Triazole analogues as potential pharmacological agents: a brief review

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Abstract

Background: A large number of studies have recently reported that, because of their significant biological and pharmacological properties, heterocyclic compounds and their derivatives have attracted a strong interest in medicinal chemistry. The triazole nucleus is one of the most important heterocycles which has a feature of natural products as well as medicinal agents. Heterocyclic nitrogen is abundantly present in most medicinal compounds. The derivatization of triazole ring is based on the phenomenon of bio-isosteres in which substituted the oxygen atom of oxadiazole nucleus with nitrogen triazole analogue.

Main text: This review focuses on recent synthetic procedure of triazole moiety, which comprises of various pharmacological activities such as antimicrobial, anticonvulsant, anti-inflammatory, analgesic, antitubercular, anthelmintic, antioxidant, antimalarial, antiviral, etc.

Conclusion: This review highlights the current status of triazole compounds as different multi-target pharmacological activities. From the literature survey, triazole is the most widely used compound in different potential activities.

Keywords: Analgesic, Anthelmintic, Anti-inflammatory, Antimicrobial, Triazole

Background

In the field of research and the synthesis of new bioactive molecule, heterocyclic chemistry plays the most important role. Medicinal chemistry is a part of the medical and pharmaceutical sciences, is concerned with the development and design, and credits the significant biologically active drug molecule. The most active biological activities have been shown among these heterocyclic molecules containing nitrogen and oxygen. Many different compounds have been prepared and exhibit different types of useful pharmacological activity [1].

To investigate a new agent is one of the most difficult tasks for the medicinal chemist. Synthesis of heterocyclic systems consisting high nitrogen has been rising over the past decade owing to their usefulness in different applications such as propellants, explosives, pyrotechnics, and especially chemotherapy. In recent years, considerable attention has been received by the chemistry of triazoles and their fused heterocyclic derivatives because of their synthetic and effective biological importance [2]. Azolic derivatives such as thiazole, triazole, oxadiazole, and thiadiazole are pharmacologically active compounds and, due to their effective use in medicinal chemistry, have been intensely studied for various biological activities [3].

Main text

Triazole

Triazole is a five-member heterocyclic ring containing two carbon and three nitrogen atoms with molecular formula C₃H₅N₃ [4]. And it is found in two isomeric forms, 1,2,3-triazole and 1,2,4-triazole, which are also known as pyrro Diazole. (Fig. 1).

Triazoles are white-to-pale yellow crystals with a weak odour, soluble in water and alcohol at a melting point of 120 °C and 260 °C [5]. In medicinal chemistry, five-member heterocyclic nitrogen-containing compounds such as triazole are of great importance due to their wide range of biological applications such as anticonvulsant [6, 7], antimicrobial [8, 9], antiviral [10, 11], antitubercular

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[12], antidiabetic [13], anti-inflammatory [14, 15], anti-proliferative [16–18], antioxidant [19], anti-urease [19], and antimalarial activities [20, 21]. (Fig. 2).

**Synthetic approaches of triazoles**

The article gives a brief review of the synthetic procedure and characterization of triazole and its pharmacological activity.

Lu yang et al. reported 4-acyl-NH-1,2,3-triazole synthesis by the use of water-mediated cycloaddition reactions of enaminone and tosilazide, requiring both a mild condition (40 °C) and practical scalability, when using the water as sole medium without any catalyst (Scheme 1) [22].

Shelke et al. had synthesized and found that, in the absence of a catalyst, the substitution of 1,2,4 triazole from hydrazine and formamide under microwave irradiation and this reaction effectively indicates excellent functional group tolerance (Scheme 2) [23].

Bechara et al. reported the synthesis of 3,4,5-Trisubstituted 1,2,4-triazole from 2° amides and hydrazides by triflic anhydride activation followed by the microwave cyclodehydration to be 1,2,4-Triazole moiety is a useful leading group of Ru-catalyzed C-H arylation (Scheme 3) [24].

Yin et al. synthesized a substituted triazole by one pot cyanimidation of aldehydes where cyanamide as nitrogen source and the NBS as an oxidant in high yield without any catalyst. The substituted product N-cyanobenzimidate may also be subjected to a cyclization reaction to produce a high yield of 1,2,4-triazole derivative (Scheme 4) [25].

Faldiman et al. reported 1,4 disubstituted 1,2,3 triazoles from azides. These are obtained with excellent yield from aromatic and aliphatic halides that are easily available without formation of potentially unstable organic azide intermediates (Scheme 5) [26].

Liu et al. reported a novel substituted 3,5-diamine-1,2,4-triazole from isothiocynate and mono-substituted hydrazines and sodium hydrogen cyanamide (Scheme 6) [27].

**Fig. 1** Different isomeric forms of triazole

**Fig. 2** Significant biological activities of triazole derivatives
**Scheme 1** Synthesis of 4-acyl-NH-1,2,3-triazole

\[
\text{R} \equiv \text{Ph} \\
\text{NH} \equiv \text{N} \\
\text{O} \equiv \text{C} \\
\text{CH}_3 \equiv \text{CH}_3
\]

\[
\text{TS-N}_3 \quad \text{Water} \quad \text{40°C}
\]

(Scheme-1)

**Scheme 2** Synthesis with substitution of 1,2,4 triazole from hydrazine and formamide

\[
\text{R-NH}_2 \quad \text{O} \quad \text{NH}_2
\]

\[
\text{R-NH}_2 \quad \text{O} \quad \text{NH}_2 \quad \text{MW}(230w,17\text{atm}),160^\circ\text{C},10\text{atm}
\]

(Scheme-2)

**Scheme 3** Synthesis of 3,4,5-Trisubstituted 1,2,4-triazole from 2 amides and hydrazides

\[
\text{R}_1 \equiv \text{H} \\
\text{R}_2 \equiv \text{H}
\]

\[
\text{H}_2\text{N} \equiv \text{N} \\
\text{H}_2\text{N} \equiv \text{N}
\]

\[
\text{Tf}_2\text{O} \quad 2\text{-FPy}
\]

(Scheme-3)

**Scheme 4** Synthesis of a substituted triazole by one pot cyanoimidation of aldehydes

\[
\text{Ar} \equiv \text{Ph} \\
\text{NCS} \equiv \text{NCS}
\]

\[
\text{OCH}_3 \equiv \text{OCH}_3
\]

\[
\text{PhNH}_2 \quad \text{CH}_3\text{OH} \quad \text{Reflux 4hr}
\]

(Scheme-4)
Zhengkaichen et al. reported a metal-free synthesis of 1,3,5-trisubstituted-1,2,4-triazoles in the presence of iodine as catalyst (Scheme 7). And it can be synthesized from hydrazones and aliphatic amines under oxidative conditions via a cascade C–H functionalization, double C–N bond formation, and oxidative aromatization [28].

**Pharmacological activities of triazole derivatives**

This article presented discusses a brief description of the various triazole activities, and the recent studies have showed the wide range of pharmacological activities available for triazole derivatives which may be divided into the following categories:

**Antimicrobial activity**

Fabrice et al. synthesized a novel series of 1,2,4-triazole-indole hybrids and evaluated their antifungal activity. All the synthesized hybrids were characterized by IR, NMR, and mass and elemental spectroscopy. The compound (2-(2,4-Dichlorophenyl)-3-(1H-indol-1-yl)-1-(1,2,4-triazol-1-yl) propan-2-ol 1a exhibited the excellent activity against *Candida*, particularly against low fluconazole susceptible species. Result showed that this compound exhibited high activity as compared with fluconazole and similar to voriconazole against *C. glabrata*, *C. krusei*, and *C. albicans* [29].

Wujec et al. synthesized the ten compounds which contain the manic base-1,2,4 triazole. The broth microdilution technique was used against Gram-positive and Gram-negative bacteria to evaluate antimicrobial activity of these compounds. The phenyl ring present in the 4-position of piperazine appears essential for antibacterial action. Compound 2a showed the potent activity with MIC value 30 μg/mL against *M. luteus* and 60 μg/mL against three different bacterial strains (*B. subtilis*, *S. aureus*, and *S. epidermidis*) [30].
Lipeeva et al. synthesized and investigated a novel series of 1,2,3-triazole-substituted coumarins and tested their in vitro antimicrobial activity against four different bacterial strains. Result showed that compounds 3a, 3b, and 3c showed potent activity against S. aureus strains with MIC values ranging between 0.16 and 0.41 μg/mL as compared with the reference drug ceftriaxone and streptomycin. The structure activity relationship of compound (carboxamidotriazolyl-benzoic acid) substitution at position C-6 of coumarin core displayed promising activity towards A. viscosus as compared with compound 3b. The compound 3b with triazolylbenzoic acid substitute in the C-7 position exhibited highest activity towards the bacterial strains of S. aureus “Viotko”, and compound 3c with the substitution of 3-ethynylcoumarin with methylanthranilate exhibited remarkable antibacterial activity against the strains of S. aureus [31].

Tang et al. synthesized the triazolyl-pterostilbene derivatives, and their antimicrobial activity was evaluated. Among all these compounds, compound 4a showed the most potent antimicrobial activity with MIC values of 1.2–2.4 μg/mL and MBC values of 19.5–39 μg/mL. On the other hand, structural activity analysis showed introduction of the phenyl group as a spacer on compound 4a exhibited significant antimicrobial activity [32].

Tingjunhong Ni et al. synthesized twenty-seven triazole derivatives containing alkynyl side chains, and their antifungal activity towards Cryptococcus and Candida species were evaluated as compared with reference drugs. The results showed that the compounds 5a and 5b demonstrated in vitro activity towards all fungi with MIC80 values in range between 0.0156 and 0.5 μg/mL, higher than ravuconazole and fluconazole. Structural relationships showed the introduction of fluoro, chloro, and cyano groups at p-position of phenyl alkynyl or pyridinyl alkynyl side chain enhances their antifungal activity [33].

Yang et al. synthesized the derivatives of quinazoline (E)-2-(4-(1H-1,2,4-triazolyl) as an antimicrobial agent. Among these compounds, in vitro antimicrobial activity was evaluated against three phytopatogenic bacteria (Xac, Xoo, and Rs) as compared with the reference bismuththiazole (BMT) drug. Among them, compounds 6a,
6b, and 6c showed better antibacterial activity against pathogen Xac and its EC50 values are 53.2, 67.7, and 70.7 μg/mL. And the antifungal activity also evaluated against the three phytopathogenic fungi. Result revealed that the compounds 6c, 6d, 6e, and 6f showed the modest inhibition activities with EC50 values 45.7 ± 1.8, 40.7 ± 2.1, 43.6 ± 1.7, and 43.1 ± 2.1 respectively against S. sclerotiorum with the reference of Hymexazol at 50 μg/mL, having >40% inhibition rate [34] where value of R in 6a. R = C(CH3)3C6H4, 6b. R = 2,6 -Cl2C6H3, 6c. R = 4 -FC6H4, 6d. R = CH3, 6e. R = (CH2)2CH3, 6f. = C6H5.

Rezki et al. reported and investigated a novel series of 2,5-disubstituted thiadiazole clubbed 1,2,4-triazole as a potential antimicrobial agent. All derivatives were characterized by IR, 1H-NMR, 13C-NMR, MS, and elemental analysis. In vitro inhibitory growth activities of three Gram-positive (+) bacteria, three Gram-negative (-) fungi, and three strains of normal pathogenic microorganism strains were tested of all these compounds. SAR studies revealed the presence of phenyl or alkyl substitution at N-4 has enhanced their antimicrobial activity towards strains of bacteria and fungi with MIC values of 8–16 μg/mL, where ciprofloxacin and fluconazole are the reference drugs (Table 1). Compounds 7a–7c were found to be the most potent antimicrobial agent [35].

Tijenonkol et al. reported the 3-[1(2H)-phthalazinone-2yl(substituted)-4-aryl-1,2,4-triazole-5-thione derivatives and evaluated their antibacterial activity and screened them against Gram (+) & Gram (-) bacterial strains and fungal strains by using the broth microdilution method. Result revealed that the compounds 8a–8e exhibited the antibacterial activity is 25% against B. subtilis. And the antifungal activity of compound 8c was found to be 25% against C. albicans. The MIC value of compound 8e towards C. albicans and C. parapsilosis was 64 μg/mL & 32 μg/mL, and compound 8d was active towards C. parapsilosis with MIC value 32 μg/mL (Table 2) [36].

Turan-Zitouni et al. synthesized 4-phenyl-cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido] thio-4H-1,2,4-triazole analogues and tested their antimicrobial activity. Among these synthesized compounds, only compound 9a showed excellent antifungal activity [37].

### Table 1 Antimicrobial activity expressed as MIC (μg/mL)

| Comp. | Gram positive | Gram negative | Fungi |
|-------|---------------|---------------|-------|
|       | Sp | Bs | Sa | Pa | Ec | Kp | Af | Ca | Gc |
| 7a    | 8  | 8  | 16 | 16 | 16 | 16 | 8  | 8  | 16 |
| 7b    | 16 | 31.5 | 16 | 16 | 16 | 16 | 16 | 16 | 31.5 |
| 7c    | 16 | 16 | 8  | 31.5 | 16 | 16 | 16 | 31.5 | 16 |
| Ciprofloxacin | < 5 | < 1 | < 5 | < 5 | < 1 | < 1 | - | - | - |
| Fluconazole       | -  | -  | -  | -  | -  | -  | < 1 | < 1 | < 1 |

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|       | Sp | Bs | Sa | Pa | Ec | Kp | Af | Ca | Gc |
| 7a    | 8  | 8  | 16 | 16 | 16 | 16 | 8  | 8  | 16 |
| 7b    | 16 | 31.5 | 16 | 16 | 16 | 16 | 16 | 16 | 31.5 |
| 7c    | 16 | 16 | 8  | 31.5 | 16 | 16 | 16 | 31.5 | 16 |
| Ciprofloxacin | < 5 | < 1 | < 5 | < 5 | < 1 | < 1 | - | - | - |
| Fluconazole       | -  | -  | -  | -  | -  | -  | < 1 | < 1 | < 1 |
Hussain et al. synthesized eleven 1,4-disubstituted-1,2,3-triazole derivatives for antibacterial activity. All the synthesized derivatives were characterized spectroscopically, and their activities were evaluated. And the preliminary results of the synthesized derivatives showed the high inhibitory effects compared with the control ciprofloxacin. Result showed that the compounds 10a and 10b were found to be potent (MIC: 5 μg/mL, MIC: 10 μg/mL respectively) antibacterials against various strains of bacteria. And the docking studies showed that the most potent is compound 10a, exhibiting high binding energy and inhibition constant [38].

Han et al. reported a new series of triazole derivatives containing different ester skeletons and evaluated as antifungal agents. The antifungal activity was investigated by utilizing the microdilution broth method. In all the synthesized compounds, compounds 11a and 11b showed the most significant activity against four important fungal pathogens (MIC80 = 2–8 μg/mL). Molecular docking studies revealed the target compounds interact with CYP51 mostly by Van der Waals and hydrophobic interactions [39].

Al-blewi et al. synthesized a novel series 1,4-disubstituted-1,2,3-triazole-sulfonamide hybrids and evaluated for their antimicrobial activity. All the synthesized hybrids were verified by mean of spectroscopic analysis. From the result, only compound 12a showed the most significant activity with MIC value range between 32 and 64 μg/mL as compared with the standard drug [40].

Antitubercular activity
Ramprasad et al. reported nineteen derivatives of quinoline-triazole hybrids and screened their antitubercular activity against Mycobacterium bovis. Result revealed that two derivatives, 13a and 13b, showed the potent antitubercular activity with MIC values 31.5 μm and 34.8 μm. SAR studies revealed that these compounds are essential for their activity due to n-octyl and 3-fluorophenyl groups presented on 1,2,3-triazole ring [41].

| Comp. | S. aureus | B. subtilis | E. coli | P. aeruginosa | C. albicans | C. parapsilosis |
|-------|-----------|------------|---------|---------------|-------------|----------------|
| 8a    | 512       | 32*        | 256     | 256           | 128         | 64             |
| 8b    | 256       | 256        | 128     | 256           | 32*         | 32*            |
| 8c    | 512       | 32*        | 256     | 256           | 512         | 512            |
| 8d    | 512       | 32*        | 256     | 256           | 64*         | 32*            |
| 8e    | 512       | 64         | 256     | 256           | 64          | 32*            |
A novel series of triazole–imidazo[2,1-b][1,3,4]thiadiazole hybrids and evaluated their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv strain reported by Ramprasad et al. From the result, two derivatives 14a and 14b demonstrated potent growth inhibition towards the bacterial strain with significant MIC value 3.125 μg/mL. Substitution of the ethyl benzyl group on 1,2,3-triazole ring enhances the inhibition activity [42].

Raju et al. synthesized 1H-pyrrolo[2,3-d]pyrimidine-1,2,3-triazole derivatives for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv strain. All synthesized hybrids exhibited significant antitubercular activity. Among these series, compounds 15a and 15b showed the remarkable MIC value 0.78 μg/mL. The molecular docking results to the exhibition of high Moldock score of these compounds. SAR studies showed that the triazole ring substituted with heteroaryl compound containing highly electronegative atoms also enhance their activity [43].

Patela et al. reported a series of N-Mannich base of 1,2,4-triazole derivatives. All the synthesized derivatives were characterized by spectral and elemental analysis and were screened for *in vitro* antitubercular activity against *M. tuberculosis*. From the result, in the primary screening, compound 16a revealed the remarkable activity (MIC = 6.25 μM) against *M. tuberculosis*. The computational studies showed a high affinity towards the active enzyme site for that Mannich derivative 16a that provides a strong platform for new structure-based design efforts [44].

Ali et al. reported and investigated seventeen new 1,2,3-triazole derivatives against *Mycobacterium tuberculosis* H37Ra (ATCC 25177 strain). The synthesized compounds were characterized by thin-layer chromatography (TLC), 1H NMR, 13C NMR, FT-IR, and mass spectrometry. Among the tested series, compound 17a substituted with the fluoro group at second position on the phenyl ring of the triazole derivatives demonstrated higher anti-mycobacterial activity with MIC = 0.78 μg/mL as compared with the first-line antitubercular drug ethambutol (MIC = 2.00 μg/mL). However, the compound 17b with the ester group also showed
significant activity (MIC = 1.56 μg/mL), in contrast with its antimicrobial activity [45].

**Anthelmintic activity**

Kharb et al. investigated fifteen novel imidazole-containing triazole derivatives and screened their anthelmintic activity towards *Pheretima posthuma* at concentrations of 0.150% and 0.300% w/v respectively as compared with the albendazole as positive control. Result revealed that, the compound 18a displayed significant anthelmintic activity as compared with the reference drug [46].

Gupta et al. reported five derivatives and evaluated for their anthelmintic activity against *P. posthuma*. From the result, compound 19a showed the potent vermicidal activity, and it exhibited the maximum paralysis time and 37.33 min of death time at 20 mg/mL concentration [47, 48].

Satyendra et al. synthesized novel di-chloro substituted benzoxazole-triazolo-thione derivatives, and their anthelmintic activities were evaluated. Among them, the compound 20a exhibited the potent anthelmintic activity against *P. posthuma* as compared with the reference albendazole at 1% concentration [49].

**Anticonvulsant activity**

Verma et al. reported a series of novel 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thione derivatives for anticonvulsant activity. Anticonvulsant activity of compound wastes by maximal electroshock (MES), subcutaneous pentylenetetrazol (scPTZ) test in mice and rat and neurotoxicity screened at 30, 100, and 300 mg/kg dose and was suspended in 30% PEG 400 by an oral route to the mice. Among all these compounds, only compound 21a exhibited significant anticonvulsant activity at 300 mg/kg at a 4-h duration [50].

Wang et al. reported a novel series of triazole-containing 7-phenyl-4,5,6,7-tetrahydrothieno[3,2-b]-pyridine derivatives and screened their anticonvulsant activity. From the result, compound 22a exhibited the potent anticonvulsant activity. Out of the therapeutic index (PI) values, compound 22a displayed better safety profile than carbamazepine and ethosuximide [51].
Zhang et al. synthesized a new series 3,4-dihydroisoquinolin containing 1,2,3-triazole compounds and investigated their anti-epileptic activity by using MES (maximal electroshock) and PTZ (pentylenetetrazole)-induced seizure test. Among the synthesized compound, only compound 23a showed excellent anti-epileptic activity with ED\textsuperscript{50} value 48.19 mg/kg. It was found to be more active than valproate but less active than carbamazepine [52].

Mahdavi et al. synthesized a novel series of 3-Amino-5-[4-chloro-2-phenoxyphenyl]-4H-1,2,4-triazoles derivatives and evaluated for their anti-epileptic activity. Result showed that the only compound 24a was found to have the most significant activity as compared with the reference drug [53].

Song et al. reported a new series of 4-(2-(alkylthio)benzo[d]oxazol-5-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one derivatives and evaluated their anticonvulsant activity. Two seizure models, the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ), were used for the anticonvulsant activity. From the result, only compound 25a was found to be most significant compound with ED\textsuperscript{50} values of 23.7 and 18.9 mg/kg, respectively. Furthermore, the seizure-preventing action of compound 25a the anticonvulsant activity confirmed by the 3-MP- and BIC-induced seizure models [54].

Dehestani et al. synthesized twelve phenacyl triazole hydrazone derivatives and screened their in vivo anticonvulsant activity by using the MES and PTZ seizure models. All synthesized derivatives are characterized by spectral analysis. Among the series, compound 26a revealed the significant activity in both models. The computational studies of compound 26a with different targets hypothesize that the compound acts mainly as a GABA\textsubscript{A} receptor [55].

Deng et al. reported a novel series of 7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-5(4H)-ones derivatives and evaluated their anticonvulsant activity. Most of the synthesized derivatives showed the significant activity in the MES model. Out of all derivatives, compound 27a displayed the most potent anticonvulsant activity with ED\textsuperscript{50} value 19.7 mg/kg [56].
Siddiqui et al. synthesized various triazoles containing thiazole derivatives. The two most active compounds 47 and 48 were tested in the Phase II anticonvulsant study for their anticonvulsant activity (ED$_{50}$) and neurotoxicity (TD$_{50}$). And anticonvulsant action was carried out by two methods mostly using the electroshock (MES) and chemoshock (scPTZ) models. From the result, compounds 28a and 28b exhibited the potent anticonvulsant activity [57].

Zheng et al. synthesized a novel series of 4-(4-substitutedphenyl)-3-methyl-1H-1,2,4-triazole-5(4H)-one derivatives and evaluated their anticonvulsant activity. All the synthesized derivatives were characterized by NMR, IR, and mass spectroscopy. Among the series, compound 29a was found to have the most promising activity with ED$_{50}$ value of 25.5 mg/kg [58].

Tariq et al. reported a novel class of N-[3-(substituted-4H-1,2,4-triazol-4-yl)]benzo-(d) thiazol-2-amine derivatives and evaluated for their in vivo anti-inflammatory activity. From the result, only compound 30a displayed the most potent in vivo anti-inflammatory activity [59].

Khan et al. reported and investigated a new series of five membered heterocyclic derivative containing three hetero atoms for their in vivo anti-inflammatory activity. Among all the synthesized compounds, only compound 32a showed the potent anti-inflammatory activity with 56.49% inhibition and the rest of the compounds showed moderate activity. And analgesic activity of all derivatives ranges between 27.50 and 65.24% as compared with the controlled drug [61].

Ahirwar et al. reported a new series of substituted benzyl groups via thio-linkage and potential merged pharmacophore containing 1,2,4-triazoles and evaluated their analgesic and anti-inflammatory activities in mice and rats, respectively. Among all these derivatives, 3-(5-(2,4-dimethylbenzylthio)-4H-1,2,4-triazol-3-yl) pyridine 31a showed excellent anti-inflammatory activity, and 3-(5-(4-nitrobenzylthio)-4H-1,2,4-triazol-3-yl) pyridine 31b showed significant analgesic activity [60].
**Zhang et al.** synthesized a novel series of pyrimidine derivatives containing triazole and investigate their anti-inflammatory activity. Result revealed that the compound 33a showed the significant anti-inflammatory activity with an inhibition rate of 49.26%. And other western blotting showed the dose-dependent NF-κB (p65) activation and MAPK (ERK) and p38-phosphorylation in dose response and concentration dependent manner is inhibited by this compound extract [62].

**Sarigol et al.** synthesized some thiazolo[3,2-b]-1,2,4-triazole-6(5H)-one derivatives and screened for their in-vivo analgesic and anti-inflammatory activity. Out of all derivatives, compound 34a had the most selective COX-2 inhibition of all tested compounds and significant analgesic and anti-inflammatory activity [63].

**Almasirad et al.** reported a new series of novel 1,2,4-triazole derivatives and screened their analgesic activity. And analgesic activity was evaluated by formalin-induced nociception test. Result revealed that the compound 35a with the inhibition rate 49.38% in early phase and 79.62% in late phase showed the potent analgesic activity [64].

**Haider et al.** synthesized a series of 1,2,3-triazole-based benzoxazolinone and screened for their COX-2 inhibitory activity. From the result, compound 36a exhibited the potent selective COX-2 inhibition (COX-1 IC\textsubscript{50} = 174.72 μM; COX-2 IC\textsubscript{50} = 2.4 μM) as compared with celecoxib. And the selective index of this compound shows the selective nature of the compound towards COX-2 inhibition. Compound 36b also exhibited the significant antinociceptive activity [65].

**Syed Shaf et al.** reported a novel series of bis-hetero cycles containing 2-mercapto benzothiazole-based 1,2,3-triazole and screened their anti-inflammatory activity. From the result, compound 37a display the significant selective COX-2 inhibition activity as compared with the standard drug and compound 37b also exhibited the comparable analgesic activity [66].
Gamal El-Din A.A. et al. described a novel series of 1-[(Aminosulfonyl)phenyl]-1H-1,2,4-triazole derivatives. All the synthesized derivatives were confirmed by different spectroscopic method. Among the tested series, compounds 38a, 38b, 38c, and 38d exhibited potent anti-inflammatory activity. SAR studies demonstrated that the substitution of 4-methoxyphenyl (38a), 4-methylphenyl (38b), 4-acetylphenyl (38c), and 3,4-dimethoxyphenyl (38d) groups also increase anti-inflammatory activity as compared with the other derivatives [67].

Tozkoparan et al. synthesized a novel series of 5-aryl-3-alkylthio-1,2,4-triazole derivatives and screened their anti-inflammatory activity. All the synthesized derivatives were characterized by spectral and elemental analysis. Among the series, compounds 39a and 39b exhibited potent analgesic and anti-inflammatory activities with no ulcerogenic effect [68].

Kaur et al. described a novel series of 1,4-diaryl-substituted triazoles was synthesized and evaluated for their COX-2 inhibition. From the result, only compound 40a displayed excellent COX-2 activity [69].

Anticancer activity
Mahanti et al. reported a series of fused acridine containing 1,2,4-triazole derivatives. And screened their anti-proliferative activity towards several human cell lines including, MCF7 (Breast), A549 (Lung), A375 (Melanoma), and HT-29 (Colon). The IC_{50} value of target compound in range between 0.11 ± 0.02 and 13.8 ± 0.99 μM as compared with the standard range 0.11 ± 0.02 to 0.93 ± 0.056 μM. Result revealed that the compounds 41a–41c exhibited the excellent anticancer activity. SAR investigations of this series revealed that introduction of 4-chloro, 3,4,5-(CH₃O)₃, and 4-CF₃CH₃ groups at para-position of the phenyl ring displayed the significant anticancer activity [70].

Al-Wahaibi et al. reported a novel series of 1,2,4-Triazolyl coumarin derivatives and evaluated their anti-proliferative activity towards human colon cancer cell line (HCT116). Result showed that the compound 42a exhibited anti-proliferative activity with IC_{50} values 4.363 μM respectively [71].

Ma et al. synthesized a new series of 1,2,3-triazole-pyrimidine-urea derivatives and evaluated their anti-proliferative activity against selected four different human tumour cell lines including MCF-7, MGC-803, EC-109, and B16-F10. The compounds 43a–43c exhibited significant growth inhibition against B16-F10 with IC_{50} values of 32 μM, 35 μM, and 42 μM among all the tested compounds [72].
Ma et al. reported a novel series of 1,2,3-triazole-pyramidine hybrid derivatives and screened their cytotoxic potential towards several tumour cell lines. Among these synthesized compounds, the compound 44a exhibited the potent and selective anti-proliferative activity with IC\textsubscript{50} values in range between 1.42 and 6.52 μM. Particularly, studies revealed that the compound 44a also inhibit the growth of EC-109 cancer cells via apoptosis-inducing activity and cell cycle arrest at G2/M phase [73].

Duan et al. synthesized a new series of 1,2,3-triazole-di-thiocarbamate hybrids and screened their anticancer activity against four different selected human cancer cell lines including MCF-7, PC-3, MGC-803, and EC-109. Among these, the compounds 45a and 45b showed significant wide-spectrum activity. Compound 45a was found to be most potent towards selected four different human cancer cell lines as compared with 5-fluorouracil [74].

Aouad et al. reported a novel series of benzothiazole-piperazine-1,2,3-triazole hybrids and investigated their anti-proliferative activity against different human cancer cell lines. Some hybrid molecules showed significant antiproliferative activity. ADME and clog P analysis method confirmed the biological profile. From the result, compound 46a exhibited the remarkable antiproliferative activity [75].

Ashwin et al. reported a novel series of 1,2,3-triazole derivatives and screened their anticancer activity against acute myeloid leukemia cell lines. Result revealed that, compound 47a exhibited the significant anticancer activity with an IC\textsubscript{50} of 2 μM towards MV4-11 cells [76].

Dhawan et al. reported a new series of coumarin-tagged β-lactam triazole hybrids and evaluated for their anticancer activity against different cancer cell lines (MDA-MB-231, MCF7, A549) and one control cell line HEK293. Among the tested series, compounds 48a and 48b exhibited excellent activity against MCF-7 cancer cell line with IC\textsubscript{50} values of 53.55 and 58.62 μM and no cytotoxicity against normal cell line. SAR studies revealed that the presence of nitro and chloro groups at C-3 position of the phenyl ring also enhance their activity against MCF-7 cell line [77].

Saftic et al. synthesized 8-triazolyd acyclovir derivatives for in vitro evaluation of cytostatic activity against Madine Darby canine kidney (MDCK I) cells and
different tumour cell lines. From the result, compound 49a with the shortest alkyl substituent at the triazole ring showed significant inhibitory activity against the CaCo-2 cell line but low cytotoxic effect on normal MDCK I cells [78].

Antidiabetic activity
Saeedi et al. reported the quinazolinone-1,2,3-triazole hybrid derivatives and screened their in vitro $\alpha$-glucosidase inhibitory activity as leading to an effective antidiabetic agent. All these derivatives displayed excellent antidiabetic activity with IC$_{50}$ values ranging between 181.0 and 474.5 $\mu$M and were found to be more potent than reference drug acarbose (IC$_{50}$ = 750.0). Result showed that the compounds 50a and 50b where 4-bromobenzyl moiety substituted to the 1,2,3-triazole ring exhibited excellent inhibitory activity with (IC$_{50}$ = 181.0 ± 1.4) and (IC$_{50}$ = 192.3 ± 1.8). Furthermore, in silico docking studies showed the binding mode of these analogues on the active site of $\alpha$-glucosidase [79].

Avula et al. synthesized a class of novel 1,2,3-triazole analogues were synthesized and evaluated their $\alpha$-glucosidase inhibitory activity in ranges between 14.2 and 218.1 $\mu$M. Result revealed that the compound 51a exhibited the most effective antidiabetic activity as compared with the reference drug. And the activity of this compound is 67 times better than the reference due to the presence of the methoxy phenyl group [80].

Wang et al. synthesized a novel series of triazine-triazole derivatives and evaluated their antidiabetic activity. All these derivatives exhibited the potent antidiabetic activity. Out of all synthesized compounds, compound 52a showed potent $\alpha$-glucosidase inhibitory activity [14].

Chinthala et al. reported a novel series of chalcone-1,2,3-triazole hybrids and screened their $\alpha$-glucosidase inhibitor activity. These hybrids exhibited the potential antidiabetic activity. Result showed that the compounds 53a, 53b, and 53c with IC$_{50}$ values of 67.77 $\mu$M, 74.94 $\mu$M, and 102.10 $\mu$M, respectively, exhibited potent $\alpha$-glucosidase inhibition. Furthermore, the docking studies showed these compounds target the $\alpha$-glucosidase in range 100.37 to 107.78 [81].
Gonzaga et al. synthesized 1-phenyl-1H-2-phenyl-2H-1,2,3-triazole derivatives and screened their α-glucosidase and porcine pancreatic α-amylase activity. All compounds tested at 500 μM, only compound 54a was found to have the most significant antidiabetic activity with 54 μM as compared with acarbose [82].

Kucukguzel et al. investigated a new series of novel thiourea containing triazole derivatives and tested their anti-HIV activity. Structures of synthesized derivatives were confirmed by elemental and spectral analysis. Result revealed that the compound 57a exhibited the significant anti-HIV activity towards Cox-sackie virus B4. SAR studies revealed that, the presence of the allyl group at N-4 of the 1,2,4-triazole ring and phenyl ring at terminal nitrogen of thioureas enhanced their activity [85].

Antiviral activity

Ju et al. reported a new class of 1,2,3-triazole oseltamivir analogues and screened their antiviral activity against three different strains (H5N1, H5N2, H5N6) in both enzymatic assay and cellular assay. From the result, compound 55a exhibited the broad-spectrum antiviral activity with IC50 value 0.12 μM, 0.049 μM, and 0.16 μM against three different strains [83].

Jordao et al. synthesized a novel series of N-amino-1,2,3-triazole compounds and screened their antiviral activity against Cantagalo virus. All derivatives were characterized by IR, 1H, and 13C spectroscopy and elemental analysis. From the result, compound 56a revealed the excellent antiviral activity [84].

Wang et al. reported a novel series of sulfanyl-triazole derivatives as an HIV-1 non-nucleoside reverse transcriptase inhibitor by using high throughput screening. It exhibited significant activities against the selected resistant mutants. From the result, compound 58a exhibited excellent anti-HIV activity [86].

Karypidou et al. synthesized a series of fused 1,2,3-triazole derivatives as potential antiviral agent. All the derivatives were screened against some variety of viruses (HIV-1, HIV-2, vaccinia virus, adenovirus-2, and coronavirus) in HEL cells and their inhibitory activity was compared with standard drugs. Among all the tested series, compound 59a (EC50 = 8.95 μM) and 59b (EC50 = 8.90 μM) exhibited the moderate activity against human coronavirus [87].
Cao et al. synthesized novel triazole derivatives for *in vitro* antiviral activity against EV71 and CVB3 in cell-based assay. All the synthesized derivatives were characterized by various spectroscopic methods including $^1$H NMR, $^{13}$C NMR, and mass spectroscopy. Among the result, only compound 60a exhibited remarkable antiviral activities against EV71 and CVB3 virus with the EC$_{50}$ value of 5.3 ± 0.7 and 10.1 ± 3.8 μg/mL as compared with the control ribavirin [88].

Mohammed et al. reported 1,2,3-triazoles as amide bio-isosteres and evaluated for their antiviral activity against H9 and MT4 cells. Result revealed that the 1,4-disubstituted-1,2,3-triazole-based derivatives 61a was found to have significant anti-HIV activity against only H9 cells (IC$_{50}$ = 1.2 μM in H9 cells) and no activity against MT4 cells [89].

**Antimalarial activity**

Oramas-Royo et al. reported and investigated a new series of 1,2,3-triazole-napthaquinone derivatives. Several of these compounds were tested for their *in vitro* antimalarial activity towards *Plasmodium falciparum* strains. From the result, compounds 62a and 62b exhibited potent antimalarial activity with IC$_{50}$ values of 0.8 and 1.2 μM. SAR studies revealed that the compound 62a bearing a fluoro group at C-3 and a methoxy group at C-4 and compound 62b with an unsubstituted phenyl ring enhanced the antimalarial activity [90].

Mohammed et al. reported 1,2,3-triazoles as amide bio-isosteres and evaluated for their antiviral activity against H9 and MT4 cells. Result revealed that the 1,4-disubstituted-1,2,3-triazole-based derivatives 61a was found to have significant anti-HIV activity against only H9 cells (IC$_{50}$ = 1.2 μM in H9 cells) and no activity against MT4 cells [89].

**Thakur et al.** synthesized a novel series of glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-dione derivatives via acid catalyzed reaction and evaluated their anti-plasmodial activity. Among them, compounds 63a and 63b exhibited the good activity against resistant strain pfk1 with IC$_{50}$ values 1.61 and 1.93 μM, respectively [91].

Thakkar et al. reported new ten compounds containing 1,2,4-triazole and evaluated their *in vitro* antimalarial activity against *P. falciparum* strain. All these synthesized derivatives were characterized by IR, $^1$H NMR, $^{13}$C NMR, mass spectroscopy, and elemental analysis. From the result, compounds 64a, 64b, and 64c exhibited the potent antimalarial activity with IC$_{50}$ values 0.282, 0.245, and 0.230 μM as compared with the reference drug chloroquine Pyrimethamine. SAR studies revealed that introduction of 4–OH, 3–NO$_2$, 4–CL in the phenyl group enhance activity [92].
Joshi et al. synthesized a novel series of quinoline triazole amide analogues and screened for their antimalarial activity against different strains (CQS D10 and CQR K1). It was concluded that the compounds $65a$, $65b$, and $65c$ showed most potent activity towards \textit{P. falciparum} CQS D10 strain with IC$_{50}$ values in the range between 349 and 1247 $\mu$M, and these compounds also exhibited similar activity against CQR K1 strain of parasite [93].

Guantai et al. synthesized a new triazole-linked chalcone and dienone hybrids and evaluated \textit{in vitro} antimalarial activity. From the result, compound $66a$ was found to have the most significant activity against D10, DD2, and W2 strains of \textit{P. falciparum} as compared with the reference drug chloroquine [94].

![Chemical structures of compounds](image-url)
Tarawneh et al. synthesized a novel series of isoxazole and triazole derivatives and evaluated for their anti-infective agent. All the compounds were screened against *P. falciparum* D6 and W2 strains. From the result, the only compound 67a exhibited the most potent activity with IC\textsubscript{50} values of 0.70 and 0.59 μM against D6 and W2 strains [95].

Miscellaneous activities
In spite of all these activities, triazoles are also active as antihypertensive agent 68a, neuroprotective agents 68b and 68c, and diuretic 68d (Table 3). Triazole nucleus was found to possess significant atypical behaviour and good potency to block 5-HT receptors and good ability of selective antagonists towards the human vasopressin V\textsubscript{1A} receptor [96–99].

Conclusion
This review article highlights research work of many researchers reported in literature for different pharmacological activities on triazole compounds. Triazole has unique moiety that is responsible for various biological activities. The importance of triazole moiety can be magnified by carrying out further studies on its possible substitution and thus to synthesize better agents that can have strong future commitments. This review has presented comprehensive details of triazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of triazole for many diseases whose treatment are difficult in the medical sciences.

Abbreviations
IC\textsubscript{50}: Half maximal inhibitory concentration; SAR: Structure–activity relationship; EC\textsubscript{50}: Median effective concentration required to induce a 50% effect; COX: Cyclooxygenase; MBC: Minimum bactericidal concentration; MIC: Minimum inhibitory concentration; PEG: Polyethylene glycol; PI: Plaque index; IR: Infrared; NMR: Nuclear magnetic resonance

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Authors’ contributions
We declare that this work was done by the authors named in this article: SLK conceived and designed the study. SK carried out the literature collection of the data and writing of the manuscript. AY and SK assisted in the data analysis and corrected the manuscript. The authors read and approved the final manuscript.

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