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1,2,3-TRIAZOLE SCAFFOLD IN RECENT MEDICINAL APPLICATIONS: SYNTHESIS AND ANTICANCER POTENTIALS[#]

Vanida Choomuenwai,[1] Ronnakorn Leechaisit,[2] Ratchanok Pingaew,[2]* Veda Prachayasittikul,[3] Supaluk Prachayasittikul,[3] and Virapong Prachayasittikul[4]

[1]Chemistry Program, Faculty of Science and technology, Nakhon Ratchasima Rajabhat University, Nakhon Ratchasima 30000, Thailand; [2]Department of Chemistry, Faculty of Science, Srinakharinwirot University, Bangkok 10110, Thailand; [3]Center of Data Mining and Biomedical Informatics, Faculty of Medical Technology, Mahidol University, Bangkok 10700, Thailand; [4]Department of Clinical Microbiology and Applied Technology, Faculty of Medical Technology, Mahidol University, Bangkok 10700, Thailand. Email: ratchanok@g.swu.ac.th

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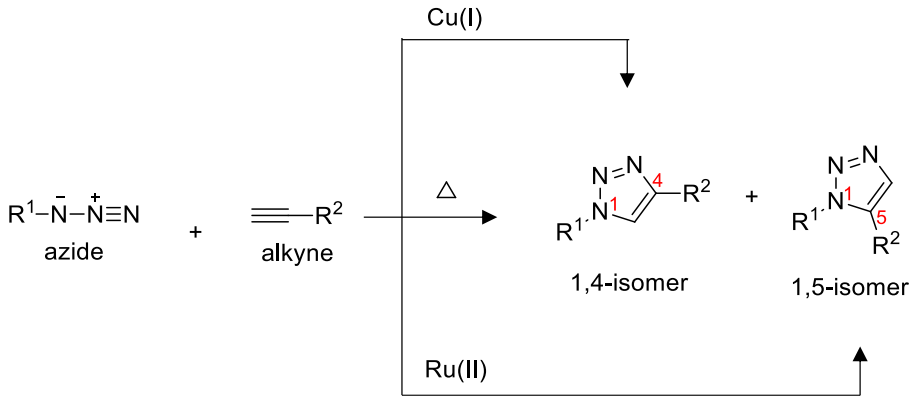
Abstract – Cancer is one of commonly concerned health problems globally and its management is challenging. Besides an availability of diverse classes of anticancer agents, the existing drugs are noted for their limitations such as considerable toxicities, low potency and responsiveness, drug resistance, and others. 1,2,3-Triazole is an attractive heterocyclic scaffold possessing considerable characteristics and is presented in many pharmacologically active molecules. Accordingly, attention has been given to this scaffold in the recent years, especially, in an area of anticancer drug development. In this review, a collection of recently reported triazole based anticancer agents are discussed along with their synthetic methods, proposed molecular targets, and mechanisms of actions. A summary of other recently reported biological activities is also provided. In overview, recent studies suggested that the 1,2,3-triazole based compounds could elicit their anticancer effects against several cancer cell lines *via* an inhibition of cancer cell growth, an induction of apoptosis, an inhibition of involved enzymes such as aromatase, kinases, and others. Some interesting results from computational studies also discussed relating to the predictions of possible molecular targets. In summary, it is suggested that the 1,2,3-triazole serves as a potential scaffold with noteworthy

opportunity for future development of novel anticancer agents to cope with current challenging issues in cancer management.

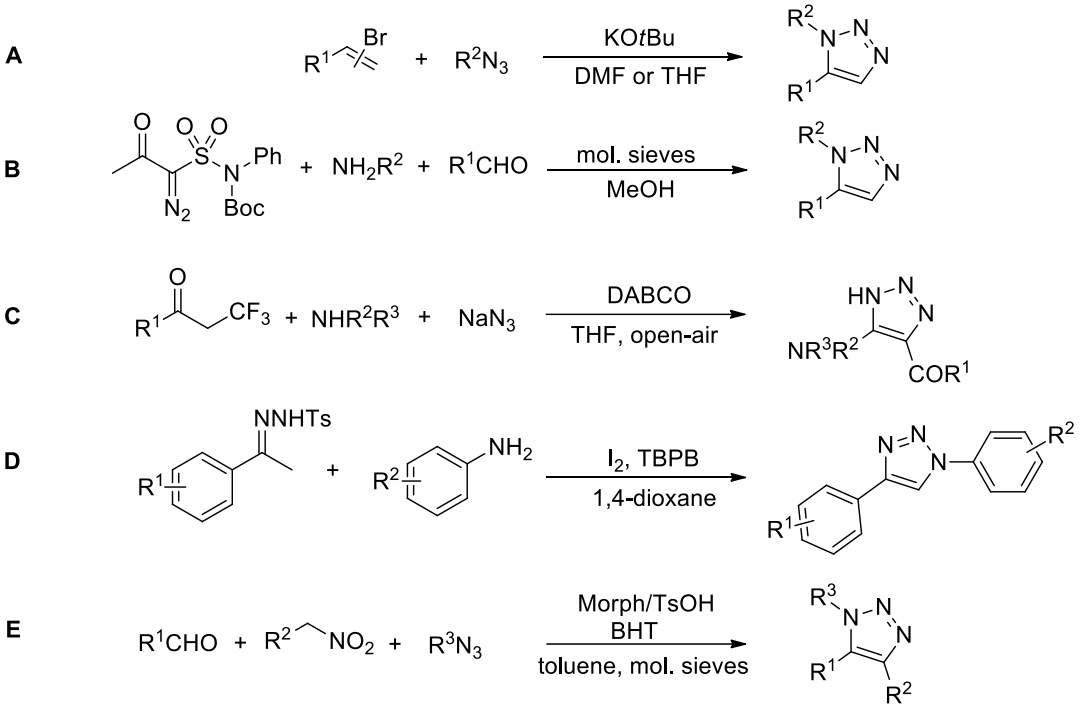
1. INTRODUCTION

Heterocyclic compounds have drawn considerable attention in an area of drug design and discovery. Azoles, for example, occupy a prominent position in modern medicinal chemistry due to their wide range of applications.[1-4] Chemical prototypes were created through the process of lead molecule development, and these prototypes need to be structurally modified to achieve more promising compounds with desirable pharmacological and pharmacokinetic properties. 1,2,3-Triazoles, a class of nitrogen heterocycles existing in several biologically active molecules, are attractive scaffold due to their distinct properties. They possess a strong dipole moment and a pi electron-deficient aromaticity as well as an ability to resist chemical and metabolic degradation.[5-7] In addition to their H-bond forming abilities against various biological targets, these frameworks can also be employed as bioisosteres with diverse functionalities, and as linkers for improving efficacy and drug-like properties of lead compounds.[8-11] Accordingly, the 1,2,3-triazole scaffold is considered a potential therapeutic architectures for the discovery and development of new pharmacologically active hybrid molecules achieving by its incorporation with other pharmacophores.[12-14] In recent years, various synthetic methodologies have been developed for the synthesis of 1,2,3-triazole ring. The scaffold can be obtained conventionally through a Huisgen cycloaddition of organic azides and substituted alkynes.[15] A non-catalytic thermal condition of unsymmetrically substituted alkynes usually resulted in both 1,4- and 1,5-regioisomeric 1,2,3-triazoles (Scheme 1). The most well-known development for improving the regioselectivity, as well as the reaction rate, of the reaction was achieved by Sharpless *via* using copper(I) salts as a catalyst.[16,17] The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), recognized as the click reaction, led to the 1,4-disubstituted 1,2,3-triazoles as solely products under exceedingly mild reaction conditions. On the other hand, 1,5-regioisomeric 1,2,3-triazoles are obtained as major products when ruthenium(II) catalysts are used instead of the Cu(I).[18]



Scheme 1. Synthesis of 1,2,3-triazole ring from azides and alkynes

In addition, other methods for the synthesis of 1,2,3-triazoles were reported such as the reaction of vinyl bromides with aryl azides mediated by base (Scheme 2A),[19] the three-component reactions of α-acetyl-α-diazomethane sulfonamides, primary aliphatic amines, and aromatic aldehydes (Scheme 2B),[20] the three-component reactions of α-CF_3 carbonyl compounds, sodium azide, and amines mediated by DABCO (Scheme 2C),[21] the oxidative reaction of *N*-tosylhydrazones with anilines mediated by I_2/TBPB (Scheme 2D),[22] and the three-component reactions of aldehydes, nitroalkanes, and organic azides (Scheme 2E)[23] as described in the literature.[24-26]



Scheme 2. Other methods for the synthesis of 1,2,3-triazoles

In drug design, the click chemistry is noted to be an effective strategy for a time saving, highly selective, and insensitive access to achieve 1,2,3-triazole derivatives with high yields, simple product isolation and a wide range of applications. The 1,2,3-triazole containing compounds exhibit numerous pharmacological properties including anti-HIV, antimicrobial, anticancer, antimalarial, antibacterial, anti-inflammatory, antituberculosis, and anti-Alzheimer.[6,27,28] Currently, a variety of 1,2,3-triazole based compounds are used as clinical and commercially available drugs such as tazobactam (antimicrobials),[29,30] cefatrizine (antimicrobials),[31] carboxyamidotriazole or CAI (anticancers),[32] mubritinib (anticancers),[33] rufinamide (anticonvulsants),[34] and *tert*-butyldimethylsilylspiroaminooxathioledioxide or TSAO derivative (HIV reverse transcriptase inhibitor)[35] as depicted in Figure 1.

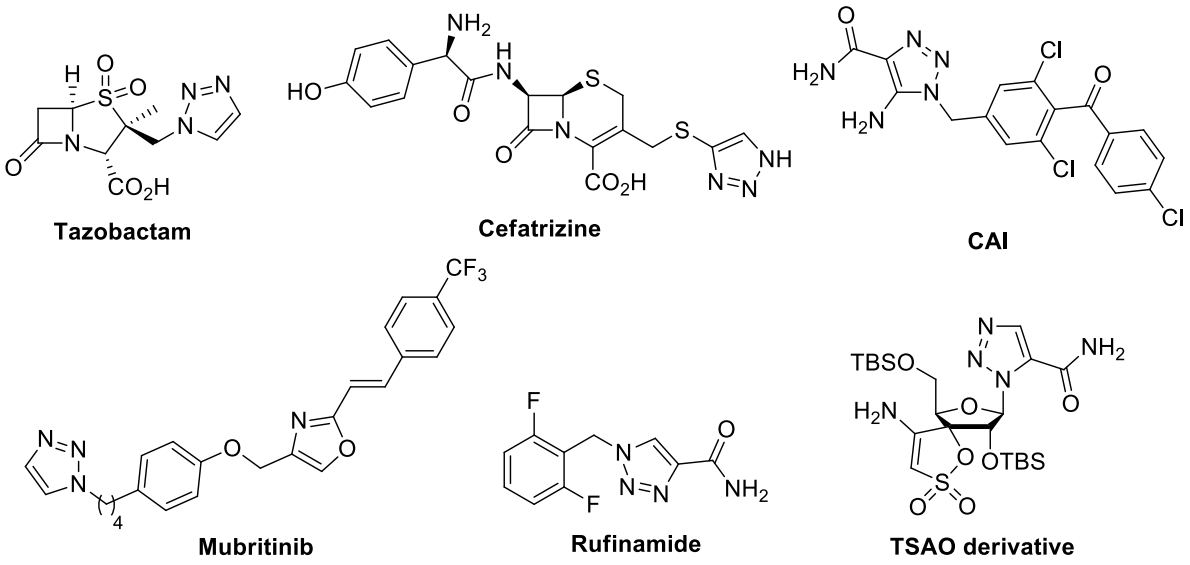


Figure 1. Clinically available 1,2,3-triazole based drugs

Cancers is one of common leading causes of mortality and its impacts on burdening human-being is widely recognized worldwide.[36] Besides undesirable side effects and toxicities, multidrug resistance against the available chemotherapeutic drugs also noted as a challenging issue in cancer management.[37] Thus, the development of novel anticancer agents with preferable efficacy and safety is considered an urgent need. Keeping in view the biological importance of 1,2,3-triazole pharmacophore, this review demonstrates an overview of current anticancer applications of 1,2,3-triazole based molecules (section 2). Summary of structure-activity relationship and *in silico* findings supporting the key roles of the triazole ring participating in ligand-target interactions is also provided (section 3). Other bioactivities of 1,2,3-triazoles are also summarized (section 4). This article would be beneficially inspiring the synthetic and medicinal chemists as well as researchers in the related fields for the future design and development of novel biologically active 1,2,3-triazoles for therapeutic applications.

2. SYNTHESIS AND ANTICANCER ACTIVITIES OF 1,2,3-TRIAZOLE BASED COMPOUNDS

Structures of 1,2,3-triazoles containing compounds with anticancer activities have been depicted in Figure 2. Their synthetic methods and anticancer activities have been outlined in Section 2.1-2.13.

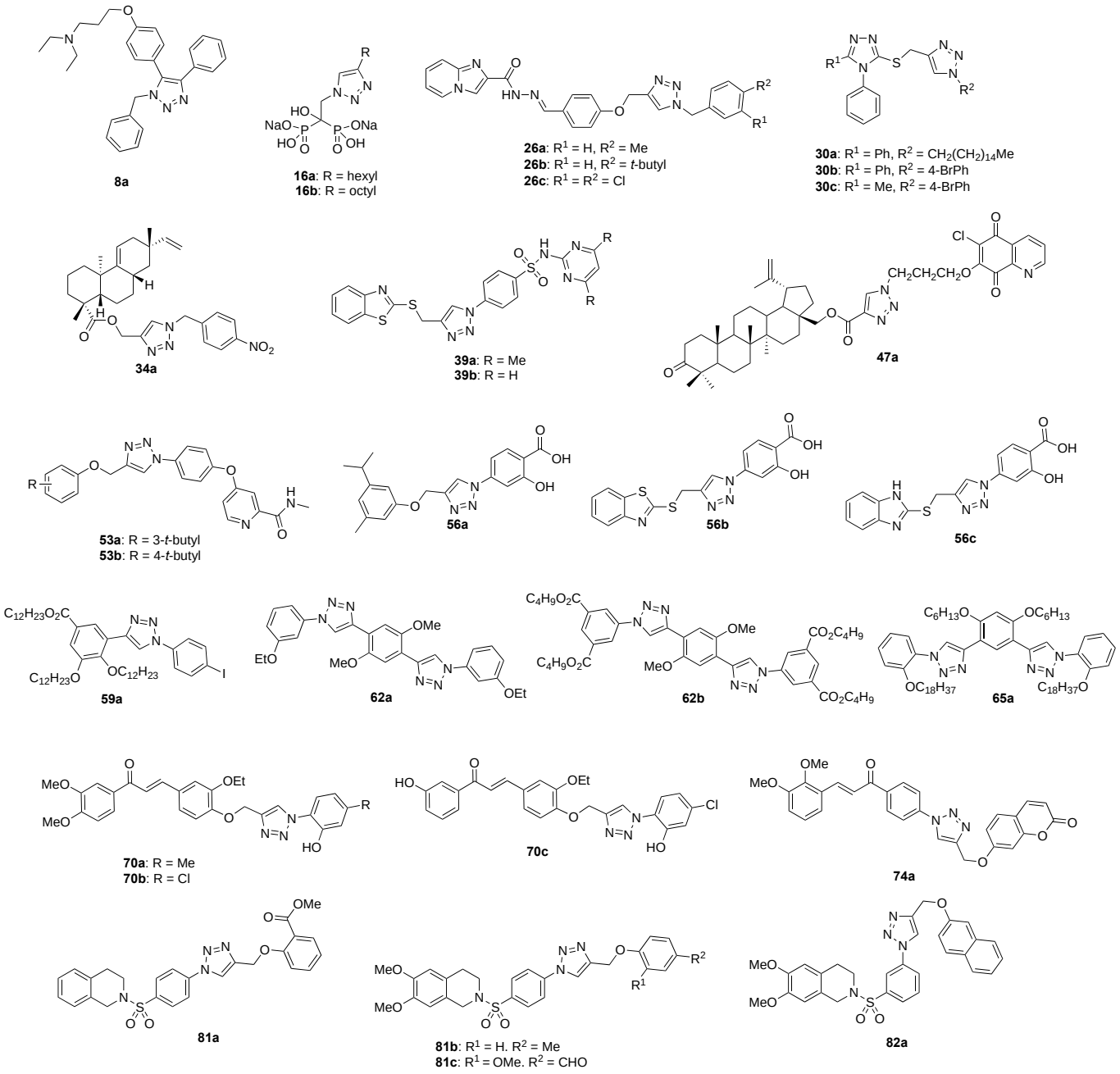
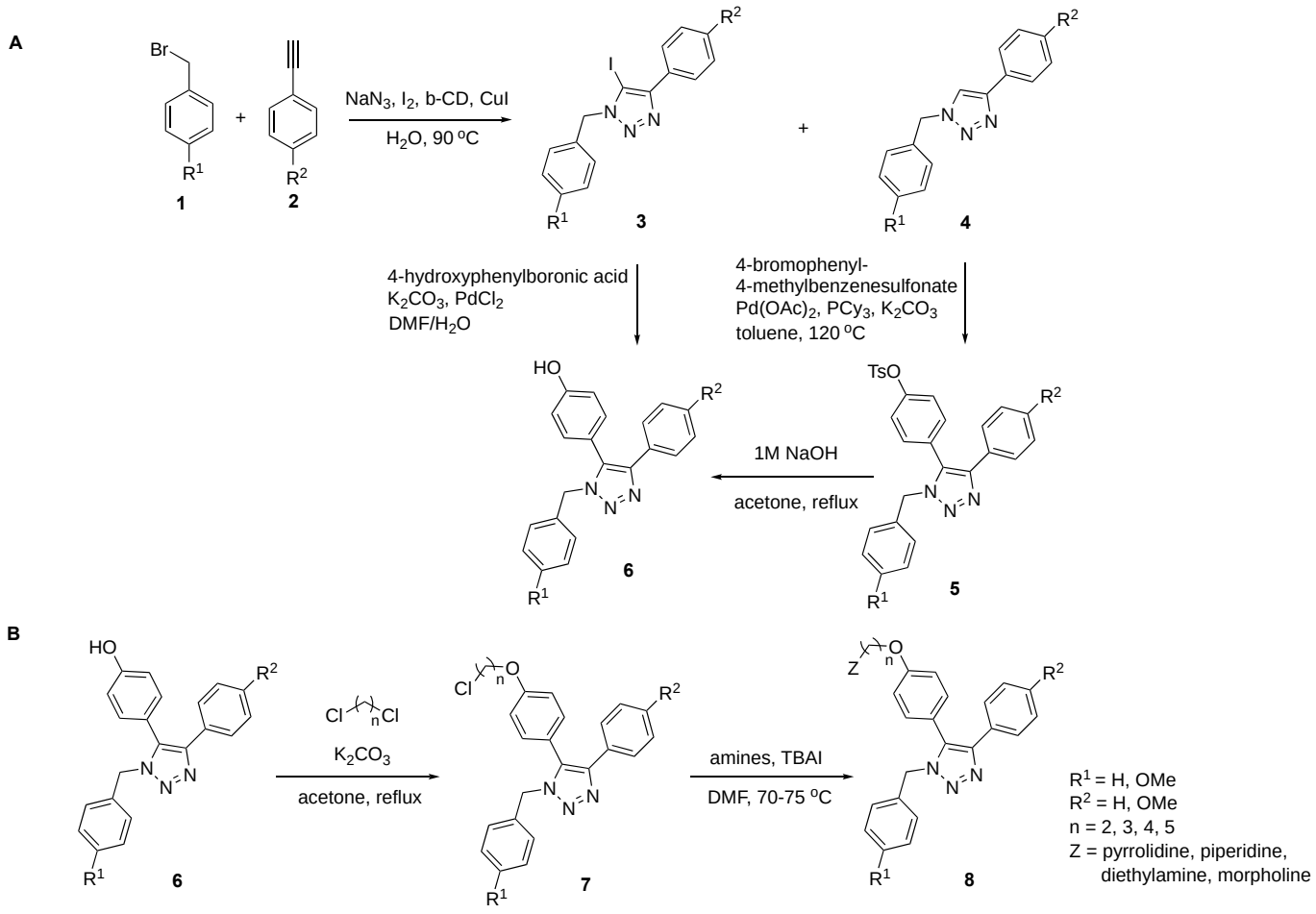


Figure 2. Structures of 1,2,3-triazole-based anticancer agents: diaryl-1,2,3-triazole **8a** (Section 2.1), bisphosphonate-1,2,3-triazoles **16a**-**16b** (Section 2.2), imidazopyridine-1,2,3-triazoles **26a**-**26c** (Section 2.3), 1,2,4-triazole-1,2,3-triazoles **30a**-**30c** (Section 2.4), acanthoic acid-1,2,3-triazole **34a** (Section 2.5), benzothiazole-1,2,3-triazoles **39a**-**39b** (Section 2.6), 1,4-quinone-betulin-1,2,3-triazole **47a** (Section 2.7), sorafenib-1,2,3-triazole analogues **53a**-**53b** (Section 2.8), salicylic acid-1,2,3-triazoles **56a**-**56c** (Section 2.9), mono- and bis-1,2,3-triazole **59a**, **62a-62b**, **65a** (Section 2.10), chalcone-1,2,3-triazoles **70a-70c** (Section 2.11), chalcone-coumarin-1,2,3-triazole **74a** (Section 2.12), *N*-sulfonylisoquinoline-1,2,3-triazoles **81a-81c, 82a** (Section 2.13)

2.1 Diaryl-1,2,3-triazoles

Dheer et al.[38] reported the synthesis of a set of diaryl-substituted 1,2,3-triazoles **8**, and investigated for their cytotoxic effects against two types of breast cancer (i.e., estrogen receptor-positive MCF-7 and estrogen receptor-negative MDA-MB-231) cell lines. Initially, 5-iodo-disubstituted-1,2,3-triazoles **3** were prepared through the in *situ* CuAAC reaction, using benzyl bromides **1** and phenylacetylenes **2** in the presence of NaN_3, Et_3N, I_2, and *β*-cyclodextrin in water. In such reaction, 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **4** was obtained as a minor product. In the next step, the Suzuki reaction was performed using 4-hydroxyphenylboronic acid to give compounds **6** (Scheme 3A). Concurrently, compound **6** was also formed by tosylation of compound **4** *via* an intermediate **5**. Then, the compounds **6** were alkylated to obtain derivatives **7**. Finally, the amination of compounds **7** with different amines like pyrrolidine, piperidine, diethylamine or morpholine to give the designed 1,2,3-triazoles **8** (Scheme 3B).

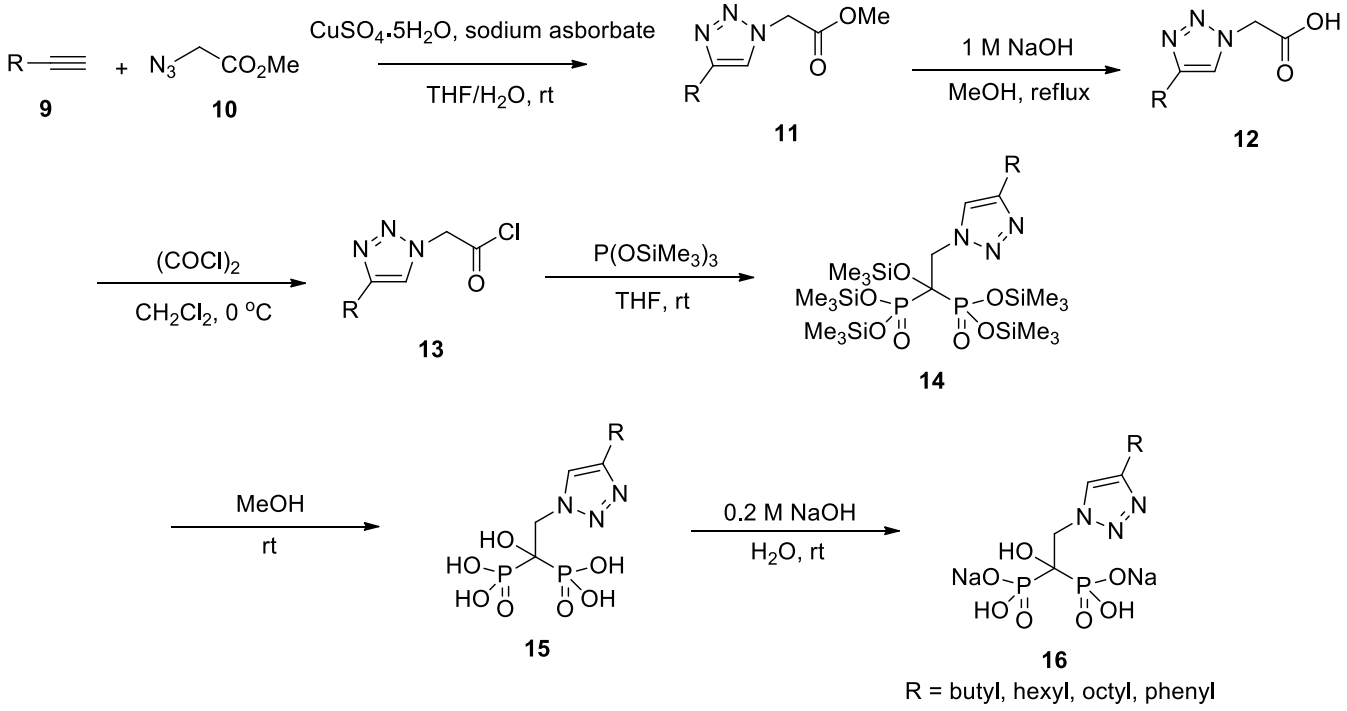


Scheme 3. Synthesis of diaryl-1,2,3-triazoles, (**A**) synthesis of compounds **6**, (**B**) synthesis of compounds **8** by amination of compounds **7**

The biological results demonstrated that compound **8a** (Figure 2) exhibited the most promising cytotoxic effects against both types of breast cancer cell lines (IC_{50}: MCF-7 = 3.5 and MDA-MB-231 = 15.54 μM) with preferable selectivity index. The cytotoxic effect was due to an ability of the compound to generate reactive oxygen species (ROS) that leads to an induction of cellular apoptosis. Molecular docking study was also carried out and showed that the compound **8a** could occupy in the binding site of ER-alpha with the same manner of 4-hydroxytamoxifen (a selective estrogen receptor modulator) suggesting that the modulation of ER-alpha could possibly be the mechanism of anticancer action of this compound.

2.2 Bisphosphonate-1,2,3-triazoles

A set of triazole bisphosphonates **16** was presented by Legigan group,[39] and their antiproliferative activities against MIA PaCa-2 (pancreas), MDA-MB-231 (breast), and A549 (lung) human tumor cell lines were assayed. The synthesis of compounds **16** is depicted in Scheme 4. First, 1,4-disubstituted triazoles **11** were prepared through the CuAAC reaction using methyl 2-azidoacetate **10** and the corresponding alkynes **9**. Hydrolysis of the methyl esters **11** followed by conversions to their corresponding acyl chlorides **13**. Treatment of the compounds **13** with $P(OSiMe_3)_3$ in THF furnished the silylated bisphosphonates **14**. Subsequently, methanolysis and neutralization of **14** led to the target compounds **16**.



Scheme 4. Synthesis of bisphosphonate-1,2,3-triazoles

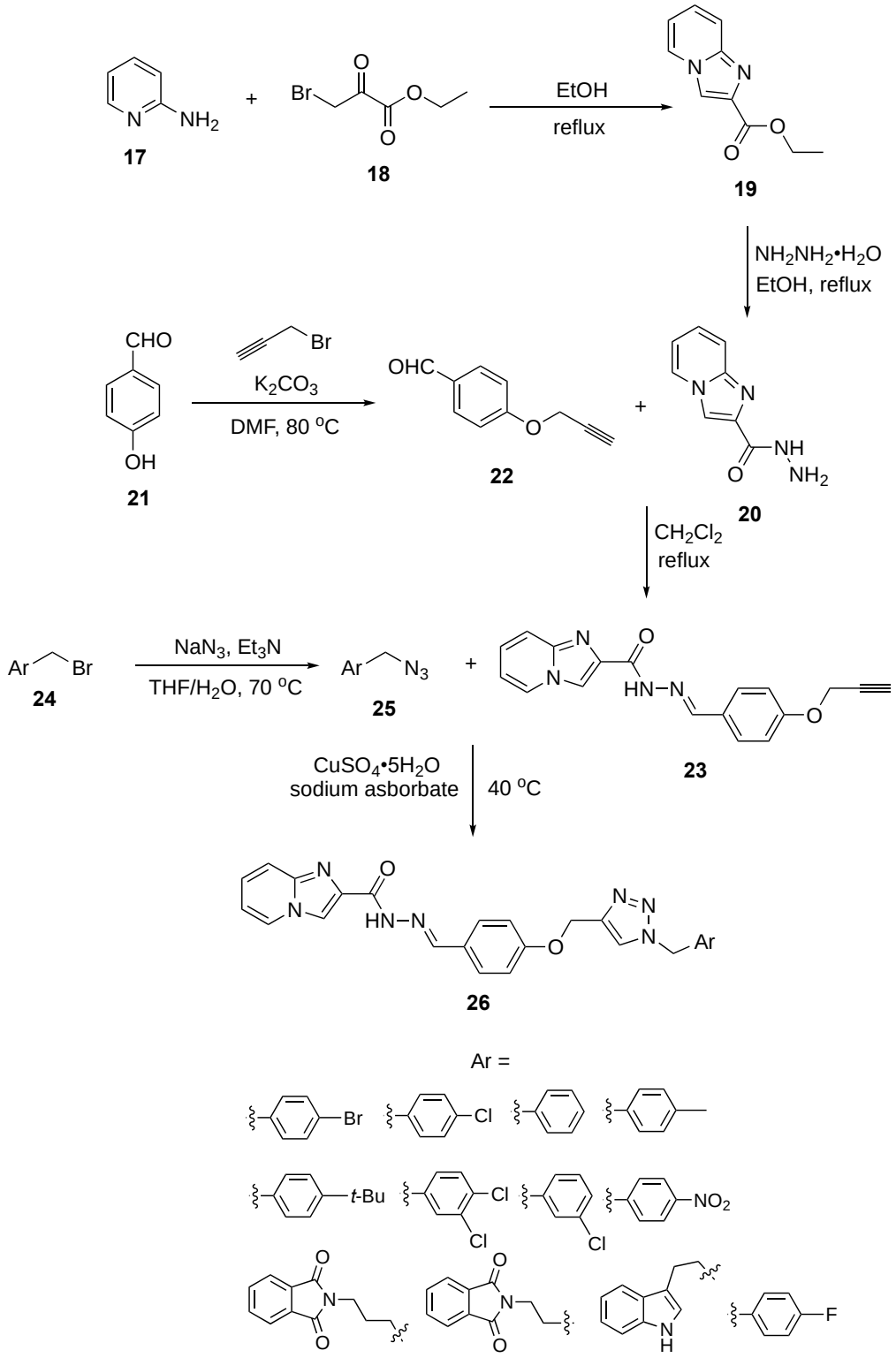
The biological investigations showed that **16a** (Figure 2) displayed notable antiproliferative activities against all the tested cancer cells (IC_{50}: 0.75-2.4 μM). Apparently, **16a** was shown to be 4- to 12-folds more

potent anticancer agent than the standard bisphosphonate drug, zoledronate. Molecular docking study of the compounds against human GGPP suggested that the triazoles **16a** and **16b** (Figure 2) bearing long alkyl chains could exhibit their antiproliferative effects through an inhibition of geranylgeranyl pyrophosphate (GGPP) biosynthesis *via* acting as GGPP synthase inhibitors.

2.3 Imidazopyridine-1,2,3-triazoles

Mesenchymal-epithelial transition factor (c-MET) is a receptor tyrosine kinase in which its abnormal activation was noted for various cancers. Recently, the development of c-MET kinase inhibitors has gained attention in cancer management.[40] A series of 12 imidazo[1,2-*a*]pyridine derivatives bearing 1,2,3-triazole moiety **26** were designed, synthesized, and evaluated as c-MET kinase inhibitors by Damghani et al.[41] The target triazoles **26** were synthesized as shown in Scheme 5. Initially, ethyl imidazo[1,2-*a*]pyridine-2-carboxylate **19** was prepared *via* the reaction of 2-aminopyridine **17** and ethyl bromopyruvate **18** in refluxing EtOH. Treatment of the compound **19** with hydrazine hydrate under reflux gave imidazo[1,2-*a*]-pyridine-2-carbohydrazide **20**. Further reaction of the hydrazide **20** and compound **22** yielded imidazo[1,2-*a*]pyridine-2-carboxylic acid (4-prop-2-ynyloxybenzylidene)hydrazide **23**. The compound **22** was prepared from 4-hydroxybenzaldehyde **21** reacting with propagyl bromide. Finally, the CuAAC of the alkyne **23** and azides **25** afforded the triazoles **26**. The starting compound **25** was prepared *via* the reaction of benzyl bromides **24** with NaN_3 in the presence of Et_3N.

Among all synthesized compounds, three derivatives from series **26** (i.e., **26a**, **26b**, and **26c**, Figure 2) were noted as the most potent c-MET kinase inhibitors (% inhibition > 50 at 25 μM). The compounds also exhibited antiproliferative effects against c-MET expressed pancreatic (AsPc-1, Suit-2, and MIA PaCa-2) and lung (EBC-1) cancer cell lines displaying low IC_{50} values within a range of 3.0 μM. Investigations on AsPc-1 cells indicated the abilities of these compounds on suppressing phosphorylation of c-MET as well as inducing apoptosis. Moreover, inhibitory effects were performed toward various types of receptor protein kinases indicated that compounds **26a**, **26b**, and **26c** are relatively selective against the c-MET kinase. *In silico* studies also suggested that these compounds could occupy in the hydrophobic back pocket of the target enzyme. Phenyl substituted moiety of the compounds was also noted to play role in an additional hydrophobic interaction toward the target contributing to potent inhibitory effect.

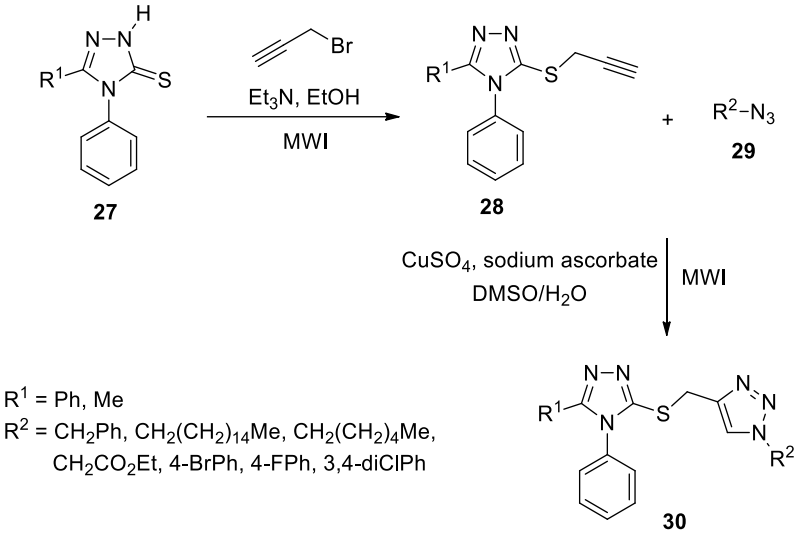


Scheme 5. Synthesis of imidazopyridine-1,2,3-triazoles

2.4 1,2,4-Triazole-1,2,3-triazoles

Conjugates of 1,2,3-triazoles linked to 1,2,4-triazoles **30** were synthesized by Ali et al.,[42] and their anticancer activities were investigated against human colon carcinoma (Caco-2 and HCT116), human cervical carcinoma (HeLa), and human breast adenocarcinoma (MCF-7) cell lines. The synthetic strategies

are depicted in Scheme 6. The target 1,2,4-triazole-1,2,3-triazole conjugates **30** were synthesized from 1,2,4-triazole units **27**. Propargylation of the precursors **27** with propargyl bromide under MWI (microwave irradiation) gave thiopropargylated 1,2,4-triazoles **28**. Finally, the CuAAC of the compound **28** with various azides **29** provided the products **30**.



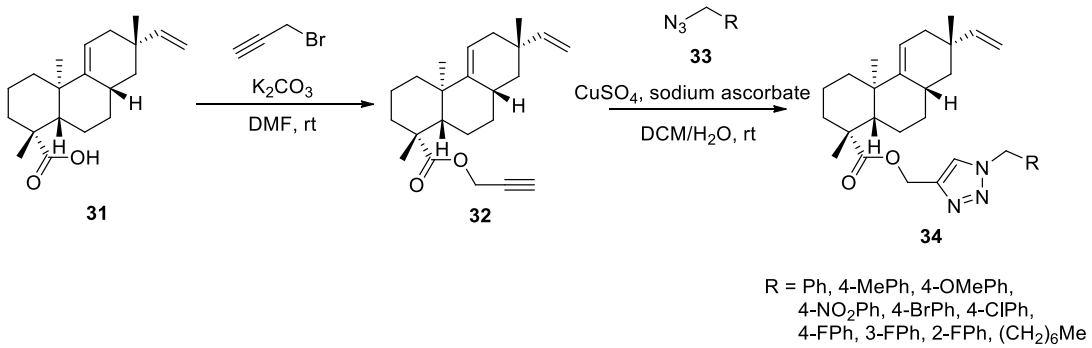
Scheme 6. Synthesis of 1,2,4-triazole-1,2,3-triazoles

Among the tested cancer cells, compounds **30a**, **30b**, and **30c** (Figure 2) showed promising activities against breast cancer MCF-7 cell line (IC_{50}: 0.31-4.46 μM). Compound **30a** was the most potent one against the MCF-7 cell line (IC_{50} = 0.31 μM). It should be noted that compound **30b** elicited the most potent activity against Caco-2 cell line (IC_{50} = 4.98 μM) while ranked as the second most potent compound against MCF-7. Cyclin-dependent kinase 2 (CDK2) played role in cell cycle in which its overexpression was noted to be involved with abnormal cell growth of several types of cancers, and its inhibition is noted as an interesting anticancer strategy.[43] Molecular docking was performed and indicated that an inhibition of the CDK2 would be a possible mechanism of anticancer action of these triazoles.

2.5 Acanthoic acid-1,2,3-triazoles

A novel series of acanthoic acid analogues containing triazole moiety (**34**) were synthesized by Kasemsuk et al.[44] through the CuAAC reaction as shown in Scheme 7. Anticancer activity against four types of cholangiocarcinoma cell lines (i.e., KKU-055, KKU-100, KKU-213, and KKU-214) were investigated. Compound **34a** (Figure 2) was noted to be the most promising compound with the highest potency against KKU-213 cell line (IC_{50} = 18 μM) as well as KKU-214 and KKU-055 (IC_{50} = 21 and 33 μM, respectively). Molecular docking against two possible target protein kinases (i.e., CDK2 and epidermal growth factor receptor (EGFR)) was performed to elucidate the possible binding modalities. Both kinases played roles in cellular growth, proliferation, and survival in which their overexpression are associated with genesis and

progression of several cancers.[45,46] *In silico* results indicated that compound **34a** could occupy within the binding site of the targets with low binding energy (CDK2 = -12.7 and EGFR = -10.8 kcal/mol). This suggested that compound **34a** may act as CDK2 and/or EGFR inhibitors to elicit its anti-cholangiocarcinoma effects. The analysis of ligand-protein interaction suggested that triazole and nitro moieties are crucial chemical features for the formation of strong hydrogen bonding while the diterpene ring structure is noted for the hydrophobic interaction against these target kinases.

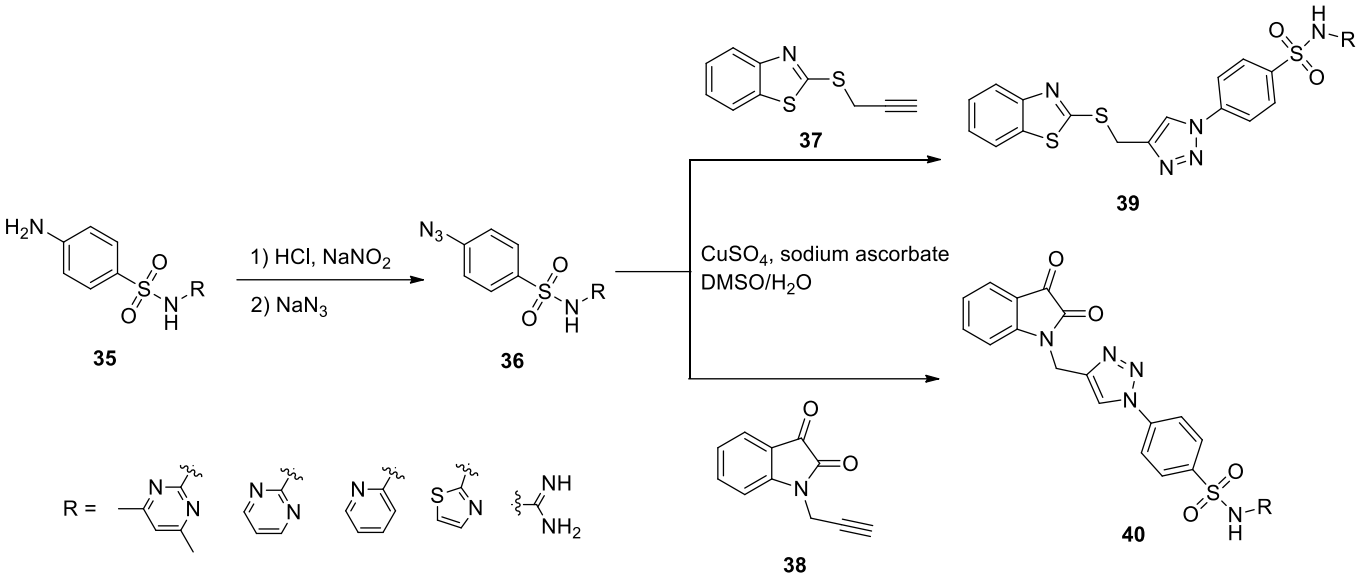


Scheme 7. Synthesis of acanthoic acid-1,2,3-triazoles

2.6 Benzothiazole/isatin-1,2,3-triazoles

Computer-aided drug discovery was employed for rational design and development of benzothiazole/isatin derivatives **39-40** by Rezki et al.[47] Scaffold hopping was performed by using the commercially available quinazoline based EGFR inhibitors (i.e., gefitinib, erlotinib, afatinib) as templates for designing target scaffolds in which the 6-membered quinazoline ring core structure, hydrophilic part, and lipophilic part were replaced by the 5-membered triazole ring, sulfonamides, and benzothiazole/isatin, respectively. Accordingly, a series of benzothiazole/isatin linked to 1,2,3-triazole moiety and terminal sulfa drugs **39-40** were synthesized and evaluated for cytotoxic activity against three types of cancer cell lines (MCF-7, HCT-116, and HepG2).[47] The synthetic route to the target 1,2,3-triazoles **39** and **40** was performed by the Click reaction of the appropriate benzothiazole or isatin based alkyne with several sulfa drugs azides as depicted in Scheme 8. The conversion of amino sulfa drugs **35** into their corresponding azides **36** was performed *via* diazotization *in situ* catalyzed by $NaNO_2$ in HCl followed by treatment with NaN_3. Then, the Click reaction of the freshly prepared sulfa drug azides **36** with propargylated benzothiazole **37** or isatin **38** led to the conjugates **39** and **40**, respectively.

The synthesized compounds **39-40** were investigated for their antiproliferative and apoptosis-inducing effect as well as inhibitory activity against EGFR. Results indicated that most of the tested compounds are potent EGFR inhibitors (IC_{50} values 103.79-712.29 nM). Among all, compounds **39a** and **39b** (Figure 2) elicited the promising effect (IC_{50}: 104.29 and 103.79 nM, respectively) with comparable activity to that of the reference drug, erlotinib (IC_{50} = 76.6 nM). Both compounds (**39a** and **39b**) displayed good antiproliferative effect against the HepG2 cell line (IC_{50}: **39a** = 1.491 μM and **39b** 1.786 μM), but weaker

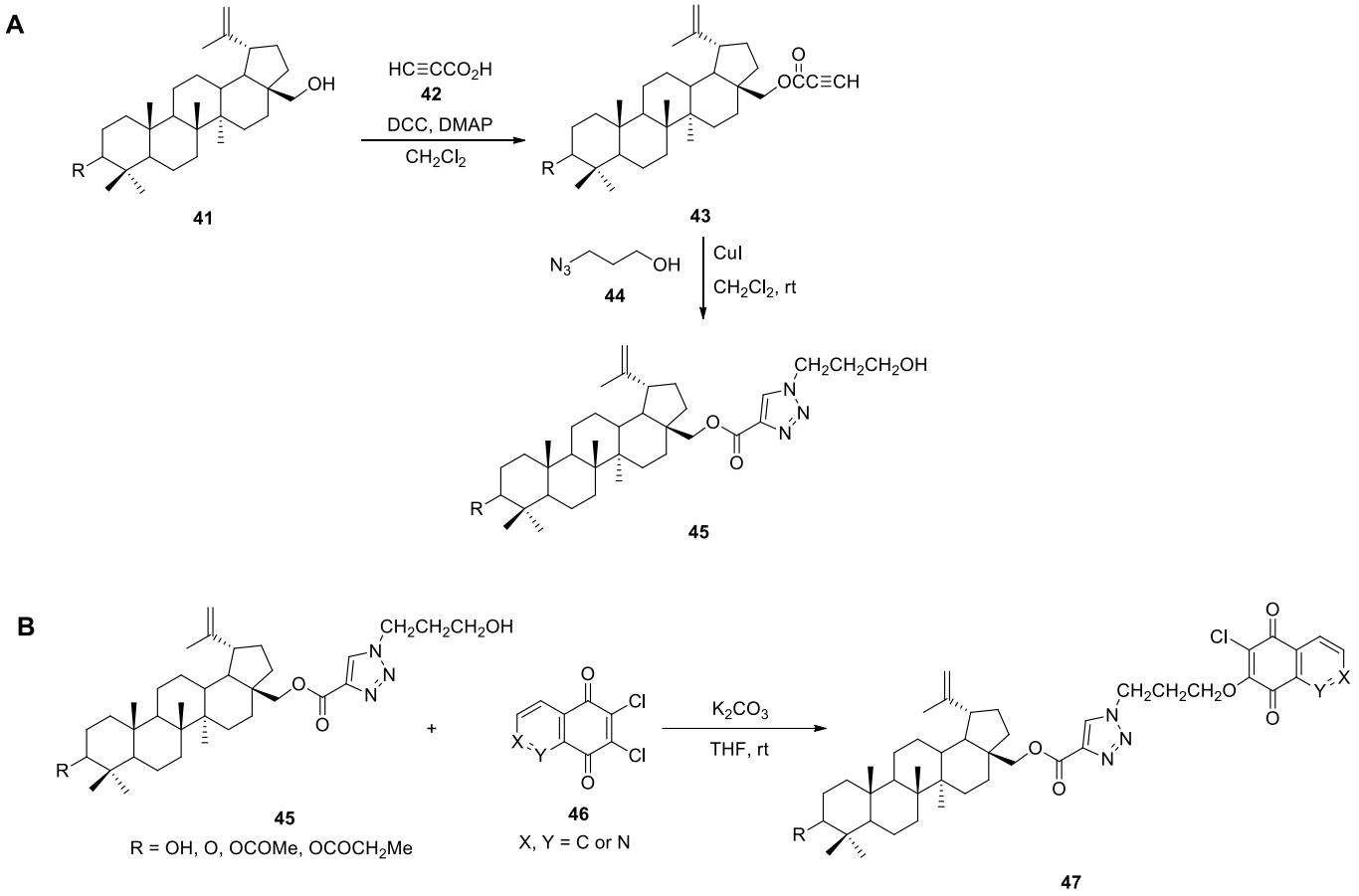


Scheme 8. Synthesis of benzothiazole/isatin-1,2,3-triazoles

inhibited the HCT-116 cell lines (IC_{50} values greater than 39 μM). Compound **39a** also showed the promising activity against the MCF-7 (IC_{50} = 2.45 μM). It also should be noted that both compounds are more potent than the reference drug staurosporine (IC_{50}: HepG2 = 16.98 and MCF-7 = 25.8 μM). Additionally, results suggested that the antiproliferative effect of these compounds could be due to an induction of cell apoptosis and cell cycle arrest at G2/M phase. Furthermore, molecular docking study was performed to reveal that **39a** and **39b** could bind at the ATP binding site of the EGFR in the same manner with the reference drug, erlotinib. The findings from ligand-target interactions also supported the scaffold-hopping guided design suggesting that the triazole moiety could be used as a representative group for the quinazoline to form a strong H-bond with the conserved Met769 residue of the EGFR.

2.7 1,4-Quinone-betulin-1,2,3-triazoles

Triazole moiety was reported as a potential linker for the design of new hybrids with improved activity and properties.[11,48] An example of the success design was reported by Kadela-Tomanek et al. in which a series of triazole-linked 1,4-quinone-betulin hybrids **47** were synthesized and reported as anticancer agents (Scheme 9).[49] The 1,4-quinone scaffold was connected to betulin derivatives using 3-hydroxypropyl-1,2,3-triazole group as a linker. The propynoyl derivatives **43** were obtained by the treatment of starting alcohol compounds **41** with propiolic acid **42** in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (Scheme 9A). Then, the obtained ester compounds **43** were converted to triazole derivatives **45** by reacting with 3-azidopropanol **44** in the presence of copper(I) iodide in CH_2Cl_2. Finally, the reaction between the triazole compounds **45** and 1,4-quinone **46** in the presence of K_2CO_3 in THF gave the hybrids **47** (Scheme 9B).



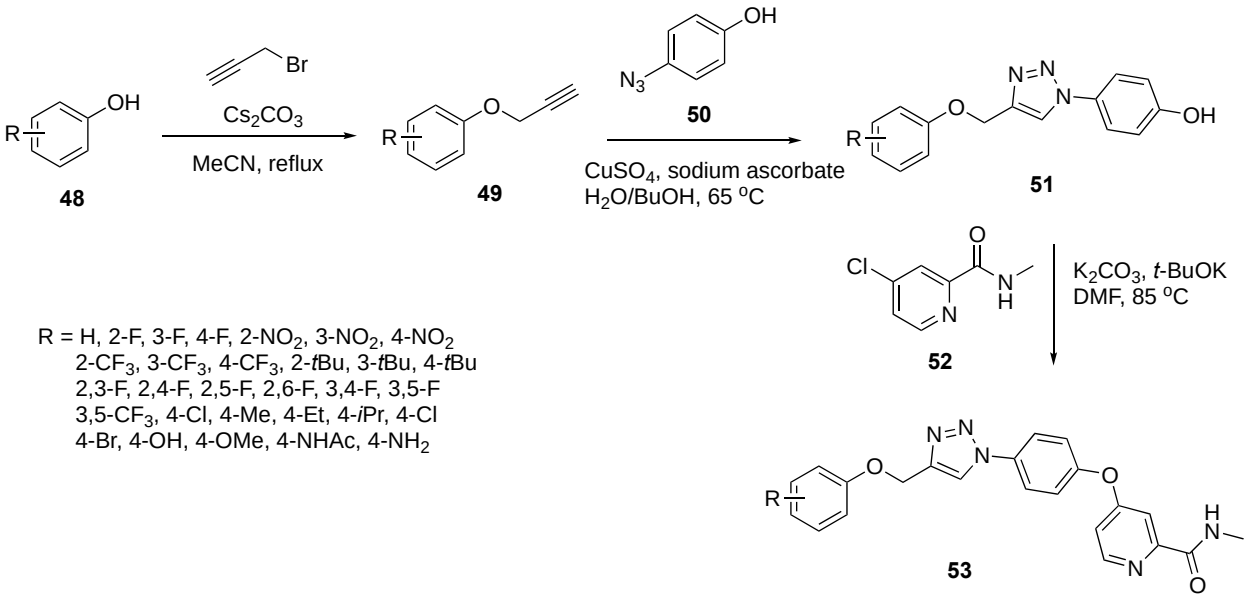
Scheme 9. Synthesis of 1,4-quinone-betulin-1,2,3-triazoles, (**A**) synthesis of compounds **45** (**B**), synthesis of hybrids **47**

The synthesized hybrids were investigated for their anticancer activities against various cancer cell lines (i.e., melanoma; Colo-829, ovarian cancer; SK-OV-3, breast cancer; T47D, MCF-7 and MDA-MB-231, colon cancer; Caco-2, and lung cancer; A549). Among the tested compounds, compound **47a** (Figure 2) was noted as the most promising compound against A549, Colo-829, and Caco-2, cell lines (IC_{50} = 1.59, 3.55, and 9.24 μM, respectively). Additionally, the compound showed non-cytotoxicity against the normal fibroblast cell line (HFF-1). An apoptotic study against A549 cell line indicated that the compound **47a** induced cancer cell death *via* an alteration of transcription activity of the cell cycle regulatory genes (i.e., p53 and p21) which leads to an increase of apoptotic (BAX) and decrease of anti-apoptotic (BCL-2) proteins, and ultimately an activation of mitochondrial apoptotic pathway. Molecular docking was performed against a possible target, DT-diaphorase (NQO1) protein which is an enzyme that catalyzes the reduction reaction of quinones to protect against cellular damages caused by free radicals. Results revealed that the compound **47a** could occupy in an active site of the enzyme, in which the triazole ring played role in hydrophobic interaction with the Phe232. This suggested that the compound **47a** could act as a substrate of NQO1. The level of NQO1 enzyme was relatively elevated in several types of cancer cells when

compared with the surrounding normal cells which suggested its potential as a target for development of selective anticancer agents.[50]

2.8 Sorafenib-1,2,3-triazole analogues

A series of 1,2,3-triazole containing sorafenib analogues **53** were prepared by Palakhachane et al.[51] *via* the Huisgen 1,3-dipolar cycloaddition and nucleophilic substitution. Initially, various phenols **48** were *O*-propargylated using propargyl bromide under basic conditions to give the corresponding alkynes **49**. Subsequently, the 1,2,3-triazole rings were constructed using the Huisgen 1,3-dipolar cycloaddition between the obtained alkynes **49** and 4-azidophenol **50**, leading to the formation of compounds **51**. The triazole-phenols **51** were coupled with 4-chloropicolinamide **52** in the presence of *t*-BuOK and K_2CO_3 to afford the target 1,2,3-triazole analogues **53** (Scheme 10).



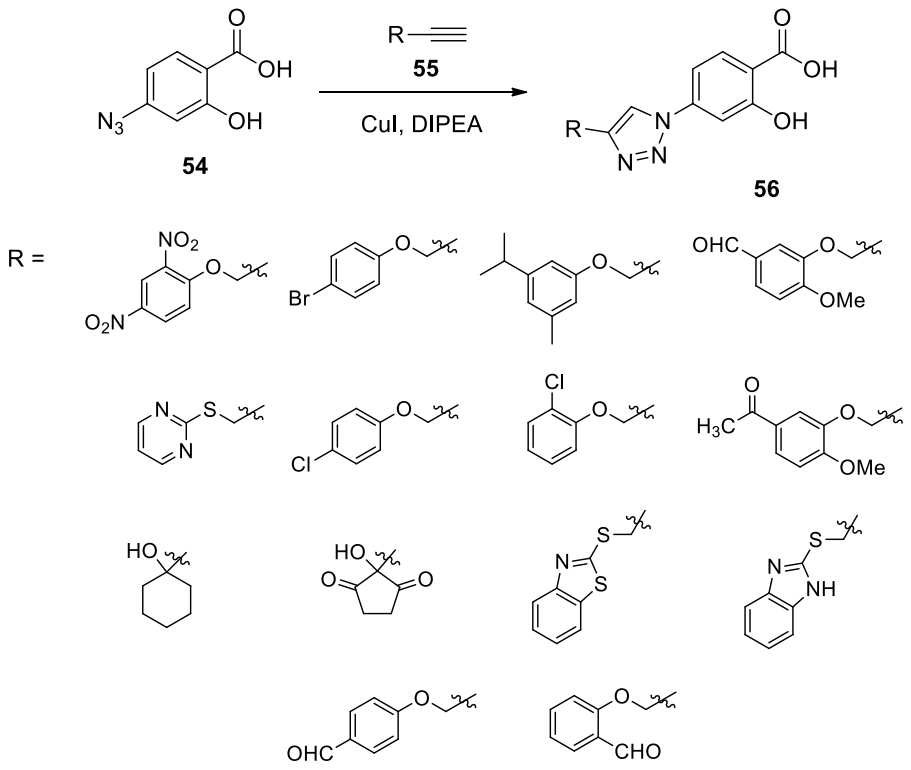
Scheme 10. Synthesis of sorafenib-1,2,3-triazole analogues

The synthesized compounds were tested against 2 types of hepatocarcinoma cancer cell lines (i.e., HepG2 and Huh7). For HepG2 cell line, compound **53a** (Figure 2) was the most potent compound (IC_{50} = 61.6 μM); however, its activity was much weaker than that of the reference drug sorafenib (IC_{50} = 3.87 μM). For Huh7 cell line, compound **53b** (Figure 2) showed potent activity against Huh7 cell line (IC_{50} = 5.67 μM) with promising selectivity index (2.6-fold higher than the sorafenib), while inactive against the HepG2. Mechanism of action of the reference drug sorafenib was reported to be *via* a multiple inhibition of kinases activities (including serine/threonine protein kinase (B-RAF) and vascular endothelial growth factor receptor (VGFR), and others which related in cell growth, proliferation, and angiogenesis).[52,53] Accordingly, molecular docking was performed to reveal possible binding mode of compound **53b** against two possible target protein kinases i.e., serine/threonine protein kinase (B-RAF) and vascular endothelial growth factor

receptor 2 (VGFR2). *In silico* results revealed that the compound **53b** could occupy within the active site of VGFR2 and B-RAF in the similar manner of those binding modes of the sorafenib. This suggested that compound **53b** is a promising compound for further development as more selective but less toxic anticancer agents for hepatocarcinoma.

2.9 Salicylic acid-1,2,3-triazoles

Signal transducer and activator of transcription 3 (STAT3) are key regulatory proteins involved in uncontrolled cell proliferation, cell differentiation, survival, and tumorigenesis.[54] Several classes of small molecules were reported to exhibit their anticancer effects *via* an inhibition of STAT3 activity; however, this is still lacking in an area of triazoles. A series of 4-(1,2,3-triazol-1-yl)salicylic acid derivatives were synthesized and reported as STAT3 inhibitors by Ríos-Malváez group.[55] Triazoles **56** were synthesized using the CuAAC of 4-azido-2-hydroxybenzoic acid **54** with the appropriate alkynes **55** (Scheme 11).



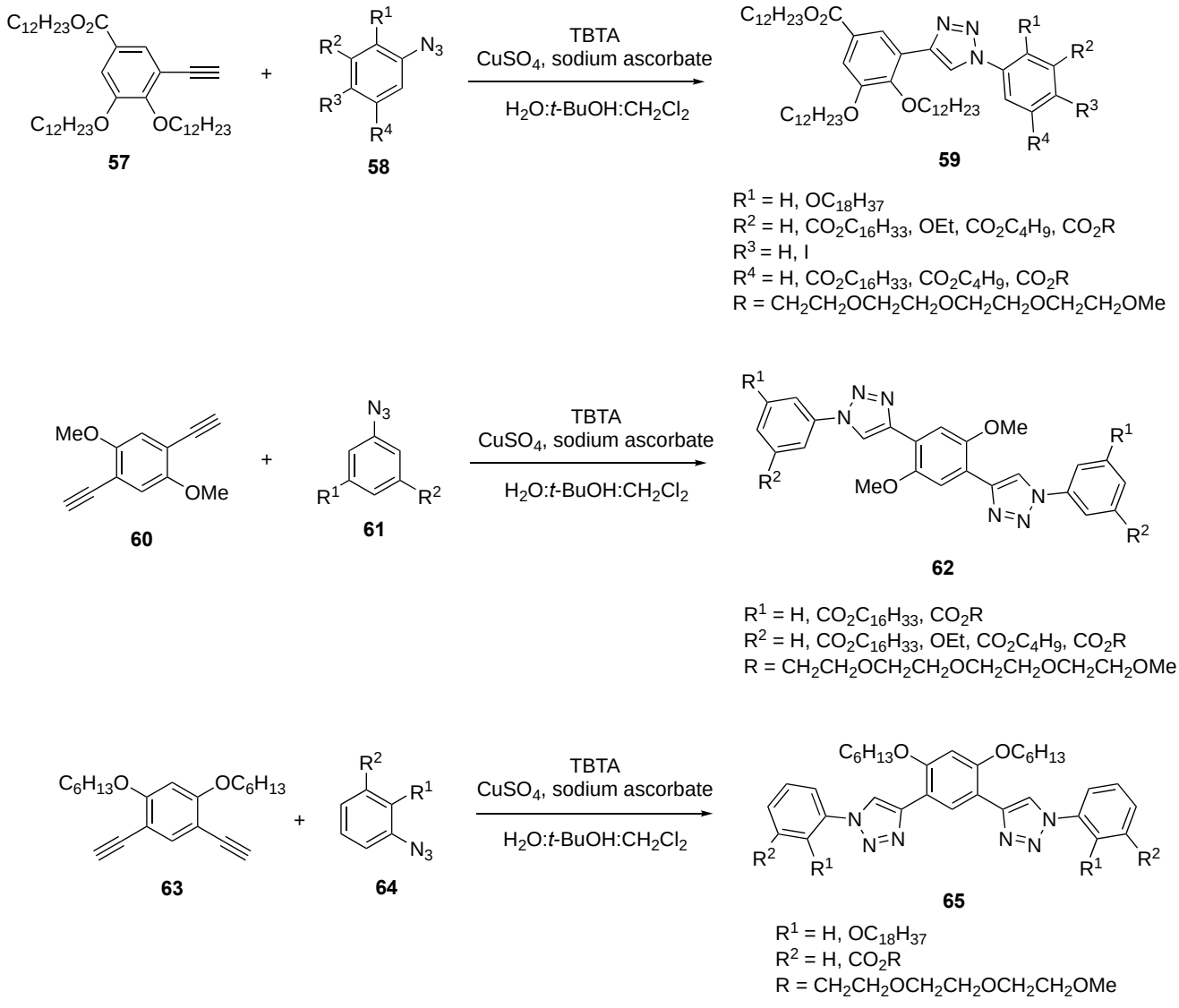
Scheme 11. Synthesis of salicylic acid-1,2,3-triazoles

The synthesized compounds **56** were studied for their antiproliferative activities against U251 (human glioblastoma), PC-3 (human prostate cancer cell line), K562 (human leukemia), HCT-15 (human colorectal adenocarcinoma), MCF-7 (human breast adenocarcinoma) and SKLU (human lung adenocarcinoma). The investigations showed that compounds **56a**, **56b** and **56c** (Figure 2) exhibited good antiproliferative effects against HCT-15, MCF-7 and U251 cell lines (% cell growth inhibition at 25 μM = 64.64%, 33.53% and 57.9%, respectively). Molecular docking results demonstrated that these derivatives could bind in the cavity

of STAT3, and the triazole moiety was noted to be essential feature for potent activity *via* its strong interaction with ARG154 residue of the target.

2.10 Mono- and bis-1,2,3-triazoles

A series of mono- and bis-1,2,3-triazole-based molecular architectures **59**, **62** and **65** were prepared *via* the CuAAC (Scheme 12) reported by Malah and co-worker.[56] Anticancer activities were investigated against 4 cancer cell lines including HepG2, MCF-7, A549, and HCT-116 using MTT assay. Cytotoxicity against normal RPE-1 cell line was also studied. Results suggested mono-1,2,3-triazole **59a** (Figure 2) as the most potent compound against HCT-116 (IC_{50} = 4.9 μM), and bis-1,2,3 triazoles **62a**, **62b**, **65a** (Figure 2) as the most potent compounds against HepG2 (IC_{50} = 27.8 μM), MCF-7 (IC_{50} = 10.0 μM), and A549 (IC_{50} = 29.9 μM), respectively. Additionally, these compounds are non-cytotoxic against the tested human normal cell, except for compound **62b** (IC_{50} RPE-1 = 80.6 μM).



R^1 = H, $OC_{18}H_{37}$
R^2 = H, $CO_2C_{16}H_{33}$, OEt, $CO_2C_4H_9$, CO_2R
R^3 = H, I
R^4 = H, $CO_2C_{16}H_{33}$, $CO_2C_4H_9$, CO_2R
R = $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OMe$

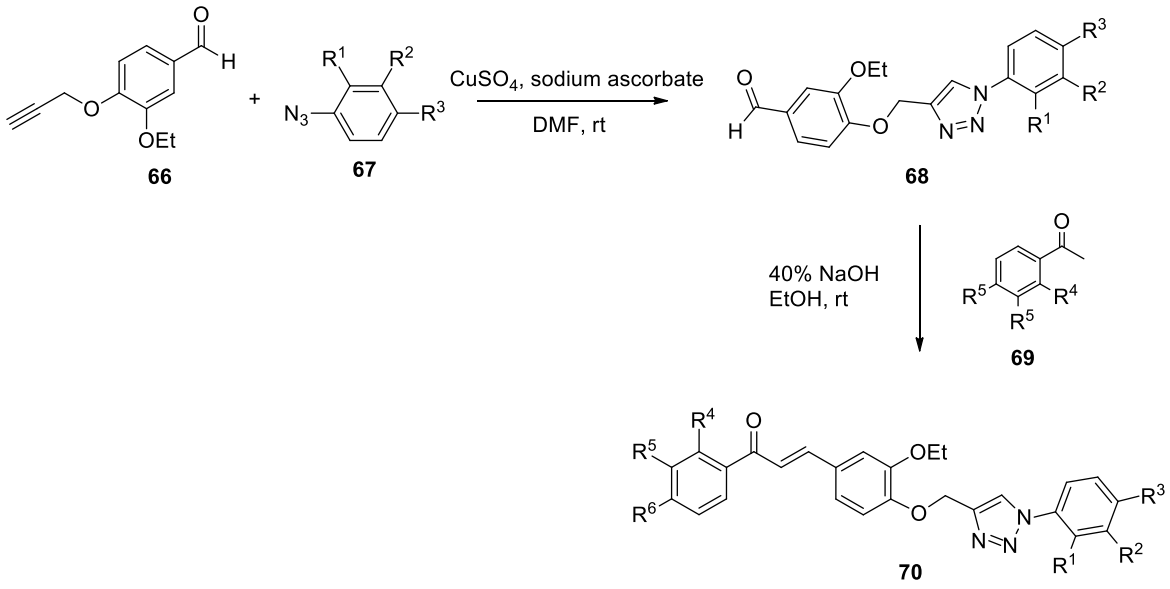
R^1 = H, $CO_2C_{16}H_{33}$, CO_2R
R^2 = H, $CO_2C_{16}H_{33}$, OEt, $CO_2C_4H_9$, CO_2R
R = $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OMe$

R^1 = H, $OC_{18}H_{37}$
R^2 = H, CO_2R
R = $CH_2CH_2OCH_2CH_2OCH_2CH_2OMe$

Scheme 12. Synthesis of mono-triazole **59** and bis-triazoles **62** and **65**

2.11 Chalcone-1,2,3-triazoles

A series of nine 1,2,3-triazole tethered chalcone hybrids **70** were designed and reported as anticancer agents by Gurrapu et al.[57] The synthetic route to the desired hybrids **70** is summarized in Scheme 13. Propargylated benzaldehyde **66** reacted with various aryl azides **67** to provide the triazoles **68**. The desired hybrids **70** were achieved by the condensation of substituted acetophenones **69** and triazoles **68** in the presence of 40% NaOH in EtOH at room temperature. Cytotoxic activity was investigated against 3 cancer cell lines (i.e., MCF-7, MDA-MB-231, and HeLa). Results suggested three compounds (**70a**, **70b**, and **70c**, Figure 2) as a promising series. These compounds exhibited moderate activities against the Hela cell (IC_{50} = 31.6-71.05 μM) and potent activities against two breast cancer cell lines (IC_{50}: MCF-7 = 0.02-1.59 μM, and MDA-MB-231 = 0.31-2.66 μM). Apparently, these set of compounds are less cytotoxic to the normal tested cell MCF-10a (IC_{50} >130 μM) than the standard drug, cisplatin (IC_{50} 24.92 μM). Among the three, compound **70b** was noted as the most promising selective and potent compound against both tested breast cancer cell lines. For activities against MCF-7, the compound **70b** exhibited lower IC_{50} value with higher selectivity index (SI) when compared to those of the reference drug, cisplatin (IC_{50}: **70b** = 0.02, cisplatin = 1.28 μM, and SI: **70b** = 6964.5, cisplatin = 19.46). Similar findings were also noted for the effects of this compound **70b** against another breast cancer MDA-MB-231 cell line, but with less promising degree (IC_{50} = 0.31 μM, and SI = 449.32). Compounds **70a** and **70c** also showed greater potency against the MDA-MB-231 cell line with lower IC_{50} values than the cisplatin, but their activities against MCF-7 and HeLa cells were weaker than those of the cisplatin. Structure-activity relationship study also suggested that the substitutions of methoxy and chloro moieties (at different positions) are considered crucial for the potent activities of these three compounds beyond other derivatives. Molecular docking was performed to elucidate the binding modes of compounds against two possible protein targets i.e., EGFR kinase and estrogen receptor-α (ERα).

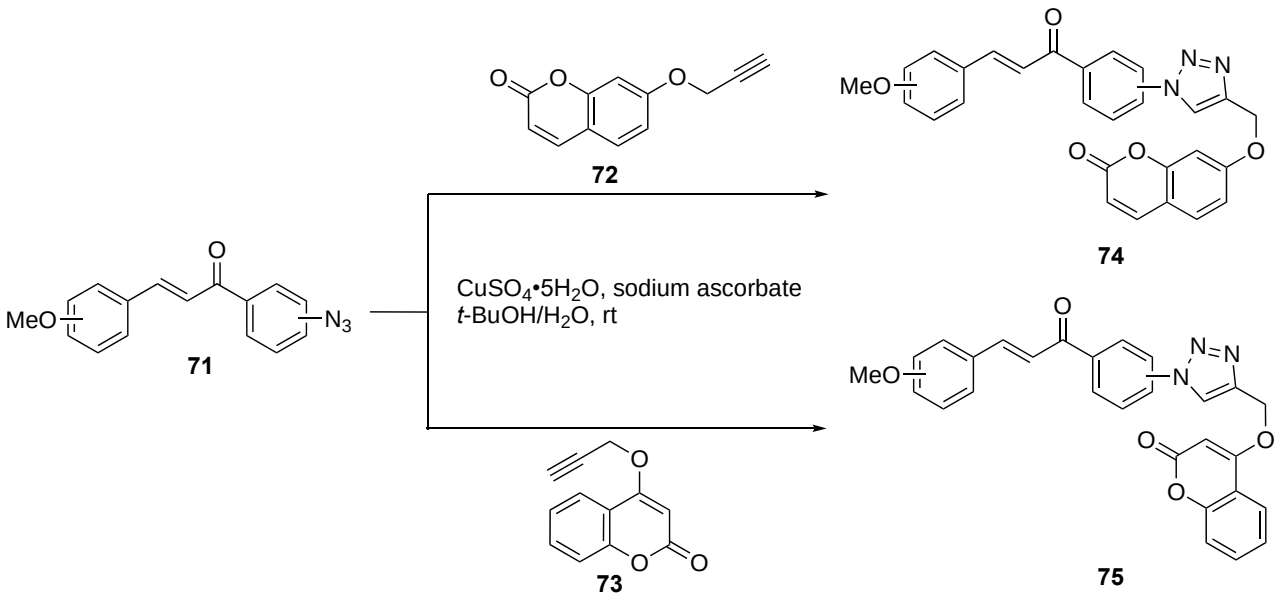


Scheme 13. Synthesis of chalcone-1,2,3-triazoles

Compound **70c** exhibited the strongest binding against EGFR. Findings from this study suggested that the triazole-chalcone hybrids could be potentially developed as selective potent anti-breast cancer agents.

2.12 Chalcone-coumarin-1,2,3-triazoles

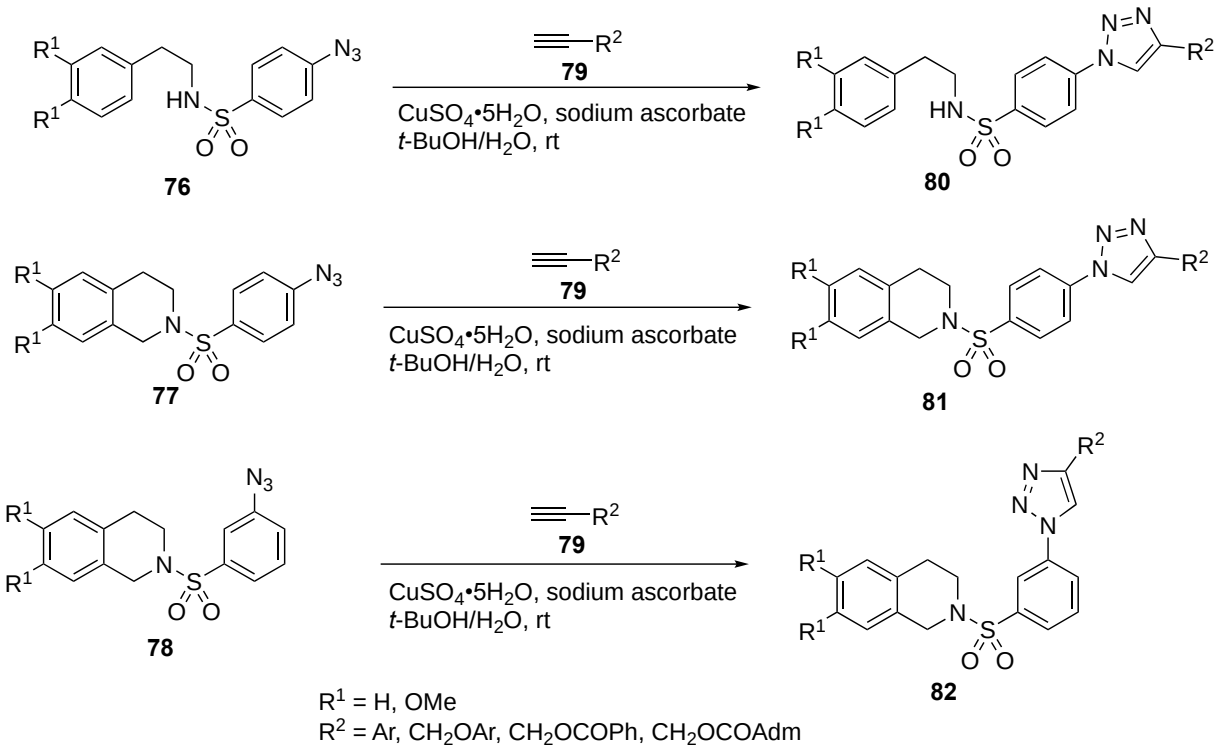
Role of triazole as a linker for bioactive hybrids was demonstrated by another published work of Pingaew et al.[58] Herein, a series of novel chalcone-coumarin derivatives **74** and **75** linked by the 1,2,3-triazole ring through the CuAAC of azidochalcone **71** with alkynes **72** and **73** (Scheme 14) were reported. Investigations on anticancer activities against four cancer cell lines (i.e., HuCCA-1, HepG2, A549, and MOLT-3) suggested that most of the synthesized compound displayed potent cytotoxic effect against the MOLT-3 cell while exhibited moderate to inactive activities against others. Among all, compound **74a** (Figure 2) displayed the promising activities against HuCCA-1, HepG2 and A549 cell lines (IC_{50} values = 4.81, 8.18 and 7.95 μM, respectively) and showed non-cytotoxicity against the normal cell. Moreover, the compound **74a** exhibited higher potency toward the HepG2 than the reference drug, etoposide (IC_{50} = 30.16 μM). Molecular docking study suggested that the compound could possibly act as a tubulin inhibitor for eliciting its cytotoxic action.



Scheme 14. Synthesis of chalcone-coumarin-1,2,3-triazoles

2.13 *N*-Sulfonylphenethylamine/isoquinoline-1,2,3-triazoles

A series of triazole-sulfonamides **80-82** were reported as anticancer agents and aromatase inhibitors by Pingaew et al.[59-62] The triazole-sulfonamides **80-82** were synthesized by the CuAAC of sulfonamide-azides **76-78** and akyne derivatives **79** as shown in Scheme 15.[59-62]



Scheme 15. Synthesis of *N*-sulfonylphenethylamine/isoquinoline-1,2,3-triazoles

Compounds **80** and **81** were investigated for their cytotoxic effects against four cancer cell lines (i.e., HuCCA-1, HepG2, A549, and MOLT-3). Findings suggested a set of three promising compounds including methylbenzoate analog **81a** (IC_{50} values: HuCCA-1 = 0.63 μM, A549 = 0.57 μM), tolyl analog **81b** (IC_{50} value: HepG2 = 0.56 μM), and benzaldehyde analog **81c** (IC_{50} value: MOLT-3 = 5.50 μM) as shown in Figure 2. Molecular docking study indicated an aldo–keto reductase 1C3 (AKR1C3) as possible anticancer target of these derivatives.[60] The AKR1C3 involves in the biosynthesis of androgen (a precursor for testosterone) within the tumor cells, and its inhibition was noted as a potential anticancer mechanism for both hormonal-dependent and hormonal-independent cancers.[63]

Brest cancer is one of the most common cancers in women worldwide, and its management is still challenging. Aromatase enzyme is a rate-limiting enzyme for estrogen biosynthesis, and its inhibition is well-known for the management of estrogen-dependent cancers.[64] Triazole ring is presented in many clinically available non-steroidal aromatase inhibitors, and its heterocyclic nitrogen atoms are noted for essential interaction with the enzyme.[65] Accordingly, compounds **80**-**82** were studied for their anti-breast cancer and aromatase inhibitory effects.[62] Aromatase inhibitory assay highlighted that compound **82a** (Figure 2), an analog bearing naphthalenyloxymethyl substituent at position 4 of the triazole ring, exhibited the promising aromatase inhibitory activity with nanomolar range of IC_{50} value (IC_{50} = 70 nM). This compound also elicited cytotoxic effect against a hormone-dependent breast cancer cell line T47-D (IC_{50} = 58.85 μM) while displayed non-cytotoxicity against the normal cell line.

3. ROLES OF THE 1,2,3-TRIAZOLE RING IN LIGAND-ANTICANCER TARGETS BINDINGS

Computational approaches (*in silico*) have been widely used as facilitating tools for elucidating structure-activity relationships and possible binding modes of the bioactive compounds against molecular targets.[66,67] Ones of which, structural-based methods (i.e., molecular docking and molecular dynamic simulation) are widely used in several steps of drug discovery including the target identification, hit identification, and lead optimization.[66,67] To demonstrate the significance of the triazole pharmacophore in anticancer drug development, a summary of *in silico* key findings regarding the possible molecular anticancer targets and binding modes of the 1,2,3-triazole-based compounds are summarized herein.

Recently, newly design 1,2,3-triazole-based anticancer agents have been reported along with their possible modes of actions against wide range types of molecular targets. Molecular docking studies suggested that the 1,2,3-triazole based compounds could occupy in the binding sites of DNA topoisomerase-II,[68] histone deacetylase 2 (HDAC2),[69] cyclooxygenase-2 (COX-2),[70] metalloproteinases (MMP-2 and MMP-9),[71] oncogenic kinase PAK1,[72] c-MET,[41] some cancer proteins,[73] carbonic anhydrase,[74] EGFR,[75] and glycogen synthase kinase-3 (GSK-3).[76]

The significant roles of the triazole ring (presented in the molecule) in the formation of ligand-binding interactions of the triazole-containing compounds were noted from several studies. The study on the binding of imidazopyridine-1,2,3-triazoles against the c-MET suggested that the triazole ring plays key role in the formation of hydrogen bond with the Lys1110 residue as well as the hydrophobic interactions with Ala1221, Leu1140, Lys1110 and Leu1157 residues of the target.[41] Significance of the nitrogen atoms contained in the triazole ring was also noted for the binding of the triazole-sulfonamide compound with the carbonic anhydrase *via* the formation of hydrogen bonds with Asn62, Lys67, and Gln92 residues.[74] Moreover, a study on the binding modes of triazole-based aromatase inhibitors suggested that the triazole ring play role in the formation of π-π stacking interaction with the Phe221 residue of the enzyme.[61,62] In addition, the role of triazole ring in the stabilized ligand-target complex and strong inhibitory effect was noted for the binding of 1,4-disubstituted 1,2,3-triazoles within the binding pockets of the MMP-2 and MMP-9[71] as well as that of the 1,2,3-triazolyl ester of ketorolac against the oncogenic kinase PAK1.[72] Molecular modeling also indicated that the triazole ring is an essential moiety which required for HDAC2 inhibitory activity of the hydroxamate-triazole compound.[69]

Besides the 1,2,3-triazole ring, some possible targets of the 1,2,4-triazole compounds were reported such as anti-apoptotic Bcl-2 protein,[77] vascular endothelial growth factor 2 (VEGF2),[78] as well as fibroblast growth factor receptor 1 (FGFR1) and Ser-/Thr-specific kinase Akt protein (Akt).[79] Additionally, the nitrogen atom of the 1,2,4-triazole ring was noted to form coordination interaction with the heme Fe ion of the aromatase enzyme contributing to the aromatase inhibitory effect.[80]

4. OTHER BIOLOGICAL ACTIVITIES

Recently, the 1,2,3-triazole based compounds were also reported for other biological activities such as antimalarial, antimicrobial, antiviral, and neuroprotective effects (as summarized in Table 1 and Figure 3).

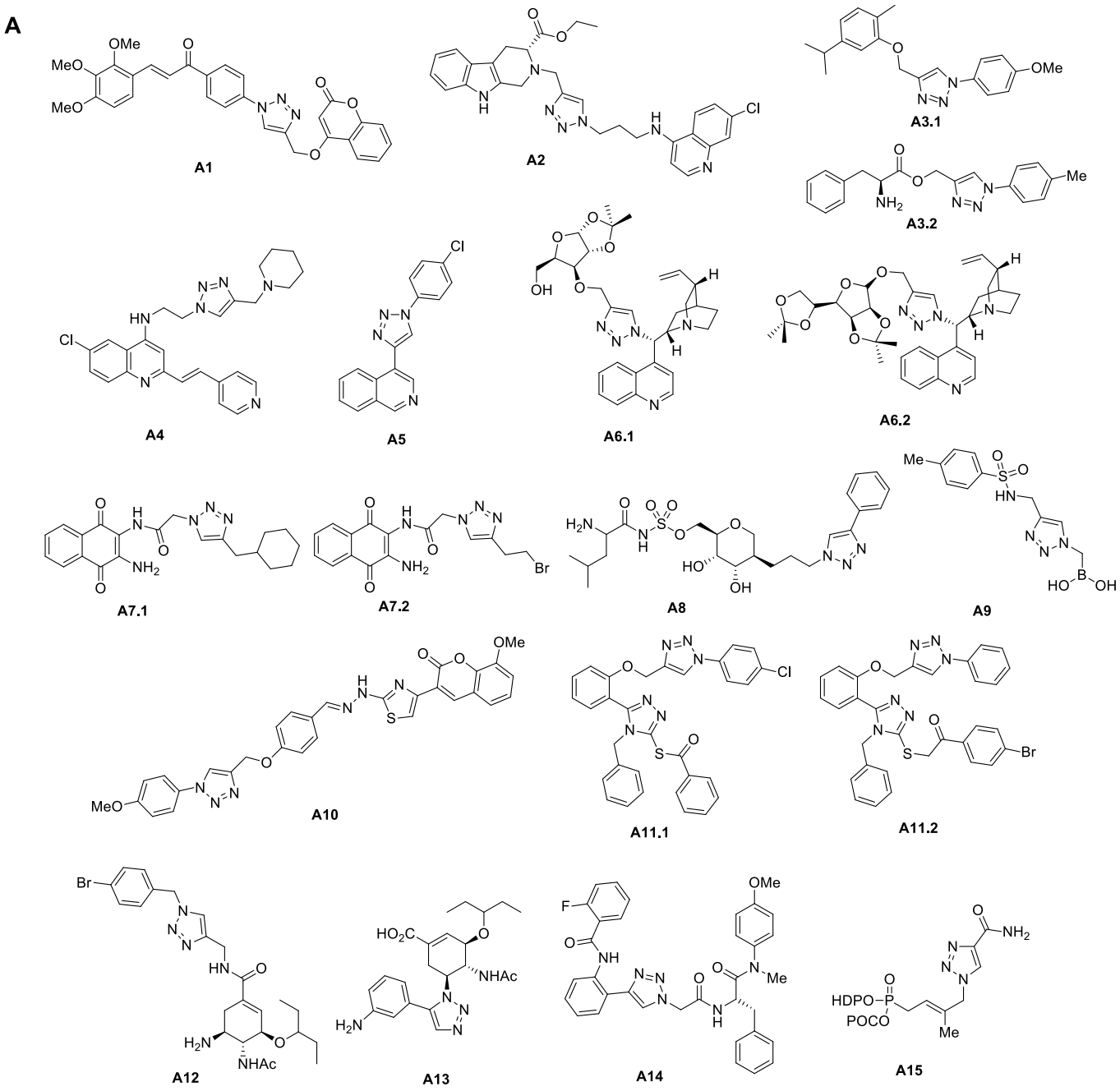


Figure 3. Summary of 1,2,3-triazoles based compounds reported as **A:** cytotoxic agents against microorganisms; antimalarial (**A1**-**A6**), antimicrobial (**A7**-**A11**), and antiviral (**A12**-**A15**) agents, and **B:** neuroprotective agents (**B1**-**B18**)

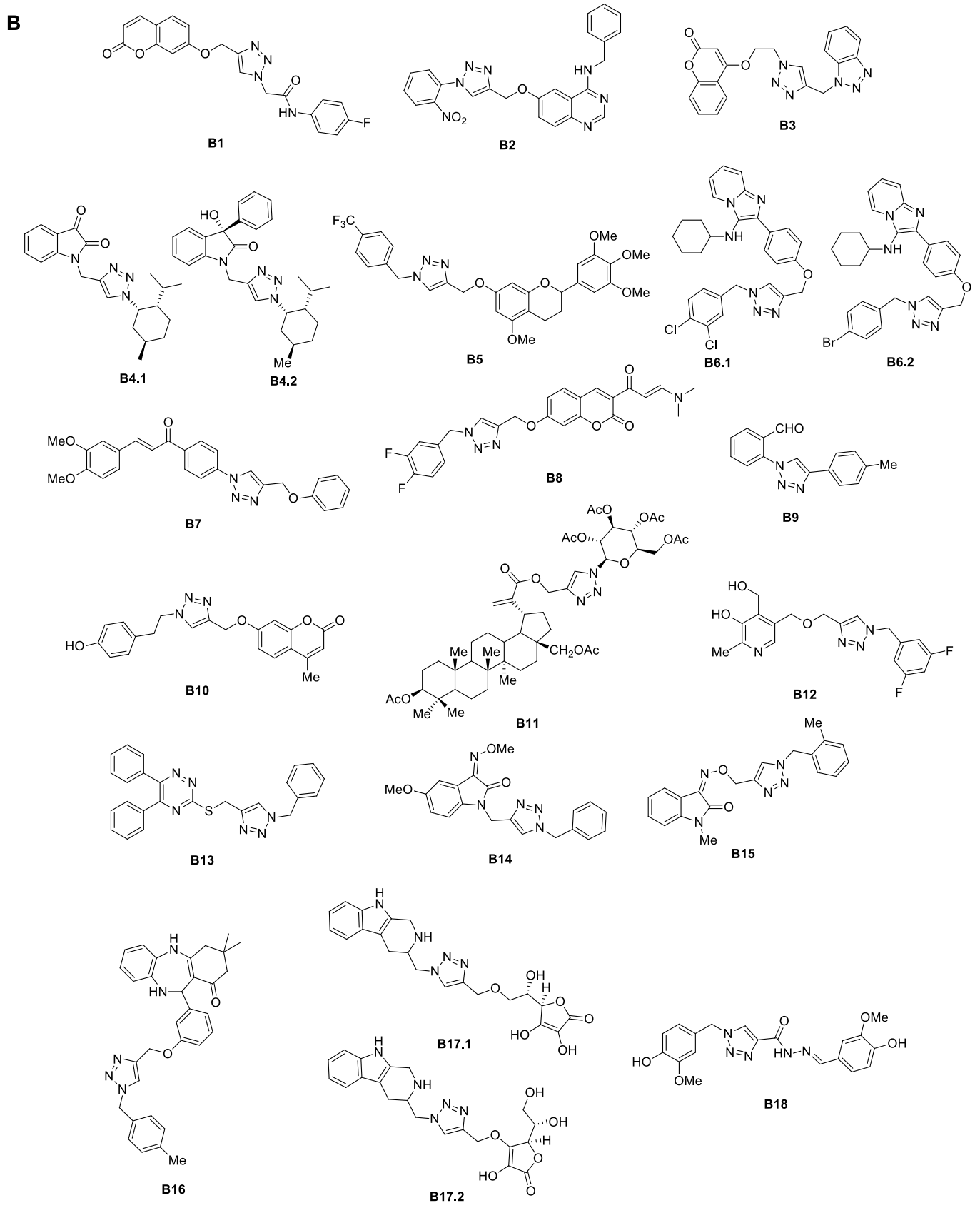


Figure 3 (cont.). Summary of 1,2,3-triazoles based compounds reported as **A:** cytotoxic agents against microorganisms; antimalarial (**A1**-**A6**), antimicrobial (**A7**-**A11**), and antiviral (**A12**-**A15**) agents, and **B:** neuroprotective agents (**B1**-**B18**)

Table 1. Summary of reported bioactivities of 1,2,3-triazoles based compounds

Bioactivity	**Class of compound**	**Structures (Figure 3)**	**References**
Antimalarial (Figure 3A)	1,2,3-Triazole containing chalcone-coumarin derivatives	**A1**	Pingaew et al.[58]
	1,2,3-Triazole containing tetrahydro-*β*-carboline-aminoquinoline derivatives	**A2**	Sharma et al.[81]
	1,2,3-Triazole containing carvacrol and phenylalanine derivatives	**A3.1** **A3.2**	Uddin et al.[82]
	1,2,3-Triazole containing pyridylvinylquinoline derivatives	**A4**	Huang et al.[83]
	1,2,3-Triazole containing isoquinoline derivatives	**A5**	Theeramunkong et al.[84]
	1,2,3-Triazole containing cinchonidine-carbohydrate derivatives	**A6.1** **A6.2**	Mishra et al.[85]
Antimicrobial (Figure 3A)	1,2,3-Triazole containing 1,4-naphthoquinone derivatives	**A7.1** **A7.2**	Nural et al.[86]
	1,2,3-Triazole containing anhydrohexitol derivatives	**A8**	Ruysscher et al.[87]
	1,2,3-Triazole containing boronic acid derivatives	**A9**	Caselli et al.[88]
	1,2,3-Triazole containing thiazole-coumarin derivatives	**A10**	Gondru et al.[89]
	1,2,3-Triazole containing 1,2,4-triazole derivatives	**A11.1** **A11.2**	Bitla et al.[90]
Antiviral (Figure 3A)	1,2,3-Triazole containing oseltamivir derivatives	**A12**	Ju et al.[91]
	1,2,3-Triazole containing oseltamivir derivatives	**A13**	Wang et al.[92]
	1,2,3-Triazole containing phenylalanine derivatives	**A14**	Sun et al.[93]
	1,2,3-Triazole containing phosphonate derivatives	**A15**	Abuduaini et al.[94]

Bioactivity	**Class of compound**	**Structures (Figure 3)**	**References**
Neuroprotective (Figure 3B)	1,2,3-Triazole containing coumarin derivatives	**B1**	Sepehri et al.[95]
	1,2,3-Triazole containing quinazoline derivatives	**B2**	Le-Nhat-Thuy et al.[96]
	1,2,3-Triazole containing coumarin-benzotriazole derivatives	**B3**	Singh et al.[97]
	1,2,3-Triazole containing isatin derivatives	**B4.1** **B4.2**	Marques et al.[98]
	1,2,3-Triazole containing flavone derivatives	**B5**	Shi et al.[99]
	1,2,3-Triazole containing imidazo[1,2-*a*]pyridin-3-amine derivatives	**B6.1** **B6.2**	Haghighijoo et al.[100]
	1,2,3-Triazole containing chalcone derivatives	**B7**	Sooknual et al.[101]
	1,2,3-Triazole containing dimethylaminoacryloyl-chromenone derivatives	**B8**	Askarani et al.[102]
	1,2,3-Triazole containing benzaldehyde derivatives	**B9**	Costa et al.[103]
	1,2,3-Triazole containing tyrosol derivatives	**B10**	Bousada et al.[104]
	1,2,3-Triazole containing betulin derivatives	**B11**	Gonzalez et al.[105]
	1,2,3-Triazole containing pyridoxine derivatives	**B12**	Pal et al.[106]
	1,2,3-Triazole containing triazine derivatives	**B13**	Yazdani et al.[107]
	1,2,3-Triazole containing indolinone derivatives	**B14**	Lan et al.[108]
	1,2,3-Triazole containing methylindolinone derivatives	**B15**	Saeedi et al.[109]

Bioactivity	Class of compound	Structures (Figure 3)	References
	1,2,3-Triazole containing benzodiazepine derivatives	**B16**	Mehrazar et al.[110]
	1,2,3-Triazole containing ascorbic acid derivatives	**B17.1** **B17.2**	Jiaranaikulwanitch et al.[111]
	1,2,3-Triazole containing *N*-acylhydrazone derivatives	**B18**	de Freitas Silva et al.[112]

5. CONCLUSION

In recent years, the 1,2,3-triazole scaffold has gained considerable interest in drug development area. Its unique and attractive characteristics have driven the design and synthesis of several therapeutic potentially active compounds. CuAAC is the method for the synthesis of 1,2,3-triazole ring. Several classes of triazole based anticancer agents and hybrids have been recently reported against several types of cancer cell lines. Possible mechanisms of actions have been proposed including an induction of apoptosis, an inhibition of cancer cell growth (antiproliferative), an alteration of cell cycle, and others. Besides experimental investigations, computational studies such as molecular docking and pharmacokinetic (ADMET) *in silico* prediction have been engaged in these studies to achieve insight information for future effective time-saving development of novel compounds. Possible molecular targets of these reported compounds were revealed such as estrogen receptor, GGPP synthase, receptor protein kinases (i.e., c-MET kinase, CDK2, and EGFR), VGFR2, and STAT3. Other biological activities of 1,2,3-triazole compounds were also reported elsewhere, and are noteworthy to be explored. Taken together, it is suggested that the 1,2,3-triazole pharmacophore is an attractive scaffold with a great opportunity for future drug design and development.

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Vanida Choomuenwai received her BSc degree in Chemistry from Thammasat University and MSc degree in Organic Chemistry from Mahidol University under the supervision of Prof. Emeritus Dr. Somsak Ruchirawat. She completed her PhD from Griffith University, Australia. Now, she is a lecturer and researcher at Chemistry Program, Faculty of Science and technology, Nakhon Ratchasima Rajabhat University. Her currently research involves Natural products, Organic synthesis, and Medicinal Chemistry.

Ronnakorn Leechaisit has received his bachelor's and master's degrees of Chemistry from Srinakharinwirot University in 2017 and 2019, respectively. Currently, he is continuing his study in Ph.D. program under the supervision of Assoc. Prof. Ratchanok Pingaew at Faculty of Science, Srinakharinwirot University.

Assoc. Prof. Dr. Ratchanok Pingaew received her Ph.D. in Organic Chemistry from Mahidol University under supervision of Prof. Emeritus Dr. Somsak Ruchirawat. She is presently associate professor at Faculty of Science, Department of Chemistry, Srinakharinwirot University. Her research interests include Synthetic Methodology and Medicinal Chemistry.

Veda Prachayasittikul received her bachelor's degree of Dentistry (first class honor) from Srinakharinwirot University in 2008. She continued her graduate study in Faculty of Medical Technology, Mahidol University under supervision of Assoc. Prof. Dr. Chanin Nantasenamat and received her Ph.D. (Medical Technology) in 2016. Currently, she is a lecturer at Center of Data Mining and Biomedical Informatics, Faculty of Medical Technology, Mahidol University. Her research interests cover areas of Computer-aided drug development (QSAR modeling), Bioactive compounds, Pharmacology, and Functional foods.

Prof. Dr. Supaluk Prachayasittikul received her bachelor's degree of Chemistry from Kasetsart University, master's degree of Organic Chemistry from Mahidol University (under supervision of Prof. Emeritus Dr. Somsak Ruchirawat), and her Ph.D. in Medicinal Chemistry from University of Illinois at Chicago (Health Science Center). She started her academic career at Faculty of Science, Department of Chemistry, Srinakharinwirot University. After her retirement, she has been invited as a research consultant at Center of Data Mining and Biomedical Informatics, Faculty of Medical Technology, Mahidol University. Presently, she still actively supervises many young generation researchers. Her research interests cover areas of Organic Chemistry, Medicinal Chemistry, Drug development, as well as Bioactive compounds.

Prof. Emeritus Dr. Virapong Prachayasittikul received his bachelor's degree of Medical Technology and master's degree of Pharmacology from Mahidol University. After received Ph.D. in Microbiology from The Chicago Medical School (USA), he started his academic path as lecturer and researcher at Faculty of Medical Technology, Mahidol University. He was awarded his Doctor of Technology (Honoris causa) from the Lund University, Sweden. He received his Prof. Emeritus and his Honorary Ph.D. in Medical Technology from Mahidol University. He is an expert in Pharmacology, Microbiology, and Medical Technology. He has actively contributed many research publications in areas of Pharmacology, Drug discovery and development, Computer-aided drug design, as well as others.