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RESEARCH ARTICLE

Pharmacological significance of triazole scaffold

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Abstract

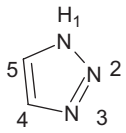
The triazole nucleus is one of the most important and well known heterocycles which is a common and integral feature of a variety of natural products and medicinal agents. Triazole nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive, antimalarial, local anaesthetic, antianxiety, antidepressant, antihistaminic, antioxidant, antitubercular, anti-Parkinson's, antidiabetic, antiobesity and immunomodulatory agents, etc. The broad and potent activity of triazole and their derivatives has established them as pharmacologically significant scaffolds. The basic heterocyclic rings present in the various medicinal agents are 1,2,3-triazole and 1,2,4-triazole. A large volume of research has been carried out on triazole and their derivatives, which has proved the pharmacological importance of this heterocyclic nucleus. The present paper is an attempt to review the pharmacological activities reported for triazole derivatives in the current literature with an update of recent research findings on this nuclei.

Keywords: 1,2,3-triazole, 1,2,4-triazole, pharmacological activities

Introduction

Triazole and its derivatives have attracted considerable attention for the past few decades due to their chemotherapeutical values [1,2]. It follows from the literature that the triazole derivatives possess a wide range of pharmacological activities such as antimicrobial [3,4], analgesic [5], anti-inflammatory, local anaesthetic [6], anticonvulsant [7], antineoplastic [8], antimalarial [9], antiviral [10], antiproliferative [11], and anticancer activities [12]. Many triazole-based derivatives are available as medicines [13].

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 at non-adjacent positions. The simplest form of the triazole family is triazole itself. Triazole is a white to pale yellow crystalline solid with a weak, characteristic odour, it is soluble in water and alcohol, melts at 120°C and boils at 260°C. It occurs as a pair of isomeric chemical compounds 1,2,3-triazole, **1**, and 1,2,4-triazole, **2** with molecular formula $C_2H_3N_3$, and a molecular weight of 69.06 [14]. The two isomers are:



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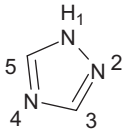

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In the past three decades the structure–activity relationship (SAR) of triazole derivatives has been extensively studied. These studies have revealed that substitutents on the triazole nucleus at the 1, 3 and 5 positions can be varied but the greatest difference in structure and properties is exerted by the groups attached to nitrogen atom at the first position. For example, a series of 1-(substituted biaryloxy)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl) propan-2-ol derivatives was synthesised by the introduction of biaryloxy side chain at the N-1 of the triazole nucleus which showed better antifungal activity than standard drug voriconazole against *Candida albicans* [15].

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Pharmacological activities

The triazole scaffold is extremely versatile and has been featured in a number of clinically used drugs, highlighting the importance of this nucleus. The most relevant and recent studies have revealed that triazole derivatives have a broad spectrum of pharmacological activities which can be classified into the following categories:

Antimicrobial activity

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including development of resistance to current antibacterial therapy and a very rapid increase of primary and opportunistic fungal infections in immunocompromised patients with AIDS or undergoing anticancer therapy and organ transplants [16–18].

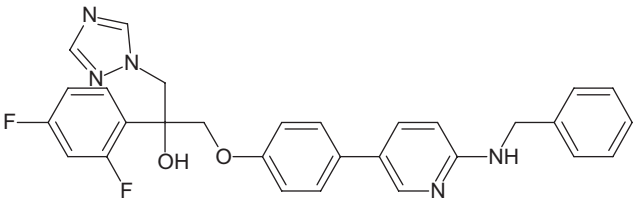
In spite of a large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistance developed in the last decades, has created a substantial medical need for new classes of antibacterial agents. A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that cross resistance with the present therapeuticals doesn't occur [19].

Systemic fungal infections are life-threatening and have become increasingly common in immuno-compromised hosts [20]. Currently triazole drugs (fluconazole, itraconazole, voriconazole and posaconazole) are most frequently used antifungals in clinical therapy. They possess a broad spectrum of activity and reduced toxicity when compared with imidazole antifungals [21,22].

However, resistance to azoles is emerging and may pose a serious health problem in future [23]. In addition, triazole drugs are often associated with hepatotoxicity and have a limited antifungal spectrum [24,25]. Consequently, it remains attractive to develop new triazole derivatives possessing broader antifungal spectra and higher therapeutic indexes.

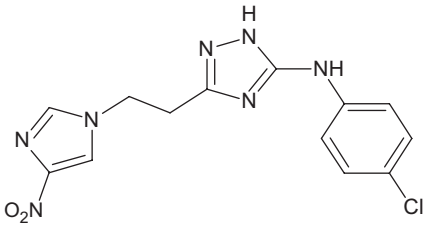
In the past few years, SAR of antifungal triazoles has been extensively studied [26,27]. Therefore, current research efforts are mainly focused on optimisation of the side chain attached to the pharmacophore. Optimisation of the side chain has led to the development of new compounds with better pharmacological activities [26,28,29].

Liu et al. synthesised a series of 1-(substituted biaryloxy)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl) propan-2-ol derivatives, **3**, and their antifungal activity was evaluated against eight human pathogenic fungi *in vitro*. Seventeen compounds showed activity between 4- and 64-fold higher than voriconazole against *Candida albicans*. Structure–activity relationship clearly suggested that introduction of a biaryloxy side chain greatly enhanced the antifungal activity of triazole analogues against *Candida* species [15].



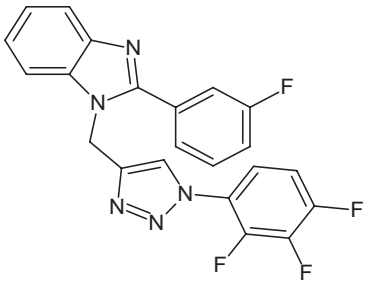
3

Demirayak et al. reported some 3-arylamino-5-[2-(substituted imidazole-1-yl or benzimidazol-1-yl) ethyl]-1,2,4-triazole derivatives (**4**) which were evaluated for antifungal activity against *Candida albicans* and *Candida glabrata* by using the tube dilution technique. The *in vitro* antifungal activity results showed that the most sensitive microorganism to the control antifungal, ketoconazol is *Candida glabrata*. Some of the compounds which possess lower minimum inhibitory concentration (MIC) values (for example, 31.25 μg/mL against *Candida glabrata*) may be considered as potential antifungal agents. No difference was observed between the anti-*Candida albicans* activities of ketoconazol and the compounds tested. *Candida glabrata* was more sensitive to both ketoconazole and the compounds tested than the *Candida albicans*, and all the compounds depicted the same MIC values for *Candida glabrata*. Hence, the tested compounds may be regarded as highly active antifungal substances against *Candida glabrata* and less active against *Candida albicans* [30]. The same class of compounds was evaluated for antimicrobial activities against *Staphylococcus aureus* NRRL B-767, *Micrococcus luteus* NRRL B-4375, *Escherichia coli* B and *Pseudomonas aeroginosa* NRRL B-23 by using the tube dilution technique. The *in vitro* antimicrobial screening results showed that the most sensitive microorganisms to the control antibiotic, chloramphenicol succinate to be *Staphylococcus aureus*. Some of the compounds which possess lower MIC values (for example, 31.25 μg/mL against *Staphylococcus aureus*) may be considered as potential antibacterial agents [30].



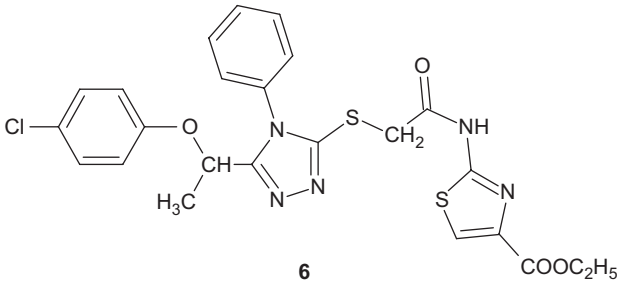
4. *N*-(4-chlorophenyl)-3-[2-(4-nitro-1*H*-imidazol-1-yl)ethyl]-1*H*-1,2,4-triazol-5-amine

Gill et al. reported some novel [1,2,3] triazoles clubbed with fluorine benzimidazole (**5**) series of H37Rv strain inhibitors which were found to be potentially active against *Mycobacterium tuberculosis* on the basis of promising results of preliminary antimicrobial study. Some of the derivatives under further evaluation are showing improved activity compared to rifampin [31].



5. 2-(3-fluorophenyl)-1-{[1-(2,3,4,-trifluorophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-benzimidazole

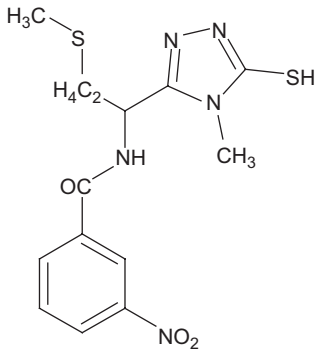
Zitouni et al. synthesised 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[*N*-(2-thiazolyl)acetamido]thio-4-*H*-1,2,4-triazole derivatives (**6**) and screened them for antimicrobial activities against *Candida albicans* (two strains), *Candida glabrata*, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.The results showed that some of the compounds have significant antifungal activities [32].



6

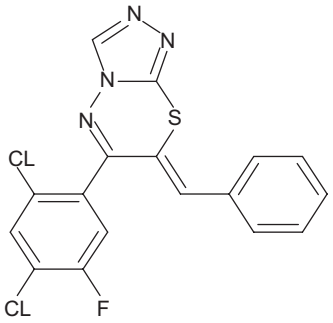
Pokrovskaya et al. investigated a series of new hybrid structures containing a fluoroquinolone (ciprofloxacin) and aminoglycoside (neomycin) antibiotics linked via 1,2,3-triazole moiety (**7**). Their antibacterial activities were determined against both Gram-negative and Gram-positive bacteria, including resistant strains. The nature of spacers in both the ciprofloxacin and neomycin parts greatly influenced the antibacterial activity. The majority of hybrids were significantly more potent than the parent neomycin and could overcome most prevalent types of resistance associated with aminoglycosides. Some hybrids inhibited bacterial protein synthesis with the potency similar to or better than that of neomycin and were up to 32-fold more potent inhibitors of DNA gyrase and toposiomerase IV than ciprofloxacin indicating a balanced dual mode of action. Significant delay in onset of resistance was observed in both *E. coli* and *B. subtilis* as compared to the treatment with ciprofloxacin-neomycin hybrid in comparison to that of each drug separately or their 1:1 mixture [33].

In another study, Pintilie et al. synthesised new 1,3,4-thiadiazole and 1,2,4-triazole` compounds containing a D,L-methionine moiety (**8**) and the potential antimicrobial effects of the synthesised 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 synthesised compounds exhibited promising activities against *Bacillus antracis* and *Bacillus cereus* [34].



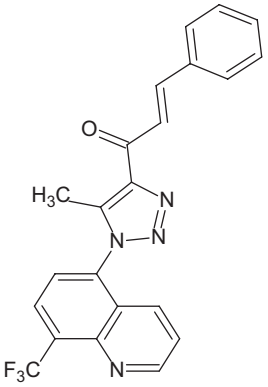
8

Holla et al. synthesised a series of 7-arylidene-6-(2,4-dichlorophenyl)-3-aryloxymethyl-anilinomethyl-1-,2,4-triazolo[3,4-b]-1,3,4-thiadiazines(**9**).The newly synthesised compounds were tested for their antimicrobial activities against *Escherichia coli, Staphylococcus aureus, Psuedomonas aeruginosa, Bacillus subtilis* and *Candida albicans* [35].



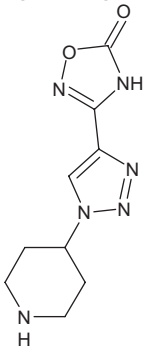
9. (7Z)-7-benzylidene-6-(2,4-dichloro-5-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine

In an another study, Holla et al. synthesised two substituted 1,2,3-triazole derivatives (**10**) which were screened for their antimicrobial activity against *Staphylococcus aureus* ATTC-25923, *Escherichia coli* ATTC-25922, *Pseudomonas aeruginosa* ATTC-27853, *Bacillus subtilis* and *Klebsiella pneumoniae* in dimethyl formamide (DMF), using disc diffusion method with ciprofloxacin as a standard. The most active compounds exhibited the maximum antibacterial activity against *Bacillus subtilis* and *Escherichia coli* as compared to *Klebsiella pneumoniae* almost equivalent to that of the standard at a concentration of 10 μg/mL [1]. The same class of compounds was evaluated for their antifungal activity against *Aspergillus flavus* NICM-524, *Aspergillus* feumigatus NICM-902, *Candida albicans* NICM-300, *Penicillium marneffei* and *Trichophyton mentagrophytes* in dimethyl sulphoxide (DMSO) by serial plate dilution method with ciclopiroxolamine as a standard. The most active compounds exhibited the maximum antifungal activity against *Aspergillus flavus* and *Trichophyton mentagrophytes* almost equivalent to the standard [1].



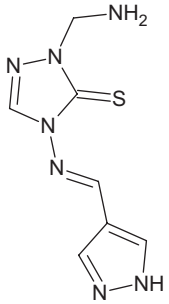
10. (2*E*)-1-{5-methyl-1-[8-(trifluorom ethyl)quinolin-5-yl]-1*H*-1,2,3-triazol-4-yl}-3-phenylprop-2-en--1-one

Sangshetti et al. designed a novel series of 1,2,3 triazole compounds possessing 1,2,4 oxadiazole ring (11) and evaluated them for their in vitro antifungal activities using the standard cup plate method. SAR for the series has been developed by comparing their MIC values with miconazole and fluconazole. One compound from the series was more potent than miconazole against Candida albicans (MIC-20) and Aspergillus flavus (MIC-10) whereas equipotent with miconazole against Fusarium oxysporum (MIC-25) and Aspergillus niger (MIC-12.5). The other compound was more potent than miconazole against Candida albicans (MIC-20) and Aspergillus niger (MIC-10) and equipotent with miconazole against Fusarium oxysporum and also it was equipotent with fluconazol against Aspergillus niger (MIC-10) [36].



11. 3-[1-(piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl]-1,2,4-oxadiazol-5(4*H*)-one

Isloor et al. screened a series of new 4-[(3-substituted-1*H*-pyrazol-4-yl)methyleneamino]-5-substituted-2-[(4-methylpiperzine-1-yl)methyl]-2*H*-1,2,4-triazole-3(4*H*)-thiones (**12**) for their antibacterial and antifungal activity. Some of the compounds were found to exhibit significant antimicrobial activity [37].



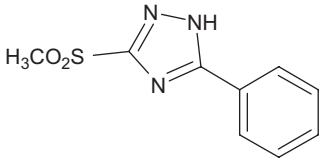
12. 2-(aminomethyl)-4-{[(E)-1*H*-pyrazol-4-ylmethylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

Analgesic and anti-inflammatory activity

Inflammation is a multifactorial process. It reflects the response of organisms to various stimuli and is related to many disorders such as arthritis, asthma, and psoriasis, which require prolonged or repeated treatment. Cyclooxygenases (COXs) are the key enzymes in prostaglandin (PG) biosynthesis from arachidonic acid (AA) that play a key role in inflammation. There are at least two COX isoforms COX-1 and COX-2. Constitutive COX-1 is responsible for providing cytoprotection in gastrointestinal (GI) tract whereas inducible COX-2 mediates inflammation [38,39].

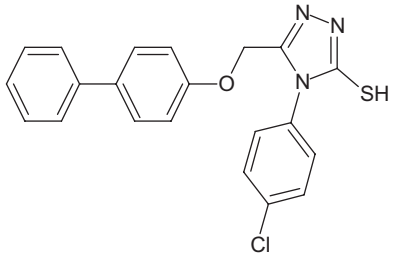
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the signs and symptoms of inflammation, particularly arthritic pain. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac, flurbiprofen and ibuprofen act via the inhibition of the COX-1 isoenzyme or the combined inhibition of COX-1 and COX-2 isoenzymes. However they show greater selectivity for COX-1 than COX-2 [40-42].

Tozkoparan et al. studied a series of 5-aryl-3-alkylthio-1,2,4-triazoles and corresponding sulphones (**13**) with the objective of developing better analgesic-anti-inflammatory compounds with minimum ulcerogenic risk. Several of these compounds showed significant activity. Alkylsulphone derivatives were found to be much more potent analgesic-anti-inflammatory agents than the corresponding alkylthio analogues. Two compounds were the most active of the series in both analgesic and anti-inflammatory activity tests. In contrast to the reference compound acetyl salicylic acid, these compounds did not induce gastric lesions in the stomach of experimental animals at the doses that exhibited analgesic/anti-inflammatory activity [43].



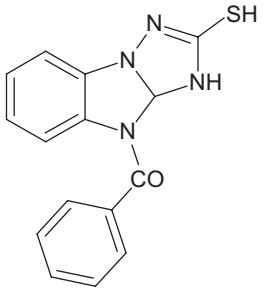
13. 3-(methylsulphonyl)-5-phenyl-1*H*-1,2,4-triazole

Kumar et al. synthesised a series of 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid (**14**), which were evaluated for their anti-inflammatory activity. These compounds also showed significant analgesic effects at equimolar oral doses relative to flurbiprofen having superior anti-inflammatory activity (81.81%) than the reference drug (79.54%) [44].



14. 5-[(biphenyl-4-yloxy)methyl]-4-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol

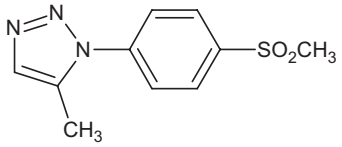
Mohamed et al. screened some new derivatives of 1,2,4-triazolo[2,3-a]benzimidazoles (**15**) for their possible anti-inflammatory and analgesic effect and most of these compounds showed potent and significant results compared to indomethacin. Moreover, ulcerogenicity and the median lethal dose of the most active compound were determined in mice; and found to be 275 mg kg^{-1} [45].



15

Abdel-Rahman et al. synthesised a series of new 1,2,4-triazole-5-thione derivatives. The newly synthesised compounds were evaluated for their anti-inflammatory and analgesic activities. Some compounds exhibited comparable anti-inflammatory activity to that of indomethacin where as other compounds were more potent analgesics than acetyl salicylic acid [46].

Wuest et al. synthesised a series of 1,4- and 1,5-diaryl substituted 1,2,3-triazoles (**16**). All compounds were tested for *in vitro* cyclooxygenase (COX) assays to determine the combined electronic and steric effects on COX-1 and COX-2 inhibitory potency and selectivity. Structure–activity relationship studies showed that compounds having a vicinal diaryl substitution pattern showed more potent COX-2 inhibition as compared to their corresponding 1,3-diaryl-substituted counterparts. In both series, compounds possessing an electron-withdrawing group (Cl and F) at the para-position of one of the aryl rings displayed higher COX-2 inhibition potency and selectivity as determined for compounds containing electron-donating groups (Me and OMe). The resultant data show, that the central carbocyclic or heterocyclic ring system as found in many COX-2 inhibitors can be replaced by a central 1,2,3-triazole unit without losing COX-2 inhibition potency and selectivity. The high COX-2 inhibition potency of some 1,2,3-triazoles having a vicinal diaryl substitution pattern along with their ease in synthesis through versatile Ru(II)-catalysed click chemistry make this class of compounds interesting candidates for further design and synthesis of highly selective and potent COX-2 inhibitors [47].



16. 5-methyl-1-[4-(methylsulfonyl)phenyl]-1*H*-1,2,3-triazole

Moise et al. evaluated some new 1,3,4-thiadiazole and 1,2,4-triazole derivatives containing a phenylalanine moiety for their anti-inflammatory activity. The anti-inflammatory screening of the triazole compounds established that the compounds possess activity comparable to other standard nonsteroidal anti-inflammatory agents [48].

Antineoplastic activity

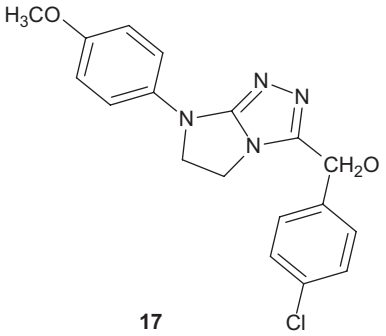
Cancer is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from benign tumours, which are self-limited, do not invade or metastasise. Most of the cancers form a tumour but some, like leukemia, do not. Cancer may affect people at all ages, even fetuses, but the risk for most of varieties increases with age [49]. Cancer causes about 13% of all deaths [50]. According to the American Cancer Society, 7.6 million people died from cancer in the world during 2007 [51].

Despite advances in cancer research, the overall survival of cancer patients remains low. Inherent and acquired resistance to treatment and the dose-limiting toxicity caused by the narrow therapeutic window of many anticancer drugs is recognised as an obstacle to the effective treatment of cancer. To search for more selective and novel compounds, a new series of triazole derivatives was designed that possess a useful therapeutic window for their cytoselective toxicity for drug-resistant cancer cells, when tested against the drug-sensitive and drug-resistant non small cell lung cancer cell lines H460 and H460taxR. Because H460taxR expresses excessive amounts of P-gp, these anticancer compounds were evidently not P-gp substrates on the basis of their cytotoxicity [52].

Antineoplastic properties of triazole derivatives can most probably be attributed to their affinity to anticancer biotargets, such as JNK-stimulating phosphatase-1 (JSP-1), tumour necrosis factor TNFα, anti-apoptotic biocomplex Bcl-XL-BH3, integrin avb3 receptor, etc. It must be emphasised, that combination of the triazole template with other heterocycles is a well known approach for the build-up of drug-like molecules, which allows new pharmacological profiles to be achieved, either by strengthening their action or lowering of toxicity [52].

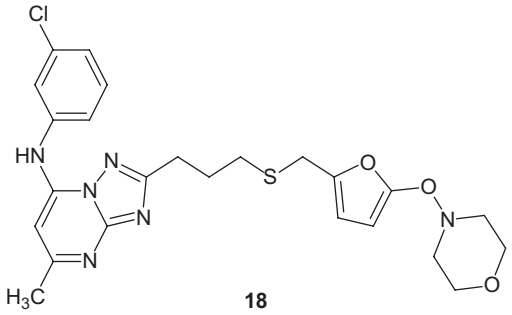
Sztanke et al. investigated 3-unsubstituted and 3-substituted-7-aryl-5*H*-6,7-dihydroimidazo[2,1-*c*][1,2,4]triazoles (**17**) which were evaluated for their cytotoxic activity against three cancer cell lines: human Caucasian colon adenocarcinoma cell line – LS180 (ECACC 87021202), human uterus carcinoma cell line – SiHa (ECACC 85060701) and human breast carcinoma cell line – T47D (ECACC 85102201) and found them to be the most effective *in vitro* against human colon adenocarcinoma cell line (LS180). Imidazotriazole was noticed to have a cytotoxic effect on the DNA structure of breast cancer cell line (T47D) when using the comet assay. One of the compounds was found to possess efficacy for DNA strand breakage in comparison to control DNA.

Moreover, there was a significant decrease in viability for the human leukaemic RPMI 8226 cells treated with different concentrations of imidazotriazoles, suggesting they may have antiproliferative properties [13].



17

Zhai et al. synthesised a series of novel *N*-anilino-5-methyl-2-(3-(5-(alkylaminomethyl)furan-2-yl-methylthio)propyl)-[1,2,4]triazolo-[1,5-*a*]pyrimidine-7-amine derivatives (**18**) and evaluated them for their *in vitro* cytotoxicity against two cancer cell lines, Bel-7402 and HT-1080. One compound possessed marked cytotoxicity and emerged as a lead compound. The activity was found to depend strongly on the substitution pattern of the side chains at C-2 position, and 4-triflouromethylanilino substituent at C-7 position was an option for anticancer potency [53].



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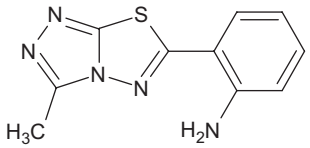
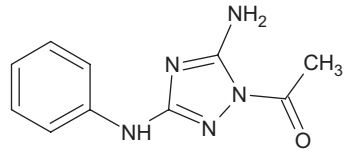
Recently, McArthur et al. demonstrated benefits with letrozole (having triazole moiety) after five years of tamoxifen. Eight hundred eighty-five women with stage I-III breast cancer who completed four to six years of tamoxifen in 2004 with no documented recurrence were given adjuvant therapy of letrozole. It was found that there was a significant increase in breast cancer survivors, especially for younger women with higher risk of this disease [54].

Ibrahim et al. studied a new series of 3,6-disubstituted[1,2,4]triazolo[3,4-b]thiadiazolederivatives (**19**). The newly synthesised compounds were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines. Some of the derivatives demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at the 10^{-5} M level and in some cases at concentrations of 10^{-7} M. In this assay, the antitumour activity of the newly synthesised compounds could not be interpreted in terms of tyrosine kinase inactivation but more likely as a relatively broad specificity for the ATP-binding domain of other kinases [55].



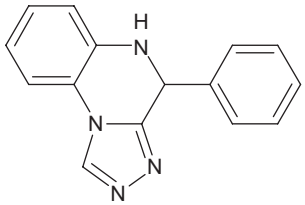
19. 2-(3-methyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)aniline

Lin et al. reported a series of 1-acyl-1*H*-[1,2,4]triazole-3-,5-diamine analogues (**20**) and found them to be cyclin-dependent kinase (CDK) inhibitors. These compounds demonstrated potent and selective CDK1 and CDK2 inhibitory activities and inhibited *in vitro* cellular proliferation in various tumour cells and also demonstrated *in vivo* efficacy in human melanoma A375 xenograft model in nude mice [56].



20. 1-[5-amino-3-(phenylamino)-1*H*-1,2,4-triazol-1-yl]ethanone

El-Hawash et al. screened a novel series of quinoxalines derived 1-substituted-4-phenyl-1,2,4-triazolo[4,3-a] quinoxalines (**21**) in order to evaluate their antitumour activity. Preliminary screening revealed that some compounds exhibited moderate to strong growth inhibition activity on various tumour panel cell lines between 10^{-6} to 10^{-5} molar concentrations. One compound showed selectivity towards CNS-cancer SF-639, leukemia CCRF-CEM, and melanoma SK-MEL-5 [57].

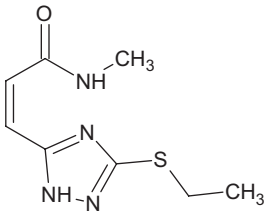


21. 4-phenyl-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinoxaline

Zhang et al. examined 6-(p-chlorophenyl)-3-[1-(p-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-s-triazolo[3,4-b]-1,3,4-thiadiazole (TDZ) for antitumour activities on two tumour lines: human hepatoma cell (SMMC-7721) *in vitro* and Sarcoma180 tumour (S180) *in vivo* resulting in the inhibition of DNA replication by 26.8% and 45.2% respectively. These results indicated that TDZ may inhibit proliferation of cancer cells by reversing SMMC-7721 cells malignant phenotypic characteristics and inducing redifferentiation. Detection of the inhibition of Sarcoma 180 tumour growth *in vivo* showed that TDZ reduced the tumour weight and 69.08% of the growth was inhibited. Thus TDZ could inhibit the proliferation of tumours *in vitro* and *in vivo* by inducing redifferentiation in the cancerous cells [58].

Pachuta-Stec et al. [59] synthesised some new N-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid (**22**) and screened them for their anticancer activity. Three compounds of this series were

found to be evidently effective against lung cell line *in vitro*. The distinctly marked antiproliferative effect of two compounds in breast carcinoma cells *in vitro* was ascertained. Moreover, the lowest cytotoxicity of one compound against the normal skin fibroblast cell line and breast carcinoma cell *in vitro* after 24- and 48-hours of incubation period was noticed in this study [59].

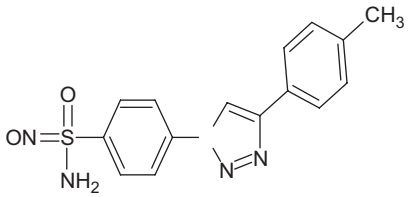


22. (2Z)-3-[3-(ethylsulfanyl)-1*H*-1,2,4-triazol-5-yl]-*N*-methylprop-2-enamide

Antiobesity activity

Obesity is a medical condition in which excess body fat is accumulated to the extent that it may have an adverse affect on health, leading to reduced life expectancy. Obesity is associated with many diseases, particularly heart disease, type 2 diabetes, breathing difficulties during sleep, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive dietary calories, lack of physical activity, and genetic susceptibility, though a limited number of cases are due solely to genetics, medical reasons, or psychiatric illness [60].

Poulsen et al. synthesised a series of 4-phenyltriazole-1-yl-benzenesulphonamide derivatives (**23**) which showed reduction in lipogenesis by the inhibition of the human mitochondrial carbonic anhydrase isoenzymes VA and VB [61].



23. 4-[4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide

Antidiabetic activity

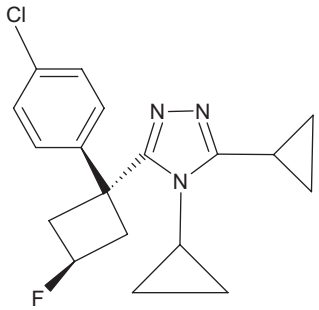
Diabetes mellitus often referred to simply as diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycaemia) [62]. Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the beta cells of the pancreas. Diabetes mellitus corresponds to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action in the body [63].

This disease develops due to a diminished production of insulin (in type 1) or resistance to its effects (in type 2 and gestational). Both lead to hyperglycaemia, which largely causes the acute signs of diabetes such as excessive urine production, resulting compensatory thirst with increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism [64].

In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly and the leading cause of non-traumatic amputation in adults, and diabetic nephropathy is the main illness requiring renal dialysis in the USA [65].

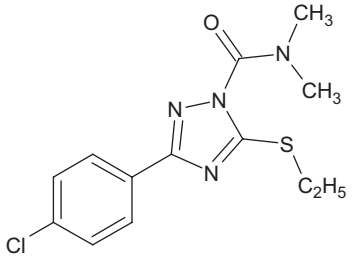
Glucocorticoids are important regulators of glucose and lipid homeostasis, acting largely via intracellular glucocorticoid receptors in the liver, adipose tissue and muscle. Glucocorticoid excess as epitomised by Cushing's syndrome can lead to insulin resistance/type 2 diabetes, dyslipidaemia and a redistribution of fat to visceral areas associated with increased cardiovascular risks [66,67]. Therefore, selective inhibition of 11β-HSDI enzyme by triazole derivatives may lead to an effective treatment for metabolic syndrome.

Zhu et al. demonstrated that 3-(phenylcyclobutyl)-1,2,4-triazole derivatives (**24**) show reduction in the blood glucose and lipid levels by the inhibition of 11β-hydroxysteroid dehydrogenase type I (11β-HSDI) [68].



24. 3-[*trans*-1-(4-chlorophenyl)-3-fluorocyclobutyl]-4,5-dicyclopropyl-4*H*-1,2,4-triazole

Ebdrup et al. studied four new classes of carbamoyl-triazoles (**25**) to demonstrate the central role of the intracellular enzyme hormone-sensitive lipase (HSL) in regulating fatty acid metabolism for the treatment of insulin resistant and dyslipidemic disorders. On the basis of a lead structure from high throughput screening, they identified methyl-phenyl-carbamoyl-triazoles as potent and efficacious HSL inhibitors to show their antidiabetic activity [69].

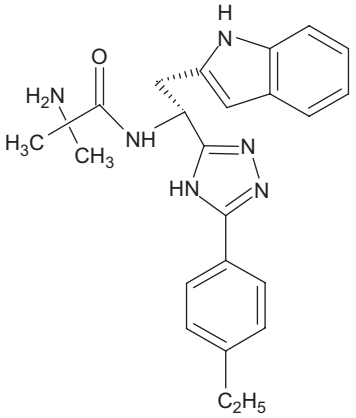


25. 3-(4-chlorophenyl)-5-(ethylsulfanyl)-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-1-carboxamide

Growth hormone receptor agonistic activity

Growth hormone (GH) is an important endocrine regulator of growth and anabolic processes [70]. The use of recombinant human GH is beneficial in the treatment of GH-deficient children [71] and has been shown to reverse some of effects of ageing in the elderly [72]. The GH releasing mechanism was found to be mediated through a G-protein coupled receptor named growth hormone secretagogue receptor type 1 a (GHS-R1a) [73]. Presence of 1,2,4-triazole moiety was found in a series of potent agonist or antagonist G-protein coupled receptor ligands [74-77].

Demange et al. investigated a novel series of growth hormone secretagogue (GHS) analogues based on the 1,2,4-triazole structure (**26**) and evaluated them for their *in vitro* binding to h GHS (a ghrelin receptor). Some compounds showed Ghrelin receptor agonistic activity and enhanced the release of growth hormone in the growth hormone deficient patients [78].

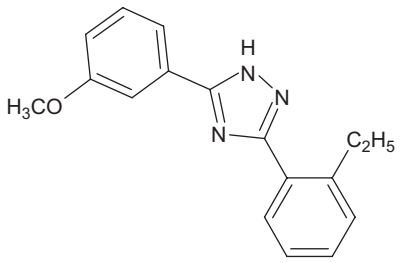


26

Immunomodulatory activity

Immunomodulators are substances having an effect on the immune system. They are of two types: immunosuppressants and immunostimulants. Immunostimulants, also known as immunostimulators, are substances (drugs and nutrients) that stimulate the immune system by inducing activation or increasing activity of any of its components. One notable example is the granulocyte macrophage colony-stimulating factor [79]. Immunosuppressive drugs or immunosuppressive agents are drugs that inhibit or prevent activity of the immune system. They are used in immunosuppressive therapy to prevent the rejection of transplanted organs and tissues (e.g., bone marrow, heart, kidney, liver), treat autoimmune diseases or diseases that are most likely of autoimmune origin (e.g., rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, Crohn´s disease, pemphigus, and ulcerative colitis) and some other non-autoimmune inflammatory diseases (e.g., long term allergic asthma control) [80].

Recently, Lindstedt et al. studied the therapeutic effects of 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1-*H*-1,2,4-triazole (ST1959) (**27**) in the treatment of autoimmune diseases. The evidence obtained in this study indicates that the beneficial effects exerted by (ST1959) rely upon a decrease in human T cell proliferation and inhibition of cytokine expression at the transcriptional level. Immunofluorescence data has shown that ST1959 inhibits the NFAT1 nuclear localisation in both Jurkat and human peripheral blood mononuclear cells resulting in the reduction of NFAT1 activity via a mechanism different from that of cyclosporin A. These findings provide new insights into the molecular mechanisms underlying the immunomodulatory activities of ST1959 [81].

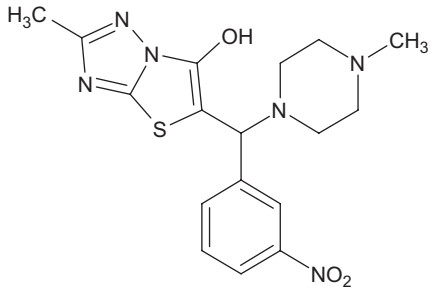


27. 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1*H*-1,2,4-triazole

Antioxidant activity

Antioxidant compounds in food play an important role as health-protecting factors. Scientific evidence suggests that antioxidants can reduce the risk for chronic diseases including cancer and heart disease. The main characteristic of an antioxidant is its ability to trap free radicals. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources. These free radicals may oxidise nucleic acids, proteins, lipids or DNA and can initiate degenerative disease. Antioxidant compounds like phenolic acids, polyphenols and avonoids scavenge free radicals such as peroxides, hydroperoxides or lipid peroxyls and thus inhibit the oxidative mechanisms that lead to degenerative diseases [82].

Recently Aktay et al. have reported promising anti-inflammatory activities together with low ulcerogenic properties of some Michael addition products of thiazolo[3,2-b]-1,2,4-triazole-5(6*H*)-ones (**28**) to investigate their antioxidant property. Some compounds with both antioxidant and anti-inflammatory activities as well as low ulcerogenic incidence, were selected for investigation of their inhibitory effect on various cyclooxygenase ezymes. Although no inhibition of cyclooxygenase-1 (COX-1) enzyme was found, yet there was a small inhibitory effect (17%) on the COX-2 enzyme. The diminished harmful effects on the stomach of these novel anti-inflammatory compounds were related to their antioxidant properties since it is ineffective on COX-1 enzyme. In conclusion, the compounds having both antioxidant and anti-inflammatory activities with a lack of COX-1 enzyme inhibitory effect may improve the gastrointestinal safety profile of such compounds [83].

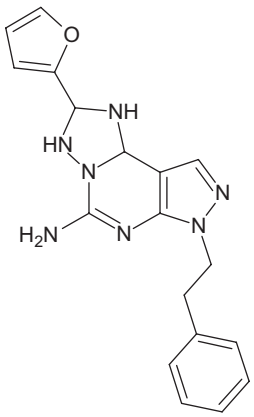


28. 2-methyl-5-[(4-methylpiperazin-1-yl)(3-nitrophenyl)methyl] [1,3]thiazolo[3,2-*b*][1,2,4]triazol-6-ol

Anti-Parkinson´s activity

Parkinson´s disease is both a chronic and progressive degenerative disease of the brain that often impairs motor skills, speech, and other functions. Parkinson´s disease belongs to a group of conditions called movement disorders. It is characterised by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunctions and subtle language problems [84].

Ongini et al. investigated a number of non-xanthine heterocycles starting from the non-selective adenosine antagonist CGS 15943, a triazoloquinazoline. Thus, replacement of the phenyl ring of CGS 15943 with a heterocyclic ring such as pyrazole or imidazole, led to a series of interesting compounds whose prototype, SCH 58261, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (**29**) has become a reference A_{2A} receptor antagonist. The relevance of the A_{2A} receptors in specific disease states, especially in the central nervous system, makes this class of adenosine receptor blockers of interest for treatment of neurodegenerative disorders such as Parkinson´s disease [85].

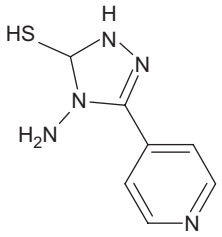


29. 2-(furan-2-yl)-7-(2-phenylethyl)-2,3,7,9b-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine

Anticonvulsant activity

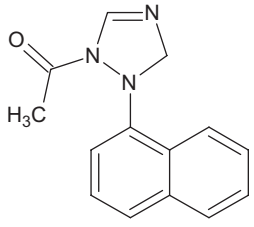
Epilepsy is a neurological disorder characterised by unprovoked seizures affecting at least 50 million people worldwide. There is a continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with the currently available antiepileptic drugs. About one third of patients do not respond well to current multiple drugs therapy. Currently employed drugs such as phenobarbital and mephobarbital are very effective in controlling the seizures but they suffer from major side effects such as sedation and hypnosis [86].

Triazole derivatives are reported to possess pronounced anticonvulsant activities. Pandeya et al. synthesised various Schiff bases such as N-[4-(4′-chlorophenyl-thiazol-2-yl] semicarbazides and 3-(4′-pyridyl)-4-amino-5-mercapto-4(*H*)-1,2,4-triazoles (**30**).The compounds were evaluated for anticonvulsant and neurotoxic properties. These compounds emerged as the most active analogues showing anti-MES and anti-PTZ activities and better than valproic acid. All the compounds showed lower neurotoxicity than phenytoin and carbamazepine [87].



30. 4-amino-3-(pyridin-4-yl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiol

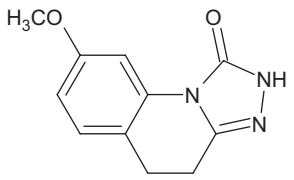
Karakurt et al. evaluated oxime and oxime ether derivatives of [1-(2-naphthyl)-2-(1,2,4-triazol-1-yl)ethanone] (**31**) as potential anticonvulsant compounds. The anticonvulsant activity of the compounds was determined by maximal electroshock and subcutaneous metrazole tests in mice and rats. Neurotoxicity was determined by the rotorod test in mice and the positional sense test, gait and stance test in rats. Although most of the O-alkyl substituted oxime ethers exhibited anticonvulsant activity, the O-arylalkyl substituted compounds were found to be inactive in the screening paradigms [88].



31. 1-[2-(naphthalen-1-yl)-2,3-dihydro-1*H*-1,2,4-triazol-1-yl]ethanone

Sun et al. screened a series of 8-alkoxy-4,5-dihydro-[1,2,4] triazole[4,3-a]quinoline-1-one derivatives (**32**) for their anticonvulsant activities. The tests demonstrated that 8-hexyloxy-4,5-dihydro-[1.2.4]triazole[4.3-a]quinoline-1-one and 8-heptyloxy-4,5-dihydro-[1,2,4] triazole[4,3-a] quinoline-1-one were the most potent anticonvulsants, having many fold better activity than that of drugs such

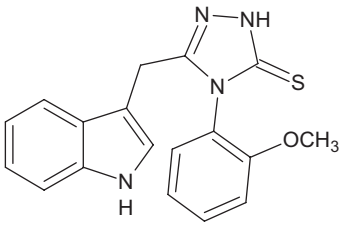
as phenytoin, carbamazepine, phenobarbital and valproate [89].



32. 8-methoxy-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinolin-1(2*H*)-one

Husain et al. investigated a series of 3,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives for their anticonvulsant activity and neurotoxicity. In anti-MES activity, seven compounds showed potent activity comparable to that of standard drugs such as phenytoin and carbamazepine whereas other compounds successfully passed the rotorod test without any sign of neurological deficit [90].

Siddiqui et al. screened a series of new 5-(*1H*-indol-3-yl)methyl-4-(substituted aryl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**33**) for their anticonvulsant activities in the MES model and compared them with the standard drugs such as phenytoin sodium and carbamazepine. Out of the 21 compounds studied, some compounds showed comparable MES activity to phenytoin and carbamazepine. One compound was found to be more potent than carbamazepine and also showed lower neurotoxicity than phenytoin [91].



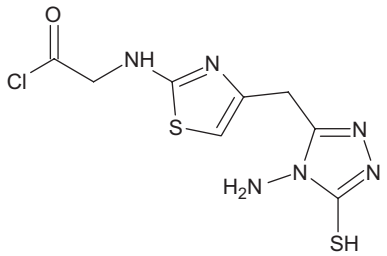
33. 5-(1*H*-indol-3-ylmethyl)-4-(2-methoxyphenyl)-2, 4-dihydro-3*H*-1,2,4-triazole-3-thione

Antitubercular activity

Tuberculosis is a chronic infectious disease caused by several species of *Mycobacterium*. The incidence of tuberculosis is increasing world wide, partly due to poverty/inequity and partly due to the HIV/AIDS pandemic, which greatly increases the risk of infection leading to overt disease. During recent years, *Mycobacterium tuberculosis* and other microorganisms have acquired increased resistance against drugs. Therefore, there is a need to develop new, potent, fast-acting antimicrobial and antimycobacterial drugs with low toxicity [92].

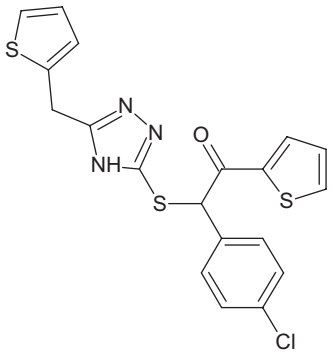
Tuberculosis is a primary cause of high mortality worldwide, despite the availability of highly active antitubercular agents. The statistics show that around three million people throughout the world die annually from tuberculosis [93,94] and today more people die from tuberculosis as ever before. Therefore the development of new drugs with activity against multi-drug resistant (MDR) TB, extensively drug resistant (XDR) TB, and the latent TB is a priority task and hopefully will reduce the current need for chemotherapy [95]. Over 10% of the newly registered pharmaceutical drugs contain one or more fluorine atoms [96]. Fluorine containing triazole derivatives and showing antitubercular activity are well documented in the literature [97].

In the 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. Shiradkar et al. synthesised various novel thiazolyl triazole derivatives (**34**) with the aim of developing novel molecules with improved potency for treating *Mycobacterium tuberculosis* H37Rv strain infections and with decreased drug resistance. They also investigated them for their antimycobacterial and antimicrobial activities. Many compounds have shown promising activity against tuberculosis [98].



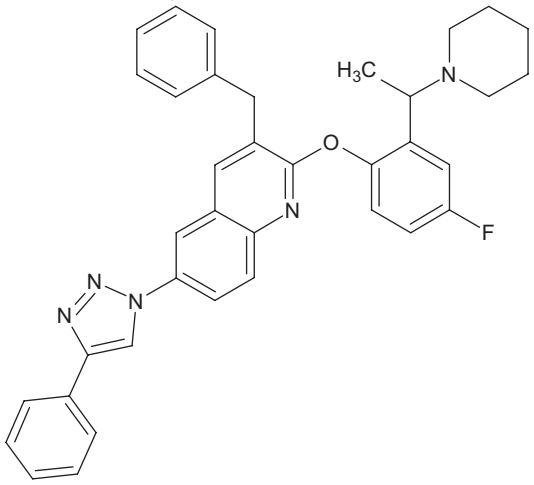
34. ({4-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl) methyl]-1,3-thiazol-2-yl}amino)acetyl chloride

The increasing clinical importance of drug-resistant mycobacterial pathogens has lent additional urgency to microbiological research and new antimycobacterial compound development. For this purpose, Kaplansikli et al. synthesised some novel 3-alkylsulphanyl-1, 2,4-triazole derivatives (**35**) and screened them for antituberculosis activity. Activity of the compounds was determined by broth micro dilution method. The micro plate Alamar blue assay, in BACTEC 12B medium and results were screened *in vitro* using the BACTEC 460 radiometric system against *Mycobacterium tuberculosis* H27Rv (ATCC 27294) at 6.25 μg/mL and the tested compounds showed considerable inhibition ranging from 58-84% [99].



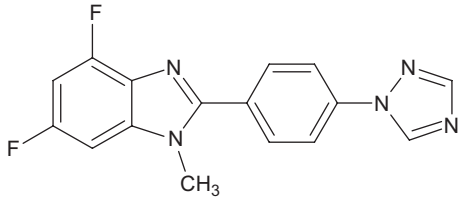
35. 2-(4-chlorophenyl)-1-(thiophen-2-yl)-2-{[5-(thiophen-2-ylmethyl) -4*H*-1,2,4-triazol-3-yl]sulfanyl}ethanone

Upadhayaya et al. designed a new series of 20 quinoline derivatives possessing triazolo (**36**) ureido and thioureido substituents and evaluated their antimycobacterial properties. Three compounds inhibited *Mycobacterium tuberculosis* H37Rv up to 96%, 98% and 94% respectively, at a fixed concentration of 6.25 μg/mL. Minimum inhibitory concentration of 3.125 μg/mL was observed for two compounds while for one compound it was found to be 6.25 μg /mL. Molecular docking calculations suggest critical hydrogen bonding and electrostatic interactions between polar functional groups (such as quinoline-nitrogen, urea-carbonyl and hydroxyl) of anti-mycobacterial (anti-TB) compounds and amino acids (Arg186 and Glu61) of ATP-synthase of *M. tuberculosis*, could be the probable reason for observed anti-mycobacterial action [100].



36

Jadhav et al. studied a series of novel 2-[4-(1*H*-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1*H*-benzo[d] imidazole derivatives (**37**) for their preliminary *in-vitro* antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhus* and then these compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth microdilution assay method. The antibacterial data suggested that the analogues with electronegative substituents emerged as the most promising antimicrobials. A few of the selected analogues are under further evaluation for secondary antitubercular screening, as they have shown better activity when compared to rifampin [101].

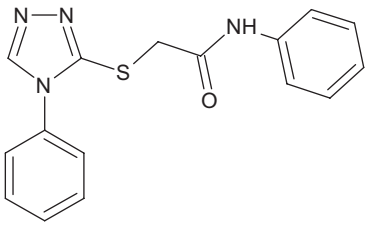


37. 4,6-difluoro-1-methyl-2-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1*H*-benzimidazole

Antiviral activity

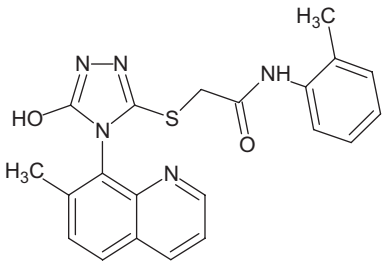
Human immunodeficiency virus type 1 (HIV-1) has been identified as the causative agent in the transmission and the development of acquired immuno deficiency syndrome (AIDS). The unique nature of the replicative cycle of HIV-1 provides many potential targets for therapeutic interventions. One of these, reverse transcriptase (RT) is a key enzyme, which is packaged within the HIV virion capsid and plays an essential and multifunctional role in the replication of the virus [102]. The RT inhibitors known to date are of two types: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The NRTIs and NtRTIs are competitive inhibitors of the 2-deoxy-nucleoside triphosphate (dNTP) binding site on RT and act as substrate decoys and chain terminators, whereas the NNRTIs bind at an allosteric site and are non-competitive with respect to the dNTP binding site [103]. The use of combinations of NRTIs, NNRTIs, and HIV protease inhibitors in a treatment regimen is termed highly active antiretroviral therapy (HAART) and is currently the best method for controlling HIV infections [104].

Wang et al. reported a novel sulphanyltriazole (**38**) as an HIV-1 non-nucleoside reverse transcriptase inhibitor via high throughput screening (HTS) cell-based assay. Chemical modifications and molecular modelling studies were carried out to establish its SAR and to understand its interactions with the enzyme. These modifications led to the identification of sulphanyltriazoles with low nanomolar potency for inhibiting HIV-1 replication and promising activities against selected NNRTI resistant mutants. These novel and potent sulphanyltriazoles could serve as advanced leads for further optimisation [105].



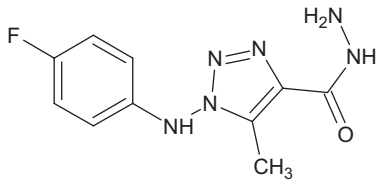
38. *N*-phenyl-2-[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetamide

De La Rosa et al. synthesised a new series of 1,2,4-triazoles (**39**) tested against several NNRTI-resistant HIV-1 isolates. Several of these compounds exhibited potent antiviral activities against efavirenz- and nevirapine-resistant viruses, containing K103N and/or Y181C mutations or Y188L mutation [106].



39. 2-{[5-hydroxy-4-(7-methylquinolin-8-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*H*-(2-methylphenyl)acetamide

Jordao et al. described the antiviral evaluation of new N-amino-1,2,3-triazole derivatives, 1-(substituted-phenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid ethyl esters, and 1-(4-substituted-phenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid hydrazides onCantagalovirusreplication.1-(4-Fluoro-phenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid hydrazide (**40**) exhibited significant antiviral effect. [107].



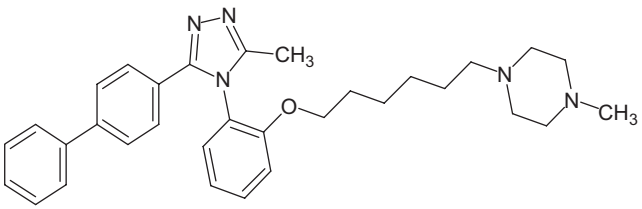
40. 1-[(4-fluorophenyl)amino]-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide

Antihypertensive activity

Hypertension, also referred to as high blood pressure is a medical condition in which blood pressure is chronically elevated. In current usage, the word "hypertension" normally refers to systemic, arterial hypertension [108]. Hypertension can be classified either as essential (primary) or secondary. Essential hypertension indicates that no specific medical cause can be found to explain the condition. About 95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma). Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure [109].

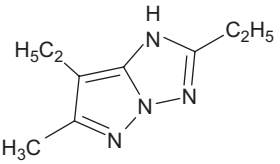
Starting at a systolic pressure of 115 mm Hg and diastolic pressure of 75 mm Hg (commonly written as 115/75 mm Hg), cardiovascular disease (CVD) risk doubles for each increment of 20/10 mm Hg [110].

Kakefuda et al. evaluated a series of 5-(4-biphenyl)-3-methyl-4-phenyl-1,2,4-triazole derivatives (**41**) as selective antagonists for human vasopressin V-1A receptor. The compounds were examined for their affinity to the cloned human V-1A receptor hV-1A and selectivity versus the cloned human V-2 receptor h-V2. One particular compound, 5-(4-biphenyl)-3-methyl-4-[2-[6-(4-methyl-1-piperazinyl)hexyloxy]phenyl]-1,2,4-triazole showed potent affinity to hV-1A and high selectivity with a 1700-fold selectivity versus h-V2, it also showed antagonist activities toward an arginine vasopressin-induced increase in diastolic blood pressure after intravenous or oral administration and long-lasting oral activity [111].



41

Okazaki et al. investigated alkyl-substituted pyrazolo [1,5-b][1,2,4]triazole derivatives (**42**) for their angiotensin II receptor antagonistic activity. Some compounds inhibited the angiotensin II-induced pressor response in rats after oral administration in the *in vivo* tests. These compounds also produced a dose-dependent decrease in blood pressure when administered orally to conscious furosemide-treated dogs, having a longer duration of action as compared to DuP753 suggesting them to be useful agents for the treatment of angiotensin II-dependent disease, such as hypertension [112].



42. 2,7-diethyl-6-methyl-1*H*-pyrazolo[1,5-*b*][1,2,4]triazole

Antidepressant activity

Depression is a central nervous system disorder characterised by inability to feel pleasure combined with physical agitation, insomnia, decreased appetite and delusional perceptions. It is mainly caused by the deficiency of excitatory neurotransmitters like serotonin, dopamine and noradrenaline in the brain [113].

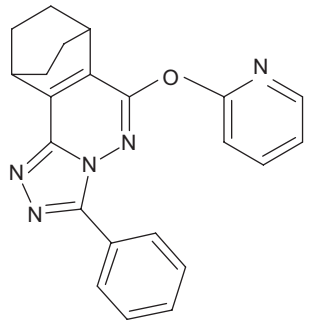
Varvaresou et al. synthesised a series of 3-[(2-Methyl-1*H*-3-indolyl) methyl]-4-aryl-4, 5-dihydro-1*H*-1,2,4-tria zole-5-thiones and their respective N-5-[2-methyl-1*H*-3-indolyl) methyl]-1,3,4-thiadiazol-2-yl-N-arylamines derivatives in order to study their antidepressant profiles. Behavioural effects, induced by the members of both the series, in conjunction with their activity in some specific tests (forced swim, pentetrazole convulsions) on mice, showed that these derivatives cross the blood-brain barrier and show antidepressant activity comparable to that of imipramine. Blood-brain barrier penetration is also supported by the lipophilicity data obtained for all analogues [114].

Antianxiety activity

Anxiety is a psychological and physiological state characterised by cognitive, somatic, emotional, and behavioural components. These components combine to create an unpleasant feeling that is typically associated with uneasiness, fear, or worry. The deficiency of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain is one of the main causes of this central nervous system disorder [115].

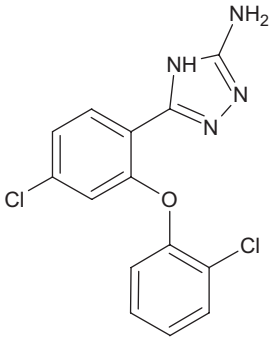
Carling et al. evaluated 6-benzyloxy-3-(4-methoxy) phenyl-1,2,4-triazolo[3,4-a]phthalazine (**43**) as a ligand with binding selectivity for the gamma-aminobutyric acid-A (GABA-A) alpha 3- and alpha 5-containing receptor subtypes over the GABA-A alpha 1 subtype. Methyl substitution of the benzo-fused ring at the 7-, 8- and 10-positions resulted in increased efficacy, although selectivity was abolished. Increased efficacy

and retention of selectivity for alpha 3 over alpha 1 was achieved with the 7,8,9,10-tetrahydro-(7,10-ethano)-phthalazine having the most binding selective GABA-A alpha 3-benzodiazepine-site partial agonists known, Although its selectivity is limited, its good pharmacokinetic profile in the rat made it a useful pharmacological tool to explore the effect of a GABA-A alpha 2/alpha 3 agonist *in vivo* [116].



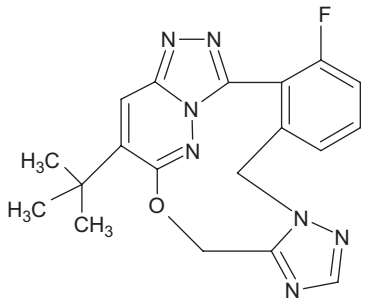
43

Akbarzadeh et al. synthesised a series of new 5-substituted analogues of 4*H*-3-(2-phenoxy)phenyl-1,2,4-triazole and its chlorinated derivatives (**44**). Conformational analysis and superimposition of energy minima conformers of the compounds on estazolam, a known benzodiazepine receptor agonist, revealed that the main proposed benzodiazepine pharmacophores were well matched. Rotarod and pentylenetetrazole-induced lethal convulsion tests showed that the introduction of an amino group in position 5 of 1,2,4-triazole ring especially in chlorinated derivatives had the best effect which was comparable with diazepam [117].



44. 5-[4-chloro-2-(2-chlorophenoxy)phenyl]-4*H*-1,2,4-triazol-3-amine

Carling et al. investigated that there is increasing evidence that compounds (**45**) with selectivity for gamma-aminobutyric acid-A (GABA-A) alpha2- and/or alpha3-subtypes may retain the desirable anxiolytic activity of nonselective benzodiazepines but possess an improved side effect profile. In this study, they have described a novel series of GABA-A alpha2/alpha3 subtype-selective agonists leading to the identification of the non-sedating anxiolytic agents in preclinical animal assays [118].



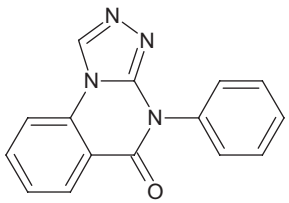
45

Antihistaminic activity

Allergies are caused by an excessive response of the body to allergens, such as the pollen released by grasses and trees. An allergic reaction indicates an excessive release of histamines by the body. Antihistamines are used for treatment of allergies. A histamine antagonist is an agent that serves to inhibit the release or actions of histamine. Antihistamine can be used to describe any histamine antagonist, but it is usually reserved for the classical antihistamines that act upon the H_1 histamine receptors [119].

Alagarsamy et al. [120] screened a series of 1-substituted-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-a]quinazolin-5-ones for their *in vivo* H_1-antihistaminic activity on guinea pigs and found that all the tested compounds protected the animals from histamine induced bronchospasm significantly. Compound 1-methyl-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-a]quinazolin-5-one emerged as the most active compound of the series and was more potent (72.76%) than the reference standard chlorpheniramine maleate (71%). Another compound of this series showed negligible sedation (10%) when compared to chlorpheniramine maleate (25%). Hence it could serve as prototype molecule for further development as a new class of H_1-antihistaminic agents [120].

In another study, Alagarsamy et al. evaluated a series of novel 1-substituted-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4*H*)-ones (**46**) for their *in vivo* H_1 antihistaminic activity on conscious guinea pigs. All the test compounds protected the animals from histamine induced bronchospasm significantly, whereas the compound 1-methyl-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5-(4*H*)-one (percentage protection 70.7%) was found to be equipotent with the reference standard chlorpheniramine maleate (percentage protection 71%). These compounds show negligible sedation (approximately 5%) when compared to the reference standard (26%). Hence they could serve as prototype molecules for future development [121].



46. 4-phenyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one

Local anaesthetic activity

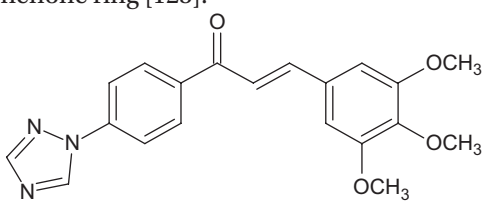
Anaesthesia has traditionally meant the condition of having sensation (including the feeling of pain) blocked or temporarily taken away. This allows patients to undergo surgery and other procedures without the distress and pain, they would otherwise experience. A local anaesthetic is a drug that causes reversible local anaesthesia and a loss of nociception. When it is used on specific nerve pathways (nerve block), effects such as analgesia (loss of pain sensation) and paralysis (loss of muscle power) can be achieved [122].

Vazzana et al. studied two sets of N-[2-(tert-amino) ethyl]- and N-[(quinolizidin-1 alpha-yl) methyl]-benzotriazol-2-ylacetamides, bearing substituents on position 5 or 5 and 6 for their local anaesthetic activities in comparison with lidocaine. Most of the prepared compounds exhibited a fairly good activity comparable or superior to that of lidocaine. The introduction of substituents on the benzene ring and the replacement of the usual tert-amino alkyl chains with the quinolizidin-1 alpha-ylmethyl (lupinyl) moiety were quite profitable for both the intensity and duration of activity. One selected compound was subjected to a large pharmacological screening and found endowed with a good level of the purported antiarrhythmic activity without any other disturbing activity [123].

Antimalarial activity

Malaria is a vector-borne infectious disease caused by protozoan parasites of the genus *Plasmodium*. Each year, there are approximately 515 million cases of malaria, killing between one to three million people, the majority of whom are young children in sub-Saharan Africa. Five species of the plasmodium parasite can infect humans and the most serious forms of the disease are caused by *Plasmodium falciparum*. Malaria caused by *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* causes milder disease in humans and is generally not fatal [124].

Mishra et al. reported the synthesis of novel 1,3-diaryl propenone derivatives (**47**) and their antimalarial activity *in vitro* against the 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 was found to be the most effective in inhibiting the 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 [125].



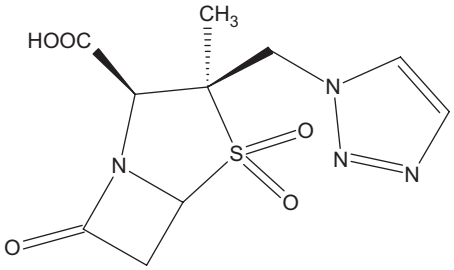
47. (2*E*)-1-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

Click chemistry of triazole: new horizons

In recent years, there has been an ever-increasing need for rapid reactions that meet the three main criteria of an ideal synthesis: efficiency, versatility, and selectivity [126]. Such rapid synthetic strategies would allow the medicinal chemist to assemble a large number of biologically active compounds in a very short period of time speeding up the process of discovery and lead optimisation [127]. The term "click chemistry" describes the reactions which are defined by a set of stringent criteria as described by Kolb et al.: "The reaction must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions, readily available starting materials and reagents, the use of no solvents or a solvent that is benign (such as water) or easily removed, and simple product isolation" [128].

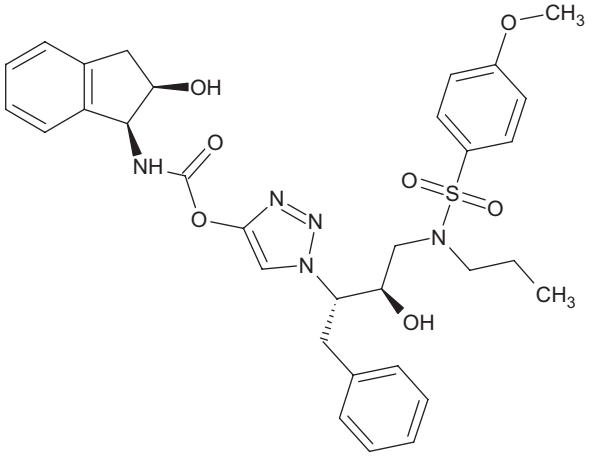
Click chemistry is increasingly being used in medicinal chemistry research because it simplifies compound synthesis and also enables a modular approach to pharmacophore design for faster lead discovery and optimisation [129]. Click chemistry has proven to be capable in helping to bridge the gaps between chemistry and biology and thus becoming a true interdisciplinary subject. Indeed, click chemistry can directly link chemistry to biology and can use biology for creating tailored synthesis [130]. Click chemistry is a modular approach that uses only the most practical and reliable chemical transformations. Among the various click chemistry reactions that are available, the union of azides and acetylenes to give triazoles deserves special recognition. The Huisgen 1,3-dipolar cycloadditions of azides and alkynes produce 1,4-disubstituted 1,2,3-triazoles. The synthesis of 1,4-substituted 1,2,3-triazoles from halides, azides, and acetylenes in the presence of copper (I) salt in one pot is well known [131]. The copper-(I)-catalysed 1,2,3-triazole formation from azides and terminal acetylenes is a particularly powerful linking reaction, due to its high degree of dependability, complete specificity, and the biocompatibility of the reactants [132,133].

A β-lactamase inhibitor, tazobactam (**48**) has been synthesised successfully by Bennett et al. utilising click chemistry. This drug is marketed in combination with the broad spectrum antibiotic piperacillin and has turned out to be a potent β-lactamase inhibitor with higher potency than clavulanic acid and sulbactam. The triazole ring appears to play a very pivotal role for its potency [134,135].



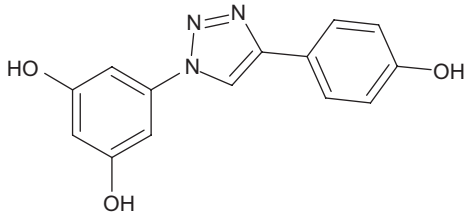
48. (2*S*,3*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylicacid 4,4-dioxide

Giffin et al. reported a triazole containing compound (**49**) as an effective molecule against the single point protease inhibitor mutants, V82F, V82A, and G48V. The biochemical and structural findings demonstrate that compound (**49**) retains high affinity for both wild-type and the PR6X multidrug-resistant protease variants. The use of azide-alkyne click chemistry synthesis allows rapid and diverse chemical modification of compound **49**. This also allows the evaluation of whether such changes improve antiviral performance against newly appearing multidrug-resistant viruses while maintaining efficacy to wild-type and previous versions of multidrug-resistant viruses [136].



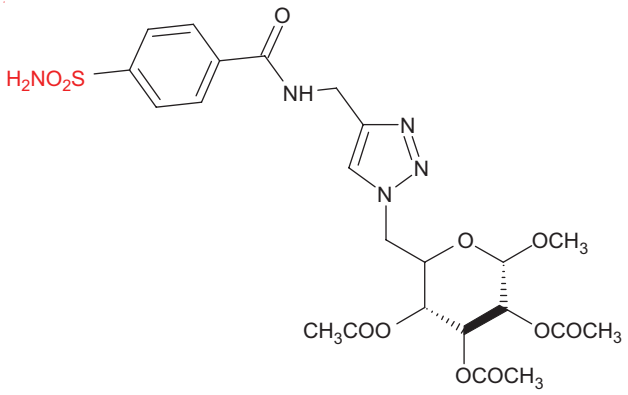
49

Pagliai et al. employed click chemistry to generate triazole-substituted resveratrol analogues (**50**). Resveratrol possesses numerous therapeutic actions including cytotoxic activity, and therefore the rapid synthesis of these triazole containing resveratrol analogues has been utilised to generate an enormous chemical database for preliminary screening of analogues with an antitumoural potential. Some of the compounds screened were found to be more potent than resveratrol as cytotoxic/antiproliferative agents [137].



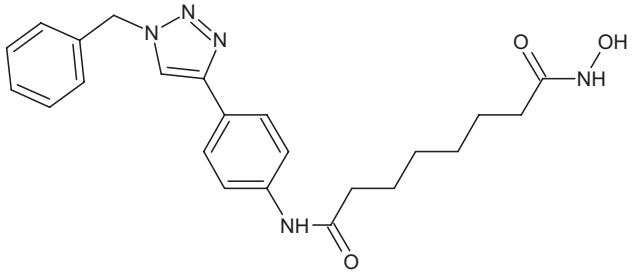
50. 5-[4-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-1-yl]benzene-1,3-diol

The quantitative structure–activity relationship (QSAR) demonstrated that the stereochemical diversity within the carbohydrate tails effectively interrogated the carbonic anhydrase (CA) active site topology, generating in some instances inhibitors with hCA IX selectivity, an important outcome in the quest for potential cancer therapy [138]. Wilkinson et al. presented a new class of CA inhibitors comprising of 28 glycosyl triazole aryl suphonamide derivatives (**51**) generated through click chemistry. These compounds were assessed for their ability to inhibit three human CA (hCA) isozymes *in vitro*: cytosolic hCA I, hCA II and transmembrane tumour-associated hCA IX. A number of derivatives were found to be selective inhibitors for the cancer associated isozyme hCA IX [139].



51

The discovery of the rules governing the inhibition of the various histone deacetylases (HDACs) isoforms is likely to be a key to identify improved therapeutics that act as epigenetic modulators of gene transcription. The synthesis of some novel triazole-based histone deacetylase inhibitors (HDACIs) (**52**) was accomplished by Chen et al. according to the synthetic protocols of click chemistry. These newly synthesised triazole based ligands were screened against a panel of pancreatic cell lines which consisted of BxPC-3, Hup T3, Mia Paca-2, Pan 04.03, and SU 86.86 cells and *Plasmodium falciparum* strains for their anticancer and antimalarial activity respectively. The results showed that the nature of substitution on the phenyl ring plays a 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 that were identified for the triazolylphenyl ligands in the inhibition of HDAC6 (IC_{50} = 1.9 nM), one compound showed significant anticancer and antimalarial activity which can be considered as a valuable candidate for further chemical modifications [140].



52

1,2,3-Triazole-based molecules are useful pharmacophores for several DNA-alkylating and cross-linking agents. Kamal et al. synthesised a series of A/C8, C/C2 and A/C8-C/C2-linked 1,2,3-triazole–PBD conjugates (**53**) by employing click chemistry approach. These molecules have exhibited promising DNA-binding affinity and anticancer activity in selected human cancer cell lines [141].

Table I. Some successful triazole based drugs available in clinical therapy [142-157].

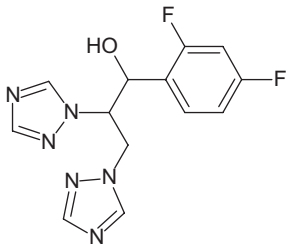
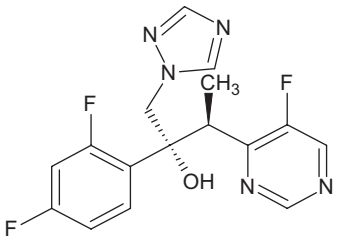
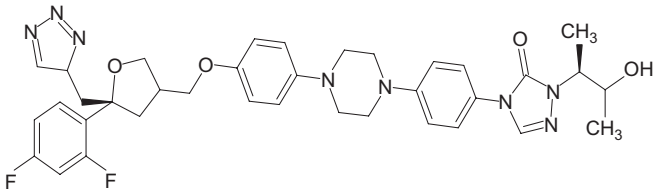
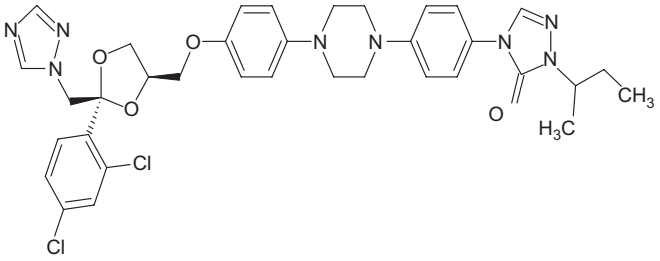
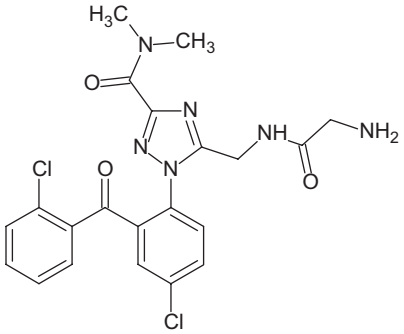
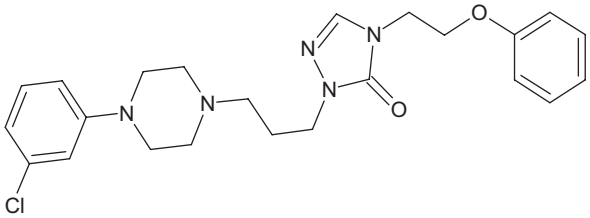
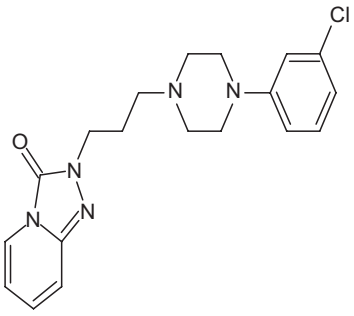
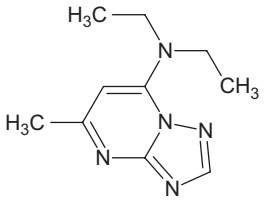
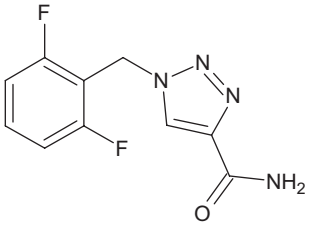
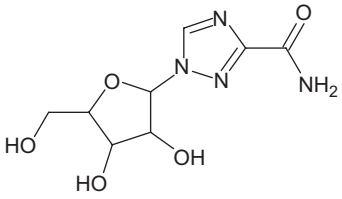
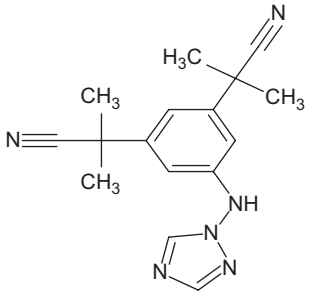
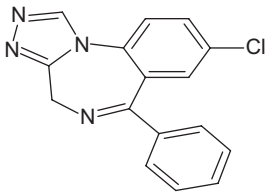
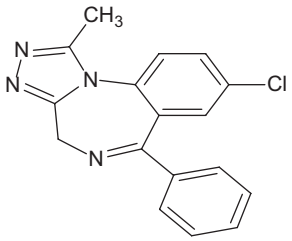
Drug	Structure	Application
Fluconazole®		Antifungal
Voriconazole®		Antifungal
Posaconazole®		Antifungal
Itraconazole®		Antifungal
Rilmazafone®		Anxiolytic
Nefazodone®		Antidepressant

Table 1. continued on next page

Table I. Continued.

Drug	Structure	Application
Trazodone®		Antidepressant
Trapidil®		Antihypertensive
Banzel®		Antiepileptic
Ribavirin®		Antiviral
Anastrozole®		Antineoplastic
Estazolam®		Sedative-Hypnotic
Alprazolam®		Tranquiliser

Conclusion

The strength of the triazole nucleus is evident from the clinically used drugs. Despite the presence of the triazole moiety in various clinically important medicinal agents, there is still further scope in this promising moiety as a number of different molecular targets are available for various 1,2,3 and 1,2,4-triazole derivatives.

A review of the diverse and potent pharmacological activities of the triazole derivatives has been presented in this paper. The information provided in this manuscript can be useful for the further study of this scaffold in order to evaluate their biological potential in a better way and for development of further pharmacologically significant medicinal agents for the treatment of various diseases.

Declaration of interest

The authors declared no conflict of interest.

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