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CLICK CHEMISTRY TOWARD THE SYNTHESIS OF ANTICANCER AGENTS

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Abstract – The copper(I)-induced synthesis of 1,2,3-triazoles using azides and alkynes (click chemistry) has become extremely significant. Click chemistry has been used in all aspects of drug discovery research. The product triazole serves as a linker as it readily combines with targets through hydrogen-bonding and dipole interaction. This review summarizes the application of click chemistry and triazoles as anticancer drugs. These types of reactions proceed with high selectivity, specificity, and yields. A variety of complex molecules are synthesized by this method.

INTRODUCTION

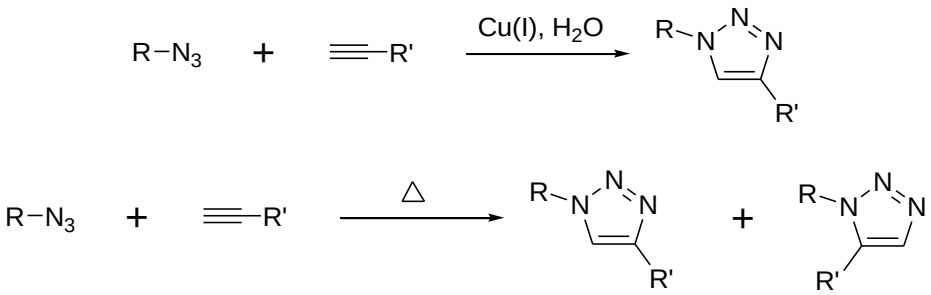
The term "click chemistry" was first introduced by Sharpless' group in 1999 at the 217th American Chemical Society annual meeting, and was first fully explained by Sharpless, Kolb, and Finn of The Scripps Research Institute in 2001.[1,2] This reaction is clean, smooth, high yielding, insensitive towards oxygen and water, wide in scope, stereospecific, simple to perform, and create less byproducts. This reaction can be conducted in easily removable or benign solvents in very high yields, with dramatic rate acceleration and a large thermodynamic driving force (>20 kcal/mol) to favor a reaction with a single reaction product. A distinct exothermic reaction makes a reactant "spring-loaded"- characterized[3] by a high thermodynamic driving force that drives it quickly and irreversibly to high yield of a single reaction product, with high reaction specificity (in some cases, with both regio- and stereo-specificity). This notion arose in response to a growing interest in capabilities for creating huge libraries of chemicals for screening in discovery research in the pharmaceuticals, materials, and other industries. Several types of reactions that meet these criteria have been identified, including thermodynamically favorable reactions

that produce only one product, such as epoxide and aziridine nucleophilic ring opening reactions, non-aldol type carbonyl reactions, such as production of hydrazones[4] and heterocycles, addtion to carbon-carbon multiple bonds, such as oxidative creation of epoxides,[5] dihydroxylation[6] and Michael additions, and cycloaddition reactions.[7,8]

PRINCIPALS OF CLICK CHEMISTRY

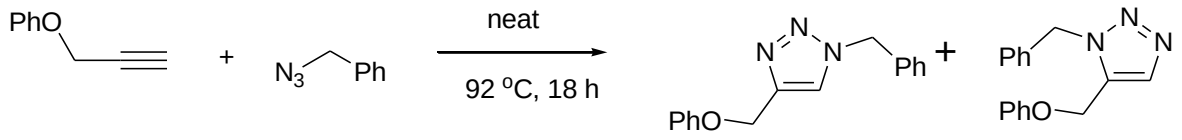
1,3-DIPOLAR CYCLOADDITION REACTION OF AZIDES AND ALKYNES

Commercially accessible monosubstituted alkynes and different types of organic azides can be easily made using a variety of functional groups. Their cycloaddition reaction produced 1,4-substituted 1,2,3-triazoles with inverse Diels-Alder reaction. Huisgen's non-catalyzed 1,3-dipolar cycloaddition produced both the 1,4- and 1,5-isomers (Scheme-1).[9]



Scheme 1. Synthesis of both the 1,4- and 1,5-Isomers

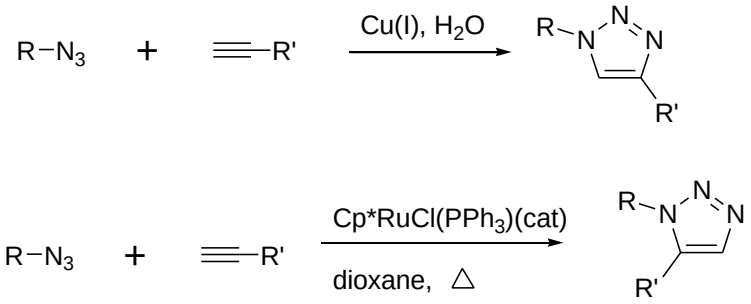
A treatment of 3-phenoxypropyne with benzyl azide without catalyst gave approximately 1:1 mixtures of both the 1,4-substituted and the 1,5-substituted regioisomers. This reaction is very exothermic, but even at high temperatures, the high activation barrier results in a relatively slow reaction rate. Another disadvantage was the creation of regioisomers, which occurs because the energy levels of the two potential HOMO-LUMO interactions of the substrates are quite similar. As a result of the heat reaction, about 1:1 mixes of both the 1,4-substituted and the 1,5-substituted regioisomers were frequently obtained (Scheme-2).[10]



Scheme 2. Formation of 1,4-Substituted and the 1,5-Substituted Regioisomers

COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITION (CuAAC)

Unfortunately, the thermal Huisgen 1,3-dipolar cycloaddition of alkynes to azides necessitates high temperatures and frequently results in mixtures of the two regioisomers (Scheme 1) containing asymmetric alkynes. The conventional 1,3-dipolar cycloaddition fails as a real click reaction in this regard. Even at ambient temperature, a copper-catalyzed version with a different mechanism can be carried out in aqueous circumstances. Furthermore, whereas the classic Huisgen 1,3-dipolar cycloaddition frequently produces mixtures of regioisomers, the copper-catalyzed reaction allows the synthesis of 1,4-disubstituted regioisomers exclusively (Scheme 3). The production of 1,5-disubstituted triazoles by ruthenium-catalyzed reactions, on the other hand, has the opposite regioselectivity. As a result, these catalyzed reactions are entirely compliant with the notion of click chemistry, with the azide-alkyne cycloaddition serving as a model click reaction.



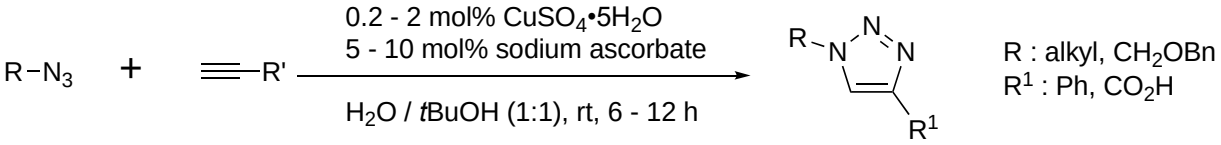
Scheme 3. The Synthesis of 1,4 and 1,5-Disubstituted Triazoles

Copper iodide catalyst is mostly used among other copper halide in various click reactions. Few reports of copper bromide catalysis are also available. Cu(I) combined with Cu(II) salts, other metal complexes or ionic liquids are also used as effective catalytic systems. Most of the reactions proceed smoothly at room temperature. However, there are many reports, which require traditional heating. A facile upon application of unconventional energy sources like microwave (MW) irradiation and ultrasound/sonication conditions are also performed. Use of co-solvent systems promotes the reactions efficiently. Alkyne is one of the indispensable components in click reactions.[11] Yang et al.[12] used calcium carbide as a source of acetylene in copper-catalyzed 1,3-dipolar cycloaddition reaction for the synthesis of 1-aryl-1,2,3-triazoles in 72 to 95% yields (Scheme 3).

MECHANISM OF CLICK CHEMISTRY USING CATALYST WITH COPPER(I) AND RUTHENIUM-COMPLEX

The union of terminal alkynes with organic azides catalyzed by copper(I) to form 1,4-disubstituted 1,2,3-triazoles has been described (Scheme 4). These have a remarkable breadth of application and fine selectivity. When compared to the uncatalyzed 1,3-dipolar cycloaddition, these copper-catalyzed azide-

alkyne cycloadditions had a rate acceleration of 10^7 to 10^8. It worked at a wide range of temperatures, was unaffected by aqueous conditions and a pH range of 4 to 12, and tolerated a wide range of functional groups. Without chromatography or recrystallization, the product can be isolated in a pure form by filtration or extraction.



Scheme 4. Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

Cu(I) salts or Cu(II) salts with sodium ascorbate as the reducing agent can be used to make the active Cu(I) catalyst.[13] The generation of oxidative homo-coupling products is prevented by adding a little amount of sodium ascorbate. In the presence of a Cu wire, disproportionation of a Cu(II) salt can also be employed to create active Cu(I). Cu(I) coordination to the alkyne is modestly endothermic in MeCN but exothermic in water, according to DFT calculations, which agrees with an observed rate acceleration in water. A 1,3-dipolar cycloaddition was not accelerated by the coordination of Cu to the acetylene. According to calculations, this reaction was even less favorable than the uncatalyzed 1,3-dipolar cycloaddition. Instead, the azide is coordinated by σ-bound copper acetylide bearing π-bound copper. The result was a unique six-membered copper metallacycle (Figure 1). A stabilizing donor ligand was provided by the second copper atom. Protonolysis delivered the triazole product and closed the catalytic cycle after ring contraction to a triazolyl-copper derivative.[14]

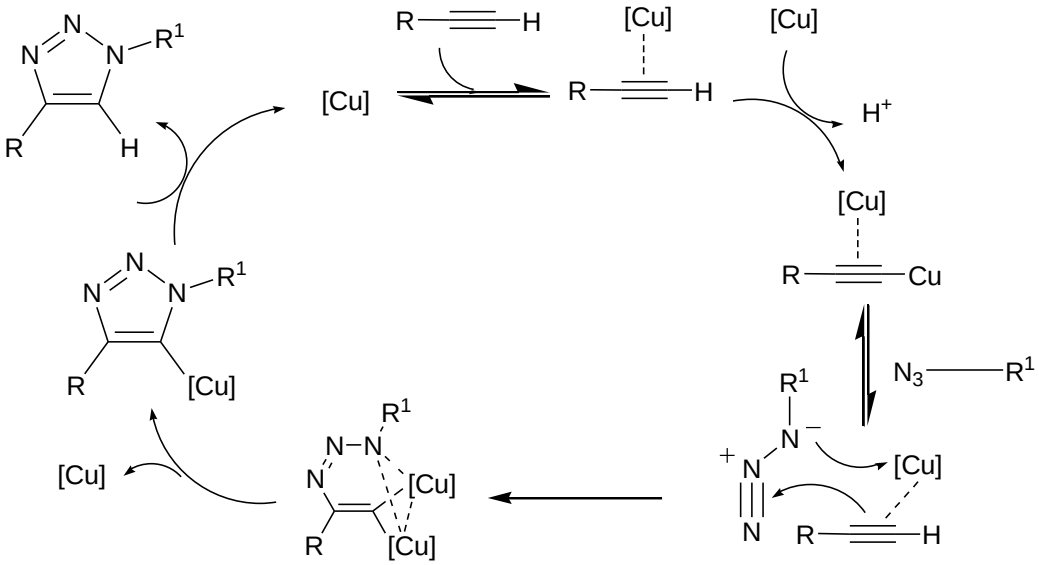
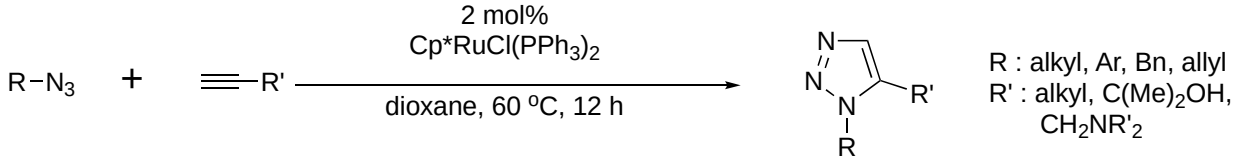


Figure 1. Mechanism of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)

RUTHENIUM-CATALYZED ALKYNE-AZIDE CYCLOADDITION

The cycloaddition of azides to terminal alkynes can be catalyzed regioselectively by (pentamethylcyclopentadienyl)ruthenium chloride [Cp*RuCl] complexes, resulting in 1,5-disubstituted 1,2,3-triazoles. In addition, unlike CuAAC, RuAAC can be utilized with internal alkynes to produce fully substituted 1,2,3-triazoles (Scheme 5).



Scheme 5. Synthesis of 1,5-Disubstituted 1,2,3-Triazoles

When 3-phenoxypropyne was treated with benzyl azide without catalyst, it gives approximately 1:1 mixtures of both the 1,4-substituted and the 1,5-substituted regioisomers. This reaction was highly exothermic, but the high activation barrier was responsible for a very low reaction rate, even at elevated temperature. Another disadvantage was the generation of regioisomers, which is caused by the substrates two probable HOMO-LUMO interactions being closely linked in terms of energy. As a result, the heat reaction frequently produced about 1:1 mixtures of the 1,4- and 1,5-substituted regioisomers.

The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) appeared to proceed by oxidative coupling of the azide and alkyne to give a six-membered product (Figure 2), with the first new carbon-nitrogen bond formed between the more electronegative carbon of the alkyne and the terminal, electrophilic nitrogen of the azide. This was followed by reductive elimination, which resulted in the formation of the triazole.[15]

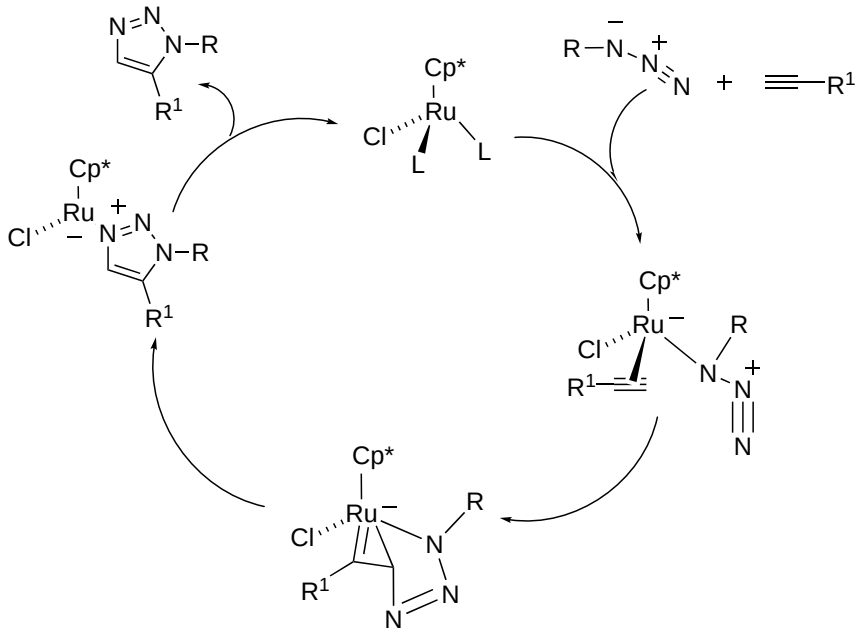
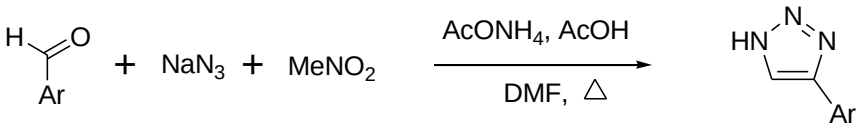


Figure 2. Mechanism of the Ruthenium-Catalyzed Azide-Alkyne Cycloaddition (RuAAC)

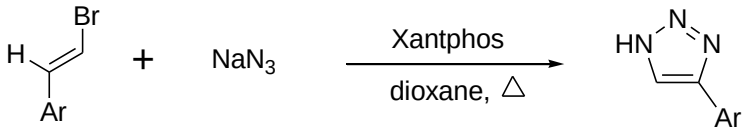
EXAMPLES USING DIFFERENT CATALYST

Cu-AAC, solid-phase synthesis, the three-component reaction of aldehydes, nitromethane, and sodium azide (Scheme 6); the reaction of enamines with 4-methylbenzenesulfonyl azide (Scheme 7); and the interaction of bromostyrenes with sodium azide in a palladium-catalyzed reaction are all methods for the synthesis of 1H-1,2,3-triazoles (Scheme 8).[16] Totobenazara and Burke reviewed novel ‘click' approaches for 1,2,3-triazoles employing classical reactions in 2015.[17]



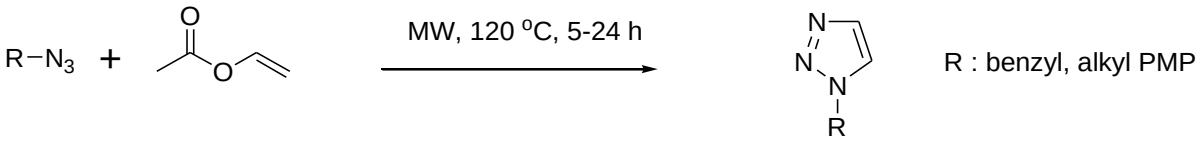
Scheme 6. Synthesis of 1*H*-1,2,3-Triazoles

Scheme 7. Synthesis of 1*H*-1,2,3-Triazoles



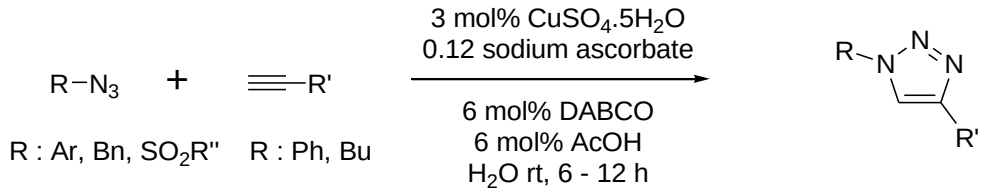
Scheme 8. Synthesis of 1*H*-1,2,3-Triazoles

Unsubstituted N-linked 1,2,3-triazoles were formed with vinyl acetate and azides by the microwave irradiation (Scheme- 9).[18]



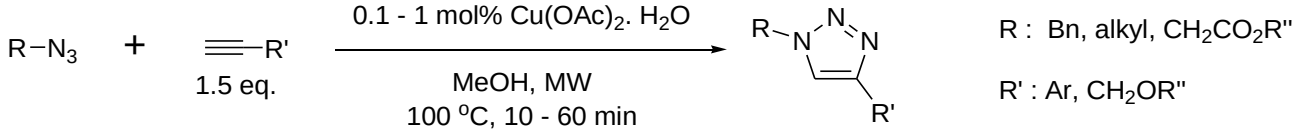
Scheme 9. Synthesis of Unsubstituted N-linked 1,2,3-Triazoles

DABCO/AcOH jointly accelerated copper(I)-catalyzed cycloaddition of azides and alkynes in water at room temperature (Scheme-10).[19]



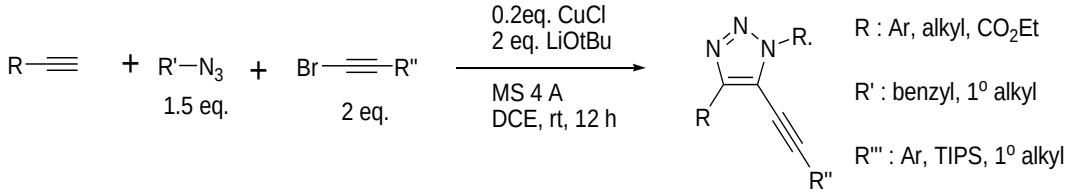
Scheme 10. Synthesis of Unsubstituted N-Linked 1,2,3-Triazoles

Heney et al. reported a new simplified protocol for copper(I) alkyne-azide cycloaddition reactions using low substoichiometric amounts of copper(II) precatalysts in methanol in which copper(II) carboxylates are reduced efficiently by methanol in the presence of alkynes to form yellow alkynylcopper(I) polymeric intermediates that react with azides, to provide 1,4-disubstituted 1,2,3-triazoles (Scheme 11).[20]



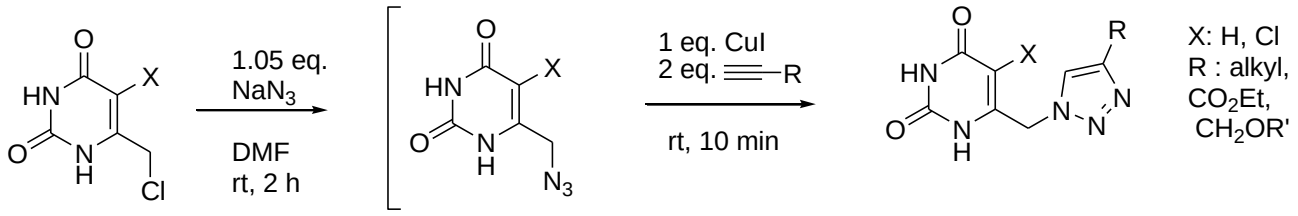
Scheme 11. Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

Xu et al. reported copper(I)-catalyzed three-component click/alkynylation. Various alkynes, organic azides, and bromoalkanes were used in a one-pot synthesis of 5-alkynyl-1,2,3-triazoles. The reaction began with a copper-catalyzed alkyne azide cycloaddition, followed by bromoalkyne interception of the cuprate-triazole intermediate generated in situ (Scheme 12).[21]



Scheme 12. Synthesis of 5-Alkynyl-1,2,3-triazoles

Jansa et al. described a one-pot synthesis of polysubstituted 6-[(1*H*-1,2,3-triazol-1-yl)methyl]uracils using the click technique, in which a stoichiometric quantity of copper iodide allowed for an effective azide-alkyne cycloaddition. Using a catalytic amount of CuI, the reaction became slow, due to chelate-like complexation of the copper catalyst with the product. A simple work-up with Na_2S was based on the low solubility of CuS (Scheme 13).[22]



Scheme 13. Synthesis of Polysubstituted 6-[(1*H*-1,2,3-Triazol-1-yl)methyl]uracils

RESEARCH ON CLICK CHEMISTRY IN THE FIELD OF PHARMACEUTICAL APPLICATIONS

The use of click chemistry is common and has widespread applications. Many scientists reported the synthesis of 1,4-substituted triazoles, peptide function modifications with triazoles, natural product and pharmaceutical modifications, macrocyclizations using Cu(I)-catalyzed triazole couplings, DNA and nucleotide modifications by triazole ligation, and carbohydrate conjugation by Cu(I)-catalyzed triazole ligation reactions. The use of click chemistry in biomedical research is fast expanding, with applications ranging from lead finding and optimization to the tagging of biological systems like as proteins, nucleotides, and complete organisms.[23-48]

The 1,2,3-triazole and 1,2,4-triazole rings are the most common heterocyclic rings found in pharmaceutical drugs.[49] Anti-HIV, anti-allergenic, antimicrobial,[50] cytostatic, virostatic, anti-inflammatory, and antibacterial actions have been discovered in 1,2,3-triazole derivatives. Obesity and osteoarthritis are also being researched with triazoles.

Kharb et al. have reviewed[51] the pharmacological activities of triazole derivatives. A review on the significant achievements in the discovery of antifungal lead structures is presented by Sheng and Zhang.[52] In particular, the structure–activity relationship of antifungal leads and perspectives for future antifungal drug discovery is provided.

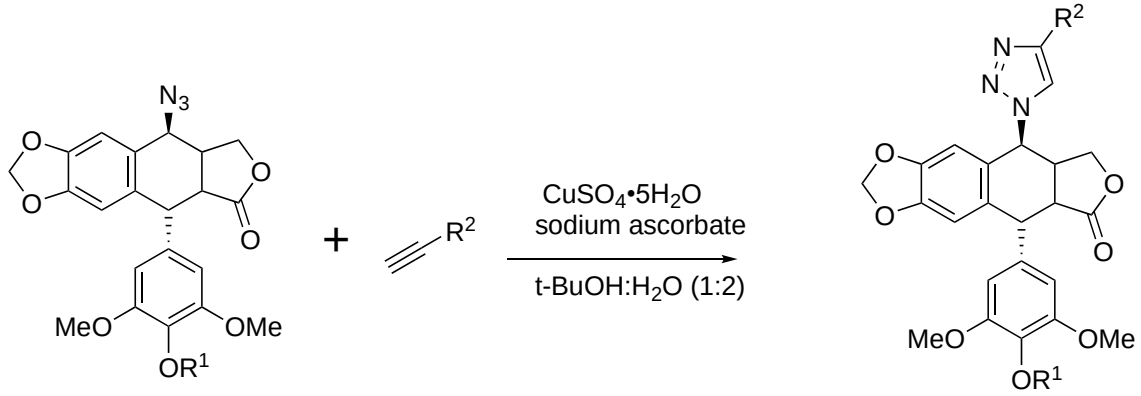
There are very few 1,2,3-triazole-containing molecules on the market or are in the last stage of clinical trials. In 2018, various biological screenings were conducted[53-56] on the basis of 1,2,3-triazole scaffolds which led to explore anticancer,[57-59] antimicrobial,[60-64] anti-infective,[65,66] and antioxidant[67-69] properties. Despite their harmful effects on native peptide function, triazole-linked derivatives were commonly utilized in peptides to simulate a trans-amide bond and were hypothesized to impact adenosine diphosphate ribosylation biology.[70,71]

PHARMACOLOGICAL APPLICATIONS OF 1,2,3-TRIAZOLES:

In both industrialized and developing countries, cancer is a major public health concern. Taxol, vinblastine, vincristine, camptothecin derivatives, topotecan and irinotecan, and etoposide derived from

epipodophyllotoxin are all in clinical usage around the world. Many anticancer drugs are in clinical trials and have shown to be effective in treating cancer. New compounds with distinct mechanisms of action must still be screened. Flavopiridol, roscovitine, combretastatin A-4, betulinic acid, and silvestrol are among the promising medications in clinical or preclinical research. However, new molecules with distinct mechanisms of action, drugs active for other diseases that may have anticancer efficacy, and new analogues of existing therapeutic treatments must also be screened.

Using a click chemistry technique, Reddy et al. produced a series of 4-[(4-alkyl)-1,2,3-triazol-1-yl]-podophyllotoxin derivatives (Scheme-14). The bulk of them were shown to be more effective than etoposide, a clinically effective cancer medication. As a heterocyclic ring, most of the compounds have a 1,2,3-triazole ring. The anticancer properties of this series are enhanced by the inclusion of methyl, ethyl, and hydroxyl groups in the triazole molecule.[72,73]



R^1 = H, Me & R^2 = Et, Pr, -CH_2OH

Scheme 14. Click Chemistry was Used to Create the Chemical Structures of Topoisomerase II Inhibitors

Chen et al. prepared carbamate derivatives of 4-(1,2,3-triazol-1-yl)podophyllotoxin for DNA topoisomerase II[74] inhibition, and then tested their cytotoxicity against the human cancer cell lines HL-60, A-549, HeLa, and HCT-8. 4′-*O*-demethyl-4-[(4-hydroxymethyl)-1,2,3-triazol-1-yl] is one of the synthetic chemicals. The most powerful action was found in the 4-deoxypodophyllotoxin cyclopentylcarbamate (Figure 3).

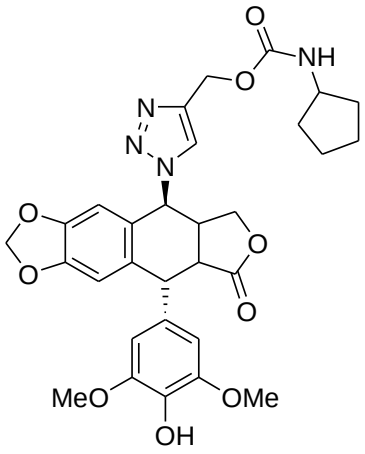


Figure 3. A Potent Cytotoxic Compound which Induced Cell Cycle Arrest in the G2/M Phase Accompanied by Apoptosis and Inhibited the Formation of Microtubules in A-549 Cells.

Mansonones are quinone-based chemicals with potent anticancer properties. Using click chemistry, Huang et al.[75-77] produced two series of novel C-9 chloro- and bromo-substituted mansonone E derivatives having a triazole group at the C-3 position. The substituents of the triazole were shown to be particularly essential for cytotoxicity in their structure-activity relationships and molecular docking studies. The triazole ring influenced the cytotoxicity of many human cancer cell lines in different ways. Almost all of the C-9 bromo-substituted derivatives showed better activity than the C-9 chloro-substituted compounds in the Topo II inhibition assay (Figure 4).

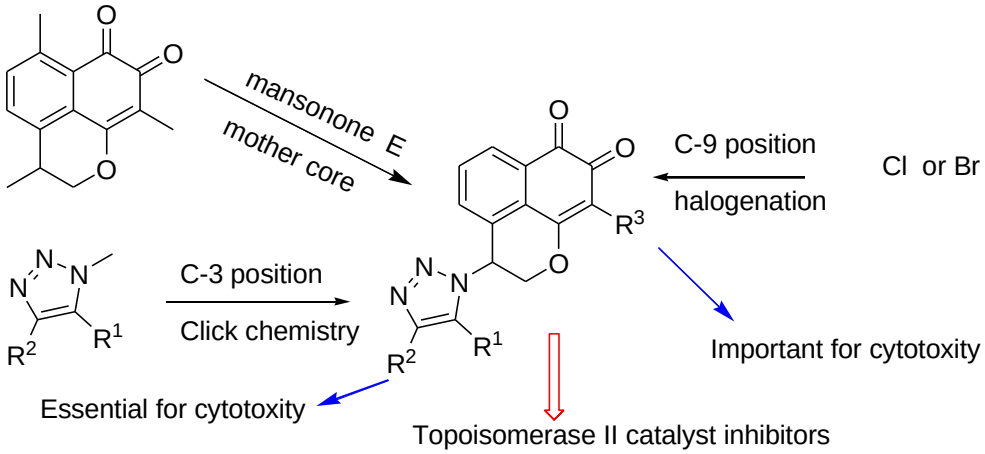
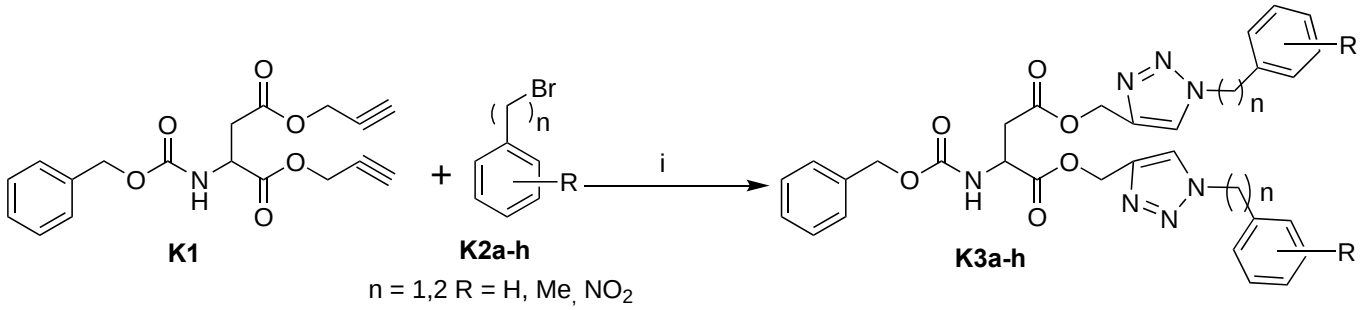


Figure 4. Two Series of Mansonone E Derivates **9**-Cl and **9**-Br with Triazoles at Position 3 through a CuAAC Click Chemistry Approach

Kaushik and Lal et al. reported the synthesis of a small library of amino acid-linked 1,4-disubstituted 1,2,3-bistriazole conjugates from the *N*-protected L-amino acids and propargyl esters through one-pot click reaction (Scheme 15). All newly synthesized compounds were tested in vitro for antimicrobial

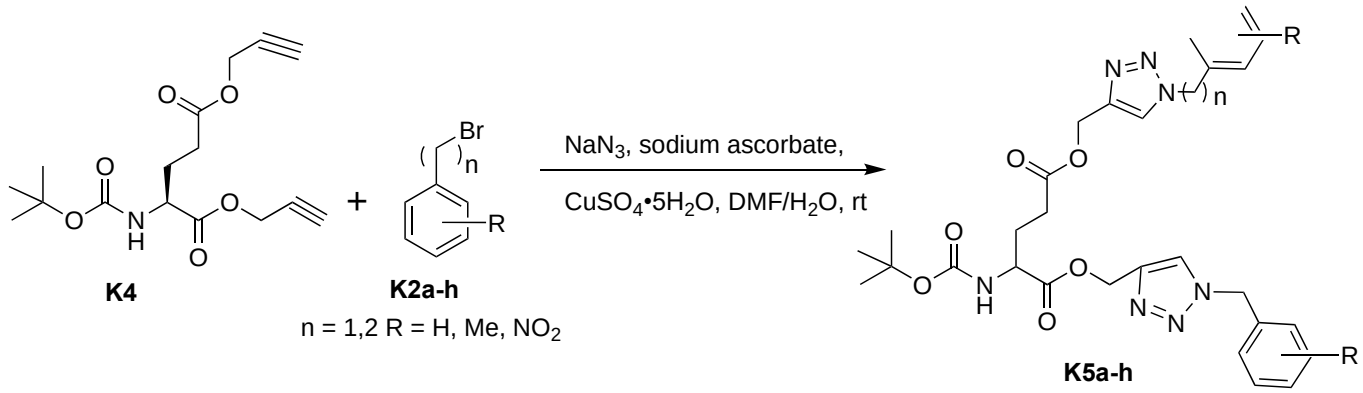
activity against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative (*Escherichia coli*) bacteria and fungi (*Candida albicans*, *Aspergillus niger*). Docking simulation of compounds (K5**a** and K5**b**, Scheme 16) showed inhibition of *Escherichia coli* topoisomerase II DNA gyrase B through hydrogen-bonding interactions.[78]

The synthesis of bisalkynes K1 and K4 was accomplished by reacting commercially available N-Cbz-L-aspartic acid and N-Boc-L-glutamic acid with propargyl bromide in presence of potassium carbonate in dry dimethylformamide (DMF). The bisalkynes so obtained were subjected to one-pot three-component reaction with various benzyl bromides (K2a–h), sodium azide, copper sulfate, and sodium ascorbate in DMF: water mixture to yield the desired bistriazoles.



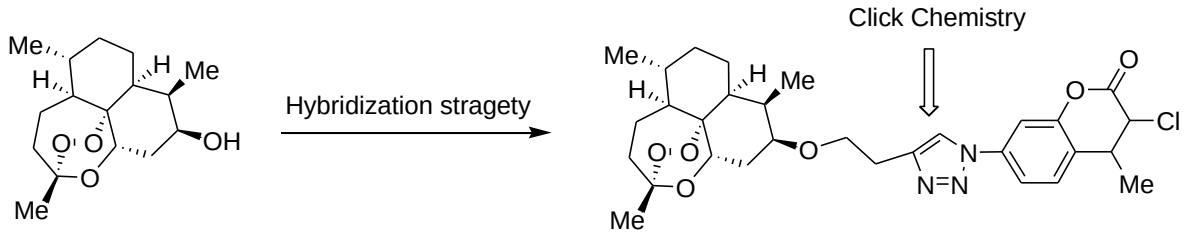
i = NaN_3, sodium ascorbate, $CuSO_4$•5$H2_O$, DMF/$H2_O$, rt. K2a: n = 1, R = H; K2b:n = 1, R = 2-Me K2c: n = 1, R = 3-Me; K2d: n = 1, R = 4-Me; K2e: n = 1, R = 2-NO_2; K2f: n = 1, R = 3-NO_2; K2g: n = 1, R = 4-NO_2; K2h: n = 2, R = H

Scheme 15. Synthesis of Aspartic Acid-based 1,4-Disubstituted 1,2,3-Bistriazoles



Scheme 16. Synthesis of Glutamic Acid-Based 1,4-Disubstituted 1,2,3-Bistriazoles

Yu et al.[79] designed and synthesized thirty four new 1,2,3-triazolo-dihydroartemisinincoumarin hybrids. These compounds were identified as great anticancer agents against two cancer cell lines (MDA-MB-231 and HT-29) (Scheme 17). The results indicated that modulation of the lateral chain dramatically affect the compound considerably.



HT- 29

Normoxia: IC_{50} > 100 μM

Hypoxia: IC_{50} = 18.52 μM

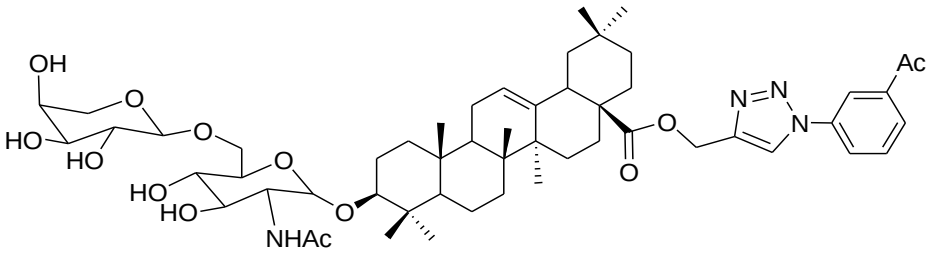
HT- 29

Normoxia: IC_{50} = 1.5 μM

Hypoxia: IC_{50} = 0.01 μM

Scheme 17. Synthesis of New 1,2,3-Triazolo-dihydroartemisinincoumarin Hybrids

Wei et al.[80] developed a variety of new antitumor albiziabioside derivatives comprising 1,2,3-triazoles and tested their anticancer capabilities in vitro and in vivo. With IC_{50} values of 5.19 μM, the target lead chemical (Figure 5) showed substantial inhibitory activity against HCT-116 cells. Furthermore, this triterpene saponin triazole derivative showed good selectivity and was efficient in MDR cancer cells, where it triggered ferroptosis and apoptosis via the mitochondrial pathway as a p53 activator. The inclusion of the triazole fragment into the triterpene skeleton significantly suppressed cancer without generating toxicity in normal cells, according to in vivo studies.



IC_{50} = 5.17 μM (HCT 116); IC_{50} = 5.83 μM (Bel-7402ADR); IC_{50} = 6.05 μM (HCT-8/Taxol)

Figure 5. 1,2,3-Triazoles Derivatives

Another series of 23 hederacolchiside A_1 derivatives were synthesized[81] via Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition. These were tested for cytotoxicity in vitro against six human cancer cell lines: PC3, HT29, HepG2, A549, HL60, and U937. The results showed that the majority of the synthesized hybrids with para- and meta-substituents were cytotoxic to HL60 and U937 cells. In comparison to the positive controls 5-fluorouracil and hederacolchiside A1, the derivative demonstrated strong anticancer potential against all examined cells. Furthermore, the lead chemical clearly suppressed the proliferation of HepG2 cells by inducing apoptosis and cell cycle arrest in the G1 and S phases, according to the results of the cell cycle and apoptosis screening (Figure 6).

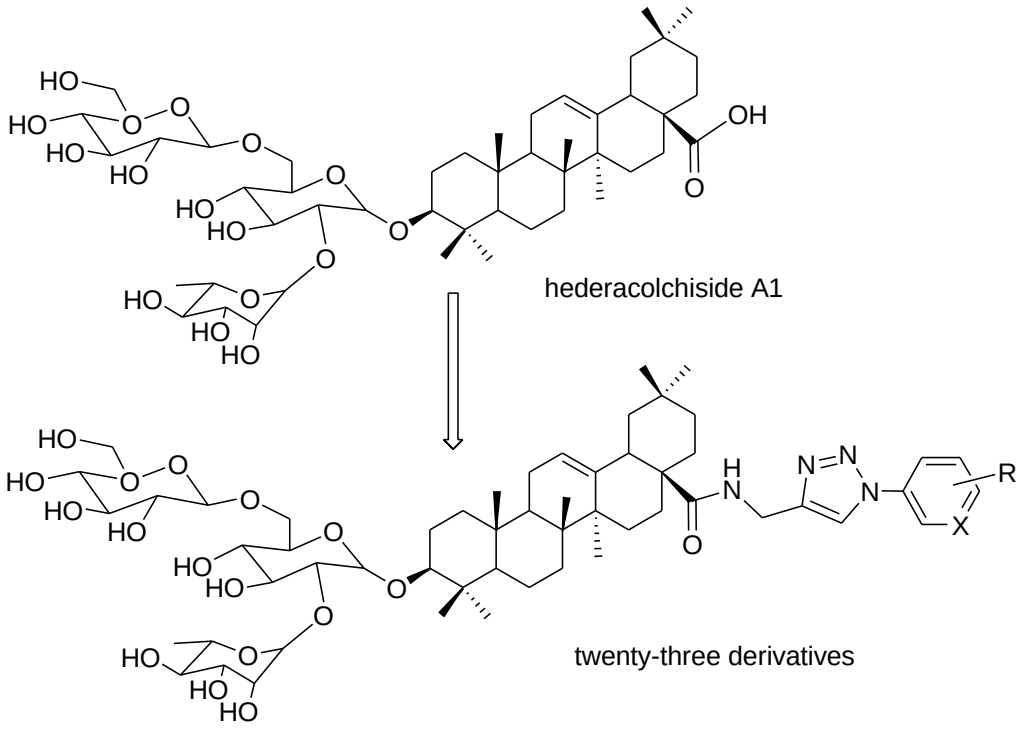


Figure 6. Some Product of Cu(I)-Catalyzed Azide-alkyne 1,3-Dipolar Cycloaddition

Wu et al. designed and synthesized[82] a series of (sixty, C_1-C_{60}) novel antitumor novel allogibberic acid derivatives containing 1,2,3-triazole pharmacophore. Aromatization of the A ring in gibberellins, production of allogibberic azides, and Huisgen 1,3-dipolar cycloaddition with alkynes are all important chemical reactions. In vitro cytotoxic activities of a number of hybrids containing the unsaturated ketone moiety were outstanding. Some hybrids were more selective to MCF-7 and SW480 cell lines, with IC_{50} values that were at least 8-fold higher than cisplatin (DDP). On the A-549, HL-60, SMMC-7721, MCF-7, and SW480 cell lines, the cytotoxic potential of all hybrid allogibberic triazole hybrids was determined to identify their anticancer capabilities. With IC_{50} values of 0.25–1.72 μM, the most powerful compounds C43 and C45 are more cytotoxic than cisplatin (DDP) against all five tumor cell lines examined. In SMMC-7721 cell lines, mechanism of action investigations revealed that the allogibberic-triazole derivative C-45 could induce S phase cell cycle arrest and apoptosis.

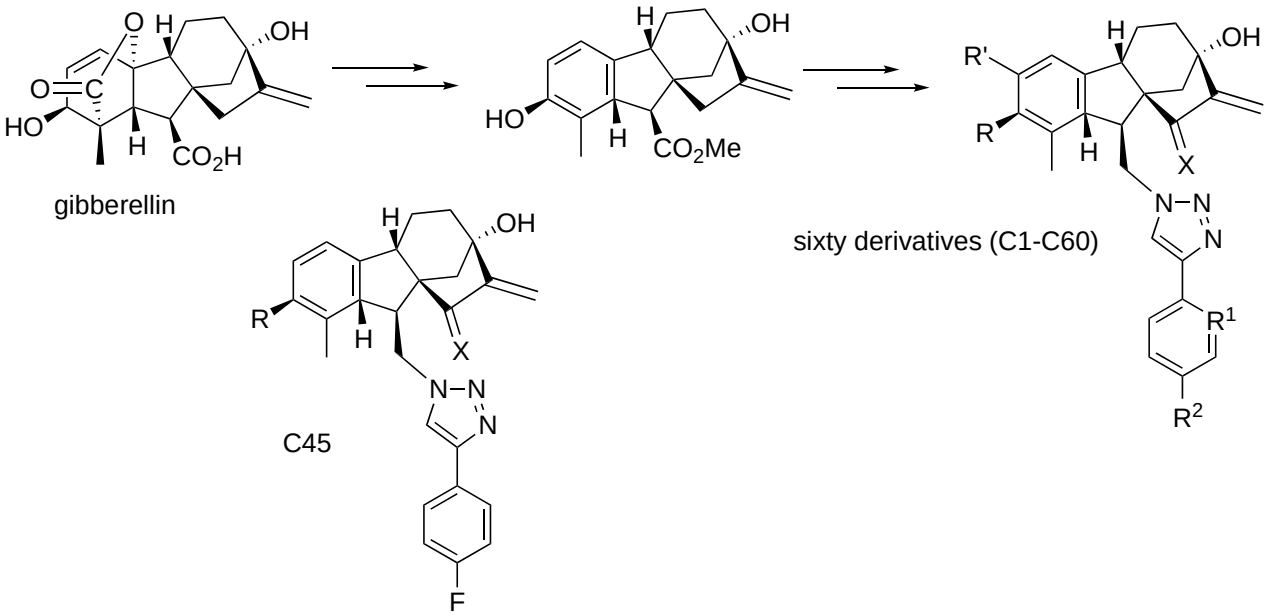
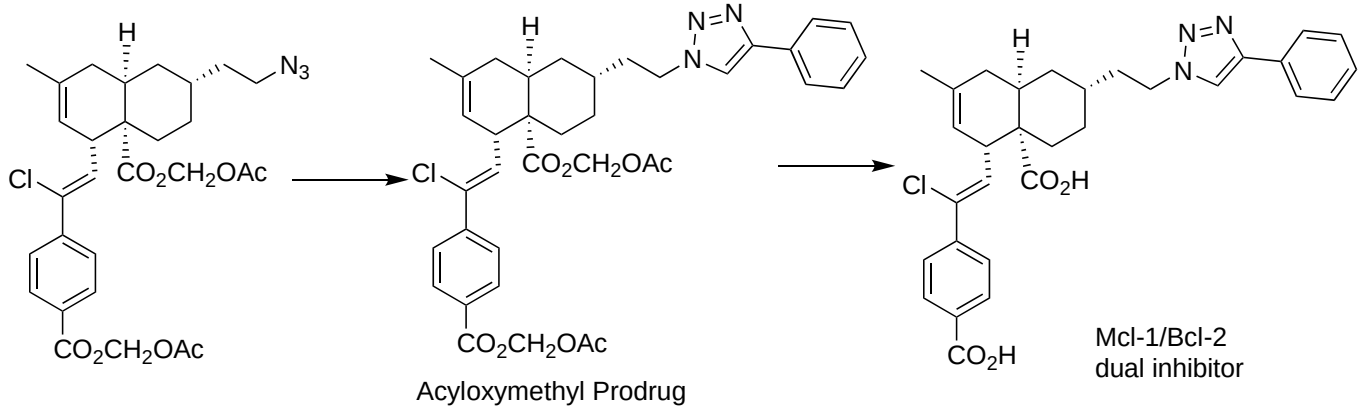


Figure 7. Some Novel Allogibberic Acid Derivatives Containing 1,2,3-Triazole Pharmacophore

Desrat and Roussi et al.[83] used specific cancer cells overexpressing one or more Bcl-2 family proteins to test thirty analogues of natural meiogynin A, a pan-Bcl-2 inhibitor, and elaborate cytotoxic chemicals. The interaction of all of the novel compounds with Bcl-xL, Mcl-1, and Bcl-2 proteins was first assessed using a fluorescence polarisation assay (FPA), which revealed that lateral chain modulation had a considerable impact on the activity of the target proteins. The cytotoxicity of the acetoxymethyl prodrugs of the two most active compounds was next tested on B cell lines. A triazole prodrug that promotes apoptosis was found to have a high cytotoxic effect on BL2 and H929 cells (Scheme-18).



Scheme 18. Synthesis of Mcl-1, and Bcl-2 Inhibitor

Bebenek et al. reported[84] other triazole-natural compound hybrids. The WST-1 assay was used to test the anticancer efficacy of triterpene derivative-linked 1,2,3-triazole moieties against amelanotic melanoma C-32, ductal carcinoma T47D, and glioblastoma SNB-19 cell lines in vitro. The IC_{50} value of hybrid

derivative 11 (0.17 μM) against the human glioblastoma SNB-19 cell line was roughly 5-fold greater than the value of the reference medication cisplatin (Figure 8).

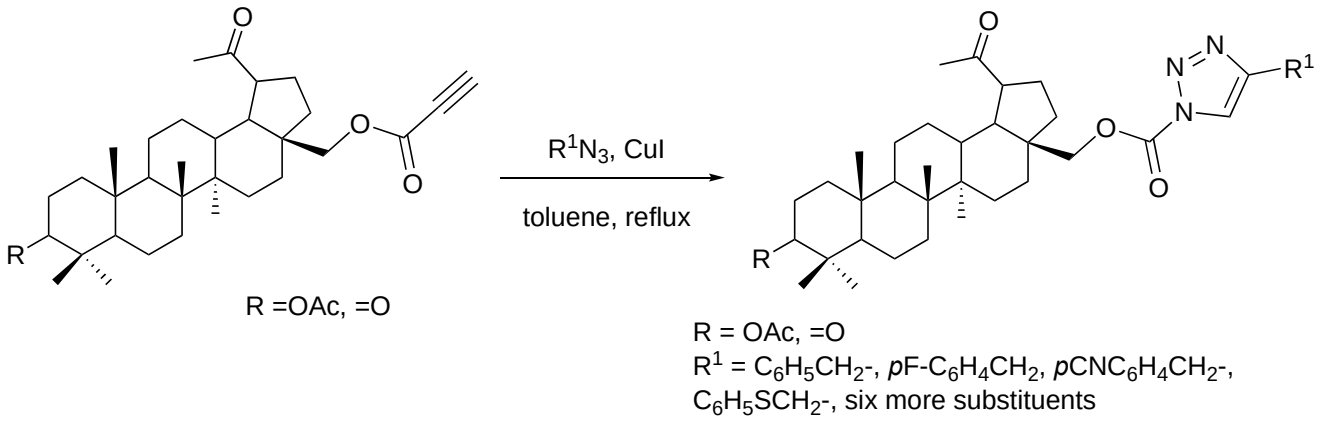


Figure 8. Some Novel Other Triazole-Natural Compound Hybrids

Bian and Lee et al. described Wogonin-based proteolysis-targeting chimaeras with the 1,2,3-triazole moiety and investigated their mechanism of action on CDK9 protein degradation in MCF-7 breast cancer cells.[85] For constructing diverse Wogonin-based PROTACs, a "click chemistry" approach was employed for the synthesis of CDK9-targeting PROTACs. The results of western blotting assays showed that compounds containing triazole group in the linker could selectively down regulate the intracellular CDK9 level. At lower doses, the most active triazole hybrid lead chemical (IC_{50}=17 μM) showed better antiproliferative potential on the MCF-7 cell line than wogonin (IC_{50}=30 μM). Western blotting demonstrated that derivatives with a triazole linker downregulated intracellular CDK9 levels preferentially. In several cancer cell lines, compound (Figures 9 and 10) was found as a selective and leading chemical degrader of CDK9 with limited antiproliferative activity.

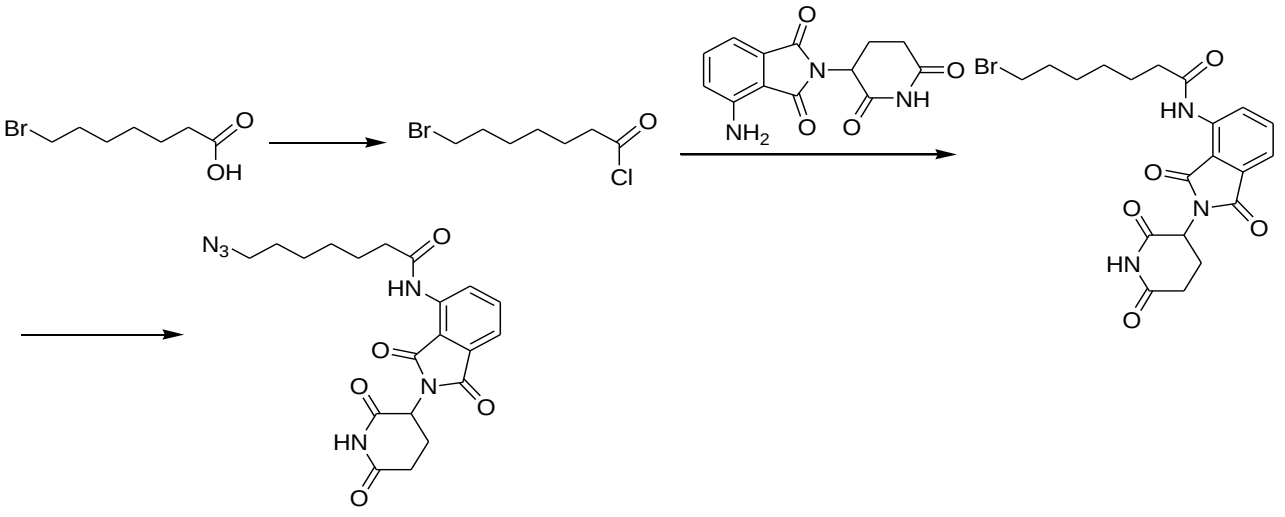


Figure 9. Some Wogonin-Based Proteolysis-targeting Chimaeras with the 1,2,3-Triazole Moiety

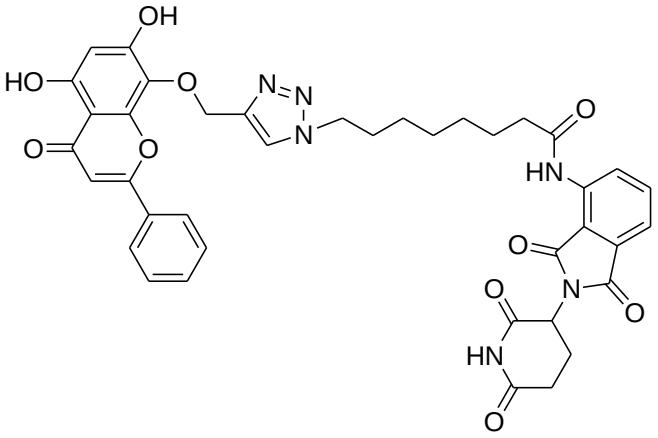


Figure 10. Triazole Compound that Showed Limited Antiproliferative Activity

Sangwan et al. examined anticancer activities in four cancer cell lines using a library of 28 bavachinin analogues, including aliphatic and aromatic ethers, epoxide, chalcone, oxime, semicarbazide, oxime ether, and triazole derivatives.[86] The IC_{50} values for the 1,2,3-triazole analogue amide (Figure 11) against A549, PC-3, HCT-116, and MCF-7 cancer cell lines were 7.72, 16.08, 7.13, and 11.67 μM, respectively. Furthermore, these compounds caused apoptosis and morphological abnormalities in cells, as well as inhibiting cell migration and colony formation.

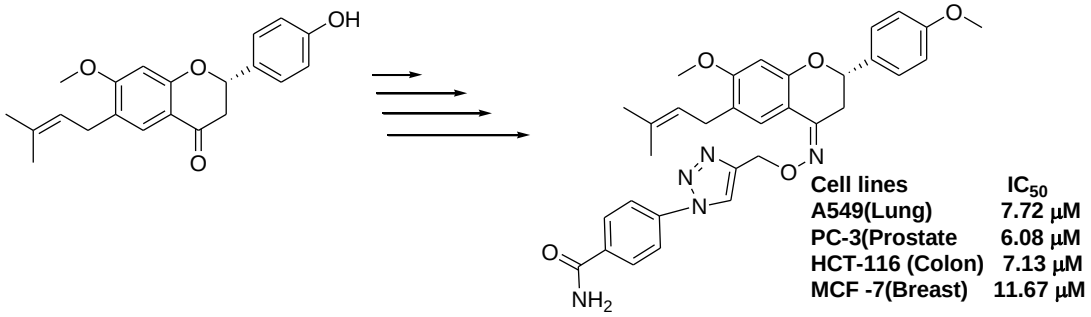
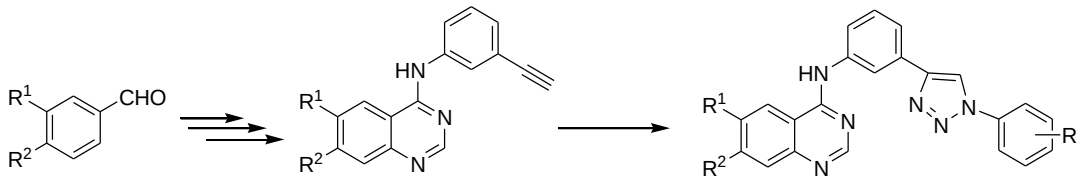


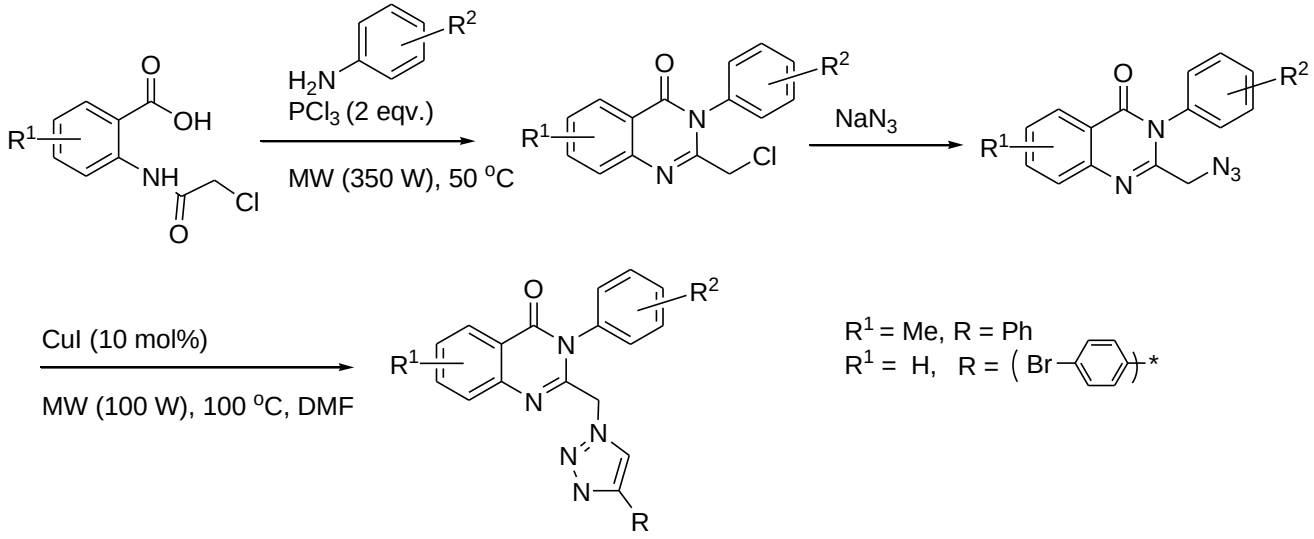
Figure 11. Some Triazole Derivatives that are Active against Cancer Cell Line

The synthesis of many series of novel dioxygenated ring fused 4-anilinoquinazolines and 4-anilinoquinazoline-substituted triazole hybrid compounds was reported by Le-Nhat-Thuy et al.[87] The biological importance of the compounds was underscored by in vitro anticancer testing, which revealed that several of them had excellent activity against three human cancer cell lines (KB, epidermoid carcinoma; HepG2, hepatoma carcinoma; SK-Lu-1, non-small lung cancer). In compared to erlotinib, the lead molecule displayed up to 100-fold greater cytotoxicity. The lead compounds, including the lead molecule (Scheme 19), were docked into the active ATP binding site of different epidermal growth factor receptor (EGFR) kinases. The interaction of H-bonds from the 1,2,3-triazole fragment and extensive hydrophobization of the di-oxygenated part of quinazolines with the ATP pocket remnants was discovered to be a key point in EGFR binding.



Scheme 19. Synthesis of Novel Dioxygenated Ring Fused 4-Anilinoquinazolines and 4-Anilinoquinazoline-Substituted Triazole Hybrid Compounds

Under microwave-assisted conditions, Sawant et al. synthesized[88] 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-ones utilizing a one-pot multicomponent method. D-ring modified triazolyl-quinazolinone analogues are created using the IC87114 scaffold, which has been shown to be the first known isoform selective inhibitor of PI3K in in vitro cytotoxicity tests against numerous cancer cell lines (HL-60, Colo-205, HCT-116, MCF-7, and A549 cells). Two triazolyl-quinazolinone compounds (Scheme 20) based on the same scaffold with PI3K specific inhibitory potential was made. In silico results suggest that these compounds have greater interaction, affinity, and inhibitory activity for PI3K than for PI3K. From a medicinal chemistry and drug development standpoint, this relocation of scaffold from PI3K to PI3K isoform can be highly valuable in unraveling molecular interactions of this new scaffold in many biological pathways.



Scheme 20. Synthesis of 1,4-Substituted 1*H*-1,2,3-Triazolo-quinazolin-4(3*H*)-ones Utilizing a One-Pot Multicomponent Method

Yang and Jiang et al. developed, produced, and tested[89] a series of non-peptide inhibitors for the fluorescence polarisation (FP) assay that target the polo-box domain (PBD) of polo-like kinase 1 (Plk1). The non-peptide triazole compound (Figure 12), which was related to the 1,4-regioisomer triazole portion, showed significant bioactivity with an IC_{50} value of 3.37 μM, which was higher than that reported for phosphate peptide (PLHSpT, IC_{50}=0.62 μM), and it showed moderate activity against the Polo-like kinase 1 PBD.

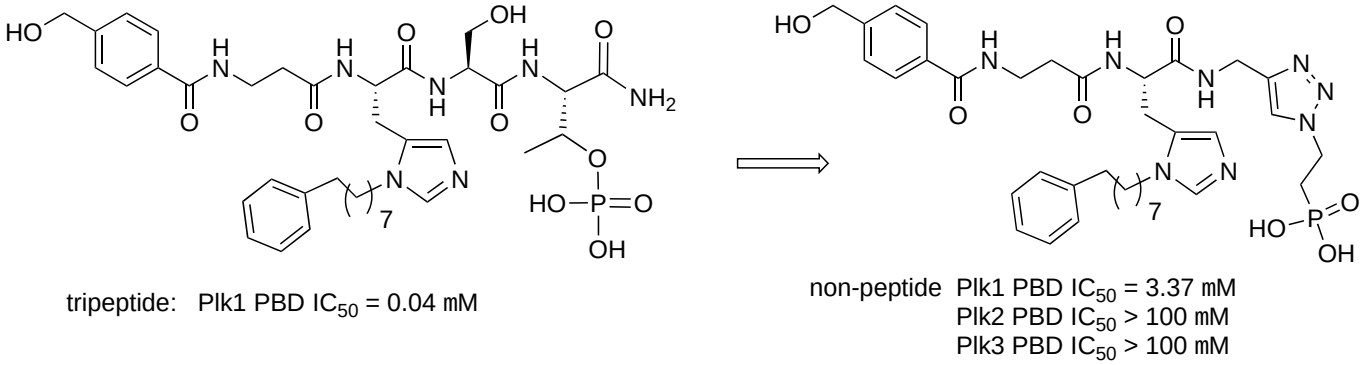
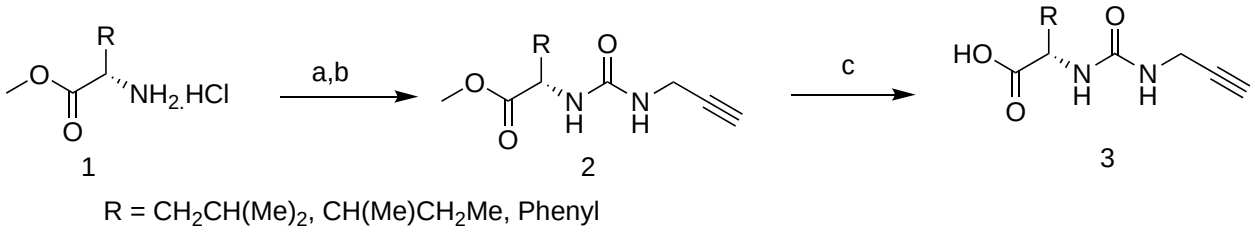


Figure 12. Some 1,4-Regioisomer Triazole Portion

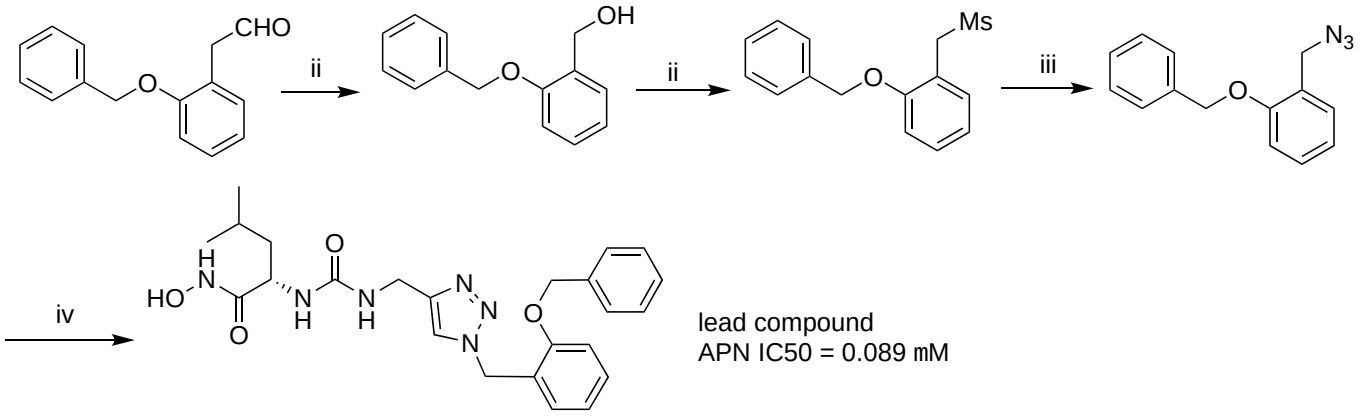
Zu and Zhang et al. developed, produced, and tested[90] a new series of leucine ureido compounds incorporating the triazole moiety as APN inhibitors. The best APN inhibition was seen in lead compound (Scheme 21), which had an IC_{50} of 0.089 - 0.007 μM, which was two orders of magnitude lower than bestatin (IC_{50} = 9.4 - 0.5 μM). This chemical also has anti-angiogenesis properties that were dose-dependent. In both the human umbilical vein endothelial cells (HUVECs) capillary tube formation assay and the rat thoracic aorta rings test, this drug showed equal anti-angiogenesis action at lower concentrations (10 μM) compared to bestatin at 100 μM. Furthermore, in vivo testing of the lead chemical revealed more promising anti-metastasis activity in the mouse H22 pulmonary metastasis model, with inhibitory rates of 71% versus 64% for bestatin.



Reagents and conditions: (a) triphosgene, $NaHCO_3$, DCM/H_2O, ice-bath, 1.5 h; (b) propargylamine, TEA, DCM, 25 °C, 12 h; (c) NH_2OK, MeOH, 25 °C, 0.5 h.

Scheme 21. Synthesis of New Series of Leucine Ureido Compounds Incorporating the Triazole Moiety as APN Inhibitors

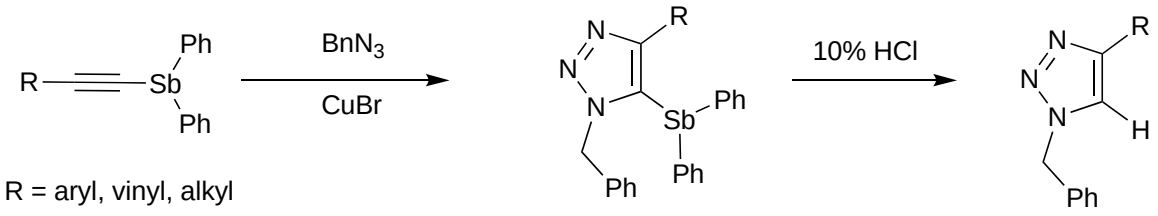
The ‘click reaction' was used by this group to synthesise leucine-ureido-triazole conjugates as aminopeptidase N inhibitors. Lead compound inhibited aminopeptidase N better than the other compounds in their investigation, with an IC_{50} of 0.089 μM. (approximately 100-fold lower than that of the positive control bestatin). Furthermore, as compared to bestatin this was demonstrated superior antiangiogenesis potency in both the HUVEC tubular structure formation bioassay and the rat aortic ring model in vitro. In addition, in vivo screening of the lead compound demonstrated more promising anti-metastasis activity in the mouse H22 pulmonary metastasis model, with inhibitory rates of 71 percent against 64 percent for bestatin.



Reagents and conditions: (i) $NaBH_4$, MeOH, ice-bath, 1 h; (ii) CH_3SO_2Cl, DCM, TEA, ice-bath, 12 h; (iii) NaN_3, DMF, 25 ^oC,12 h; (iv) 3, $CuSO_4$•$5H_2O$, sodium ascorbate, DMSO/H_2O (4:1), 25 ^oC, 2 h

Scheme 22. Synthesis of New Series of Leucine Ureido Compounds Incorporating the Triazole Moiety

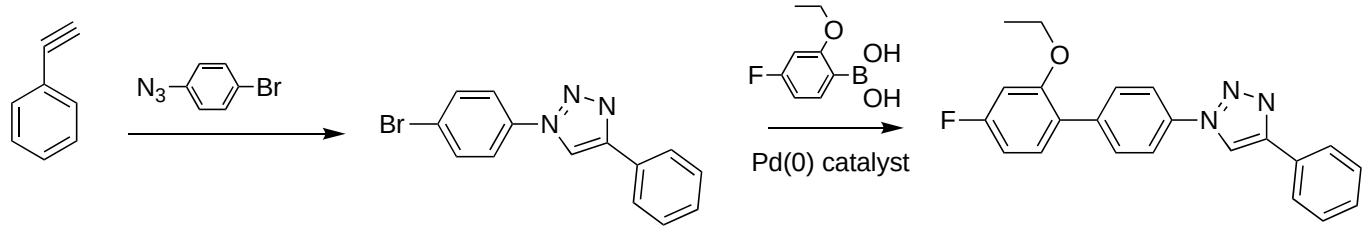
Yamada et al. reported[91] the synthesis of trisubstituted 5-organostibano-1*H*-1,2,3-triazoles by the Cu-catalyzed azide-alkyne cycloaddition of various ethynylstibanes with benzylazide in the presence of CuBr (5 mol%) under aerobic conditions. The anticancer properties of eight cultivated tumour cell lines, including human solid tumour cell lines such as colon, stomach, and breast cancers, were assessed.



Scheme 23. Synthesis of Trisubstituted 5-Organostibano-1*H*-1,2,3-Triazoles

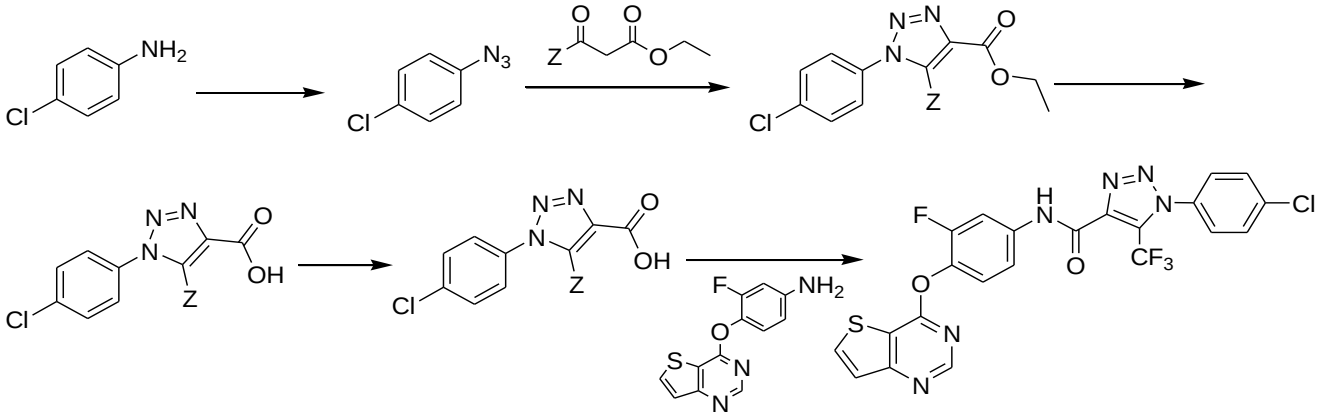
Gilandoust et al.[92] used a copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC) process to synthesize 1,4-disubstituted 1,2,3-triazoles and 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives, which were then tested for anticancer efficacy against MCF7 cells. Compound 1-(2′-ethoxy-4′-fluoro-[1,1′-biphenyl]-4-yl)-4-

phenyl-1*H*-1,2,3-triazole demonstrated activity against MCF7, BT474, MDA-MB-231, and Ishikawa cells (IC_{50} values of 1.69, 4.08, 4.81, and 1.97 μM, respectively) (Scheme 24).



Scheme 24. Synthesis of 1,4-Disubstituted 1,2,3-Triazoles and 1,2,4-triazolo[1,5-*a*]pyrimidine Derivatives.

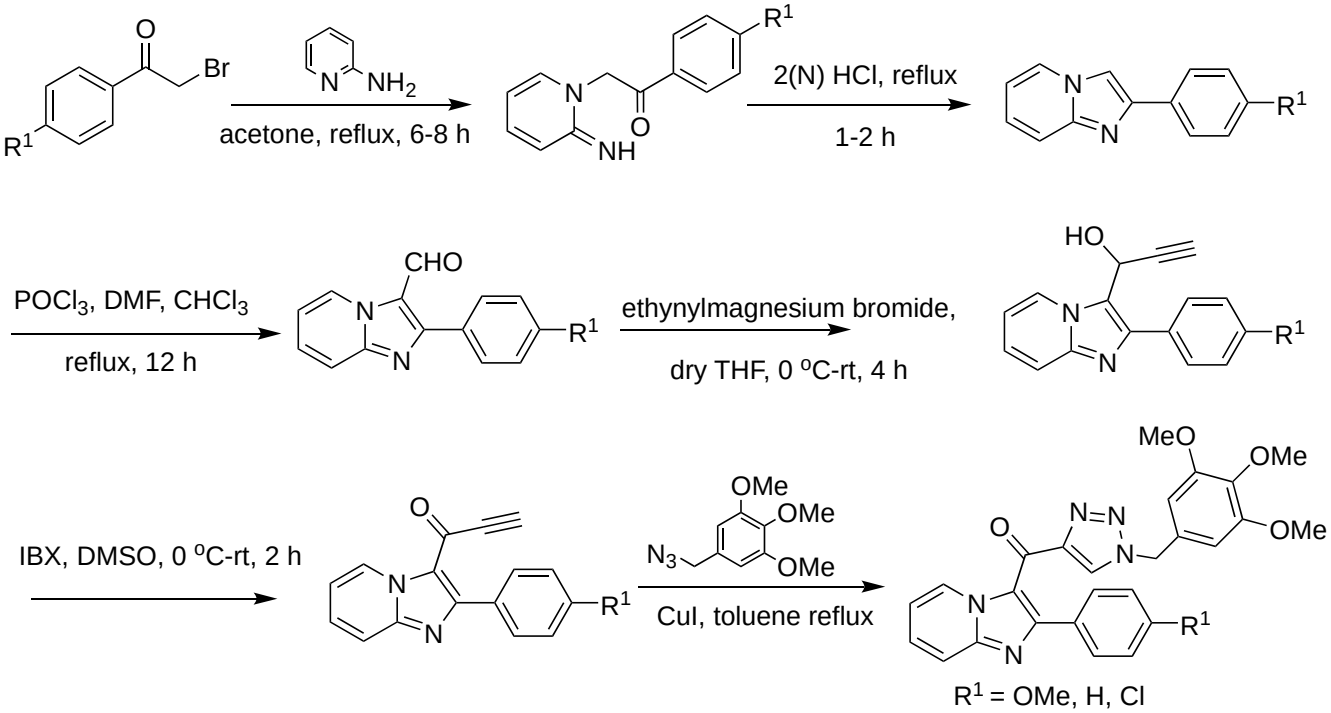
Five series of N-methylpicolinamide moiety and thienopyrimidine moiety containing triazoles were found by Zhu et al.[93] All target compounds were tested for IC_{50} values against three cancer cell lines (A549, HepG2, and MCF-7) and some of them were also tested for activity against the kinases c-Met, Flt-3, VEGFR-2, c-Kit, and EGFR. Furthermore, SARs and docking investigations revealed that the thieno[3,2-*d*]pyrimidine carrying triazole moiety was the activity's preferred structure. The activity of the Cl atom on the 4-C position of the aryl group was particularly high. With IC_{50} values of 0.9 -0.1 μM, 0.5 - 0.1 μM, and 1.1- 0.2 μM, respectively, the most promising compound showed 3.7–5.4-fold more activity than the lead drug Foretinib against A549, HepG2, and MCF-7 cell lines, and enzyme-based experiments revealed that promising compound inhibits c-Met selectively, with IC_{50} values of 16 nM, which showed equal activity to Foretinib (14 nM). Furthermore, enzyme-based tests revealed that one drug inhibited c-Met selectively, with an IC_{50} of 16 nM, similar to foretinib (14 nM).



Scheme 25. Synthesis of Thienopyrimidine Moiety Containing Triazoles

Kamal et al. used click chemistry to design, manufacture, and test[94] a library of new imidazopyridine linked triazole hybrid conjugates against four cancer cell lines: human lung (A549), human prostate (DU-145), human colon (HCT-116), and breast (MDA-MB 231) cancer. With an IC_{50} of 0.51 μM in A549 lung cancer cells and 1.04μ M in prostate cancer cell line, the most active molecule showed strong anticancer

potential (DU-145). Equimolar mixes of substituted 2-bromoacetophenones and 2-aminopyridine were refluxed for 4–5 hours to yield 2-arylimidazopyridine linked triazoles, followed by addition of 2 N HCl under reflux conditions. Vilsmeier–Haack reaction on the equivalent 2-arylimidazopyridine yielded the intermediate imidazopyridine aldehydes. These aldehydes were then treated with ethynylmagnesium bromide in THF to produce intermediate hydroxyl aryl compounds, which were then oxidised with IBX in DMSO to yield the keto–alkynyl precursors. Following that, the required compounds were made by reacting the precursors with substituted benzyl azides (Scheme 26).



Scheme 26. Synthesis of Imidazopyridine-Triazole Hybrids

Bistrovic et al. described[95] a series of novel amidino 2-substituted benzimidazoles linked to 1,4-disubstituted 1,2,3-triazoles by implementation of microwave and ultrasound irradiation in click reaction and subsequent condensation of thus obtained 4-(1,2,3-triazol-1-yl)benzaldehyde with *o*-phenylenediamines. *In vitro* anti-proliferative screening of compounds (Figure 13) performed on human cancer cell lines revealed that *p*-chlorophenyl-substituted 1,2,3-triazolyl-*N*-isopropylamidine and benzyl-substituted 1,2,3-triazolyl-imidazoline-benzimidazoles had selective and potent cytostatic activities in the low nM range against non-small cell lung cancer cell line A549, which could be attributed to induction of apoptosis and primary necrosis.

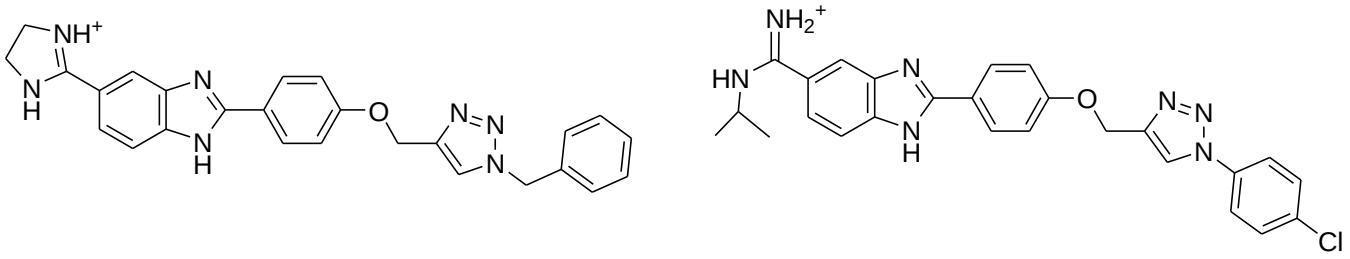
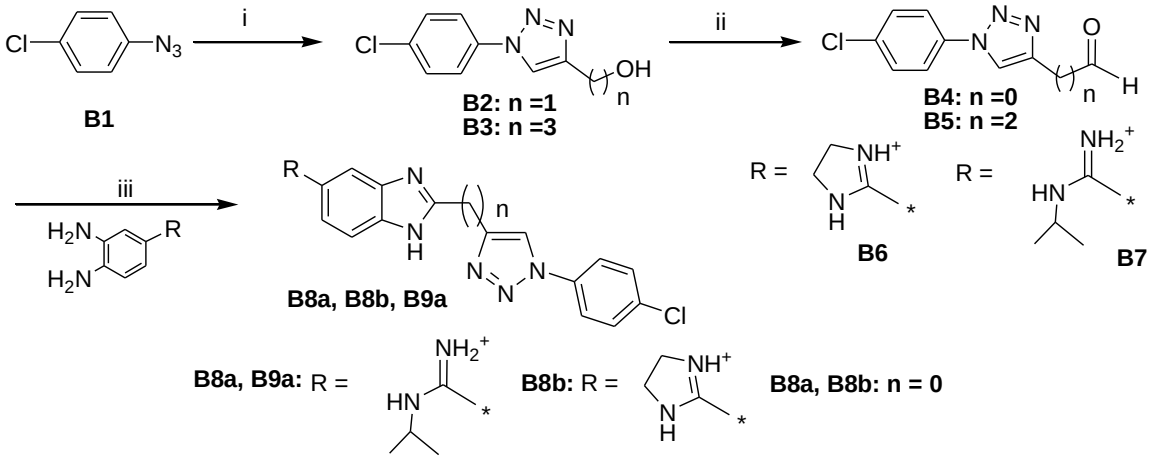


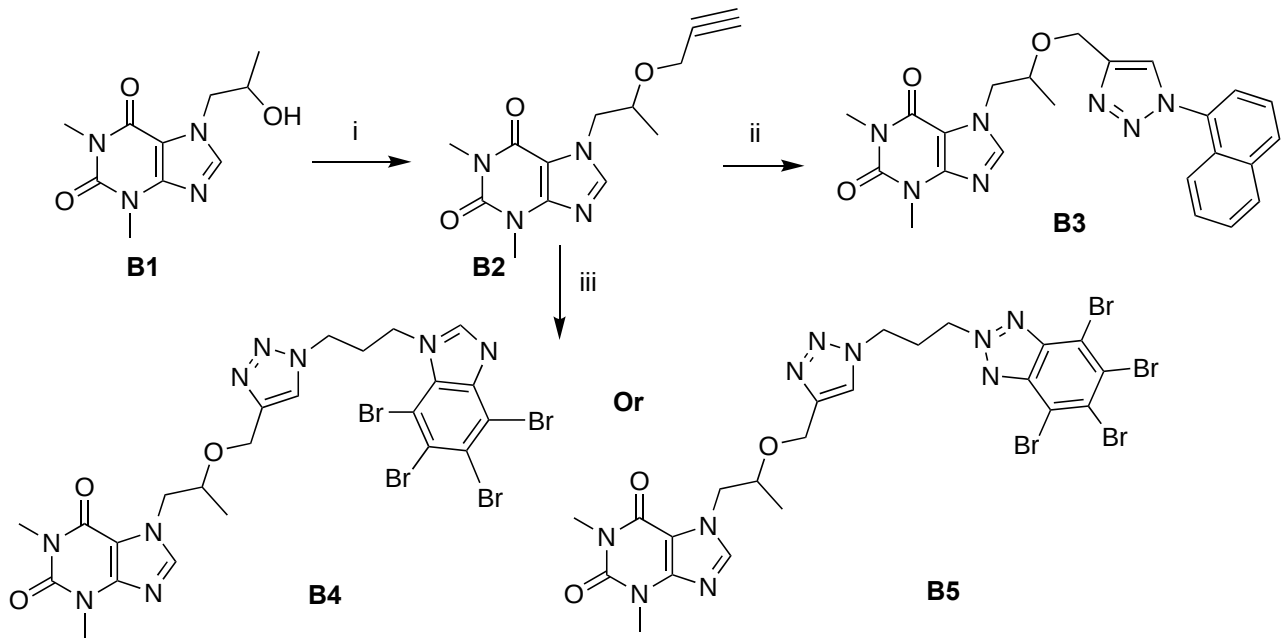
Figure 13. Some Anti-Proliferative Compounds with 1,2,3-Triazoles



(i): propargyl alcohol/4-pentyn-1-ol, $Cu(OAc)_2$, MeOH, 80 ^oC, US, 1.5 h; (ii): $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to rt 45 min; (iii): a) 1,2-phenylenediamine (5 and 6), $NaHSO_3$, EtOH, reflux, 6 h; b) HCl/MeOH, rt, 4 h.

Scheme 27. Series of Novel Amidino 2-Substituted Benzimidazoles Linked to 1,4-Disubstituted 1,2,3-Triazoles

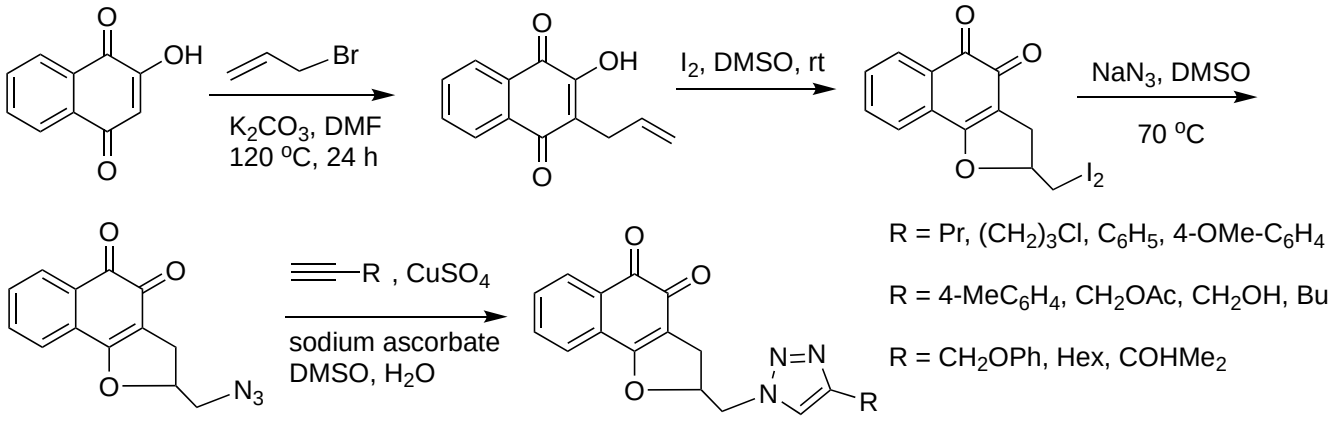
Borowiecki et al. created[96] sixteen novel 1,3-dimethylxanthine derivatives (proxyphylline analogues) and found that three of them have antifungal and anticancer activities in common. Proxyphylline with a 1-(10*H*-phenothiazin-10-yl)propan-2-yl and polybrominated benzimidazole, or benzotriazole moiety was selectively cidal against *Candida albicans*, but not against normal mammalian Vero cell line in vitro (IC_{50} 280 μM) or *Galleria mellonella* in vivo. These compounds (B3-B5: Scheme-28) also showed considerable antineoplastic activity (EC_{50} = 80 μM) against human breast adenocarcinoma (MCF-7) cell line and significant activity (EC_{50} = 6.3-6.5 μM) against peripheral blood T lymphoblast (CCRF-CEM).



(i) NaH (2 equiv., as 60% w/w dispersion in mineral oil), dry THF, 10 min at 0-5 ^{o}C, then 30 min at rt (under Ar-atmosphere), then TBAI (0.1 equiv.), propargyl bromide (2 equiv., as 80% w/w solution in PhMe), 20 min at 0-5 ^{o}C, then 2 h at rt; (ii) 30 (1.1 equiv.), $CuSO_4$•$5H_2O$ (0.01 equiv.), sodium ascorbate (0.02 equiv.), $MeCO_2H$ (0.1 equiv.), *tert*-BuOH/H_2O (1:2, v/v), 10 min at rt; (iii) 37 or 38 (1.1 equiv.), $CuSO_4.5H_2O$ (0.1 equiv.), sodium ascorbate (0.2 equiv.), $MeCO_2H$ (0.2 equiv.), DMF/tert-BuOH/H_2O (5:1:2, v/v), 30 min at 50 ^{o}C.

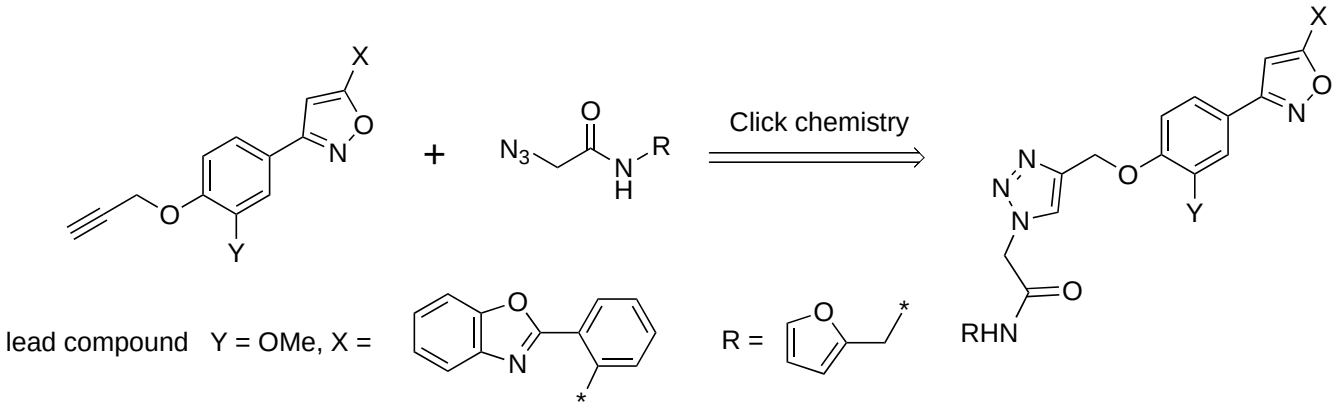
Scheme 28. Synthesis of Proxyphylline 1,2,3-Triazolic Ethers B3-B5

Costa et al.[97] synthesized (Scheme -29) 35 1,4-naphthoquinones tethered to 1,2,3-1*H*-triazoles, and tested their anticancer activity and molecular processes in a variety of assays, including in vitro and in vivo models of OSCC and normal oral human cells. The lead drug was the most efficient against OSCC cells among the 35 triazole naphthoquinones produced, with high cytotoxicity (35 μM), selectivity (SI 6) and low acute toxicity in animals, and so should be considered for future cancer therapy.



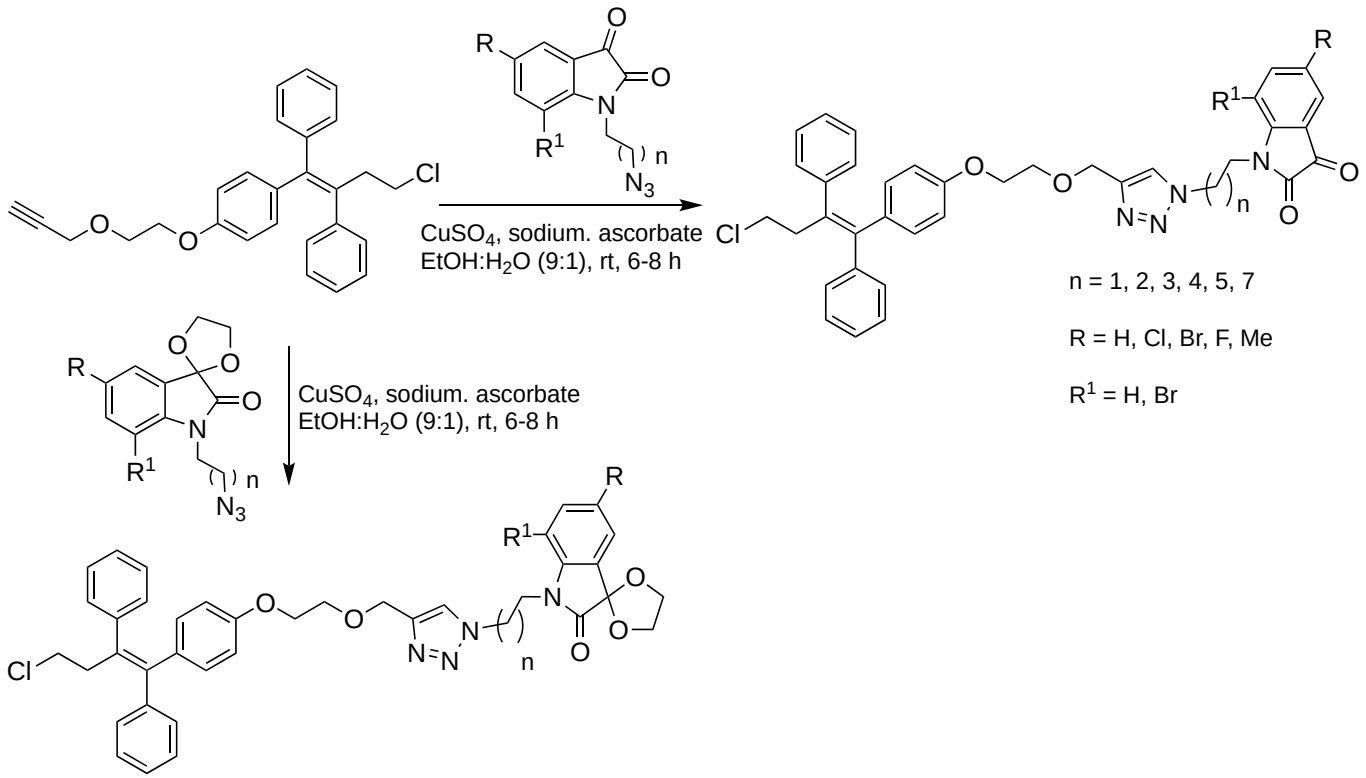
Scheme 29. Synthesis of 1,4-Naphthoquinones Tethered to 1,2,3-1*H*-Triazoles

Dadmal et al. synthesized[98] a series of 1,2,3-triazole and isoxazole-linked benzothiazole/benzoxazole compounds and tested their anticancer efficacy against HeLa (cervical) and A549 (lung) cell lines, with the HEK-293 cell line serving as a reference. Inhibition values for the lead drug in this investigation are good (Scheme 30, IC_{50}=1.768 [HeLa] and 2.594 μM [A549]). The cell cycle of the HeLa and A549 cell lines was also studied. On A549 cells, the triazole derivative was more potent, and the cell death percentage in the subG1 phase was 49.43 percent in the cell cycle experiment. When compared to the reference medications TAK-165 and GW-610, compound (42.58 percent) showed considerable and elevated apoptotic potency in the subG1 phase in HeLa cells.



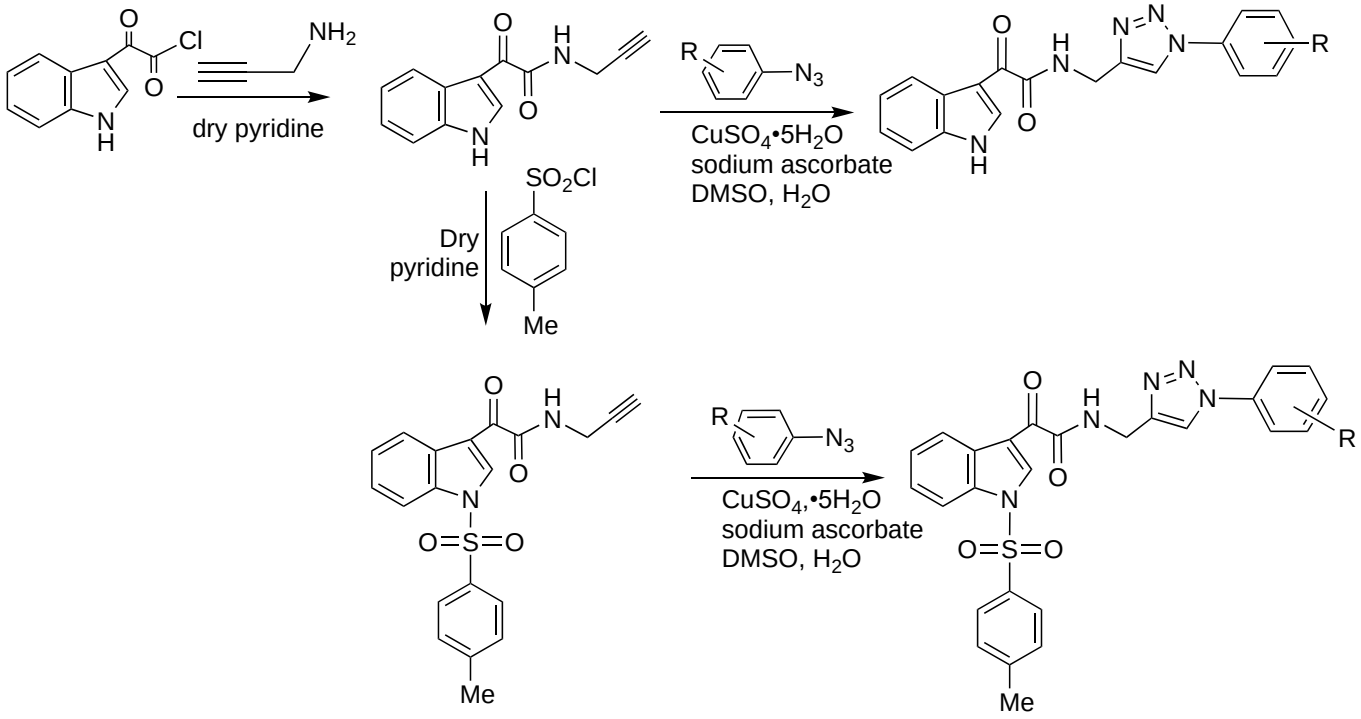
Scheme 30. Series of 1,2,3-Triazole and Isoxazole-linked Benzothiazole/Benzoxazole Compounds

Kumar et al. synthesized[99] a library of 1*H*-1,2,3-triazole-tethered ospemifene–isatin and ospemifene–spiroisatin conjugates and tested them against MCF-7 and MDA-MB-231 cell lines for anti-proliferative activity. The assessment investigations found that final compound (Scheme 31) was the most effective against the MCF-7 cell line, with an IC_{50} value of 1.56 μM. The structure–activity relationship (SARs) analysis revealed that conjugates with a bromo-substituent of the isatin ring, as well as ethyl/propyl as the spacer, were active against the MCF-7 cell line, with the most potent compound being 30 times more potent than Tamoxifen.



Scheme 31. Synthetic Route to 1*H*-1,2,3-Triazole Tethered Ospemifene–Isatin/Ospemifene–Spiroisatin Conjugates

Using a click chemistry approach, Shahar Yar et al. synthesized a set of two series containing 42 compounds[100] of 1, 2, 3-tethered indole-3-glyoxamide derivatives, which were then tested for their in vitro cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX) inhibitory activities as a cancer chemotherapy. In this study, final compound (Scheme 32) showed dual inhibition of COX-2 and 5-LOX, as well as substantial antiproliferative potential on the prostate cancer cell line DU145, a great COX-2SI, and satisfactory anti-inflammatory activity in vivo with no ulcerogenic effects. Furthermore, final compound interfered with microtubule dynamics, acting as a microtubule-destabilizing agent, as evidenced by its influence on tubulin polymerization which is also occupy the colchicines binding site of tubulin polymer, according to in silico molecular docking studies, and has high binding affinities for COX-2 and 5-LOX.



Scheme 32. Synthesis of 1, 2, 3-Tethered Indole-3-glyoxamide Derivatives

Based on the N-arylpiperidine-4-carboxamide derivative connected to the triazole ring, Schlapbach et al. published[101] a new and highly selective MALT1 protease inhibitor. MALT1 inhibitors demonstrated activity in a mechanistic Jurkat T cell activation test as well as in the B-cell lymphoma line OCI-Ly3, suggesting that they could be used to treat autoimmune disorders and B-cell lymphomas with a dysregulated NF-B pathway. Furthermore, the pharmacokinetic parameters of this chemical series in rats revealed extremely high clearance. Among the other examined substituents, the para-substituent tethered to a 1,2,3-triazole moiety was found to be the most advantageous.

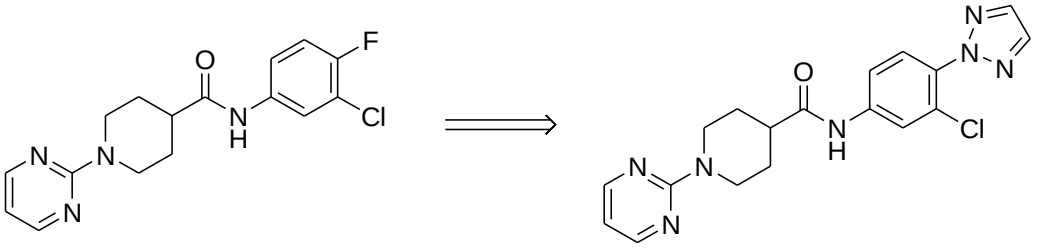
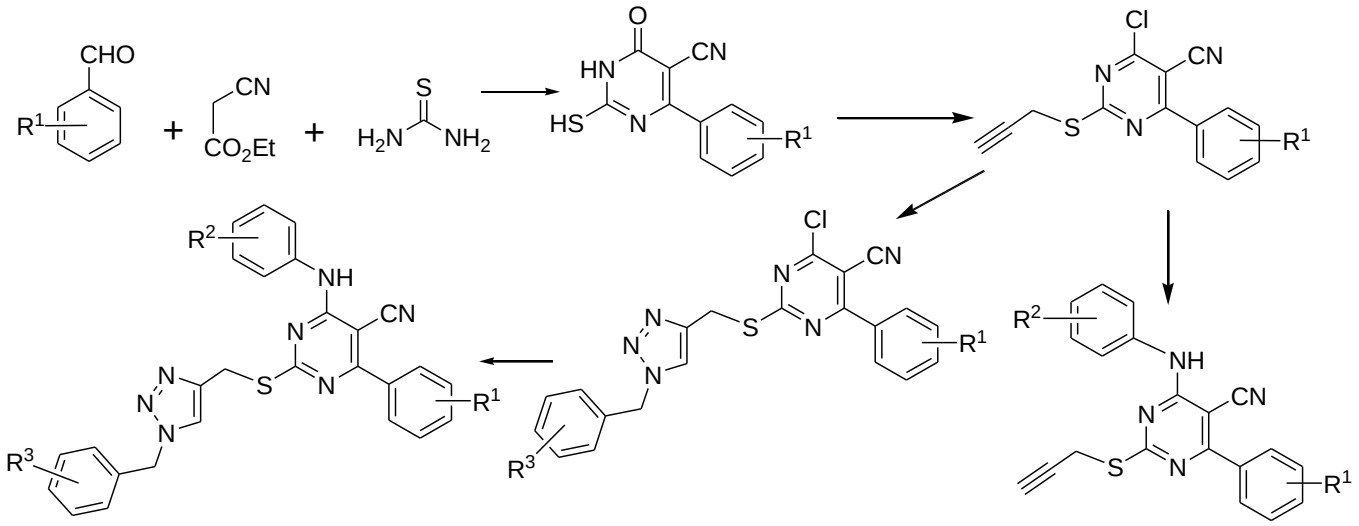


Figure 14. N-Arylpiperidine-4-carboxamide Derivative

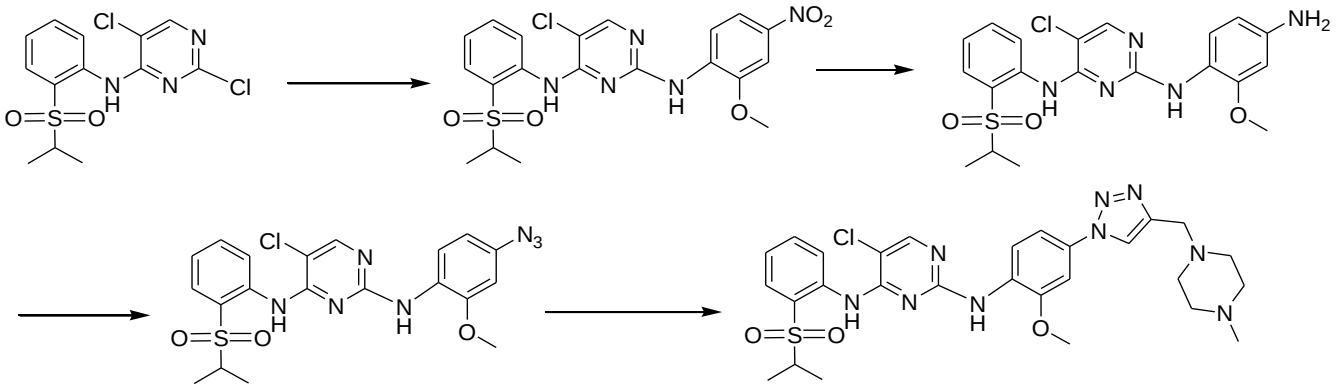
Liu et al. created[102] a series of pyrimidine-based hybrid compounds with a 1,2,3-triazole moiety and tested them for MDR reversal activity. The majority of target compounds had reversal potency ranging from moderate to high. Lead compound had the most strong reversal activity of the bunch, almost 7 times more active than Verapamil (VRP). The lead compound could clearly reverse paclitaxel (PTX) resistance

in SW620/AD300 cells by enhancing PTX accumulation and prolonging PTX maintenance, according to further mechanistic studies. The findings suggest that 1,2,3-triazole-pyrimidine-based compounds could be a promising starting point for the creation of novel ABCB1-dependent MDR modulators (Scheme 33).



Scheme 33. Synthesis of Pyrimidine-Based Hybrid Compounds with a 1,2,3-Triazole Moiety

Based on the cocrystal structure of ceritinib with ALKWT, Zhai and Ghong et al.[103] developed and synthesized two series of 2,4-diarylaminopyrimidine (DAAP) analogues containing thiazole or 1,2,3-triazole moieties (PDB 4MKC) to overcome crizotinib-resistant mutations, as well as the binding model of ceritinib with ALKG1202R for novel anaplastic lymphoma kinase (ALK) and proto-oncogene tyrosine-protein kinase ROS (ROS1) dual inhibitors. The trizole drug (Scheme 34) inhibited ROS1-positive HCC78 (IC_{50}=40 nM), anaplastic lymphoma kinase-dependent H2228 (IC_{50}=95 nM) cell lines, and KARPAS299-positive HCC78 (IC_{50}=40 nM).



Scheme 34. Synthesis of 2,4-Diarylaminopyrimidine (DAAP) Analogues Containing Thiazole

SOME REPRESENTATIVE 1,2,3-TRIAZOLES AS ANTI-CANCER AGENTS

2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl)aniline which inhibited tubulin polymerization with IC_{50} = 4.8 μM.

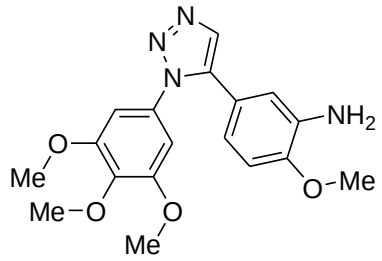


Figure 15

3-(4-(4-Phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzo[*d*]isoxazole which was found to be one of the most potent antiproliferative agent with an IC_{50} of 2 μM against MV4-11 cells using MTT assay.

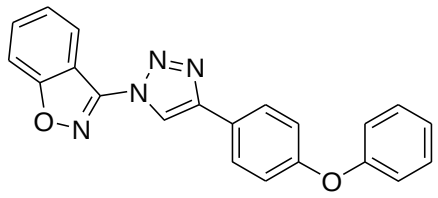


Figure 16

4-[Phenyl-1-(1-phenylethyl)]-1*H*-1,2,3-triazole which is displayed good cytotoxic activity against HL 60 cells with IC_{50} values of 1.15 μM.

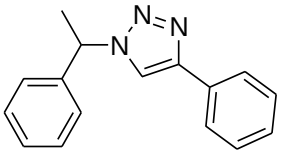


Figure 17

3-(4-{(4-Pyridinyl)-5-(4-fluorophenyl)}-4*H*-1,2,4-triazol-3-yl-thio)-N-isopropylpropan-1-amine and

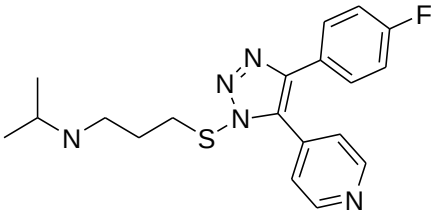


Figure 18

N-(5-benzylthiazol-2-yl)-4-(4-methyl-1*H*-1,2,3-triazole-1-yl)benzamide having lowest IC_{50} values induced DNA damage through apoptosis which was probably the biochemical basis for excellent cytotoxicity of these compounds.

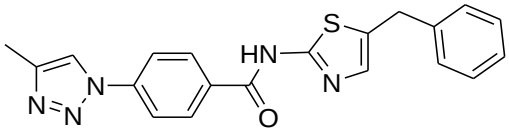


Figure 19

3-{1-N-(2-Cyanophenyl)-1*H*-1,2,3-triazol-4yl}methyloxy betulinic acid.

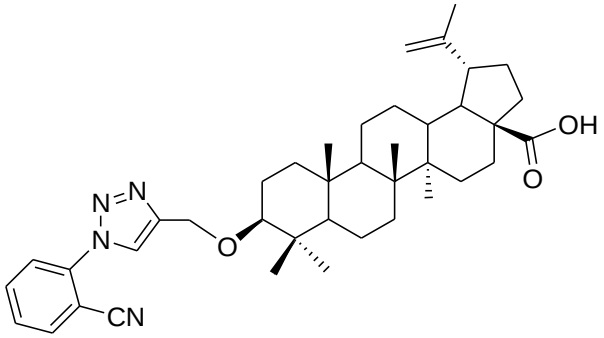


Figure 20

3-{1-N-(5-Hydroxy-naphth-1yl)-1*H*-1,2,3-triazol-4yl}methyloxybetulinic acid displayed impressive IC_{50} = 2.5 and 3.5 μM respectively against leukemia cell line HL-60, in short, showing 5–7-fold higher potency than betulinic acid.

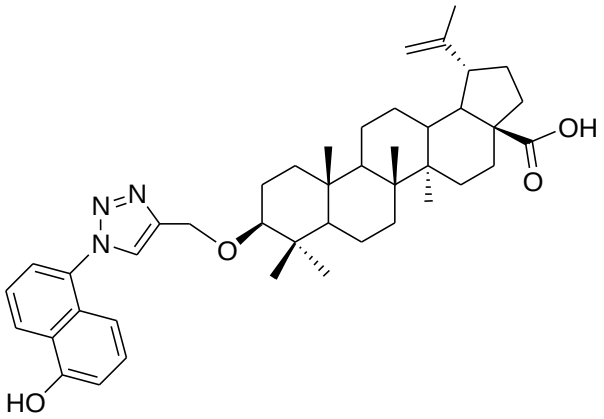


Figure 21

(1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl piperazine-carbodithioate displayed impressive IC_{50} = 2.5 and 3.5 μM respectively against leukemia cell line HL-60, in short, showing 5–7-fold higher potency than betulinic acid.

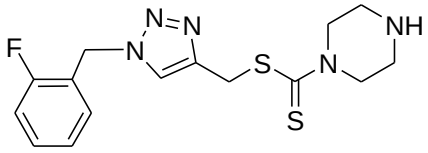


Figure 22

[1-(4-Fluorobenzyl)-1*H*-1,2,3-triazole-4-yl)methyl-4-dimethylcarbamoyl)piperazine-1-carbodithioate and 1-(benzo[*b*]thiophen-2-yl)-4-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole showed broad-spectrum anticancer activity with IC_{50} values ranging from 1.62 to 20.84 μM and 0.76 to 13.55 μM, respectively against MGC-803 cells.

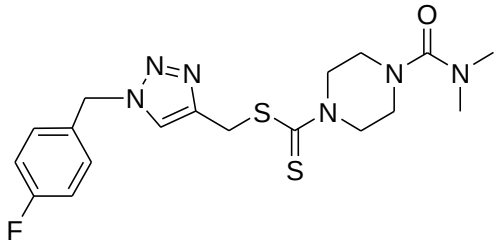


Figure 23

1-(Benzo[b]thiophen-2-yl)-4-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole was found to be the most potent against triple negative Hs578T breast cancer cell lines and was also the most effective inhibitor of tubulin polymerization.

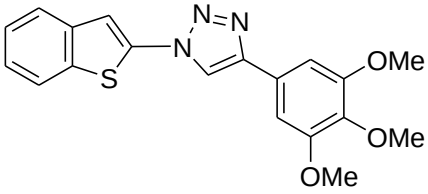


Figure 24

N-((1-3-Phenoxybenzyl)-1*H*-1,2,3-triazole-4-yl)methyl)picolinamide was the foundational compound for further study which induced M-phase arrest in HeLa cells at 5 μM concentration.

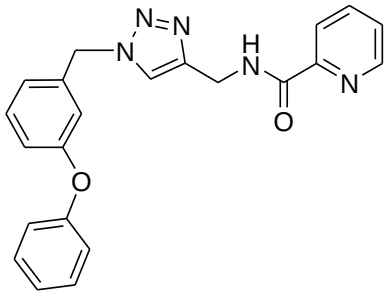


Figure 25

(5,6-Dihydrooxazolo[3,2-*e*][1,2,3]triazol-3-yl)(4-methoxyphenyl)methanone was found to be the most potent derivative with IC_{50} values lower than 1.9 lg/ml against A431 and K562 human tumor cell lines.

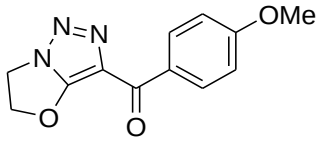
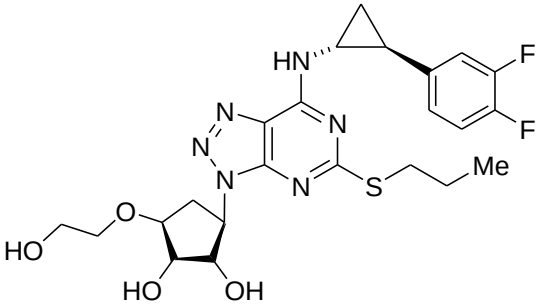
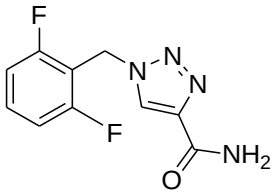
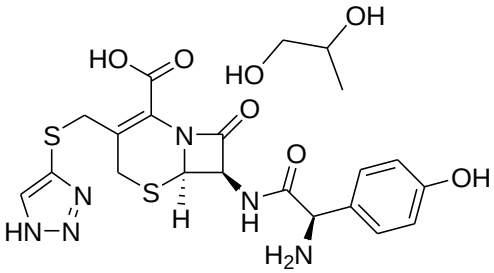
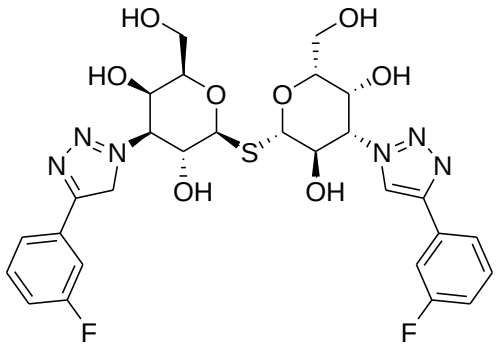
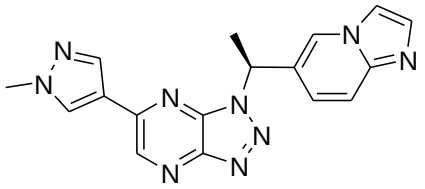
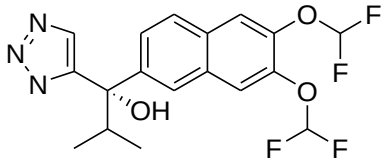
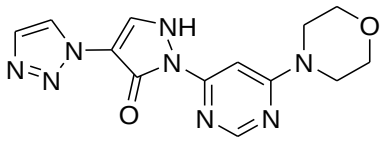
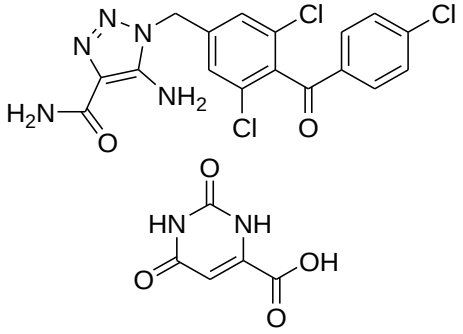
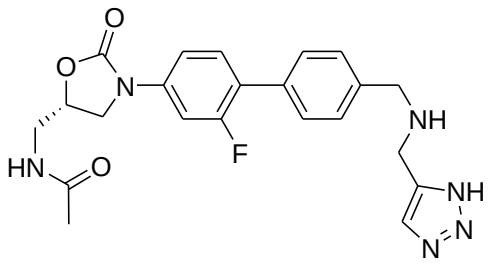
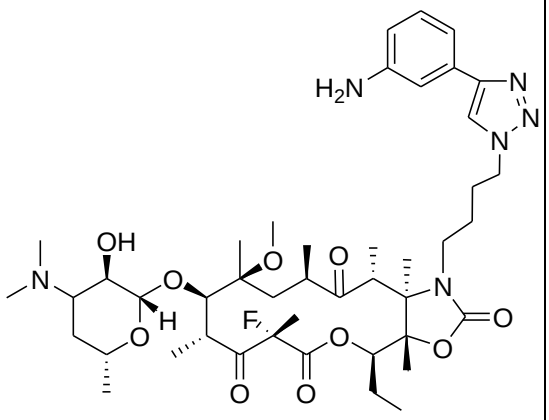


Figure 26

TABLE I. SOME TRIAZOLE BASED DRUGS AVAILABLE IN CLINICAL THERAPY USING CLICK CHEMISTRY

Drug	Structure	Application
Ticagrelor		Ticagrelor is used for the prevention of thrombotic events (for example stroke or heart attack) in different categories of patients.
Rufinamide		Rufinamide is an anticonvulsant medication to treat seizure disorders like Lennox-Gastuat syndrome, a form of childhood epilepsy.
Cefatrizine propylene glycol		Cefatrizine Propylene Glycolate is the propylene glycol from cefatrizine, a semi-synthetic, first-generation cephalosporin with strong activity against gram-positive cocci except enterococci.

TD - 139		*TD139* is a highly potent, specific inhibitor of the galactoside binding pocket of galectin-3. *TD139* is formulated for inhalation, which enables direct targeting the fibrotic tissue in the lungs, while minimizing systemic exposure.
Savolitinib		Savolitinib (HMPL-504) is a powerful and highly selective cMET small molecule tyrosine kinase inhibitor with outstanding preclinical tolerance profile and robust pharmacokinetics.
Seviteronel		Seviteronel, the nonsteroidal inhibitors, has been used in trials studying the treatment of CRPC, Prostate Cancer, and Castration-resistant Prostate Cancer.
Molidustat		*Molidustat* (BAY 85–3934) is a novel, orally bioavailable HIF-PH inhibitor that mimics hypoxia by stabilizing HIF-α subunits.
Carboxy-amidotriazole orotate		The *orotate* salt form of *carboxyamidotriazole* (CAI), an orally bioavailable small molecule with potential antiangiogenic and antiproliferative activities.

Radezolid		*Radezolid* is a second-generation oxazolidinone antibiotic discovered by Melinta scientists using proprietary, *structure*-based design, to achieve higher ribosomal binding affinity, minimal off-target activity, and a broader spectrum of antimicrobial activity than is currently available in the class.
Solithro mycin		*Solithromycin* is a new ketolide antibiotic, based on the macrolide antibiotic structure, being studied for use in CABP. It has efficacy in vitro against the common causative pathogens in CABP including Streptococcus pneumoniae, Haemophilus influenzae, and atypical pathogens.

PROSPECTS AND APPLICATION OF CLICK CHEMISTRY

Click chemistry is a stringent criterion that used to construct novel and useful pharmacophores to facilitate and in many other applications in the future. The use of click chemistry has found tremendous advantages over traditional synthetic techniques for the modular, rapid, clean and efficient synthesis of various biomolecules. Click chemistry in many is insensitive to oxygen. The high yields with basic purification procedures can lead to photochemical and thermal initiation. Many other applications include in modification of peptide function with triazoles, modification of natural products and pharmaceuticals, drug discovery, macrocyclizations using Cu(I)-catalyzed triazole couplings, modification of DNA and nucleotides by triazole ligation, supramolecular chemistry: calixarenes, rotaxanes, and catenanes, dendrimer design, carbohydrate clusters and carbohydrate conjugation by Cu(1)-catalyzed triazole ligation reactions, polymers, material science, nanotechnology and bioconjugation. The versatility of the reaction can be expanded by the synthesis of NH-1,2,3-triazole derivatives. Click chemistry made the use of azidomethylpivalate to the desired derivative of NH-1, 2, 3-triazole that is amenable for further derivatization. It can be concluded that click chemistry reaction has high potential if exploited appropriately. It links various types of chemistry with biology and can tailor various useful synthesis in

future. Because of the dependability, specificity, and biocompatibility of 1,2,3-triazole, click chemistry is one of the most powerful methods for constructing heteroatom linkages for chemistry and biology in anticancer drug creation and study.

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