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A REVIEW ON MULTISTEP SYNTHESIS STRATEGIES OF AZOLE-BASED ANTIBACTERIAL AGENTS

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Abstract:
This article reviews current multistep synthesis strategies of azole-based antibacterial agents. In recent years, extensive use of chemical agents in treating different diseases resulted in the development of drug resistance. The war on multidrug resistance has resulted in the most significant loss to the world's economy. Thus, the expansion of development of novel and potential candidates such as azoles and its derivatives is an escalating area in the field of medicinal chemistry. Azole compounds are increasingly being considered necessary in drug discovery paradigms as a number of them serve as lead compounds for the discovery of potent therapeutic agents. They have been used to treat bacterial, fungal, malarial, viral, and other general infections. They have also been known for their anticancer and anti-inflammatory activities. Their efficacy has been attributed to their electron-rich property, resulting in the formation of non-covalent bonds to the receptor proteins. Current research has given us a significant collection of synthetic strategies in the progress of azole compounds. This review article describes the survey of literature regarding multistep synthetic methods in the preparation of azole-based compounds and their antibacterial properties in the.

Keywords: *Antibacterial agents, azole derivatives, multistep synthesis and antifungal agents.*

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INTRODUCTION:

Organic chemists have given exceptional attention to the synthesis of heterocyclic compounds as it is a significant part of the overall pharmaceutically important compounds. Over 50% of the total organic chemistry research is about the synthesis and development of heterocyclic compounds. Many of the biologically active compounds consume heterocycles as the precursor scaffold.1 Many heterocyclic compounds, including amino acids or peptides conjugated heterocycles,2 Schiff bases derived from heterocycles,3 coumarin heterocyclic derivatives,4 spiro heterocyclic compounds,5 azoles, azines, and azepines derivatives,6–8 imidazoles,9 pyrroles,10,11 indoles,12,13 quinolines,14–17 are known for their biological activity. Among the classes of compounds described above, azoles have gained special attention as therapeutic agents. Azoles are a broad class of five-membered heterocycles with one nitrogen atom and at least one non-carbon atom (i.e. nitrogen, sulfur, or oxygen) as part of the ring.18 Azoles or their derivatives are known to possess antibacterial.6 anticancer,19,20 antifungal,19–21 anti-inflammatory,22,23 antimalarial,24,25 anti-trypanosomal,26–28 anti-tuberculosis,29–31 and antiviral activities.32–34 This wide range of activity exhibited by the azoles and their derivatives results from their electron-rich property. This special nature enables the formation of non-covalent interactions such as hydrogen bonds, coordination bonds, ion-dipole, cation-p, p-p stacking, hydrophobic, and van der Waals interactions with enzymes and receptors.35 For decades, azole-based drugs have been used in treating different diseases. Anticancer drugs such as Dacarbazine,36 Zoledronic acid,37 and Tipifarnib38 (Figure 1) were effectively used to treat different types of cancers. Azathioprine39 is a commonly used immunosuppressant. It is used in rheumatoid arthritis, Crohn's disease, ulcerative colitis, and kidney transplants to prevent rejection. A highly exploited and commercialized use of azoles is their activity against Fungus. A wide variety of antifungal azoles have been commercialized and used for many years. Janssen Pharmaceutica in 1981 produced Ketoconazole, FDA approved drug for systemic use40; this was followed by the development of different azoles such as Fluconazole and Itraconazole. Disadvantages associated with these drugs are long-term side effects, toxic effects due to drugdrug interactions, development of drug resistance, and unfavorable pharmacokinetics. The second generation of antifungal azoles was prepared to overcome these issues, consisting of Voriconazole and Ravuconazole41–43 (Figure 2). There is one challenge that researchers continue to face is the development of drug resistance. It is a reduction in the effectiveness of treating a disease using an antimicrobial or an antineoplastic agent. Another term used to describe the condition is drug tolerance, which indicates a drug's reduced activity due to repeated use. The lion's share of the drug resistance reported against the antimicrobial azoles. Unrestricted use of azole-based hydrophilic compounds resulted in the induction of resistant strains.44 Many studies indicated that the drug resistance could evolve in conditions where there is an insufficient intracellular content of azole. This can occur due to impermeability issues, inactivated uptake systems, multidrug resistance genes, and induction of resistance by cytochrome P450-dependent-14-a-demethylase.45–48 other problems like Liver toxicity, hormone-related issues, phototoxic effects, hair loss are few other commonly associated side effects of azole drugs.49 Apart from these, specific drugs such as Dacarbazine, Azathioprine, Ketoconazole are well known for their various adverse effects.[1,2]

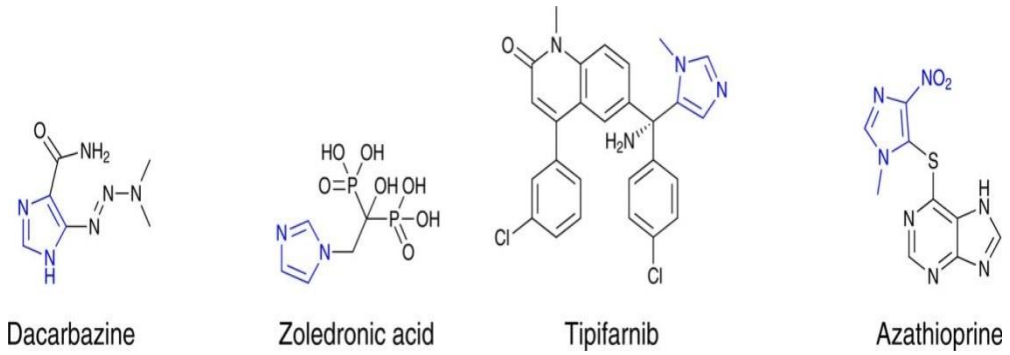


Figure1: Commercial anticancer drugs and immunosuppressant azathioprine

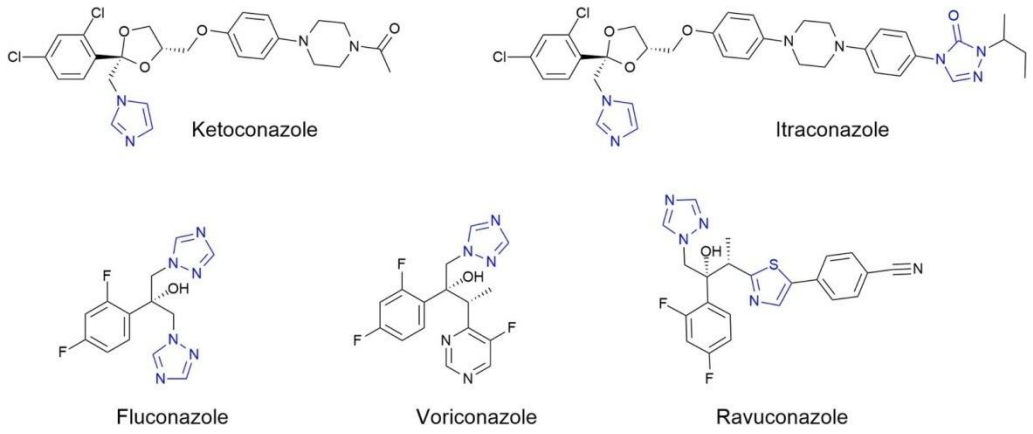


Figure 2. First-andsecond-generation antifungal azoles

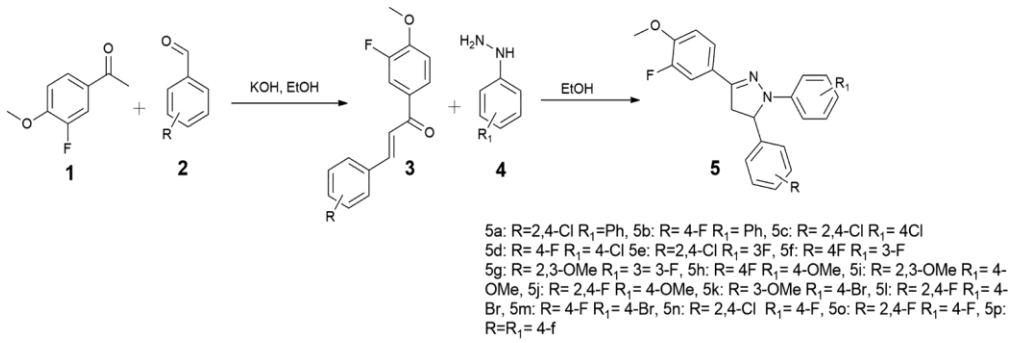
Difficulties discussed above led to new azole compounds with improved biological activity, lesser side effects, and superior quality. This review is a compilation of progress in the synthesis and biological evaluation of new Antibacterial azole derivatives in the last past years. [3]

MULTISTEP SYNTHESIS AND ANTIBACTERIAL EVALUATION OF AZOLE DERIVATIVES

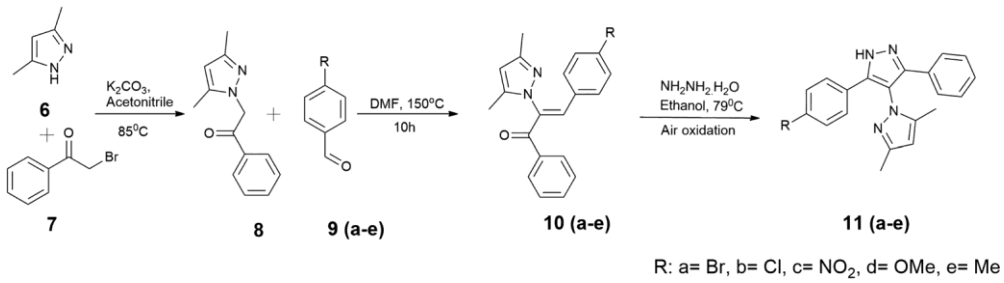
Synthesis and antibacterial evaluation of diazole derivatives

A series of 1,3,5-triaryl-4,5-dihydro-1H-pyrazole derivatives were synthesized from 3-fluoro-4-methoxy acetophenone (1) (Scheme 1), and the synthesized compounds were screened for their antibacterial activity. A mixture of 4-methoxy-3-fluoroacetophenone (1), substituted aromatic aldehydes (2), and potassium hydroxide in ethanol was stirred at room temperature for 10–12 h. The obtained product (3) was further treated with phenylhydrazine or substituted phenyl hydrazines hydrochloride (4) and refluxed for 8–10 h to get the 1,3,5-triaryl-4,5-dihydro-1H-pyrazole derivatives (5). The antibacterial activity of 1,3,5-triaryl-4,5-dihydro-1H-pyrazole products (5a–p) was evaluated against two Gram-negative bacteria, namely, Escherichia coli (NCIM-2256) and Pseudomonas aeruginosa (NCIM-2036), and two Gram-positive bacteria, namely, Staphylococcus aureus (NCIM-2901), and Bacillus subtilis (NCIM-2063), using Ampicillin and Ciprofloxacin as standard drugs. All the compounds showed lesser activity than Ciprofloxacin against all the tested bacterial strains. However, compared to Ampicillin, except (5h) and (5i), all showed good activity against B. subtilis. Compounds (5f, n, m, p) are said to have broad-spectrum activity against Gram-positive and negative bacteria.51 Claisen–Schmidt condensation followed by Michael's addition reaction was used to synthesize a series of azole derivatives by Rani et al. (2017). A mixture of 3,5-dimethyl-1H-pyrazole (6), 2- bromo acetophenone (7), and potassium carbonate in acetonitrile was refluxed at 85 C for 5 h to obtain the product (8). This was then refluxed at 155 C with 4-substituted benzaldehyde (9) in N,N-dimethylformamide (DMF) for 10 h in the presence of a strong base like sodium hydride. Final products (11a–e) were formed by the reaction of (10a–e) with hydrazine hydrate, respectively (Scheme 2). (11a–e) were screened for their antibacterial activity against five bacterial strains, three grampositive B. subtilis, B. cereus, S. aureus, and two gram-negative, E. coli, P. fluorescens. All the compounds tested showed moderate to excellent inhibition against both types of bacteria except in the case of P. fluorescens. Compounds were found to be more effective against gram-positive bacteria compared to gram-negative bacterial strains. Structure-activity relationship (SAR) studies revealed that compounds with electron donor groups such as chloro/methoxy derivatives (11b–d) are more active.52 A series of novel naphthalimide-derived metronidazoles were designed and synthesized for the first time and studied for antibacterial activity. The synthesis was carried out by J. Kang associates through a multistep synthetic procedure as outlined in Scheme 3. 53 Commercially available naphthalic anhydride (12) was used as the starting material. Compound (12) was treated with aq. NH3 to produce intermediate (13), then further reacted with chloroacetone in DMF under basic conditions to afford (14). The compound's bromination yielded compound (15). This was coupled with 2-methyl-5-nitroimidazole in DMF using potassium carbonate as the base. The reduction of Nitroimidazole coupled product (16) with sodium borohydride followed by the N-alkylation with various alkyl amines in dimethyl sulphoxide using potassium carbonate as base and copper (I) oxide as a catalyst, produced a series of amino-type substituted naphthalimide metronidazoles (17a–g). Antibacterial studies revealed that compounds (17a–g) had better antibacterial activity than

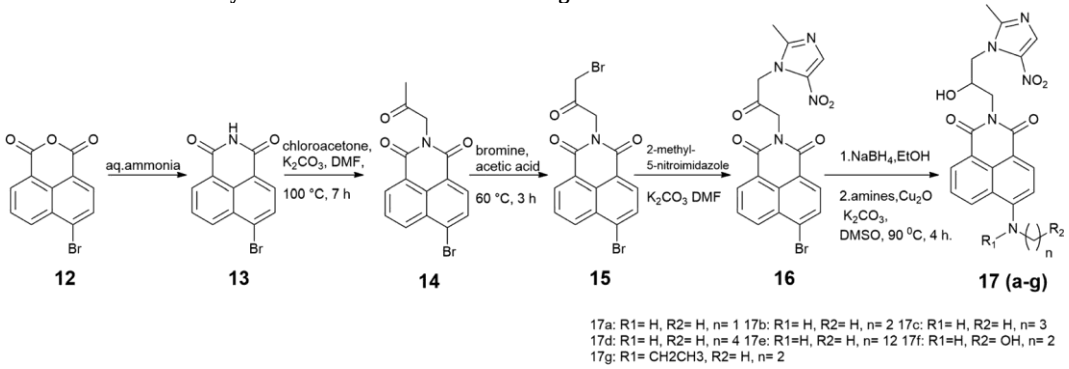
compounds (16), implying the amino group's positive effect on its biological activity. Among the (17) series of compounds, (17b) showed relatively good broad-spectrum activity. An excellent Minimum Inhibitory Concentration (MIC) value of 0.002 mmol/mL was shown against P. vulgaris, which was 95-fold more potent than reference drug Metronidazole. Compound (17b) also exhibited better activity against S. dysenteriae and E. coli (DH52) with MIC values 0.01 and 0.04 mmol/mL, respectively in comparison with Chloromycin (MIC ¼ 0.05 and 0.10 mmol/mL, respectively). A ciprofloxacin-azole hybrid series was prepared and their in vitro biological activities were carried out by the team lead by Z. Xu in 2017. Hybrids (22a–b) were synthesized as shown in Scheme 4. 54 Azole (18) was first alkylated with 1,2-dibromoethane or 1,3-dibromopropane in the presence of K2CO3. N-(2-bromoethyl/3-bromopropyl) azole (20) was treated with 8-OMe ciprofloxacin at room temperature in the presence of K2CO3 to obtain the 8-OMe ciprofloxacin-azole hybrid. All the tested compounds showed a similar spectrum of activity to that of Ciprofloxacin and the standard levofloxacin. Apart from this observation, it was also concluded that ethylene imidazole hybrid (22a) has much better activity than the corresponding propylene imidazole hybrid (22b).[4,5]



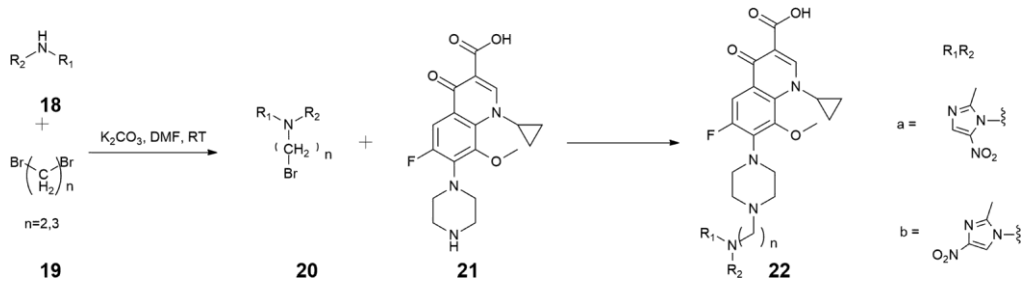
Scheme1.Synthesisof 1,3,5-triaryl-4,5-dihydro-1*H*-pyrazolederivatives



Scheme2.Synthesis of azole derivatives through Claisen Schmidt condensation and Micheal addition



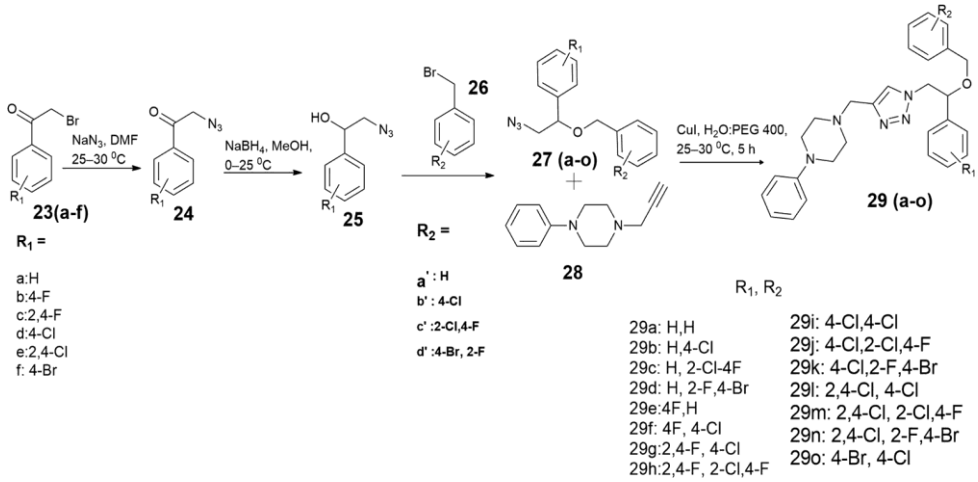
Scheme 3: Synthetic route of naphtha imide-derived metronidazoles.



Scheme 4.Synthesis of 8-OMeciprofloxacin-hydrazone/azolehybrids

Synthesis and antibacterial evaluation of triazole derivatives

A bio isosteres replacement strategy was adopted to synthesize new Piperazine-triazole derivatives by Khedar et al. The group reported the synthesis of various compounds (29a–o) (Scheme 5) and their corresponding HCl salts by passing dry HCl to tackle the solubility issue. A significant step in the synthesis of the compounds was the click chemistry step, where compounds (27a–o) reacted with (28) in the presence of CuI and PEG400 at room temperature for 5 h. The synthesized compounds (29a–o) were screened for antibacterial activities against Gram-negative **E. coli** and **P. putida**, Gram-positive **S. aureus**. Compounds were evaluated at concentrations ranging from 0.5 to 128 mg/mL. MIC values of each of the compounds were assessed comparing with that of the chloramphenicol. Among the tested compounds (29c) with phenyl and 4-fluoro-2-chlorobenzyloxy substitutions showed the highest antibacterial activity against Gram þ ve and ve bacteria. In the case of the salts, (29a) and (29c) were found to improve their action against the bacteria, implying the HCl salt's better solubility to that of the corresponding compounds. Compounds (29d, g, l, j, k) showed no activity, and the rest of the compounds were insufficient in their activity.55 5-(1H-1,2,3-triazolyl)-, 5-(4-methyl-1H-1,2,3-triazolyl)-, 5-(5-methyl-1H-1,2,3-triazolyl)-, and 5-imidazolyl-methyl oxazolidinone analogs were synthesized by Philips et al. (2015). Selected compounds among the synthesized were tested for their antibacterial activity and their inhibitory activity against monoamine A and B oxidases (MAO). This is to avoid any possible toxicity of the compound as their structural similarity with that of the Toloxatone, A known MAO inhibitor. Within the large library of compounds synthesized, the unsubstituted-1H-1,2,3-triazolyl and 4- methyl-1H-1,2,3-triazolyl-N-glycinyl derivatives (30a–h) (Figure 3) showed potent antimicrobial activity and revealed a lack of inhibitory activity against both MAO-A and -B at the tested concentrations of 50 and 200 mM.56 [6,7]



Scheme 5.synthesize new piperazine-triazole derivatives.

.A D-glucose-derived 1,2,3-triazole derivative was synthesized, and the antibacterial activity was evaluated by Zhang et al. (2015). A series of novel derivatives were synthesized through the 1,3-dipolar cycloaddition reactions (Scheme 6). Compound (32) was synthesized in more than 80% yield by the reaction of methyl-4,6-O-benzylidene-a-D-glucopyranoside with propargyl bromide in the presence of NaH using dry Tetrahydrofuran (THF) as the solvent. The cycloaddition of acetylenic compound (32) with aryl azides with catalyst copper sulfate and sodium ascorbate in the tertiary butanol-H2O solvent at room temperature gave 1,4-disubstituted triazole compounds (33a–k) in good yield. Deprotection was carried out using 5% HCl.

The formed HCl salts of the compounds (34a-k) were neutralized using 25% aq. NH3 to yield D-glucose-derived 1,2,3-triazoles (35a-k). [8, 9]

Benzylidene-protected glucose-derived bis-triazoles showed no antibacterial activity; however, some of the deprotected derivatives and their HCl salts showed moderate to excellent antibacterial activities. Among all the compounds, (35c) glucose triazole bearing chloro moiety at meta position of aromatic ring showed perfect inhibitory activity against S. aureus with an MIC50 value of 27.8 mM. Compound (34k), an HCl salt showed excellent activity against B. subtilis with an MIC50 value of 11 mM superior to the protected glucose triazole (33k) and deprotected derivative (35k). Compounds (35g), (35h), and their corresponding salts (34g), (34h) could significantly inhibit the growth of B. proteus and E. coli at concentrations ranging from 12.5 to 52 mM. Zhang et al. (2015) reported the synthesis and antibacterial activities of a series of Azolylthioether quinolones. Synthetic route for the target molecules is shown in Scheme 7. N-alkylation of commercially available quinolones with 2-(chloromethyl) oxirane resulted in intermediates formation (37a–c). This was further reacted with commercially available azoles in acetonitrile in the presence of potassium carbonate as a base at 70 C to produce the target Quinolone azoles (39a–f), (40a–f), all the compounds were tested for antibacterial activity, and it was evident that all groups of compounds (39a–f), (40a–f) had good antibacterial activity. Among all tested compounds, (39e), (40d), and (40f) compounds exhibited broad antimicrobial and excellent antibacterial activities compared to other compounds. Imidazolyl thioether functionalized compound (39e) gave the best antibacterial activity against P. aeruginosa and methicillin-resistant S. aureus (MRSA) with MIC values of 0.2510 mg/mL, which was more active than Clinafloxacin (MIC ¼ 1 mg/mL). Tetrazolyl thioether substituted imidazolyl thioether, which yielded compounds (39b), (39d), (39f) resulted in lower activity against the tested bacterial strains. However, compounds (40d) and (40f) bearing benzyl triazole-thioether groups displayed fairly good antibacterial activities with the MIC values in the range of 0.25–32 mg/mL in comparison with reference drug chloramphenicol (MIC ¼ 8–32 mg/mL).57 [10,11]

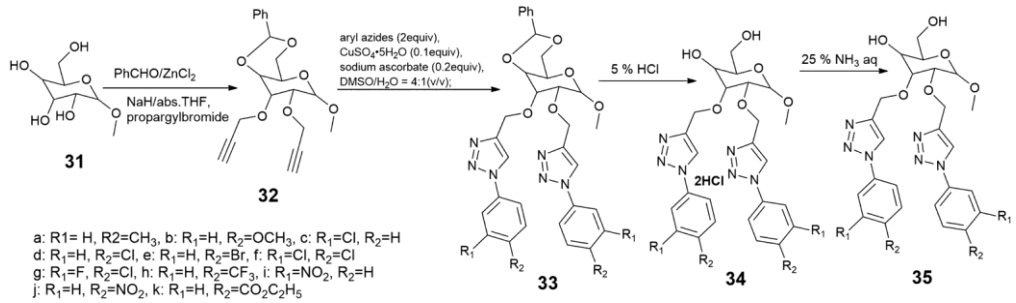
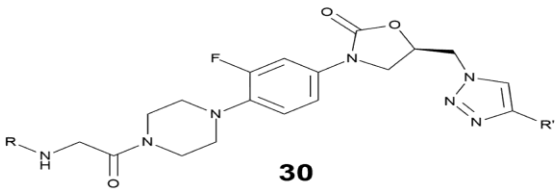
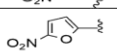
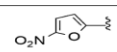
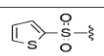
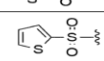


Figure 3.Piperazine- triazolederivatives

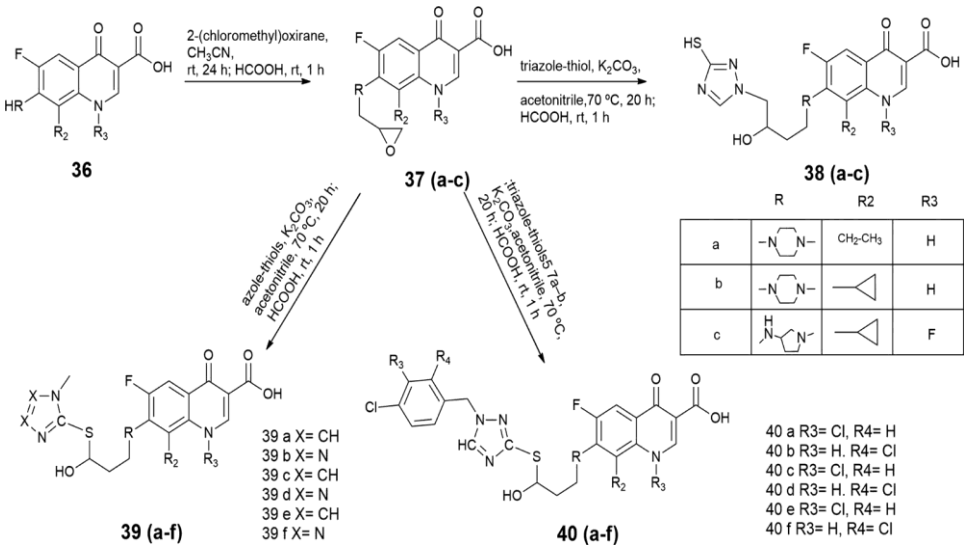


	R	R'
30a	PhCO	H
30b	PhCO	CH_3
30c		H
30d		CH_3
30e		H
30f		CH_3
30g		H
30h		CH_3

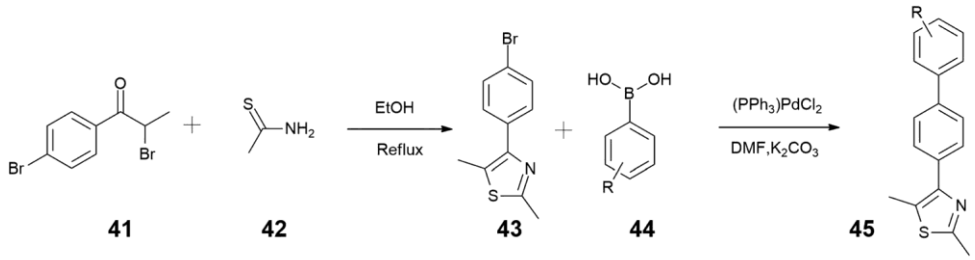
Scheme 6. SynthesisofD-glucose-derived1,2,3-triazolederivatives.

Synthesis and antibacterial evaluation of thiazole and oxazole derivatives

Trisubstituted thiazoles were synthesized and evaluated for their antimicrobial activity by Reddy et al. Reaction of 2-bromo-1-(4-bromophenyl)propan-1-one (41) with thioacetamide (42) gave compound (43). Further, Suzuki reaction between (43) and aryl boronic acids (44a–l) in the presence of palladium chloride (PdCl2), triphenylphosphine (PPh3), and potassium carbonate in DMF gave the corresponding thiazole derivatives (45a–l). Most of the compounds were formed with comparatively good yields. The reaction of trifluoro substituted boronic acid with Bromophenylthiazole moiety gave the highest yield of about 90% (Scheme 8). [12, 13]

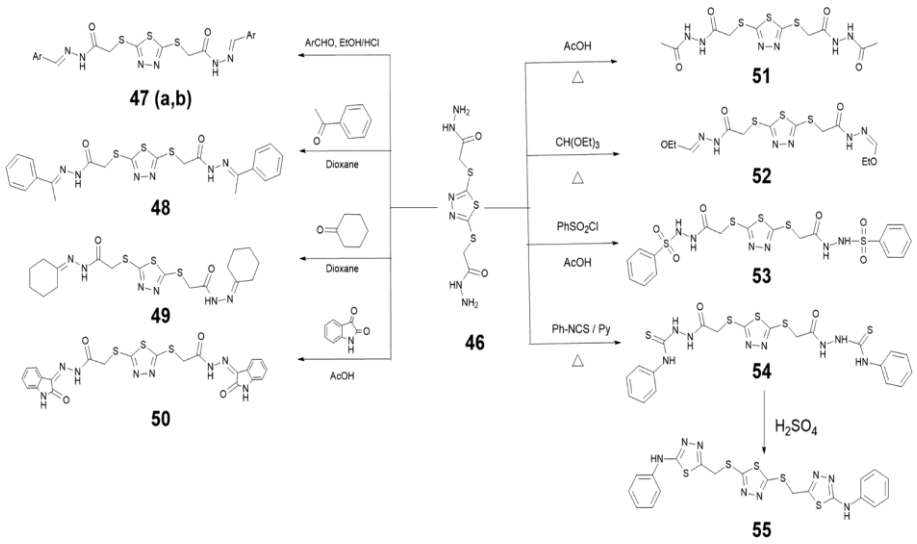


Scheme7.Syntheticroutesofazolylthioetherquinolones

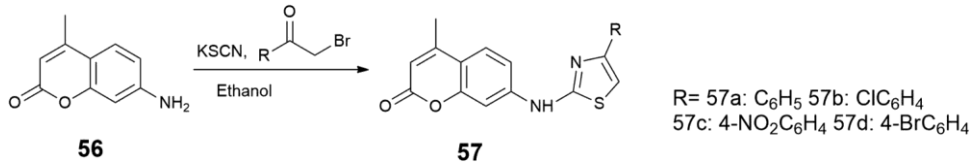


Scheme8.Synthesisoftrisubstitutedthiazolederivatives

All the compounds (45a–l) were tested for the antibacterial activity against B. subtilis (ATCC6633) S. aureus (ATCC-19433), E. coli (ATCC-8739), P. vulgaris (ATCC-29213), and the result revealed that compound (45l) showed the highest activity and lowest MIC value against both Gram-positive and Gram-negative bacteria. This most increased tri-methyl substituted compound's activity attributed to the highest LUMO energy through SAR study.58 Abo-Bakr and Hashem reported a new series of 2,5-disubstituted-1,3,4-thiadiazoles starting from 2,5-bis(mercapto-acetichydrazide)-1,3,4-thiadiazole (46) along with different reagents namely ethoxymethylene malononitrile, ethoxymethylene ethyl cyanoacetate, triethyl orthoformate, phenyl isothiocyanate, carbon disulfide, isatin, acetophenone, cyclohexanone, different aldehydes, and different anhydrides as shown in Scheme 9. [14,15]



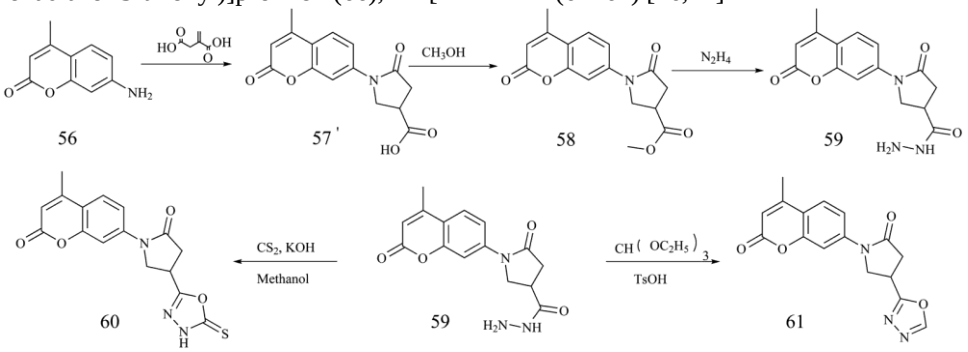
Scheme 9.Synthesis of 1,3,4-thiadiazole derivatives



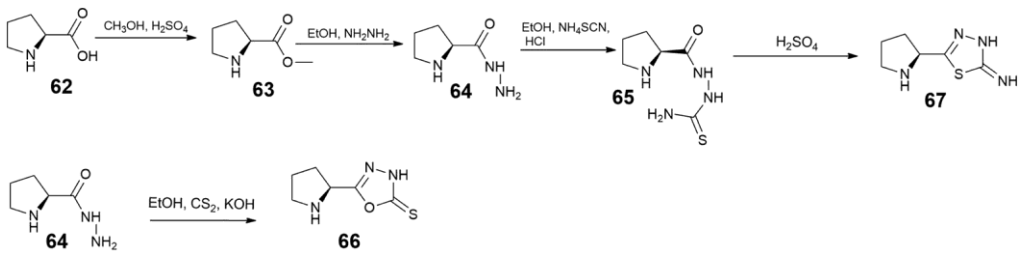
Scheme10.Synthesisof*N*-1,3-thiazolesubstituted-7-amino-4-methyl-2*H*-chromen-2-ones

The reaction of hydrazide (46) with aromatic aldehydes, acetophenone, and cyclohexanone in dioxane with drops of hydrochloric acid under reflux condition yielded corresponding Schiff bases (47a,b), (48), (49) and isatin under reflux in acetic acid gave the corresponding (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide derivative (50). Similarly, heating of compound (46) with acetic acid yielded acetylated derivative (51). Treatment with excess triethyl orthoformate on water bath gave the ethoxymethylene hydrazide (52). Phenylsulphonyl hydrazino derivative (53) was prepared by adding benzenesulfonyl chloride to the dihydrazide at room temperature. 2,5-Bis(phenylamino thiocarbonyl hydrazino carbonylmethyl sulfanyl)-1,3,4-thiadiazole (54) was prepared by boiling compound (47) with phenylisothiocyanate in ethanol. The intramolecular cyclodehydration of compound (54) has been performed in an acidic medium by adding concentrated sulfuric acid with stirring at 0 C to give the product 2,5-bis-(5-phenylamino-[1,3,4] thiadiazol-2-yl-sulfanylmethyl)-[1,3,4] thiadiazole (55). Antibacterial activity of the synthesized compounds was evaluated against E. coli (ATCC25922) as Gram-negative bacteria and Enterococcus faecalis (ATC29212) Gram-positive bacteria. A paper disk assay method was adopted for the evaluation. Ceftriaxone 30 mg/disk was used as a positive control. The synthesized compounds had moderate to good activity. Among the tested compounds (49, 50) showed good activity against E. coli with inhibition zone diameters 12 mm and 15 mm, respectively, and compounds (50, 52) exhibited excellent activity against E. faecalis with inhibition zone diameters 13 mm for both the compounds in comparison with the inhibition zone of 25 mm for the Ceftriaxone control.59 N-1,3-thiazole substituted 7-amino-4-methyl-2H-chromen-2-ones (Scheme10) were synthesized by Anusevicius et al. (2016), and antibacterial activity of the formed compounds was tested using different strains of bacteria. Substituted a-halo ketones and potassium thiocyanate were heated to 60 C in ethanol for 4 h followed by the addition of 7-amino-4-methyl-2H-chromen-2-one (56) and further refluxed for 40 h. The formed N-1,3-thiazole substituted compounds (57a–d) were isolated and recrystallized. Starting from compound (56), a series of reactions resulted in the formation of 1-(4-methyl-2- oxo-2H-chromen-7-yl)-5-oxopyrrolidine-3-carbohydrazide (59), which was then converted into three more azole derivatives as shown in Scheme 11. 1-(4-Methyl-2-oxo-2H-chromen-7-yl)4- (1,3,4-oxadiazole-2-yl)pyrrolidine-2-one (61) synthesized by refluxing hydrazide (59) with an excess of triethoxymethane in the presence of 4-methylbenzenesulfonic acid as a catalyst, whereas compound (60) 1,3,4-oxadiazole was prepared by

heating at reflux a mixture of hydrazide (59), carbon disulfide, and potassium hydroxide in methanol. The antibacterial assay showed a mixed trend in the activity against different strains of tested bacteria. Compounds (57 a,b,d) showed activity against E. coli, whereas compounds (57a-b) and (60) exhibited activity against X. campestris. Other reported compounds showed less or no antibacterial activity against the tested strains. None of the other compounds displayed any antibacterial activity against Rhizobium radiobacter. 60 Antibacterial activity of two synthesized azole derivatives of proline namely 2-[2-(1,3,4-oxadiazol-5-thionyl)]proline (66), 2-[2-(1,3,4-thiadiazol-5-thionyl)] proline (67) were carried out by Amarouche et al. A common synthetic pathway was adopted for the synthesis of the mentioned compounds as depicted in Scheme 12. All the six compounds (62–67) were evaluated for their antibacterial activity using the paper disk diffusion method against Gram-positive S. aureus and B. cereus and Gram-negative bacteria, E. coli and P. aeruginosa. All the compounds displayed little or no activity against Gram-positive S. aureus, whereas B. cereus was affected by all the compounds. Gram-negative bacteria, E. coli and P. aeruginosa were affected by all the compounds (64–67) [16,17]



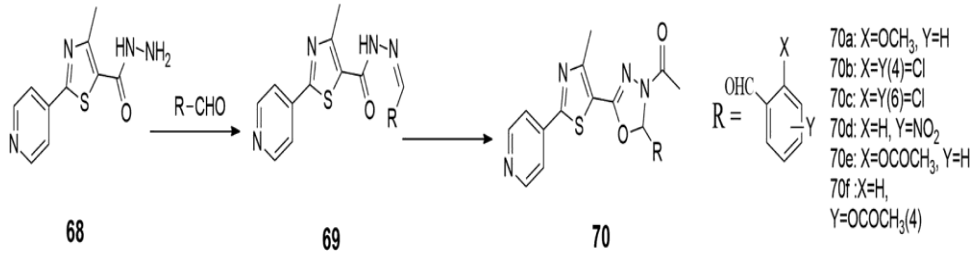
Scheme11. Synthesis of *N*-substituted 7-amino-4-methyl-2*H*-chromen-2-ones.



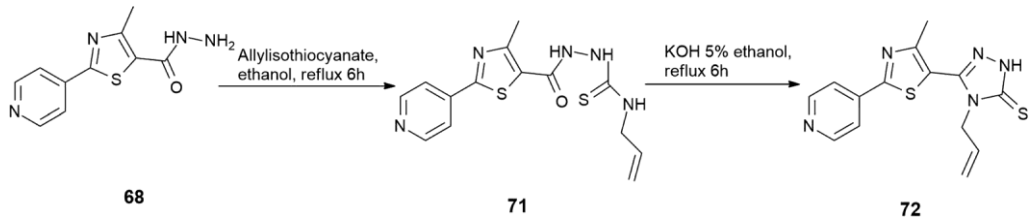
Scheme12. Synthetic pathway for azole derivatives of proline.

Synthesis and antibacterial evaluation of hybrid azoles

A new series of 4-methyl-2-(pyridine-4-yl)-thiazole-5-yl-azoles were synthesized Oniga et al. (2015) starting from 4-methyl-2-(pyridine-4-yl) thiazole-5-carbohydrazide (68). A library of compounds were synthesized (Scheme 13),62 by reacting 4-methyl-2-(pyridine-4-yl) thiazole-5- carbohydrazide (68) with different aromatic and heterocyclic aldehydes in absolute ethanol under reflux condition for 3 h. The obtained compound (69) was further refluxed for 2 h with Ac2O to form the final product (70). The target compounds were synthesized in good yields and further evaluated for their biological activities. All compounds were tested for their antibacterial activity against two Gram-negative (Salmonella typhimurium ATCC 13311, E. coli ATCC 25922) and three Gram-positive (Listeria monocytogenes ATCC 35152, S. aureus ATCC 25923, B. cereus ATCC 13061) bacterial strains. Among the tested compounds (70e) showed excellent antibacterial activity against Candida albicans, S. aureus, and B. cereus. 2(4-pyridyl)-5-thiazolyl-N-allyl-hydrazine carbo-thioamide (71) and 2(4-pyridyl)-5-thiazolyl-1,3,4-triazole-5-thione (72) (Scheme 14) showed promising antibacterial activity against L. monocytogenes and B. cereus.



Scheme 13. Synthesis of 4-methyl-2-(pyridine-4-yl)-thiazole-5-yl-azoles.



Scheme 14. Synthesisof 2(4-pyridil)-5-thiazolyl-1,3,4-triazol-5-thione

Microbial Thiazolium and Triazolium Side-Chain Polymethacrylates with mono and bis-cationic quaternary ammonium cations were prepared by controlled N-alkylation of 1,2,3-triazole and 1,3-thiazole. N-butyl quaternized polymethacrylates were synthesized through a sealed tube reaction at 700 C. Purging of argon gas for 15 min was done in the sealed tube before the reaction followed by charging of 1 equivalent of PMTA and 1-Iodobutane (74), 3.5 equivalent for PMTA-1 (73) (Scheme 15), 5 equivalent for PMTA-4 (76) (Scheme 16) in dry DMF. A time-kill efficiency test was carried out for the synthesized compounds using Gram-negative P. aeruginosa and Gram-positive S. aureus bacteria strains according to the Clinical Laboratory Standards Institute (CLSI) micro broth dilution reference method. Time-kill experiments showed both classes of copolymer, i.e. PMTA-1 (75) and PMTA-4 (76) has very high killing-efficiency (>3-log reduction) against both microorganisms at very low exposure times, achieving 100% killing in less than 1 h for both PMTA series and, in the case of the PMTA-4 series, in less than 15 min at 2 MIC.63 Sekhar et al. have demonstrated the synthesis of 1,3-/1,4-phenylene linked bis(azoles) and conducted antimicrobial activity studies of the synthesized compounds. E-cinnamohydrazide (78), terephthalic acid (79) or isophthalic acid (80) along with POCl3 were subjected to ultrasound irradiation for 50–70 min at room temperature to obtain compounds (81a–c) and (82a–c), respectively. These compounds were further treated with thiourea under ultrasonication for 90–120 min, to get compounds (83a–c), (85a–c), and with hydrazine hydrate under ultrasonication for 60–80 min to acquire and (84a–c), (86a–c), respectively (Scheme 17). [18-20]

CONCLUSION:

This article briefly demonstrated various synthetic multistep strategies for synthesizing azolebased compounds, which are potential antibacterial agents. They expand the scope of medicinal chemistry research and overcome existing challenges such as drug resistance. Two major concepts covered in most of the reactions studied: (1) development of new candidate based on the structural similarity to the existing molecules; (2) modification of existing drug candidates or bio isosteres replacement, and repurposing them for suitable medicinal application. Molecules synthesized based on these strategies were effective in inhibiting the growth of both pathogenic and nonpathogenic bacteria. Compounds such as azolopyrimidines, naphthalimide-derived metronidazoles, azolylthioether quinolones showed better antibacterial activity than the standard drugs. Few of the reported molecules showed broader activity against bacteria. Only one research showed cytotoxic assays along with antibacterial assay, which was the synthesis of piperazine-triazole derivatives. A major drawback was the lack of advanced studies, such as cytotoxicity of the synthesized compounds. Except few, all the research involved evaluating antibacterial activity only, avoiding the chances of identifying potent drug lead molecules. Also, the incorporation of in silico modeling and computeraided studies can increase the research's pace and reduce costs. Nonetheless, here we have made an effort to compile synthetic protocols and antibacterial screening of azole-based compounds reported in

the last 5 years. Therefore, this work signifies an important supplement in the development of antibacterial azole-based compounds.

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