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Review Article

A RECENT UPDATE: ANTIMICROBIAL AGENTS CONTAINING PYRAZOLE NUCLEUS

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ABSTRACT

Objective: In this review, we report antimicrobial candidates containing pyrazole nucleus integrated with various functionalities.

Methods: research results by numerous scientists have been summarized from international journals indexed in reputed database such as Scopus and Web of Science.

Results: Pyrazole derivatives are much of interest as potent bioactive molecules. They have shown large bioactivities especially antimicrobial performance against broad spectrum of bacterial strains.

Conclusion: Several designed pyrazole derivates possessed good to superior antimicrobial activities.

Keywords: Antimicrobial, Antibacterial, Antifungal, Pyrazole, Bioactive.

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INTRODUCTION

Microbial spread and infection as the major cause of illness in human are main problems occurred in both developing and developed countries [1-3]. It leads a large number of dead every year [4,5]. This condition is deteriorated by the emergence of multidrugs resistance (MDR) phenomena. Old antibiotics such as tetracyclines, methicillin, aminoglycosides, macrolides, and penicillin have become less and less effective day by day [6,7]. For example, drug-resistant *Mycobacterium tuberculosis* and *Staphylococcus aureus* are found [8,9]. Therefore, continuation in developing antimicrobial agents with an attractive structural motif and activity toward organic synthesis is a great challenge.

Recently, researcher's attention has been paid to heterocycles containing nitrogen atom, particularly pyrazoles and their derivatives [10]. They have been found to denote versatile biological activities such as monoamine oxidase inhibitor [11,12], antihepatotoxicity [13,14], antileishmanial [15-17], anti-inflammatory [18-20], antiproliferative [21], tissue non-specific alkaline phosphatase inhibitor [22], cyclin-dependent kinase inhibitor [23], anticancer [24-27], antimicrobial [28-30], and antioxidant [31-33]. Development of novel chemical structures of pyrazole derivatives is currently a trending topic due to their wonderful biological actions [34-37]. In this paper, we will focus on the diverse structure of pyrazole derivatives and related compounds (e.g. pyrazolines, pyrazolinones, and pyrazolones) synthesized in the past few years and their performance as potent antimicrobial candidates.

DISCUSSION

Research in 2013

The synthesis of some new pyrazolopyridines from 4-(dimethylaminomethylene)-1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-5(4*H*)-one was investigated by El-Borai *et al.* [38]. Among the synthesized compounds, (1) exhibited remarkable antimicrobial activity against *Escherichia coli*, *Enterobacter cloacae,* and *Serratia* with inhibition zone diameter of 19, 19, and 17 nm (at 10 mg/ml sample concentration), respectively [Fig. 1]. Gaikwad *et al.* developed three series of thiazole-substituted pyrazole derivatives and investigated their antimicrobial potency [39]. The result highlighted that compound (2) exhibited strong activity against all the tested organism. However, compound (3)-(6) showed good action against *S. aureus* with inhibition values of 24.41–27.13 mm (at 128 µg/ml). Introduction of F, Cl, Br, and NO_2 groups to the phenyl ring enhanced antibacterial and antifungal capability [38]. Preparation and characterization of novel sulphapiperazine containing arylazopyrazoles were performed by Shah *et al.* [40]. Through antibacterial evaluation, 50 µg/ml of compound (7) resulted inhibition zone diameter of 84, 54, 80, 67, and 70 mm against *Bacillus subtilis*, *S. aureus*, *Salmonella typhi,* and *E. coli*, respectively. It was denoted as the most active agent in this series. At 1000 µg/ml, compound (7) also showed the highest antifungal activity with an inhibition zone of 78, 76, 77, 66, and 64 mm against *Penicillium expansum*, *B. theobromine, Nigrosspora* sp., *Trichothesium* sp., and *R. nigricun*, respectively [40].

A novel bioactive thiazolyl-pyrazoline derivatives were designed by Sharifzadeh *et al.* through one-pot three-component reactions [41]. Compounds (8) and (9) were noted to have moderate activity against *Pseudomonas aeruginosa* with inhibition zone diameter of 19 mm at sample concentration of 1000 µg/ml. Three series of new 1, 2, 4-triazoles and benzoxazoles containing pyrazole moiety were investigated in term of their antimicrobial performance [42]. Among the screened products, compounds (10) and (11) which contain 2, 5-dichlorothiophene and 2, 4-dichlorophenyl substituent, respectively, on pyrazole ring emerged as potent antimicrobial agents. These compounds have minimum inhibition concentration (MIC) values in the range of 1.6125–6.2500 µg/ml against five tested microbes. Some new pyrazolinone and pyrazole analogs containing quinoline nucleus were synthesized by Amir *et al.* [43]. From antimicrobial evaluation result, compound (12) was denoted as the most excellent agent with MIC values of 6.25 µg/ml (against *E. coli*, *Aspergillus niger,* and *Candida albicans*) and 12.5 µg/ml (against *S. aureus*). Compounds bearing electron withdrawing group such as fluoro and bromo at phenyl ring substituent of pyrazolinone and pyrazole nucleus showed better activity than compounds with electron donating group [43]. Compound (13) was chosen as the most potent antimicrobial agent in a new series of 6-amino-1-(1,3-diphenyl-1*H*-pyrazole-4-yl)methyleneamino)-4-(aryl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles [44]. The synthesis of some novel pyrazole and pyrazole derivatives bearing benzensulfonamide moiety was done by Hassan [45]. Compound (14) exhibited the highest activity against *C. albicans* strains with MIC value of 12.5 µg/ml. New derivatives of

pyrazole-3-carboxylates, 1, 3, 4-oxadiazoles and 5-aminopyrazole-4-carboxylates were synthesized by Siddiqui *et al.* [46]. Furthermore, 12 novel compounds were also screened for their antimicrobial efficacy. Compound (15) was observed to denote significant activity against *A. niger* with MIC value of 12.5 µg/ml. It has the same performance with standard drug clotrimazole.

Research in 2014

A new series of 2-*H*/methyl-3-phenyl-5-alkyl/aryl/heteroaryl-7-trifluoromethylpyrazolo (1,5-a) pyrimidines were developed by Aggarwal *et al.* and were tested for their antimicrobial activity [47]. All tested compounds possessed moderate antibacterial activity against *S. aureus* and *B. subtilis* as Gram-positive bacteria [Fig. 2]. Among them, compounds (16) and (17) were selected as the most potent agent with inhibition zone diameter between 15.6 and 19.3 mm. Kumar *et al.* synthesized some new pyrimidine pyrazole heterocycles [48]. Following antifungal evaluation, compounds (18) and (19) showed synergy with standard drug ketoconazole at 1:8 (6.25:50.0 µg/ml) and 1:4 (25:100 µg/ml) against *Aspergillus fumigatus* (ITCC 4517) and *A. fumigatus* (VPCI 190/96), respectively.

Lavanya *et al.* reported the synthesis of some novel (1,4-phenylene) bis (arylsulfonylpyrazoles and isoxazoles) by 1,3-dipolar cycloaddition of nitrile imines and nitrile oxides [49]. In pyrazole series, compound (20) exhibited promising activity against both of Gram-positive and Gram-negative bacteria. However, among the synthesized compounds, the study revealed that compound which contains isoxazole nucleus has better activity than compound with pyrazole ring. Malladi *et al.* developed new analogs of 2,5-disubstituted-1, 3, 4-oxadiazoles bearing pyrazole skeleton [50]. Following *in vitro* evaluation of antimicrobial performance, compounds (21) and (22) were noted to have appreciable activity against *E. coli*, *S. aureus,* and *P. aeruginosa* strains with diameter of zone inhibition in the range of 9–13 mm. These compounds also showed remarkable antifungal activity against different strains of *Aspergillus flavus*, *C. keratinophilum,* and *C. albicans* [50].

One-pot multicomponent synthesis and biological benefit of some new quinazolin-4(*3H*)-one integrated with 1,3-diphenyl-1*H*-pyrazole system were studied by Mehta *et al.* [51]. Among the prepared compounds, compound (23) was chosen as the most prominent agent against some Gram-positive and Gram-negative bacteria. Furthermore, this compound exhibited excellent action as anti-*M. tuberculosis* with 98% of inhibition using Rifampicin and Isoniazid as positive controls. From a novel series of 2-(5-methyl-1,3-diphenyl-1*H*-pyrazole-4-yl)-5-phenyl-1,3,4-oxadiazoles developed by Ningaiah *et al.*, compound (24) was selected as the most potent antimicrobial agent [52]. Compound (25) showed most excellent antibacterial activity in a new series of 5-(thiophen-2-yl)-phenyl pyrazolines synthesized by Rani and Mohamad [53]. The hybrid of pyrazole-quinoline-pyridine as a novel class of antimicrobial candidates was developed by Sangani *et al.* [54]. Based on antimicrobial evaluation in term of MIC values, compounds (26) and (27) were denoted as the most promising candidates. Mishra *et al.* studied the synthesis and antibacterial action of 3-substituted pyrazole derivatives [55]. Compound (28–30) showed moderate to feeble inhibition against both Gram-positive and Gram-negative bacteria.

Research in 2015

Polysubstituted and condensed pyrazolopyranopyrimidine and pyrazolopyranotriazine were developed by Hafez *et al.* and were subsequently found to exhibit activity against certain microbial strains [56]. Compound (31) was the most active antifungal agent. It has better performance than fluconazole [Fig. 3]. Meanwhile, compound (32) exhibited excellent activity against bacteria which was higher or equal to MIC of norfloxacin [56]. Synthesis and antimicrobial screening of acetyl sulfonamide pyrazoles, substituted 4,5-dihydropyrazole-1-carbothioamide and 4,5-dihydropyrazole-1-isonicotinoyl derivatives were presented by Hamada and Abdo [57]. Compound (33) showed most potent activity against *S. aureus* and *C. albicans* with inhibition zones of 21 and 24 mm, respectively. The presence of pharmacophores

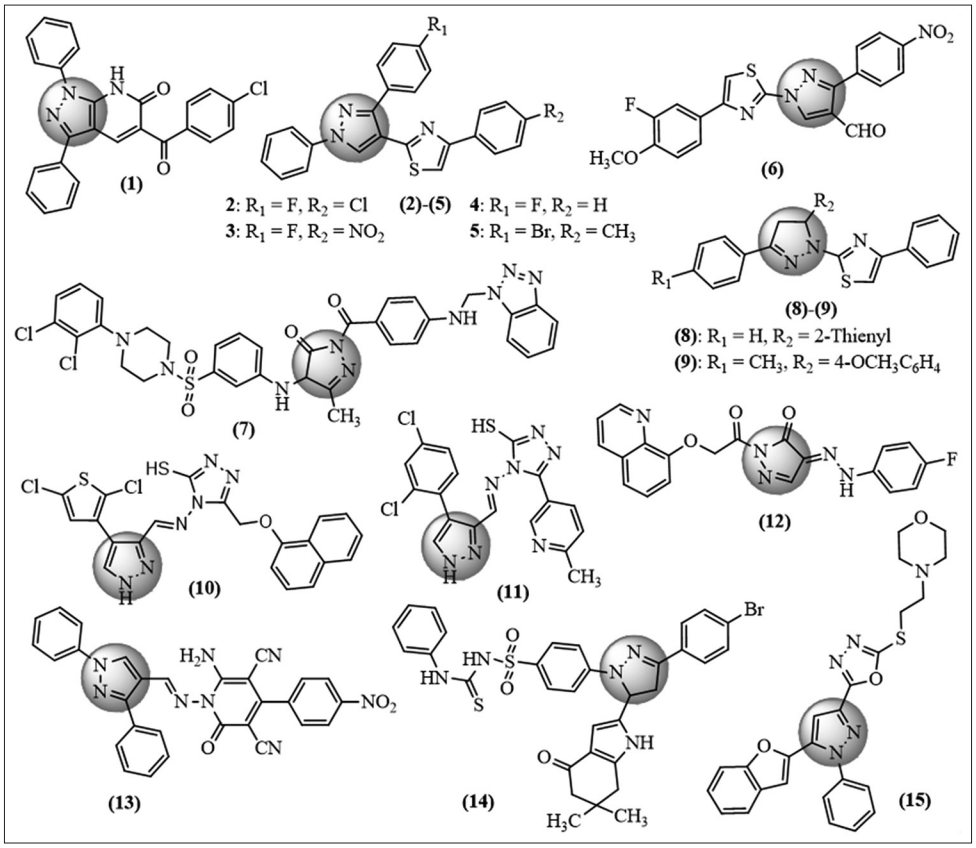

Fig. 1: Structure of compounds (1)–(15)

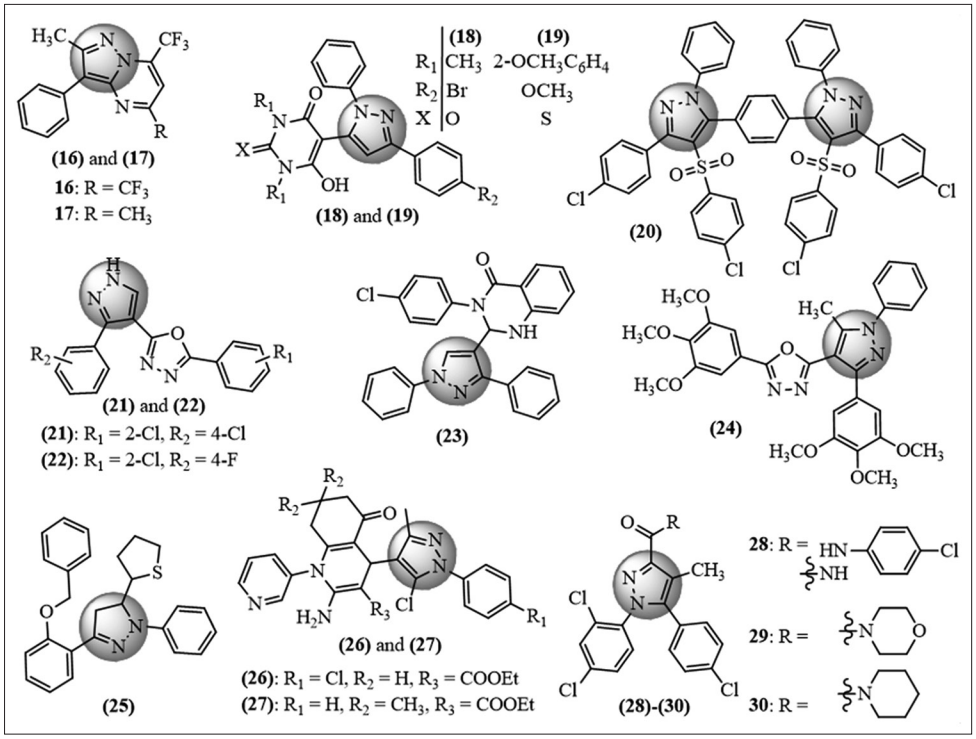

Fig. 2: Structure of compounds (16–30)

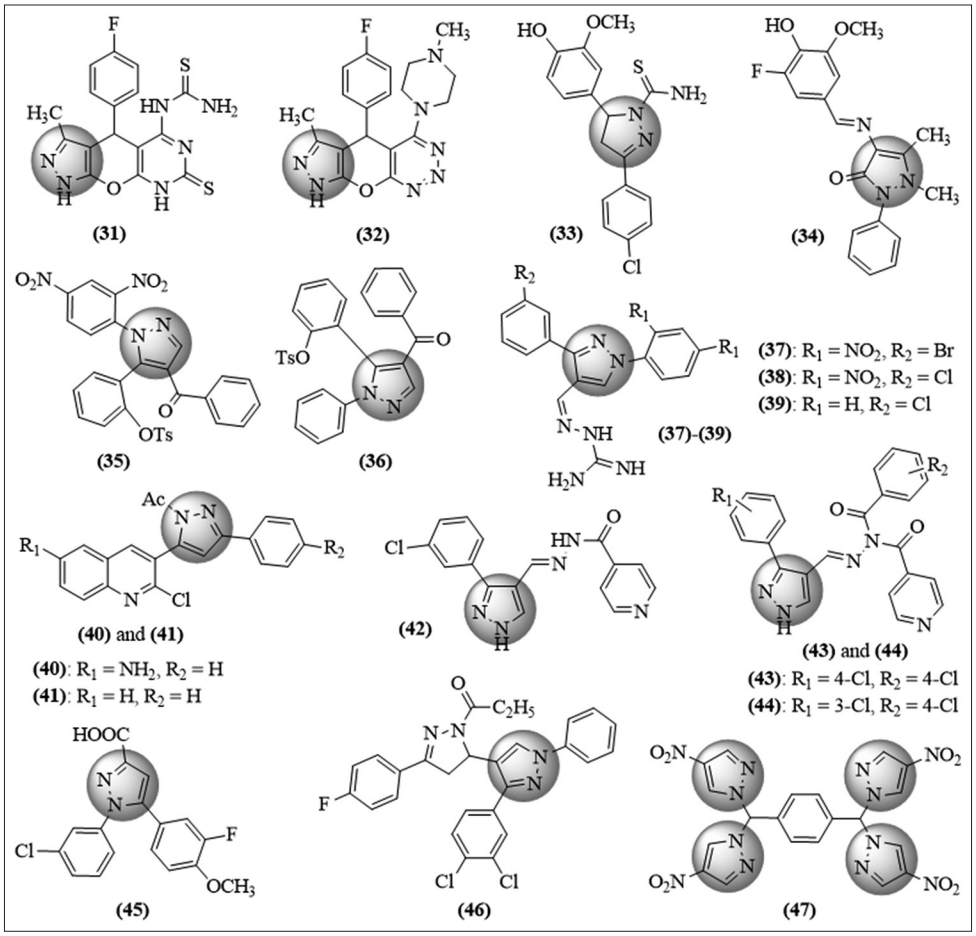

Fig. 3: Structure of compounds (31–47)

with lipophilic properties such as chloro and bromo enhances the antimicrobial efficacy.

A remarkable antibacterial effect against *S. pneumoniae*, *E. faecalis,* and *H. influenzae* of (34) was recorded by İskeleli *et al.* [58]. Unfortunately, it has no antifungal effect for selected fungal isolates. The multicomponent cyclo-condensation reaction of 1-phenyl-3-(2-(tosyloxy)phenyl) propane-1,3-dione, N,N-dimethylformamide dimethyl acetal and hydrazine or hydroxylamine hydrochloride or 2-aminothiophenol or 2-aminophenol or benzene-1,2-diamine was used to prepare some novel pyrazole, isoxazole, and other heterocyclic models [59]. In pyrazole series, compound (35) was denoted to give appreciable activity against all tested microbes. Compound (36) has similar performance to compound (35) except against fungi *Fusarium oxysporum;* no effect was observed [59]. Preparation and biological testing of 1,3-diaryl pyrazoles bearing aminoguanidine or furan-2-carbohydrazide functionalities have been done by Li *et al.* [60]. Most of the prepared compounds exhibited promising action against several Gram-positive and Gram-negative bacteria with MIC values between 1 and 64 µg/ml. Specifically, compounds (37–39) were highlighted as the most active candidates against both bacterial and fungal strains with MIC values of 1 or 2 µg/ml. A novel series of pyrazoles decorated with 2-chloroquinoline nucleus have been synthesized and evaluated for antimicrobial activity by Miniyar *et al.* [61]. Among the series, compound (40) moderately inhibited *A. fumigatus*, *P. notatum,* and *B. subtilis* with MIC 48, 46, and 44 µg/ml, respectively, whereas compound (41) was noted as an active agent against *E. coli*, *P. notatum,* and *B. subtilis* with MIC 43, 57, and 54 µg/ml, respectively [61].

Nayak *et al.* successfully designed a novel series of isonicotinohydrazide based pyrazole derivatives [62]. Following *in vitro* evaluation of antibacterial activity, three derivatives (42–44) showed high performance against the tested bacteria having zone inhibition in the range of 15–25 mm. Raundal *et al.* have synthesized and characterized novel 1,5-disubstituted pyrazole and isoxazole derivatives [63]. All the prepared compounds have been investigated for the antibacterial and antifungal potency. Interestingly, all the tested samples perform good activity, however, compound (45) possess highest performance. In the study conducted by Viveka *et al.*, the design synthesis and antibacterial activity of some novel pyrazolyl-pyrazolines have been developed [64]. The bioactivity test revealed that compound (46) that contains N-propionyl pyrazolyl-pyrazoline could be identified as the most promising candidate for an antibacterial agent with zone inhibition diameter within 15–28 mm against Gram-positive and Gram-negative bacteria. The compounds with multi-pyrazole nucleus and their application as antibacterial agents have been synthesized and evaluated by Wang *et al.* [65]. Compound (47) was found to be the most active with superior area of zone inhibition of 431.81 and 222.14 mm 2 against *S. aureus* and *B. subtilis,* respectively.

Research in 2016

Phenyl-pyrazolines and isoniazid-pyrazolines were prepared by Ahmad *et al.* starting from *p*-acetamidophenol initial substrate [66]. Newly obtained pyrazolines showed interesting antibacterial activity toward bacterial and fungal strains [Fig. 4]. Specifically, compound (48) exhibited excellent antibacterial potency against *S. aureus* and *P. aeruginosa* with MIC 3.12 µg/mL. On the other hand, compound (49) has been identified as the most potent antifungal performance against *A. niger* and *C. albicans* (MIC 3.12 µg/mL) [66]. Akondi *et al.* described the in water synthesis of pyrazolone derivatives containing 2-naphtol skeleton using Ce/SiO_2 composite catalyst [67]. Overall, compound (50) was recorded as the most potent antimicrobial candidate through *in vitro* assay against *Micrococcus luteus*, *B. subtilis*, *Salmonella paratyphi*, *S. typhi*, *C. albicans,* and *Trichoderma viride* with zone of inhibition between 20 and 28.5 mm. In addition, it moderately inhibits the growth of *S. mutans* and *P. aeruginosa* (14.5 and 13.5 mm, respectively). Pyrazole compounds integrated with 1,4-benzothiazine moiety have been developed by Dabholkar and Gavande [68]. Through antimicrobial assay, compound (51) was found to be the most promising candidate in this series against some Gram-positive, Gram-negative bacteria, and fungi with zone of inhibition in the range of 10–17 mm.

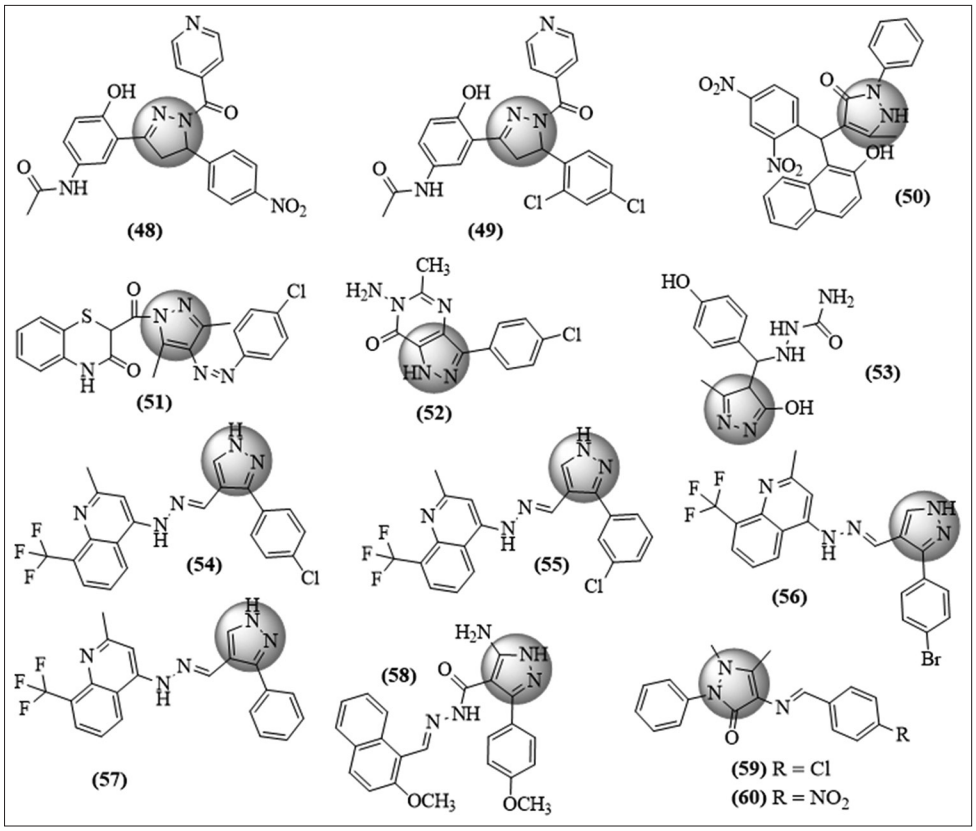

Fig. 4: Structure of compounds (48–60)

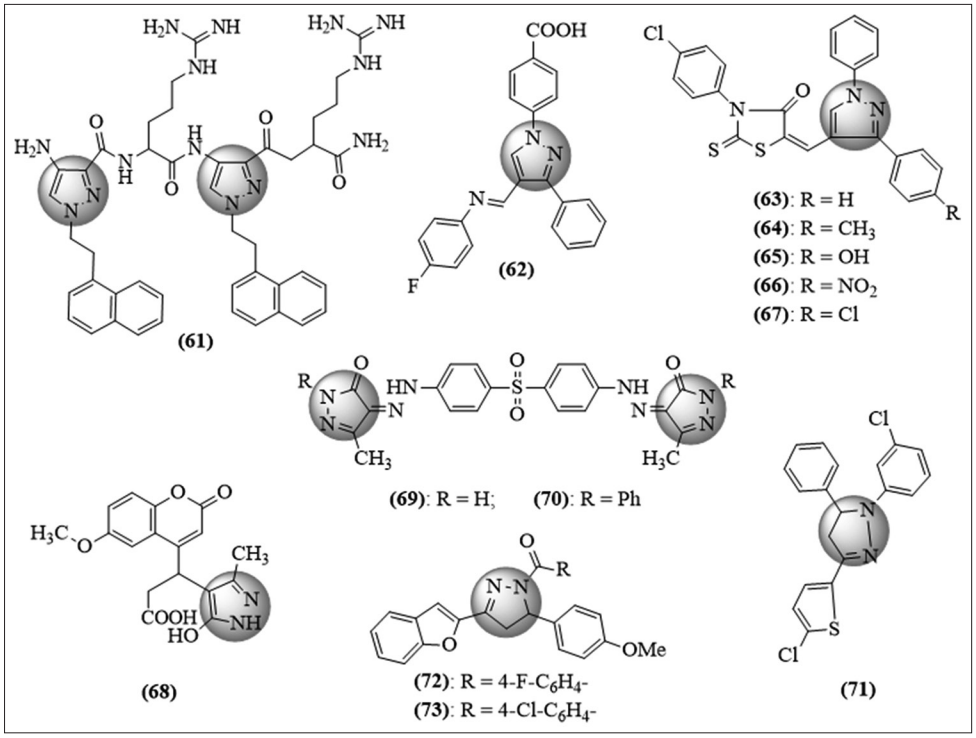

Fig. 5: Structure of compounds (61–73)

Antimicrobial assessment was carried out for newly synthesized pyrazole derivatives containing oxa/thiadiazolyl or pyrazolyl moieties and pyrazolopyrimidine derivatives [69]. Among the prepared compounds, there were seven candidates that showed excellent activity compared to standard drug. However, compound (52) was selected as the best agent. Surendra Kumar *et al.* explored the synthesis of novel pyrazole analogs and screened them for antimicrobial potency [70]. Compound (53) was found to be the most promising candidate against Gram-negative bacterial strain of *E. coli* (MIC 0.25 µg/mL and zone of inhibition 28 mm). Quinoline-pyrazole hybrid derivatives containing fluorine moiety were synthesized and screened for antibacterial activity by Nayak *et al.* [71]. From *in vitro* test, it was found that compound (54–57) exhibited substantial inhibitory activity against bacterial strains with inhibition zone diameter within 15-24 mm. Refat and Fadda reported the synthesis and antimicrobial activity of some novel hydrazide, pyrazole, triazine, isoxazole, and pyrimidine derivatives [72]. Surprisingly, pyrazole (58) was denoted as the most potent compound within this research result. It could be concluded that pyrazole is one of the lead compounds for antimicrobial agent. A series of Schiff's bases of substituted (4*E*)-4-(benzylideneamino)-1,2-dihydro-2,3-dimethyl-1-phenylpyrazol-5-ones have been prepared starting from 4-AAP and benzaldehyde derivatives [73]. Based on Kirby–Bauer protocol for antimicrobial assay, it was noted that compounds (59) and (60) exhibited the high activity against bacterial as well as fungal strains, such as *B. subtilis*, *P. aeruginosa*, and *A. niger*. Schiff's bases containing 4-Cl and 4-NO_2 moieties presented good inhibitory activity [73].

Research in 2017

Ahn *et al.* reported the first route to pyrazole-arginine derived from novel synthesized N-alkyl/aryl pyrazole amino acids [74]. Compound (61) proved to be a promising lead compound of antimicrobial agent against MDR bacteria, such as methicillin-resistant *S. aureus* (MRSA), MDR *P. aeruginosa* (MDRPA), and vancomycin-resistant *Enterococcus faecium* (VREF) strains [Fig. 5]. Compared to melittin as reference drug, it showed 2-folds, 2-4-folds, and 4-folds of better activity against MRSA, MDRPA, and VREF, respectively. A superior antimicrobial activity with zone of growth inhibition up to 85 mm against *Acinetobacter baumannii* was displayed by 4-(4-formyl-3-phenyl-1*H*-pyrazol-1-yl) benzoic acid, a compound in a series prepared by Allison *et al.* [75]. A new series of pyrazole derivatives containing 2-thioxothiazolidine-4-one were studied by Bhatt and Sharma [76]. Antimicrobial evaluation of the synthesized products revealed that compounds (63–65) were found as promising candidate for anti-*S. aureus* activity. Furthermore, compound (66) showed a potent activity against *E. coli* strains. Meanwhile, a very good activity against *C. albicans* was showed by compound (64) and (67). Chougala *et al.* developed an eco-friendly and green method of multicomponent reaction for the synthesis of coumarin-based pyrano [2,3-*c*]pyrazole derivatives [77]. All synthesized compounds have shown the interesting result to be drug candidates. Compound (68) was found having excellent activity against Gram-positive and Gram-negative bacteria (minimum inhibitory concentration [MIC] 0.78–6.25 µg/mL).

Mehta *et al.* developed new mono and bisphenyl integrated bispyrazole and bispyrazolone derivatives, then evaluated their antimicrobial performance [78]. Compound (69) and (70) demonstrated good inhibitory activity against some bacterial strains with zone of inhibition in the range of 19–27 mm. The title compound 1-(3-chlorophenyl)-3-(5-chlorothiophen-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole was prepared and screened for antimicrobial activity by Prabhudeva *et al.* [79]. *In vitro* test of the ligand (71) revealed that this compound has moderate inhibitory activity against *B. subtilis* and *A. flavus*. Meanwhile, against *S. aureus* and *E. coli*, it showed good performance with MIC 20 µg/mL, same with Streptomycin as positive control. A novel class of 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole derivatives was designed by Rangaswamy *et al.* [80]. Using well plate method for antimicrobial assay, compound (72) and (73) exhibited good inhibitory activity against *E. coli*, *S. aureus,* and *P. aeruginosa*.

CONCLUSION

Several developed pyrazole derivatives possessed good to superior antimicrobial activities. This current review provides important information for the upcoming design of new antimicrobial agents based pyrazole skeleton.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

Bayu Ardiansah responsible for collecting data from literatures and writing the manuscript.

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