JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A review on the recent advancements in biological activity of triazoles and tetrazoles

P. M. Jadhav* & Premkumar R. Mali

*Department of Chemistry, Shri Muktanand College, Gangapur, Aurangabad (MS) India.
Department of Chemistry, Agasti Arts, Commerce and Dadasaheb Rupwate Science College, Akole, Dist - Ahemednagar, (MS) India.
***Corresponding author email**: jadhavpm767@gmail.com

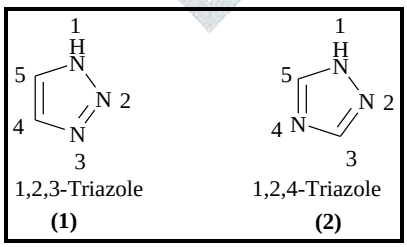
Abstract:

Triazoles and tetrazoles are the biologically significant five-membered heterocycles constituting the skeletons of several commercially marketed drugs and other heterocyclic compounds having a diverse range of biological activities including antimicrobial, antioxidant, anticancer, antidiabetic, and another potential. This review accounts for the recent advancements in biological activities of triazoles and tetrazoles derivatives.

Keywords: Biological activity, Triazoles, Tetrazoles, Nanocatalyst

Introduction:

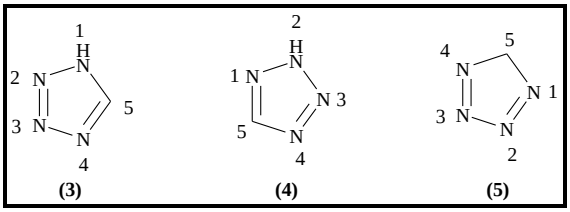
Triazole is a five-membered heterocyclic compound bearing three nitrogen and two carbon atoms. It exists in two isomeric forms - 1, 2, 3-triazole (**1**) and 1, 2, 4-triazole (**2**). The 1, 2, 3 isomer contains the three nitrogen atoms adjacent to one another, whereas, the 1, 2, 4 isomer possesses the two nitrogen atoms adjacent to each other, and the third nitrogen is present between the two carbon atoms.



1,2,3-triazole and its derivatives are well documented for various biological activities such as antimicrobial, analgesic, anti-HIV, anti-inflammatory, anti-allergic, anticancer, antimalarial, and anti-tubercular[1,2]. The 1,2,4-triazoles also play an important role in medicinal chemistry possessing various biological activities such as antimicrobial, antimalarial, anticancer, antioxidant, and antimycotic activities[3]. The triazole ring has been proven medicinally important scaffold in terms of various commercially marketed drugs

such as alprazolam, rizatriptan, trazodone, hexaconazole, and so on. Thus the small triazole nucleus bears several biological activities and remained a privileged scaffold for medicinal chemists.

Tetrazoles are the heterocyclic compounds possessing a 5-membered ring comprised of four nitrogen atoms and one carbon atom existing in three different isomeric forms (**3**), (**4**), (**5**):



The heterocyclic compounds bearing tetrazole moiety have attracted the attention of medicinal and organic chemists due to their unique structure in various antihypertensive, anti-allergic, antibiotic, and anticonvulsant agents[4-5]. These tetrazoles also find extensive applications in photography, recording systems, as well as biological sciences[6-7].

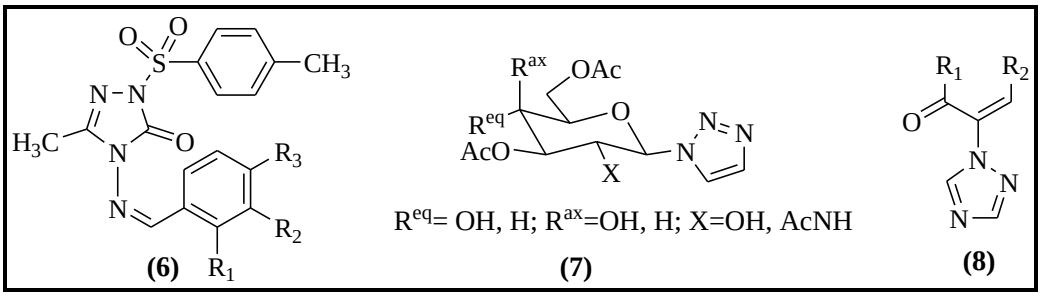
Structural modifications of the triazole and tetrazole rings can lead to improving biological activities with improved potency and lesser toxicity. The present chapter provides an overview of recent updates in the biological potential and various methods for the synthesis of triazole and tetrazole based heterocycles using nanomaterials as catalysts.

Biological significance of triazoles and tetrazoles:

The Schiff bases of 4-amino-1, 2, 4-triazoles (**6**) were synthesized by the condensation of 4-amino-1, 2, 4-triazol-3-ones with aromatic aldehydes under ultrasound irradiation and documented for antioxidant activity by the DPPH method. The DPPH inhibition values of the compounds were found in the range of 71.2 to 96.4% at 1.20 μM concentration. Molecular docking of the synthesized compounds with the active site of ACE revealed good inhibitory effects of the triazole Schiff's bases[8].

The glycosyl 1, 2, 3-triazoles (**7**) were synthesized by reaction of the corresponding azides with vinyl acetate under microwave irradiation. It was found that the deprotected glucosyl and galactosyl triazoles did not display inhibitory activity at 1 mM. Among the screened samples, the GlcNAc-triazole was found to be hydrolyzed by *Talaromyces flavus* CCF 2686 β-N-acetylhexosaminidase. Furthermore, the β-GlcNAc triazole acted as a strong ligand of rat and human natural killer cell-activating receptors[9].

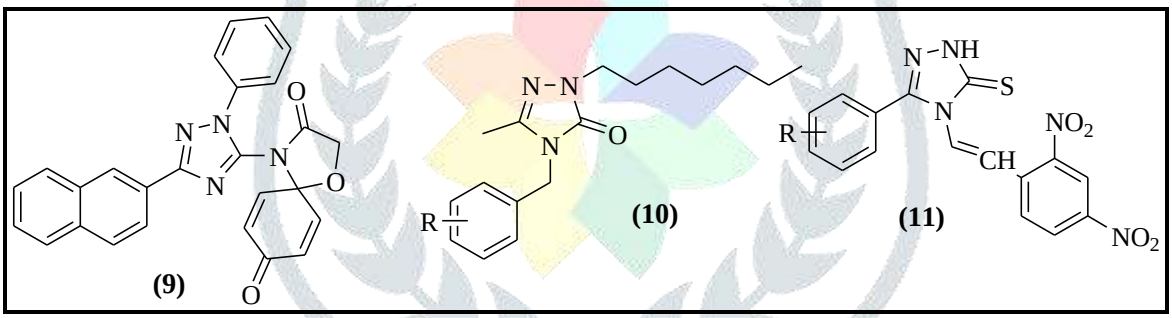
The 1,2,4-triazoles (**8**) were evaluated for antimicrobial activity by Stingaci *et al.* The compounds were highly active against *Xanthomonas campestris.* The antifungal activity of these compounds was found to be better than the reference drugs[10].



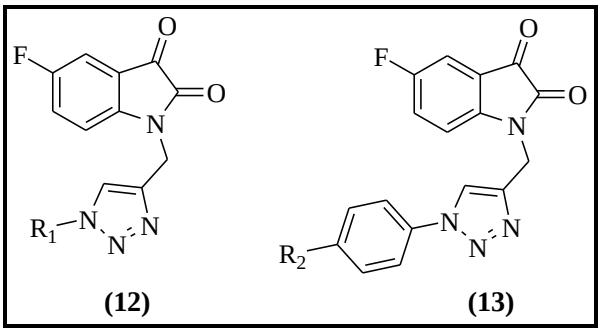
1, 2, 4-triazole-spirodienone (**9**) was found as a promising pharmacophore for anticancer activity. It showed a remarkable *in vitro* cytotoxic activity by arresting the cell cycle and showed induction in apoptosis in MDA-MB-231 cells[11].

The 1, 2, 4-triazoles (**10**) were evaluated for tyrosinase inhibition potential by S. Akin *et al*. The inhibition mechanism of these compounds was reversible and uncompetitive on the tyrosinase activity. The most promising compound was found to bind weakly with the receptor via interactions with His244, His263, Phe264, and Val283[12].

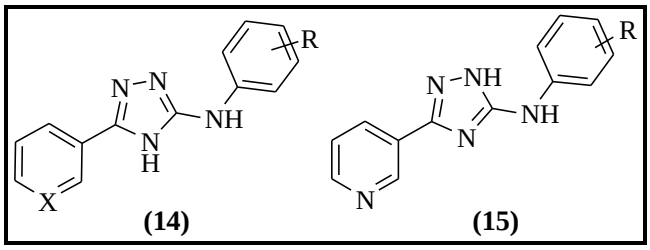
The Schiff bases containing 1, 2, 4-triazole-3(4H)-thione (**11**) were documented for antifungal activity. These compounds were observed to be more effective against *Wheat gibberellic* as compared to the fluconazole standard. The more active compounds were evaluated for enzyme inhibition efficacy against the receptor CYP51 by docking[13].



The 1H-1,2,3-triazol-4-yl indoline-2,3-diones (**12**), (**13**) were found to be highly active against *S. Epidermidis*, *B. Subtilis*, *E. Coli*, & *P. Aeruginosa* bacterial strains. Some of them exhibited better antifungal potential than the standard Fluconazole against *A. Niger* and *C. Albicans.* Results demonstrated the key role of the triazole unit in these compounds for high antimicrobial activities[14].



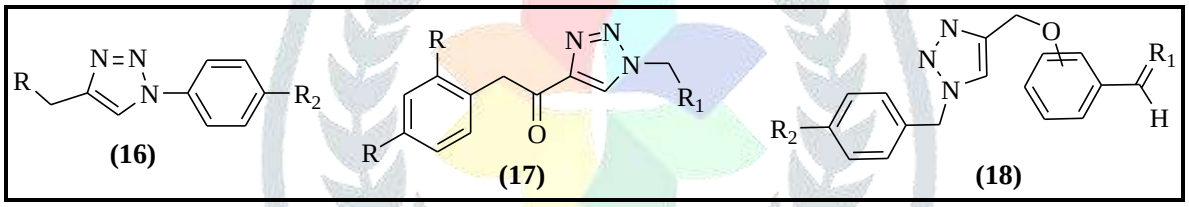
The 3-amino-1, 2, 4-triazole scaffold containing compounds (**14**) and (**15**) were evaluated for anticancer activity against cancer cell lines using MTT assay. In addition, these compounds exhibited good anti-angiogenic activity indicating their highly promising dual anticancer activity [15].



The 1, 2, 3-triazoles (**16**) were synthesized via azide-alkyne click chemistry approach and evaluated for anti-leishmanial activity against the promastigote form of *Leishmania donovani*. Three of these compounds were identified for a promising antileishmanial activity and were non-cytotoxicity towards macrophage cells. The molecular docking study supported good interactions with the key residues in the catalytic site of trypanothione reductase[16].

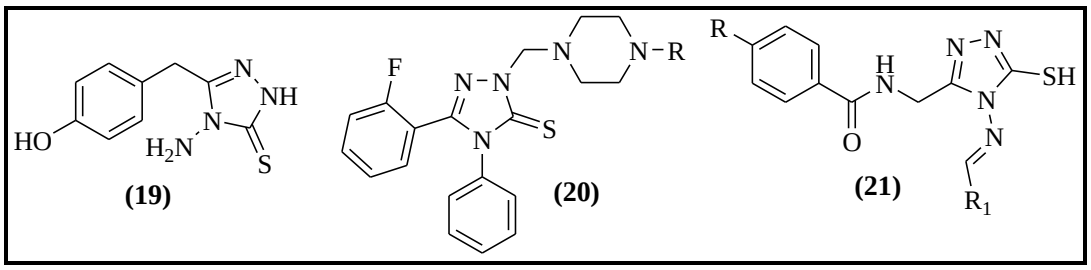
The 1,4-disubstituted triazole or a-ketotriazole (**17**) derivatives synthesized by the copper-catalyzed [3+2] cycloaddition of alkynes with different azides bearing a lipophilic chain mimicking the substrate were able to inhibit InhA. One of the compounds exhibited a minimum inhibitory concentration inferior to 2 mg/mL against *Mycobacterium tuberculosis* H37Rv [17].

The disubstituted-1, 2, 3-triazole-thiosemicarbazone hybrid molecules (**18**) exhibited an excellent potency result for *B. Subtilis* and *P. Aeruginosa* bacterial strains as compared to reference drug ciprofloxacin. Antibacterial activity results were supported by molecular docking and DFT studies[18].



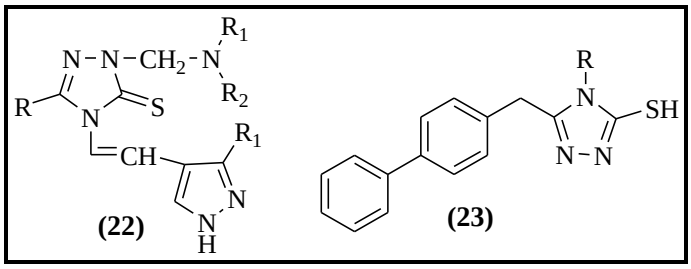
The triazoles (**19**) were reported for an inhibitory potential of cyclin-dependent kinase 5 enzyme [19]. The fluorine and piperazine moiety bearing 1,2,4-triazole thione derivatives (**20**) synthesized by the Mannich reaction of triazole intermediates, substituted piperazines, and formaldehyde was documented for significant fungicidal activity against *Cercospora arachidicola*, *Physalospora piricola*, and *Rhizoctonia cerealis* at 50 mg/mL[20].

The Schiff bases of 1, 2, 4-triazole derivatives (**21**) synthesized by the condensation of *N*-[(4-amino-5-sulfanyl-4*H*-1, 2, 4-triazol-3-yl)methyl]-4-substituted-benzamides with various aldehydes exhibited a good antibacterial and antifungal activity[21].

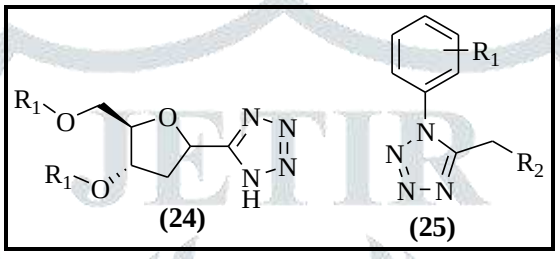


The 1, 2, 4-triazole-3(4H)-thiones (**22**) were screened for antibacterial and antifungal activity by A. M. Isloor *et al*. Some of the compounds were found to exhibit significant antimicrobial activity[22].

Khan *et al.* developed the triazole heterocyclic derivatives (**23**) for analgesic, ulcerogenic and anti-inflammatory activity[23] .

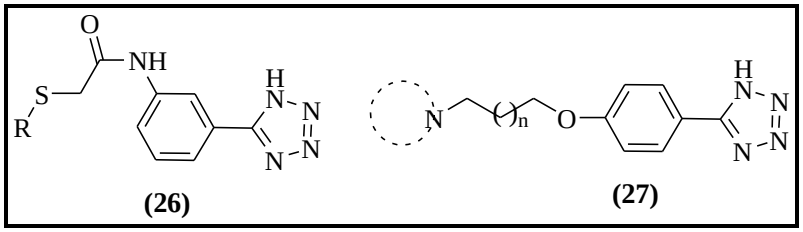


S. Penjarla, *et al.* documented tetrazoles (**24**) possessing C-nucleoside analogs for antitumor activity[24]. The newly synthesized drug candidate (**25**) was demonstrated for *in vitro* anticancer potential by N. Dhiman *et al.* [25].

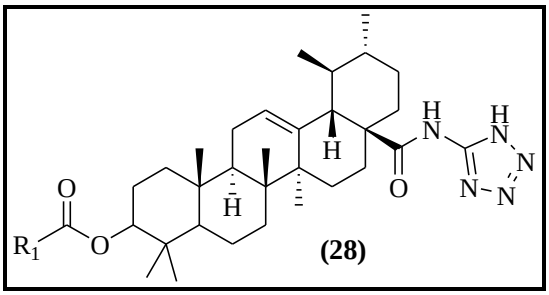


N. Maheshwari *et al.* documented a series of 1*H*-tetrazole derivatives (**26**) for protein tyrosine phosphatase 1B (PTP1B) inhibitory activity. Among the series, the 5-Cl substituted benzothiazole analogs revealed a considerable PTP1B inhibition with an IC50 of 1.88 μM aligned with reference standard suramin (IC50≥10 μM). In addition, an excellent *in vivo* anti-diabetic activity of these compounds was also observed as compared to the standard drugs - glimepiride and metformin. Studies revealed the necessity of the presence of tetrazole moiety for the enhancement of non-carboxylic inhibitors of PTP1B through anti-diabetic potential[26].

Inspired by the chemical structure of cilostazol, a selective phosphodiesterase 3A (PDE3A) inhibitor, the new hybrids of nucleobases and tetrazoles (**27**) were synthesized and studied for inhibitory activity on PDE3A as well as their cytotoxicity on HeLa and MCF-7 cancerous cell lines by M. Shekouhy *et al.* The obtained results showed a linear correlation of the inhibitory effect of the synthesized compounds and their cytotoxicity. In some cases, the PDE3A inhibitory effects of synthesized compounds are higher than the cilostazol. Some of the synthesized compounds revealed higher cytotoxicity against the HeLa and MCF-7 cancerous cell lines[27].



Zhang *et al.* documented 31 ursolic acid bearing a tetrazole moiety (**28**) for probable anti-tumor activities as HIF-1α transcriptional inhibitor. The structure-activity relationships of these compounds through HIF-1α recommended the existence of a tetrazole group at C-28 to enhance their inhibitory activities[28].



(28)

Conclusion:

In summary, triazoles and tetrazoles are the biologically significant five-membered heterocyclic compounds which are the core structures of several commercially marketed drugs and other heterocyclic compounds of great biological significance. This review article summarizes the various biological activities of triazole and tetrazole based heterocyclic.

References:

[1] A. Sahu, P. Sahu, R. Agrawal, 2020. A Recent review on drug modification using 1, 2, 3-triazole. Current Chemical Biology, 14, 2, 71-87.

[2] B. Zhang, 2019. Comprehensive review on the anti-bacterial activity of 1, 2, 3-triazole hybrids. European Journal of Medicinal Chemistry, 168, 357-372.

[3] V. Sharma, B. Shrivastava, R. Bhatia, M. Bachwani, R. Khandelwal, J. Ameta, 2011. Exploring potential of 1, 2, 4-triazole: A brief review. Pharmacology, 1, 1192-1222.

[4] Sarvary A, Maleki A, 2015, A review of syntheses of 1, 5-disubstituted tetrazole derivatives. Molecular Diversity, 19, 1, 189-212.

[5] Aljamali NM, Mahmood RM, Baqi RA, 2020. Review on preparation and application fields of triazole & tetrazole derivatives. International Journal of Analytical and Applied Chemistry, 6, 1, 50-60.

[6] Dürr CJ, Lederhose P, Hlalele L, Abt D, Kaiser A, Brandau S, Barner-Kowollik C., 2013. Photo-induced ligation of acrylonitrile-butadiene rubber: selective tetrazole-ene coupling of chain-end-functionalized copolymers of 1, 3-butadiene. Macromolecules., 46, 15, 5915-5923.

[7] Z. Li, L. Qian, L. Li, J.C. Bernhammer, H.V. Huynh, J.S. Lee, S.Q. Yao, 2016. Tetrazole photo click chemistry: reinvestigating its suitability as a bioorthogonal reaction and potential applications. Angewandte Chemie International Edition, 55, 6, 2002-2006.

[8] I. Saadaoui, F. Krichen, B.B. Salah, R.B. Mansour, N. Miled, A. Bougatef, M. Kossentini, 2018. Design, synthesis and biological evaluation of Schiff bases of 4-amino-1,2,4-triazole derivatives as potent angiotensin-converting enzyme inhibitors and antioxidant activities. Journal of Molecular Structure, S0022-2860, 31429-7. DOI: 10.1016/j.molstruc.2018.12.008.

[9] K. Slamova, P. Marhol, K. Bezouška, L. Lindkvist, S. G. Hansen, V. Kr̆en, H. H. Jensen, 2010. Synthesis and biological activity of glycosyl-1H-1,2,3-triazoles. Bioorganic & Medicinal Chemistry Letters, 20, 4263-4265.

[10] E. Stingaci, M. Zveaghinteva, S. Pogrebnoi, L. Lupascu, V. Valica, L. Uncu, A. Smetanscaia, M. Drumea, A. Petrou, A. Ciric, J. Glamoclija, M. Sokovic, V. Kravtsov, A. Geronikaki, F. Macaev, 2020. New vinyl-1, 2, 4-triazole derivatives as antimicrobial agents: Synthesis, biological evaluation, and molecular docking studies. Bioorganic & Medicinal Chemistry Letters, S0960-894X; 30479-0.

[11] L. Luo, J.J. Jia, Q. Zhong, X. Zhong, S. Zheng, G. Wang, L. He, 2020. Synthesis and anticancer activity evaluation of naphthalene-substituted triazole spirodienones. European Journal of Medicinal Chemistry S0223-5234;31011-4: https://doi.org/10.1016/j.ejmech.2020.113039.

[12] S. Akın, E.A. Demir, A. Colak, Y. Kolcuoglu, N. Yildirim, O. Bekircan, 2018. Synthesis, biological activities and molecular docking studies of some novel 2,4,5-trisubstituted-1,2,4-triazole-3-one derivatives as potent tyrosinase inhibitors. Journal of Molecular Structure, S0022-2860; 30884-6. doi:10.1016/j.molstruc.2018.07.065.

[13] S. Wu, W. Zhang, L. Qi, Y. Ren, H. Ma, 2019. Investigation on 4-amino-5-substituent-1, 2, 4-triazole-3-thione Schiff bases an antifungal drug by characterization (spectroscopic, XRD), biological activities, molecular docking studies, and electrostatic potential (ESP). Journal of Molecular Structure, 1197, 171-182.

[14] S. Deswal, Naveen, R.K. Tittal, D.G. Vikas, K. Lal, A. Kumar, 2020. 5-Fluoro-1H-indole-2, 3-dione-triazoles- synthesis, biological activity, molecular docking, and DFT study. Journal of Molecular Structure, 1209, 127982.

[15] O. Grytsai, O. Valiashko, M. Penco-Campillo, M. Dufies, A. Hagege, L. Demange, S. Martial, G. Pages, C. Ronco, R. Benhida, 2020. Synthesis and biological evaluation of 3-amino-1,2,4-triazole derivatives as potential anticancer compounds. Bioorganic Chemistry, 104, 104271.

[16] M.M. Masood, P. Hasan, S. Tabrez, B.B. Ahmad, U. Yadava, C. G. Daniliuc, Y. A. Sonawane, A. Azam, A. Rub, M. Abid, 2017. Anti-leishmanial and cytotoxic activities of amino acid-triazole hybrids: Synthesis, biological evaluation, molecular docking and in silico physicochemical properties. Bioorganic & Medicinal Chemistry Letters, S0960-894X; 30298-6; DOI: http://dx.doi.org/10.1016/j.bmcl.2017.03.049.

[17] C. Menendez, S. Gau, C. Lherbet, F. Rodriguez, C. Inard, M.R. Pasca, M. Baltas, 2011. Synthesis and biological activities of triazole derivatives as inhibitors of InhA and antituberculosis agents. European Journal of Medicinal Chemistry, 46, 5524-5531.

[18] Naveen, R.K. Tittal, V.D. Ghule, N. Kumar, L. Kumar, K. Lal, A. Kumar, 2020. Design, synthesis, biological activity, molecular docking and computational studies on novel 1,4-disubstituted-1,2,3-triazole-thiosemicarbazone hybrid molecules. Journal of Molecular Structure, 1209, 127951.

[19] A.K. Srivastava, A. Kumar, N. Misra, P.S. Manjula, B.K. Sarojini, B. Narayana, 2016. Synthesis, spectral (FT-IR, UV-visible, NMR) features, biological activity prediction and theoretical studies of 4-amino-3-(4-

hydroxybenzyl)-1H-1,2,4-triazole-5(4H)-thione and its tautomer. Journal of Molecular Structure, 1107, 137-144.

[20] L-Y. Zhang, B-L. Wang, Y-Z. Zhan, Y. Zhang, X. Zhang, Z-M. Li, 2016. Synthesis and biological activities of some fluorine- and piperazine-containing 1, 2, 4-triazole thione derivatives. Chinese Chemical Letters, 27, 1, 163-167

[21] Y.J. Mange, A.M. Isloor, S. Malladi, S. Isloor, H-K. Fun, 2013. Synthesis and antimicrobial activities of some novel 1, 2, 4-triazole derivatives. Arabian Journal of Chemistry, 6, 177-181.

[22] A.M. Isloor, B. Kalluraya, P. Shetty, 2009. Regioselective reaction: Synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1, 2, 4-triazoles. European Journal of Medicinal Chemistry, 44, 3784-3787.

[23] S.A. Khan, S.M. Imam, A. Ahmad, S.H. Basha, A. Husain, 2017. Synthesis, molecular docking with COX 1& II enzyme, ADMET screening and in vivo anti-inflammatory activity of oxadiazole, thiadiazole and triazole analogues of felbinac. Journal of Saudi Chemical Society, S1319-6103; 30064-9; DOI: http://dx.doi.org/10.1016/j.jscs.2017.05.006

[24] S. Penjarla, S. K. Sabui, D. S. Reddy, S. Banerjee, P. Y. Reddy, S. Penta, Y. S. Sanghvi, 2020. An efficient synthesis tetrazole and oxadiazole analogs of novel 2'-deoxy-nucleosides and their antitumor activity. Bioorganic & Medicinal Chemistry Letters, S0960-894X; 30723-X. DOI: https://doi.org/10.1016/j.bmcl.2020.127612

[25] N. Dhiman, K. Kaur, V. Jaitak, 2020. Tetrazoles as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. Bioorganic & Medicinal Chemistry, S0968-0896; 30429-6.

[26] N. Maheshwari, C. Karthikeyan, S. V. Bhadada, A. K. Verma, C. Sahi, N.S. H. N. Moorthy, P. Trivedi, 2019. Design, synthesis and biological evaluation of some tetrazole acetamide derivatives as novel non-carboxylic PTP1B inhibitors. Bioorganic Chemistry, 92, 103221.

[27] M. Shekouhy, S. Karimian, A. Moaddeli, Z. Faghih, Y. Delshad, A. Khalafi-Nezhad, 2020. The synthesis and biological evaluation of nucleobases/tetrazole hybrid compounds: A new class of phosphodiesterase type 3 (PDE3) inhibitors. Bioorganic & Medicinal Chemistry, 28, 115540.

[28] L-H. Zhang, Z-H. Zhang, M-Y. Li, Z-Y. Wei, X-J. Jin, H-R. 2019. Piao Synthesis and evaluation of the HIF-1α inhibitory activities of novel ursolic acid tetrazole derivatives. Bioorganic & Medicinal sChemistry Letters, 29, 1440-1445.