Review Article

Antimicrobial efficacy of Quinolines and Naphthyl-substituted 1, 2, 4-Triazoles

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Abstract

The antimicrobial activity of novel quinoline and naphthyl substituted 1,2,4-triazole derivatives has been reported by various researchers on different test microbes. The synthesis involved the preparation of diverse 1,2,4-triazole compounds bearing quinoline and naphthyl moieties through efficient synthetic methodologies. The structural characterization of the synthesized compounds reported using spectroscopic techniques such as 1H NMR, 13C NMR, and FT-IR spectroscopy, confirming the desired molecular structures. Subsequently, the antimicrobial potential of these compounds has been studied against a panel of pathogenic microorganisms including bacteria and fungi using standard agar diffusion and broth microdilution methods. Studied has been confirmed promising antimicrobial activity of several synthesized compounds, with some exhibiting notable inhibition zones and minimal inhibitory concentrations against tested microbial strains. These reported findings suggest the potential of quinoline and naphthyl substituted 1,2,4-triazole derivatives as promising candidates for further development as antimicrobial agents, warranting further investigation into their mechanism of action and pharmacological properties. This review is compile the various new chemical entities with antimicrobial properties, which could address the growing concerns regarding antimicrobial resistance in clinical settings.

Keywords: Antimicrobial activity, Quinoline, Naphthyl, 1,2,4-triazole and Structure-activity relationship

Introduction

Triazole derivatives possess a large significance in medicinal chemistry and numerous heterocyclic triazole compounds having different biological activities. Triazole is a five membered basic compound, containing two carbon and three nitrogen atoms having molecular formula $C_2H_3N_3$ (Siddiqui et al., 2011). In many developing countries large portion of population, depends on the traditional system of medicine to treat variety of disease (McGaw et al., 2000).

The 1,2,3-triazole is measured to be the most stable compound in relationship to all other compounds possessing three adjacent nitrogen atoms. Triazole derivatives possess wide variety of pharmacological activities such as antifungal, antibacterial, antiviral, anticancer, anticonvulsant, anti-inflammatory, antioxidant, anti-tubercular, anti-malarial, anti-nociceptive and other anticipated activities (Padmaja et al., 2012).

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The resolute appearances of microbial infections followed by the expansion of several resistant bacterial and fungal strains against clinically used antimicrobial arsenal have urged medicinal communities to look for new incorporations into the current armamentarium. Severe chances of microbial infections among immunosuppressive individuals due to the HIV infection, cancer treatments and organ transplantations actuated additional urgency to generate new antimicrobial agents. The development of resistance to currently used antibacterial therapy has obliged the scientists, chemists, and biologists, to further search for more effective agents with less or no side effects. This is even more relevant to the present day scenario as the primary and opportunistic bacterial and/or fungal infections still continue to escalate with the increased number of immune compromised patients (mostly due to the diseases such as AIDS, cancer, and also as a consequence of long-term therapy after transplants) (Padmaja et al., 2012).

The term "privileged structures" was coined by Evans and co-workers and since then has proven to be an effective

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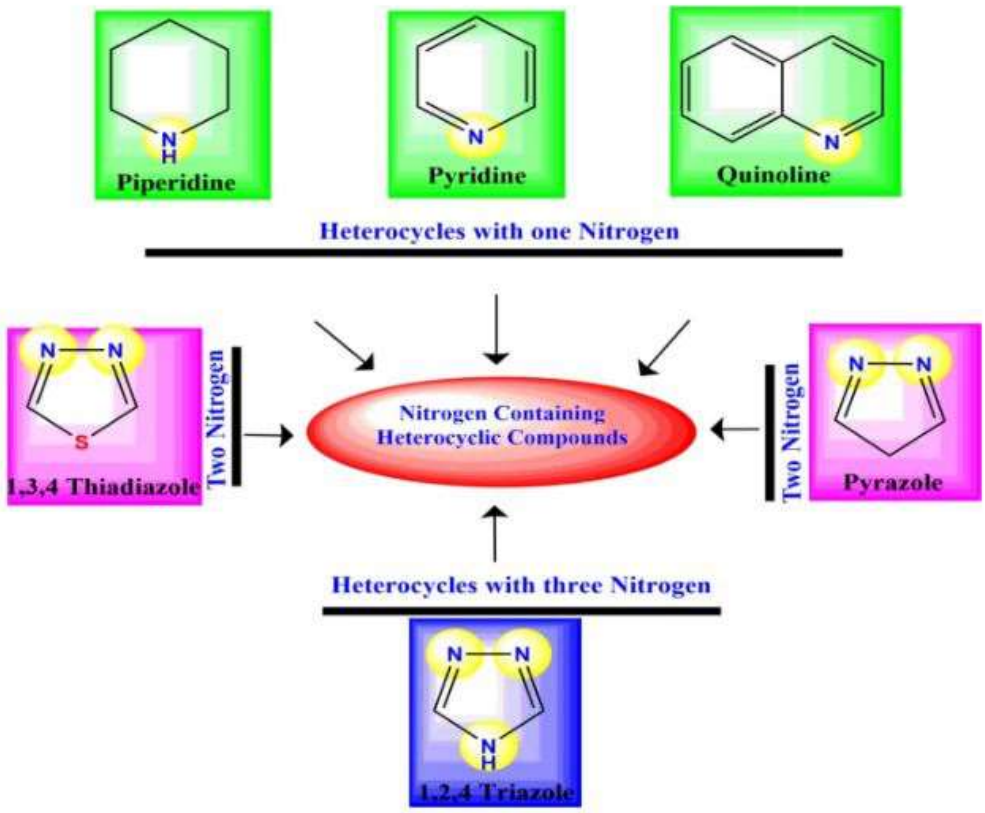

Figure 1. Nitrogen containing heterocyclic compounds

approach in drug discovery process. Among the reported privileged structures, the quinoline scaffold constitutes one of the most explored heterocyclic systems due to its broad range of pharmacological activities of special interest are the anticancer properties of quinoline derivatives. Thus, the quinoline ring is utilized in clinically used anticancer drugs, such as *camptothecin* and its analogues, e.g., topotecan, which are known as topoisomerase inhibitors or multitarget kinase inhibitors, including lenvatinib and cabozantib, whereas omipalisib and dactolisib are currently under clinical trials as agents targeting the phosphoinositide 3-kinase (PI3K). It is worth noting, however, that the antiproliferative effects of the quinoline-containing compounds may also result from cell cycle arrest, apoptosis DNA intercalation inhibition of angiogenesis inhibition of proteasome and disruption of tubulin polymerization (Sidoryk et al., 2015).

Chemistry

The synthetic route for key intermediate methanesulfonic acid 2-[1-(4-methoxy-phenyl])-3-methyl-5-oxo-1,5-dihydro-[1,2,4]-triazol-4-yl]-ethylester (**7**) is depicted. This intermediate is prepared from 4-methoxy aniline through the sydnone by two ring transformation reaction following the literature method (Latthe et al., 2007). The synthetic route followed for the preparation of the new compounds is outlined. The reaction of methanesulfonic acid 2-[1-(4-methoxy-phenyl])-3-methyl-5-oxo-1,5-dihydro-[1,2,4]-triazol-4-yl]-ethylester (**7**) with substituted piperidine, piperazines, and phenols in the presence of Cs_2CO_3 gave [1,2,4]-triazolo piperidine (**8**), [1,2,4]-triazolo piperazines (**9a-c**) and [1,2,4]-triazolo phenylethers (**10a-e**) in moderate to good yields. It has been tried similar conditions for anilines and instead of the desired products **11a-c**, and obtained alkene (**12**), the structure of which is confirmed by ^{1}H NMR and LCMS. This indicates that anilines are less reactive towards nucleophilic substitution. Hence in the presence of Cs_2CO_3 dehydromethylsulphonation is preferred over substitution reaction. Triethylamine first reacts with **7** and forms more reactive quaternary salt, from Cs_2CO_3 to triethyl amine (Foroumadi et al., 2006).

Antimicrobial activity of heterocyclic compounds

Some heterocyclic chemicals and heterocyclic compounds show some antimicrobial activity. Some antimicrobial agents are safe, potent and they must be encouraged. Further all future efforts to produce an effective antimicrobial agent must strictly take the following things as major concerns (Gennnaro and Remington's, 2000).

The *in vitro* antimicrobial activity was carried by using the disc diffusion method .All the newly synthesized compounds were evaluated for their antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*,

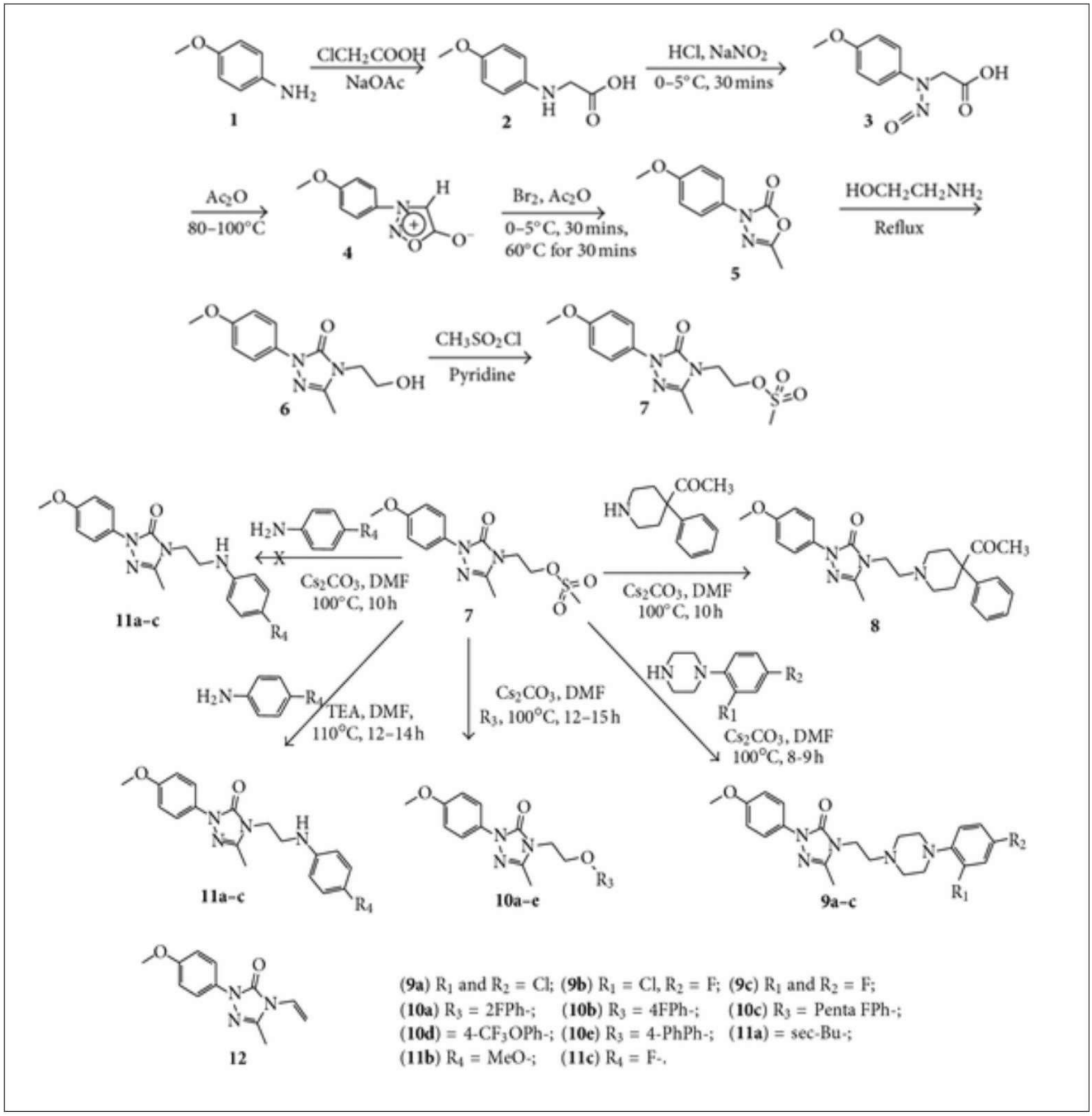

Figure 2. Synthetic route for various Triazoles derivatives

Staphylococcus epidermidis, *Escherichia coli,* and *Pseudomonas aeruginosa*. The antifungal activity was evaluated against *R. oryzae*, *A. niger*, *A. flavus*, *C. albicans,* and *S. cerevisiae*. The minimum inhibition concentration (MIC) was determined by using the twofold serial dilution method with 64-well microtest plates (Snow and Abeywardane, 2007). The test compounds were dissolved in dimethylformamide (DMF). Further dilutions were made at the required concentrations of 300, 150, 75, 37.5, 18.75, 9.75, 6.25, 3.125, and 1.56µg/mL, respectively. Streptomycin and Penicillin were used as reference standards for antibacterial activity and Amphotericin-B as reference standard for antifungal activity. The standard drugs were selected based on our previous work in order to compare the activity (Ozden et al., 2007).

Bacteria are the simplest and smallest unicellular organism originate independently or in bunches. The huge number of extremely effective and comparatively non-toxic drugs

available for the management of bacterial infections has provided tough contest for the medicinal chemist, challenging to synthesis of new antimicrobial agents. These antibacterial agents are classified in two types on the basis of their mode of action as bactericidal and bacteriostatic activities.

The 1-(1H-1,2,4-triazolyl)-2-(2,4-diflurophenyl)- 3-(4-substituted-1-piperazinyl)-2-propanol derivatives on the basis of the active site of lanosterol 14α-demethylase exhibited in vitro antifungal activities. Some of these compounds had higher antifungal activity than fluconazole and some compounds showed good MIC values less than 0.125μg/mL and more potent than fluconazole. Compound had excellent effectiveness against a broad range of pathogenic fungal stains including *Aspergillus fumigates* (Jubie et al., 2010).

The compound showed comparable or superior activity than the reference drug Some ciprofloxacin analogues compound showed antimicrobial activity. In these compounds ciprofloxacin have been incorporated to the series of Schiff bases of 1,2,4-triazole via Mannich reaction. The compounds showed in vitro antimicrobial activity against gram positive and gram negative bacteria like *B. subtilis, K. pneumoniae*, and ciprofloxacin (Chun et al., 2004).

Unsubstituted and 3-substituted-7-aryl-5H-6,7-dihydroimidazo [2,1-c][1,2,4]triazoles compound were exhibited their antifungal activity against A. niger and Fusarium oxysporum. Among these compounds, 7-(3- chlorophenyl)-6,7-dihydro-5Himidazo[2,1-c] [1,2,4]triazole-3-thiol was showed the most significant activity (Sztanke et al., 2018).

Among these compounds, 7-(3- chlorophenyl)-6,7-dihydro-5Himidazo[2,1-c] [1,2,4]triazole-3-thiol was showed the most significant activity. Compounds were evaluated as antimicrobial agents against against *Esherichia coli, P. auroginosa*, *Yersinia pseudotuberculosis, Klepsiella pneumonia, Enterococcus fecalis, Staphylococcus aureus* and *Bacillus cereus* and ampicillin was used as control antibiotics. These compounds were showed good antibacterial activity against S. aureus34. The 1,2,4-triazole-3-thiol metronidazole derivatives. were showed anti microbial agents against G-positive, G-negative bacteria and fungal. With the exception of Clostridium sporogenes the antimicrobial activity was significantly lower than that of the reference antimicrobials (Haythem et al., 2010).

A series of N,N-bis(1,2,4-triazole-1-yl methyl) amine, condensation of 1- (hydroxyl-methyl) with different amines were evaluated for their antifungal activity against budding yeast *Saccharomycces cerevisiae* and their antibacterial activity was found most active (Hanane et al., 2010).

Some 4-Aryl triazole derivative were found as antibacterial agents against *B. cereus, P. aeriginosa, K. pneumoniae, Micrococcus flavus* and *Citrobactor freundii* and antifungal agents against *Candida tropicalis, C. albicans, Cryptococcus neofomans, Trichospor onbeigelii*, and *A. flavus* (Prajapati et al., 2013).

Some 1,3,4-thiadiazol-2-ylmethyl-1,2,4- triazoles were showed microbial activities.

Some compounds of them showed good activity against a variety of microorganisms60. A series of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazo l-2-yl]-3-methylthio-6,7-dihydrobenzo thiophen-4(5H)ones were showed in vitro antimicrobial activity. Some of these compounds exhibited a good activity against S. aureus, S. epidermidis and Bacillus subtilis (Tehranchian et al., 2005).

A derivatives of 1-(substituted biaryloxy)- 2-(2,4-difluoro phenyl)-3-(1H-1,2,4-triazol-1- yl) propan-2-ol derivatives were showed antifungal activity against eight human pathogenic fungi in vitro. Most compounds showed activity between 4- and 64-fold higher than voriconazole against *C. albicans*. Activity suggested that introduction of a biaryloxy side chain greatly improved the antifungal activity of triazole (Liu et al., 2007).

The comparison of the biological activity of psedomonoas aeruginosa and Escherichia coli (G-) becteria and staphylococcus aureus and bacillis (G+). The data are listed the biological activity of some metal comparison are higher than the free ligand (Raja et al., 2011).

Third and fourth series involve reaction of α- and β-naphthol with 4-(Bromomethyl)phenol and alkyl halides. It is a two-step reaction furnished through one-pot synthesis. Firstly, 4- (Bromomethyl) phenol reacts with 1-(2-chloroethyl) pyrrolidine hydrochloride, 1-(2-chloroethyl) piperidine hydrochloride and 4- (2-chloroethyl) morpholine hydrochloride producing phenoxy ethyl derivatives, which in turn reacts with α- and β-naphthol fabricating corresponding naphthyloxy phenoxyethyl derivatives. The synthesized series constituted simple, but novel, naphthyloxy and naphthylphenoxy derivatives which were synthesized with the concept of showcasing promising antimicrobial potency (Kaur el al., 2014).

The chemical structure was elucidated by spectral methods. The number of signals in the 1H-NMR spectra of azo compound (L1) was observed due to the 10 protons back to the three aromatic rings were observed in the δ ~7.53-8.51 ppm range. Some of these doublet signals appeared at chemical shift (δ ~8.49-8.51ppm) for H13+15 due to the withdrawing induced by the keto group. The other triplet signals appeared at the field (δ ~8.01-7.98, 7.92-7.94 and 7.78-7.80 ppm) due to protons H9, H6, and H3, respectively

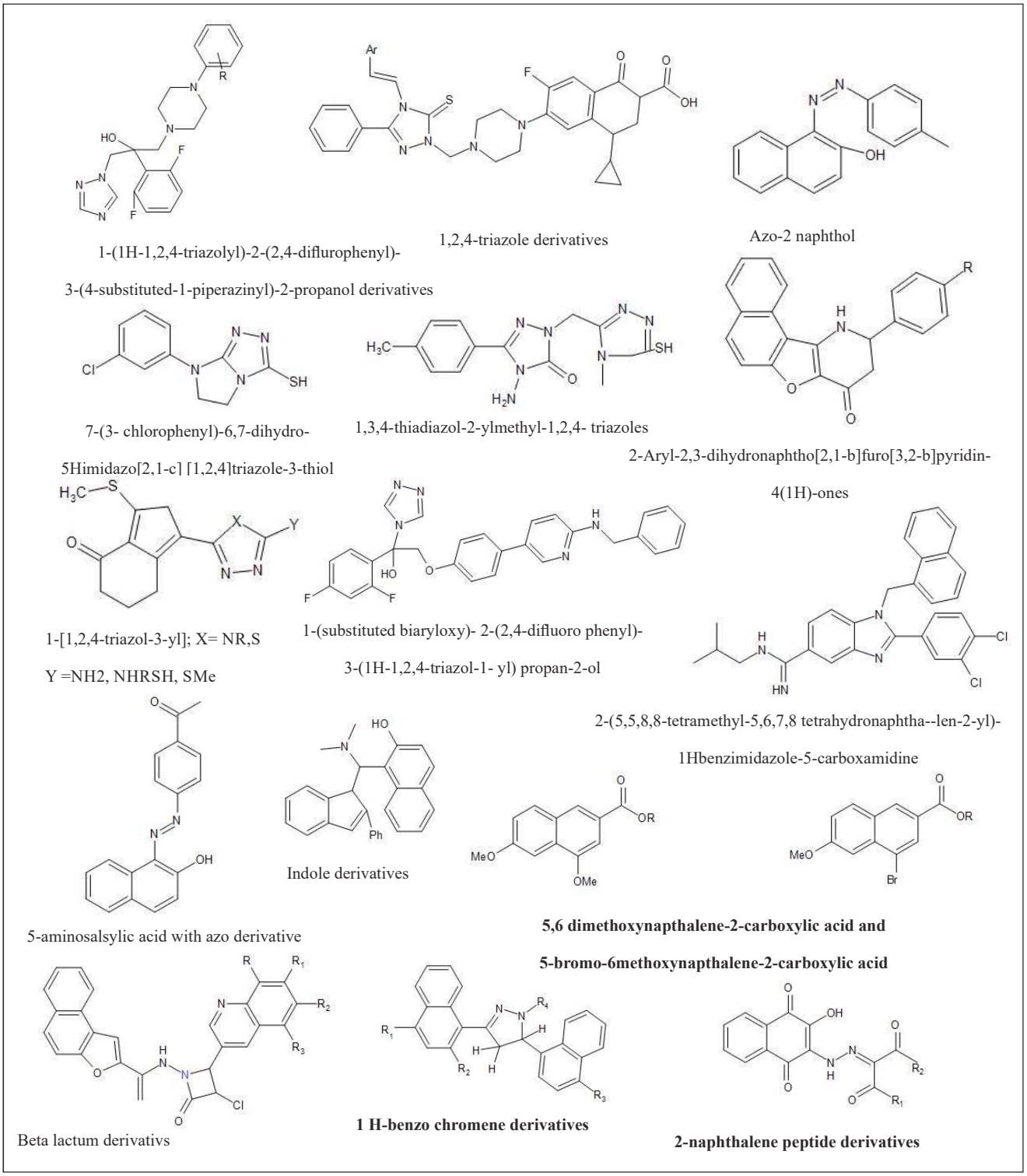

Figure 3. Structures of different heterocyclic compounds showed Antimicrobial activity

while the singlet signal of hydroxyl group showed at (d ~6.83 ppm). At a lower field, Me-keto appeared at (d ~ 2.41 ppm). In the 13C-NMR spectra, the signal of the carbonyl keto (C-17) appeared at 196 ppm, while the signals back to 16 aromatic carbon atoms were observed at a range of 117-142 ppm. At this time, the signal of the methyl group was shown at. Azo-Schiff compound (L2) was prepared via condensation of 5-aminosalsylic acid with azo derivative (L1) in an acidic solution, according figure (Jarad, 2012).

The indole framework is a medicinally relevant scaffold and

has been widely identified as a privileged structure of pharmacophore. Indole scaffold is present in thousands of isolated natural products and also synthetic compounds constitute an important class of therapeutic agents in medicinal chemistry such as antimicrobial and antituberculosis products (Pajouhesh et al., 1983).

In view of structure and in continuation of our research on the synthesis of biologically active molecules in present investigation, we report the synthesis, antioxidant, antimicrobial, antitubercular, and anticancer activities of novel indole derivatives(Saundane et al.,2013).

All the newly synthesized compounds (above) were assessed for their in vitro antibacterial activity against four representative bacterial species, namely, *Escherichia coli* (MTCC-723), *Staphylococcus aureus* (ATCC-29513), *Klebsiella pneumonia* (NCTC-13368), and *Pseudomonas aeruginosa* (MTCC-1688) using gentamycin as reference. Determination of MIC was done using the serial dilution method (Barry, 1980).

The tested azo-2 naphthol and 2-napthol against five representative human pathogenic microorganisms i.e. *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa* and *Streptococcus faecalis*. Both azo-2 naphthol and 2-napthol were found equally effective against all the organisms tested (Mkpenie et al., 2008).

The prepared several 2-(5,5,8,8-tetramethyl-5,6,7,8 tetrahydronaphtha--len-2-yl)-1Hbenzimidazole-5-carboxamidine analogues and evaluated for their antibacterial and antifungal activities against S. aureus, Methicillin-resistant S. aureus (MRSA)(Zeynep et al., 2006).

The compound 2-hydroxy-1-napthalene with 6,7-dihydro-13H dibenzo [e,n] doxomin-2,11 diamine were studied on the Gram-negative bacteria like Escherichia coli (ATCC 25922) and Pseudomonas aeruginosa (ATCC 27853), the Gram-positive bacteria like S. aureus (ATCC 25923), MRSA (clinical isolate), Enterococcus faecalis (ATCC 29212) and fungi like Candida krusei (ATTC 6258) and Candida albicans (ATCC 10231). The compound was found to have potent antibacterial and antifungal activity(Nagaraja et al.,2006).

The compound synthesized 2-Aryl-2,3-dihydronaphtho[2,1-b]furo[3,2-b]pyridin-4(1H)-ones were synthesized from2-hydroxy-1-naphthonitrile and characterized on the basis of chemical, analytical and spectral data. The compounds screened for antibacterial and antifungal activity were found effective against human pathogenic Gram positive and Gram negative bacteria and fungi (Nagaraja et al., 2006).

The substituted several new 1 H-benzo chromene derivatives with 2-napthols and found them to possess enhanced biological activity against bacterial, fungal and viral pathogens of human 15. Azarifar et al., 16 the syntheses of twenty-four 3, dinaphthalene -1-yl substituted 2-pyrazolines containing certain groups as substituent's both on the naphthalene and pyrazoline rings. The compounds were tested in vitro for antimicrobial activity against Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Proteus mirabillis, Shigella dysentry and Salmonella typhii at a temperature of 37 °C (±1°C). It was observed that 81% of the total samples tested showed antimicrobial activity against all the organisms tested (Ahemed et al., 2002).

The reported that 5-bromo-6methoxynapthalene-2-carboxylic acid and 5,6 dimethoxynapthalene-2-carboxylic acid were having antibacterial activity against some pathogenic bacteria under in-vitro conditions(Goksu et al.,2005).

The important structural features affecting the antimicrobial activity of 15- residue derivatives of lactoferricins. His investigations were based on an alanine-scan of a 15 residue bovine lactoferricin derivative that revealed the absolute necessity of two tryptophan residues for antimicrobial activity. They prepared a synthetic 15-residue derivative of bovine lactoferricin (LFB). containing naphthalene derivative and concluded that 2-naphthalene peptide more active than 1- naphthalene isomers; 2, the naphthalene moiety in 2-Nal is pointing more away from the b-carbon atom than in 1-Nal, giving 2-Nal a more elongated shape; 2-Nal thereby has a longer side chain than 1-Nal, and was able to penetrate deeper into the cell membrane of bacteria, thus offering an explanation as to why the 2-Nal peptides display a higher antimicrobial activity than the 1-Nal peptides(Strom et al.,2002)

Conclusion

Many different triazole derivatives have been prepared from its useful pharmacological activities. In the present review, reported the different pharmacological activities of triazole derivatives. Triazole derivatives possess a wide range of pharmacological activities such as anticancer, anticonvulsant, antimicrobial, antitubercular, antimalarial, anti-inflammatory, antioxidant, analgesic etc. In general triazole ring, substitution at 1,4 and 1,3 positions with electronegative group will possess more active compounds. Some triazole compounds are in therapeutic uses like, Itraconazole, Voriconazole, Fluconazole, Posaconazole (antifungal), Ribavirin (antiviral), Trapidil (antihypertensive and aasodilator), Rilmazafone (anxiolytic), Nefazodone, Trazodone (antidepressant), Estazolam (sedativehypnotic), Rufinamide (antiepileptic),

Anastrozole (antineoplastic), Alprazolam (tranquillizer). These diverse pharmacological activities of triazole are the milestone for the new research. Modifications in triazole ring displayed valuable biological activities and these modifications can be utilized to develop more effective agents for future explorations.

Conflict of interest: None

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