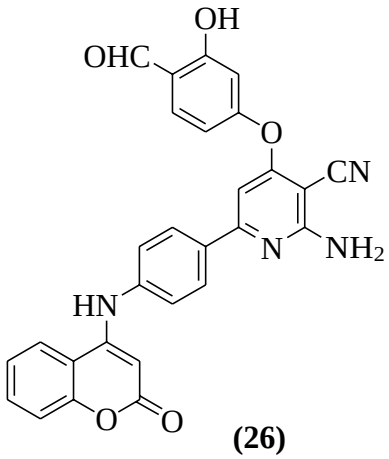
(24)

Zheng *et al* synthesized a novel series of 1,3-diphenyl-1*H*-pyrazoles functionalized with phenylalanine derived rhodanine derivatives **(25)** and were evaluated for their antibacterial activity. Some compounds exhibited stronger activity than the standard drugs Norfloxacin and Oxacillin against Methicillin-resistant *Staphylococcus aureus* and *quinolone resistant S. aureus.* In conclusion one compound at (MIC 1mg/mL) exhibited stronger activity as compared with the reference drugs [29].



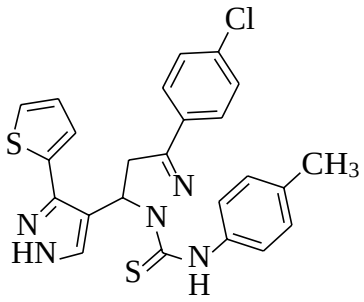
(25)

Patel *et al* synthesized a series of 4-[4-(1- acetyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-phenylamino]- chromen-2-one derivatives **(26)** .The newly synthesized compounds were evaluated for their antimycobacterial activity and antimicrobial activity against eight bacteria (*S. aureus, B. cereus, E. coli, P. aeruginosa, K. pneumoniae, S. typhi, P. vulgaris,* and *S. flexneri)* and four fungi *(A. niger, C. albicans, A. fumigatus,* and *A. clavatus* .The results revealed that one compound showed potent activity at MIC of 100 µg/mL in comparision of Ciprofloxacin as a standard drug [30].



(26)

Bakr *et al* synthesised 1-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde derivatives **(27)** . The antimicrobial activities of the synthesized compounds were evaluated. Ciprofloxacin (50 µg/ml) and Ketoconazole (50 µg/ml) were used as standards for antibacterial and antifungal activity respectively. Various derivatives showed good antibacterial activities against all the tested pathogen including gram-positive, gram-negative bacteria and yeast with minimal inhibitory concentration (MIC) that ranged between 33.3 µg/ml and 41.6 µg/ml . One compound showed an excellent antibacterial activity at MIC value of 20.8 µg/ml against *Staphylococcus aureus* ATCC 29213 and *Enterobacter Cloaca* ATCC3047 bacterias [31].



(27)

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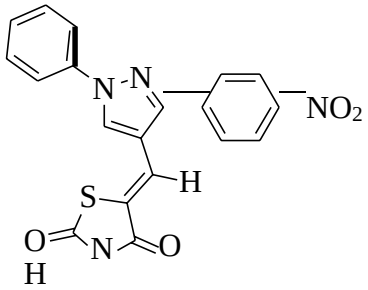
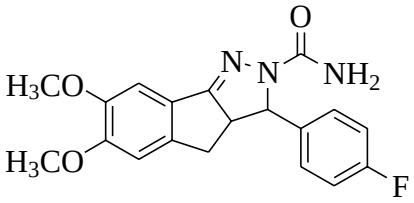
Parkash *et al* synthesized a series of 5-((3-aryl-1-phenyl-1*H*-pyrazol-4- yl)methylene)thiazolidine-2,4-diones derivatives **(28)** by Knoevenagel condensation. All compounds were screened for their *in vitro* antibacterial (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli)* activity and compared with the commercially available antibiotic Ciprofloxacin. One compound was found to be most potent member among all the compounds showing at MIC of 16 µg/ml against *S. aureus* and 32 µg/ml against *B. subtilis.* All the synthesized compounds were tested for their *in vitro* antifungal activity against *Aspergillus niger* and *A. flavus* activity and compared with standard drug Fluconazole [32].



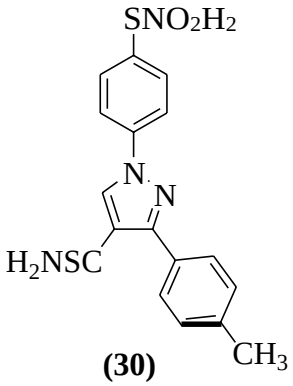
(28)

Jawed *et al* synthesized a series of 4-dihydro-3*H*-indenopyrazole-2carboxamide/carbothioamide analogues **(29)** and evaluated their antibacterial activity against *Bacillus subtilis* and *Escherichia coli* and antifungal activity against *Phytophthora infestanse*, *Aspergillus niger* and *Aspergillus fumigates* .One compound was found to be the most active compound against various bacterial strains with MIC of 2-4 µg/ml as compared with the standard drug Ciprofloxacin [33].



(29)

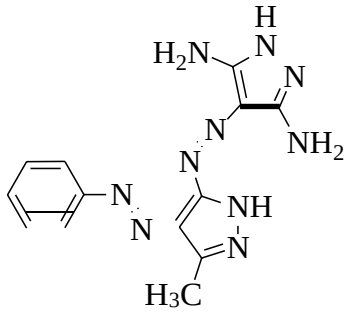
Sharma *et al* synthesized 4-functionalized pyrazoles carbothioamides derivatives **(30)** and evaluated for their *in vitro* antibacterial activity against pathogenic bacterial stains namely, *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 121) as Gram-positive bacteria and Escherichia *coli* (MTCC 1652), *Pseudomonas aeruginosa* (MTCC 741) as Gram-negative bacteria, and *in vitro* antifungal activity against two pathogenic fungal stains namely, *Aspergillus niger* and *Aspergillus flavus*. One compound was the most potent compound which showed the maximum zone of inhibition of 21.6 mm and against *B. subtilis* as compared with the standard drug Ciprofloxacin [34].



(30)

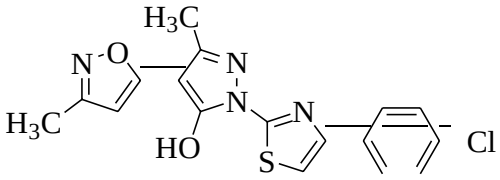
Karci *et al* synthesized a series of pyrazolyl hydrazono malononitriles of aniline derivatives **(31)** **.**The antimicrobial activities of the newly synthesized compound was evaluated against *Bacillus subtilis* (NRRL B-3711), *Staphylococcus aureus* (ATCC 25923), *Micrococcus luteus* (NRRL B-1018),

Enterococcus faecium (NRRL B-2354), *Escherichia coli* (ATTC 25922) and *Proteus vulgaris* and found their MIC values within the range 3.90– 2000 mg/ml. Results showed that one of the synthesized compounds had important antibacterial activities when compared with control antibiotic Streptomycin against not only gram negative but also gram-positive bacteria. This compound showed potent antimicrobial activity against *B. subtilis, S. aureus* and *M. luteus* at the dose of 125 mg/ml [35].



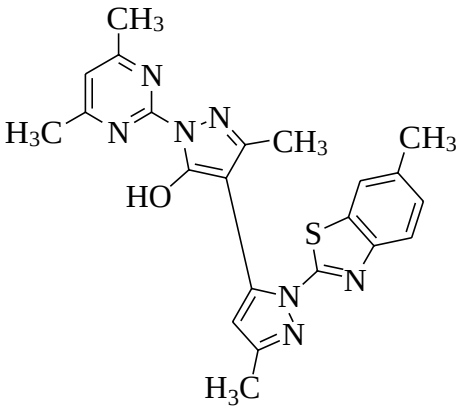
(31)

Mor *et al* synthesized a series of isoxazolyl thiazolyl pyrazoles derivatives **(32)** and were assayed for their *in vitro* antibacterial activity against Gram-positive *Bacillus subtilis, Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* and *in vitro* antifungal activity against *Candida albicans* and *Aspergillus niger*. Most of the synthesized compounds showed good antibacterial activity with MICs ranging from 1.435 to 1.778 µg/ml in the comparison of Norfoxacin and Fluconazole were used as the standard drugs respectively. However, one compound was found to exhibit the promising antibacterial activity against *S. aureus* bacteria [36].



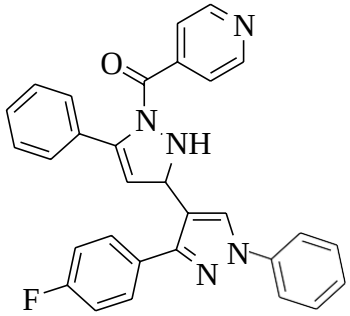
(32)

Aggarwal *et al* reported the synthesis of 5-Hydroxy-3-methyl-1-(4,6-dimethylpyrimidin-2-yl)pyrazol-4-yl-1,3-butanedione derivatives **(33)** and were screened for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), and their antifungal activity against yeasts *Candida albicans* and *Saccharomyces cerevisiae*. Ciprofloxacin was used as the standard antibacterial drug and Amphotericin B as standard antifungal drug .One compound exhibited the most promising results, showing the lowest MIC of 32 µg/mL against *S. aureus*, 16 µg/mL against *B. subtilis*, and 64 µg/mL against *S. cerevisiae* [37].



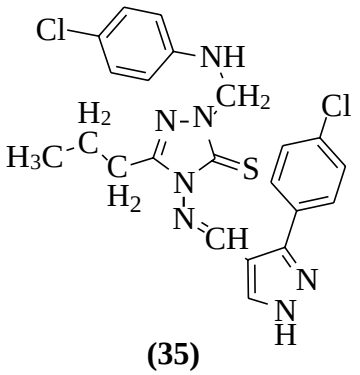
(33)

A series of (3-phenyl-5-(1-phenyl-3-aryl-1*H*pyrazol- 4-yl)-4 methanones derivatives **(34)** were synthesized by **Kumar *et al.*** All the newly synthesized compounds were evaluated for their antibacterial and antifungal activity against five standard bacterial species including gram-positive (*Staphylococcus aureus, Bacillus pumilis,* and *Bacillus subtilis*) and gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria and standard fungi (*Candida albicans, Candida tropicalis, Aspergillus niger,* and *Aspergillus flavus*). The MIC values studied for reference bacterial (*Staphylococcus aureus, Bacillus pumilis, Bacillus subtillus, Escherichia coli,* and *Pseudomonas aeruginosa*) and three fungal (*Candida albicans, Aspergillus niger,* and *Aspergillus flavus)* stains at concentration ranges from 1.562 to 800 µg/mL. One compound was showed good antimicrobial activity comparable with that of standard drugs Ciprofloxacin and Fluconazole [38].



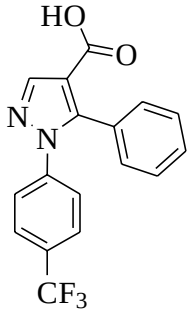
(34)

In the present investigation, a series of new 4[(3-substituted-1*H*-pyrazol-4-yl)methyleneamino]-5-substituted-2-[(4-methylpiperzine-1-yl)methyl]-2H-1,2,4-triazole-3(4*H*)-thiones derivatives **(35)** were synthesized by the **Isloor *et al*** .All the newly synthesized Mannich bases were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed *S. aureus, B. subtilis, E. coli and P. aeruginosa* and for antifungal activity *C. albicans* used as organism.One compound showed excellent activity against fungal stain *Candida albicans* at 3 mg/ml concentration as compared with reference drug Ampicillin [39].



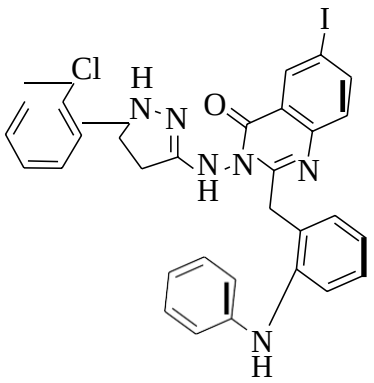
(35)

In the present study, a novel series of Pyrazole derivatives **(36)** were synthesized by **Chandrakantha *et al*** through condensing ethyl- 3-(dimethylamino)-2-(phenylcarbonyl)prop-2-enoate. All the newly synthesized compounds were screened for their antibacterial properties against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa.* Among the screened samples, showed excellent antibacterial activity against all the tested bacterial stains at concentrations of 50, 25, 12.5, 6.25, 3.125, and 1.6125 µg/ml as compared to the standard drug Ceftriaxone . Finally, One compound was showed excellent activity at concentrations of 105 mg/ml against *S. aureus, B. subtilis, E. coli,* and *P. aerogenosa* suspension as compared with the standard drug Ceftriaxone [40].



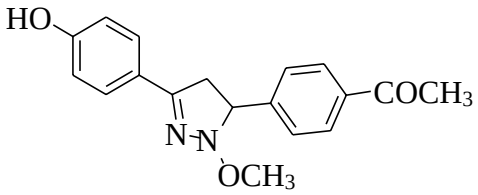
(36)

Patel *et al* synthesized the several pyrazolyl-quinazolin-4(3*H*)-ones derivatives (**37)** and evaluated both gram positive as well as gram negative bacteria. One compound showed excellent activity against gram positive bacteria *S. aureus* and *B. subtilis* and gram negative bacteria *P. aeruginosa* as compared to standard drug Penicillin- G. The most of the compounds showed good antifungal activity as compared to Fluconazole except compounds which displayed moderate antifungal activity against *C. albicans* and *A. niger*. One compound showed excellent activity against both fungi along with compounds zone of inhibition at concentration 10 µg/mL as compared with standared drug Fluconazole [41].



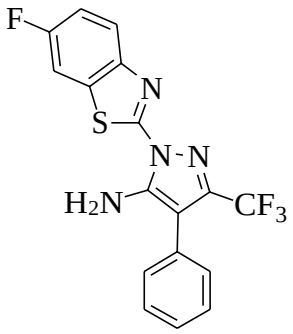
(37)

Chimenti *et al* synthesised a series of N1-substituted 3,5-diphenyl pyrazolines derivatives **(38)** were prepared and evaluated for their antibacterial activity. All synthesized compounds were showed little or no activity against different species of Gram-positive and Gram-negative bacteria of clinical relevance and against various stains of pathogenic fungi. The same derivatives exhibited a significant degree of activity against a range of *H. pylori* stains, including those resistant to the reference compound Metronidazole. Among the prepared compounds those with an N1-acetyl group and a 4-methoxy substituent in the 5-phenyl ring showed the best activity against *H. pylori* M**e**tronidazole resistant stains in the MIC range of 1–4 µg/mL [42].



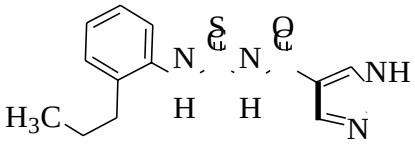
(38)

Kumar *et al* synthesized a series of 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles derivatives **(39)** in a regioselective manner. All the compounds were tested for their antibacterial property against Gram-positive and Gram-negative bacteria like *Bacillus subtilis* (NRRL B-3711), *Staphylococcus aureus* (ATCC 25923), *Micrococcus luteus* (NRRL B-1018), *Enterococcus faecium* (NRRL B-2354), *Escherichia coli* (ATTC 25922), *Proteus vulgaris*. Some compounds were more effective in inhibiting *E. coli* and *P. aeruginosa*. The antibacterial activity of these compounds compared with three commercial antibiotics namely Cefaclor and Cefuroxime axetial, One of the compound showed comparable activity with standard drugs [43].



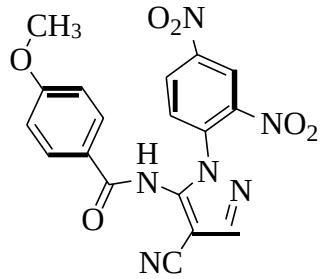
(39)

A series of N-(1-methyl-1*H*-pyrazole-4-carbonyl)-thiourea derivatives **(40)** were prepared by **Nitulescu *et al*** and evaluated for antibacterial and antifungal activities. The tested microorganisms were represented by Gram-positive (*Bacillus subtilis, Enterococcus faecalis, Staphylococcus aureus*) and Gram-negative (*Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae* and *Escherichia coli*) reference or recently isolated stains. The quantitative assay of the minimal inhibitory concentration starting from 1,000 to 1.95 µg/ml. One compound showed potent activity as compared to the respective standard drug Ciprofloxacin [44].



(40)

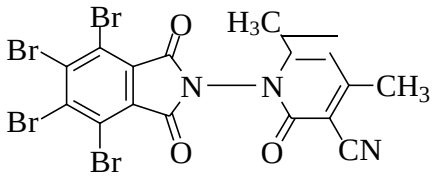
Sadeghian *et al* reported a series of 5-amido-1-(2,4-dinitrophenyl)-1*H*-4-pyrazolecarbonitriles derivatives **(41)** and were evaluated for antibacterial activity against *Bacillus subtilis* , *Staphylococcus aureus* , *Micrococcus luteus* , *Enterococcus faecium* , *Escherichia coli* , *Proteus vulgaris*. Final results showed that some compounds exhibit better antibacterial activity against *Staphylococcus aureus* and *Staphylococcus aureus* with minimum inhibition concentration (MIC) values of 3.8-15.3 µg/mL. One compound showed potent activity as compared to the standard drug Cloxacillin [45].



(41)

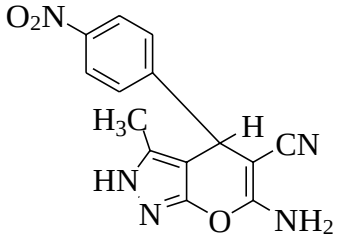
Khidre *et al* reported a new series of 1- substituted amino-4,6-dimethyl-2-oxo-pyrazole-3-carbonitrile derivatives **(42)**. The antibacterial and antifungal activities of the synthesized compounds were evaluated. Some compounds showed a comparable effect to a well known antibacterial and antifungal agents. The activity of the tested samples studied against the *Staphylococcus aureus* (RCMB000106)

and *Bacillus subtilis* (RCMB 000107) as Gram positive bacteria and *Pseudomonas aeruginoca* (RCMB 000102), *Escherichia coli* (RCMB 000103) as Gram negative bacteria. Penicillin G and Streptomycin were used as standard drugs against Gram positive and Gram negative bacteria. Also the same compounds showed the highest activity against *B. subtilis* with zones of inhibition 25.4 -26.4 respectively [46].



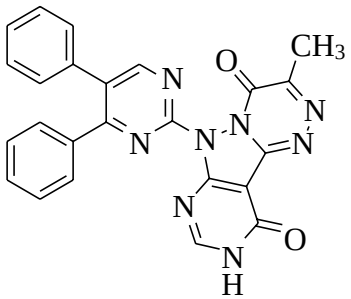
(42)

Bihani *et al* synthesized a series of aryl-3-methyl-2,4-dihydropyrano pyrazole-carbonitriles derivatives **(43)** . All the newly synthesized compounds screened for their antibacterial properties against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa.* Among the screened samples, showed excellent antibacterial activity against all the tested bacterial strains at MIC 25 µg/ml as compared with the reference drug Ampicillin [47].



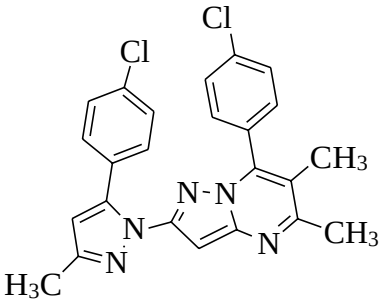
(43)

Ali *et al* synthesized a series of 3-methylthio-pyrazolo pyrimidine derivatives **(44)** and screened for their in *vitro* antibacterial and antifungal activities. The antimicrobial activities were carried out against three bacterial stains, *Staphylococcus aureus* (MTCCB 737), *Staphylococcus epidermi*dis (MTCCB 1824) and *Escherichia coli* (MTCCB 1652) and three fungal stains, namely *Aspergillus fumigatus, Aspergillus niger* and *Alternaria alternata.* The preliminary screening results indicated that some compounds showed antimicrobial activity from moderate to good MIC at 0.41 mg/mL as compared with the standard drug Bleomycin [48].



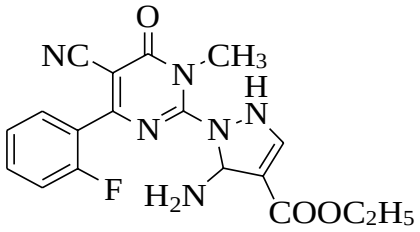
(44)

A novel series of pyrazol-10-ylpyrazolopyrimidines derivatives **(45)** were synthesized by **Aggarwal *et al*** and screened for their antibacterial activity against gram-positive and gram-negative bacterias and antifungal activity against phytopathogenic fungi. Some compounds were manifested rather broad antibacterial activity than standard antimicrobial drug Ampicillin. One lead compound at the minimum inhibitory concentration of 10 mg/ml-200 mg/ml exhibited equipotent antimicrobial and antifungal activity against all tested microorganisms when compared with standard drugs Ciprofloxacin and Fluconazole [49].



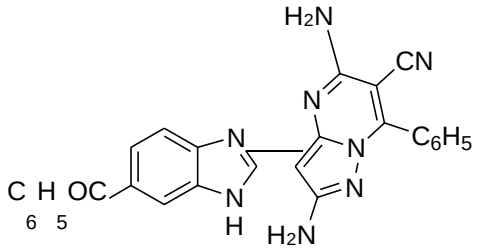
(45)

Ramesh *et al* synthesized a novel series of dihydropyrimidines with their hydrazine derivatives and subsequently their pyrazole derivatives **(46)** and were evaluated for their *in vitro* antibacterial activity against pathogenic bacterial stains namely, *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 121) as Gram-positive, *Escherichia coli* (MTCC 1652) , *Pseudomonas aeruginosa* (MTCC 741) as Gram-negative , and *in vitro* antifungal activity against pathogenic fungal stains namely, *Aspergillus niger* and *Aspergillus flavus*. One of novel compound showed potent *in vitro* antibacterial and antifungal activity at MIC value of 14.72 μg ml^{-1} against all species of Gram positive bacteria and Gram negative bacteria as compared with standard drugs Ciprofloxacin and Fluconazole [50].



(46)

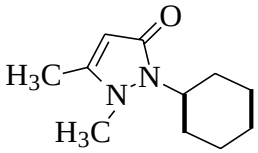
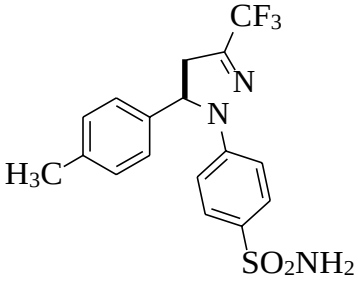
Pyrazolo pyrimidines derivatives **(47)** were synthesized by **Zaharan *et al***. Most of the synthesized compounds found to possess various antimicrobial and antifungal activities and evaluated for their *in vitro* antibacterial activity against pathogenic bacterial stains namely, *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 121) as Gram-positive , *Escherichia coli* (MTCC 1652), *Pseudomonas aeruginosa* (MTCC 741) as Gram-negative , and *in vitro* antifungal activity against pathogenic fungal stains namely, *Aspergillus niger* and *Aspergillus flavus* with minimal inhibitory concentration (MIC) values 100–250 g ml. However, one of the tested compound showed superior antimicrobial activity than the reference drug Ampicillin [51].

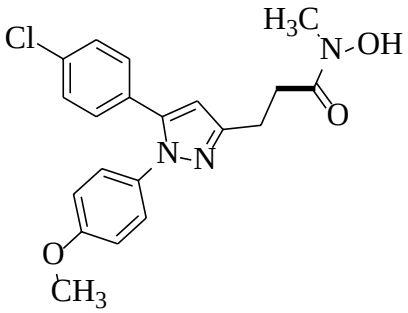
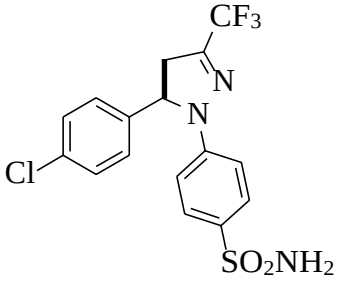
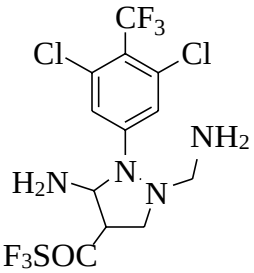
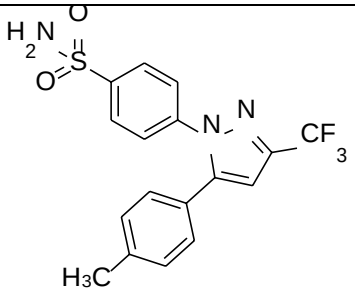
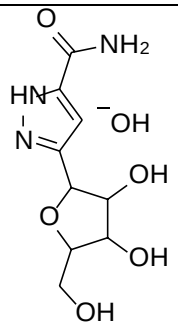


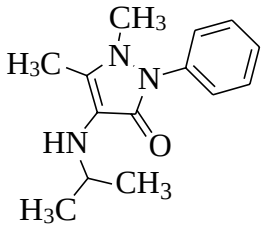
(47)

Some successful pyrazole based drugs available in clinical therapy have been summarized in the **Table no. 1.**

Table No.1: Some successful Pyrazole Based Drugs Available in Clinical Therapy [52-65].

S. No.	Brand Name	Chemical Structure	Pharmacological Use
1.	Phenazone®		Antipyretic
2.	Celecoxib®		Anti-inflammatory

3.	Tepoxalin®		Anti-inflammatory
4.	Lonazolac®		Anti-inflammatory
5.	Fibronil®		Antimicrobial
9.	Celecoxib®		Anti-inflammatory
10.	Pyrazofurin®		Antimicrobial

11.	Ramifenazone®		Antimicrobial

CONCLUSION

This review article has presented updated and comprehensive scientific information on novel pyrazole analogues having potent antimicrobial activities due to their different mode of action based on the recent literature survey. The exclusive facts provided in this manuscript may be utiliized further by medicinal chemists working in the area of antibiotic research programme to explore the antimicrobial potential of novel pyrazole derivatives for drug design and develpoment of antimicrobial agents for future to prevent the global death toll due to microbial infections.

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