REVIEW

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.

Introduction

The medicinal chemists have considered the synthesis of 1, 2, 3-triazole based heterocycles as the corner stone 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

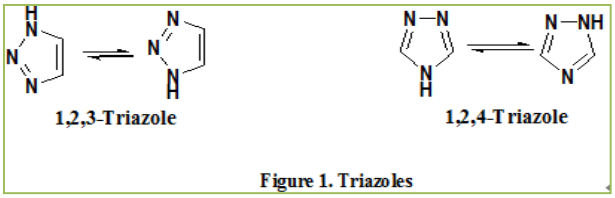


Figure 1. Triazoles

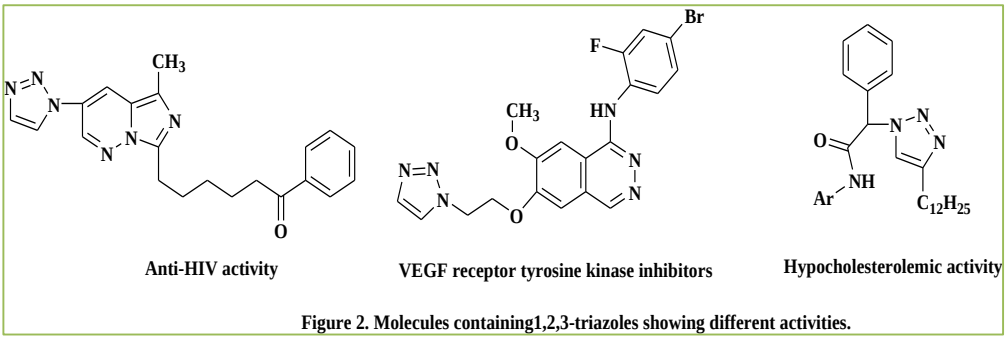


Figure 2. Molecules containing1,2,3-triazoles showing different activities.

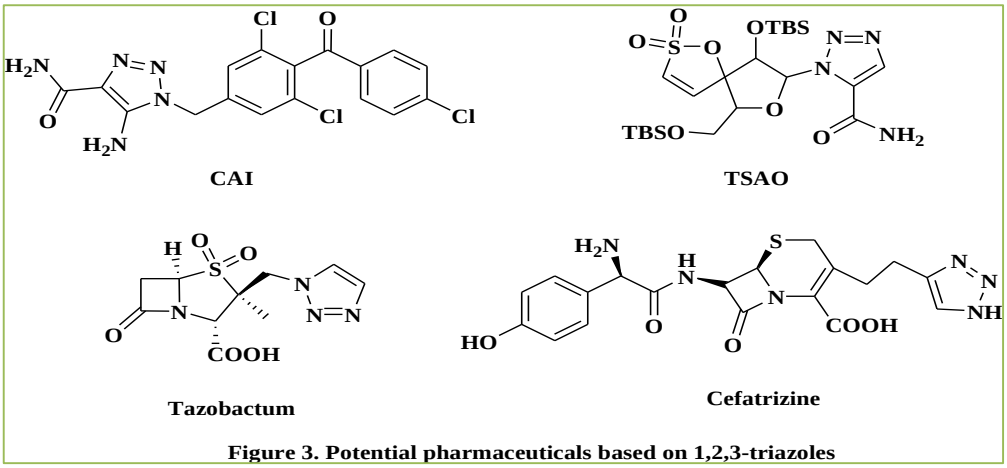


Figure 3. Potential pharmaceuticals based on 1,2,3-triazoles

of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$.

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-traizoles are shown below [17].

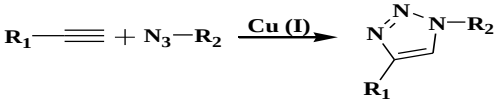
Potential pharmaceuticals (**Figure 3**) based on 1, 2, 3-triazoles include the anticancer compound carboxyamidotriazole (CAI) [18], the nucleoside derivative non-nucleoside reverse transcriptase inhibitor tert-butyldimethylsilylspiroaminooxathioledioxide (known as TSAO), β-lactum antibiotic Tazobactum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

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

Scheme 1

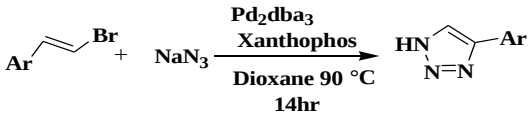
The most popular reaction that has been adapted to produce the 1, 2, 3-triazole moiety is the 1, 3-dipolar cycloaddition also known as Huisgen cycloaddition, between an azide and a terminal alkyne. Although this reaction was discovered at the start of the 20th century, its detailed mechanism was described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



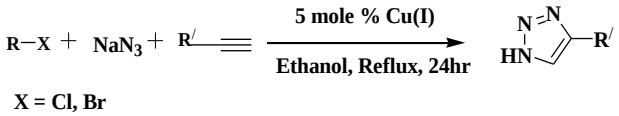
Scheme 2

A palladium catalysed synthesis of 1, 2, 3-triazoles from alkenyl halides and sodium azides added a new chapter in the Palladium chemistry [23].



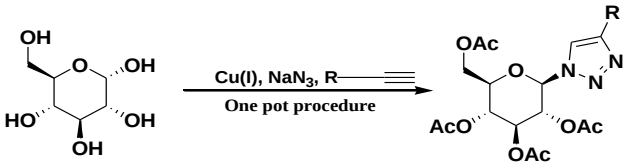
Scheme 3

The terminal alkynes 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.



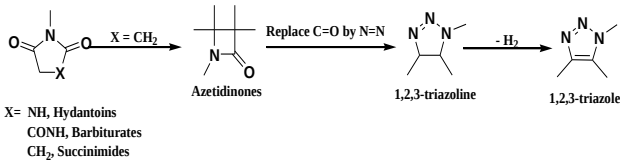
Scheme 4

An efficient one pot synthesis of 1, 2, 3-triazole linked glycoconjugates involving 1, 3-dipolar cycloaddition in 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.



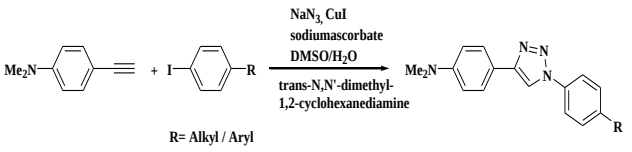
Scheme 5

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].



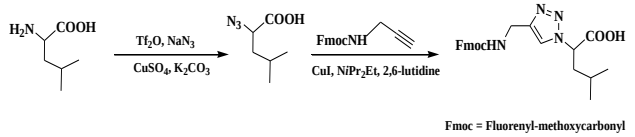
Scheme 6

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



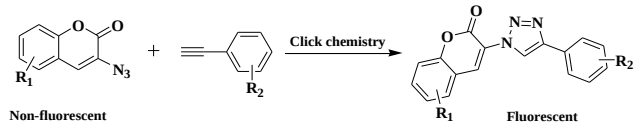
Scheme 7

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



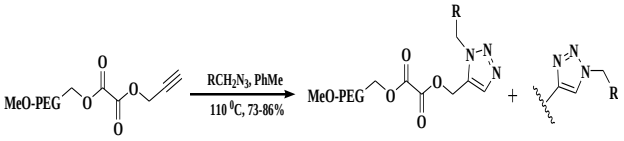
Scheme 8

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



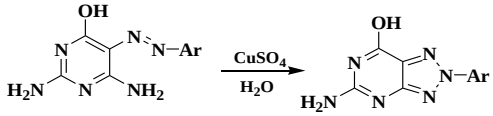
Scheme 9

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



Scheme 10

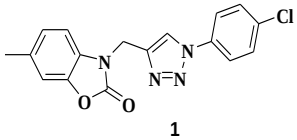
Condensed 1, 2, 3-triazoles can be synthesized by the oxidation of arylazo heterocycles having an amino group in the *ortho* position [31].

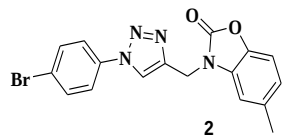


Pharmacological significance of 1, 2, 3-triazoles

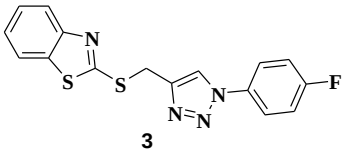
Anti-inflammatory activity

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 vivo* 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].



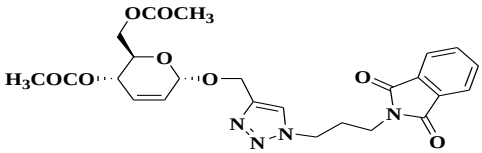


Shafi *et al* have synthesized novel bis-heterocycles encompassing 2-mercapto benzothiazole and 1, 2, 3-triazoles and evaluated them for their anti-inflammatory activity by using biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema method. The compound **3** exhibited a selective index (COX-2/COX-1) of 0.44 against celecoxib which exhibited a selective index of 0.0028 [33].



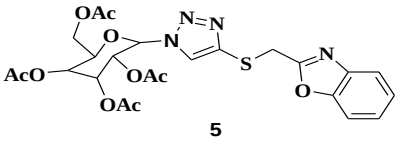
3

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].



4

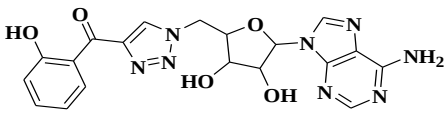
Silva *et al* carried out the synthesis and anti-inflammatory activity of novel glucosyl triazoles from a reaction of 2, 3, 4, 6-tetra-*O*-acetyl-β-D-glucopyranosyl azide and terminal alkynes using ultrasound energy. The compound **5** exhibited potent anti-inflammatory activity with an inhibition of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



5

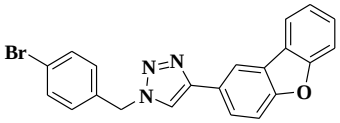
Antitubercular activity

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].



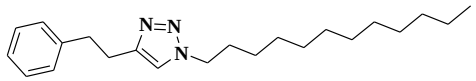
6

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].

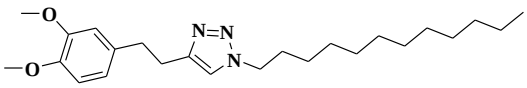


7

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].

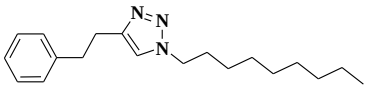


8



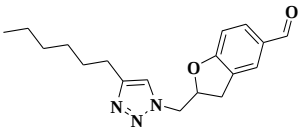
9

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].



10

Tripathi *et al* have synthesized 1, 4-disubstituted-1, 2, 3-triazoles by [3+2] cycloaddition of different 2-(azidomethyl)-dihydronaptho(benzo)furans with different alkynes and screened them against *Mycobacterium tuberculosis* H_{37}Rv. 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].

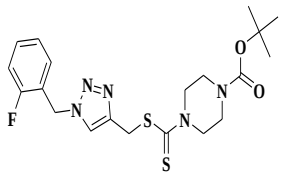


11

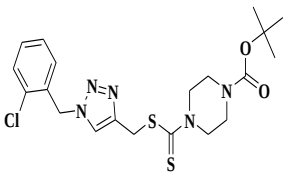
Anticancer activity

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].

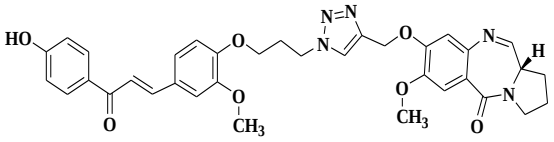


12



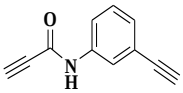
13

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].

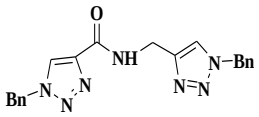


14

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].

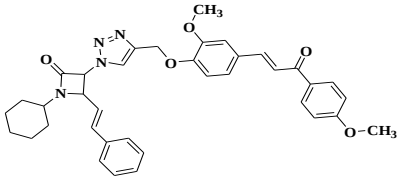


15



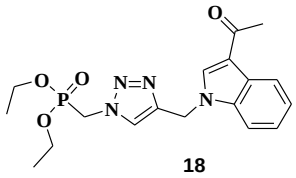
16

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].



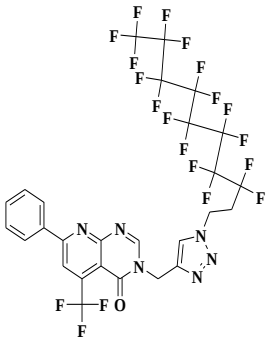
17

G1owacka *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].

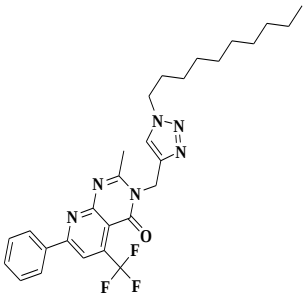


18

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].

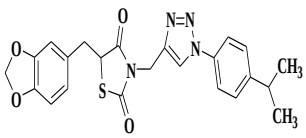


19

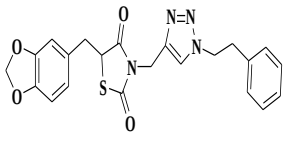


20

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].



21

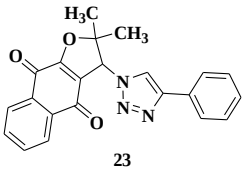


22

Antileishmanial activity

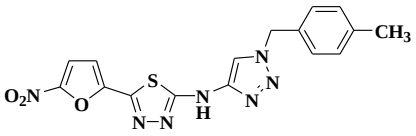
Guimarães *et al* have carried out the synthesis of ten α-lapachone-based 1,2,3-triazoles, seven 1,4-naphthoquinones coupled to 1,2,3-triazoles and five nor-β-lapachone-based 1,2,3-triazoles. These compounds were evaluated for their activity against promastigote forms of antimony-sensitive and -resistant 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 IC_{50} values were found to be in a range of 1.0 to 50.7 μM. The compound **23** exhibited an IC_{50} of 1.00 μM in comparison to the standard drug Potassium antimonyl tartrate whose IC_{50} was found to be 86.1 μM against *Leishmania infantum* [48].



23

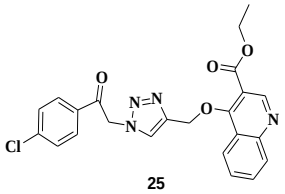
Tahghighi *et al* utilised the click chemistry approach to synthesize novel 5-(5-nitrofuran-2-yl)-1, 3, 4-thiadiazol-2-amines by introducing N-[(1-benzyl-1H-1, 2, 3-triazol-4-yl) methyl] nucleus on the C-2 amine of thiadiazole ring. The synthesized compounds were evaluated for their *in vitro* anti-leishmanial activity against promostigote form of the *Leishmania major*. The compound **24** exhibited an IC_{50} of 12.20 μM in comparison to the standard drug glucantime whose IC_{50} was 68.30 mM [49].



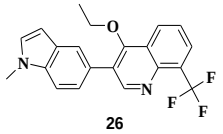
24

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* [50].

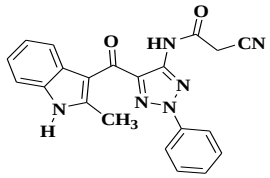


25



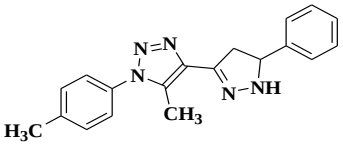
26

Behbehani *et al* have synthesized a series of novel indole containing 1, 2, 3-triazole, pyrazole and pyrazolo[1,5-a]pyrimidine 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* [51].



27

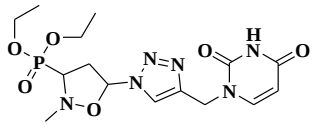
Abdel-Wahab *et al* have carried out the synthesis of novel pyrazolyl-1,2,3-triazoles and 1,2,3-triazol-4-yl-pyrazolylthiazoles using 1-tolylyl-4-acetyl-5-methyl-1,2,3-triazole as a precursor through a series of multistep reactions. The compound **28** was found to exhibit MIC of 8.25μg/ml against *S. aureus* [52].



28

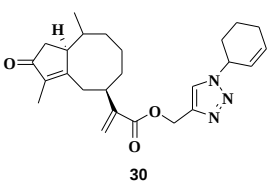
Antiviral activity

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 cytostatic activity at a higher micromolar range [53].



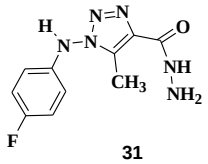
29

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 IC_{50} of 2.82 μg/ml against the Anti-influenza A virus (Strain A/FM/1/47/H1N1) as compared to oseltamivir whose IC_{50} was 2.81 μg/ml [54].



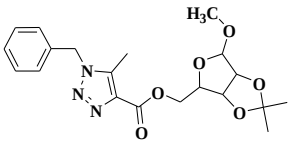
30

Jordaˇo *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].

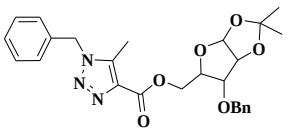


31

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].



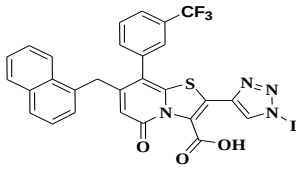
32



33

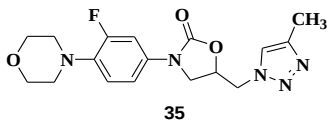
Antibacterial activity

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].



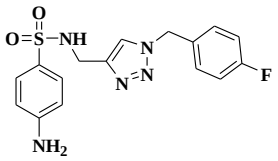
34

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].



35

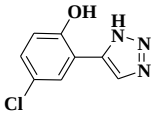
Wang *et al* have synthesized sulfanilamide based 1, 2, 3-triazoles and screened them for their *in vitro* antibacterial (*S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*) and antifungal (*C. albicans* and *C. mycoderma*) activities. The compounds **36** exhibited MIC (μg/ml) of 256 against *C.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



36

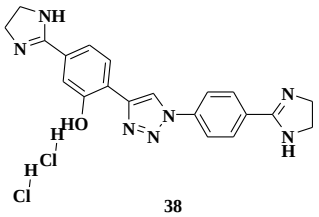
Miscellaneous

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].



37

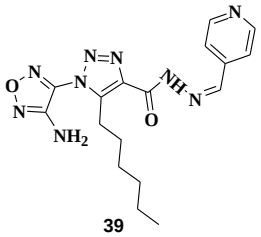
Bakunov *et al* have synthesized sixty novel dicationic 1, 2, 3-triazoles by the Pinner method from the corresponding dinitriles, using copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The synthesized compounds were screened for their *in vitro* antiprotozoal activity against *Trypanosoma brucei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



38

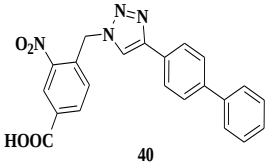
Olesen *et al* have synthesized 1-(4-Aminofurazan-3-yl)-5-dialkylaminomethyl-1*H*-[1, 2, 3] triazole-4-carboxylic acid derivatives as selective GSK-3 inhibitors. Glycogen synthase kinase-3 (GSK-3) is a protein-serine kinase involved in the hormonal control of several regulatory proteins. It helps in 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].

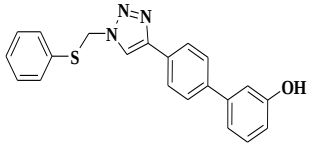


39

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-lipoxygenase and 5-lipoxygenase. The compounds **40** and **41** exhibited an IC_{50} value of 3.2 μM against mPGES-1and IC_{50} of 0.4 μM on 5-LOX protein respectively [68].



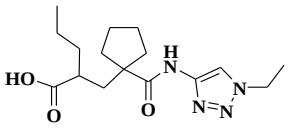
40



41

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].



42

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

1. Dalvie DK, Kalgutkar AS, Khojasteh-Bakht SC, Obach RS, Donnell JP. Biotransformation reactions of five-membered aromatic heterocyclic rings. Chem Res Toxicol 2002; 15: 269-299.
2. Bock VD, Perciaccante R, Jansen TP, Hiemstra H, Van Maarseveen JH. Click chemistry as a route to cyclic tetrapeptide analogues: synthesis of cyclo-[Pro-Val-psi(triazole)-Pro-Tyr]. Org Lett 2006; 8: 919-922.
3. Bock VD, Speijer D, Hiemstra H, Van Maarseveen JH. 1,2,3-Triazoles as peptide bond isosteres: synthesis and biological evaluation of cyclotetrapeptide mimics. Org Biomol Chem 2007; 5: 971-975.
4. Bourne Y, Kolb HC, Radic Z, Sharpless KB, Taylor P, Marchot P. Freeze-frame inhibitor captures acetylcholinesterase in a unique conformation. Proc Natl Acad Sci USA. 2004; 101: 1449-1454.
5. Whiting M, Muldoon J, Lin YC, Silverman SM, Lindstron W, Olson AJ, *et al*. Inhibitors of HIV-1 protease by using in situ click chemistry. Angew Chem Int Ed 2006; 45: 1435-1439.
6. Horne WS, Yadav MK, Stout CD, Ghadiri MR. Heterocyclic peptide backbone modifications in an alpha-helical coiled coil. J Amer Chem Soci 2004; 126: 15366-15367.
7. Kolb HC, Finn MG, Sharpless KB. Click Chemistry in Glycoscience: New Developments and Strategies. Angew Chem Int Ed 2001; 40: 2004-2021.
8. Kolb HC, Finn MG, Sharpless KB. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. Angew Chem 2001; 113: 2056-2075.
9. Pieters RJ, Rijkers DTS, Liskamp RMJ.Application of the 1.3-Dipolar cycloaddition reaction in chemical biology: approaches towards multivalent carbohydrate and peptide and peptide based polymers. QSAR Comb Sci 2007; 26: 1181-1190.
10. Nuzzi A, Massi A, Dondoni A. Model Studies Toward the Synthesis of Thymidine Oligonucleotides with Triazole Internucleosidic Linkages Via Iterative Cu(I)-Promoted Azide-Alkyne Ligation Chemistry. QSAR Comb Sci 2007; 26: 1191-1199.
11. Neil EJO, DiVittorio KM, Smith BD. Phosphatidylcholine-derived bolaamphiphiles via click chemistry. Org Lett 2007; 9: 199-202.
12. Gierlich J, Burley GA, Gramlich PME, Hammond DM, Carell T. Click chemistry as a reliable method for the high-density postsynthetic functionalization of alkyne-modified DNA. Org Lett 2006; 8: 3639 -3642.
13. Tron GC, Pirali T, Billington RA, Canonico PL, Sorba G, Genazzani AA. Click chemistry reactions in medicinal chemistry: applications of the 1,3-dipolar cycloaddition between azides and alkynes. Med Res Rev 2008; 28: 278-308.
14. Wang P, Du J, Rachakonda S, Byoung-Kwon C, Tharnish PhM, Stuyver LJ, *et al*. Synthesis and structure-activity relationships of novel anti-hepatitis C agents: N3,5'-cyclo-4-(beta-D-ribofuranosyl)-vic-triazolo[4,5-b]pyridin-5-one derivatives. J Med Chem 2005; 48: 6454-6460.
15. Betti L, Biagi G, Giannaccini G, Giorgi I, Livi O, Lucacchini A, *et al*. Novel 3-aralkyl-7-(amino-substituted)-1,2,3-triazolo[4,5-d]pyrimidines with high affinity toward A1 adenosine receptors. J Med Chem 1998; 41: 668-673.
16. Biagi G, Giogi I, Livi O, Scartoni V, Betti L, Giannaccini G, *et al*. New 1,2,3-triazolo[1,5-a]quinoxalines: synthesis and binding to benzodiazepine and adenosine receptors. II. Eur J Med Chem 2002; 37: 565-571.
17. Sandip GA, Suleman RM, Vandana SP. Click chemistry: 1,2,3-triazoles as pharmacophores. Chem Asian J 2011; 6: 2696-2718.

18. Soltis MJ, Yeh HJ, Cole KA, Whittaker N, Wersto RP, Kohn EC. Identification and characterization of human metabolites of CAI [5-amino-1-1(4'-chlorobenzoyl-3,5-dichlorobenzyl)-1,2,3-triazole- 4-carboxamide). Drug Metab Dispos 1996; 24: 799-806.
19. Sheng C, Zhang W. New lead structures in antifungal drug discovery. Curr Med Chem 2011; 18: 733-766.
20. Huisgen R, Guenter S, Leander M. 1.3-Dipolare cycloadditionen,XXXII. Kinetik der additionen organischer azide an CC-mehrfachbindungen. Chem Ber 1967; 100: 2494-2507.
21. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. A stepwise huisgen cycloaddition process: copper (I)-catalyzed regioselective "ligation" of azides and terminal alkynes. Angew Chem Int Ed 2002; 41: 2596-2599.
22. Dorner S, Westermann B. A short route for the synthesis of “sweet” macrocycles via a click-dimerization-ring-closing metathesis approach. Chem Commun 2005; 14: 2852-2854.
23. Barluenga J, Valdes C, Beltran G, Escribano M, Anzar F. Developments in Pd catalysis: synthesis of 1H-1,2,3-triazoles from sodium azide and alkenyl bromides. Angew Chem Int 2006; 45: 6893-6896.
24. Miaoa T, Wang L. Regioselective Synthesis of 1,2,3-Triazoles by Use of a Silica-Supported Copper(I) Catalyst Synthesis 2008; 14: 363-368.
25. Srinivas C, Xie F, Qian W. One-pot synthesis of triazole-linked glycoconjugates. Tetra Lett 2005; 13: 2331-2336.
26. Pankaja KK. Triazolines. 14. 1,2,3-Triazolines and triazoles, a new class of anticonvulsants. Drug design and structure-activity relationships. J Med Chem 1988; 31: 196-203.
27. Watzke A, Kohn M, Gutierrez-Rodriguez M, Wacker R, Schroder H, Breinbauer R. Site Selective Protein Immobilization by Staudinger-Ligation. Angew Chem 2006; 118: 1436-1440.
28. Horne WS, Stout CS, Ghadiri MR. A heterocyclic peptide nanotube**.** J Am Chem Soc 2003; 125: 9372-9376.
29. Pore VS, Aher NG, Kumar M, Shukla PK. Design and synthesis of fluconazole/bile acid conjugates using click reaction. Tetrahedron 2006; 62: 11178-11186.
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.
31. Boyer J. Monocyclic Triazoles and Benzotriazoles, in: R. Elderfield (editor), Heterocyclic Compounds [Russian translation], Vol. 7, Izd. Mir, Moscow (1965), p. 296.
32. Haider S, Alam MS, Hamid H, Shafi S, Nargotra A, Mahajan P, *et al*. Synthesis of novel 1,2,3-triazole based benzoxazolinones: Their TNF-a based molecular docking with in-vivo anti-inflammatory, antinociceptive activities and ulcerogenic risk evaluation. Eur J Med Chem 2013; 70: 579-588.
33. Shafi S, Alam MM, Mulakayala N, Mulakayala C, Vanaja G, Kalle AM *et al*. Synthesis of novel 2-mercapto benzothiazole and 1,2,3-triazole based bis-heterocycles: Their anti-inflammatory and anti-nociceptive activities. Eur J Med Chem 2012; 49: 324-333.
34. Assis SPO, da Silva MT, de Oliveira RN, Lima VLM. Synthesis and Anti- Inflammatory Activity of New Alkyl-Substituted Phthalimide 1H-1,2,3-Triazole Derivatives. The Sci World J. doi:10.1100/2012/925925.
35. Silva GB, Guimarães BM, Assis SPO, Lima VLM, Oliveira RN. Ultrasound-Assisted Synthesis of 1-N-β-D-Glucopyranosyl-1H-1,2,3-triazole Benzoheterocycles and their Anti-Inflammatory Activities. J Braz Chem Soc 2013; 24: 914-921.
36. Somu RV, Boshoff H, Qiao C, Bennett EM, Barry CE, Aldrich CC. Rationally designed nucleoside antibiotics that inhibit siderophore biosynthesis of Mycobacterium tuberculosis. J Med Chem 2006; 49: 31-34.
37. Yempala T, Sridevi JP, Yogeeswari P, Sriram D, Kantevari S. Rational design and synthesis of novel dibenzo[b,d]furan-1,2,3-triazole conjugates as potent inhibitors of Mycobacterium tuberculosis. Eur J Med Chem 2014; 71: 160-167.
38. Menendez C, Chollet A, Rodriguez F, Inard C, Pasca MR, Lherbet C. Chemical synthesis and biological evaluation of triazole derivatives as inhibitors of InhA and antituberculosis agents. Eur J Med Chem 2012; 52: 275-283.
39. Menendez C, Gau S, Lherbet C, Rodriguez F, Inard C, Pasca MR *et al*. Synthesis and biological activities of triazole derivatives as inhibitors of InhA and antituberculosis agents. Eur J Med Chem 2011; 46: 5524-5531.
40. Tripathi RP, Yadav AK, Ajay A, Bisht SS, Chaturvedi V, Sinha SK. Application of Huisgen (3 þ 2) cycloaddition reaction: Synthesis of 1-(2,3-dihydrobenzofuran-2-yl-methyl [1,2,3]-triazoles and their antitubercular evaluations. Eur J Med Chem 2010; 45: 142-148.
41. Duan YC, Ma YC, Zhang En, Shi XJ, Wang MM, Ye XW, *et al*. Design and synthesis of novel 1,2,3-triazole-dithiocarbamate hybrids as potential anticancer agents. Eur J Med Chem 2013; 62: 11-19.
42. Kamal A, Prabhakar S, Ramaiah MJ, Reddy PV, Reddy CR, Mallareddy A, *et al*. Synthesis and anticancer activity of chalcone-pyrrolobenzodiazepine conjugates linked via 1,2,3-triazole ring side-armed with alkane spacers. Eur J Med Chem 2011; 46: 3820-3831.
43. Elamari H, Slimi R, Chabot GG, Quentin L, Scherman D, Girard C. Synthesis and in vitro evaluation of potential anticancer activity of mono- and bis-1,2,3-triazole derivatives of bis-alkynes. Eur J Med Chem 2013; 60: 360-364.
44. Singh P, Raj R, Kumar V, Mahajan MP, Bedi PMS, Kaur T, *et al*. 1,2,3-Triazole tethered β-lactam-Chalcone bifunctional hybrids: Synthesis and anticancer evaluation. Eur J Med Chem 2012; 47: 594-600.
45. G1owacka IE, Balzarini J, Wróblewski AE. The synthesis, antiviral, cytostatic and cytotoxic evaluation of a new series of acyclonucleotide analogues with a 1,2,3-triazole linker. Eur J Med Chem 2013; 70: 703-722.
46. Kurumurthy C, Rao PS, Swamy BV, Kumar GS, Rao PS, Narsaiah B, *et al*. Synthesis of novel alkyltriazole tagged pyrido[2,3-d]pyrimidine derivatives and their anticancer activity. Eur J Med Chem 2011; 46: 3462-3468.
47. Chinthala Y, Domatti AK, Sarfaraz A, Singh SP, Arigari NK, Gupta N, *et al*. Synthesis, biological evaluation and molecular modeling studies of some novel thiazolidinediones with triazole ring. Eur J Med Chem 2013; 70: 308-314.
48. Guimarães TT, Pinto FR, Lanza JS, Melo MN, Monte-Neto RL, Melo IMM, *et al*. Potent naphthoquinones against antimony-sensitive and -resistant Leishmania parasites: Synthesis of

novel α- and nor- α -lapachone based 1,2,3-triazoles by copper-catalyzed azide-alkyne cycloaddition. Eur J Med Chem 2013; 63: 523-530.

49. Tahghighi A, Razmi S, Mahdavi M, Foroumadi P, Ardestani SK, Emami S, *et al*. Synthesis and anti-leishmanial activity of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines containing N-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] moieties. Eur J Med Chem 2012; 50: 124-128.
50. Garudachari B, Isloor AM, Satyanarayana MN, Fun HK, Hegde G. Click chemistry approach: Regioselective one-pot synthesis of some new 8-trifluoromethylquinoline based 1,2,3-triazoles as potent antimicrobial agents. Eur J Med Chem 2014; 74: 324-332.
51. Behbehani H, Ibrahim HM, Makhseed S, Mahmoud H. Applications of 2- arylhydrazononitriles in synthesis: Preparation of new indole containing 1,2,3-triazole, pyrazole and pyrazolo[1,5-a]pyrimidine derivatives and evaluation of their antimicrobial activities. Eur J Med Chem 2011; 46: 1813-1820.
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.
53. Piotrowska DG, Balzarini J, Glowacka IE. Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a 1,2,3-triazole linker. Eur J Med Chem 2012; 47: 501-509.
54. He YW, Dong CZ, Zhao JY, Ma L, Li YH, Aisa HA. 1,2,3-Triazole-containing derivatives of rupestonic acid: Click-chemical synthesis and antiviral activities against influenza viruses. Eur J Med Chem DOI: 10.1016/j.ejmech.2014.02.029.
55. Jorda˜o AK, Afonso PP, Ferreira VF, Souza MCBV, Almeida MCB, Beltrame CO, *et al*. Antiviral evaluation of N-amino-1,2,3-triazoles against Cantagalo virus replication in cell culture. Eur J Med Chem 2009; 44: 3777-3783.
56. Silva F, Souza MCBV, Frugulhetti IIP, Castro HC, Souza SL, Souza TM, *et al*. Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. Eur J Med Chem 2009; 44: 373-383.
57. Bengtsson C, Lindgren AEG, Uvell H, Almqvist F. Design, synthesis and evaluation of triazole functionalized ring-fused 2-pyridones as antibacterial agents. Eur J Med Chem 2012; 54: 637-646.
58. Phillips OA, Udo EE, Hamid MEA, Varghese R. Synthesis and antibacterial activity of novel 5-(4-methyl-1H-1,2,3-triazole) methyl oxazolidinones. Eur J Med Chem 2009; 44: 3217-3227.
59. Wang XL, Wan K, Zhou CH. Synthesis of novel sulfanilamide-derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities. Eur J Med Chem 2010; 45: 4631-4639.
60. Yamamoto S, Hayaishi O. Tryptophan pyrrolase of rabbit intestine. D- and L-tryptophan-cleaving enzyme or enzymes. J Biol Chem 1967; 242: 5260-5266.
61. Sono M, Roach M, Coulter E, Dawson J. Heme-Containing Oxygenases. Chem Rev 1996; 96: 2841-2888.
62. Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, Brown C, Mellor AL. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science 1998; 281: 1191-1193.
63. Hwu P, Du MX, Lapointe R, Do M, Taylor MW, Young HA. Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation. J Immunol 2000; 164: 3596-3599.
64. Terness P, Bauer TM, Röse L, Dufter C, Watzlik A, Simon H, *et al*. Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: mediation of suppression by tryptophan metabolites. J Exp Med 2002; 196: 447-457.
65. Rohrig UF, Majjigapu SR, Grosdidier AL, Bron S, Stroobant V, Pilotte L, *et al*. Rational Design of 4-Aryl-1,2,3-Triazoles for Indoleamine 2,3-Dioxygenase 1 Inhibition. J Med Chem 2012; 55: 5270-5290.
66. Bakunov SA, Bakunova SM, Wenzler T, Ghebru M, Werbovetz KA, Brun R, *et al*. Synthesis and Antiprotozoal Activity of Cationic 1,4-Diphenyl-1H-1,2,3-triazoles. J Med Chem 2010; 53: 254-272.
67. Olesen PH, Sørensen AR, Ursø B, Kurtzhals P, Bowler AN, Ehrbar U, *et al*. Synthesis and in Vitro Characterization of 1-(4-Aminofurazan-3-yl)-5-dialkylaminomethyl-1H-[1,2,3]triazole-4-carboxylic Acid Derivatives. A New Class of Selective GSK-3 Inhibitors. J Med Chem 2003; 46: 3333-3341.
68. Simone RD, Chini MG, Bruno I, Riccio R, Mueller D, Werz O, *et al*. Structure-Based Discovery of Inhibitors of Microsomal Prostaglandin E2 Synthase-1, 5-Lipoxygenase and 5-Lipoxygenase-Activating Protein: Promising Hits for the Development of New Anti-inflammatory Agents. J Med Chem 2011; 54: 1565-1575.
69. Pryde DC, Maw GN, Planken S, Platts MY, Sanderson V, Corless M, *et al*. Novel selective inhibitors of neutral endopeptidase for the treatment of female sexual arousal disorder. Synthesis and activity of functionalized glutaramides. J Med Chem 2006; 49: 4409-4424.