1, 2, 3-Triazoles: scaffold with medicinal significance

Saqlain Haider, Mohammad Sarwar Alam, Hinna Hamid

Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University) New Delhi, 110 062, India

Correspondence: Mohammad Sarwar Alam
E-mail: msalam@jamiahamdard.ac.in or msalam5555@gmail.com
Received: February 05, 2014
Published online: July 12, 2014

Despite a significant work on 1, 2, 3-triazoles, continuous efforts are still being made to identify novel heterocyclic compounds with potent bioactivities. This review may help the medicinal chemists to develop new leads possessing 1, 2, 3-triazoles nucleus with higher efficacy. This review throws light on the detailed synthetic approaches which have been used for the synthesis of triazoles since the early development in the area of triazole chemistry. This has been followed by the in depth analysis of the triazoles with respect to their medicinal significance.

To cite this article: Saqlain Haider, et al. 1, 2, 3-Triazoles: scaffold with medicinal significance. Inflamm Cell Signal 2014; 1: e95. doi: 10.14800/ics.95.

Copyright: © 2014 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

Introduction

The medicinal chemists have considered the synthesis of 1, 2, 3-triazole based heterocycles as the cornerstone of medicinal chemistry due to their important biological activities. This could be understood from the fact that even in the early part of the twentieth century the researchers started working on the possibility of using 1,2,3-triazolo[4,5-d]pyrimidines (8-azapurines) for the treatment of cancer and malignant tumors [1]. 1, 2, 3-triazoles cause peptidomimetic inhibition of tyrosinase, an enzyme which causes the browning of plant based foodstuffs and human skin diseases [2, 3].

The features possessed by the 1, 2, 3-triazoles make them pharmaceutically important molecules. They are stable to reduction and oxidation as well as to hydrolysis in acidic and basic conditions, which indicates their high aromatic stabilization. 1,2,3-triazoles have a high dipole moment (about 5 D) [4] and are able to participate actively in hydrogen bond formation as well as in dipole-dipole and π stacking interactions [5] which helps them in binding easily with the biological targets [6] and improves their solubility.

The click chemistry approach invented by Sharpless [7] using copper (I)-catalyzed azidealkyne cycloaddition (CuAAC) has resulted in the production of large number of 1, 4-disubstituted 1, 2, 3-triazoles in very high yields [8]. The copper(I)-catalyzed azidealkyne cycloaddition (CuAAC) approach has been widely used in the different spheres of the science such as bioconjugation [9], oligonucleotide synthesis [10], construction of bolaamphiphilic structures [11], DNA labelling [12] and drug discovery [13]. In the present scenario of a continuous requirement for better drugs in shorter times, it is a challenging task to prepare new molecules that combine high activity and selectivity, drug-likeness and good pharmacokinetic properties. Triazoles are heterocyclic compounds (Figure 1) featuring five member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-membered ring. Triazole refers to either one...
of a pair of isomeric chemical compounds with molecular formula C₆H₃N₅.

The search for new biologically active compounds in the series of condensed 1, 2, 3-triazoles is still continuing. Thus for example, substances acting against the hepatitis C virus [14] and compounds inhibiting benzodiazepine and adenosine receptors were found [15, 16]. Some biologically active compounds (Figure 2) containing 1, 2, 3-triazoles are shown below [17].

Potential pharmaceuticals (Figure 3) based on 1, 2, 3-triazoles include the anticancer compound carboxamidotriazole (CAI) [18], the nucleoside derivative non-nucleoside reverse transcriptase inhibitor tert-butylidimethylsilylspiroaminooxahiolethiodioxide (known as TSAO), β-lactum antibiotic Tazobactum [19] and Cefatrizine.

Methods for the synthesis of 1, 2, 3-triazoles

Scheme 1

The most popular reaction that has been adapted to produce the 1, 2, 3-triazole moiety is the 1, 3-dipolar cycloaddition also known as Huisgen cycloaddition, between an azide and a terminal alkyne. Although this reaction was discovered at the start of the 20th century, its detailed mechanism was described by Huisgen in the 1960s [20].

This reaction is catalysed by the copper (I) metal and thus most often carried out in the presence of copper (II) salts e.g. copper sulfate pentahydrate [21] or copper acetate [22] using sodium ascorbate or metallic copper as a reducing agent which reduces the copper (II) to copper (I). The solvent used for this reaction contains a mixture of tert-butanol and water. By using this solvent system the requirement of a base to generate copper acetylide species is eliminated and the same can be used for the lipophilic compounds.
A palladium catalysed synthesis of 1, 2, 3-triazoles from alkenyl halides and sodium azides added a new chapter in the Palladium chemistry [23].

\[
\text{Ar} + \text{NaN}_3 \xrightarrow{\text{Pd}_2(\text{dba})_3, \text{Xanthophos}} \text{Dioxane 90 °C} \xrightarrow{14 \text{hr}} \text{HN} \equiv \text{Ar} \equiv \text{N=Ar}
\]

Scheme 3

The terminal alkyne react with a mixture of benzyl or alkyl halides with sodium azide in ethanol to produce 1, 4-disubstituted 1, 2, 3-triazoles in good yields [24]. It is catalysed by copper immobilized on 3-aminopropyl functionalised silica gel.

\[
\text{R} - \text{X} + \text{NaN}_3 + \frac{5 \text{ mole % Cu(I)}}{\text{Ethanol, Reflux, 24 hr}} \rightarrow \text{HN} \equiv \text{Ar} \equiv \text{N=Ar}
\]

\(X = \text{Cl, Br}\)

Scheme 4

An efficient one pot synthesis of 1, 2, 3-triazole linked glycoconjugates involving 1, 3-dipolar cycloaddition in the presence of Cu(I) as a catalyst has been reported [25]. It is an easy method to prepare neoglycoconjugates derived from unprotected saccharides or peracetylated saccharides.

Scheme 5

Pankaja synthesized a family of closely related 1, 2, 3-triazoles as anticonvulsant agents in which the dicarboximide moiety was lacking from the triazole ring, unlike the traditional anticonvulsant agents [26].

Scheme 6

Terminal alkyne on reaction with iodosobenzene and mixture of sodium azide, cuprous iodide and sodium ascorbate gives 1, 2, 3-triazole [27].

Scheme 7

Primary aliphatic amines undergo diazo transfer to form azides which are converted into 1, 2, 3-triazoles under appropriate reaction conditions [28].

Scheme 8

Non-fluorescent 3-azide coumarins can be converted into fluorogenic probes by reacting them with alkyne. This method is used to generate fluorescent DNA probes used in the molecular biology [29].

Scheme 9

The organic azides undergo cycloaddition with immobilized alkyne on polystyrene resins resulting in the formation of 1, 2, 3-triazoles [30].

Scheme 10

Condensed 1, 2, 3-triazoles can be synthesized by the oxidation of arylazo heterocycles having an amino group in the ortho position [31].

Pharmacological significance of 1, 2, 3-triazoles

Anti-inflammatory activity

Haider et al have synthesized a library of benzoxazolinone based 1, 2, 3-triazoles using click chemistry approach and screened them for their in vitro and in vivo anti-inflammatory activity. The compound 1 exhibited potent in vitro anti-inflammatory activity of 81.39% inhibition at 3 h post-carrageenan and 80.62% inhibition 5 h post-carrageenan administration in comparison to indomethacin which exhibited 79.06% and 82.25% inhibition after 3 h and 5 h, respectively. The compound 2 exhibited significant TNF-α inhibitory activity with 50.95% inhibition as compared to the standard drug indomethacin which exhibited 64.01% inhibition [32].
Shafi et al have synthesized novel bis-heterocycles encompassing 2-mercapto benzothiazole and 1, 2, 3-triazoles and evaluated them for their anti-inflammatory activity by using biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema method. The compound 3 exhibited a selective index (COX-2/COX-1) of 0.44 against celecoxib which exhibited a selective index of 0.0028 [33].

Assis et al have synthesized 1, 2, 3-triazole based phthalimide derivatives by the 1,3-dipolar cycloaddition reaction of N-(azido-alkyl)phthalimides with terminal alkynes and screened them for their anti-inflammatory activity. The compound 4 exhibited potent anti-inflammatory activity with 69% inhibition as compared with ibuprofen which showed 68% inhibition of inflammation [34].

Silva et al carried out the synthesis and anti-inflammatory activity of novel glucosyl triazoles from a reaction of 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl azide and terminal alkynes using ultrasound energy. The compound 5 exhibited potent anti-inflammatory activity with an inhibition of 64.70% in comparison to ibuprofen which exhibited 77% inhibition [35].

### Antitubercular activity

Somu et al carried out the synthesis of the compound 6 which was found to be the inhibitor of Mycobacterium tuberculosis. Its activity is due to the inhibition of the adenylate forming enzyme MbtA, which is involved in biosynthesis of the mycobactins [36].

Yempala et al have synthesized a series of novel dibenzofuran based 1, 2, 3-triazole derivatives using click chemistry approach and screened them for their in vitro anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv. The compound 7 was found to be most potent antitubercular agent with lowest cytotoxicity against the HEK-293T cell line [37].

Menendez et al have synthesized a series of 1,2,3-triazoles as inhibitors of Mycobacterium tuberculosis H37Rv. Compounds 8 and 9 were found to be good inhibitors of Mycobacterium tuberculosis with MIC values of 0.50 and 0.25 μg/mL, respectively [38].

Menendez et al have synthesized and screened the phenethyl based 1, 2, 3-triazoles as the inhibitors of Mycobacterium tuberculosis H37Rv. The compound 10 was found to exhibit a potent antitubercular activity with MIC of 5 μg/mL as compared to triclosan which exhibited the MIC of 10 μg/mL [39].

Tripathi et al have synthesized 1, 4-disubstituted-1, 2, 3-triazoles by [3+2] cycloaddition of different 2-(azidomethyl)-dihydropaphtho(benzo)furans with different alkynes and screened them against Mycobacterium tuberculosis H37Rv. The synthesized compounds exhibited potent antitubercular activities with MIC ranging from 12.5 to 3.12 μg/ml. The compound 11 exhibited a potent MIC of 6.25 μg/ml [40].

### Anticancer activity

Duan et al have synthesized a series of novel 1, 2, 3-triazole-dithiocarbamate hybrids and screened them against four selected human tumor cell lines i.e. MGC-803, MCF-7, PC-3, EC-109. Most of the compounds especially 12 and
13 exhibited potent anticancer activity with IC_{50} values ranging from 0.73 to 11.61 μM and 0.49 to 12.45 μM, respectively against the different tumor cell lines [41].

Kamal et al. have synthesized novel chalcone-pyrrolo[2,1-c] [1,4]benzodiazepine (PBD) derivatives using alkane spacers and linked through a 1,2,3-triazole moiety. The synthesized compounds showed a promising anticancer activity with MIC ranging from <0.1-2.92 μM. The compound 14 was found to be the most potent with MIC ranging from 0.12-2.03 μM against different cancer cell lines [42].

Elamari et al. have synthesized a series of bis-alkyne amides derived from propiolic acid and evaluated them for their in vitro cytotoxic activity using B16 melanoma cells. The cytotoxic activity of the compounds 15 and 16 was found to be 0.3μM and 0.28 μM respectively [43].

Singh et al. have synthesized a series of novel 1, 2, 3-triazole based β-lactam-chalcone bifunctional hybrids using click chemistry approach. The synthesized compounds were screened against four human cancer cell lines viz A-549(lung), PC-3(prostate), THP-1(leukemia), and Caco-2(colon). The compound 17 was nearly twice as active as 5-flourouracil against of THP-1 cell lines [44].

Glowacka et al. have synthesized a series of novel acyclonucleotide analogues with a 1,2,3-triazole linker using diethyl azidomethyl-, 2-azido-1-hydroxyethyl-, 2-azidoethyl-, 3-azidopropyl-, 3-azido-2-hydroxypropyl-, 4-azidobutyl-and 3-azido-1-hydroxypropylphosphonates and some alkynes using microwave conditions. The cytotoxicity of the synthesized compounds was evaluated against murine leukaemia L1210, human T-lymphocyte CEM and human cervix carcinoma HeLa cells. The compound 18 was found to exhibit an IC_{50} (μM) of 2.78 [45].

Kurumurthy et al. have synthesized a series of novel alkyltriazole tagged pyrido[2,3-d]pyrimidine derivatives starting from 2,3-active functional pyridine 1 via cyclization and propargylation followed by reaction with alkyl or perfluoroalkyl azides under Sharpless conditions. All the compounds were screened for anticancer activity against three cancer cell lines viz U937, THP-1 and Colo205. The compounds 19 and 20 were found to exhibit potent anticancer activity with an IC_{50} (μg/ml) of 8.16 and 6.20 respectively against U937 cancer cell line [46].

Chinthala et al. have carried out the synthesis of a series of thiazolidine-2, 4-dione based 1, 2, 3-triazole derivatives. The synthesized compounds exhibited a potent anticancer activity towards human cancer cell lines IMR-32 (neuroblastoma), Hep-G2 (hepatoma) and MCF-7 (breast). The compounds 21 and 22 exhibited an IC_{50} (µg/ml) of 97.52 and 52.64 against the IMR 32 cell line [47].

Antileishmanial activity

Guimarães et al. have carried out the synthesis of ten α-lapachone-based 1,2,3-triazoles, seven 1,4-naphthoquinones coupled to 1,2,3-triazoles and five nor-β-lapachone-based 1,2,3-triazoles. These compounds were evaluated for their activity against promastigote forms of antimony-sensitive and -resistant strains of (syn. Leishmania chagasi) Leishmania amazonensis and
Leishmania infantum. These compounds were evaluated for their toxicity against the mammalian cells. The synthesized compounds exhibited more potent antileishmanial activity than the antimonial drug. The IC₅₀ values were found to be in a range of 1.0 to 50.7 μM. The compound 23 exhibited an IC₅₀ of 1.00 μM in comparison to the standard drug Potassium antimonyl tartrate whose IC₅₀ was found to be 86.1 μM against Leishmania infantum.

Tahghighi et al utilised the click chemistry approach to synthesize novel 5-(5-nitrofuran-2-yl)-1, 3, 4-thiadiazol-2-amines by introducing N-((1-benzyl-1H-1, 2, 3-triazol-4-yl) methyl) nucleus on the C-2 amine of thiadiazole ring. The synthesized compounds were evaluated for their in vitro anti-leishmanial activity against promastigote form of the Leishmania major. The compound 24 exhibited an IC₅₀ of 12.20 μM in comparison to the standard drug glucantime whose IC₅₀ was 68.30 mM.

Antimicrobial activity

Garudachari et al have carried out the synthesis of 8-trifluoromethylquinoline based 1,2,3-triazoles derivatives with the help of multi-step reactions by click chemistry approach. The synthesized compounds were screened for their in vitro antimicrobial activity by well plate method (zone of inhibition). The antibacterial study was done against Escherichia coli, Bacillus subtilis and Pseudomonas aeruginosa and the antifungal study was done against Aspergillus flavus, Chrysosporium keratinophilum and Candida albicans. The results of the antibacterial study showed that the compound 25 exhibited a zone of inhibition of 14 mm in comparison to ciprofloxacin which showed a zone of inhibition of 22 mm against Escherichia coli. The antifungal study showed that the compound 26 displayed a zone of inhibition of 9 mm as compared to fluconazole which showed a 13 mm zone of inhibition against Aspergillus flavus.

Bebeheini et al have synthesized a series of novel indole containing 1, 2, 3-triazole, pyrazole and pyrazolo[1,5-alpyrimidine derivatives and screened them for their antimicrobial activities. The antimicrobial activity was done against Gram negative bacteria, Gram positive bacteria and Yeast. The compound 27 exhibited a zone of inhibition of 9.3 mm against B. subtilis.

Abdel-Wahab et al have carried out the synthesis of novel pyrazolyl-1,2,3-triazoles and 1,2,3-triazol-4-yl-pyrazolylthiazoles using 1-tolyl-4-acetyl-5-methyl-1,2,3-triazole as a precursor through a series of multistep reactions. The compound 28 was found to exhibit MIC of 8.25μg/ml against S. aureus.

Antiviral activity

Piotrowska et al have reported the synthesis and the antiviral activity of novel isoxazolidine nucleotide analogues with a 1, 2, 3-triazole linker. The synthesized 1, 2, 3-triazole based isoxazolidine phosphonates were evaluated for their in vitro activity against a variety of DNA and RNA viruses. However the synthesized compound 29 exhibited cyostatic activity at a higher micromolar range.

He et al have carried out the synthesis of novel 1, 2, 3-triazole-containing derivatives of rupestonic acid and screened them for their antiviral activity against influenza virus using oseltamivir and ribavirin as the standard drug. The compound 30 exhibited an IC₅₀ of 2.82 μg/ml against the Anti-influenza A virus (Strain A/FM/1/47/H1N1) as compared to oseltamivir whose IC₅₀ was 2.81 μg/ml.
Jordaño et al have synthesized N-amino-1,2,3-triazole derivatives i.e. 1-(4-substituted-phenylamino)-5-methyl-1H-[1,2,3]-triazole-4-carboxylic acid hydrazides and 1- (substitutedphenylamino)-5-methyl-1H-[1,2,3]-triazole-4- carboxylic acid ethyl esters and screened them against Cantagalo virus replication. The compound 31 exhibited an inhibition of 55.70% on the virus progeny production [55].

Silva et al have carried out the synthesis and the in vitro HIV-RT inhibitory activity of 1-benzyl-1H-1, 2, 3-triazole derivatives of carbohydrates. The compounds 32 and 33 exhibited a CC_{50} (μM) 837.5 and 724.06 as compared to the standard drug AZT whose CC_{50} was found to be 126.00 [56].

### Antibacterial activity

Bengtsson et al used Sonogashira couplings followed by Huisgen 1, 3-dipolar cycloadditions to synthesize fused 2-pyridone based 1,2,3-triazoles. The synthesized compounds were evaluated for their antibacterial activity by whole cell pili dependent biofilm assay. The compound 34 showed a potent antibacterial activity with an EC_{50} of 9μM [57].

Phillips et al have synthesized novel 5-(4-methyl-1, 2, 3-triazole)methyl oxazolidinones and screened them for their in vitro antibacterial activity against the Gram-positive and Gram-negative bacteria using linezolid and vancomycin as standard. The compound 35 exhibited MIC (μg/ml) of 4.00 [58].

Wang et al have synthesized sulfanilamide based 1, 2, 3-triazoles and screened them for their in vitro antibacterial (S. aureus, B. subtilis, E. coli, P. aeruginosa) and antifungal (C. albicans and C. mycoderma) activities. The compounds 36 exhibited MIC (μg/ml) of 256 against C. albicans and 64 against S. aureus respectively [59].

### Miscellaneous

Indoleamine 2, 3-dioxygenase 1 (IDO1) is an important target used for the treatment of diseases such as cancer [60]. IDO1 catalyzes the initial and rate limiting step in the catabolism of tryptophan (Trp) involved in the kynurenine pathway [61]. By depleting Trp and accumulating Trp catabolites, IDO1 exerts a local immunosuppressive effect on T lymphocytes and its inhibition may enhance the effectiveness of cancer treatments [62-64]. Röhrig et al have designed the synthesis of 4-Aryl-1, 2, 3-triazoles as the inhibitors of indoleamine 2,3-dioxygenase 1. The compound 37 was found to be the most potent with an IC_{50} value of 80 nM in a cellular assay on hIDO1, 2 nM in an assay on mIDO1, 330 nM and 71 nM respectively in an enzymatic assay on hIDO1 at pH 6.5 and pH 7.4 [65].

Bakunov et al have synthesized sixty novel dicarboxylic 1, 2, 3-triazoles by the Pinner method from the corresponding dinitriles, using copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The synthesized compounds were screened for their in vitro antiproteozal activity against Trypanosoma brucei rhodesiense, Plasmodium falciparum and Leishmania donovani. Eight of the synthesized compounds exhibited antiproteozal activity with IC_{50} values below 10 nM. The compound 38 exhibited potent antiplasmodial activity with IC_{50} value of 0.6 nM [66].

Olesen et al have synthesized 1-(Aminofurazan-3-yl)-5-dialkylaminomethyl-1H-[1, 2, 3] triazole-4-carboxylic acid derivatives as selective GSK-3 inhibitors. Glycogen synthase kinase-3 (GSK-3) is a protein-serine kinase involved in the hormonal control of several regulatory proteins. It helps in the phosphorylation and inactivation of glycogen synthase, the regulatory enzyme of glycogen synthesis in mammals. The synthesized compounds were...
screened in a GSK-3 inhibition assay at 100 μM ATP giving IC_{50} in the range from 0.1 to 10 μM. The compound 39 exhibited a potent GSK-3 inhibition with an IC_{50} value of 0.10 μM [67].

Simone et al have done the in silico molecular docking study and synthesized 1, 2, 3-triazoles and screened them for their inhibitory activity against microsomal prostaglandin E2 synthase which helps in the activation of 1, 5-lipoxgenase and 5-lipoxynase. The compounds 40 and 41 exhibited an IC_{50} value of 3.2 μM against mPGES-1 and IC_{50} of 0.4 μM on 5-LOX protein respectively [68].

Endopeptidase (NEP) is an enzyme responsible for the female sexual arousal disorder.

Pryde et al have carried out the synthesis of a library of compounds as endopeptidase (NEP) inhibitors. The compound 42 exhibited potent activity of 82 nm against NEP [69].

Acknowledgements

The authors thank Dr. G.N. Qazi, Vice-Chancellor, Jamia Hamdard for providing necessary research facilities to the Department of Chemistry. One of the authors (SH) is also thankful to CSIR for awarding the senior research fellowship.

Conflict of interest

The authors declare that there is no conflict of interest.

References


30. Freeze S, Norris P. Synthesis of carbohydrate-derived 1,2,3-triazoles using 1,3-dipolar cycloaddition on a soluble polymer support. Heterocycles 1999; 51: 1807-1817.


48. Guimarães TT, Pinto FR, Lanza JS, Melo MN, Monte-Neto RL, Melo IMM, et al. Potent naphthoquinones against antimyoglobin-sensitive and -resistant Leishmania parasites: Synthesis of


52. Abdel-Wahab BF, Latif EA, Mohamed HA, Awad GEA. Design and synthesis of new 4-pyrazolin-3-yl-1,2,3-triazoles and 1,2-3-triazol-4-yl-pyrazolin-1-ylthiazoles as potential antimicrobial agents. Eur J Med Chem 2012; 52: 263-268.


54. HeYW, Dong CZ, Zhao JY, Ma L, Li YH, Aisa HA. 1,2,3-Triazole-containing derivatives of rupestronic acid: Click-chemical synthesis and antiviral activities against influenza viruses. Eur J Med Chem DOI: 10.1016/j.ejmech.2014.02.029.


