Recent Advances in the Medicinal Chemistry of Tetrazole as antibacterial agents: A Comprehensive Study

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Abstract

Bacterial infections are rapidly increasing worldwidely and there is a massive increase in incident of invasive bacterial infections in the last two decades. Development of drug resistane bacteria like multidrug-resistant strains, intractable pathogens and newly arising pathogenic organisms are increasing the patients with bacterial infections. Tetrazole hybrids, has a wide range of biological activities, can be used as a previliged scaffold for the development of new lead molecule. Tetrazole moiety can be hybridized with other molecules to develop new molecules with potential anti bacterial activity. Various tetrazole based molecules have been designed, synthesized and screened for anti bacterial activity in recent years. Some of them are possessing promising activity against various gram positive as well as gram negative bacterias. Tetrazole has various biological activities like 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 summaizes the recent advances and development in medicinal chemistry of tetrazole hybrids for the development of potential anti bacterial agent. This review will provide rationale of various researchers to design more effective tetrazole based clinical candidates.

Keywords: Tetrazole derivatives, Antibacterial activity, Biological activity, Molecular docking

1. 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 anti bacterial 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] and etc[11] are the various types of heterocylce based compounds 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 like anticancer[20], antifungal[21], antiviral[22-23], antimalarial[24], antialzheimer[25-26], antitubercular[27], anti-inflammatory[28] and antibacterial[29]. Various bacterial infections are mainly caused by the *Streptococcus* species *viz. Streptococcus pyogenes* (*S. pyogenes*), *Streptococcus agalactiae* (*S. agalactiae*), *Streptococcus anginosus* (*S. anginosus*), *Streptococcus intermedius* (*S. intermedius*), and *Streptococcus constellatus* (*S. constellatus*), *Staphylococcus aureus* (*S. aureus*, including methicillin-susceptible *S. aureus*/MSSA and methicillin-resistant *S. aureus*/MRSA), *Bacillus subtilis* (*B. subtilis*), *Escherichia coli* (*E. coli*), *Klebsiella pneumonia* (*K. pneumonia*) and *Enterococcus faecalis* (*E. faecalis*)[30-37]. Tetrazole derivatives are found to have potential role upon various types of gram positive and gram negative bacterias. Various tertazole based drugs are clinically available like Cefamandole[38] (**2**), Ceftezole[39] (**3**), Tedizolid[40] (**4**) are used as antibacterial agents and other tetrazole based drugs like Losartan[41] (**5**) and Valsartan[42] (**6**) are used as anti hypertensive agents (**Figure 1**). In this review, basically we have tried to enlighten up the recent advances of tetrazole derivatives as anti bacterial agents. This review will give an overview of emergence of tetrazole hybrids as potential inhibitor of various bacterial pathogens like gram positive as well as gram negative bacterias.

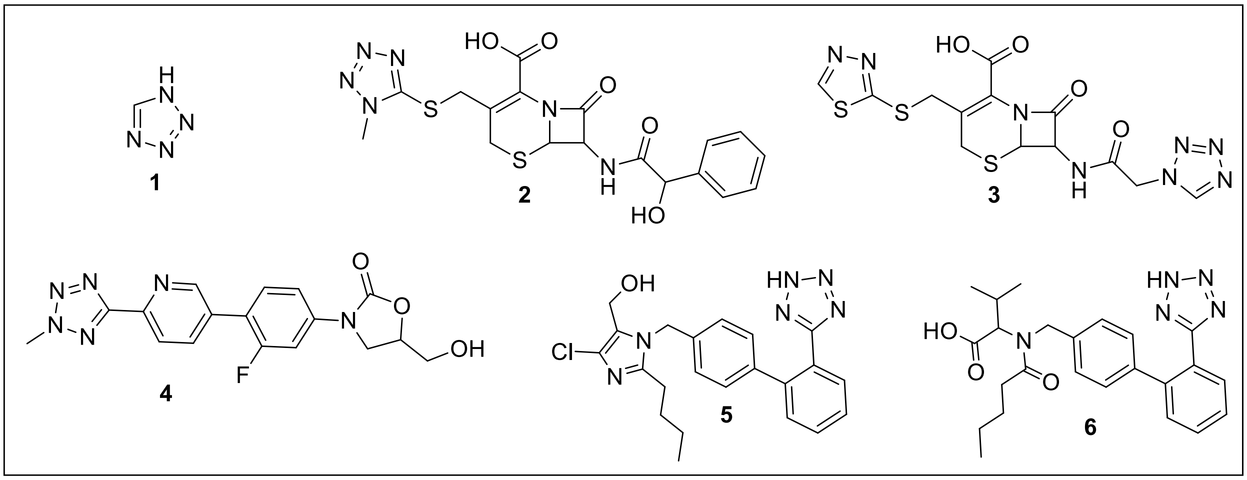


Figure 1

Tetrazole containing clinical available drugs

2. Recent Advances in Medicinal Chemistry of Tetrazole Derivatives as Antibacterial Agents

Ashok D *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 evalualted their antibacterial activity upon 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 (*A. niger*, *A. flavus* and *F.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 concetration 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

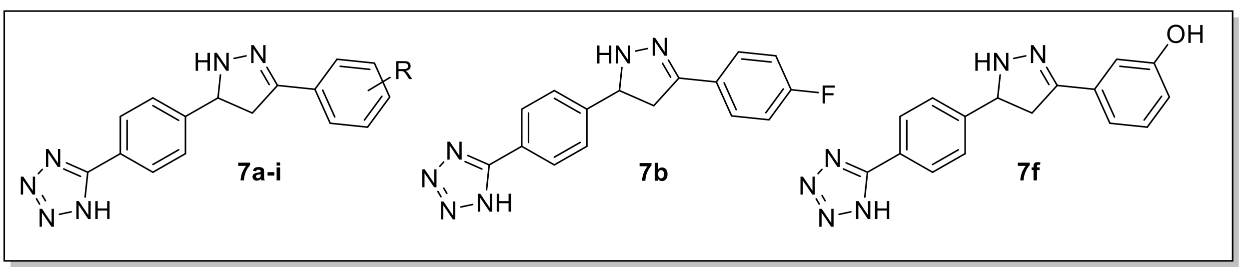


Figure 2: Pyrazole clubbed tetrazole derivatives as antibacterial agents

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 bacterias 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 A.A. *et al.*, designed, synthesized new derivatives of Triazole, Tetrazole, and Spiropyrimidine-Thiadiazole (**8-21d**) and evaluated their anti bacterial potential against two strains of gram positive bacteria (*M. luteus*, *Rhodo pseudomonas fp.* and *B. cereus*) and three strains of gram negatives bacteria (*E. coli* and *S. typhi*). They have also assessed their anti fungal potential upon four strains of fungus i.e. *A. alternata*, *A. flavus*, *C. albicans* and *C. lunata* (**Figure 3**). Results of *in vitro* anti bacterial 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 anti bacterial (MIC = 1-7 μmol/cm^3) as well as anti fungal compounds (MIC = 1-3 μmol/cm^3)[44].

Sathe B.P. *et al.*, designed, synthesized new tetrazole derivatives containing azodye (**22a-k**) and evaluated their antibacterial potential upon 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, S. boydii, E. aerogenes, P. aerogenosa* and *S. 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 5-30 mm whereas standard Tetracycline has zone of inhibition in range of 20-33 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 MICs of above mentioned four best compounds against four bacterial strains *B. subtilis*, *S. typhi*, *E. coli*, *S. abony* and one fungal strains *C.albicans*. It was

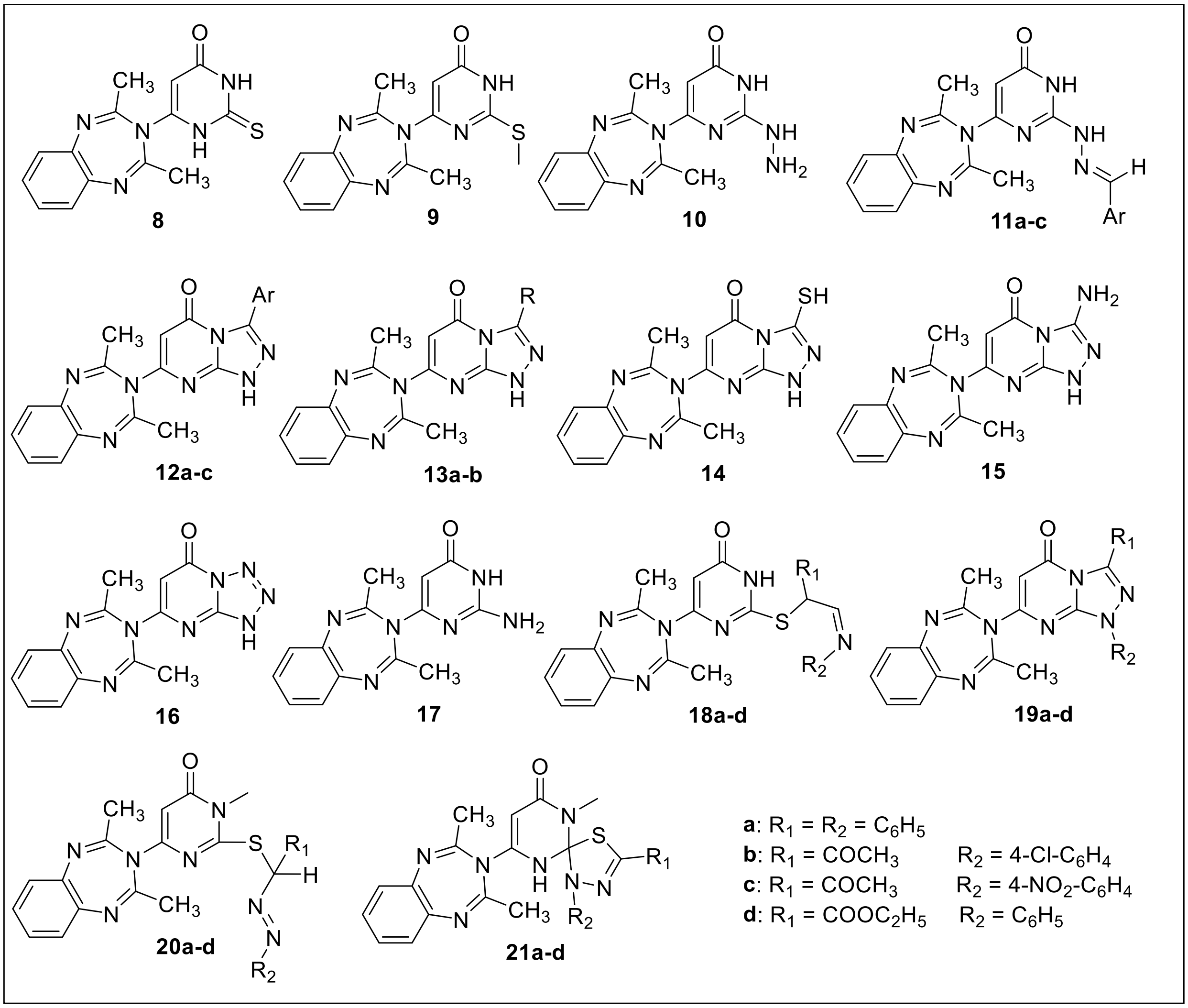


Figure 3: Triazole, tetrazole, and spiropyrimidine-thiadiazole as antibacterial agents

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 like Val167, Thr165, Arg136, Ser121, Val120, Gly119 and Ala96[45].

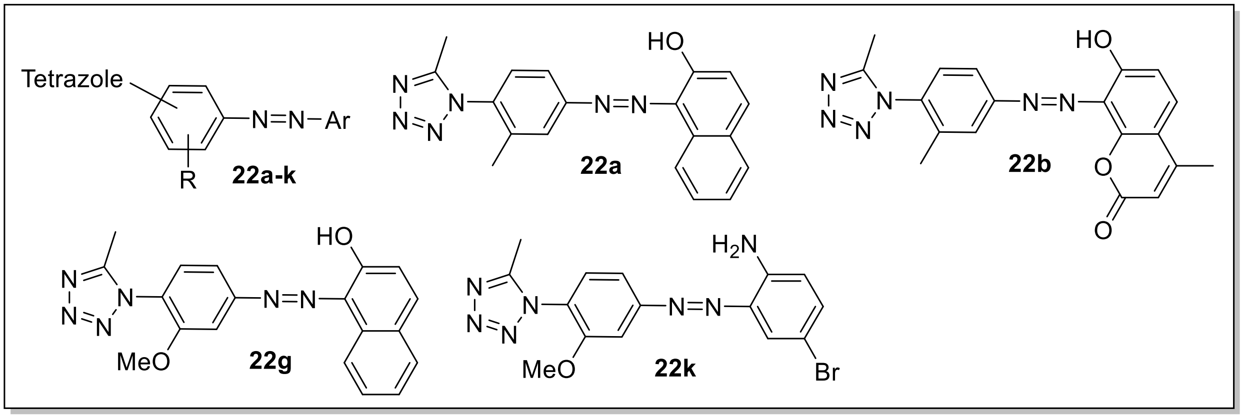


Figure 4: Azodye containing tetrazoles as antibacterial compounds

Ozkan H. *et al.*, designed, synthesized Sulfonamide derivatives (**23**, **24a-g**, **25** & **26a-b**) with Tetrazole and Oxadiazole Rings and evaluated their antibacterial activity upon 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** & **26a-b**, **Figure 5**) were also assayed for their antifungal activity upon two fungal strains (*S. 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 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. pnemoniae* 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* anti fungal assay against *S. cerevisiae* and *C.* albicans and revealed that none of the compounds possessed anti fungal 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 has 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 anti fungal 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

DPPH assay and it was assessed that none of the compounds were had antioxidant property as compared to BHT (butylated hydroxytoluene)[46].

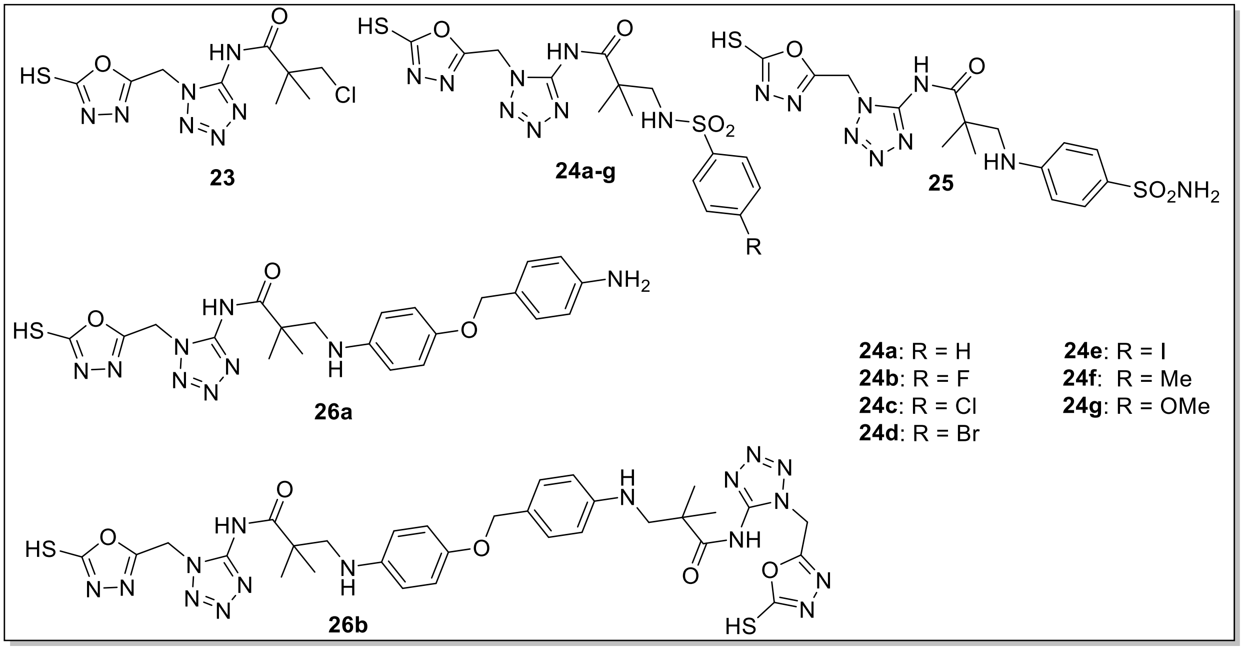


Figure 5: Sulfonamide appended tetrazoles as antibacterial and antifungal agents

Bahrin L.G. *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 modelling 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 bistetrazolybimesitylene crystallizes with space group *P*21/*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].

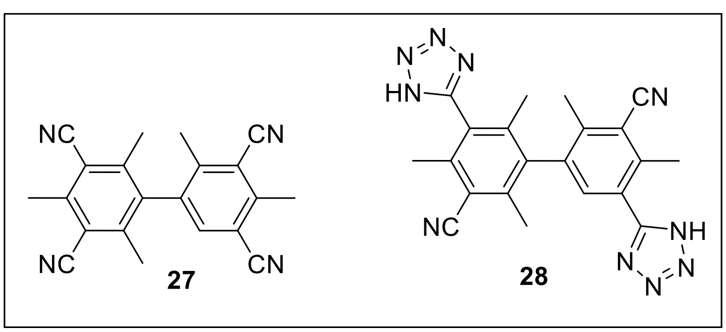


Figure 6: Bimesitylene and bimesitylene bistetrazole for bacterial infections

Andrejević T.P. *et al.*, designed, synthesized three molecule of 1-benzyl-1*H*-tetrazoles with silver(I) complexes (**29-31**, **Figure 7**) and evaluated them for anti bacterial activity against *S. aureus*, *L. monocytogenes*, *M. luteus* and *P. aeruginosa*. They have also evaluated the anti fungal

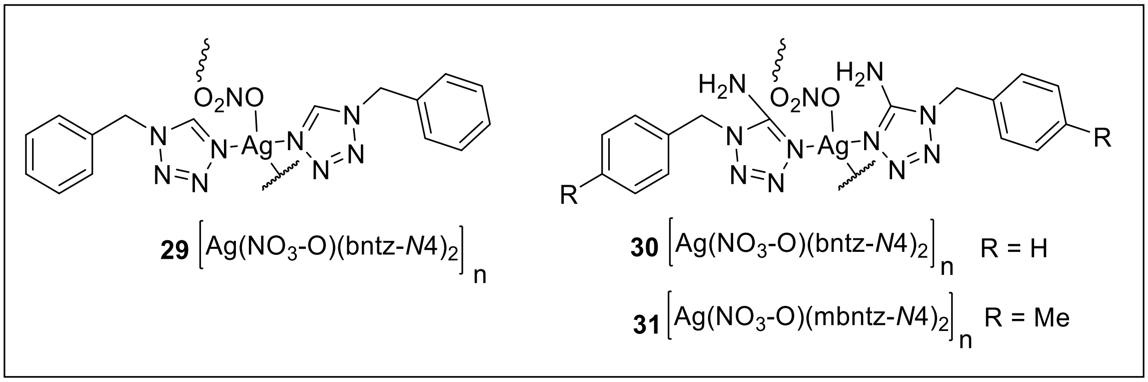


Figure 7: Silver complex of tetrazole as antibacterial agents

activity of all the compounds (**29-31**) against *C. albicans*, *C. glabrata*, *C. krusei* and *C. parapsilosis*. Structural analysis of all the three compounds was done by using X-ray analysis. Results of *in vitro* assay against bacterial strains revealed that none of the compouds 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 R. *et al.*, designed, synthesized tetrazole-heterocycle hybrids (**32a-m**) and evaluated their anti bacterial activity against four bacterial strains (*K. pneumoniae*, *P. aeruginosa*, *S. aureus* and *S. pyrogenes* and also evaluated their anti fungal 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. pyrogenes* as compared to Amikacin [zone of inhibition = 18.2 mm (*S. aureus*) and 18.1 mm (*S. pyrogenes*)]. 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 D. *et al.*, designed, synthesized and evaluated the new derivatives of 1*H*-tetrazol-5-amine (**33a-n**, **Figure 9**) for antibacterial activity upon different strains of *S. aureus, S. epidermidis*, *B. subtilis*, *B. cereus*, *E. hirae*, *E. faecalis*, *M. luteus*, *E. coli*, *P. vulgaris*, *P. aeroginosa* and *B. 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

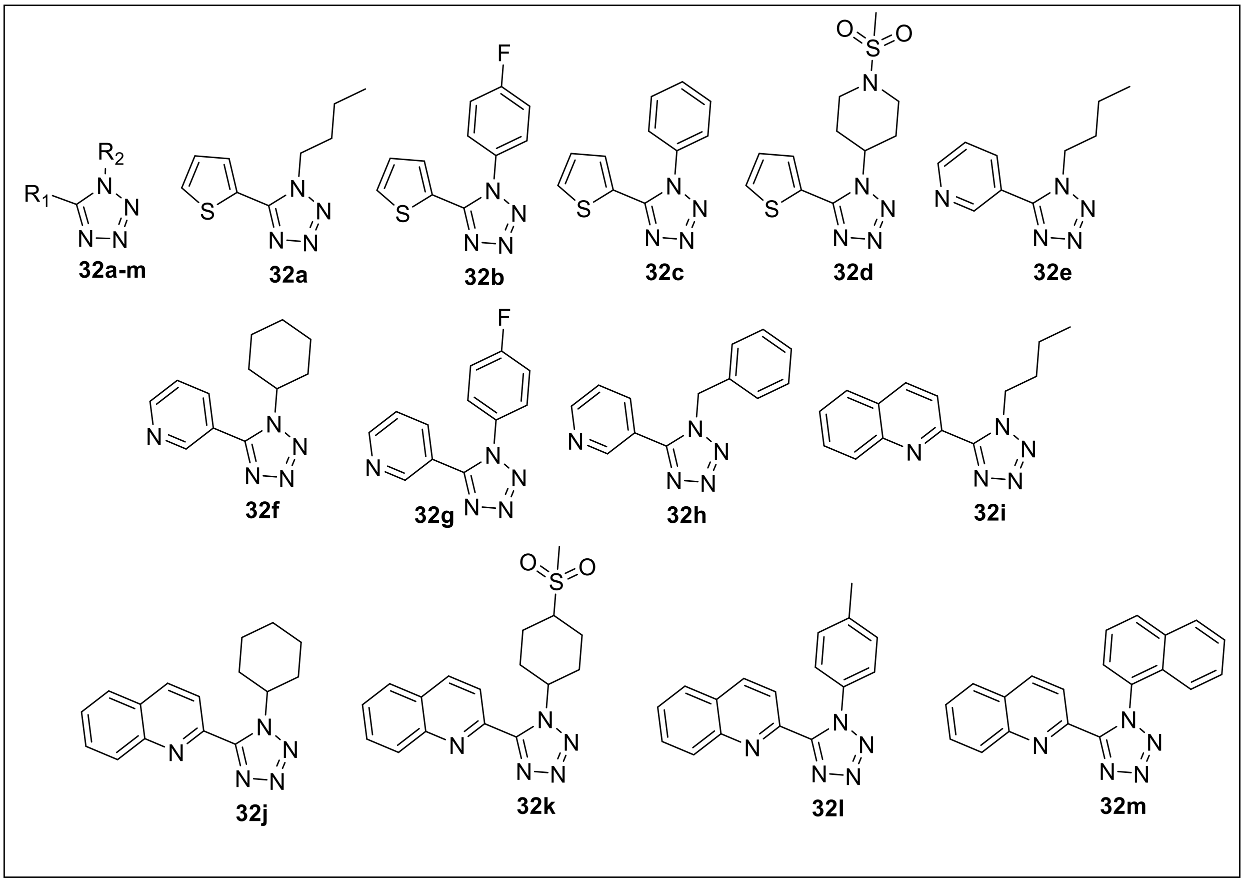


Figure 8: Tetrazole heterocyclic hybrids as antibacterial agents

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 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 like Gly85 and Thr173[50].

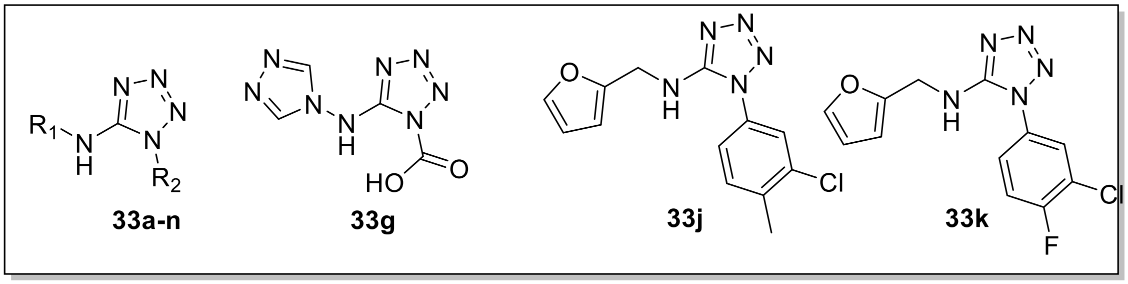


Figure 9: Tetrazole amines as antibacterial agents

1,5-disubstituted tetrazole derivatives are known to have various biological activities like anti tubercular, anti-inflammatory, antiviral, antibacterial and many more[51-53]. Inspired from above, Soliman H.A. *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) upon two gram positive bacterial strains (*Bacillus subtilis* & *Staphylococcus aureus*), two gram negative bacterial strains (*Escherichia coli* & *Pseudomonas aeuroginosa*) and one fungal strain (*Candida albicans*) using agar diffusion method. Results of *in vitro* assay against all the bacterial strains revealed that compounds (**34a-**i)

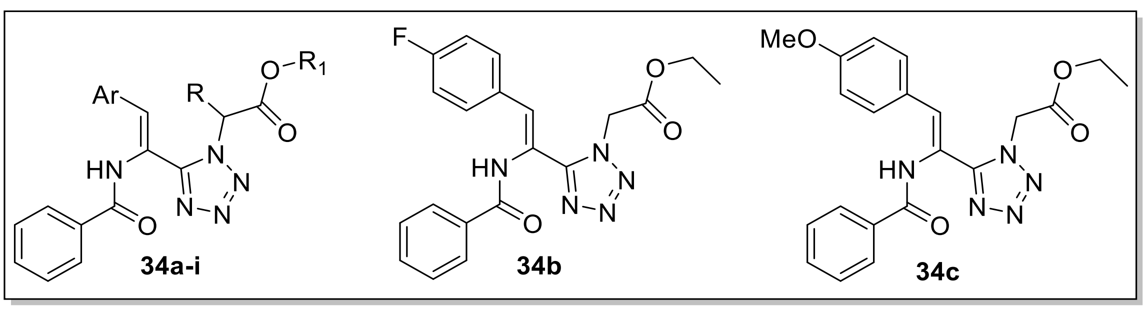
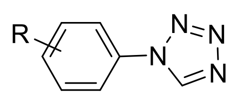


Figure 10: 1,5-Disubstituted tetrazoles as antibacterial agents

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, compound **34b** and **34c** was the best compound with zone of inhibition of 18,17,15,16 & 13 mm and 18,16,14,16 & 13 mm against *B. subtilis, S. aureus, E. coli, P. aeuroginosa* & *C. albicans,* respectively. Further they carried out anticancer activity upon breast cancer cell line (MCF-7) and it was established that none of the compound was potent for anti cancer activity having IC_{50} value in range of 40.2-84.7 µM[54].

Khan F.A.K. *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 bacterias (*P. aeruginosa* and *E. coli*). They have also predicted their ADMET properties (**Figure 11**). All the compounds (**35a-l**) were synthesized via 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



35a-l

35a: R = H
35b: R = 2-OH
35c: R = 4-OH
35d: R = 4-Cl
35e: R = 2,4-DiCl
35f: R = 4-Br
35g: R = 3-NO_2
35h: R = 4-NO_2
35i: R = 4-Me
35j: R = 4-OMe
35k: R = 4-COOH
35l: R = 4-CF_3

Figure 11: 1-Substituted tetrazoles as antibacterial agents

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 Ampcillin (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].

Baghershiroudi M. *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** has weaker activity against *P. aeruginosa* with MIC value of 6.25 µg/mL each as compared to ciprofloxacin (MIC = 0.39 µg/mL)[56].

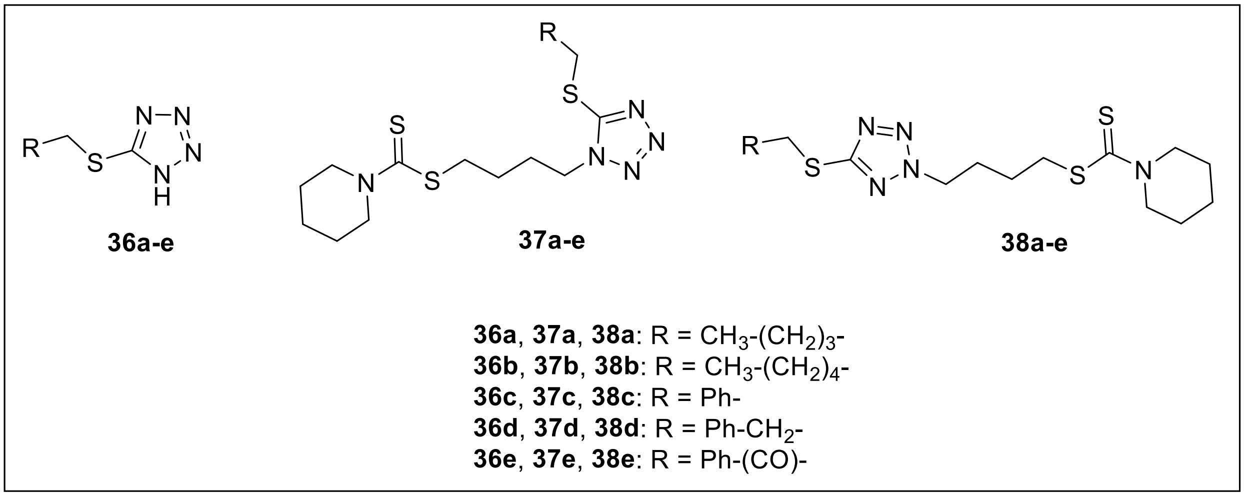


Figure 12: Sulfanyltetrazoles as antibacterial agents

Baghershiroudi M. *et al.*, designed, synthesized sulfanyltetrazole compounds based upon 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**), compound **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 but still compound **39d** was the best compound against all the tested bacterial strains[57].

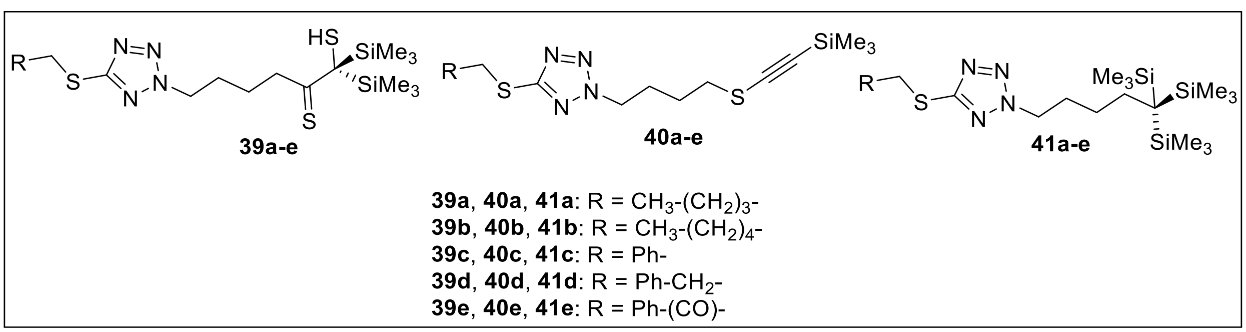
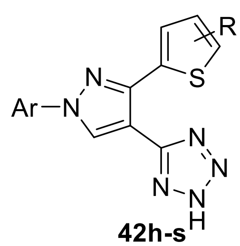


Figure 13: Sulfanyltetrazole appended organosilicon as antibacterial agents

Kumbar M.N. *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 anti bacterial activity against a panel of bacterial strains i.e. *E. faecalis*, *S. aureus*, *E. coli* and *P. auregenosa*. 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 lower concentration of 1.56-3.12 µg/mL whereas Ciprofloxacin has MIC of 6.25 µg/mL. Compounds **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. auregenosa* with MIC value of 3.12 and 1.56 µg/mL, respectively as compared to Ciprofloxacin (MIC = 6.25 µg/mL). Further, they analysed anti-inflammatory activity using RAW mouse murine cancer cell line at three different concentration levels viz., 1, 5 and 10 µg/mL. From the results, it was established that all compounds (**42h-s**) inhibited the production of nitric oxide (NO) in a dose dependent manner. Further, docking study was performed upon all the compounds (**42h-s**) against active site of COX-2 using Surflex-dock programme 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 like Tyr355, His90, Phe518 and Arg120[58].



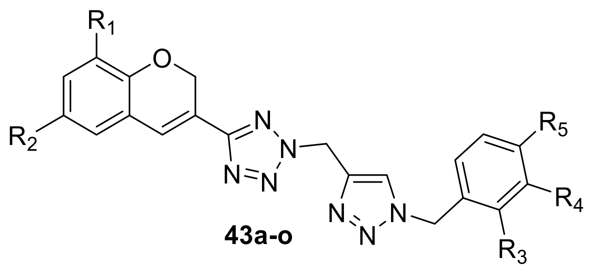
42h-s

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

Figure 14: Thiophene clubbed tetrazoles as antibacterial agents

Srinivas B. *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 upon 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 comaprison 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].



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

Dileep K. *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 Ciproflooxacin (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].

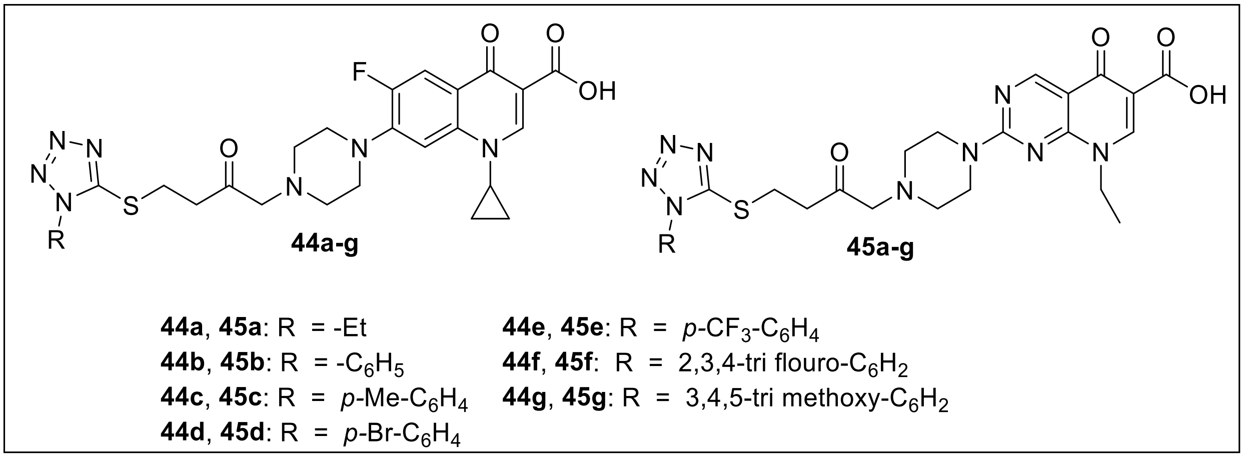


Figure 16: Pipemidic and Ciprofloxacin based tetrazoles as antibacterial agents

Dofe V.S. *et al.*, designed, synthesized derivatives of tetrazole-based pyrazole (**46a-f**) and pyrimidine (**47a-f**) and evaluated their anti bacterial activity against four bacterial strains (*S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*) and anti fungal 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

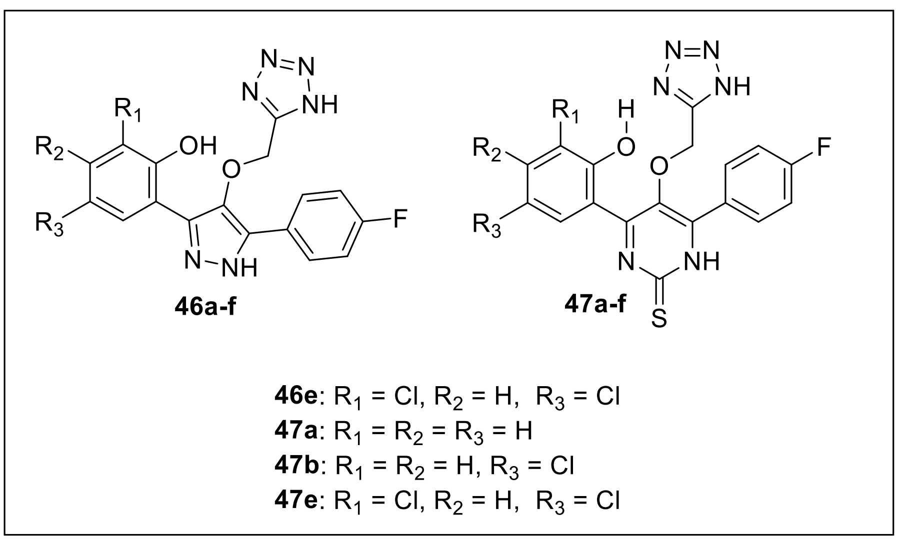


Figure 17: Pyrazole and pyrimidine based tetrazoles as antibacterial agents

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 as compared to Chloramphenicol (MIC = 50 µg/mL). Results of anti fungal 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 oth the fungal strains with MIC value in range of 50-100 µg/mL[61].

3. Conclusion

Tetrazole moiety, which have 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 emergnce of drug resistance bacterias especially multi drug resistant strains put a serious burden upon world health system. That is why need of an efficacious moleule 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* anti bacterial profile against various pathogens like *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. intermedius*, *S. constellatu*, *Staphylococcus*, *B. subtilis*, *E. coli*, etc. have been discuused 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 hybirds 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.

4. Conflict of Interest

The author declares no conflict of interest.

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