



Review article

Recent accomplishments on the synthetic/biological facets of pharmacologically active 1*H*-1,2,3-triazolesSumit Kumar ^a, Bharvi Sharma ^a, Vishu Mehra ^b, Vipin Kumar ^{a,*}^a Department of Chemistry, Guru Nanak Dev University, Amritsar, 143005, Punjab, India^b Department of Chemistry, Hindu College, Amritsar, Punjab, 143001, India

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ABSTRACT

The continuous demand of medicinally important scaffolds has prompted the synthetic chemists to identify simple and efficient routes for their synthesis. 1*H*-1,2,3-triazole, obtained by highly versatile, efficacious and selective "Click Reaction" has become a synthetic/medicinal chemist's favorite not only because of its ability to mimic different functional groups but also due to enhancement in the targeted biological activities. Triazole ring has also been shown to play a critical role in biomolecular mimetics, fragment-based drug design, and bioorthogonal methodologies. In addition, the availability of triazole containing drugs such as fluconazole, furacyclin, etizolam, voriconazole, triazolam etc. in market has underscored the potential of this biologically enriched core in expediting development of new scaffolds. The present review, therefore, is an attempt to highlight the recent synthetic/biological advancements in triazole derivatives that could facilitate the in-depth understanding of its role in the drug discovery process.

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Contents

1. Introduction	1
Anti-proliferative 1 <i>H</i> -1,2,3-triazoles	2
Anti-plasmodial/malarial 1 <i>H</i> -1,2,3-triazoles	11
Anti-mycobacterial/tubercular 1 <i>H</i> -1,2,3-triazoles	16
Anti-microbial profile of 1 <i>H</i> -1,2, 3-triazole	24
Conclusion	29
Declaration of competing interest	29
References	29

1. Introduction

Synthetic medicinal chemistry of biologically relevant heterocycles has been a continuous source of inspiration and attracts continuous attention of chemists and biologists all around the world. Amongst the various processes in drug development, one key step is the systemic incorporation of heterocyclic fragments with relevant physicochemical properties to obtain the fine-tuned

and potent compounds [1]. Synthetic tailoring of heterocyclic scaffolds via manipulation of polarity, hydrogen bonding and lipophilicity has led to improved pharmacological/physicochemical properties eventually leading to clinical drugs candidates or drug-like molecules [2]. Synthesizing new molecular assemblies with well-defined biological targets remains an extremely exigent task and requires refinements in conventional synthetic tactics [3,4]. Click Chemistry, an approach to link substrate of choice with specific biomolecules is one of the most desirable synthetic methodologies that remains in brain and heart of most synthetic organic chemist. Huisgen's 1,3-cycloaddition, a reaction between an azide and alkyne to afford 1,2,3-triazole, is considered as a revolutionary

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work in the field of azole chemistry [5]. This was further accelerated by the Nobel laureate K. Barry Sharpless (Nobel prize laureate in chemistry, 2001) who referred, to this 1,3-dipolar cycloaddition as "the cream of the crop" of "Click Chemistry" [6–8]. The term "Click Chemistry" as a class of biocompatible reactions was initially coined by K. B. Sharpless in 1998 and fully explained in 2001 [5,6]. According to Sharpless *et al.*, click chemistry has been associated with various attributes that include simple reaction conditions, wide scope, high yields, insensitivity to oxygen and water, use of either no solvent or water and easily removable solvents, strongly exothermic by virtue of stabilized product, no by-products and simple product isolation [9–11]. These salient features resemble the salient aspects of chemical biology and hence click chemistry has played a key role in total synthesis of natural product [12].

Triazoles synthesized by means of click reaction consist of five-membered ring with two carbon and three nitrogen atoms, and can be divided into two categories viz. 1,2,3- and 1,2,4-triazoles as depicted in Fig. 1 [13]. In 2001, Meldal and Sharpless research laboratories individually synthesized regioselective 1,4-disubstituted 1,2,3-triazoles using Cu(I) salts as a catalyst. On the other hand, Ru/Rh catalyzed 1,3-dipolar cycloaddition afforded the corresponding 1,4-isomer [14]. In recent years, Cu (I) promoted azide-alkyne cycloaddition (CuAAC) has proven to be a powerful tool for the affording new pharmacologically active entities [12–15]. Triazole containing scaffolds exhibit numerous pharmacological properties such as anti-microbial, anti-cancer, anti-malarial, anti-bacterial, anti-alzheimer and anti-tubercular activities [16–18]. The advent of pharmaceutical compounds possessing 1,2,3-triazole core including anticancer carboxyamidotriazole (CAI), anti-bacterial Tazobactam, antibiotic Cefatrizine, has led the way for the development of 1,2,3-triazole containing compounds. A list of drugs containing 1,2,3-triazole core is depicted in Fig. 2 [19].

Triazoles are considered as the fundamental building blocks and can be employed as bio-isosters for modifying active molecules [20]. Triazole may act as the bio-isosters of functional groups such as amide, ester and carboxylic acid and can mimic the various amino acids [21]. Molecular Hybridization (MH) is considered as a strategy in drug design and development involving amalgamation of pharmacophoric moieties of different bio-active molecules to produce a hybrid compound with improved affinity and efficacy compared to the parent drugs. The approach has resulted in scaffolds with modified selectivity, dual modes of action and low incidence of side effects. The emergence of click reaction has further revolutionized the concept of MH as it is one of the straightforward methods of coalescing two pharmacophores to yield the desired hybrid in high yields without the formation of any side-products using simple purification techniques.

Keeping in view of the biological importance of triazoles, the present review entails the recent developments (2017–2019) in synthetic/medicinal attributes of 1H-1,2,3-triazole containing heterocycles and has been further categorized on the basis of their biological activities into following sections:

1.2 Anti-proliferative 1H-1,2,3-triazoles

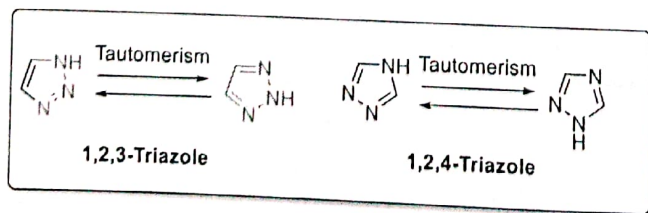


Fig. 1. Chemical structures of 1,2,3-triazole and 1,2,4-triazole.

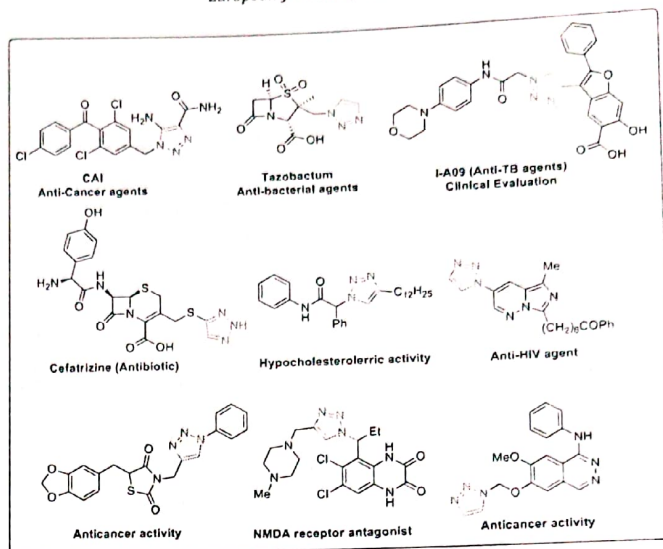


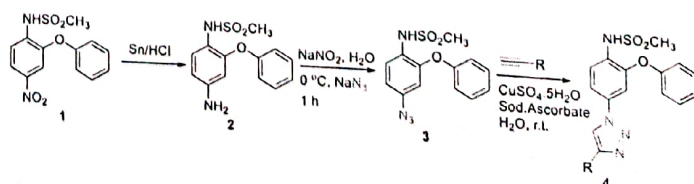
Fig. 2. 1,2,3-triazole containing available drugs.

- 1.3 Anti-plasmodial/malarial 1H-1,2,3-triazoles
- 1.4 Anti-mycobacterial/tubercular 1H-1,2,3-triazoles
- 1.5 Anti-microbial 1H-1,2,3-triazoles

Anti-proliferative 1H-1,2,3-triazoles

Mareddy and co-workers have synthesized and evaluated a series of 1H-1,2,3-triazole-nimesulides against A549, HepG2, HeLa, DU145 and HEK293 cancer cell lines [22]. The precursor azides were synthesized *via* reduction of nimesulide **1** followed by diazotization with sodium nitrite and subsequent treatment with sodium azide. Cu promoted cycloaddition between substituted alkynes and nimesulide-azide afforded the desired product **4** as illustrated in Scheme 1. The compound **4a** exhibited low IC₅₀s of 7.8 and 7.5 μM on HeLa and HepG2 cells, while **4b** was active on DU145 and A549 cells with IC₅₀ of 5.9 and 6.7 μM respectively (Fig. 3). The promising compounds among the series were also tested against normal cells *i.e.* HEK293 (Human embryonic kidney cells) and were found to be non-cytotoxic. An insight into Structure-Activity-Relationship (SAR) data revealed that the introduction of –OCH₂– in the hybrids improved their flexibility as well as anti-proliferative activity.

C-14 dehydroabiatic acid (DHAA)-1,2,3-triazoles were synthesized by Hou *et al.* and evaluated against SK-OV-3 (ovary), PC-3 (prostate), MDA-MB-231 (breast) and MCF-7 (breast) cancer cell lines [23]. The key steps of synthesis involved the esterification of **5** yielding **6** which on subsequent nitration provided a mixture (3:2) of **7** and **8**. The reduction of **8** with Fe/NH₄Cl with subsequent reaction with chloroacetyl chloride afforded **10**. Nucleophilic substitution of **10** with sodium azide afforded the key intermediate **11**. Final step of the synthesis involved Cu (I) promoted 1,3-



Scheme 1. Synthesis of a library of 1H-1,2,3-triazole-nimesulide hybrids.

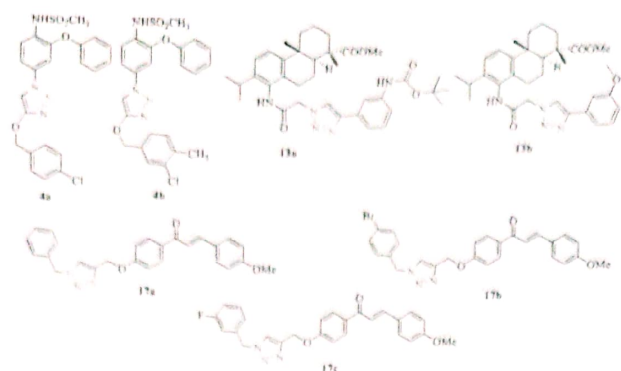
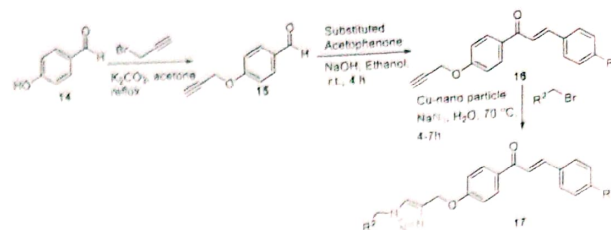


Fig. 3. Promising anti-proliferative 1H-1,2,3-triazole linked nimesulide (**4a-b**), DHAA (**13a-b**) and chalcone hybrids (**17a-c**) hybrids.

cycloaddition reaction between various aliphatic and aromatic alkynes and azide linked DHAA **11** affording **12** and **13** in good yields as elucidated in Scheme 2. The potent hybrids from the synthesized library were **13a** and **13b** and with IC_{50} s ranging between 0.8 and 1.9 μ M on the panel of tested cell lines (Fig. 3). The most potent compound **13a** was chosen to infer into the mechanistic studies and evaluated against several proteins using western blotting assay. It has been demonstrated that **13a** induced apoptosis in the cancer cells. Furthermore, SAR studies demonstrated that the introduction of substituents on C-4 position of the triazole ring have critical role in enhancing activity profile.

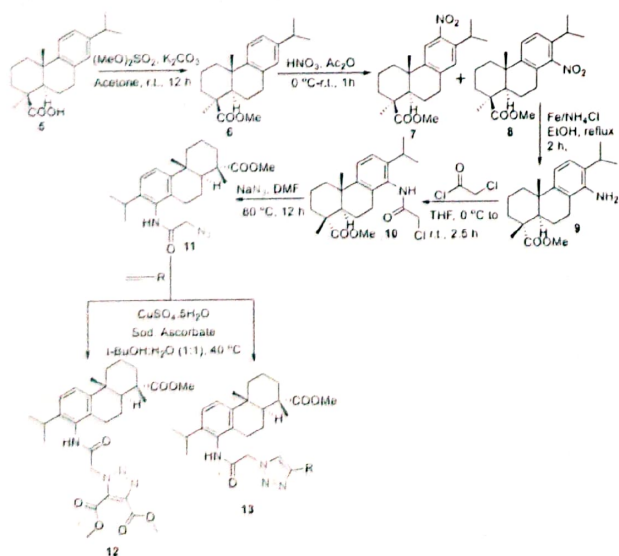
A series of triazole linked chalcones were synthesized and evaluated on a panel of human cancer cell lines by Yadav and co-workers [24]. Synthetic methodology involved an initial base promoted propargylation of **14** to afford **15**, which upon aldol condensation with substituted acetophenones resulted in the formation of *O*-propargylated substituted chalcones **16**. The use of Cu-nanoparticles as catalyst for click reaction afforded the desired 1H-1,2,3-triazoles **17** (Scheme 3). The most promising scaffolds from the synthesized series exhibited IC_{50} values in the range of 4–11 μ M against the evaluated cancer cell lines. Compound **17a** exhibited IC_{50} of 4 μ M against pancreatic cancer cells i.e. MIA-Pa-Ca-2 and has



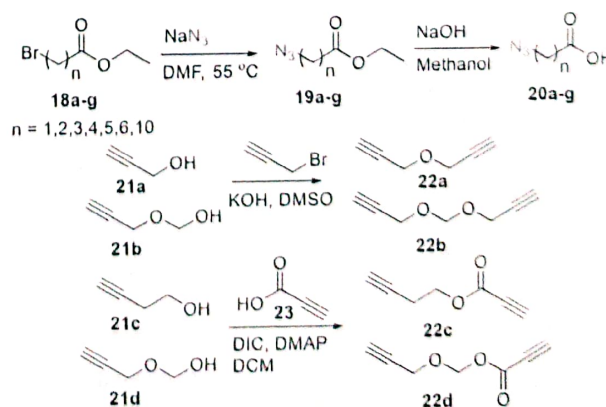
Scheme 3. Synthesis of chalcone linked 1,2,3-triazoles.

comparable activity to that of reference drug, (PI 103; IC_{50} = 6 μ M) and was non-cytotoxic nature against normal epithelial FR2 cells (Fig. 3). Compound **17a** was able to induce apoptosis and G2/S arrest and triggered mitochondrial potential loss in pancreatic cancer.

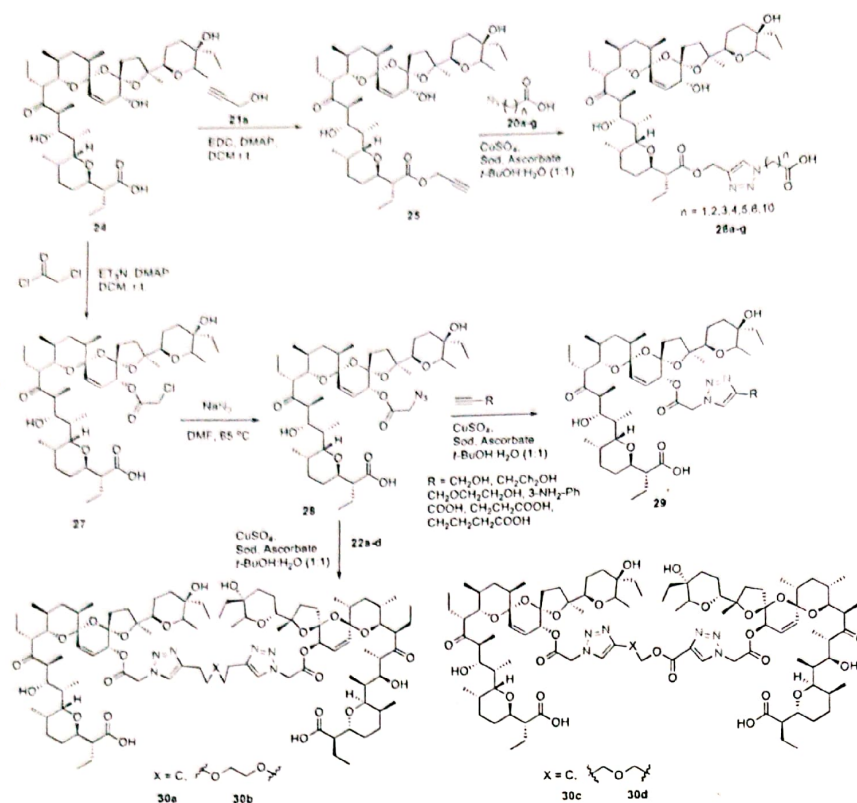
Synthesis of Salinomycin-1,2,3-triazoles were disclosed by Huang et al. along with their evaluation against breast cancer cell lines i.e. MCF-7 and MDA-MB-231 [25]. The precursors' **20a-g** were synthesized via nucleophilic substitution of **18a-g** using sodium azide to result in **19a-g** followed by de-esterification. The precursors' **22a-b** were prepared via reaction of **21a** and **21b** with propargyl bromide while **22c-d** were synthesized via reaction of **21c** and **21d** with **23** (Scheme 4). The targeted salinomycin-triazole hybrids **26a-g** were synthesized via reaction of propargyl alcohol **21a** with salinomycin **24** in the presence of DIC (*N,N'*-diisopropylcarbodiimide) and DMAP (4-dimethylaminopyridine) to yield **25** with subsequent Cu-promoted click reaction with **20a-g**. The treatment of salinomycin **24** with chloroacetyl chloride in the presence of DMAP afforded **27** which upon reaction with sodium azide afforded **28**. Cu (I) promoted click reaction between **28** and substituted alkynes resulted in the formation of **29**. Similarly, the reaction between intermediate **28** and substituted alkynes **22a-d** provided the desired hybrids **30a-d** (Scheme 5). Growth inhibition studies against breast cancer MCF-7 cells demonstrated that the synthesized dimers were 3.27–4.97 folds more potent compared to that of triazole linked monomers. The most active compounds from the synthesized series have been illustrated in Fig. 4. SAR analysis of the compounds **26** indicated the direct dependence of spacer length on the cytotoxic profile of the synthesized compounds. Further SAR studies among hybrids **29** displayed a reverse trend with cytotoxicity decreasing with the increase in alkyl chain length on MCF-7 cells while the effect reverses on MDA-MB-231 cell line. The most active compound among the series, **29a** displayed IC_{50} 3.96 μ M against MCF-7 and 1.94 μ M



Scheme 2. Synthetic route for 1,2,3-triazole dehydroabietic acid (DHAA) hybrids.



Scheme 4. Synthetic route for the precursor's **20** and **22**.



Scheme 5. Synthesis of targeted monomer and dimers triazole linked salinomycin hybrids.

against MDA-MB-231. Furthermore, compound **30d** carrying two salinomycin units observed to be more potent against MCF-7 as compared to MDA-MB-231 with an IC_{50} value of 0.60 μ M.

A Library of triazole tethered substituted benzofuro[3,2-b]quinolones (T-BFQs) were explored for their G-quadruplex binding abilities and antitumor activities by Zeng and co-workers [26]. Synthetic methodology for the desired derivatives **34** encompassed an initial reaction between 11-chlorobenzofuro[3,2-b]quinoline **31** and propargyl amine **32** followed by Cu (I) promoted 1,3-cycloaddition reaction with various azides as depicted in Scheme 6. T-BFQs have shown G-quadruplex stability with interactive activities and were evaluated in cellular and *in vivo* experiments for complete investigation. Results revealed that the derivatives possess good inhibitory activities against tumor cells through down-regulation of transcription of *c-myc* gene and expression in raji cells presumably through the stabilization of *c-myc* G-quadruplex structure. Highly potent compounds from series **34a** and **34b** are illustrated in Fig. 4 and exhibited IC_{50} s ranging from 0.02 to 5.53 μ M against raji cells, A549 and CA46 cells respectively with lower cytotoxicity against mesangial cells. SAR studies revealed that the *in situ* induction of protonated terminal amino groups and aza heterocyclic rings enhanced the G-quadruplex stabilizing efficiency. Furthermore, stronger stabilizing ability to the *c-myc* G-quadruplex was observed for compounds with longer side chains. Molecular modelling of compounds **34a** and **34b** via solution state NMR spectroscopy with *c-myc* G-quadruplex further supported the mechanistic pathways and binding interactions.

Triazole coupled nitroimidazole-isatin and nitroimidazole-isatin thiosemicarbazone hybrids were synthesized by Kumar and co-workers as elucidated in Scheme 7 [27].

Synthetic protocol involved an initial alkylation of substituted isatins **35** with dibromoalkanes with subsequent treatment with sodium azide to afford isatin-azides **37**. The second precursor, viz. *N*-propargylated nitroimidazole **39** was synthesized via base-promoted *N*-propargylation of nitroimidazole. Cu-promoted azide-alkyne cycloaddition between **37** and **39** afforded the desired nitroimidazole-isatin conjugates **40a-i** which were subsequently refluxed with thiosemicarbazone in ethanol to furnish the corresponding thiosemicarbazides **41a-i**. The synthesized compounds were evaluated against breast cancer cell lines MCF-7 and MDA-MB-231 cell lines using MTT assay. The most active compound of series **40a** ($R = Cl$, $n = 5$) exhibited IC_{50} values of 20.76 and 16.06 μ M against MCF-7 and MDA-MB-231 cell lines respectively, thereby indicating the compounds to be ~2 folds active against MCF-7 and ~5 folds against MDA-MB-231 cell lines as compared to the standard drug Tamoxifen (TAM) (Fig. 4). The inclusion of thiosemicarbazone moiety however resulted in loss of cytotoxic activity. Further, the docking studies of synthesized compounds with Insulin-like growth factor 1 (IGF-1) attributed to the fact that the activities resulted from hydrophobic and Van der Waals interactions between residues Val80 and Asp103 with the alkyl linker and methyl group of imidazole ring, respectively.

Utilizing CuAAC, Singh et al. has synthesized a series of isatin-ferrocene conjugates with an aim of probing their anti-proliferative SAR against MCF-7 and MDA-MB-231 cells [28]. The methodology involved an initial synthesis of spiroindoline-oxirane-2-ones **43** via base-promoted *N*-alkylation of **35** with methyl iodide or benzyl bromide to yield *N*-alkylated isatins **42** with subsequent treatment with trimethylsilyl iodide. Epoxide ring opening of **43** with sodium azide resulted in the synthesis of precursor, 3-