Review Article

Recent advances in the medicinal chemistry of tetrazole as antibacterial agents: a comprehensive study

Pinky Arora[1], Vikrant Rahi[2], Navneet Kaur[3], Shubham Kumar[2]*

[1]Faculty of Medical Lab Sciences, PCTE Group of Institutes, Ludhiana, Punjab, India, [2]Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Ludhiana, Punjab, India, [3]Faculty of Biotechnology, PCTE Group of Institutes, Ludhiana, Punjab, India

Correspondence:
Shubham Kumar, Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Ludhiana, Punjab, India.
E-mail: shubham@pcte.edu.in

How to cite this article: Arora P, Rahi V, Kaur N, Kumar S. Recent advances in the medicinal chemistry of tetrazole as antibacterial agents: a comprehensive study. Pharmaspire 2021;13(1):42-53.

Source of Support: Nil,

Conflicts of Interest: None declared

ABSTRACT

Bacterial infections are rapidly increasing world widely and there is a massive increase in incident of invasive bacterial infections in the past two decades. Development of drug resistance bacteria such as multidrug-resistant strains, intractable pathogens, and newly arising pathogenic organisms is increasing the patients with bacterial infections. Tetrazole hybrids, has a wide range of biological activities, can be used as a privileged scaffold for the development of new lead molecule. Tetrazole moiety can be hybridized with other molecules to develop new molecules with potential antibacterial activity. Various tetrazole based molecules have been designed, synthesized and screened for antibacterial activity in recent years. Some of them are possessing promising activity against various Gram-positive as well as Gram-negative bacteria. Tetrazole has various biological activities such as anticancer, antifungal, antiangiogenic, antiviral, antimalarial, antitubercular, and antibacterial and thus, this has prompted the medicinal chemist to design and develop tetrazole based molecule with the desired biological profile. This review summarizes the recent advances and development in medicinal chemistry of tetrazole hybrids for the development of potential antibacterial agent. This review will provide rationale of various researchers to design more effective tetrazole based clinical candidates.

Keywords: Antibacterial activity, biological activity, molecular docking, tetrazole derivatives

INTRODUCTION

Bacterial infections are one of the major infections in the modern world and it is responsible for majority of infections at the hospital and community level. Antibacterial drugs are the one of the crucial weapon for the treatment of bacterial infections.[1,2] One of the major issues for antibacterial drugs is the development of resistance of pathogen to the available drugs and thus it becomes a problematic to treat the bacterial infections.[3,4] Imidazole,[5] triazole,[6] tetrazole,[7] pyrazole,[8] oxazole,[9] thiazole,[10] etc.,[11] are the various types of heterocycle based compounds which are available for the treatment of bacterial infections but still development of resistance occurs. Tetrazole (**1**) derivatives[12] are an important class of heterocyclic chemistry along with the various types of applications in chemistry, coordination chemistry, agriculture, photography industry, energetic materials, and drug development.[13-17] Tetrazole moiety has poly nitrogen electron rich structural features which are responsible for the binding of tetrazole derivatives with various types of binding and interaction with receptors or enzyme through weak interactions, including hydrogen bounds, hydrophobic effect, coordination bonds, or Van der Waals force.[18,19] Tetrazole derivatives have a wide range of activity such as anticancer,[20] antifungal,[21] antiviral,[22,23] antimalarial,[24] anti-Alzheimer,[25,26] antitubercular,[27] anti-inflammatory,[28] and antibacterial.[29] Various bacterial infections are mainly caused by the *Streptococcus* species, namly, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*, *Staphylococcus aureus*, including methicillin-susceptible *S. aureus*/and methicillin-resistant *S. aureus*/), *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia,* and

Access this article online

Website: www.isfcppharmaspire.com

P-ISSN: 2321-4732
E-ISSN: XXXX-XXXX

Enterococcus faecalis.[30-37] Tetrazole derivatives are found to have potential role on various types of gram positive and gram negative bacteria. Various tetrazole based drugs are clinically available such as Cefamandole[38] (**2**), Ceftezole[39] (**3**), and Tedizolid[40] (**4**) which are used as antibacterial agents and other tetrazole based drugs such as Losartan[41] (**5**) and Valsartan[42] (**6**) are used as antihypertensive agents [Figure 1]. In this review, basically we have tried to enlighten up the recent advances of tetrazole derivatives as antibacterial agents. This review will give an overview of emergence of tetrazole hybrids as potential inhibitor of various bacterial pathogens such ass Gram-positive as well as Gram-negative bacteria.

RECENT ADVANCES IN MEDICINAL CHEMISTRY OF TETRAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS

Ashok *et al*. designed and synthesized 5-[4-(3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)phenyl]-1*H*-tetrazole derivatives (**7a-i**) and evaluated their antibacterial activity on two Gram-positive bacterial strains (*S. aureus* and *B. subtilis*) and two Gram-negative bacterial strains (*E. coli* and *K. pneumoniae*). They have also evaluated anti-fungal activity of all the compounds (**7a-i**) against three strains of fungi (*Aspergillus niger*, *Aspergillus Flavus,* and *Fusarium oxysporum*). All compounds (**7a-i**) have promising antibacterial activity against *S. aureus* with zone of inhibition of 13–22 mm and 14–32 mm at concentration of 20 and 40 μg/mL, respectively [Figure 2]. Among the synthesized compounds, compound **7f** was the most potent compound against *S. aureus* with zone of inhibition of 22 and 32 mm as compared to Gatifloxacin having zone of inhibition of 20 and 30 mm at concentration of 20 and 40 μg/mL, respectively. Results of *in vitro* assay against *B. subtilis* revealed that compound **7f** was the most potent compound with zone of inhibition of 23 and 40 mm at conc. of 20 and 40 μg/mL, respectively, whereas Gatifloxacin has zone of inhibition of 20 and 40 mm at conc. of 20 and 40 μg/mL, respectively. Compounds **7f** was also potent against both the Gram-negative bacteria with zone of inhibition of 16 and 21 mm against *E. coli* and 14 and 20 mm against *K. pneumoniae* at same concentrations whereas Gatifloxacin has zone of inhibition of 15 and 20 mm against *E. coli* and 10 and 18 mm against *K. pneumoniae* at same concentration. Results of *in vitro* assay against fungus strain revealed that compounds **7b** and **7f** were the potent compounds with zone of inhibition of 14.5 and 15.5 mm against *A. niger* and 17 and 17.7 mm against *F. oxysporum*, respectively, whereas Amphotericin B has zone of 14 and 15.2 against *A. niger* and *F. oxysporum*, respectively. It was also established that only compound **7a** was the most potent compound against *A. flavus* with zone of inhibition of 13.6 mm as compared to Amphotericin B (Zone of inhibition = 12.5 mm).[43]

Abu-Hashem and El-Shazly, designed, synthesized new derivatives of Triazole, Tetrazole, and Spiropyrimidine-Thiadiazole (**8-21d**) and evaluated their antibacterial potential against two strains of Gram-positive bacteria (*Micrococcus luteus*, *Rhodopseudomonas* fp. and *Bacillus cereus*) and three strains of Gram-negative bacteria (*E. coli* and *Salmonella typhi*). They have also assessed their antifungal potential on four strains of fungus, that is, *Alternaria alternata*, *A. flavus*, *Candida albicans,* and *Cochliobolus lunata* [Figure 3]. Results of *in vitro* antibacterial assay revealed that compounds **20a-d** and **21a-d** with MIC values in range of 1–11 μmol/cm^3 exhibited promising inhibitory activity against all the tested bacterial strains whereas reference drug Levofloxacin has MIC values in range of 2–5 μmol/cm^3. Except **20a-21d**, compounds (**8-19d**) possessed very low and weaker activity against all the tested strains (MIC = 9–38 μmol/cm^3). Compounds **20a-21d** (MIC = 1–9 μmol/cm^3) were also found to be shown comparable and similar activity against all the tested strains of fungal as compared to reference drug Nystatin (MIC = 1–3 μmol/cm^3) whereas all others compounds (**8-19d**) had shown poor activity against all the tested fungal strains. Overall compounds **21a-d** were found to be the most potent and promising antibacterial (MIC = 1–7 μmol/cm^3) as well as antifungal compounds (MIC = 1–3 μmol/cm^3).[44]

Sathe *et al*., designed, synthesized new tetrazole derivatives containing azodye (**22a-k**) and evaluated their antibacterial potential on five Gram-positive bacterial strains (*S. aureus, B. cereus, B. megaterium*, *M. glutamicum,* and *B. subtilis*) as well as six Gram-negative strains (*E. coli, S. typhi, Shigella boydii, Enterobacter aerogenes, Pseudomonas aerogenosa,* and *Salmonella abony*). They performed agar diffusion method to determine the zone of inhibition of compounds (**22a-k**, Figure 4) and it was assessed that all the compounds have moderate to weaker inhibitory activity with zone of inhibition varies from 5 to 30 mm whereas standard Tetracycline has zone of inhibition in range of 20

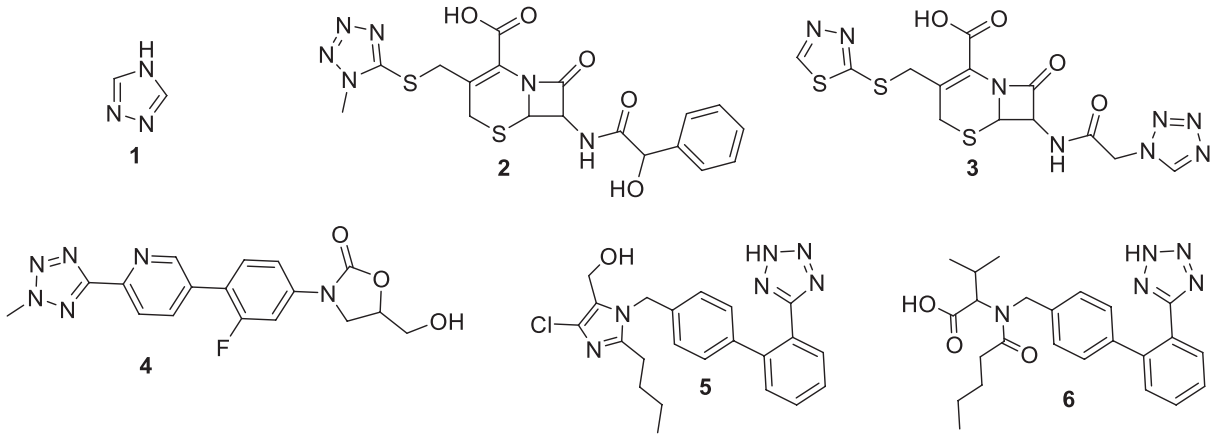


Figure 1: Tetrazole containing clinical available drugs

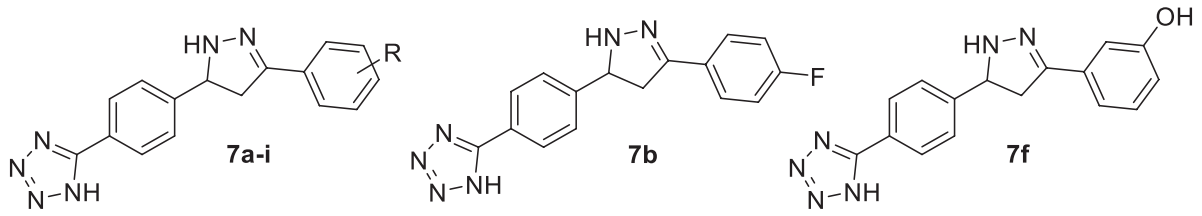


Figure 2: Pyrazole clubbed tetrazole derivatives as antibacterial agents

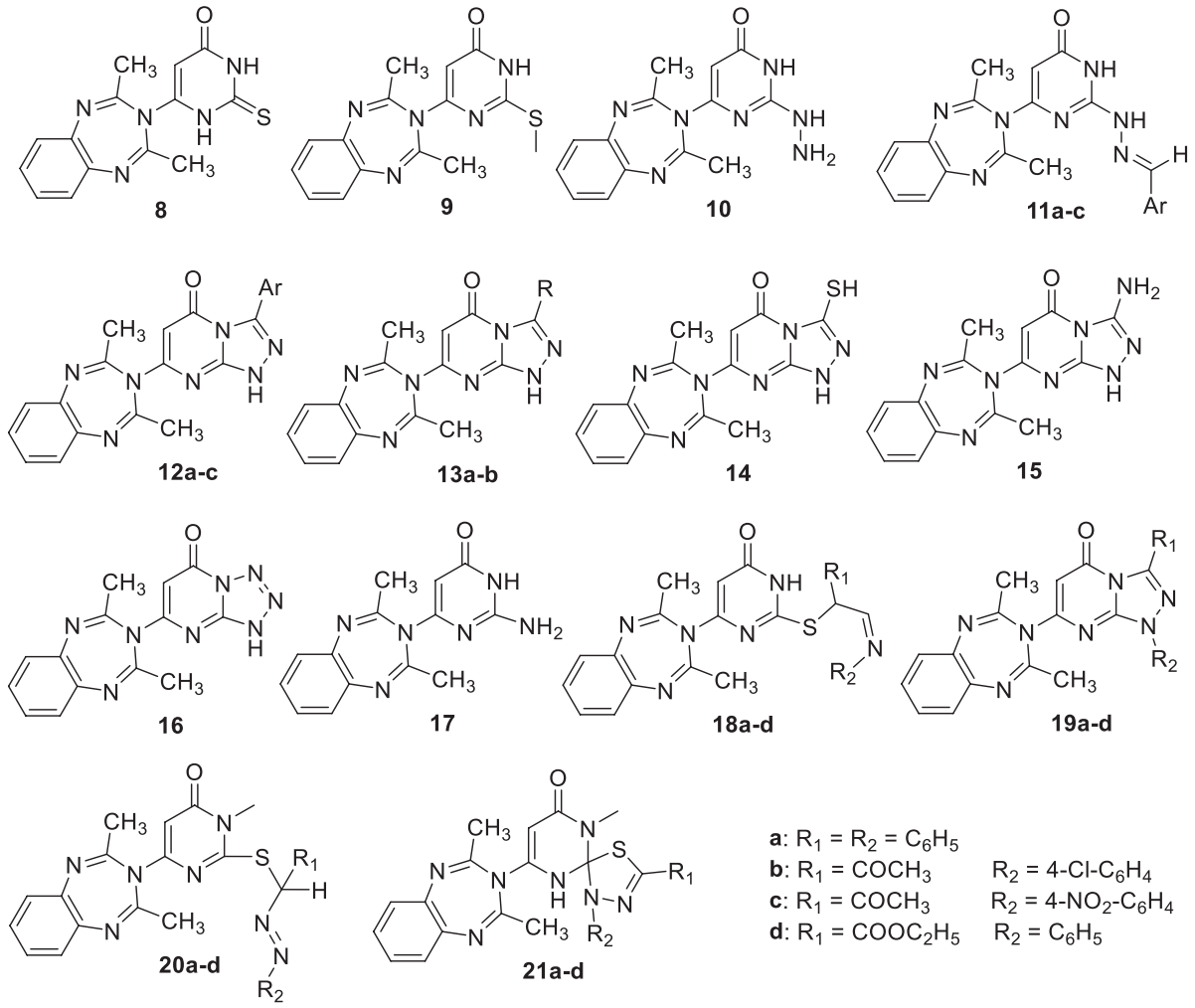


Figure 3: Triazole, tetrazole, and spiropyrimidine-thiadiazole as antibacterial agents

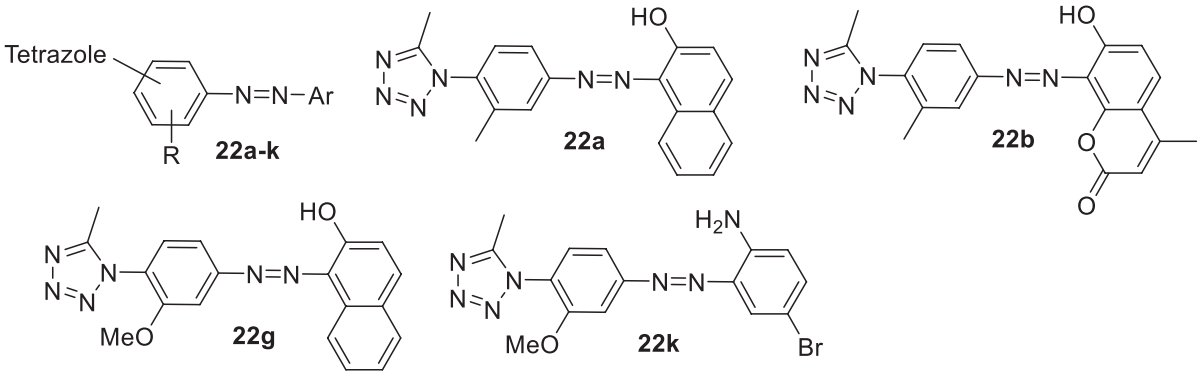


Figure 4: Azo dye containing tetrazoles as antibacterial compounds

to 33 mm against all the evaluated bacterial strains. Compounds **22a**, **22b**, **22g,** and **22k** were found to be best compounds with zone of inhibition in range of 6–30 mm against all the bacterial strains. Then, they determined the minimum inhibitory concentration (MICs) of above mentioned four best compounds against four bacterial strains *B. subtilis*, *S. typhi*, *E. coli*, and *S. abony* and one fungal strains *C. albicans*. It was established that compounds **22a**, **22b**, **22g,** and **22k** have the weaker antibacterial activity with MIC values of 16–95 μg/mL as compared to Tetracycline (MIC 2.25–4.0 μg/mL). Results for fungal strain revealed that all the four compounds also have poor activity with MIC values in range of 55–98 μg/mL as compared to Fluconazole (MIC = 12.5 μg/mL). Overall, it was established that compound **22k** was the most promising compound with zone of inhibition of 8–30 mm and MICs of 16–55 μg/mL. Further, they carried out the docking study of best four compounds (**22a**, **22b**, **22g,** and **22k**) was carried out against DNA gyrase subunit b using GLIDE module software. Results of docking study revealed that compounds **22a**, **22b**, **22g,** and **22k** (glide score of −8.882 to −8.172) have occupied the active site of enzyme while interacting with various key residues such as Val167, Thr165, Arg136, Ser121, Val120, Gly119, and Ala96.[45]

Ozkan *et al.,* designed, synthesized Sulfonamide derivatives (**23**, **24a-g**, **25,** and **26a-b**) with Tetrazole and Oxadiazole Rings and evaluated their antibacterial activity on two Gram-positive (*S. aureus* and *B. subtilis*) as well as two Gram-negative (*K. pnemoniae* and *E. coli*) strains. All the compounds (**23**, **24a-g**, **25,** and **26a-b**, Figure 5) were also assayed for their antifungal activity on two fungal strains (*Saccharomyces cerevisiae* and *C. albicans*). From the results, it was evaluated that all the compounds were shown to have moderate to weaker inhibitory activity against all the tested bacterial strains with zone of inhibition in the range of 14–40 mm. Among all the compounds, compounds **24b** and **24c** have the similar and comparable activity against *S. aureus* with zone of inhibition of 41 and 38 mm, respectively, as compared to Ciprofloxacin (zone of inhibition = 40 mm). Compound **24c** has also shown to have comparable activity against *B. subtilis* with zone of inhibition of 38 mm in comparison to Ciprofloxacin (zone of inhibition = 42 mm). Compound **24g** has shown the similar level of activity against *K. pneumoniae* as compared to Ciprofloxacin (zone of inhibition = 37 mm). Compounds **24b** and **24d** were the most potent compounds with zone of inhibition of 40 and 41 mm, respectively, in comparison to Ciprofloxacin (zone of inhibition = 39 mm). Further, they performed *in vitro* antifungal assay against *S. cerevisiae* and *C. albicans* and revealed that none of the compounds possessed antifungal activity. Only compound **24b** has the moderate activity against *S. cerevisiae* with zone of inhibition of 37 mm as compared to reference drug Ketoconazole (zone of inhibition = 40 mm). Then, they estimated the MIC value of all the compounds through *in vitro* assay and it was assessed that only compound **24b** (MIC = 4.125 μg/mL) has the similar activity against *S. aureus* as compared to Ciprofloxacin (MIC = 4.125 μg/mL) whereas none of the compound was potent against *B. subtilis*. Various compounds (**24a-c**, **24f-g,** and **25**) with MIC value of 8.25 μg/mL have shown equipotent activity against *K. pnemoniae* in comparison to Ciprofloxacin (MIC = 8.25 μg/mL) whereas only compound **24b** (MIC = 4.125 μg/mL) has shown similar activity in comparison to Ciprofloxacin (MIC = 4.125 μg/mL). Results of antifungal assay revealed that compound **24e** was equipotent as Ketoconazole with MIC of 8.25 μg/mL. Further, they assessed the antioxidant activity of all the compounds using 2,2-diphenyl-1- picrylhydrazyl (DPPH) assay and it was assessed that none of the compounds were had antioxidant property as compared to butylated hydroxytoluene.[46]

Bahrin *et al.,* designed, synthesized two derivatives bimesitylene (**27**) and bimesitylene bistetrazole (**27**) and evaluated their antibacterial potential against *S. aureus* and *E. coli* as well as antifungal potential against *C. albicans* [Figure 6]. They also carried out the computational modeling of both the compounds. Initially, they carried out the X-ray analysis using single-crystal X-ray diffraction analysis and assessed that compound **27** and **28** crystallizes in the asymmetric part as one molecular unit of 3,3′,5,5′-tetracyanobimesitylene and

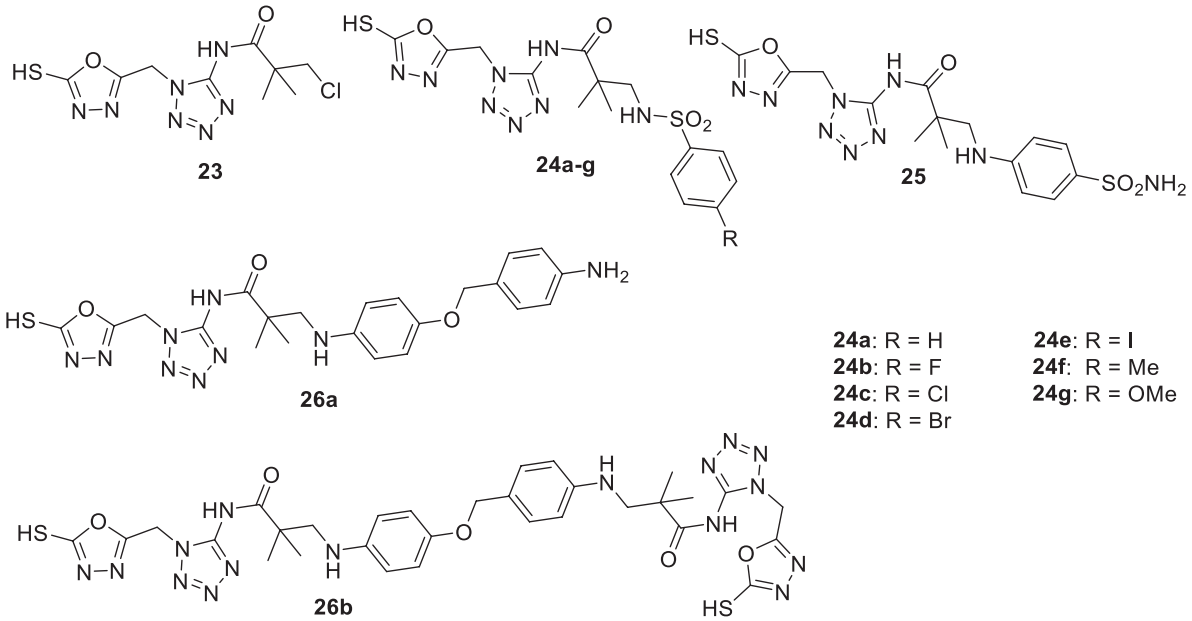


Figure 5: Sulfonamide appended tetrazoles as antibacterial and antifungal agents

bistetrazolybimesitylene crystallizes with space group *P21/n* and *C2/c* of monoclinic system, respectively. Compound **28** was further optimized using computational approaches DFT with the B3LYP and LSDA methods. Results of antibacterial assay of both the compounds revealed that none of the compounds has shown antibacterial activity against both the tested strains. Further, it was assessed that compound **28** has selective antifungal activity with zone of inhibition 4 mm at 20 mg/mL whereas compound **27** did not showed antifungal activity. They concluded that antifungal activity of compound **27** was due to presence of tetrazole ring.[47]

Andrejević *et al.,* designed, synthesized three molecule of 1-benzyl-1*H*-tetrazoles with silver(I) complexes (**29-31**, Figure 7) and evaluated them for antibacterial activity against *S. aureus*, *Listeria monocytogenes*, *Micrococcus luteus,* and *Pseudomonas aeruginosa*. They have also evaluated the antifungal activity of all the compounds (**29-31**) against *C. albicans*, *Candida glabrata*, *Candida krusei,* and *Candida parapsilosis*. Structural analysis of all the three compounds was done using X-ray analysis. Results of *in vitro* assay against bacterial strains revealed that none of the compounds were active against any of the bacterial strains at concentration >500 μg/mL. All the three compounds had shown inhibiting activity against all the bacterial strains with MIC values of 2–8 μg/mL. All the three silver complexes were shown to inhibit both the *albicans* and non *albicans* strains of *Candida* at MIC value of 0.16–1.25 μg/mL. Among all the three strains, compound **30** (MIC = 0.62–2 μg/mL) was more active as compared to others two. Further, they have estimated the cytotoxic effects of all the three compounds against human fibroblast cell line (MRC5) and results revealed that none of the compounds had shown cytotoxic effects.[48]

Sribalan *et al.*, designed, synthesized tetrazole-heterocycle hybrids (**32a-m**) and evaluated their antibacterial activity against four bacterial strains (*K. pneumoniae*, *P. aeruginosa*, *S. aureus,* and *S. pyrogenes)* and also evaluated their antifungal potential against *C. albicans* [Figure 8]. Except **32f**, all compounds (**32a-m**) have shown activity against *K. pneumoniae* and compound **32e** was the most potent compound against same strain with zone of inhibition of 17.2 mm as compared to standard drug Amikacin (zone of inhibition = 17.2 mm). Only a few compounds (**32d**, **32h,** and **32j-k**) were shown activity against *P. aeruginosa* (zone of inhibition = 3.9–12 mm) but none of them were potent as compared to Amikacin (zone of inhibition = 17 mm). Compound **32e** was found to possessed the promising activity with zone of inhibition of 15 mm against *S. aureus* whereas compound **32k** (zone of inhibition = 15.9 mm) has moderate activity against *S. pyogenes* as compared to Amikacin (zone of inhibition = 18.2 mm [*S. aureus*] and 18.1 mm [*S. pyogenes*]). None of the compounds were shown promising activity against fungal strain *C. albicans*. Further, they assessed the anti-inflammatory activity of compounds **32a-m** and it was established that compound **32b** and **32h** found to have anti-inflammatory property in a dose-dependent manner at different concentration of 50, 100, 200, and 400 μg/mL. Further, they predicted the ADMET properties of all compounds (**32a-m**) and it was found that all compounds were had drug likeness properties with no violation of Lipinski's rule of five. Further, they performed the docking study against bacterial DNA gyrase, COX-1, and COX-2 using Auto-Dock software (version 4.2). From the docking results, it was established that compound **32m** has the maximum binding energy of −9.06 kcal/mol.[49]

Szulczyk *et al.*, designed, synthesized and evaluated the new derivatives of 1*H*-tetrazol-5-amine (**33a-n**, Figure 9) for antibacterial activity on different strains of *S. aureus*, *Staphylococcus epidermidis*, *B. subtilis*, *B. cereus*, *Enterococcus hirae*, *E. faecalis*, *M. luteus*, *E. coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa,* and *Bordetella bronchiseptica*. Among all the compounds (**33a-n**), compounds **33j** and **33k** were the promising compounds with MICs in range of 1–208 μM against all the tested strain whereas compound **33k** was the most potent compound against *E. faecalis, M. luteus*, *E. coli,* and *P. vulgaris* with MICs in range of 1–7 μM. Further, they selected three compounds **33g**, **33j,** and **33k** for the activity against hospital strains of *S. aureus*, *S. epidermidis*, *P. aeruginosa,* and *E. coli* and from the results it was established that the activity against Gram-positive strains were in the range of 7–56 μM whereas compounds **33j** and **33k** were possessed the activity against Gram-negative strains with MICs in range of 7–111 μM. Further, they determined the cytotoxic activity of few selected compounds **33b-c**, **33e-f,** and **33h-k** against adult human skin (HaCaT) and human epithelial lung carcinoma cell line (A549). Results revealed that all the

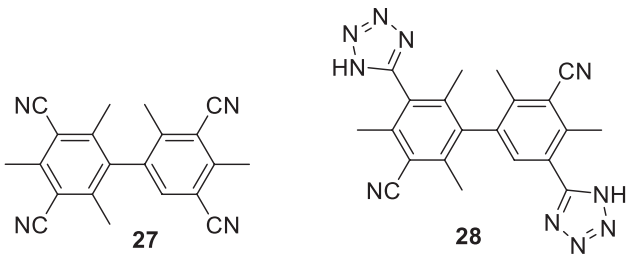


Figure 6: Bimesitylene and bimesitylene bistetrazole for bacterial infections

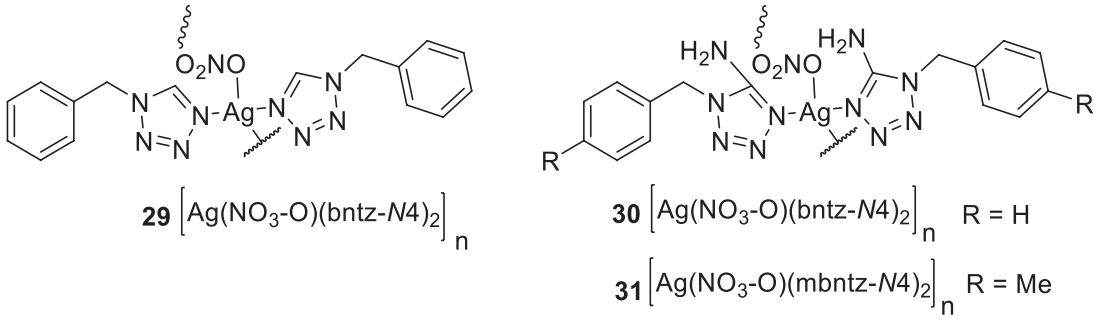


Figure 7: Silver complex of tetrazole as antibacterial agents

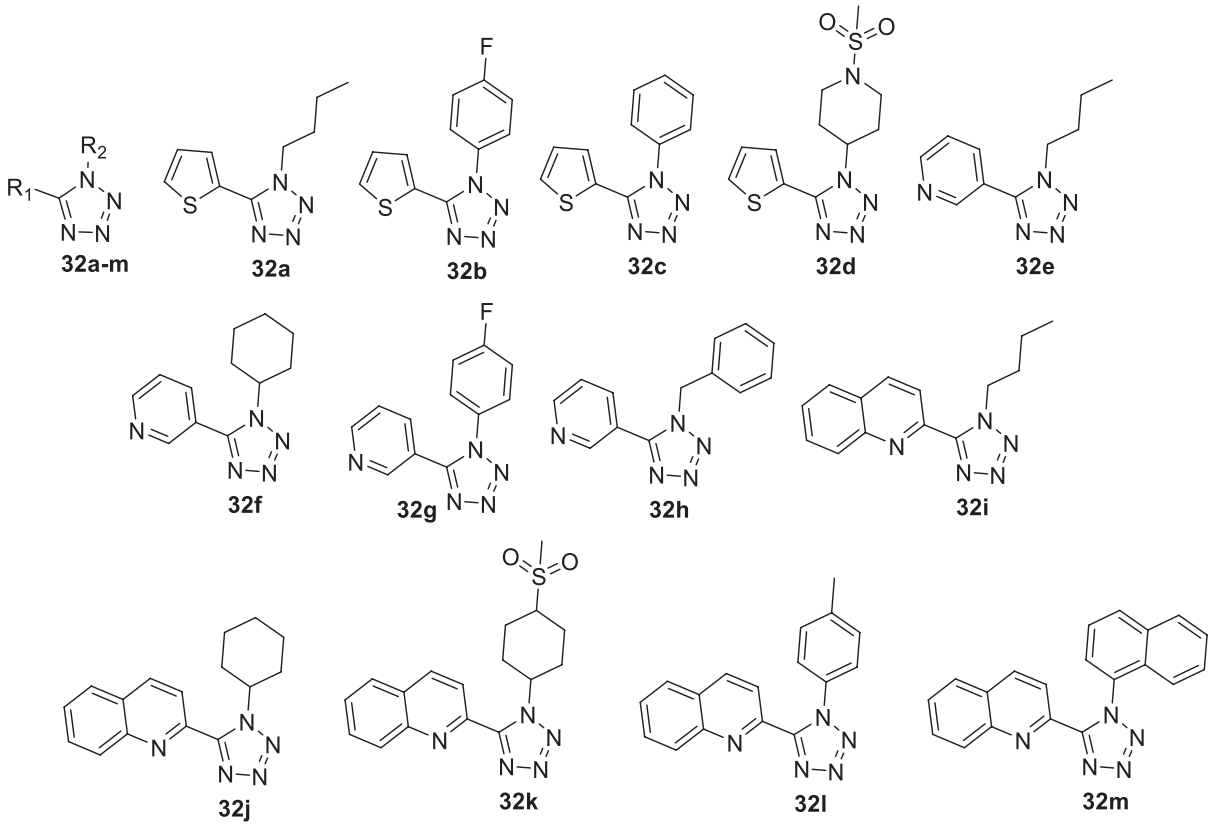


Figure 8: Tetrazole heterocyclic hybrids as antibacterial agents

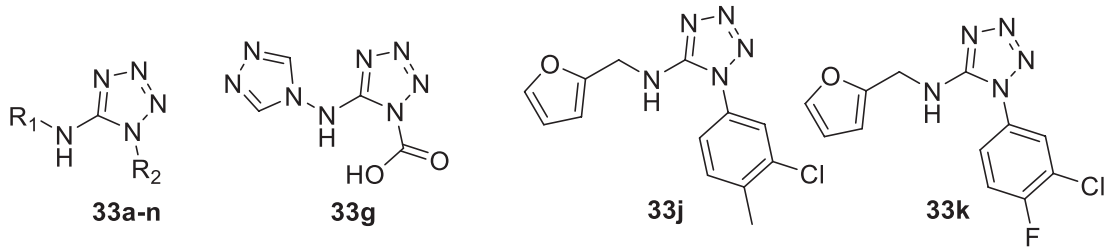


Figure 9: Tetrazole amines as antibacterial agents

compounds were non cytotoxic with CC_{50} <60 μM. when compared the DNA gyrase supercoiling inhibition of compound **33j** and **33k** and results revealed that compound **33k** found to be better inhibitor with IC_{50} value of 0.9 μg/mL as compared to Ciprofloxacin (IC_{50} = 3.5 μg/mL). They have also compare the inhibition of topoisomerase IV (topIV) and results revealed that compound **33k** again inhibited topIV with IC_{50} value of 2.6 μg/mL as compared to Ciprofloxacin (IC_{50} = 1.70 μg/mL). Results of molecular docking studies revealed that all compounds have binding energy varies from −3.25 to −7.02 kcal/mol whereas most potent compound **33k** has interaction with various key residues such as Gly85 and Thr173.[50]

1,5-disubstituted tetrazole derivatives are known to have various biological activities such as antitubercular, anti-inflammatory, antiviral, antibacterial, and many more.[51-53] Inspired from above, Soliman *et al.,* designed, synthesized 1,5-disubstituted tetrazole derivatives (**34a-I**, Figure 10) and evaluated their antimicrobial as well as anticancer activity. They have estimated the antibacterial potential of compounds (**34a-**i) on two Gram-positive bacterial strains (*B. subtilis* and *S. aureus*), two Gram-negative bacterial strains (*E. coli* and *P. aeruginosa*), and one fungal strain (*C. albicans*) using agar diffusion method. Results of *in vitro* assay against all the bacterial strains revealed that compounds (**34a-**i) had zone of inhibition of 13–18 mm and this showed that all the compounds were moderate to weaker inhibitor of these bacterial strains. Results against fungal strain revealed that compounds (**34a-**i) were slightly active against *C. albicans* with zone of inhibition of 11–13 mm. Overall, it was assessed that among all the compounds, compounds **34b** and **34c** were the best compound with zone of inhibition of 18, 17, 15, 16, and 13 mm and 18, 16, 14, 16, and 13 mm against *B. subtilis, S. aureus*, *E. coli*, *P. aeruginosa,* and *C. albicans*, respectively. Further they carried out anticancer activity on breast cancer cell line (MCF-7) and it was established that none of the compound was potent for anticancer activity having IC_{50} value in the range of 40.2–84.7 μM.[54]

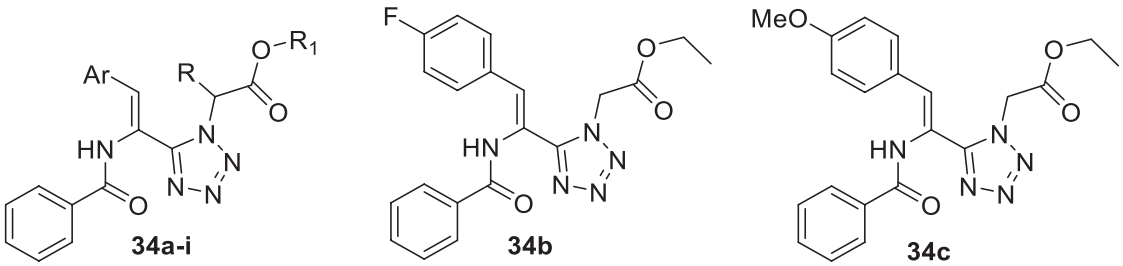


Figure 10: 1,5-Disubstituted tetrazoles as antibacterial agents

Khan *et al.*, designed, synthesized 1-substituted-1*H*-1,2,3,4-tetrazoles (**35a-l**) and evaluated them for their antibacterial activity against two strains of Gram-positive bacteria (*B. subtilis* and *S. aureus*) and two Gram-negative bacteria (*P. aeruginosa* and *E. coli*). They have also predicted their ADMET properties [Figure 11]. All the compounds (**35a-l**) were synthesized through one pot facile synthesis. Results of *in vitro* assay revealed that among all the compounds (**35a-l**), compounds **35c** and **35i** (MIC = 97.2 and 94.6 μg/mL) were the potent compound against *P. aeruginosa* as compared to Ampicillin (MIC = 100 μg/mL). Compounds **35e** and **35f** were the *li* with MIC value of 71.40 and 96.40 μg/mL, respectively, in comparison to Ampicillin (MIC = 100 μg/mL). Many compounds (MIC = 70.30–190.10 μg/mL) possessed promising activity against *B. subtilis* whereas compound **35e** (MIC = 70.30 μg/mL) was the most potent compound as compared to Ampicillin (MIC = 250 μg/mL). Compound **35c** with MIC value of 80.30 μg/mL was the most potent compound against *S. aureus* as compared to Ampicillin (MIC = 250 μg/mL). Further, they have predicted the ADMET properties of compounds **35a-l** and revealed that all the compounds (**35a-l**) have drug likeness properties and no violation of Lipinski's rule of five was observed.[55]

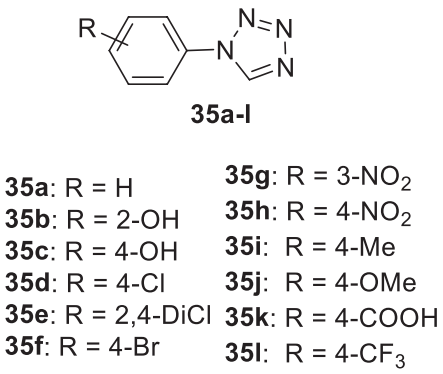
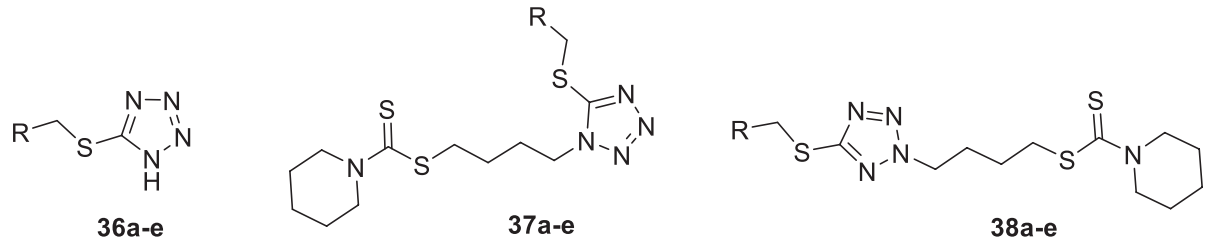


Figure 11: 1-Substituted tetrazoles as antibacterial agents

Baghershiroudi *et al.*, designed, synthesized sulfanyltetrazole derivatives (**36a-e**) bearing piperidine dithiocarbamate (**37a-e** and **38a-e**, Figure 12) and evaluated their antibacterial activity against *S. aureus*, *E. coli*, *S. typhi,* and *P. aeruginosa*. Compounds **37d** and **38d** were the potent compound against *S. aureus* with MIC value of 1.56 and 0.78 μg/mL but not that much potent as compared to ciprofloxacin (MIC = 0.195 μg/mL), respectively. Both the compounds **37d** and **38d** were also the best compound against *E. coli* with 3.12 and 1.56 μg/mL which was very poor in comparison to ciprofloxacin (MIC = 0.024 μg/mL), respectively. Compounds **37d**, **38d,** and **38e** (MIC = 3.12-6.25 μg/mL) were the best compound against *S. typhi* but very poor as compared to ciprofloxacin (MIC = 0.098 μg/mL). Compound **37d** and **38d** have weaker activity against *P. aeruginosa* with MIC value of 6.25 μg/mL each as compared to ciprofloxacin (MIC = 0.39 μg/mL).[56]

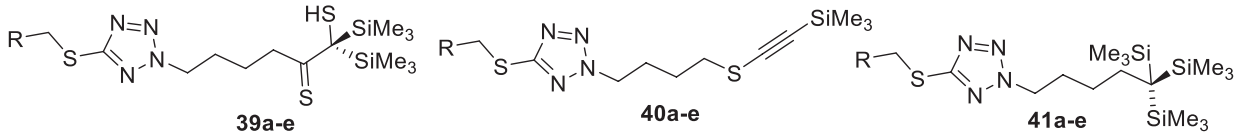
Baghershiroudi *et al.*, designed, synthesized sulfanyltetrazole compounds based on the organosilicon (**39a-41e**) and estimated their antibacterial activity against *S. aureus*, *E. coli*, *S. typhi,* and *P. aeruginosa*. Among all the compounds (**39a-41e**, Figure 13), compounds **39d** and **39e** have the moderate activity against *S. aureus* with MIC value of 3.91 and 7.81 μg/mL when compared to reference drug ciprofloxacin (MIC = 0.244 μg/mL). Only a few compounds have shown activity against *P. aeruginosa* and among them compound **39d** has the lowest MIC of 31.25 μg/mL. This was very poor as compared to ciprofloxacin (MIC = 0.488 μg/mL). They concluded that although the activity of all the compounds was weaker as compared to ciprofloxacin still compound **39d** was the best compound against all the tested bacterial strains.[57]

Kumbar *et al.,* designed, synthesized a series of new 5-(1-Aryl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-1H-tetrazoles derivatives (**42h-s**, Figure 14) and evaluated their antibacterial activity against a panel of bacterial strains, that is, *E. faecalis*, *S. aureus*, *E. coli* and *P. aeruginosa*. Structure analysis of all the compounds (**42h-s**) was confirmed by performing X-ray analysis using Bruker SHELXTL-97 Software Package. Among all the compounds (**42h-s**), compound **42n** and **42s** inhibited the *E. faecalis* at 3.125 and 1.56 μg/mL, respectively, as compare to Ciprofloxacin (MIC = 6.25 μg/mL). Compounds **42j**, **42i**, **42k,** and **42s** were found to have strong inhibition against *S. aureus* at the lower concentration of 1.56–3.12 μg/mL whereas Ciprofloxacin has MIC of 6.25 μg/mL. Compound **42n** was the most potent compound against *E. coli* with MIC of 0.78 μg/mL as compared to Ciprofloxacin (MIC = 3.12 μg/mL). Compounds **42n** and **42p** were found to be strong inhibitor of *P. aeruginosa* with MIC value of 3.12 and 1.56 μg/mL, respectively, as compared to Ciprofloxacin (MIC = 6.25 μg/mL). Further, they analyzed anti-inflammatory activity using RAW mouse murine cancer cell line at three different concentration levels, namely, 1, 5, and 10 μg/mL. From the results, it was established that all compounds (**42h-s**) inhibited the production of nitric oxide in a dose-dependent manner. Further, docking study was performed on all the compounds (**42h-s**) against active site of COX-2 using Surflex-dock program of Sybyl-X 2.0 software. Results showed that compound **42q** has the highest D score of −114.786 and possessed interaction with key residues such as Tyr355, His90, Phe518, and Arg120.[58]



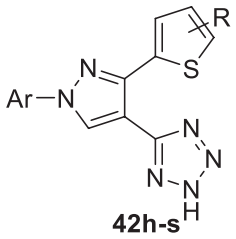
36a, **37a**, **38a**: R = CH_3-$(CH_2)_3$-
36b, **37b**, **38b**: R = CH_3-$(CH_2)_4$-
36c, **37c**, **38c**: R = Ph-
36d, **37d**, **38d**: R = Ph-CH_2-
36e, **37e**, **38e**: R = Ph-(CO)-

Figure 12: Sulfanyltetrazoles as antibacterial agents



39a, **40a**, **41a**: R = CH_3-$(CH_2)_3$-
39b, **40b**, **41b**: R = CH_3-$(CH_2)_4$-
39c, **40c**, **41c**: R = Ph-
39d, **40d**, **41d**: R = Ph-CH_2-
39e, **40e**, **41e**: R = Ph-(CO)-

Figure 13: Sulfanyltetrazole appended organosilicon as antibacterial agents



42h: R = H, Ar = C_6H_5
42i: R = H, Ar = 4-Br-C_6H_4
42j: R = H, Ar = 4-Cl-C_6H_4
42k: R = 5-Cl, Ar = C_6H_5
42l: R = 5-Cl, Ar = 4-Br-C_6H_4
42m: R = 5-Cl, Ar = 4-Cl-C_6H_4
42n: R = 5-Br, Ar = C_6H_5
42o: R = 5-Br, Ar = 4-Br-C_6H_4
42p: R = 5-Br, Ar = 4-Cl-C_6H_4
42q: R = 5-OMe, Ar = C_6H_5
42r: R = 5-OMe, Ar = 4-Br-C_6H_4
42s: R = 5-OMe, Ar = 4-Cl-C_6H_4

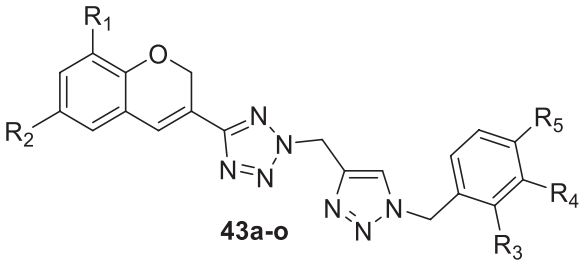
Figure 14: Thiophene clubbed tetrazoles as antibacterial agents

Srinivas *et al.,* designed, synthesized new 2-((1-Benzyl-1*H*-1,2,3-Triazol-4-yl)methyl)-5-(2*H*Chromen-3-yl)-2*H*-Tetrazoles derivatives (**43a-o**) and evaluated their antibacterial activity on two bacterial strains (*E. coli* and *S. aureus*). Results of *in vitro* assay revealed that compounds (**43a-o**, Figure 15) possessed good to moderate activity with MICs in range of 8.5–19.5 μg/mL against *E. coli* whereas compounds **43b** and **43m** were the potent compounds having MIC 8.5 μg/mL in comparison to Ciprofloxacin (MIC = 12 μg/mL). All compounds (**43a-o**) have shown moderate to potent inhibitory activity against *S. aureus* with MICs in range of 6.5–19.5 μg/mL whereas compounds **43c**, **43h,** and **43m** were the potent compound with MIC values of 7.5, 7.5, and 6.5 μg/mL, respectively, as compared to Ciprofloxacin (MIC = 11 μg/mL). Further, they established the antioxidant property of all the compounds (**43a-o**) using DPPH assay, H_2O_2 assay, and Iron chelating assay. Results of DPPH assay revealed compound **43e** as the most promising compound with IC_{50} value of 78.74 μg/mL as compared to ascorbic acid (IC_{50} = 77.13 μg/mL). Results of H_2O_2 assay and iron chelating assay revealed various

compounds as the most promising compound with IC_{50} values in range of 68.05–182.05 μg/mL as compared to ascorbic acid with IC_{50} = 154.34 μg/mL and 109.15 μg/mL against H_2O_2 assay and iron chelating assay, respectively. Compound **43a** was the most promising compound for antioxidant activity with IC_{50} value of 68.05 μg/mL in iron chelating assay. Further, they carried out the docking study of all the compounds and results revealed that docking energy of all the compounds varies from –11.525 to –85.163 kcal/mol.[59]

Dileep *et al.,* designed, synthesized new derivatives of tetrazole by clubbing ciprofloxacin (**44a-g**) and pipemidic acid (**45a-g**) and evaluated all the compounds against a panel of bacterial strains *E. coli*, *B. subtilis*, *B. megaterium*, *M. luteus*, *S. typhi,* and *P. aeruginosa*. Initially, they estimated the zone of inhibition of all the compound (**44a-g**, Figure 16) and assessed that many compounds has moderate to weaker activity against all the bacterial strains (zone of inhibition = 10–37 mm) as compared to Pipemidic acid (zone of inhibition = 22–27 mm) and Streptomycin (zone of inhibition = 19–31 mm), but none of the compound has potent activity in comparison to Ciprofloxacin (zone of inhibition = 35–45 mm). From the results, it was also noticed that tetrazole derivatives of ciprofloxacin (**44a-g**) were more potent than tetrazole derivatives of pipemidic acid (**45a-g**). Then, they estimated the MIC value of compounds **44a-g** through *in vitro* assay and revealed that compounds **44a-g** (MIC = 15.6 μg/mL) were shown to have potent activity against all the bacterial strains (except *P. aeruginosa*) as compared to Ciprofloxacin (MIC = 7.8 μg/mL) and Streptomycin (MIC = 15.6 μg/mL) whereas none of the compounds had shown potent activity against *P. aeruginosa*. Further, they evaluated anticancer potential of all the compounds against cervix (SiHa), breast (MDA-MB-231) and pancreatic carcinoma cell lines (PANC-1). It was assessed that compounds **44c**, **44d**, **45c**, **45d,** and **45f** exhibited potent activity against SiHa cell line with GI_{50} value of 0.06–0.08 μM as compared to Tamoxifen (GI_{50} = 0.12 μM). Compounds **44a**, **44c–g**, **45a**, **45b,** and **45d–f** exhibited potent activity against MDA-MB-31 cell lines (GI_{50} = 0.08-0.02 μM) as compared to Tamoxifen (GI_{50} = 0.24 μM) whereas only **45d** has potent activity against PANC-1 with GI_{50} value of 0.07 μM as compared to Tamoxifen (GI_{50} = 0.15 μM). From the data, it was assessed that compound **45d** has potent activity against all the tested cell lines.[60]

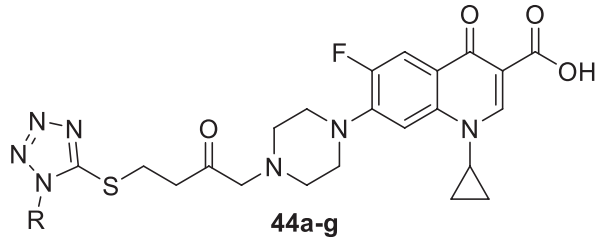
Dofe *et al.*, designed, synthesized derivatives of tetrazole-based pyrazole (**46a-f**) and pyrimidine (**47a-f**) and evaluated their antibacterial activity against four bacterial strains (*S. aureus*, *B. subtilis*, *E. coli,* and *P. aeruginosa*) and antifungal activity against two fungal strains *C. albicans* and *A. niger* [Figure 17]. Compounds were synthesized using conventional heating and ultrasound irradiation methods. Results of *in vitro* assay against *S. aureus* revealed that compounds **46e**, **47a**, **47b,** and **48e** were potent activity with MIC value of 25–50 μg/mL as compared to Chloramphenicol (MIC = 50 μg/mL). None of the compounds were shown to have potent activity against *B. subtilis* and *P. aeruginosa* (MIC = 50–200 μg/mL) as compared to Chloramphenicol (MIC 25–50 μg/mL). Compound **46e** was the equipotent compound



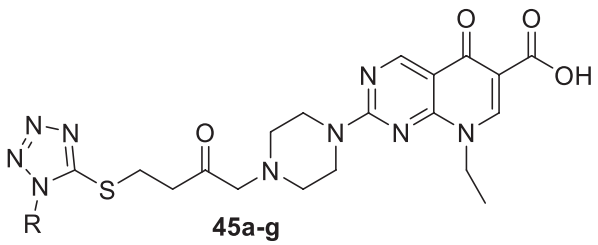
43a-o

43a: $R_1 = R_2 = R_3 = R_4 = R_5 = H$
43b: $R_1 = R_2 = R_3 = R_4 = R_5 = Cl$
43c: $R_1 = R_2 = R_3 = R_4 = H, R_5 = Cl$
43e: R_1 =OMe, $R_2 = R_3 = R_4 = R_5 = H$
43h: $R_2 = Me, R_1 = R_3 = R_4 = R_5 = H$
43m: $R_2 = R_3 = R_5 = Cl, R_4 = R_1 = H$

Figure 15: Chromen based tetrazole derivatives as antibacterial agents



44a-g



45a-g

44a, **45a**: R = -Et
44b, **45b**: R = $-C_6H_5$
44c, **45c**: R = *p*-Me-C_6H_4
44d, **45d**: R = *p*-Br-C_6H_4
44e, **45e**: R = *p*-CF_3-C_6H_4
44f, **45f**: R = 2,3,4-tri flouro-C_6H_2
44g, **45g**: R = 3,4,5-tri methoxy-C_6H_2

Figure 16: Pipemidic and Ciprofloxacin based tetrazoles as antibacterial agents

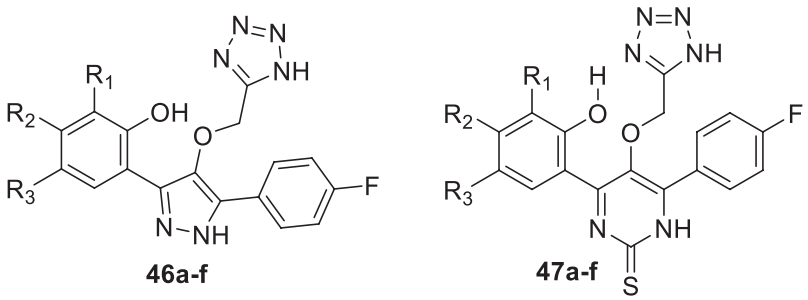


Figure 17: Pyrazole and pyrimidine based tetrazoles as antibacterial agents

as compared to Chloramphenicol (MIC = 50 μg/mL). Results of antifungal activity revealed that only compound **47e** was the most potent compound against *A. niger* with MIC value of 12.5 μg/mL and equipotent against *C. albicans* (MIC = 50 μg/mL) as compared to reference drug Clotrimazole (MIC = 25–50 μg/mL). Compound **47a** was the equipotent compound as compared to Clotrimazole against *A. niger* whereas all others compounds were having poor activity against both the fungal strains with MIC value in the range of 50–100 μg/mL.[61]

CONCLUSION

Tetrazole moiety, which has used in various different drugs with different biological activities, can be used as pharmacophore for the development and discovery of various new clinical candidates. Tetrazole motifs have ability to interact with various key biological targets or biomolecules and this type of interaction is responsible for the different biological profile of tetrazole based drugs. This ability to interact with various biological targets makes tetrazole derivatives attractive lead molecules for design and development of heterocyclic compounds in the field of drug discovery. There is a heavy increase and widely emergence of drug resistance bacteria especially multi drug resistant strains put a serious burden upon world health system. That is why need of an efficacious molecule is still awaited and tetrazole is that kind of scaffold which can provide a clinical candidate with appropriate biological profile. Various tetrazole based hybrids exhibiting promising *in vitro* antibacterial profile against various pathogens such as *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. intermedius*, *S. constellatus*, *Staphylococcus*, *B. subtilis*, and *E. coli* have been discussed in this review. Apart from this, Cefamandole, Ceftezole, Tedizolid, Losartan, and Valsartan are some of the tetrazole based clinically available drug candidates. This review covers recent advances in the medicinal chemistry of tetrazole based hybrids as potential antibacterial agents. This review will provide enriched rationale for the development of tetrazole hybrids with higher activity, lower toxicity as well as multiple mechanism of action. We hope this literature will inspire various researchers by providing the useful information and thus they can utilize tetrazole nucleus for the design as well as the development of clinically viable molecules.

REFERENCES

1. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 2010;74:417-33.
2. Tambo-Ong A, Chopra S, Glaser B, Matsuyama K, Tran T, Madrid P. Mannich reaction derivatives of novobiocin with modulated physiochemical properties and their antibacterial activities. Bioorg Med Chem Lett 2011;21:5697-700.
3. Scheffler R, Colmer S, Tynan H, Demain A, Gullo V. Antimicrobials, drug discovery, and genome mining. Appl Microbiol Biotechnol 2012;97:969-78.
4. Genin M, Allwine D, Anderson D, Barbachyn MR, Emmert DE, Garmon SA, *et al*. Substituent effects on the antibacterial activity of nitrogen-carbon-linked (azolylphenyl) oxazolidinones with expanded activity against the fastidious gram-negative organisms *Haemophilus influenzae* and *Moraxella acatarrhalis*. J Med Chem 2000;43:953-70.
5. Rani N, Sharma A, Singh R. Imidazoles as promising scaffolds for antibacterial activity: A review. Mini Rev Med Chem 2013;13:1812-35.
6. Shalini K, Kumar N, Drabu S, Sharma P. Advances in synthetic approach to and antifungal activity of triazoles. Beilstein J Org Chem 2011;7:668-77.
7. Wang S, Wang Y, Xu Z. Tetrazole hybrids and their antifungal activities. Eur J Med Chem 2019;170:225-34.
8. Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot YN, Al-Aizari FA, *et al*. Synthesis and pharmacological activities of pyrazole derivatives: A review. Molecules 2018;23:134.
9. Kakkar S, Narasimhan B. A comprehensive review on biological activities of oxazole derivatives. BMC Chem 2019;13:16.
10. Sadek B, Al-Tabakha M, Fahelelbom K. Antimicrobial prospect of newly synthesized 1,3-thiazole derivatives. Molecules 2011;16:9386-96.
11. Zhang L, Peng X, Damu G, Geng R, Zhou C. Comprehensive review in current developments of imidazole-based medicinal chemistry. Med Res Rev 2013;34:340-437.
12. Wei C, Bian M, Gong G. Tetrazolium compounds: Synthesis and applications in medicine. Molecules 2015;20:5528-53.
13. Gao H, Shreeve J. Azole-based energetic salts. Chem Rev 2011;111:7377-36.
14. Lim S, Sunohara Y, Matsumoto H. Action of fentrazamide on protein metabolism and cell division in plants. J Pestic Sci 2007;32:249-54.
15. Łodyga-Chruścińska E. Tetrazole peptides as copper (II) ion chelators. Coord Chem Rev 2011;255:1824-33.
16. He Y, Cai C. Tetrazole functionalized polymer supported palladium complex: An efficient and reusable catalyst for the room-temperature Suzuki cross-coupling reaction. Catal Lett 2010;140:153-9.

17. Zhang H, Gan L, Wang H, Zhou C. New progress in azole compounds as antimicrobial agents. Mini Rev Med Chem 2016;17:122-66.
18. Aziz H, Saeed A, Jabeen F, Din N, Flörke U. Synthesis, single crystal analysis, biological and docking evaluation of tetrazole derivatives. Heliyon 2018;4:e00792.
19. Chen Y, Shoichet B. Molecular docking and ligand specificity in fragment-based inhibitor discovery. Nat Chem Biol 2009;5:358-64.
20. Kumar C, Parida D, Santhoshi A, Kota A, Sridhar B, Rao V. Synthesis and biological evaluation of tetrazole containing compounds as possible anticancer agents. Medchemcomm 2011;2:486.
21. Qian A, Zheng Y, Wang R, Wei J, Cui Y, Cao X, *et al*. Design, synthesis, and structure-activity relationship studies of novel tetrazole antifungal agents with potent activity, broad antifungal spectrum and high selectivity. Bioorg Med Chem Lett 2018;28:344-50.
22. Zhan P, Liu H, Liu X, Wang Y, Pannecouque C, Witvrouw M, *et al*. Synthesis and anti-HIV activity evaluation of novel N'-arylidene-2-[1-(naphthalen-1-yl)-1H-tetrazol-5-ylthio] acetohydrazides. Med Chem Res 2009;19:652-63.
23. Yeung K, Qiu Z, Yang Z, Zadjura L, D'Arienzo CJ, Browning MR, *et al*. Inhibitors of HIV-1 attachment. Part 9: An assessment of oral prodrug approaches to improve the plasma exposure of a tetrazole-containing derivative. Bioorg Med Chem Lett 2013;23:209-12.
24. Kalaria P, Karad S, Raval D. A review on diverse heterocyclic compounds as the privileged scaffolds in antimalarial drug discovery. Eur J Med Chem 2018;158:917-36.
25. Kushwaha P, Fatima S, Upadhyay A, Gupta S, Bhagwati S, Baghel T, *et al*. Synthesis, biological evaluation and molecular dynamic simulations of novel benzofuran-tetrazole derivatives as potential agents against Alzheimer's disease. Bioorg Med Chem Lett 2019;29:66-72.
26. Hameed A, Zehra S, Abbas S, Nisa RU, Mahmood T, Ayub K, *et al*. One-pot synthesis of tetrazole-1,2,5,6-tetra hydro nicotinonitriles and cholinesterase inhibition: Probing the plausible reaction mechanism via computational studies. Bioorg Chem 2016;65:38-47.
27. Gao C, Chang L, Xu Z, Yan XF, Ding C, Zhao F, *et al*. Recent advances of tetrazole derivatives as potential anti-tubercular and anti-malarial agents. Eur J Med Chem 2019;163:404-12.
28. Lamie P, Philoppes J, Azouz A, Safwat N. Novel tetrazole and cyanamide derivatives as inhibitors of cyclooxygenase-2 enzyme: Design, synthesis, anti-inflammatory evaluation, ulcerogenic liability and docking study. J Enzyme Inhib Med Chem 2017;32:805-20.
29. Dai L, Zhang H, Nagarajan S, Rasheed S, Zhou C. Synthesis of tetrazole compounds as a novel type of potential antimicrobial agents and their synergistic effects with clinical drugs and interactions with calf thymus DNA. Medchemcomm 2015;6:147-54.
30. Randhawa E, Woytanowski J, Sibliss K, Sheffer I. *Streptococcus pyogenes* and invasive central nervous system infection. SAGE Open Med Case Rep 2018;6:2050313.
31. Chen S. Genomic insights into the distribution and evolution of Group B *Streptococcus*. Front Microbiol 2019;10:1447.
32. Waite R, Qureshi M, Whiley R. Modulation of behaviour and virulence of a high alginate expressing *Pseudomonas aeruginosa* strain from cystic fibrosis by oral commensal bacterium *Streptococcus anginosus*. PLoS One 2017;12:e0173741.
33. Tong S, Davis J, Eichenberger E, Holland T, Fowler V. *Staphylococcus aureus* infections: Epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603-61.
34. Lakhundi S, Zhang K. *Methicillin-resistant Staphylococcus aureus*: Molecular characterization, evolution, and epidemiology. Clin Microbiol Rev 2018;31:18.
35. Ramos-Silva P, Serrano M, Henriques A. From root to tips: Sporulation evolution and specialization in *Bacillus subtilis* and the intestinal pathogen clostridioides difficile. Mol Biol Evol 2019;36:2714-36.
36. Thakur N, Jain S, Changotra H, Shrivastava R, Kumar Y, Grover N, *et al*. Molecular characterization of diarrheagenic *Escherichia coli* patho types: Association of virulent genes, serogroups, and antibiotic resistance among moderate-to-severe diarrhea patients. J Clin Lab Anal 2018;32:e22388.
37. Bolocan AS, Upadrasta A, de Almeida Bettio PH, Clooney AG, Draper LA, Ross RP, *et al*. Evaluation of phage therapy in the context of *Enterococcus faecalis* and its associated diseases. Viruses 2019;11:366.
38. Neu H. Cefamandole, a cephalosporin antibiotic with an unusually wide spectrum of activity. Antimicrob Agents Chemother 1974;6:177-82.
39. Yotsuji A, Mitsuyama J, Hori R, Yasuda T, Saikawa I, Inoue M, *et al*. Mechanism of action of cephalosporins and resistance caused by decreased affinity for penicillin-binding proteins in *Bacteroides fragilis*. Antimicrob Agents Chemother 1988;32:1848-53.
40. Ferrández O, Urbina O, Grau S. Critical role of tedizolid in the treatment of acute bacterial skin and skin structure infections. Drug Des Devel Ther 2016;11:65-82.
41. Hosoya T, Kuriyama S, Yoshizawa T, Kobayashi A, Otsuka Y, Ohno I. Effects of combined antihypertensive therapy with losartan/hydrochlorothiazide on uric acid metabolism. Intern Med 2012;51:2509-14.
42. Giles T, Cockcroft J, Pitt B, Jakate A, Wright H. Rationale for nebivolol/valsartan combination for hypertension. J Hypertens 2017;35:1758-67.
43. Ashok D, Nagaraju N, Lakshmi B, Sarasija M. Microwave assisted synthesis of 5-[4-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenyl]-1H-tetrazole derivatives and their antimicrobial activity. Russ J Gen Chem 2019;89:1905-10.
44. Abu-Hashem A, El-Shazly M. Synthesis and antimicrobial evaluation of novel triazole, tetrazole, and spiropyrimidine-thiadiazole derivatives. Polycycl Aromat Comp 2019;41:1-20.
45. Sathe BP, Phatak PS, Rehman NN, Dixit PP, Khed-Kar VM, Vedpathak SG, *et al*. Synthesis, anti-microbial evaluation and molecular docking studies of some novel tetrazole containing azodye derivatives. Chem Bio Inter 2019;9:96-113.
46. Özkan H, Demirci B. Synthesis and antimicrobial and antioxidant activities of sulfonamide derivatives containing tetrazole and oxadiazole rings. J Heterocycl Chem 2019;56:2528-35.
47. Bahrin L, Clima L, Shova S, Rosca I, Cojocaru C, Bejan D, *et al*. Synthesis, structure, computational modeling, and biological activity of two novel bimesitylene derivatives. Res Chem Intermed 2018;45:453-69.
48. Andrejević T, Nikolić A, Glišić B, Wadepohl H, Vojnovic S, Zlatović M, *et al*. Synthesis, structural characterization and antimicrobial activity of silver(I) complexes with 1-benzyl-1H-tetrazoles. Polyhedron 2018;154:325-33.
49. Sribalan R, Banuppriya G, Kirubavathi M, Padmini V. Synthesis, biological evaluation and *in silico* studies of tetrazole-heterocycle hybrids. J Mol Struct 2019;1175:577-86.
50. Szulczyk D, Dobrowolski M, Roszkowski P, Bielenica A, Stefańska J, Koliński M, *et al*. Design and synthesis of novel 1H-tetrazol-5-amine based potent antimicrobial agents: DNA topoisomerase IV and gyrase affinity evaluation supported by molecular docking studies. Eur J Med Chem 2018;156:631-40.
51. Myznikov L, Hrabalek A, Koldobskii G. Drugs in the tetrazole series. Chem Inform 2007;38:42264.
52. Rajasekaran A, Thampi P. Synthesis and analgesic evaluation of some 5-[β-(10-phenothiazinyl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles. Eur J Med Chem 2004;39:273-9.
53. Uchida M, Komatsu M, Morita S, Kanbe T, Yamasaki K, Nakagawa K. Studies on gastric antiulcer active agents. III. Synthesis of 1-substituted 4-(5-tetrazolyl) thio-1-butanones and related compounds. Chem Pharm Bull 1989;37:958-61.
54. Soliman H, Kalmouch A, Awad H, Wahed NA. Synthesis of new tetrazole derivatives and their biological evaluation. Russ J Gen Chem 2018;88:1726-33.
55. Khan F, Zaheer Z, Sangshetti J, Ahmed R. Facile one-pot synthesis, antibacterial activity and *in silico* ADME prediction of 1-substituted-1 H -1,2,3,4-tetrazoles. Chem Data Coll 2018;15-16:107-14.
56. Baghershiroudi M, Safa K, Adibkia K, Lotfipour F. Synthesis and antibacterial evaluation of new sulfanyltetrazole derivatives bearing piperidine dithiocarbamate moiety. Synth Commun 2018;48:323-8.
57. Baghershiroudi M, Safa K, Adibkia K, Lotfipour F. Bulky organosilicon compounds based on sulfanyltetrazoles: Their synthesis and *in vitro* antibacterial

evaluation. J Iran Chem Soc 2018;15:1279-86.

58. Kumbar M, Kamble R, Dasappa J, Bayannavar PK, Khamees HA, Mahendra M, *et al*. 5-(1-Aryl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-1H-tetrazoles: Synthesis, structural characterization, hirshfeld analysis, anti-inflammatory and anti-bacterial studies. J Mol Struct 2018;1160:63-72.
59. Srinivas B, Kumar P, Reddy PN, Venu S, Shyam P, Krupadanam GD. Design, synthesis, antioxidant and antibacterial activities of novel 2-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-(2HChromen-3-yl)-2H-tetrazoles. Russ J Bioorg Chem 2018;44:244-51.
60. Dileep K, Polepalli S, Jain N, Buddana S, Prakasham R, Murty M. Synthesis of novel tetrazole containing hybrid ciprofloxacin and pipemidic acid analogues and preliminary biological evaluation of their antibacterial and antiproliferative activity. Mol Divers 2017;22:83-93.
61. Dofe V, Sarkate A, Shaikh Z, Gill C. Ultrasound-assisted synthesis and antimicrobial activity of tetrazole-based pyrazole and pyrimidine derivatives. Heterocycl Commun 2018;24:59-65.