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New Insights into Chemistry and Anti-Infective Potential of Triazole Scaffold

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Abstract: Research and development for novel substances possessing anti-infective activity have attracted considerable attention due to the escalating resistance towards conventional antibiotics. Therefore, the discovery and development of effective antimicrobial drugs with novel mechanism of action have become an insistent task for infectious diseases research programs. Triazole scaffold has been consistently rewarded as a promising versatile lead molecule with a pivotal position in modern medicinal chemistry. The literature reveals that this heterocyclic moiety has drawn attention of the chemists, pharmacologists, microbiologists and other researchers owing to its indomitable biological potential as anti-infective agents. The present communication is a cogent attempt to review the chemistry and antimicrobial activities of triazole derivatives reported in recent scientific literature. The biological profiles of these new triazole derivatives represent a fruitful matrix for further development as promising and superior anti-infective medicinal agents.

Keywords: 1,2,3-triazole, 1,2,4-triazole, antibacterial, antifungal, antiviral, antimycobacterial, antimalarial activity.

1. INTRODUCTION

New and reemerging infectious diseases will continue to pose serious global health threats well into the 21st century and according to the world health organization (WHO) report, these are still the leading cause of death among humans worldwide [1]. Approximately one third of the human death toll, i.e. about 17 million people per year, has to be attributed to infections caused by pathogenic viruses, bacteria, fungi and parasites. Five of the leading causes of deaths worldwide related to infectious diseases in humans are pneumonia, acquired immunodeficiency syndrome (AIDS), chronic liver disease, chronic obstructive lung disease, and neoplastic diseases like stomach cancers, cervical cancers and liver cancers. AIDS pandemic has been devastating, with the WHO reporting 2.1 million deaths due to AIDS whereas another 1.6 million deaths due to tuberculosis and 880,000 deaths due to malaria occur every year which represent the severity of these infectious diseases [2, 3].

Nosocomial infections have also increased dramatically in the past few years. The majority of these infectious diseases are caused by *staphylococci*, *enterococci* or *Pseudomonas aeruginosa*. Patients treated with intensive care medicine, and the growing number of immuno-compromised persons due to chemotherapy, AIDS or organ transplantations, represent a high risk group potentially susceptible to these pathogens [4-6].

Antimicrobial resistance is an under-appreciated threat to public health in nations around the globe. With globalization booming, it is important to understand the international patterns of resistance [7]. According to laws of Darwinian evolution, antimicrobial use creates a selection pressure on microorganisms: weak ones are killed, but stronger ones might adapt and survive. When pathogenic microorganisms can multiply beyond some critical mass in the face of invading antimicrobials, treatment outcome is compromised; this phenomenon is referred as antimicrobial resistance (AMR) [8-11]. Treatment of infections is increasingly compromised by ability of bacteria to develop resistance to antibiotics through mutations or the acquisition of resistance genes. Several mechanisms have been characterized, through which bacteria become resistant to antibiotics [12]: (i) production of enzymes that digest/metabolize the antibiotic; (ii) efflux pumps that eliminate the drug from the cell; (iii) modifications to the cellular target of the antibiotic that prevent binding; (iv) activation of an alternate pathways that bypasses drug action; and (v) particularly for Gram-negative bacteria, down-regulation or elimination of transmembrane porins through which drugs enter the cell [13].

Resistance mechanisms may develop over months or years. Once established, a single resistance mechanism can often allow a bacterium to resist multiple drugs [14]. It remains unclear whether resistance is reversible, and thus whether drug effectiveness is a renewable or non-renewable resource [15-18]. Drug resistance raises the cost of treatment for infectious diseases and increases the rate of morbidity and mortality from such diseases [19-26].

Escherichia coli and *Klebsiella pneumoniae* are the most common Gram-negative pathogens that infect hospitalized patients [27]. The management of such infections has become complicated due to generation of a variety of β-lactamases by these microorganisms. β-Lactamases are either Type 1 or non-Type 1 enzymes. Type 1 β-lactamases are produced through chromosomally mediated mechanisms. Non-Type 1 β-lactamase resistance takes several forms, of which the transfer of extended-spectrum β-lactamases (ESBLs) between bacteria is becoming increasingly clinically relevant [28, 29]. Bacteria that produce ESBLs should be considered resistant to all penicillins, cephalosporins other than cephamycins (e.g., cefoxitin and cefotetan), and aztreonam [30]. Moreover, third-generation cephalosporins, such as cefotaxime and ceftriaxone, with reported minimum inhibitory concentration (MICs) in the susceptible range against ESBL-producing bacteria, may fail *in vivo* [31]. Presently, carbapenems, such as imipenem and meropenem, are the most stable antibiotic class in the presence of ESBLs, so these agents are reserved for patients with severe infections with risk factors for ESBLs [32].

Enterococci develop resistance by acquiring resistance genes from plasmids of other microorganisms and through intrinsic mechanisms [33]. Enterococcal plasmids can transfer resistance to other Gram-positive bacteria, which present a mechanism for spreading vancomycin resistance in the staphylococci and streptococci species. Gentamycin or streptomycin can be used in treatment of vancomycin-resistant enterococcal infections [34].

Antibiotics are known as the second most commonly prescribed category of drugs and in terms of usage, the most widely used antibiotics are penicillins and cephalosporins, followed by fluoroquinolones [35]. Inappropriate antibiotic use and antibiotic resistance are now major global issues because it is widely accepted that there is a direct correlation between the use of antibiotics and development of antibiotic resistance [36]. More than 90% of strains of *Staphylococcus aureus* in American hospitals are resistant to penicillin and β-lactam antibiotics. The economic impact of antimicrobial resistance is substantial. The estimated annual cost of

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antimicrobial resistance in hospitals due to *Staphylococcus aureus* is $122 million and of nosocomial infections is $4.5 billion. The effective dissemination to healthcare professionals of the significance of the intangible costs and collateral damage associated with antibiotic use remains one of the most compelling challenges [37]. In addition to this, systems need to be developed that raise and sustain an awareness of the principles of prudent antibiotic use among healthcare professionals. Therefore, physicians must now select antibiotics with the specific needs of an individual patient in mind but also in a manner that does not breed further drug resistance [38, 39].

The biological, immunological, and physiological consequences of the interaction of pathogenic microbes with hosts have begun to be appreciated during the last two decades and provide opportunities to develop new therapeutic options [40]. These new approaches will synergize with antibiotic use in ways that will lead to better clearance of infectious organisms from tissues [41-43]. Many scientists believe that the new age of antibiotic discovery will be driven by revolutionary developments in combinatorial chemistry, genetics, structural biology, bioinformatics, and genetic engineering [44-46]. Merging of advances in high throughput screening with combinatorial chemistry offers opportunities for formulating new paradigms for antibiotic development during the times ahead [47, 48].

Discovery of antibiotics is one of the greatest events in the history of medicine which has a profound effect on human life. Research for drug discovery takes about 10-15 years for a new chemical entity to become a drug, which costs about $ 800 million for a single drug. At the present time, large pharmaceutical companies are not much involved in antibiotic drug discovery because of unfavorable returns. About twelve thousand antibiotics are known today [49]. Approximately, 55% of antibiotics were produced by the genus Streptomyces which is within the filamentous bacterial group (Actimomycetes), 11% from other actinomycetes, 12% from nonfilamentous bacteria and 22% from filamentous fungi [50].

According to a report published in 2009, the antibiotics market generated sales of US$42 billion globally, representing 46% of sales of anti-infective agents (which also include antiviral drugs and vaccines) and 5% of the global pharmaceutical market. However, the antibiotics market is maturing; it showed an average annual growth of 4% over the past 5 years, compared with a growth of 16.7% and of 16.4% for antiviral drugs and vaccines, respectively [51]. The cephalosporin class of antibiotics is the largest in terms of sales, generating $11.9 billion. This class represents 28% of the total antibiotic market. With sales of $7.9 billion, the second largest drug class is the broad-spectrum penicillins whereas the third largest drug class is fluoroquinolones having sales of $7.1 billion, accounting for 17% of the total antibiotic market (Table **1**).

Table 1. World Antibiotic Market [52, 53]

Antibiotic	World market in US$ (billions)
Cephalosporins	11.9
Penicillins	7.9
Fluoroquinolones	7.1
Macrolides	4.8
Tetracyclines	1.6
Aminoglycosides	1.0
Trimethoprims	0.3

Today, resistance mechanisms against nearly all of the antimicrobial agents have emerged, leading to the evolution of epidemic multiresistant microbial strains that spread within hospitals, nations and even around the world. Therefore, the development of more effective new antimicrobial agents against the most severe pathogens that use novel targets has become an urgent issue [54-60].

The pharmacologically important heterocycles derived from triazole paved the way towards active research in triazole chemistry. A number of attempts have been made to improve the pharmacological activities of these compounds by varying the substitution on the triazole nucleus [61]. The triazole nucleus is one of the oldest and the most potent heterocyclic compounds, having been incorporated into a wide variety of therapeutically significant drug candidates including antibacterial [62], antifungal [63], antitubercular, antiviral, antimalarial, antimigrane, antileishmanial, anti-inflammatory [64], analgesic [65], antihypertensive, local anaesthetic, antianxiety, antidepressant, antihistaminic, antioxidant, antiparkinson's, antidiabetic, antiobesity, immunomodulatory, antiepileptic [66] and antineoplastic agents etc. [67-69].

2. CHEMISTRY

Small ring systems containing nitrogen, sulphur and oxygen have been under investigation for a long time because of their important medicinal activities [70]. Five-membered rings containing more than one nitrogen as heteroatom are the heterocycles which represent the largest and the most diverse group of the heterocyclic compounds. It is variation in the number and positions of these nitrogen atoms which lead to the structural diversity of this group of heterocycles, resulting in the formation of some important members like diazoles (pyrazole and imidazole), triazoles (1,2,3- and 1,2,4-triazole) and tetrazoles containing two, three and four nitrogen atoms in the rings respectively. Heterocyclic compounds are common and integral structural features of a variety of natural products and medicinal agents, having a wide range of applications such as pharmaceuticals, agrochemicals and veterinary products [71].

Triazole, also known as pyrrodiazole is one of the classes of organic heterocyclic compounds, containing a five membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms. It is a white to pale yellow crystalline solid with a weak characteristic odour, soluble in water and alcohol, melts at 120°C, boils at 260°C, with molecular formula $C_2H_3N_3$, having molecular weight of 69.06. It occurs as a pair of isomeric chemical compounds 1,2,3 and 1,2,4-triazole (Fig. **1**) which are the basic heterocyclic rings present in various pharmacologically important medicinal agents [72].

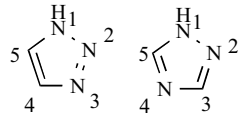


Fig. (1). Chemical structures of 1,2,3 and 1,2,4-triazole.

The most common approaches which have been employed for synthesis of various triazole derivatives are discussed in the following text:

2.1. Methods of Synthesis of 1,2,4-triazoles

2.1.1. Pellizari Reaction

In this reaction, thermal condensation of an acylhydrazide with an amide or (better) a thiomide, for example benzoyl hydrazide and thio benzamide at 140˚C yields 3,5-diphenyl -1,2,4-triazole (Fig. **2**) [73].

2.1.2. Einhorn –Brunner Reaction

Hydrazide or a mono substituted hydrazine is condensed with a di-acylamine in the presence of a weak acid, for example phenyl

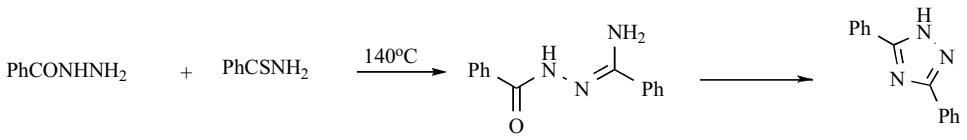


Fig. (2). Synthesis of 3,5-diphenyl -1,2,4-triazole.

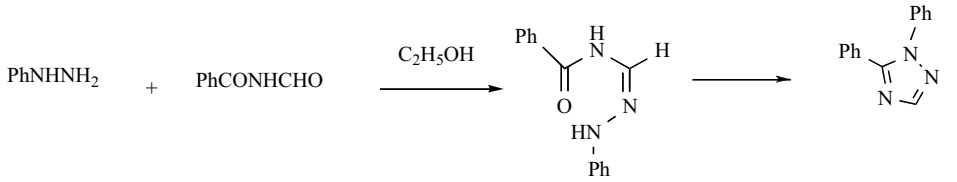


Fig. (3). Synthesis of 1,5-diphenyl-1,2,4-triazole.

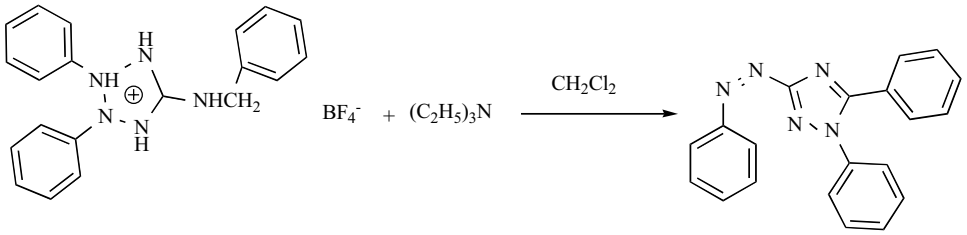


Fig. (4). Synthesis of 1,2,4-triazole.

hydrazine and *N*-formyl benzamide. Reaction gave 1,5-diphenyl-1,2,4-triazole (Fig. **3**) in good yields [72].

2.1.3. Recently, various 1,2,4-triazoles have been prepared by the reaction of 5-(benzylamino)tetrazolium salt with triethylamine in the presence of dichloromethane at room temperature (Fig. **4**) [74].

2.1.4. The synthesis of 1,2,4-triazoles can be carried out by the reaction of pyridyl-3-carbohydrazide with potassium hydroxide and carbon disulphide to yield potassium 3-aroyldithiocarbazate salt which is refluxed with ammonia to yield 3-(3'-pyridyl)-1,2,4-triazole-5-thiol in moderate to higher yields (Fig. **5**) [75].

2.2. Methods of Synthesis of 1,2,3-triazoles

2.2.1. 1*H*-1,2,3-triazoles can be prepared by the 1,3-dipolar cycloaddition of wide variety of organic azides XN_3 (X= alkyl, vinyl, aryl, acyl, arene, sulphonyl, etc.) to acetylenes (Fig. **6**) [76].

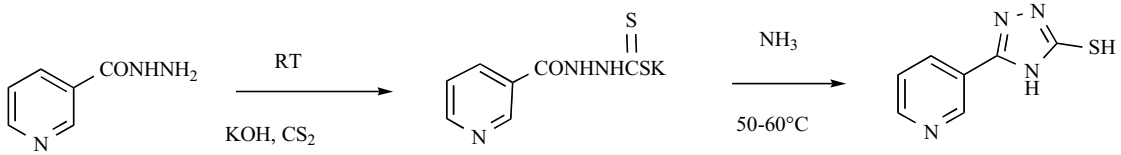


Fig. (5). Synthesis of 3-(3'-pyridyl)-1,2,4-triazole-5-thiol.

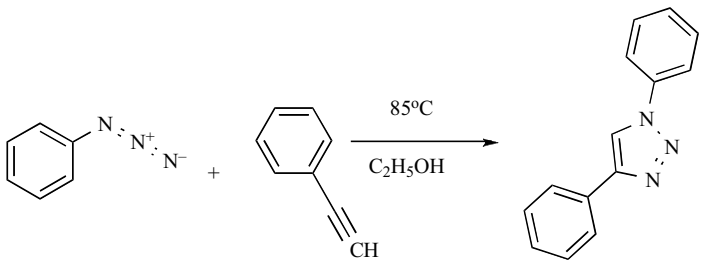


Fig. (6). Synthesis of 1,2,3-triazole.

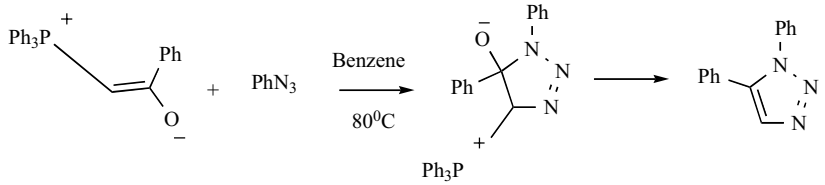


Fig. (7). Synthesis of 1,5-diphenyl-1,2,3-triazole.

2.2.2. Several other compounds can react with azides to give 1*H*-1,2,3-triazoles; these include enolate anions, enol ethers, enamines and alpha-acyl phosphorus ylides etc. For example, the ylide react with the azido benzene in solution at 80°C to give 1,5-diphenyl-1,2,3-triazole (Fig. **7**) [73].

2.2.3. One-pot synthesis of 1,2,3-triazole is done in the absence of any catalysts and additives, from benzyl and alkyl halides, sodium azide and alkynes in the presence of water. For example, the reactions of terminal arylalkynes, sodium azide with benzyl chlorides and bromides give the corresponding regiospecific 1,4-disubstituted triazoles in excellent yields (Fig. **8**) [77].

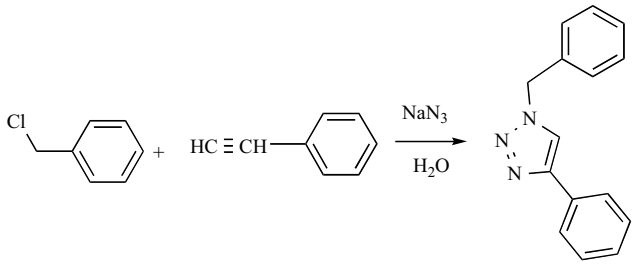


Fig. (8). Synthesis of 1,4-disubstituted-1,2,3-triazole.

2.2.4. Various 1,2,3-triazoles are prepared *via* click chemistry by the Huisgen [3 + 2] cycloaddition between alkynes and azides catalyzed by copper(I) salts in the presence of sodium ascorbate (Fig. **9**) [78].

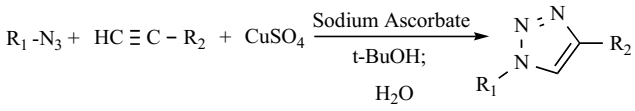


Fig. (9). Synthesis of 1,4-disubstituted-1,2,3-triazole.

2.2.5. 1,2,3-triazoles can be prepared by 1,3-dipolar cycloaddition reactions of 9-azidoacridines with various acetylenes like dimethylacetylene dicarboxylate under solvent-free conditions by using microwave irradiation method (Fig. **10**) [79].

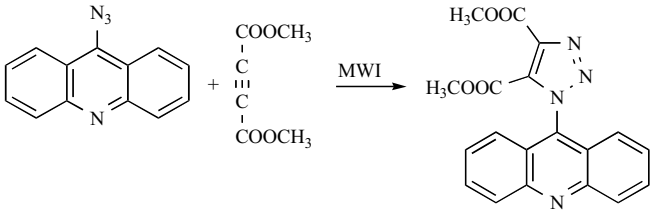


Fig. (10). Synthesis of 1,4,5-trisubstituted-1,2,3-triazole.

2.2.6. 2*H*-1,2,3-triazoles can be made by the oxidative cyclization of copper (II) salts of the bis-phenyl hydrazones of 1,2-diketones, for example the cyclization of bis-phenyl hydrazones of α-keto aldehydes gives 2*H*-1,2,3-triazoles (Fig. **11**) [80].

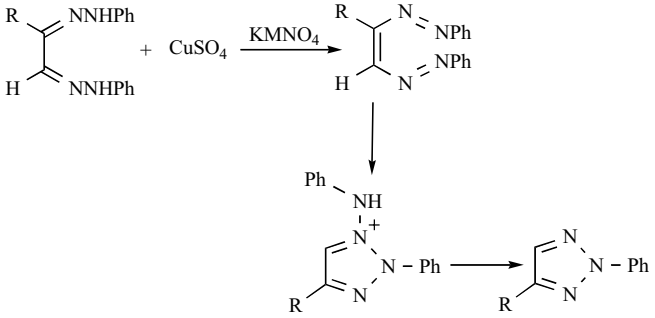


Fig. (11). Synthesis of 2,4-disubstituted-1,2,3-triazole.

2.3. Chemical Reactions of Triazoles

Triazole nucleus undergoes following types of chemical reactions:

2.3.1. Electrophilic Substitution Reaction

Electrophilic Substitution reactions at carbon are relatively uncommon in the triazole because the number of carbon atoms is less and electrophiles preferentially attack at nitrogen atom [80]. Bromination (Fig. **12**) and methylation (Fig. **13**) are the examples as follows:

Bromination

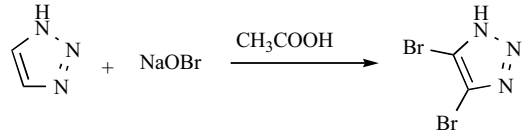


Fig. (12). Bromination of triazole.

Methylation

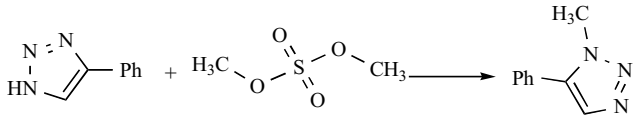


Fig. (13). Methylation of triazole.

2.3.2. Nucleophilic Substitution Reaction

Nucleophilic substitution reactions of carbon substituents which are good leaving groups take place in triazoles for example 5-chloro-1-substituted triazoles can be converted into other 5-substituted triazoles by nucleophilic substitution reactions (Fig. **14**) [81].

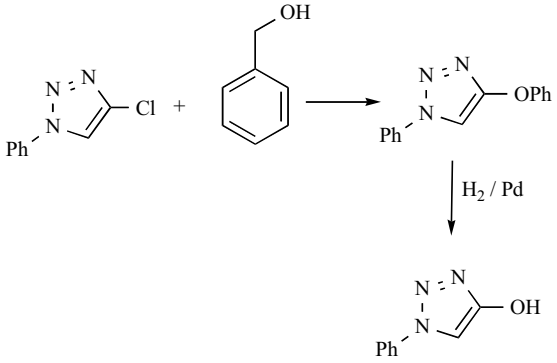


Fig. (14). Nucleophilic substitution reaction of triazole.

2.3.3. Decomposition of 1,2,3- Triazole

Triazole exists as an isomeric pair of 1,2,3 and 1,2,4-triazoles which is chemically stable under normal temperature conditions. It undergoes thermal decomposition at a temperature of above 295ºC by liberating nitrogen containing products and oxides of carbon. It readily reacts with strong oxidizers or strong acids causing product decomposition. Thermal stability of triazole varies with the type of substitution to the triazole ring for example metal chelated and halogen substitution of the triazole ring make it for a particularly heat sensitive material. It is soluble in water, methanol, ethanol and chloroform, and sparingly soluble in ethyl acetate. It is insoluble in ether and acetone. Aqueous solutions are neutral. Triazole is decomposed to aziridine at 500°C with a loss of molecular nitrogen by so called ring chain tautomerism involving Dimorth rearrangement. The photolysis or thermolysis of 1-substituted-1,2,3-triazole gives 1*H*-aziridine intermediate (Fig. **15**) [82].

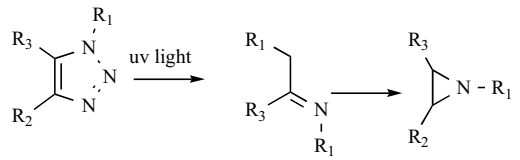


Fig. (15). Photolytic decomposition of 1,2,3-triazole.

2.3.4. Formation of Diquartenary Salt

1-Methyl-1,2,4-triazole is successively methylated at N-4 and N-2 by an excess of trimethyloxonium tetraflouroborate to give the diquartenary salt (Fig. **16**) [80].

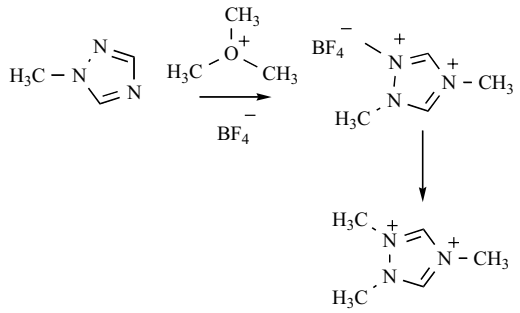


Fig. (16). Formation of diquartenary salt of triazole.

3. SPECTRAL CHARACTERISTICS

The spectroscopic characterization of triazoles has been established by various instrumental methods of analysis like ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR) and mass spectroscopy. Brief discussion of spectral features is presented as follows:

3.1. UV Spectroscopy

The UV spectrum (measured in ethanol) of 1,2,3-triazole shows absorption maximum at 210 nm whereas the wavelength for absorption maximum of 1,2,4-triazole in UV (measured in dioxane) is 205 nm [83].

3.2. IR Spectroscopy

The IR (KBr) spectrum of the triazole shows peaks at 3298-3249 cm^{-1}, N-H stretching; 2934-2923 cm^{-1}, CH stretching; 1628-1621 cm^{-1}, C=N stretching [84, 85].

3.3. NMR Spectroscopy

The ^{1}H-NMR spectrum of 1,2,3-triazole (in DMSO-d_6) shows peaks at δ 13.15 (H-2), δ 7.91 (H-4) and δ 7.91 (H-5). The ^{13}C-NMR (in DMSO-d_6) spectrum of 1,2,3-triazole shows peaks at δ 130.3 (C-4) and δ 130.3 (C-5). The ^{1}H-NMR spectrum of 1,2,4-triazole (in HPMT) shows a CH- signal at δ 8.17 and an NH-signal at δ 15.1. Only one signal at δ 147.4 is observed in the ^{13}C-NMR spectrum (in methanol-d_4) because of time averaging due to tautomerism. However, at 34°C, the CH-signal is observed to split into two peaks at δ 7.92 for 3-H and δ 8.85 for 5-H [86].

3.4. Mass Spectroscopy

The mass spectra of 1,2,4-triazole shows that fragmentation pattern of l,2,4-triazole nuclei (Fig. **17**) are analogous to the fragmentation modes reported for pyrrole. The extent to which these fragmentations account for the peaks in the mass spectra depends on the substituents of the 1,2,4-triazoles. The possible application of fragmentation modes of pyrrole to 1,2,4-triazole nuclei is complicated when hydrogen is bonded to one of the ring nitrogens because of the possible tautomerism [87, 88].

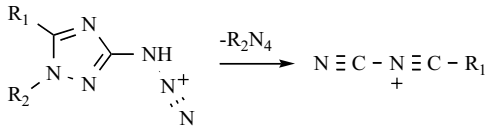


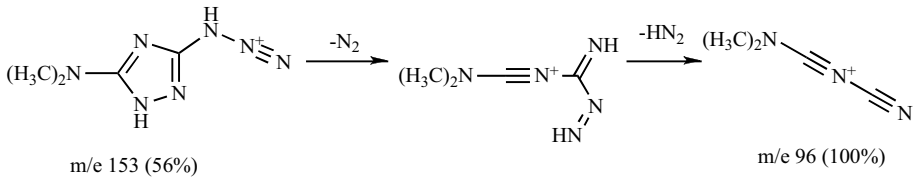
Fig. (17). Fragmentation pattern of l,2,4-triazole.

The existence of M-1 peaks in the spectra of such compounds is due the fact that the hydrogen atoms are β, instead of α, to the ring. The loss of nitrogen in the decomposition of azides by the electron impact is common. The base peak usually corresponds to the remaining ion. The fragmentation of the C-azido-1,2,4-triazoles (Fig. **18**) leads primarily, to stable nitrilium ions. The mass spectra of C-azido-1,2,4-triazoles are characterized by a strong peak corresponding to the molecular ion and base peak which together account for 28-48% of the total ionization at 70 eV. The mass spectrum of C-azido-5-dimethylamino-1,2,4-triazole contains meta stable peaks which illuminate the transitions leading to its base peak. These transitions, can be rationalized by charge delocalization in the molecular ion on the azide group. Even though, the peak representing the M-N_2 species is not present in the spectrum, a metastable peak indicates the loss of nitrogen and is a typical of the azides. The additional loss of HN_2 forms a species corresponding to the base peak, which can be represented by the stable nitrilium ion. The formation of nitrilium ions is likely for all the C-azido-1,2,4-triazoles, since in every case, the base peak corresponds to the loss of molecule of nitrogen plus 1-N, 2-N, and any group attached to them [89].

3.5. X-Ray Diffraction Spectroscopy

The triazolyl ring is planar with C atom lying only 0.063 A° from the mean plane. All four C-N distances are shorter than a normal single bond (1.47 A°). The N-N bond is also shorter than a normal single bond (1.45 A°). The three atoms bonded to N-1 are almost co planer with it. Taken together, these data indicate extensive delocalization within the heterocyclic ring. The most noteworthy feature of the heterocyclic ring is the asymmetry of the exocyclic angles at N-1 (30.80°). A similar pattern has been observed in related triazole systems and it appears to be a function of a triazolyl ring itself rather than the influence of any inter or intramolecular interactions as shown in the 3D X-ray crystal structure of 4-(4-Chlorophenoxy)-2-(1,1dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol (Fig. **19**) [90].

The X-ray diffraction study of 3-mono and 3,5-disubstituted 1,2,4-triazoles having nonequivalent substiuents in crystals exist as a tautomer in which the electron acceptor substituent NO_2 occupies the 3-position, while the electron donor substituent NH_2 resides in



m/e 153 (56%) m/e 96 (100%)

Fig. (18). Fragmentation pattern of C-azido-1,2,4-triazole.

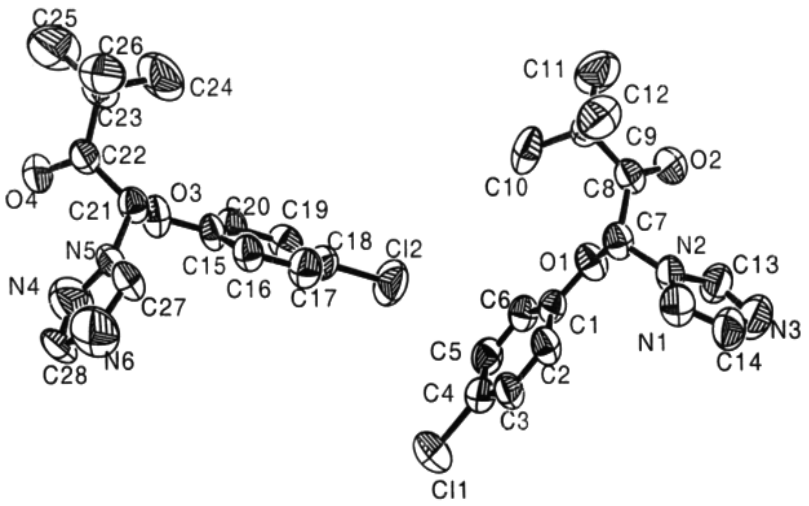


Fig. (19). ORTEP diagram describing 3D X-ray crystal structure of 4-(4-chlorophenoxy)-2-(1,1dimethylethyl)-1H-1,2,4-triazole-1-ethanol.

the 5-position. Symmetric 3,5-disubstituted 1,2,4-triazoles could give rise to tautomeric equilibrium between the 1H and 2H-structures even in crystal. One of the ammonium cations is located in the symmetry centre. Around the cations are placed three independent triazole anions, whose geometrical parameters are almost identical. Triazole rings are practically plannar (with an accuracy of 0.01 A˚). The nitro groups are located in the planes bound with the triazole cycle (deviation is less than 1 A˚). All the hydrogen atoms of the NH bond participate in hydrogen coupling [91].

4. ANTI-INFECTIVE ACTIVITY PROFILE

The triazole scaffold is an extremely versatile lead molecule that has been incorporated in a number of pharmacologically significant anti-infective medicinal agents like antibacterial, antifungal, antimalarial, antimycobacterial and antiviral drugs, many of which are used clinically for the treatment of various microbial diseases such as pneumonia, tuberculosis, candidiasis, AIDS, hepatitis, influenza and malaria etc.

The literature survey of the most relevant and recent studies based on triazole derivatives have revealed that they have a broad spectrum of antimicrobial activities and have been classified into the following categories in this paper:

4.1. Antibacterial and antifungal activity

4.2. Antiviral activity

4.3. Antimycobacterial activity

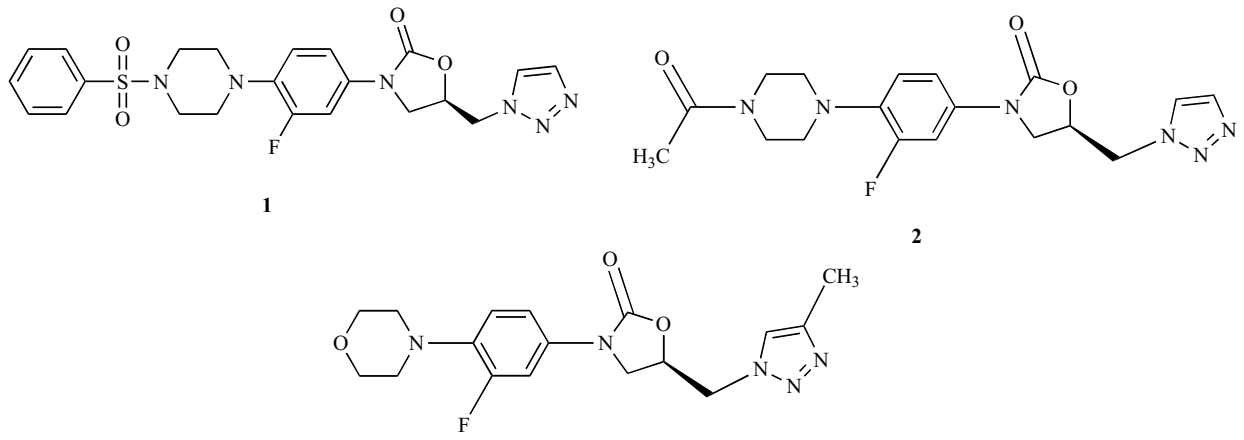
4.4. Antimalarial activity

4.1. Antibacterial and Antifungal Activity

There is an increasing demand for new antimicrobial agents due to the increasing resistance towards conventional antibiotics [92-94] and a very rapid increase of primary and opportunistic bacterial and fungal infections in immunocomprimised patients such as those affected with AIDS (over 90%), bone marrow and organ transplant patients, and cancer patients [95-99]. Therefore, the discovery and development of effective antibacterial and antifungal drugs with novel mechanism of action have become an urgent task for infectious diseases research programs [100-104]. The current standards of therapies in antifungals are the fungicidal (but toxic) polyene, amphotericin B, and the safe (but fungistatic) azoles like triazoles [105-107]. In particular, the latter drugs are important antifungal agents widely used for AIDS-related mycotic pathologies [108-111]. Despite the important advances in this field, there is a continuing increase in the incidence of fungal infections, together with a gradual rise in azole resistance. This scenario highlights the urgent need for new and effective antifungal agents [112-114].

Various novel triazole derivatives have been synthesized and evaluated recently for their antimicrobial activities against the bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Yersinia pseudotuberculosis*, *Klebsiella pneumonia*, *Enterococcus hirae*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Proteus vulgaris*, *Bodetella bronchiseptica*, *Bacillus subtilis*, *Bacillus cereus*, the yeast fungi like *Candida albicans*, *Candida parapsilosis* and *Candida tropicalis* [115-117]. Triazole drugs (fluconazole, itraconazole, voriconazole and posaconazole) are among most frequently used antifungals in clinical therapy. They possess a broad spectrum of activity and reduced toxicity when compared with imidazole antifungals [118, 119].

Phillips *et al* studied a series of novel arylcarbonyl- and arylsulfonyl-piperazinyl-5-triazolylmethyl oxazolidinones (Fig. (**20**): **1-3**) for their antibacterial activity against a panel of Gram-positive and Gram-negative bacterial clinical isolates. The arylcarbonyl oxazolidinone derivatives **1** showed strong *in vitro* antibacterial activity against susceptible and resistant Gram-positive pathogenic bacteria and were more active than the arylsufonyl derivatives [120]. Further, they evaluated a series of new piperazinyl-5-triazolylmethyl oxazolidinones **2** containing long chain acyl group at the piperazine N-4-position for antibacterial activity against a number of clinical isolates of Gram-positive and Gram-negative bacteria. Derivatives having long chain acyl groups with nine or more number of carbon atoms showed significant decrease in antibacterial activity [121]. In continuation of their work, they reported synthesis of a series of 5-(4-methyl-1,2,3-triazole) methyl oxazolidinones **3** and tested them for their antibacterial activity against a panel of Gram-positive and Gram-negative clinical isolates in comparison with linezolid and vancomycin. Most of the compounds demonstrated strong to moderate *in vitro* antibacterial activity against susceptible and resistant Gram-positive pathogenic bacteria. Antibacterial activity varied with substitutions at the phenyl C-4 position, with bulky alkylcarbonyl and alkoxycarbonyl substitutions on the piperazine N-4 was proved to be detrimental to antibacterial activity. Whereas the presence of the 4-methyl-1,2,3-triazole moiety in the acyl-piperazine containing analogs resulted in increased protein binding, and decreased antibacterial activity particularly against *Streptococcus pneumoniae* strains [122].



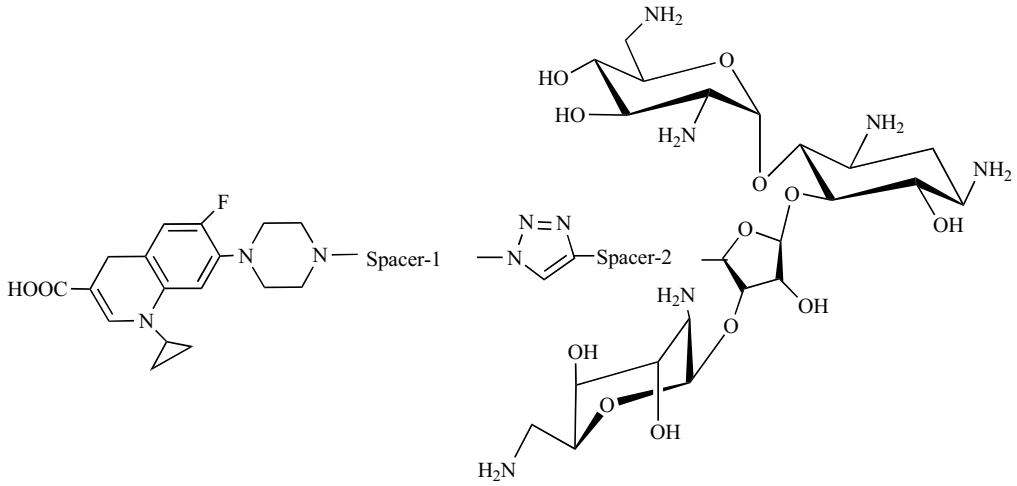
1 **2** **3**

Fig. (20). Chemical structures of 5-triazolylethyl oxazolidinones.

A combination of two different drugs in one molecule has been employed as a strategy to overcome the current resistance and in addition to reduce the appearance of new resistant strains. With this strategy, each drug moiety is designed to bind independently to two different biological targets and synchronously accumulate at both target sites. Pokrovskaya *et al* hypothesized that the Cipro-NeoB hybrids, because of the presence of the highly positively charged NeoB, could afford favorable binding to that of Cipro to these ternary complexes by forming additional contacts to DNA and/or DNA-protein interface and as such exhibit better inhibition and improved antibacterial activity. The Cipro-NeoB hybrids involved the two pharmacophores linked through different spacers: spacer-1 in the Cipro part and spacer-2 in the NeoB part. These hybrid structures were having high potency against both Gram-negative and Gram-positive bacteria including MRSA. They also showed that new hybrids exhibited the dual mode of action by inhibiting both targets: bacterial protein synthesis and topoisomerase/gyrase. The antibacterial activity of a series of new hybrid structures containing fluoroquinolone (ciprofloxacin) and aminoglycoside (neomycin) antibiotics linked *via* 1,2,3-triazole moiety **4** (Fig. **21**) against both Gram-negative and Gram-positive bacteria, including resistant strains was determined by Pokrovskaya *et al*. 1,2,3-triazole moiety appears to be a linker group between ciprofloxacin and neomycin with the help of spacers which means that it only act as structural rule of linkage for the observed antibacterial activity. The nature of spacers in both the ciprofloxacin and neomycin parts greatly influenced the antibacterial activity. It is pertinent to mention here that there was a significant delay in onset of resistance in both *E. coli* and *B. subtilis* to the treatment with ciprofloxacin-neomycin hybrid in comparison to that of each drug separately or their 1:1 mixture [123].

A series of mannich bases of 4-substituted 5-[4-(4-X-phenylsulfonyl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **5** (Fig. **22**) was synthesized by Almajan *et al.* The potential antibacterial effects of the synthesized compounds were investigated against *Acinetobacter baumanii*; *Citrobacter freundii*; *Pseudomonas aeruginosa*; *Enterococcus faecalis*; *Staphylococcus aureus*; *Staphylococcus epidermidis*; *Bacillus subtilis* strains. Some of them exhibited promising activities against *A. baumanii* and *B. subtilis* [124].

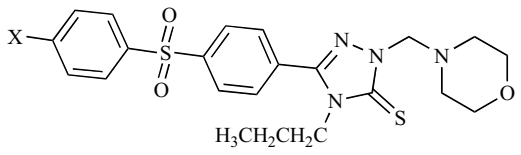
Patil *et al* investigated a series of novel 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2,4-dihydro-[1,2,4]triazolo-3-ones (Fig. (**23**): **6**) and their corresponding sulfones (Fig. (**23**): **7**) with the objective of developing better antimicrobial agents. The newly synthesized compounds were screened for their antimicrobial



Ciprofloxacin Cipro-Neo B Hybrids Neomycin B

4

Fig. (21). Chemical structure of ciprofloxacin and neomycin antibiotic linked by 1,2,3-triazole moiety.



X=H, Cl, Br

5

Fig. (22). Chemical structure of 4-substituted 5-[4-(4-X-phenylsulfonyl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The antifungal activity was tested against *Rhizopus oryzae, Aspergillus niger*, *Aspergillus flavus*, *Candida albicans* and *Saccharomyces cerevisiae*. The compound with fluoro substitution on phenyl ring exhibited significant activity against *S. aureus*, where as the compound with methoxy group on phenyl ring showed moderate activity against *B. subtilis* and *E. coli*. Among all the compounds synthesized, two compounds (**6** and **7**) exhibited significant antibacterial activity with MIC values of 9.75 and 9.37 µg/mL respectively when compared with standard drug streptomycin having MIC value of 7.81 µg/mL [125].

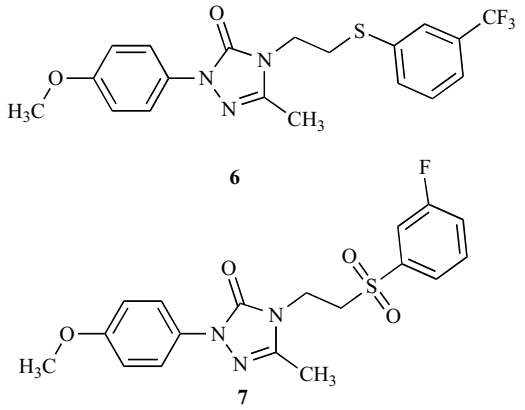


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Fig. (23). Chemical structures of 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2,4-dihydro-[1,2,4]triazolo-3-ones.

The screening for antibacterial activity of C-5-substituted triazole-oxazolidinones **8** (Fig. **24**) against *Mycobacterium smegmatis* ATCC 14468, *Bacillus subtilis* ATCC 6633, and *Enterococcus faecalis* ATCC 29212 was done by Demaray *et al*. Notably, the 3-(4-acetyl-phenyl)-5-(1*H*-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one showed 4-fold lower MIC value than measured for isoniazid [126].

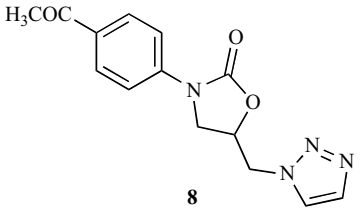

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Fig. (24). Chemical structure of 3-(4-acetyl-phenyl)-5-(1*H*-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one.

Al-Omar *et al* synthesized some novel 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles **9** (Fig. **25**) and related derivatives and tested for *in vitro* antibacterial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli* and *Pseudomonas aeuroginosa*. Several derivatives showed good or moderate activities, particularly against the tested Gram-positive bacteria. The antimicrobial activity results of the 4-arylideneaminotriazoles revealed that the aryl substituents greatly influenced the antimicrobial activity. The halo and hydroxyl derivatives were highly active particularly against the tested Gram-positive bacteria, while the nitro and methoxy derivatives were generally inactive. In addition, the hydroxy derivatives and showed marked activity against the tested Gram-negative bacteria. The 4-fluoro and 4-bromo derivatives were significantly active against *Candida albicans*. Compound **9** showed excellent antibacterial activity with MIC value of 2 µg/mL when compared with standard drug gentamicin having MIC value of 2 µg/mL [127]. In continuation of this work, he further reported the synthesis of new 5-(2-thienyl)-1,2,4-triazoles **10** (Fig. **25**) and 5-(2-thienyl)-1,3,4-oxadiazoles as well as some other related derivatives and tested them for their *in vitro* activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeuroginosa* and the yeast-like pathogenic fungus *Candida albicans*. None of the synthesized compounds were proved to be significantly active against *Candida albicans* when compared with standard drug clotrimazole. Compound **10** showed excellent antibacterial activity with MIC value of 1 µg/mL when compared to standard drug ampicillin having MIC value of 0.5 µg/mL [128].

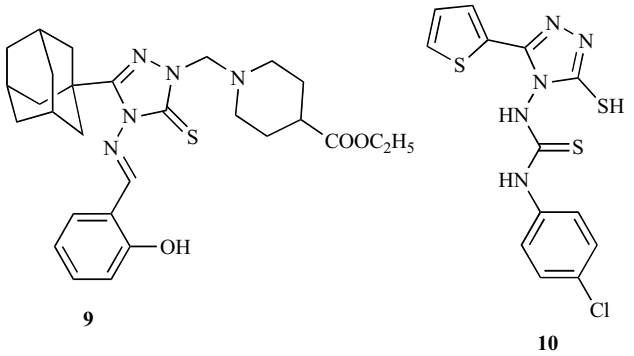

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Fig. (25). Chemical structure of 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazole and 5-(2-thienyl)-1,2,4-triazole.

Pandey *et al* performed synthesis of a series of novel fused heterocyclic systems, viz. triazolo[4,3-a]-quinazolin-7-ones **11** (Fig. **26**) [1,2,4,5]-tetrazino[4,3-a]-quinazolin-8-ones and indolo[2,3-c][1,2,4]-triazino[4,3-a]-quinazolin-8-ones and screened them for their antibacterial activity against Gram-negative bacteria e.g. *Escherichia coli*, *Pseudomonas aeruginosa* and Gram-positive bacteria e.g. *Streptococcus pneumoniae*, *Bacillus subtilis*, as well as for antifungal activity against fungal stains such as *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger*. Some compounds exhibited potent antibacterial and antifungal activity [129].

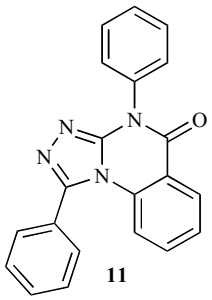

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Fig. (26). Chemical structure of triazolo[4,3-a]-quinazolin-7-one.

A series of 2,4-dichloro-5-fluorophenyl bearing thiazolo-triazoles **12** (Fig. **27**) starting from 3-(2,4-dichloro-5-fluorophenyl)-

4*H*-1,2,4-triazole-3-thiol was synthesized by Karthikeyen. Some of the synthesized compounds were tested for their anti-inflammatory, analgesic and antimicrobial activities. Three compounds exhibited potent antibacterial activity whereas other compounds demonstrated significant antifungal activity [130].

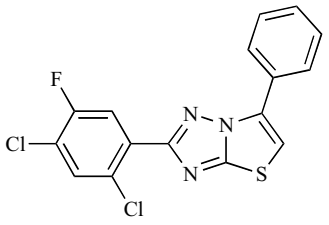

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Fig. (27). Chemical structure of 2,4-dichloro-5-fluorophenyl bearing thiazolotriazole.

Onkol *et al* investigated some new 3-[(1(2*H*)-phthalazinone-2-yl(methyl/ethyl]-4-aryl-1,2,4-triazole-5-thione and 2-[[1(2*H*)-phthalazinone-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives for their antimicrobial properties against two Gram-positive bacteria (*S. aureus*, *B. subtilis*), two Gram-negative bacteria (*P. aeruginosa*, *E. coli*) and two yeast-like fungi (*C. albicans* and *C. parapsilosis*) using the broth microdilution method. Compounds were found to be active against *B. subtilis* and the fungi. Derivatives carrying a 1,3,4-thiadiazole ring generally showed higher antimicrobial activity against *B. subtilis* and the fungi when compared to other synthesized compounds [131].

Vatmurge *et al* evaluated some novel 1,2,3-triazole-linked beta-lactam bile acid conjugates **13** (Fig. **28**) *in vitro* for their antifungal and antibacterial activities. 1,2,3-Triazole moieties are attractive connecting units, as they are stable to metabolic degradation and capable of hydrogen bonding, which can be favorable in binding of biomolecular targets and solubility. This study shows that triazole just serves as a structural rule of linkage for the observed antifungal and antibacterial activities. Most of the compounds exhibited significant antifungal and moderate antibacterial *in vitro* activity against all the tested strains [132].

A series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl) imidazo[2,1-b]thiazol-3-yl)methyl)-3*H*-1,2,4-triazole-3-thiones and 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazoles **14** (Fig. **29**) were synthesized by Guzeldemirci *et al*. The synthesized compounds were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* as well as for antifungal activity against *Candida albicans*, *Candida parapsilosis*, *Candida krusei*, *Trichophyton mentagrophytes*, *Microsporum gypseum* and *Trichophyton tonsurans* using the microbroth dilution method. One compound showed the highest antibacterial activity against *Staphylococcus aureus* with MIC value of 32 μg/mL when compared with standard drug levofloxacin having MIC value of 0.12 μg/mL [133].

A series of new 5-[2-(substituted sulfamoyl)-4,5-dimethoxy-benzyl]-4-aryl-triazole-3-thiones **15** (Fig. **30**) was investigated by Ezabadi *et al* for *in vitro* antifungal and antibacterial activity. All tested compounds showed significant antifungal activity against all the micromycetes, compared to the commercial fungicide bifonazole. Differences in their activity were found to be dependent on the substitution of different reactive groups. More specifically, high antifungal activity among synthetic analogues was shown by compounds with *N*-dimethylsulfamoyl functionality. All the compounds tested against bacteria showed the comparable activity to the commercial agent streptomycin, except for *Enterobacter cloacce* and *Salmonella* species. Chloramphenicol depicted lower bactericidal effects than these synthetic compounds. It is apparent from results that different compounds reacted in different manners against bacteria. Gram-negative bacteria seem to be more sensitive to these compounds than Gram-positive species. An effort was made to correlate the above-mentioned differences in activity with lipophilicity studies. Furthermore, molecular modeling was used to obtain the main conformational features of this class of molecules for future structure-activity relationship studies [134].

A series of novel perfluoroalkyl-1*H*-1,2,3-triazol-4-yl substituted quinazolines **16** (Fig. **31**) was screened by Mani Chandrika *et al* for *in vitro* antibacterial activity against Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*) and Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*) bacteria. The theoretical results suggest that, the formation of *anti* product is more feasible and stable than *syn* both kinetically and thermodynamically. This might be mainly due to the steric repulsions arising due to the bulky fluorous alkyl tag attached to the triazole ring. This observation indicates that triazole act as a structural rule of linkage for the observed antibacterial activity. One compound was identified as most active antibacterial compound against *Bacillus subtilis* with MIC value of 18.75 μg/mL when compared with standard drug streptomycin having MIC value of 6.25 μg/mL. This result indicates that this compound can be considered as an interesting lead compound for the synthesis of novel antibacterial agents for future [135].

The synthesis of new 1,3,4-thiadiazole and 1,2,4-triazole compounds containing a D,L-methionine moiety was reported by Pintilie *et al*. The potential antimicrobial effects of the synthesized compounds were investigated using the *Staphylococcus aureus* ATCC 25923, *Bacillus antracis* ATCC 8705, *Bacillus cereus* ATCC 10987, *Sarcina lutea* ATCC 9341 and *Escherichia coli* ATCC 25922 strains. The newly synthesized compounds exhibited promising activities against *Bacillus antracis* and *Bacillus cereus* [136].

The analgesic, antiinflammatory, antibacterial and antifungal activity of 1-acylthiosemicarbazides, 1,2,4-triazole-5(4*H*)-thiones **17** (Fig. **32**) 1,3,4-thiadiazoles and hydrazones containing 5-methyl-

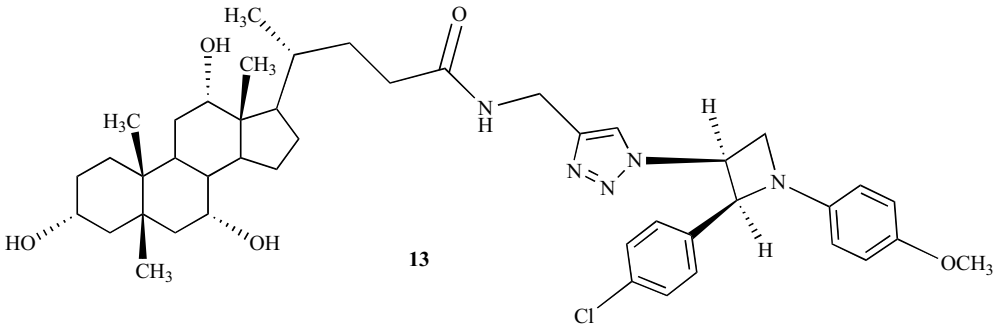

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Fig. (28). Chemical structure of 1,2,3-triazole-linked beta-lactam bile acid conjugates.

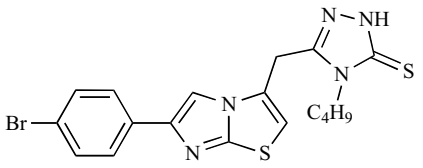

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Fig. (29). Chemical structure of 2-alkyl/arylamino-5-((6-(4-bromophenyl) imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazol.

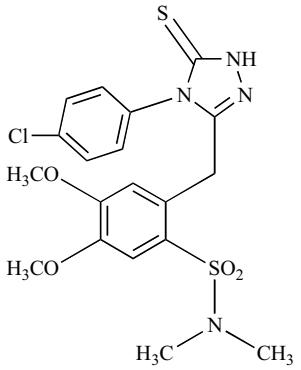

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Fig. (30). Chemical structure of 5-[2-(substituted sulfamoyl)-4,5-dimethoxy-benzyl]-4-aryl-triazole-3-thione.

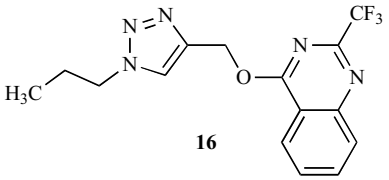

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Fig. (31). Chemical structure of perfluoroalkyl-1*H*-1,2,3-triazol-4-yl substituted quinazoline.

2-benzoxazolinones was demonstrated by Salgin-Goksen *et al*. While most compounds were exhibiting high activity, some of them were found to be moderately active against bacteria and fungi [137].

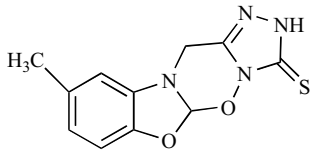

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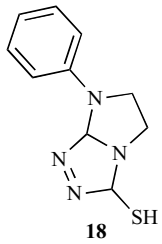
Fig. (32). Chemical structure of 1-acylthiosemicarbazides, 1,2,4-triazole-5(4*H*)-thione.

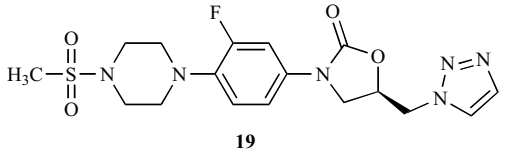
The antimicrobial activities of 1-aryl-2-methylthio-imidazolines and the 7-(4-methylphenyl)-3-methylthio-5*H*-6,7-dihydroimidazo [2,1-c][1,2,4]triazole were revealed by Sztanke *et al*. All tested compounds showed MIC in the range of 11.0-89.2 µM. 1-Aryl-2-methylthio-imidazolines were found to be equipotent to chloramphenicol *in vitro*, whereas 7-(4-methylphenyl)-3-methylthio-5*H*-6,7-dihydroimidazo[2,1-c][1,2,4]triazole showed superior activity (MIC) to ampicillin [138]. Further, they evaluated 3-unsubstituted and 3-substituted-7-aryl-5*H*-6,7-dihydroimidazo[2,1-c][1,2,4]triazoles **18** (Fig. **33**) for their antimicrobial activities. Three tested compounds revealed significant antimicrobial activities with MIC values in the range of 30.9-44.0 µM. One compound showed superior antibacterial activity to ampicillin and chloramphenicol *in vitro*, whereas other compound displayed superior antifungal activity to miconazole [139].



18

Fig. (33). Chemical structure of 3-substituted-7-aryl-5H-6,7-dihydroimidazo [2,1-c][1,2,4]triazole.

A new series of oxazolidinones containing triazolyl group **19** (Fig. **34**) was synthesized by Fan *et al* and tested for *in vitro* antibacterial activity by MIC determination against a panel of resistant and susceptible Gram-positive organisms. Most of the analogs in this series displayed activity superior to linezolid and vancomycin *in vitro*. Further, *in vivo* efficacies of the selected oxazolidinones were also reported [140].

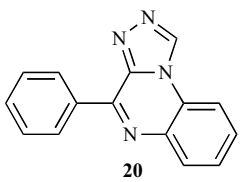


19

Fig. (34). Chemical structure of oxazolidinone containing triazolyl group.

Singh *et al* screened some Schiff's bases derived from 1,2,4-triazoles as well as their metal complexes incorporating cobalt(II), nickel(II), copper(II) and zinc(II) for antibacterial activity against three Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus subtilis*) and two Gram-negative (*Salmonella typhi* and *Pseudomonas aeruginosa*) bacterial strains, and results were compared with the activity of the free ligands. The metal complexes were found to be more potent against one or more bacterial strains than the free ligands [141].

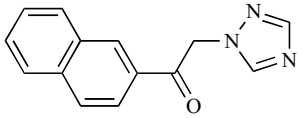
Two novel series of quinoxalines derived from 3-phenylquinoxalin-2(1*H*)-one and 2-hydrazino-3-phenylquinoxaline, namely 1-substituted-3-phenylquinoxaline-2(1*H*)-ones, 2-(3-oxo-3,3a,4,5,6,7-hexahydroindazol-2-yl)-3-phenylquinoxaline, *N*-cyclopentylidene or benzylidene-*N*′-(3-phenylquinoxaline-2-yl)hydrazines, 1-substituted-4-phenyl-1,2,4-triazolo[4,3-a]quinoxalines **20** (Fig. **35**) were synthesized by El-Hawash *et al* in order to evaluate their antitumor and antimicrobial activities. Preliminary screening showed that four compounds exhibited a moderate to strong growth inhibition activity on various tumor panel cell lines. One compound showed selectivity towards CNS-cancer SF-639, leukemia CCRF-CEM, and melanoma SK-MEL-5 (GI_{50} = 4.03, 6.46, and 4.17 µM, respectively). On the other hand, the *in vitro* microbiological data revealed that the prepared compounds showed mild antimicrobial activity [142].



20

Fig. (35). Chemical structure of 1-substituted-4-phenyl-1,2,4-triazolo[4,3-a]quinoxaline.

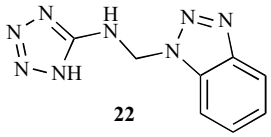
Karakurt *et al* studied oxime and oxime ether derivatives of [1-(2-naphthyl)-2-(1,2,4-triazol-1-yl) ethanone] **21** (Fig. **36**) as potential anticonvulsant and antimicrobial compounds. In addition to anticonvulsant tests, all compounds were also evaluated against the following microorganisms: *S. aureus*, *E. coli*, *P. aeruginosa*, *E. faecalis*, *C. albicans*, *C. parapsilosis*, and *C. krusei* using microdilution broth method for possible antibacterial and antifungal activities. Although most of the O-alkyl substituted oxime ethers exhibited both anticonvulsant and antimicrobial activities, the O-arylalkyl substituted compounds were found to be inactive in both screening paradigms [143].



21

Fig. (36). Chemical structure of [1-(2-naphthyl)-2-(1,2,4-triazol-1-yl) ethanone].

Rajasekaran *et al* presented the synthesis of several novel 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzo[d][1,2,3]triazoles **22** (Fig. **37**). The titled compounds were evaluated for their *in-vitro* antibacterial and antifungal activity. All synthesized compounds exhibited moderate antibacterial activity against *Bacillus subtilis* and moderate antifungal activity against *Candida albicans* [144].



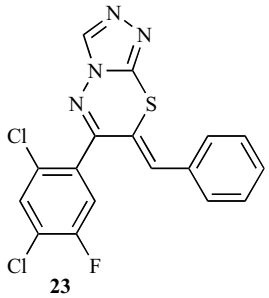
22

Fig. (37). Chemical structure of 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzo[d] [1,2,3]triazole.

The synthesis of some novel N- and S-β-D-glucosides of 5-pyridin-3-yl-1,2,4-triazoles was accomplished by Khalil *et al*. Antimicrobial screening of fourteen selected compounds was carried out against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli* [145].

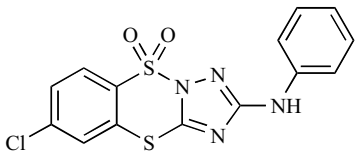
Holla *et al* investigated a series of 7-arylidene-6-(2,4-dichloro-5-fluorophenyl)-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines for their antibacterial activities against Gram-positive and Gram-negative bacteria. Among the tested compounds, one compound showed the highest degree of antibacterial activity against *S. aureus* and evaluation of the 50 % lethal dose (LD_{50}) value of this compound was carried out [146]. Further in the proceeding year, they revealed the antibacterial activities of a series of some novel 2-(2-furyl)4-quinolinecarboxylic acids, 2-(5-nitro-2-furyl)4-quinolinecarboxylic acids, 4-(3-aryloxymethyl-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazolo-6-yl)-2-(furyl)quinolines and 4-(3-aryloxymethyl-1.2,4-triazolo[3,4-b]-1,3,4-thiadiazolo-6-yl)-2-(5-nitro-2-furyl)quinolines. It was observed that compounds containing nitrofuran moiety showed excellent antibacterial activity [147]. As a continuation of their work, they described the synthesis of a series of 7-arylidene-6-(2,4-dichlorophenyl)-3-aryloxymethyl/anilinomethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines, **23** (Fig. **38**). These compounds were tested for antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Psuedomonas aeruginosa* and *Candida albicans* and exhibited mild antibacterial activity [148].

Some new derivatives of 1-alkyl-2-alkylthio-1,2,4-triazolobenzimidazole were studied by Mohamed *et al* for their antibacterial and antifungal activities. Most of the tested compounds depicted comparable results with those of ampicillin and fluconazole reference drugs. The study indicated that, the antibacterial as well as the antifungal activities of the test compounds were improved with increase in the bulkiness of the introduced alkyl groups. Also, some active antibacterial compounds were tested for their antimycobacterial activity. All the test compounds showed equipotent antitubercular activity as that of isoniazid (INH) as a reference drug [149].



23

Fig. (38). Chemical structure of 7-arylidene-6-(2,4-dichlorophenyl)-3-aryloxymethyl/anilinomethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine.

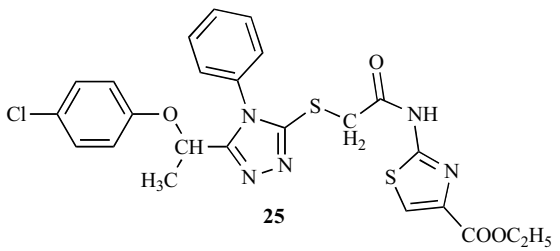


24

Fig. (39). Chemical structure of 2-arylamino-8-chloro-5,5-dioxo[1,2,4] triazolo[2,3-b][1,4,2]benzodithiazine.

Pomarnacka *et al* developed two series of 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-arylsemicarbazides and 2-arylamino-8-chloro-5,5-dioxo[1,2,4]triazolo[2,3-b][1,4,2]benzodithiazines **24** (Fig. **39**) in order to evaluate their biological activity. Some compounds were tested for their antibacterial activity and exhibited good MIC and MBC values against *Staphylococcus aureus* (3.9-31.5 μg/mL) [150].

The increasing clinical importance of drug-resistant fungal and bacterial pathogens has lent additional urgency to microbiological research and new antimicrobial compound development. For this purpose, some new 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4*H*-1,2,4-triazole derivatives **25** (Fig. **40**) were prepared by Turan-Zitouni *et al* and evaluated for antifungal and antibacterial activity. Their antimicrobial activities against *Candida albicans* (two strains), *Candida glabrata*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* were investigated. The results showed that some of the compounds possess very strong antifungal activity [151].

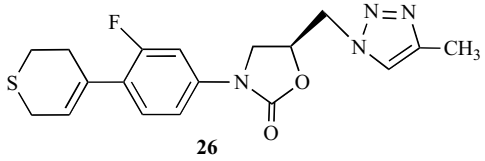


25

Fig. (40). Chemical structure of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazole.

Oxazolidinones represent a new and promising class of antibacterial agents. Current research in this area is mainly

concentrated on improving the safety profile and the antibacterial spectrum. Many oxazolidinones, including linezolid, are inhibitors of monoamine oxidase A (MAO-A), which presents an undesired side effect. Recently, it was found that the 1,2,3-triazole is a good replacement for the conventional acetamide functionality found in oxazolidinones. Reck *et al* disclosed the findings that 1,2,3-triazoles **26** (Fig. **41**) bearing a substituent like methyl, small substituted methyl, bromo, or a linear (sp-hybridized) group at the 4th position are good antibacterials with reduced or no activity, within the detection limit of the assay, against MAO-A. The results were especially promising for the development of oxazolidinones with an improved safety profile. The structure activity relationship of MAO-A can be rationalized on the basis of docking studies to a MAO-A/MAO-B homology model [152].



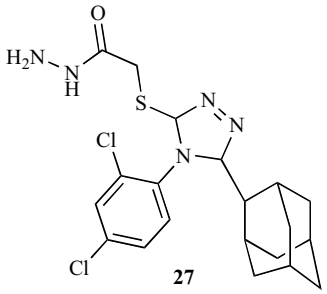
26

Fig. (41). Chemical structure of 1-substituted-1,2,3-triazole bearing methyl group.

Synthesis of some new 3-aryl/hetryl-5,7-dimethyl-1,2,4-triazolo [4,3-a]pyrimidines was accomplished by Prakash *et al*. Nine new compounds were tested *in vitro* for their antibacterial activity. Two compounds, namely 3-(4'-pyridyl)-5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidine and 3-(3',4'-dimethoxyphenyl)-5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidine were associated with substantially higher antibacterial activity than some commercial antibiotics against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Salmonella typhi* at MIC value of 10 µg/mL [153].

Screening of two novel series of imidazo[2',1':5,1]-1,2,4-triazolo[4,3-c]quinazolines bearing 5-thioxo-1,2,4-triazoles and 4-oxothiazolidines for their *in vitro* antibacterial activity against various Gram-positive and Gram-negative bacteria was done by Nasr *et al*. Some test compounds were found to possess potent antibacterial activities. One compound exhibited much higher potency than the reference standard ciprofloxacin, against both types of bacteria, particularly, Gram-positive organisms [154].

Garoufalias *et al* described synthesis of a novel series of substituted hydrazones and thiazolidinones starting from *N*-[4-(2,4-dichlorophenyl)-5-adamantyl-1*H*-1,2,4-triazol-3-ylmercaptoacetyl] hydrazine **27** (Fig. **42**). The new compounds were tested for antimicrobial and antifungal activity and some of them exhibited moderate activity against *Candida albicans* [155].

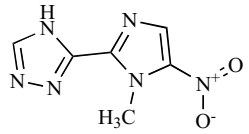


27

Fig. (42). Chemical structure of N-[4-(2,4-dichlorophenyl)-5-adamantyl-1*H*-1,2,4-triazol-3-ylmercaptoacetyl]hydrazine.

Synthesis of unsymmetrically 1,1'-disubstituted ferrocenes by condensation reactions of 1,1''-diacetylferrocene with different heteroaromatic amines such as, 2-amino-1,3,4-thiadiazole, 5-aminotetrazole and 3-amino-1,2,4-triazole was carried out by Chohan *et al*. The synthesized compounds were screened against pathogenic bacterial strains e.g., *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, showing moderate activity as antibacterials *in vitro* [156].

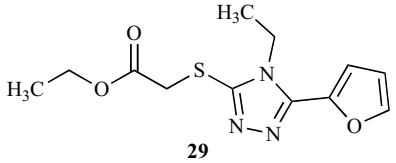
Various 5-(1-methyl-5-nitro-2-imidazolyl)-4*H*-1,2,4-triazoles **28** (Fig. **43**) were evaluated *in vitro* by Shafiee *et al* for their antibacterial and antifungal activities. Two compounds exhibited significant effects against *Bacillus subtilis* at MIC ranges of 0.5-1 µg/mL and moderate effects against *Staphylococcus aureus* [157].



28

Fig. (43). Chemical structure of 5-(1-methyl-5-nitro-2-imidazolyl)-4*H*-1,2,4-triazole.

Ulusoy *et al* synthesized ethyl 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetate **29** (Fig. **44**), 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide and a series of new *N*-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercapto-acetic acid hydrazides. The newly synthesized compounds were evaluated *in vitro* for antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Escherichia coli* ATCC 8739, *Shigella flexneri*, *Salmonella typhi*, *Proteus mirabilis* and for antifungal activity against *Candida albicans* ATCC 10231 using disk diffusion and microdilution methods. One compound showed antibacterial activity against some bacteria. The *in vitro* antimycobacterial activity of the new compounds against *Mycobacterium tuberculosis* H37Rv was evaluated employing the BACTEC 460 radiometric system. The highest inhibition observed was 61% at > 6.25 µg/mL [158]. Further, they evaluated a series of 4-(alkylidene/arylidene) amino-2,4-dihydro-5- (2-thienyl)-3*H*-1,2,4-triazole-3-thiones for *in vitro* antimicrobial activity against various bacteria and fungi. Some of the compounds demonstrated antimicrobial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Trichophyton rubrum*, *Trichophyton mentagrophytes var. erinacei* NCPF-375 and *Microsporum canis* (MIC 50-6.25 mg/mL). The *in vitro* antimycobacterial activity of the new compounds was also investigated. Some of the compounds showed varying degrees of inhibition (2-40%) against *Mycobacterium tuberculosis* H37Rv in the primary screen that was conducted at 12.5 mg/mL using the BACTEC 460 radiometric system [159].



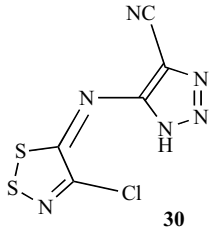
29

Fig. (44). Chemical structure of ethyl 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetate.

Baraldi *et al* demonstrated antibacterial, antifungal and antitumor activity of some novel *N*-heteroimmine-1,2,3-dithiazoles and their triazolo- **30** (Fig. **45**), imidazo-, and pyrazolopyrimidine derivatives. Although all these, *N*-heteroimines were devoid of significant antibacterial activity, yet they depicted significant antifungal activity [160].

The synthesis and evaluation of new 1,2,4-triazoles as antimicrobial agents was described by Bhat *et al*. To evaluate *in-vitro* antibacterial activity, compounds were evaluated against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus typhi* by the disc

diffusion method. To evaluate antifungal activity, some of the compounds were screened for activity against *Aspergillus niger* 88 and *Aspergillus niger* 90 and others were screened for activity against *T. rubrum* TR1, *T. rubrum* R6, *T. rubrum* R7 and *T. mentagrophyte* M1, using the cup plate method. Results showed that triazoles with a pyrazine moiety at position 3 were more active as antitubercular and antifungal agents compared to triazoles which had a pyrazine moiety at position 4 of the molecule [161].



30

Fig. (45). Chemical structure of N-heteroimmine-1,2,3-dithiazole containing triazolo derivative.

Ersan *et al* prepared *N*-[(alpha-methyl)benzylidene]-(3-substituted-1,2,4-triazol-5-yl-thio) acetohydrazides and tested for antimicrobial activity. The prepared compounds exhibited only poor activity against Gram-positive and Gram-negative bacteria with MIC > or = 400 µg/mL. Moderate activity was observed against *Candida* species with MICs in range 100-400 µg/mL [162].

Some of the triazole derivatives having significant antibacterial and antifungal activities have been listed in the Table **2**.

4.2. Antiviral Activity

Most of the antiviral drugs now available are designed to combat with human immunodeficiency virus (HIV), herpes viruses (best known for causing cold sores and genital herpes, but actually causing a wide range of diseases), the hepatitis B and C viruses and influenza A and B viruses [163-165]. Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV which lead to AIDS [166-168].

Symptoms of AIDS are primarily result of infections caused by bacteria, viruses, fungi and parasites that are normally controlled by the elements of the immune system that HIV damages [169, 170]. Opportunistic infections are common in people with AIDS which include pneumocystis pneumonia, tuberculosis, candidiasis and encephalitis etc. [171, 172]. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid, and breast milk [173].

When several such drugs, typically three or four, are taken in combination, the approach is known as highly active antiretroviral therapy, or HAART. The American National Institutes of Health and other organizations recommend offering antiretroviral treatment to all patients with AIDS. There are different classes of antiretroviral drugs that act at different stages of the HIV life cycle like nucleoside and nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) etc. [174]. Current treatment for HIV infection consists of highly active antiretroviral therapy, or HAART. This has been highly beneficial to many HIV-infected individuals since its introduction in 1996 when the protease inhibitor-based HAART initially became available [175]. Recent optimal HAART options consist of combinations consisting of at least three drugs belonging to at least two types, or classes, of antiretroviral agents. Typical regimens consist of two NARTIs or NRTIs with either a PI or NNRTI [176].

AIDS is now a pandemic. In 2007, it was estimated that 33.2 million people lived with this disease worldwide, and that AIDS had killed an estimated 2.1 million people, including 330,000 children [177]. Over three-quarters of these deaths occurred in sub-Saharan Africa, retarding economic growth and destroying human capital. HIV and AIDS affect economic growth by reducing the availability of human capital. Without proper nutrition, health care and medicine that is available in developed countries, large numbers of people suffer and die from AIDS-related complications. The forecast is that, this will probably cause a collapse of economies and societies in countries with a significant AIDS population [178].

Wang *et al* reported a novel sulfanyltriazole **31** (Fig. **46**) as an HIV-1 NNRTI *via* high throughput screening (HTS) using a cell-based assay. Chemical modifications and molecular modeling studies were carried out to establish their structure activity relationship (SAR) and to understand interactions with the enzymes. These modifications led to the identification of sulfanyltriazoles with low nanomolar potency for inhibiting HIV-1 replication and promising activities against selected NNRTI resistant mutants. The SAR results suggested that substitution on carboxamide phenyl ring has significant effect on antiviral activity and it was also found during the SAR studies that substitution of an electron-withdrawing groups like chloro, flouro, nitro, cyano and triflouromethyl is favored at the ortho position of the phenyl ring for good antiviral activity. EC_{50} value of standard antiviral drug efavirenz against K103/L100I is only 2.5 µM whereas one of sulfanyltriazole derivatives exhibited EC_{50} value of 182 nM, suggesting the antiviral potential of sulfanyltriazoles to overcome the K103 related NNRTI resistant mutants. These novel and potent sulfanyltriazoles could serve as advanced leads for further optimization [179].

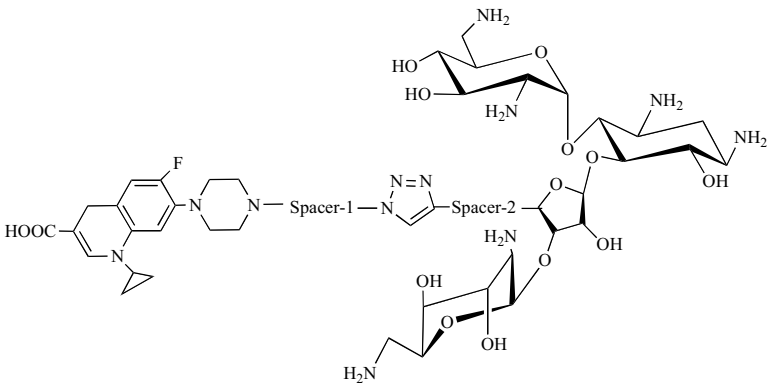
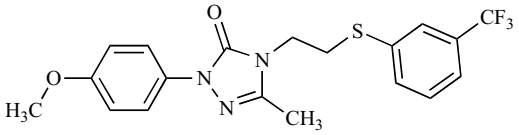
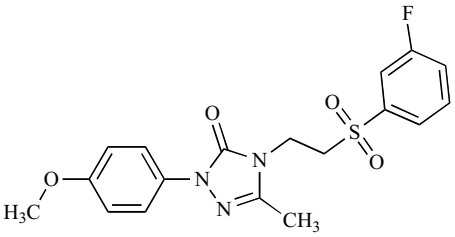
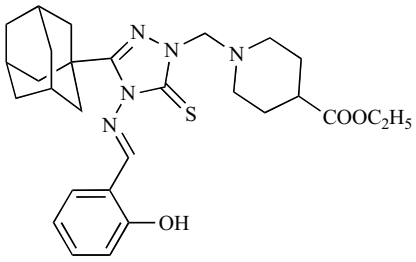
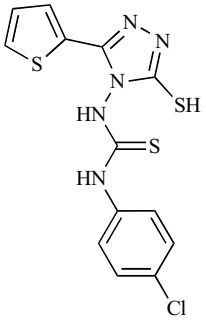
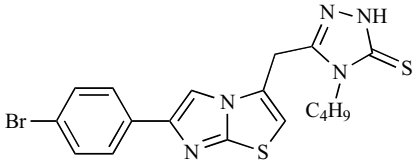
A series of HIV-1 integrase inhibitors containing a novel metal binding moiety consisting of 8-hydroxy-1,6-naphthyridine core and either an oxadiazole or triazole **32** (Fig. **47**) was identified by Johns *et al*. The design of the key structural components was based on two-metal coordination pharmacophores. This report presents initial structure-activity data showing that the new chelation architecture delivers potent inhibition of HIV-1 integrase enzymes in both enzymatic and antiviral assays [180].

Wan *et al* synthesized novel ethynyltriazole ribonucleosides **33** (Fig. **48**). Two compounds inhibited hepatitis C virus (HCV) replication efficiently by interfering in nucleic acid synthesis. Most interestingly, notable selective antiviral activity was achieved for one compound by modulating the ribose sugar moiety into deprotected and protected forms while retaining a similar trifluoromethylphenylethynyltriazole as the nucleobase. Preliminary structure-activity relationship study revealed that not only the ribose moiety but also CF_3 group at para position of phenyl ring and rigid triple bond functionality contributed critically to the observed antiviral activity of one compound against HCV. Therefore this compound constitutes promising lead in search for new antiviral candidates [181].

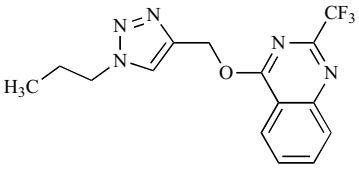
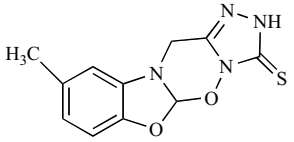
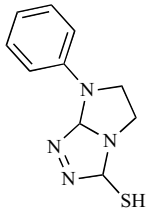
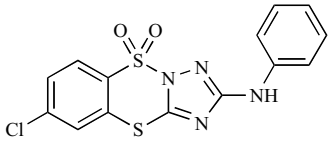
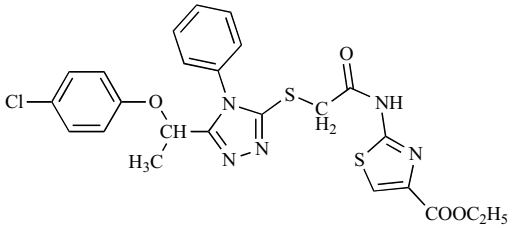
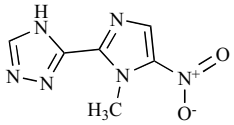
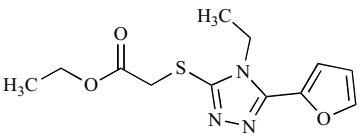
Synthesis and antiviral activity of a series of novel 1,2,3-triazole nucleosides **34** (Fig. **49**) linked to DNA nucleobases against selected RNA viruses was reported by Chittepu *et al*. Melting experiments demonstrated that such 1,2,3-triazole nucleosides have a negative impact on the duplex stability. The nucleobases attached to the triazole ring cannot involve in base pair formation with opposite bases because of the structural variations induced by triazole ring. Stacking of such nucleosides when positioned at end of oligonucleotides retains stability of DNA duplexes. Duplex structures were studied by molecular modelling which support the results of melting experiments [182].

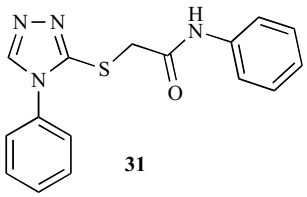
Al-Soud *et al* prepared a series of 1,5-dialkyl-1,2,4-triazole derivatives of acetic acid alkylidene hydrazides, the acid, 1,5-dialkyl-3-(5-mercapto-4-*N*-aryl-1*H*-[1,2,4]-triazol-3-ylmethylene)-1*H*-[1,2,4] triazoles, their 1,3,4-oxadiazole analogues, as well as

Table 2. Some Triazole Derivatives Having Antibacterial and Antifungal Activities

Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
1.	 Ciprofloxacin Cipro-Neo B Hybrids Neomycin B	MIC = 0.02 µg/mL	Inhibited bacterial protein synthesis by inhibiting DNA gyrase and toposiomerase IV	[123]
2.		MIC = 9.75 µg/mL	Inhibition of lipid biosynthesis in *S. aureus* and *E. coli*	[125]
3.		MIC = 9.37 µg/mL	Inhibition of lipid biosynthesis in *S. aureus* and *E. coli*	[125]
4.		MIC = 2 µg/mL	Inhibition of *P. aeuroginosa* and *B. subtilis*	[127]
5.		MIC = 1 µg/mL	Inhibition of *C. albicans*, *P. aeuroginosa* and *B. subtilis*	[128]
6.		MIC = 32 µg/mL	Inhibition of *C. albicans* and *T. tonsurans*	[133]

(Table 2). Contd…..

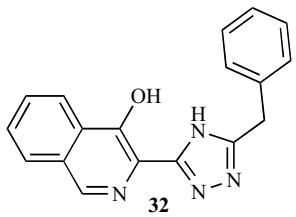
Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
7.		MIC = 18.75 µg/mL	Inhibition of synthesis of bacterial folic acid	[135]
8.		MIC = 128 µg/mL	Inhibition of *Candida krusei, Candida albicans* and *Candida parapsilosis*	[137]
9.		MIC = 30.9 µg/mL	Inhibition of *Staphylococcus aureus*, *Aspergillus niger* and *Fusarium oxysporum*	[139]
10.		MIC = 3.9 µg/mL	Inhibition of cell growth of *Staphylococcus aureus*	[150]
11.		MIC = 4 µg/mL	Inhibition of cell growth of *Candida albicans, Candida glabrata*	[151]
12.		MIC = 1 µg/mL	Inhibition of cell growth of *Staphylococcus aureus* and *Bacillus subtilis*	[157]
13.		MIC = 6.25 µg/mL	Inhibition of cell growth of *Staphylococcus aureus*, *Staphylococcus epidermidis*	[158]



31

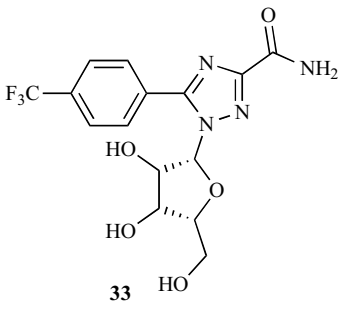
Fig. (46). Chemical structure of sulfanyltriazole.

1,2,4-triazolo-indoles. Most of target compounds were evaluated for their antiviral activity. No *in vitro* antiviral activity against HIV-1, HIV-2, *herpes simplex* virus (HSV)-1 and HSV-2 was found for all of the synthesized compounds [183]. Further, they evaluated a series of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **35** (Fig. **50**) and thiadiazine analogues for their antiviral activity against the replication of HIV-1 and HIV-2 activity in MT-4. However, two compounds showed EC_{50} = 2.11 and 1.97 µg/mL. Results suggested that these compounds act by inhibiting non nucleoside reverse transcriptase enzymes and these can be considered as a new lead in the development of antiviral agents [184].



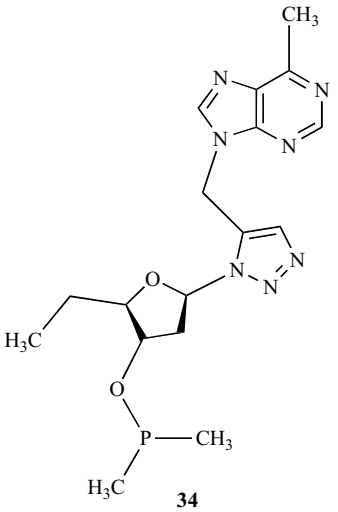
32

Fig. (47). Chemical structure of 8-hydroxy-1,6-naphthyridine containing triazole.



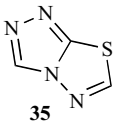
33

Fig. (48). Chemical structure of ethynyltriazole ribonucleoside.



34

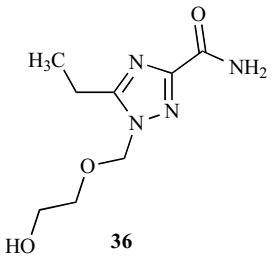
Fig. (49). Chemical structure of 1,2,3-triazole nucleosides.



35

Fig. (50). Chemical structure of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole.

Synthesis of novel acyclic triazole nucleosides with various ethynyl moieties appended on the triazole nucleobase **36** (Fig. **51**) was reported by Zhu *et al*. One of the compounds inhibited HCV subgenomic replication by inhibiting viral polymerase with a 50% effective concentration (EC_{50}) of 22 μg/mL. A preliminary SAR study suggests that appended phenyl ring as well as rigid triple bond linker contributes considerably to the anti-HCV activity [185].

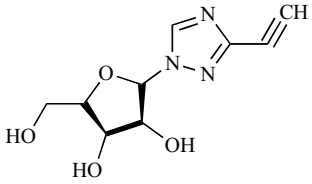


36

Fig. (51). Chemical structure of acyclic triazole nucleoside.

Abdel-Aal *et al* prepared a number of new N-arylaminomethyl-1,3,4-oxadiazole derivatives and their sugar (5-N-arylaminomethyl-1,3,4-oxadiazol-2-yl) hydrazones. The novel acyclo-C-nucleosides were prepared by heterocyclization of sugar hydrazones with acetic anhydride. A number of the synthesized compounds were tested for their antiviral activity against HSV-1 and hepatitis-A virus (HAV). Results revealed that two sugar hydrazones showed higher antiviral activity compared to other hydrazones and their acetylated derivatives [186].

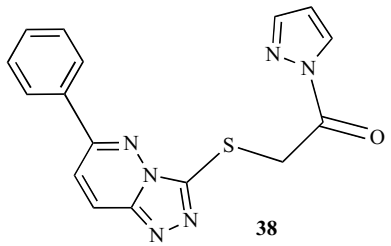
There are no Food and Drug Administration (FDA) approved drugs for treatment of hemorrhagic fever with renal syndrome (HFRS), a serious human illnesses caused by Hantaviruses. Clinical studies using βribavirin (RBV) to treat HFRS patients suggest that it provides an improved prognosis when given early in the course of disease. Given the unique antiviral activity of RBV and lack of other lead scaffolds, Chung *et al* reported a diverse series of 3-substituted 1,2,4-triazole-β-ribosides and identified one with antiviral activity, 1-β-d-ribofuranosyl-3-ethynyl-[1,2,4]triazole (ETAR) **37** (Fig. **52**). ETAR showed an EC_{50} value of 10 and 4.4 μM for Hanta virus (HTNV) and Andes virus, respectively. ETAR was phosphorylated in Vero E6 cells to its 5'-triphosphate and reduced cellular GTP levels. In contrast to RBV, ETAR did not increase mutation frequency of HTNV genome, which suggests its different mechanism of action than RBV. ETAR is an exciting and promising lead compound that may be elaborated in further synthetic investigations as a framework for the rational design of new antivirals for treatment of HFRS [187].



37

Fig. (52). Chemical structure of 1-ß-d-ribofuranosyl-3-ethynyl-[1,2,4] triazole (ETAR).

Shamroukh *et al* prepared some novel 3-S-substituted-6-phenyl-[1,2,4]triazolo[4,3-b]pyridazine derivatives. Furthermore, preparation of 1-[2-(6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylsulfanyl)-acetyl]-1*H*-pyrazole derivative **38** (Fig. **53**) and 5-(6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylsulfanylmethyl)-[1,3,4]oxadiazole derivatives was described. Some of the prepared products revealed a promising antiviral activity against HAV. Plaque reduction infectivity assay was used to determine virus count reduction as a result of treatment with the test compounds. Structure-activity correlation of the obtained results revealed that 6-phenyl-[1,2,4]triazolo[4,3-b]pyridazine-3(2*H*)-thione showed more HAV activity than the S-alkylated compounds. While addition of other rings e. g., a pyrazole ring or an oxadiazole ring increased the activity percentage of HAV reduction. One compound showed the highest effect on HAV with EC_{50} value of 20 μg/mL in comparison to standard drug amantadine [188].



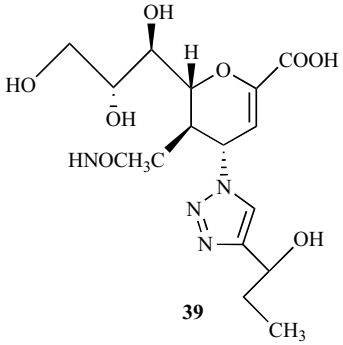
38

Fig. (53). Chemical structure of 1-[2-(6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylsulfanyl)-acetyl]-1*H*-pyrazole.

With the emergence of HIV strains resistant or cross-resistant to nearly all antiretroviral regimen, novel therapy approaches have to be considered. As a part of their current work on viral mutagenic

compounds, Vivet-Boudou *et al* evaluated the nucleoside mutagenic activity of 1-(2' -deoxy-beta-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (2' -deoxy-ribavirin) and its 5' -triphosphate derivative on HIV-1 NL4-3 in CEMx174 cell culture. After 2.5 months, no reduction on HIV-1 viability was observed. On the other hand, *in vitro* experiments with purified HIV-1 RT demonstrated that the triphosphate analog can be incorporated opposite to several natural nucleosides [189].

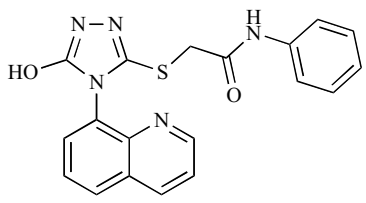
Inhibitory activities of sixteen novel 4-triazole-modified zanamivir analogues **39** (Fig. **54**) were determined by Li *et al* against avian influenza virus (AIV, H5N1). The SAR studies had reported that alkyl and alkoxy groups are more favorable substituents on the phenyl ring as compared to large aromatic or halogen substituents for better antiviral activity. One compound exerted promising inhibitory activity with EC_{50} of 6.4 μM, which is very close to that of zanamivir (EC_{50} = 2.8 μM). Molecular modeling provided useful information about the binding model between inhibitors and neuraminidase, which are in good agreement with inhibitory activities [190].



39

Fig. (54). Chemical structure of 4-triazole-modified zanamivir analogue.

The antiviral screening of a new series of 1,2,4-triazoles **40** (Fig. **55**) against several NNRTI-resistant HIV-1 isolates was done by De La Rosa *et al*. Various substitutions at the phenyl ring attached to 5-position of the triazole showed that the presence of an ortho or para substituent on phenyl ring improved antiviral activity with the biggest effect being observed when the substituent was placed at para position. Para substituents like methyl and methyl carboxylate showed similar good activity, while trifluoromethoxy and isopropyl exhibited a reduced activity. The range of substitutions allowed at the position 5 of our triazole proved to be narrow as only methyl, ethyl, and trifluoromethyl substituents showed good activity on the wild type virus, and methyl group was the only substitution exhibiting sub-micromolar potency against K103NY181C mutant virus in this series of compounds. Several of these compounds exhibited potent antiviral activities against efavirenz and nevirapine-resistant viruses, containing K103N and/or Y181C mutations or Y188L mutation [191].

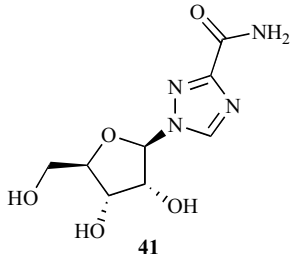


40

Fig. (55). Chemical structure of 1,2,4-triazole.

A new series of ribavirin analogues in which six-membered anhydrohexitol ring was combined with the triazolyl carboxamide moiety of ribavirin was revealed by Van Aerschot *et al*. Within this series some analogues were endowed with strong antiviral properties, particularly against herpes viruses [192].

Zhang *et al* disclosed the finding that ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) **41** (Fig. **56**) is a nontoxic antiviral agent currently licensed for the treatment of severe respiratory syncytial virus (RSV) associated with lower respiratory tract infections. Furthermore they demonstrated that ribavirin potentiates virus-induced interferon (IFN)-stimulated response element (ISRE) signaling to enhance the expression of antiviral IFN-stimulated response genes (ISGs), suggesting a mechanism for efficacy of combined treatment with ribavirin and IFN in other chronic viral diseases [193].



41

Fig. (56). Chemical structure of ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide).

Eighteen compounds of 7-(substituted phenyl)-2-substituted-6,7-dihydro-4*H*-[1,2,4]triazolo[1,5-a]pyrimidin-5-one derivatives were synthesized and evaluated for their anti-HIV-1 and anti-HSV-1 activities by Abdel-Hafez *et al* as an effort to develop new non-nucleoside antiviral agents. Complete inhibition of proliferation of HIV-1 viruses was achieved by some compounds where as other compounds exhibited potential activity against HSV-1 with 88% reduction in viral plaques [194].

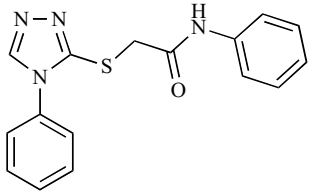
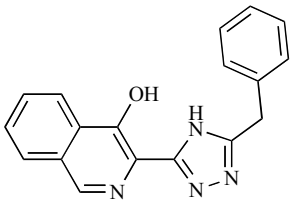
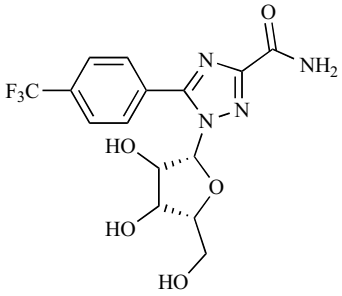
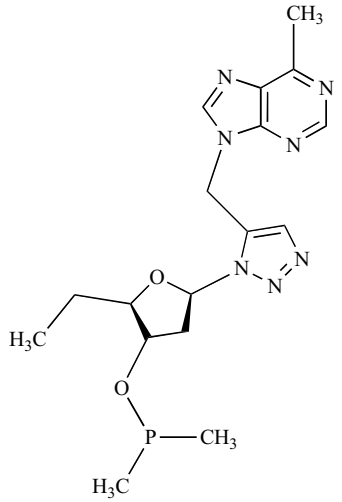
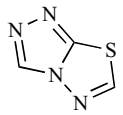
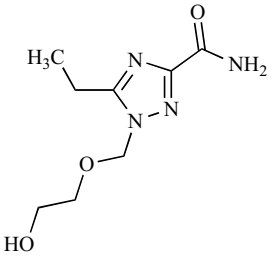
Some of the triazole derivatives depicting significant antiviral activity have been listed in the Table **3**.

4.3. Antimycobacterial Activity

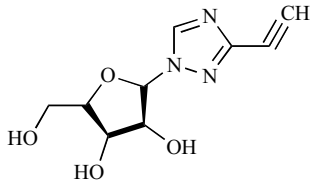
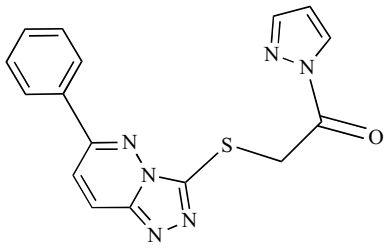
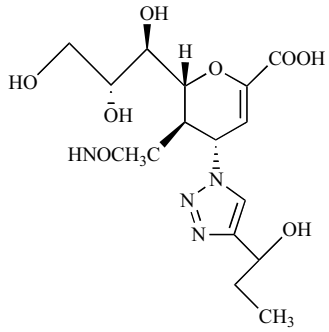
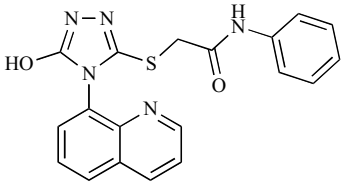
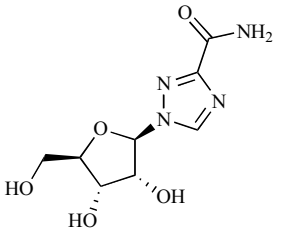
Tuberculosis (TB) is a common and often deadly infectious disease in humans caused by mycobacteria, particularly by *Mycobacterium tuberculosis* [195-197]. Tuberculosis usually attacks the lungs (as pulmonary TB) but can also affect central nervous system, lymphatic system, circulatory system, genitourinary system, gastrointestinal system, bones, joints, and even skin [198-200]. Incidence and prevalence tuberculosis is increasing world wide, partly due to poverty and partly due to the HIV/AIDS pandemic, which greatly increases risk of infectious proceeding to overt disease [201-204]. Tuberculosis is still a prime cause of high mortality worldwide, despite the availability of highly active antitubercular agents [205, 206]. The WHO declared TB a global health emergency in 1993. According to WHO, nearly 2 billion people that is one third of the world's population-have been exposed to the tuberculosis pathogen. Annually, 8 million people become ill with tuberculosis, and 2 million people die from the disease worldwide. The annual incidence rate varies from 356 per 100,000 in Africans to 41 per 100,000 in the Americans. Tuberculosis is world's greatest infectious killer of women of reproductive age and leading cause of death among people with HIV/AIDS [207-209]. Many countries use Bacillus Calmette-Guerin (BCG) vaccine as part of their TB control programs, especially for infants. According to the WHO, this is the most often used vaccine worldwide, with 85% of infants in 172 countries immunized in 1993. This was the first vaccine for TB, developed at the Pasteur Institute in France between 1905 and 1921 [210, 211].

Several new vaccines to prevent TB infection are being developed. The first recombinant tuberculosis vaccine rBCG30,

Table 3. Triazole Derivatives Depicting Antiviral Activity

Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
1.		EC_{50} = 182 nM	Inhibition of viral non nucleoside reverse transcriptase enzymes.	179
2.		IC_{50} = 0.011 µM	HIV-1 Integrase inhibition	180
3.		EC_{50} = 14.1 µM	Interefere in viral nucleic acid synthesis	181
4.		EC_{50} = 15 µM	Destabilizing effect on the viral DNA Duplexes	182
5.		EC_{50} = 1.97 µg/mL	Inhibiting of viral non nucleoside reverse transcriptase enzymes	184
6.		EC_{50} = 50 µg/mL	Inhibition of viral polymerase	185

(Table 3). Contd…..

Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
7.		EC_{50} = 10 μM	Inhibition of viral RNA polymerase	187
8.		EC_{50} = 20 μg/mL	Inhibition of viral replication	188
9.		EC_{50} = 6.4 μM	Inhibition of viral neuraminidase	190
10.		EC_{50} = 0.022 μM	Non-nucleoside reverse transcriptase inhibiton	191
11.		EC_{50} = 10 μg/mL	Inhibition of viral RNA polymerase	193

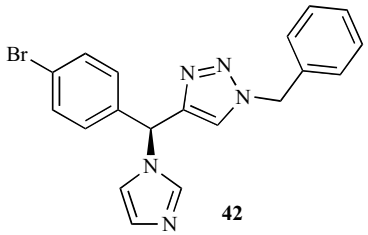
entered clinical trials in the United States in 2004, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). In 2005, a study showed that a DNA TB vaccine given with conventional chemotherapy can accelerate the disappearance of bacteria as well as protect against re-infection in mice; it was expected to take four to five years to be available for humans [212]. A very promising TB vaccine, MVA85A, is currently in phase II trials in South Africa by a group led by Oxford University, and is based on a genetically modified vaccinia virus [213]. All of these vaccines have been successfully tested in humans and are now in extended testing in TB-endemic regions. In order to encourage further discovery, researchers and policymakers are promoting new economic models of vaccine development including prizes, tax incentives and advance market commitments [214, 215].

Drug-resistant TB is a public health issue in many developing countries, as treatment is longer and requires more expensive drugs. Multi-drug-resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective first-line TB drugs: rifampicin and INH. Therefore development of new drugs with activity against multi drug resistant (MDR) TB, extensively drug resistant (XDR) TB, and latent TB is a priority task, which will shorten the current chemotherapy [216]. The directly observed treatment short-course (DOTS) strategy of tuberculosis treatment based on clinical trials done in the 1970s by Tuberculosis Research Centre, Chennai, India, focusing on a neglected area of infectious disease control is now showing promising results in effectively treating all TB cases in the community [217].

The synthesis of novel triazole derivatives and investigation of their chemical and biological behavior have gained more attention in recent decades because of their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv. The current work which describes the synthesis of triazole derivatives with encouraging

antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv has been included in the following text:

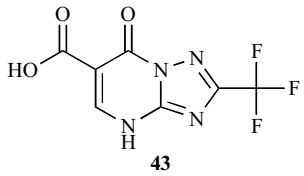
Castagnolo *et al* synthesized a series of novel enantiomerically pure azole derivatives **42** (Fig. **57**). The new compounds, bearing an imidazole and a triazole moiety, were evaluated as antimycobacterial agents. One of them proved to have activity against *Mycobaterium tuberculosis* comparable to those of the classical antibacterial/antifungal drugs such as econazole and clotrimazole [218].



42

Fig. (57). Chemical structure of 1,4-disubstituted-1,2,3-triazole.

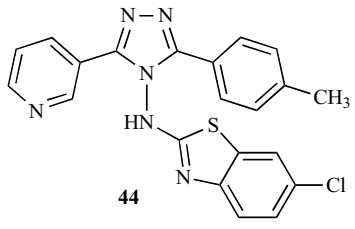
A series of fluorinated 1,2,4-triazolo[1,5-a]pyrimidine-6-carboxylic acid derivatives was designed and synthesized by Abdel-Rahman *et al*. These compounds were screened against *Mycobacterium tuberculosis* H37Rv strain at 6.25 µg/mL concentration. One compound, the 7-oxo-2-(trifluoromethyl)-4,7-dihydro-1,2,4-triazolo[5,1-a]pyrimidine-6-carboxylic acid **43** (Fig. **58**) was found to be a very potent inhibitor, being able to inhibit 92% growth of *M. tuberculosis* H_{37}Rv at 6.25 µg/mL concentration. At the same time, it proved to be nontoxic to mammalian cells (IC_{50} > 62.5 µg/mL *in vero* cells) [219].



43

Fig. (58). Chemical structure of 7-oxo-2-(trifluoromethyl)-4,7-dihydro-1,2,4-triazolo[5,1-a]pyrimidine-6-carboxylic acid.

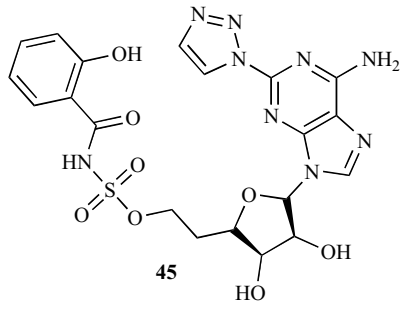
Patel *et al* synthesized 3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-substituted-1,3-benzothiazol-2-amino)-4*H*-1,2,4-triazole analogs **44** (Fig. **59**) and evaluated for antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv strain using Lowenstein-Jensen medium and antimicrobial activity against various bacteria and fungi using broth microdilution method. Some compounds emerged as promising antimicrobials. It was also observed that the promising antimicrobials have proved to be better antituberculars. One compound showed better antitubercular activity with MIC value of 25 µg/mL when compared with standard drug rifampicin having MIC value of 40 µg/mL [220].



44

Fig. (59). Chemical structure of 3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-substituted-1,3-benzothiazol-2-amino)-4*H*-1,2,4-triazole.

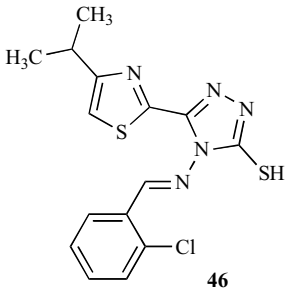
Gupte *et al* demonstrated synthesis, biochemical, and biological evaluation of a systematic series of 2-triazole derivatives **45** (Fig. **60**) of 5'-O-[N-(salicyl)sulfamoyl]adenosine (Sal-AMS) and described them as inhibitors of aryl acid adenylating enzymes (AAAE) involved in siderophore biosynthesis by *Mycobacterium tuberculosis*. SAR revealed a remarkable ability to tolerate a wide range of substituents at the 4-position of the triazole moiety, and a majority of the compounds possessed subnanomolar apparent inhibition constants. However, the *in vitro* potency did not always translate into whole cell biological activity against *M. tuberculosis*, suggesting that intrinsic resistance plays an important role in the observed activities [221].



45

Fig. (60). Chemical structure of 2-triazole derivative of 5'-O-[N-(salicyl)sulfamoyl]adenosine.

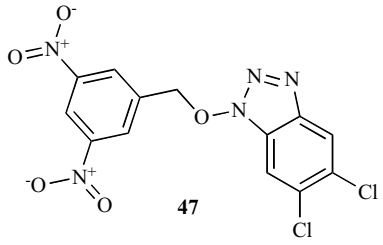
Kumar *et al* studied a series of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole **46** (Fig. **61**) and 1,3,4-oxadiazole derivatives for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth dilution assay method. One compound exhibited promising antitubercular activity with MIC value of 4 µg/mL when compared with standard drug INH having MIC value of 0.25 µg/mL. This result indicates that it deserve more consideration as potential antitubercular agent [222].



46

Fig. (61). Chemical structure of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole.

A series of 1-nitrobenzyloxybenzotriazoles was synthesized and tested against four *Mycobacterium* strains by Augustynowicz-Kopec *et al*. Particularly high antimycobacterial activity, comparable with that of isoniazide, was found for 5,6-dichloro-1-(3,5-dinitrobenzyloxy)-1*H*-benzotriazole **47** (Fig. **62**) [223].

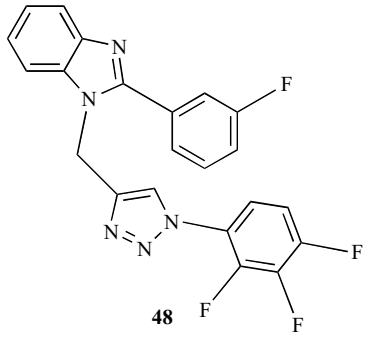


47

Fig. (62). Chemical structure of 5,6-dichloro-1-(3,5-dinitrobenzyloxy)-1*H*-benzotriazole.

Gill *et al* investigated a series of novel clubbed [1,2,3] triazoles **48** (Fig. **63**) with fluorine benzimidazole series of H37Rv strain

inhibitors, potentially useful for the treatment of tuberculosis on the basis of promising results of preliminary antimicrobial study. Evaluation of the structure activity relationship (SAR) of substitution within this series has followed the identification of a range of compounds. As a part of SAR studies, they had incorporated fluoro substituent at positions 2, 3 & 4 in different variations on the phenyl ring attached to triazole nucleus. Replacement of fluoro with trifluoromethyl group resulted in a substantial loss of biological activity. This loss may indicate retardation in the intracellular transport due to highly electronegativity in one region. In case of electron donating groups, like methyl substitutions resulted in loss of activity. The biological data generated revealed that compounds having an electron-withdrawing group like fluoro attached to triazole nucleus may prove a template for anti tuberculosis activity for further development. Some of the derivatives are under further evaluation showing better and considerable activity compared to rifampin [224].

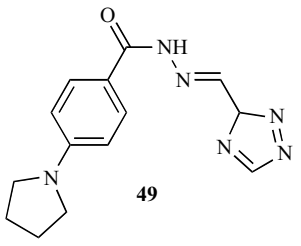


48

Fig. (63). Chemical structure of clubbed [1,2,3] triazole with fluorine benzimidazole.

Singh *et al* prepared 5-azido-5-deoxy-xylo-, ribo-, and arabinofuranoses and their intermediate 5-azido-5-deoxy glycofuranoses which on 1,3-cycloaddition with different alkynes afforded the corresponding sugar triazoles in very good yields. The synthesized sugar triazoles were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv, where one of the compounds displayed mild antitubercular activity *in vitro* with MIC 12.5 μg/mL [225].

A novel series of 4-pyrrol-1-yl benzoic acid hydrazide analogs, derived 5-substituted-2-thiol-1,3,4-oxadiazoles, 5-substituted-4-amino-1,2,4-triazolin-3-thione **49** (Fig. **64**) and 2,5-dimethyl pyrroles were designed and synthesized in good yields by Joshi *et al*. Compounds were evaluated for their preliminary *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria and for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth dilution assay method. Some compounds exhibited very good antibacterial and antitubercular activities [226].

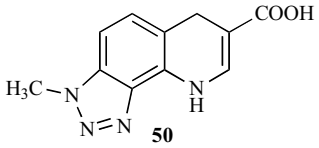


49

Fig. (64). Chemical structure of 5-substituted-4-amino-1,2,4-triazolin-3-thione.

A series of 4-arylidenamino-4*H*-1,2,4-triazole-3-thiol derivatives were evaluated by Ozdemir *et al* for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294), using the BACTEC 460 radiometric system and BACTEC 12B medium. One compound showed significant activity at 6.25 μg/mL with a 87% inhibition [227].

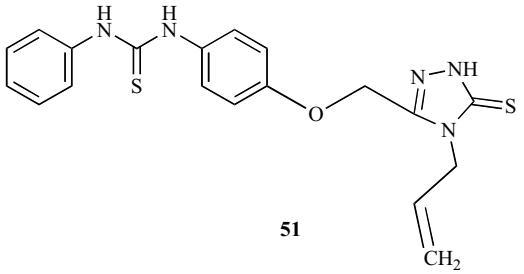
Carta *et al* reported activity of 3-methyl-9-substituted-6-oxo-6,9-dihydro-3*H*-[1,2,3]-triazolo[4,5-h]quinolone carboxylic acids **50** (Fig. **65**) and their esters as a new class of antiinfective agents against MDR *Mycobacterium tuberculosis*. In antitubercular screening against H37Rv and clinically isolated strains of *M. tuberculosis* several derivatives showed MIC_{90} in the range 0.5-3.2 μg/mL. Preliminary SAR studies suggested that in general the presence of an alkyl substituent on triazole nucleus was more favorable than propenyl or benzyl groups for better antitubercular activity. One compound showed no cytotoxicity and proved to be the most potent derivative exhibiting MIC_{90}=0.5 μg/mL against all *M. tuberculosis* strains and infected human macrophages (J774-A1) tested [228].



50

Fig. (65). Chemical structure of 3-methyl-9-substituted-6-oxo-6,9-dihydro-3*H*-[1,2,3]-triazolo[4,5-h]quinolone carboxylic acid.

A series of novel N-alkyl/aryl-N'-[4-(4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione-5-yl)phenyl]thioureas and three S-alkylated representatives of the former, N-alkyl/aryl-N'-[4-(3-aralkylthio-4-alkyl/aryl-4*H*-1,2,4-triazole-5-yl)phenyl]thioureas was screened by Kucukguzel *et al* for antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv as well as *Mycobacterium fortuitum* ATCC 6841 which is a rapid growing opportunistic pathogen. Some compounds were found to possess the same MIC value as that of tobramycin against *M. fortuitum* ATCC 6841 whereas other compounds had positive response against *M. tuberculosis* H37Rv at varying degrees. One compound was identified as the most potent derivative of the series with an MIC value of 6.25 μg/mL and selectivity index of 1.6 [229]. Further, they designed a series of novel 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and several related thioureas, N-alkyl/aryl-N'-{4-[(4-alkyl/aryl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methoxy]phenyl}thioureas **51** (Fig. **66**) for evaluation of their antimycobacterial potency. All compounds were evaluated *in vitro* for antimycobacterial against *Mycobacterium tuberculosis* H37Rv. One compound was the most active compound with 79% inhibition against *M. tuberculosis* H37Rv [230].

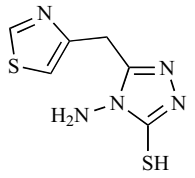


51

Fig. (66). Chemical structure of N-alkyl/aryl-N'-{4-[(4-alkyl/aryl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methoxy]phenyl}thiourea.

In last few decades, though significant progress has been made in the treatment and control strategies of tubercular infections by introducing new diagnostic and monitoring tools and combination therapy, it still continues to be a severe problem. Thus with the aim of developing novel molecules with improved potency for treating

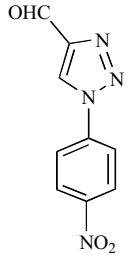
Mycobacterium tuberculosis H37Rv strain infections and with decreased probability of developing drug resistance, Shiradkar *et al* reported the synthesis of thiazolyl triazole derivatives **52** (Fig. **67**) by microwave organic reaction enhancement method (MORE) and results of investigations of their antimycobacterial and antimicrobial activities have shown promising activity for many compounds [231].



52

Fig. (67). Chemical structure of thiazolyl triazole derivative.

Costa *et al* described the synthesis, *in vitro* anti-*Mycobacterium tuberculosis* profile, and the SAR study of new N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes **53** (Fig. **68**). In order to investigate the influence of the difluoromethylene group on the anti-*Mycobacterium* activity of these compounds, fluorination of triazoles with diethylaminosulphur trifluoride (DAST) converted the corresponding carbaldehyde compounds into new difluoromethyl derivatives in excellent yields. Two compounds were screened for the inhibitory activity against *Mycobacterium tuberculosis* H37Rv and both of them were able to inhibit the growth of the mycobacterium. Interestingly, these compounds exhibited the best inhibition with MIC values of 2.5 µg/mL, similar to pharmaceuticals currently used in the treatment of tuberculosis. Their SAR study indicated the importance of the hydrogen bond acceptor subunit, the position in the aromatic ring, the planarity of triazole and phenyl rings in these compounds, and a correlation between the uniform highest occupied molecular orbital (HOMO) coefficient distribution and the anti-tubercular activity. The significant activity of two compounds pointed them as promising lead molecules for further synthetic and biological exploration [232].



53

Fig. (68). Chemical structure of N-substituted-phenyl-1,2,3-triazole-4-carbaldehyde.

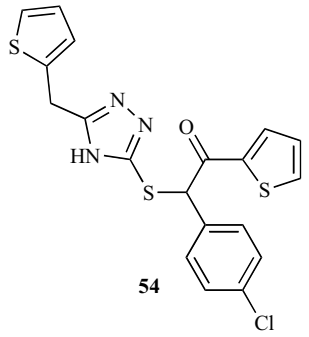
Banfi *et al* investigated different series of imidazole and triazole derivatives having an azomethine linkage to pyridine-2-carboxamidohydrazone to develop new antimycobacterial and antifungal drugs that act by binding to sterol 14α-demethylase (14DM). MICs of the compounds were evaluated by reference assay and as well as employing recently developed Microdilution Resazurin Assay (MRA). It was found that halogenated derivatives showed good activity; most of the compounds had inhibitory action against *Mycobacterium tuberculosis* reference and clinical strains, with MICs in the range 4-64 mg/L. Molecular modelling investigations showed that the active new compounds may interact at the new potent site of mycobacterial cytochrome P450-dependent sterol-14α-demethylase and that the calculated binding free energy values are in agreement with the corresponding MIC values [233].

Sanna *et al* synthesized a series of 3-aryl substituted-2-(1*H*(2*H*)-benzotriazol-1(2)-yl)acrylonitriles for a preliminary *in vitro* evaluation of antitubercular activity. In this work, it was reported that the several compounds showed an interesting activity in the preliminary screening with a percent growth inhibition of the virulent *Mycobacterium tuberculosis* between 40 and 99% at the concentration of 12.5 µg/mL. The most effective derivatives were also tested *in vitro* against *M. avium* [234].

A series of 3-benzylsulfanyl derivatives of 1,2,4-triazole and 4-methyl-1,2,4-triazole were evaluated by Klimesova *et al* for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*, *M. avium*, and two strains of *M. kansasii*. The activities were expressed as minimum inhibitory concentrations. The compounds exhibited only a moderate or slight antimycobacterial activity. MICs fall into a range of 32≥ 1000 µmol/L. The most active substances bear two nitro groups or a thioamide group on the benzyl moiety. As regards to cytotoxicity effect, the evaluated compounds can be considered as moderately toxic [235].

Zahajska *et al* prepared a set of four types of benzazoles, 1,2,4-triazole, and pyridine-2-carbonitrile/-2-carbothioamide substituted with 1-naphthylmethylsulfanyl or pyridylmethylsulfanyl to modify the structure of benzylsulfanyl derivatives of the captioned heterocycles. The compounds were evaluated for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*, *M. avium*, and two strains of *M. kansasii*. The activities were expressed as the MIC. The MIC values were in the range of 2 to >1000 µmol/L. Introduction of a pyridyl moiety into the molecule generally decreased the activity. A naphthyl moiety did not affect the activity when substituted with a phenyl ring. The most active substances were 4-(3-pyridylmethylsulfanyl)pyridine-2-carbothioamide (MIC = 2 - >62.5 µmol/L) and 4-(1-naphthylmethylsulfanyl) pyridine-2-carbothioamide (MIC = 2 - >32 µmol/L) [236].

Kaplancikli *et al* synthesized new 3-alkylsulfanyl-1,2,4-triazole derivatives **54** (Fig. **69**) and evaluated them for antitubercular activity by broth microdilution assay, the Microplate Alamar Blue Assay, in BACTEC 12B medium. Results were obtained by screening *in vitro*, using BACTEC 460 Radiometric System against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) at 6.25 µg/mL and the tested compounds showed considerable inhibition ranging from 58-84% [237].



54

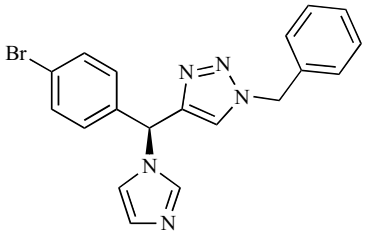
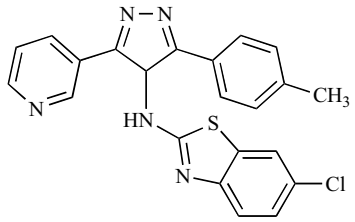
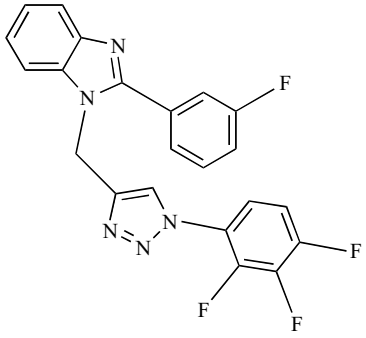
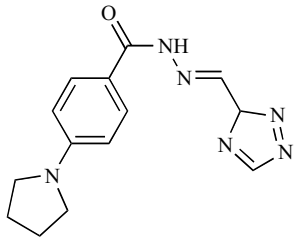
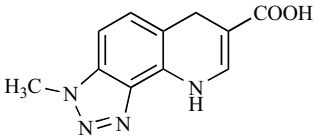
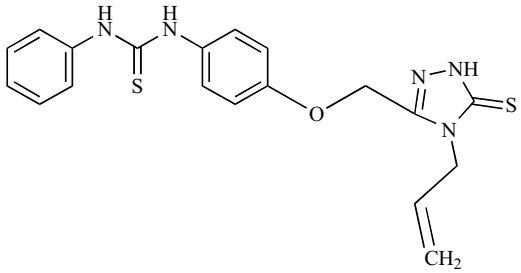
Fig. (69). Chemical structure of 3-alkylsulfanyl-1,2,4-triazole derivative.

Some of the triazole derivatives having significant antimycobacterial activity have been listed in the Table **4**.

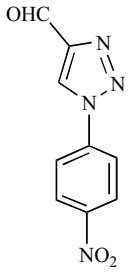
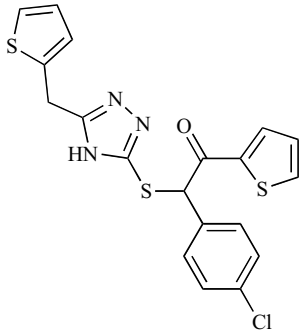
4.4. Antimalarial Activity

Malaria is a vector-borne infectious disease caused by protozoan parasites of the genus *Plasmodium*. In humans, malaria is caused by *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi*. The most common cause of infection is *P. falciparum* which is responsible for about 80% of all malaria cases, and is also responsible for about 90% of the deaths from malaria [238].

Table 4. Some Triazole Derivatives Having Antimycobacterial Activity

Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
1.		MIC = 16 µg/mL	Inhibition of cell growth of *Mycobacterium tuberculosis*	[218]
2.		MIC = 25 µg/mL	Inhibition of biosynthesis of *Mycobacteria*l lipids	[220]
3.		MIC = 6.25 µg/mL	inhibition of proliferation of H37Rv strain of *Mycobacterium tuberculosis*	[224]
4.		MIC = 16 µg/mL	Inhibition of cell growth of *Mycobacterium tuberculosis*	[226]
5.		MIC = 0.5 µg/mL	Inhibition of DNA gyrase	[228]
6.		MIC = 2.5 µg/mL	Inhibition of cell growth of *Mycobacterium tuberculosis*	[230]

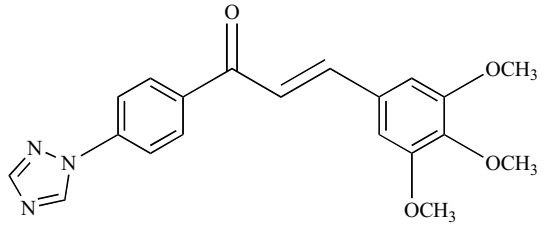
(Table 4). Contd…..

Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
7.		MIC = 2.5 µg/mL	Inhibition of cell growth of *Mycobacterium tuberculosis*	[232]
8.		MIC = 6.25 µg/mL	Inhibition of cell growth of *Mycobacterium tuberculosis*	[237]

Malaria in humans develops *via* two phases: an exoerythrocytic and an erythrocytic phase. The exoerythrocytic phase involves infection of the hepatic system, or liver, whereas the erythrocytic phase involves infection of the erythrocytes, or red blood cells. The parasites multiply within red blood cells, causing symptoms that include signs of anemia (light-headedness, shortness of breath, tachycardia, etc.), as well as other general symptoms such as fever, chills, nausea, flu-like illness, and, in severe cases, coma, and death [239].

Each year, there are approximately 350–500 million cases of malaria, killing between one and three million people, the majority of whom are young children in Sub-Saharan Africa. Ninety percent of malaria-related deaths occur in Sub-Saharan Africa [240]. Pregnant women are especially attractive to the mosquitoes, and malaria in pregnant women is an important cause of stillbirths, infant mortality and low birth weight, particularly in *P. falciparum* infection, but also in other species infection, such as *P. vivax* [241, 242]. Since 2001, the WHO has recommended use of artemisinin-based combination therapy (ACT) as first-line treatment for uncomplicated malaria in areas experiencing resistance to older medications. The most recent WHO treatment guidelines for malaria recommend four different ACTs [243]. The current scientific studies suggest that the major molecular target of artemisinin and its analogs is sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), a calcium pump in the endoplasmic reticulum [244, 245].

Mishra *et al* described the synthesis of novel 1,3-diaryl propenone derivatives and their antimalarial activity *in vitro* against asexual blood stages of human malaria parasite, *Plasmodium falciparum*. Chalcone derivatives were prepared *via* Claisen-Schmidt condensation of substituted aldehydes with substituted methyl ketones. The chloro-series, 1,2,4-triazole substituted chalcone **55** (Fig. **70**) was found to be the most effective in inhibiting the *in vitro* growth of *P. falciparum in vitro* while pyrrole and benzotriazole substituted chalcones showed relatively less inhibitory activity. This is probably the first report on antiplasmodial activity of chalcones with azoles on acetophenone ring [246].



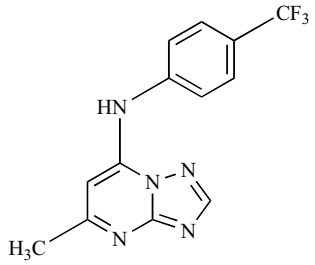
55

Fig. (70). Chemical structure of 1,2,4-triazole substituted chalcone.

Gujjar *et al* recently synthesized phenyl-substituted triazolopyrimidines **56** (Fig. **71**) leading to identification of analogs with low predicted metabolism in human liver microsomes and which showed prolonged exposure in mice. The preliminary SAR studies had reported that unsubstituted phenyl compound is completely inactive. Single position ortho substituted phenyl compounds are likewise inactive, while meta substitutions significantly improve activity over the unsubstituted phenyl derivative. Compounds that contain ortho substitution in combination with substitutions at the meta or para position typically have poor activity, although it is improved over ortho substitution alone. The most active single substituted compounds in the series contained para substituents, with larger hydrophobic residues being preferred: CF_3, > Br>OCF_3>CH_3, NO_2, F, Cl. Finally, combinations of para and meta substitutions on phenyl ring attached to triazole nucleus yielded compounds with the best antimalarial activity. One compound containing para-trifluoromethylphenyl group suppressed growth of *P. berghei* in mice after oral administration. This study provides the first proof of concept that dihydrofolate dehydrogenase (DHODH) inhibitors can suppress *Plasmodium* growth *in vivo*, validating DHODH as a new target for antimalarial chemotherapy [247].

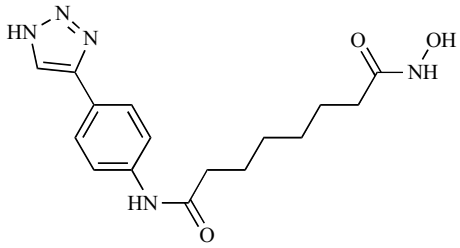
Discovery of the rules governing inhibition of various histone deacetylase (HDAC) isoforms is likely to be key in identifying improved therapeutics that act as epigenetic modulators of gene

transcription. In a report published in the year 2008, Chen *et al* presented results on the modification of the CAP region of a set of triazolylphenyl-based histone deacetylase inhibitors (HDACIs) **57** (Fig. **72**) and showed that nature of substitution on the phenyl ring plays a pivotal role in their selectivity for HDAC1 versus HDAC6, with low to moderate selectivity (2 to 51-fold) being achieved. In light of the valuable selectivity and potency, identified for the triazolylphenyl ligand in the inhibition of HDAC6 (IC_{50} = 1.9 nM), this compound represented a valuable research tool and a candidate for further chemical modifications. Lastly, these new HDACIs were studied for antimalarial activity, which serve to validate the superior activity of the HDACI 10c [248].



56

Fig. (71). Chemical structure of phenyl-substituted triazolopyrimidine.

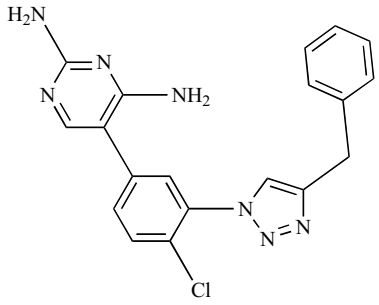


57

Fig. (72). Chemical structure of triazolylphenyl derivative.

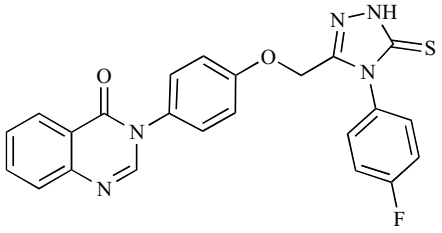
As part of research efforts to improve the quality of current chemotherapy of *Pneumocystis carinii* pneumonia, Chan *et al* reported a structure-based design project to optimise activity, species selectivity and pharmaceutical properties of triazenyl-pyrimethamine TAB (IC_{50}= 0.17 μM; rat liver DHFR IC_{50}/*P. carinii* DHFR IC_{50}=114). This concern led them to design, synthesise and evaluate four new series of pyrimethamine derivatives bearing triazole **58** (Fig. **73**) triazolium, triazinium and amino moieties at the 3'-position of para-chlorophenyl ring. Such stabilised 'triazene' derivatives address potentially compromised pharmaceutical profile of TAB and the 3'-amine substituted agents afford conformationally flexible substitutes. The benzylamino-pyrimethamine derivative (IC_{50}= 0.12 μM, rat liver DHFR IC_{50}/*P. carinii* DHFR IC_{50}: 5.26) was most potent and was the only *P. carinii*-selective antifolate agent of this new series [249].

Endeavors to find new agents with promising antimalarial activity are still a high priority task due to increasing malarial emergency of chloroquine resistant *Plasmodium falciparum* strains. Some new 3-[4-(4-substituted phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4 triazol-3-ylmethoxy)-phenyl]-2-phenyl-3*H*-quinazolin-4-one **59** (Fig. **74**) derivatives were synthesized by Havaldar *et al* and sensitivity of chloroquine-resistant *Plasmodium falciparum* malarial parasite to newly synthesized compounds was evaluated *in vitro* by using triturated Hypoxanthine incorporation assay. The compounds were tested for antimalarial activity and only one compound that is 3-{4-[4-(4-fluoro-phenyl)-4*H*-[1,2,4]triazol-3-yl-methoxy]-phenyl}-2-phenyl-3*H*-quinazolin-4-one was found to be most active against *Plasmodium falciparum* strains and its 50% inhibitory concentration IC_{50} value was 1.2 μM [250].



58

Fig. (73). Chemical structure of pyrimethamine derivative bearing triazole.



59

Fig. (74). Chemical structure of 3-[4-(4-substituted phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4 triazol-3-ylmethoxy)-phenyl]-2-phenyl-3*H*-quinazolin-4-one.

Some of the triazole derivatives with significant antimalarial activity have been listed in the Table **5**.

Very recent examples used in this manuscript demonstrate the usefulness of triazole derivatives in a broad range of therapeutical fields such as antibacterial, antifungal, antiviral, antimycobacterial and antimalarial activity, thereby confirming that these compounds can still have a place in the tool-kit of the modern medicinal chemist to synthesize novel anti-infective agents. Some important triazole based anti-infective drugs which are available in clinical practice have been reported in the Table **6**.

CONCLUSION

This review is an attempt to address the vistas of anti-infective potential of strategically placed triazole scaffold in medicinal chemistry and drug development. The plethora of research efforts carried out focus that myriad spectrums of promising anti-infectious actions are exhibited by triazole derivatives. Information provided in this manuscript can be found useful for further investigations on this scaffold in order to harness its optimum antimicrobial potential. Moreover, rational design and development of the novel anti-infective agents incorporating this nucleus can help in dealing with escalating problems of the microbial resistance and also to meet the need for an effective antimicrobial therapy for the treatment of various deadly infectious microbial diseases.

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Prof. Om Prakash, Director, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India is duly acknowledged for his valuable suggestions. Prof. Vinod Sharma, Principal, CT Institute of Pharmaceutical Sciences, Jalandhar, India is duly acknowledged for the necessary help and support during this work.

Table 5. Some Triazole Derivatives with Significant Antimalarial Activity

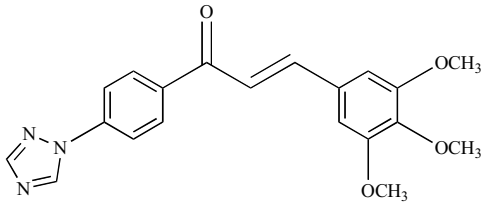
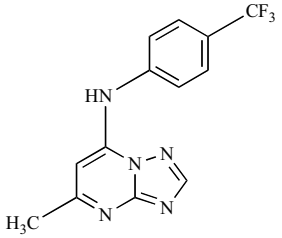
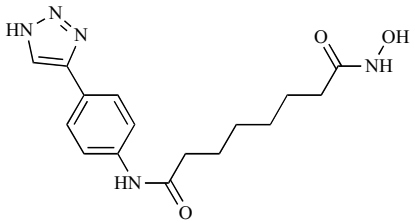
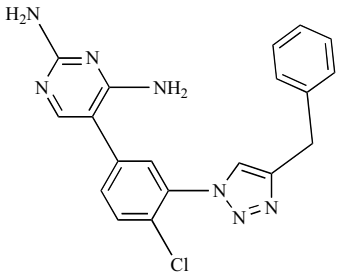
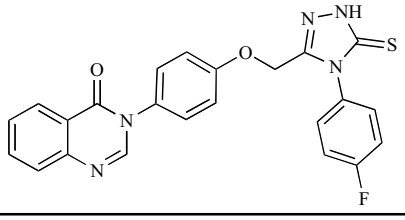
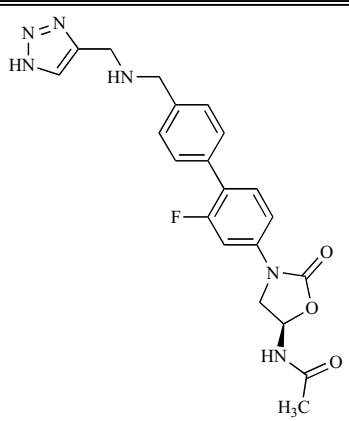
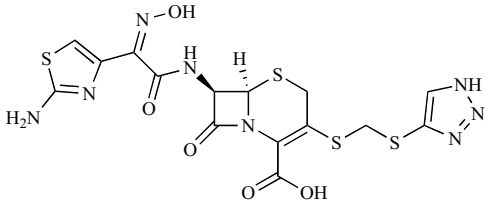
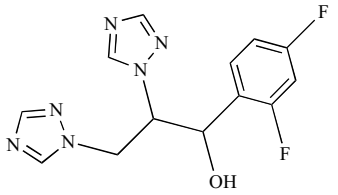
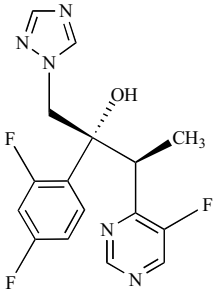
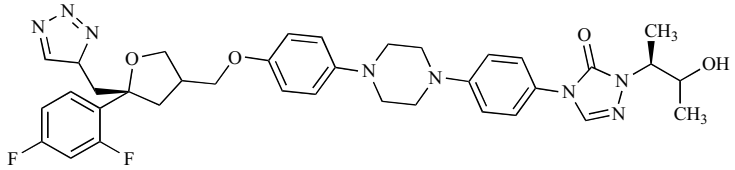
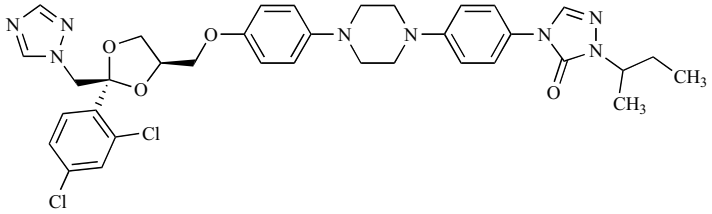
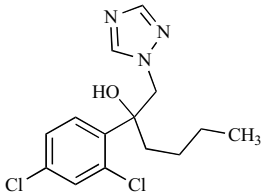
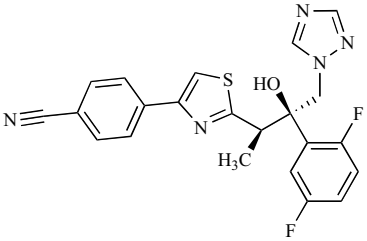
Sr. No.	Chemical structure	Potency	Target / Mechanism of action	Ref. No.
1.		IC_{50} = 1.17 µM	Inhibition of histone deacetylase	[246]
2.		IC_{50} = 0.27 µM	Inhibition of dihydrofolate dehydrogenase	[247]
3.		IC_{50} = 1.9 nM	Inhibition of histone deacetylase	[248]
4.		IC_{50} = 0.17 µM	Inhibition of dihydrofolate reductase	[249]
5.		IC_{50} = 1.2 µM	Inhibition of dihydrofolate reductase	[250]

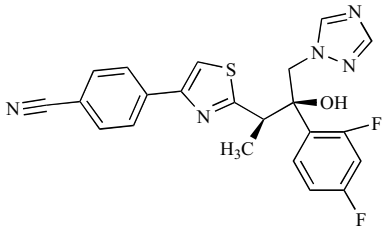
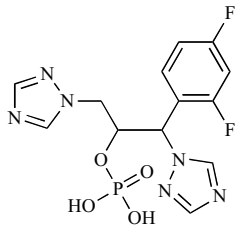
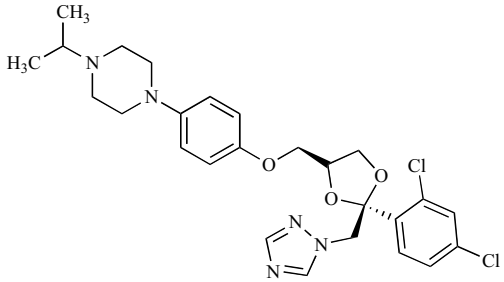
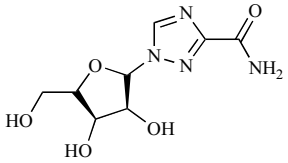
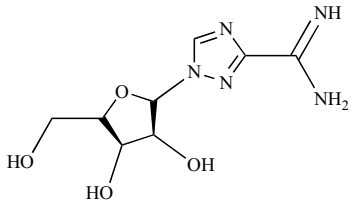
Table 6. Some Successful Triazole Based Anti-Infective Drugs Available in Clinical Therapy [251-259]

Sr. No.	Name of the Drug	Structure	Application
1.	Radezolid®		Antibacterial

(Table 6). Contd…..

Sr. No.	Name of the Drug	Structure	Application
2.	Cefmatilen®		Antibacterial
3.	Fluconazole®		Antifungal
4.	Voriconazole®		Antifungal
5.	Posaconazole®		Antifungal
6.	Itraconazole®		Antifungal
7.	Hexaconazole®		Antifungal
8.	Isavuconazole®		Antifungal

(Table 6). Contd…..

Sr. No.	Name of the Drug	Structure	Application
9.	Ravuconazole®		Antifungal
10.	Fosfluconazole®		Antifungal
11.	Terconazole®		Antifungal
12.	Ribavirin®		Antiviral
13.	Taribavirin®		Antiviral

ABBREVIATIONS

AAAE = Aryl acid adenylating enzymes
AIDS = Acquired immunodeficiency syndrome
AIV = Avian influenza virus
AMR = Antimicrobial resistance
BCG = Bacillus Calmette-Guerin
DAST = Diethylaminosulphur trifluoride
DHODH = Dihydroorotate dehydrogenase
DNA = Deoxy ribonucleic acid
DOTS = Directly observed treatment short-course
EC_{50} = 50% Effective concentration
ESBLs = Extended-spectrum β-lactamases
ETAR = 1-β-d-Ribofuranosyl-3-ethynyl-[1,2,4]triazole
FDA = Food and drug administration
HAART = Highly active antiretroviral therapy
HAV = Hepatitis-A virus
HCV = Hepatitis C virus
HDAC = Histone deacetylase
HDACI = Histone deacetylase inhibitor
HFRS = Hemorrhagic fever with renal syndrome
HIV = Human immunodeficiency virus
HOMO = Higher occupied molecular orbital
HSV = Herpes simplex virus
HTNV = Hanta virus
HTS = High throughput screening
IFN = Interferon
INH = Isoniazid
IR = Infrared

ISGs = Interferon -stimulated response genes
ISRE = Interferon-stimulated response element
MAO = Monoamine oxidase
MDR = Multi drug resistant
MDR-TB = Multi-drug-resistant tuberculosis
MIC = Minimum inhibitory concentration
MORE = Microwave organic reaction enhancement
MRA = Microdilution Resazurin Assay
NIAID = National Institute of Allergy and Infectious Diseases
NMR = Nuclear magnetic resonance
NNRTI = Non-nucleoside reverse transcriptase inhibitors
NRTI = Nucleoside reverse transcriptase inhibitors
PI = Protease inhibitors
RBV = Ribavirin
RSV = Respiratory syncytial virus
SAR = Structure activity relationship
TB = Tuberculosis
UV = Ultraviolet
WHO = World health organization
XDR = Extensively drug resistant

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