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Recent Advances in Pyrazole Derivatives as Potential Antimicrobial Agents

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Abstract: The antimicrobial drug resistant against various bacterial strains have become a challenging situation for health due to which many classical antibiotics become inactive nowadays. To overcome this challenge, various antimicrobial agents have been developed to treat the infectious diseases spread by bacteria over the last decades. In the ongoing battle against bacterial infections, the need for new and effective antibacterial agents is paramount. Heterocyclic compounds regarded for drug discovery due to their drug like properties and structural characteristics. Pyrazole, a five-membered heterocyclic compound, has garnered significant attention in recent years due to its potential as an antibacterial agent. This review aims to explore the current research on pyrazole derivatives, highlight the efficacy and mechanisms of action of pyrazole as an antibacterial agent, which will be beneficial for medicinal chemists.

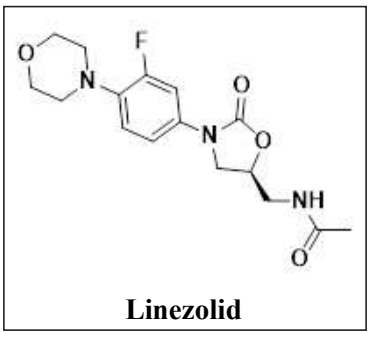
Keywords: Antimicrobial, *E. Coli,* Pyrazole, *S. Aureus, Streptococcus pneumonia*.

I. Introduction

Bacterial infection has been a persistent threat and infinite financial burden to the human healthcare system [1]. The emerging resistance of various bacteria to the presently available antibiotics became a global challenge [2–4]. The major concern is the resistance caused by few gram-positive bacteria like vancomycin-resistant *Enterococcus faecalis,* penicillin-resistant *Streptococcus pneumonia and* methicillin-resistant *Staphylococcus aureus* [5–7]. Additionally, due the shortage of new therapeutic drugs, this resistance became global problem [8-9]. Due to microbial transformations, the antibiotic drugs became less effective. To overcome this difficulty, identification of novel antibiotic drugs became the first priority these days [10]. In recent years, emergence of new antibiotic agents has gained substantial importance because of their ability to fight against several bacterial strains [11]. However, excessive use of these antibiotic agents results in the emergence of drug resistant bacteria, thus posing the major challenge to the modern healthcare [12-15]. These superbug bacteria cause the multi drug resistance, thus compelling us to develop more effective and alternative antibiotic agents.

II. Pyrazole Moiety with Antimicrobial Activity

Linezolid (Fig. 1), belongs to the oxazolidinone family and was the first marketed antibacterial drug. This unique antibiotic agent inhibits the bacterial translation by binding with 50S subunit of ribosome at the initiation phase. It has shown the activities against almost all pathogens like penicillin-resistant *Streptococcus pneumonia and* vancomycin-resistant *Enterococcus faecium* [16]. Interestingly, many fused pyrazoles have also shown remarkable biological and pharmacological properties as purine analogues [17–21].



Linezolid

Fig. 1

Pyrazole derivatives are so important scaffolds for antibiotic drugs that several reviews have been published in recent years elucidating the biological properties of pyrazole derivatives [22-28] and their Schiff bases (Fig. 2) [29]. In this review we will focus on the literature related to the anti-bacterial properties of pyrazole.

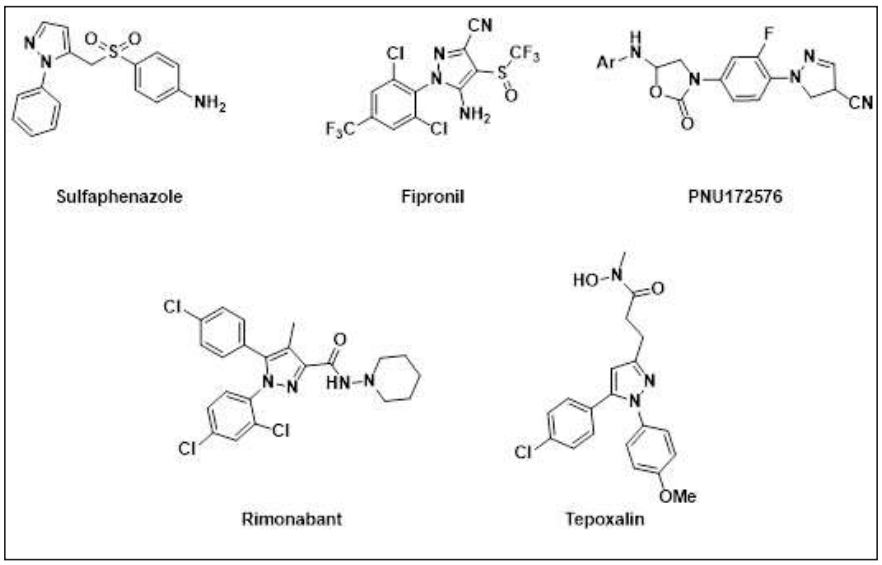


Fig. 2

G Daidone *et al.* prepared a series of novel 4-diazopyrazole derivatives and were tested anti HIV and anticancer effect. Although these derivatives did not show much activity against HIV, moderated activity against tumor cell lines (IC_{50} 2.4-20 μM) but have shown promising anti-bacterial properties against gram positive, gram negative and few stains of fungi (IC_{50} 0.8-12.5 μM) [30].

G. Menozzi *et al.* synthesised a number of pyrazole analogues and find a lead compound 3. But it showed very moderate antibacterial activity [31]. In order to enhance antibacterial activities same group prepared a series of chloro and fluoro derivatives of compound 1. These derivatives have shown interesting antimicrobial activities [32]. The compounds 2, 3 and 4 (Fig. 3) showed similar or superior inhibitory effect against gram positive bacteria compared to bifonazole. To rationalized the pharmacological result, docking studies of these derivatives have also been carried out.

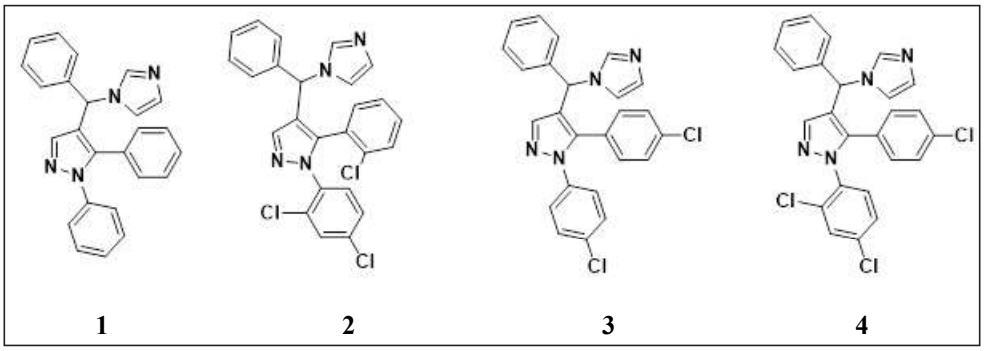


Fig. 3

Mannich bases of some pyrazole derivatives have been synthesised by non-conventional techniques like microwave-assisted reactions. These synthesised derivatives were screened for their analgesics, anti-inflammatory, antioxidant and anti-bacterial activities. The synthesised compounds were 1.06 times more effective compared to standard drugs like ciprofloxacin against gram-negative bacteria (compound 5, Fig. 4 was found to be most promising). A trend of activity was observed in these compounds that electron-donating substituents improved the antibacterial activity and most of the derivatives have shown better activity against gram-negative bacteria as compared to gram-positive bacteria [33].

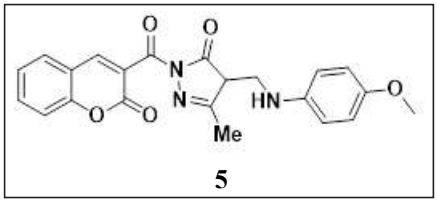
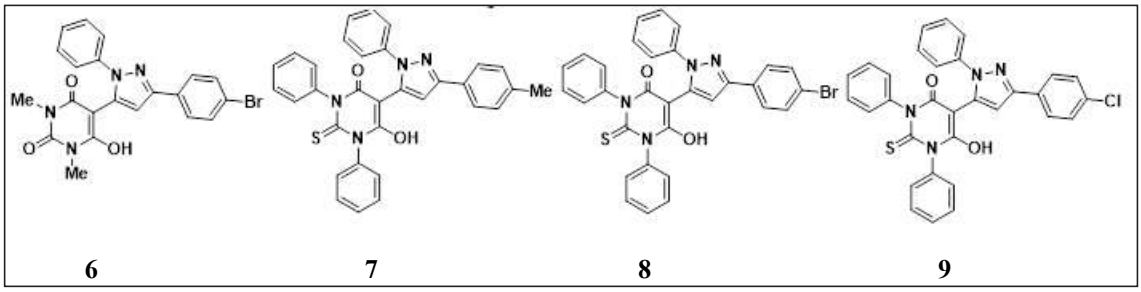


Fig. 4

Recently R. Kumar *et al.* showed the importance of combination therapy and novel heterocycles can serve as additional

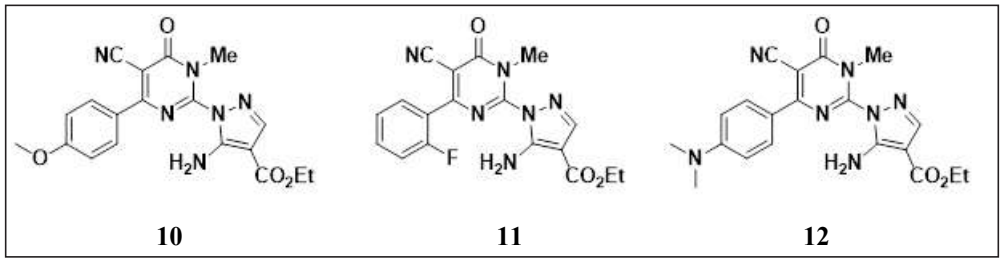
supplement to the existing antimicrobial therapy. They have synthesized the pyrimidine pyrazole derivative by using oxidative cyclisation of chalcones. The most active compound 6 has MIC 31.25 μg/mL against *Staphylococcus aureus* and *Bacillus cereus*. Antibacterial activities showed by 7, 8, and 9 (Fig. 5) was 62.50, 125.00, and 500.00 μg/mL respectively. The combination of synthesized compounds with antibiotic drugs showed synergetic effect against *A. fumigatus* [34].



6 **7** **8** **9**

Fig. 5

B. Ramesh *et al.* synthesized dihydroprimidines and their derivatives and tested for antimicrobial activities. The findings were quite interesting. The pyrazole derivatives of dihydropyrimidines 10, 11 and 12 (Fig. 6) very potent anti-bacterial activity against both Gram-positive and gram negative bacteria, while the other derivatives showed the moderate antibacterial activities. The study reveals that the pyrazole ring is responsible for the increased anti-bacterial activity and halogenation increase the antibacterial activity [35].



10 **11** **12**

Fig. 6

Yang *et al.* synthesized a series of oxazolidinone derivatives and their toxicities and antibacterial activities were evaluated. The study showed the increased effect substitution on pyrazolyl ring. All synthesized compounds have shown excellent antibacterial activities (MIC 0.25-2 μg/mL). Lead compound 13 (Fig. 7) displayed promising safety profile and water soluble salt with less bone marrow suppression [36].

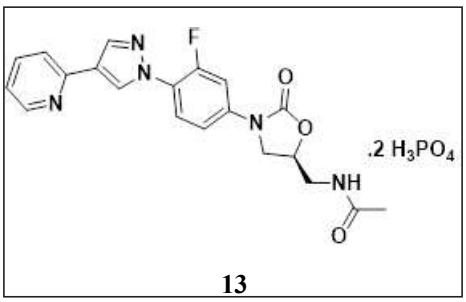


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Fig. 7

Y.-R. Li *et al.* synthesized three different series of pyrazole derivatives containing furan-carbohydrazide and aminoguanidine moieties. These derivatives were evaluated for their anti-inflammatory and anti-bacterial activities and showed strong inhibition (MIC 1.64 μg/mL) against gram positive, gram negative as well as resistant strains. Compound 14, 15 and 16 (Fig. 8) were most potent (MIC 1-2 μg/mL). Compound 18 also showed more potent anti-inflammatory activity than ibuprofen and indomethacin [37].

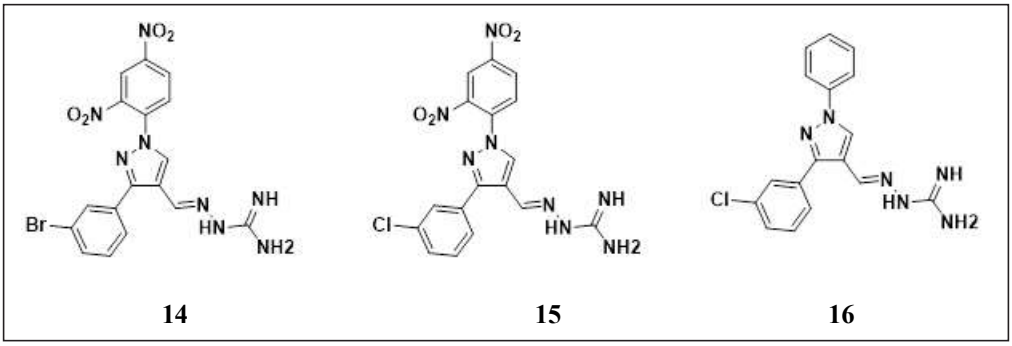


Fig. 8

Metronidazole based agents for antibacterial activities have been synthesised and found to inhibit the tyrosyl-tRNA synthetase with low cytotoxicity and potent antibacterial activity. Compound 17 was the most potent (IC_{50} 0.92 µM) against TryRS, MIC value of 0.98 µg/mL against *P. aeruginosa* and 1.96 µg/mL against *E. coli*. To find the reasons for antibacterial activity, docking studies were also performed which indicates the inhibition of tryRS may be main factor responsible for the antibacterial activities [38]. As we can see, the compound 18 with 4- methoxy substituent in the benzene ring fragment (A) exerted the highest inhibitory activity against TyrRS with an IC_{50} of 0.92 µm and afforded over 60-fold improvement over the unsubstituted analog 18.

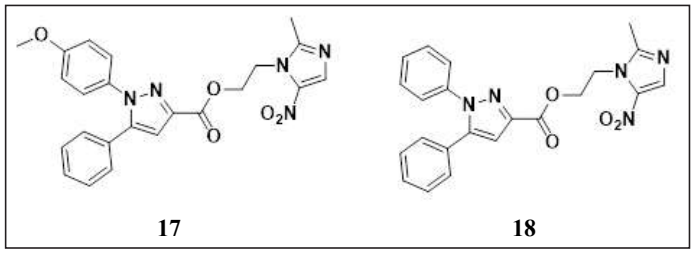


Fig. 9

The pyrazole-arginine based peptidomimetic 19 were synthesised first time by Bang *et al.* methodical modification like charge, length of peptide chain or hydrophobicity a short peptide py11 was identified as potent antibacterial agent against antibiotic resistant bacteria, gram negative bacteria (*E. Coli*, *P. aeruginosa*) and gram positive bacteria (*S. epidermidis*, *S. aureus*). The study also showed that with increase in charge and hydrophobicity will increase the antibacterial activity [39].

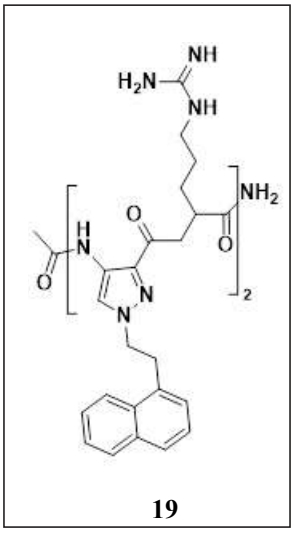


Fig. 10

Jimmy *et al.* recently reported targeting histidine kinase could inhibit the bacterial growth as this kinase is essential for the growth of bacteria. For this, they have synthesised and screened diaryl pyrazole Hsp90 inhibitors against histidine kinase present in *C. crescenrus*. The synthesized derivatives were potent against both gram-positive and gram-negative bacteria, most potent were 20, 21 and 22 (MIC 17.5, 12.3 and 11.2 µM). These derivatives were almost 10 times more potent for yeast Hsp90 compare to CckA [40].

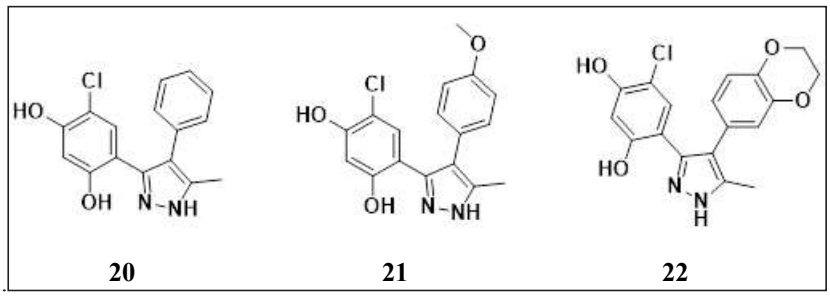


Fig. 11

S. Hassan *et al.* synthesised the fused pyrazole derivatives and their Schiff bases. All the synthesized compounds were screened for their anti-bacterial activities against MDR bacteria. The most potent were the Schiff base 23 showed MIC 7.81 µg/mL against *S. aureus* and 3.91 µg/mL against *S. epidermis* [41]. Compound 24 (a pyrazolo[1,5-a]pyrimidine) also exhibited promising activity against the *Staphylococcus aureus*.

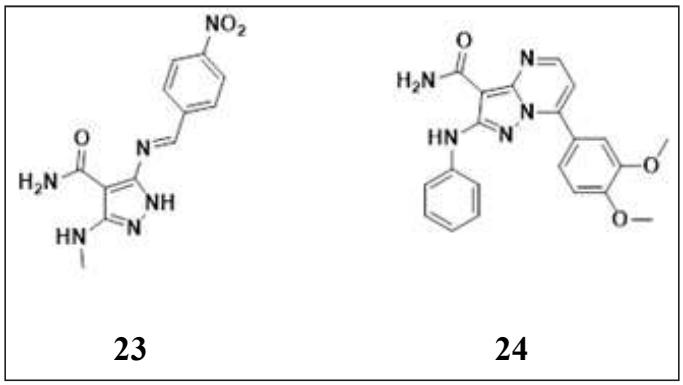


Fig. 12

A series of novel pyrazole derivatives were synthesised by Ibrahim *et al.* in 2008 and their antibacterial screening has been performed. Compound 25 showed potent anti-bacterial activity against gram positive bacteria and fungi. Compound 26 displayed more potency against *C. albicans*. While compound 27 is potent against almost all microorganisms except *C. albicans* [42].

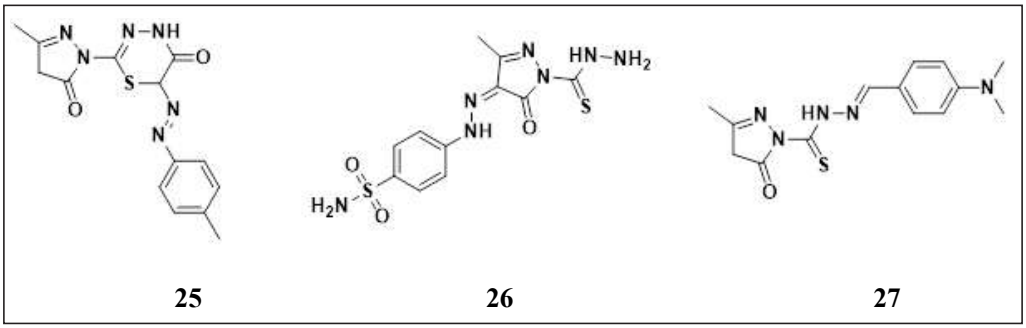
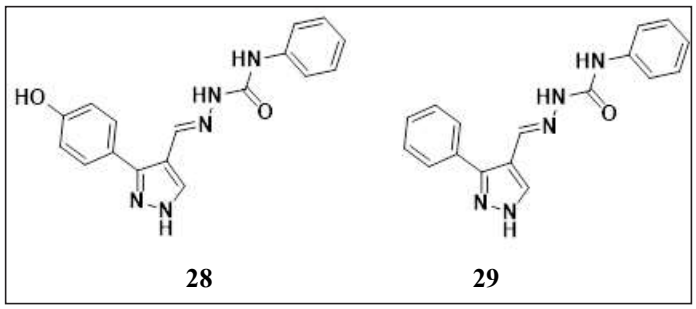


Fig. 13

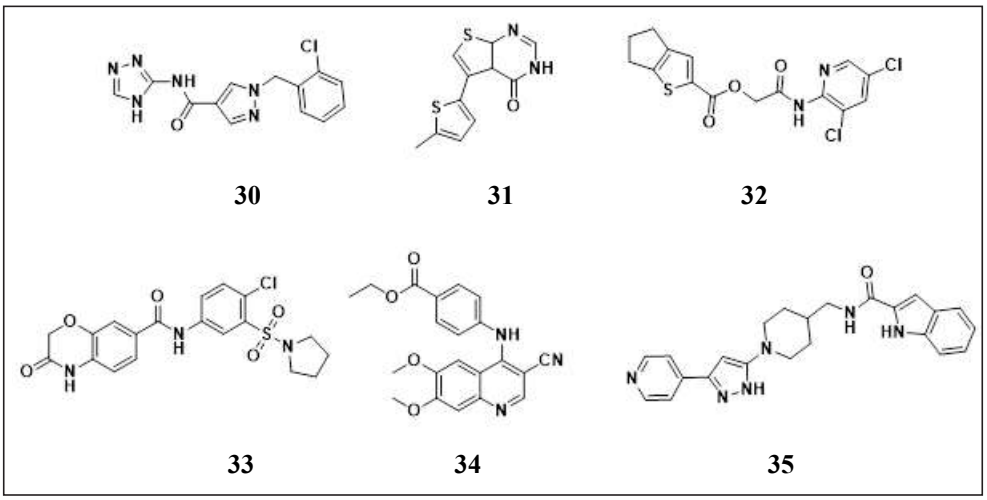
Liang *et al.* recently synthesised a series of pyrazole derivative having (thio) semicarbazide moiety. These compounds were screened for dual antimicrobial and inflammatory activities. Around 11 compounds have showed anti-bacterial activities (MIC 8-128 µg/mL). Compound 28 and 29 were most potent against *S. pneumoniae* and *S. aureus* with MIC=8µg/mL [43].



28 **29**

Fig. 14

W. Zhong *et al.* recently identified TrmD inhibitors having diverse scaffold by using bioluminescence based high throughput screening. A library of 116350 compounds was screened and 61 TrmD inhibitors were identified. Many of these inhibitors were comprising pyrazole scaffold. Almost all the pyrazole derivatives (30-35, Fig. 15) were found to be active against various strains of bacteria [44].

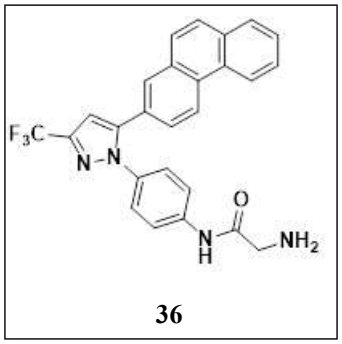


30 **31** **32**

33 **34** **35**

Fig. 15

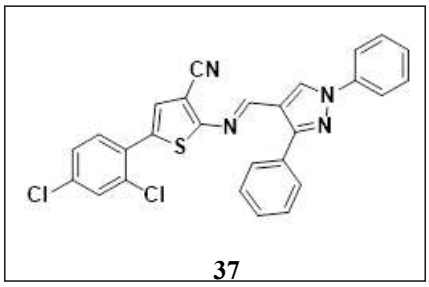
W. T. Barker *et al.* showed that an inhibitor of eukaryotic kinase, meridian in D, can modify the activities of both Gram negative and Gram positive bacteria. Commercially available libraries of gram negative bacilli were utilised for pilot screening of kinase inhibitors. The results identified a pyrazole derivative (OSU 03012) compound 36 (Fig. 16) as an active inhibitor of PDK-1 in colistin sensitive strains [45].



36

Fig. 16

Nayak *et al.* recently synthesize novel pyrazole Schiff bases having thiophene moiety and screened them for their activities against different strains of bacteria (compound 37, Fig. 17 was found to be most potent). The library of synthesised derivatives were not only showed potent antibacterial activities but also showed anti-inflammatory as well as anti-tubercular activities [46].



37

Fig. 17

Khan *et al.* prepared two series of pyrazole derivatives containing 1-substituted carbamoyl and thiocarbomoyl moieties. Almost all the prepared derivatives not only showed the moderate antibacterial activities (zone of inhibition 11-27 mm) but also showed anti-cancer properties [47]. The compounds 38, 39 and 40 (Fig. 18) were most promising.

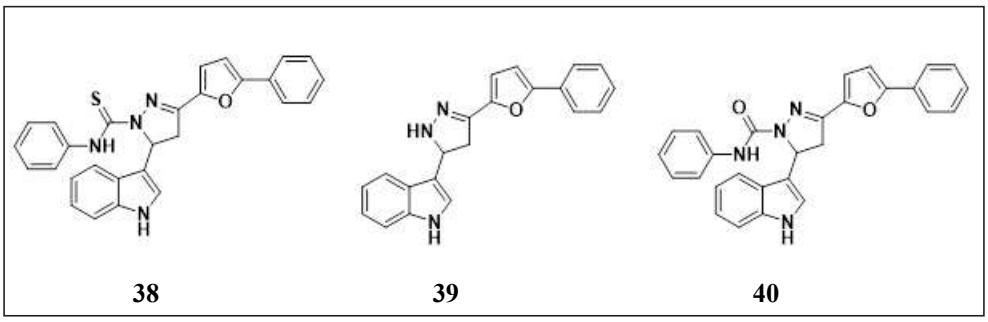


Fig. 18

Despite the promising potential of pyrazole as an antibacterial agent, further research is needed to optimize its activity, improve its selectivity, and investigate its potential toxicity and resistance mechanisms. Moreover, in vivo studies and clinical trials are required to evaluate the efficacy and safety of pyrazole compounds in treating bacterial infections in humans.

III. Conclusion

Pyrazole compounds represent a new and exciting class of antibacterial agents with broad-spectrum activity and synergistic effects when used in combination with existing antibiotics. The ability of pyrazole to target multiple essential bacterial processes makes it a promising candidate for combating drug-resistant bacteria. However, more research is necessary to fully understand the potential of pyrazole as an antibacterial agent and to translate these findings into effective clinical therapies. With continued investigation and development, pyrazole may play a significant role in the fight against bacterial infections in the future.

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