REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Triazoles as Promising Small Molecules Anticancer Agents

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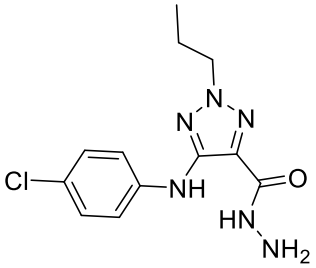
Abstract

The 1,2,3-triazole scaffold has emerged as a pivotal heterocyclic motif in medicinal chemistry due to its unique physicochemical properties, synthetic accessibility, and broad spectrum of biological activities. These five-membered nitrogen-rich rings are most commonly synthesized via the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), a prototypical "click" reaction that offers regioselective access to 1,4-disubstituted triazoles under mild conditions. The resulting triazole ring is chemically stable, metabolically resilient, and capable of mimicking amide bonds, making it a valuable bioisostere in drug design. Biologically, 1,2,3-triazoles have demonstrated diverse pharmacological profiles, including antimicrobial, anticancer, antiviral, anti-inflammatory, and enzyme inhibitory activities. Their ability to engage in hydrogen bonding and π–π stacking interactions enhances their binding affinity to biological targets. Moreover, triazole-containing compounds have been successfully incorporated into peptidomimetics, nucleoside analogs, and targeted drug delivery systems. Recent advances in metal-free and biocompatible triazole synthesis have further expanded their utility in chemical biology and pharmaceutical development. This abstract highlights the dual significance of 1,2,3-triazoles as both versatile synthetic intermediates and potent pharmacophores, underscoring their continued relevance in the discovery and optimization of therapeutic agents.

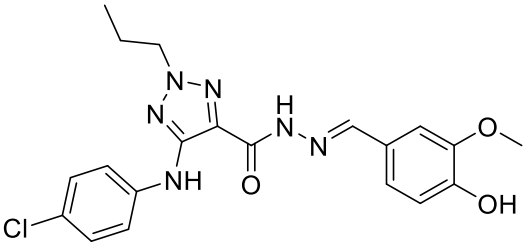
Keywords: Heterocycles, 1,2,3-triazole, Anticancer.

Triazoles as anticancer agents

A series of 2-propyl-1,2,3-triazole compounds **1** and **2** were designed, synthesized, and evaluated for their antitumor activity against breast cancer cell lines, MCF-7 and MDA-MB-231. Compounds **1** and **2** exhibited significant antitumor effect against both cell lines, with IC_{50} values ranging from 5.36 to 18.01 µM, compared to doxorubicin (6.72 µM). The most promising compounds were further assessed for EGFR inhibition, showing IC_{50} values of 0.16 and 0.15 µM, respectively, in comparison to gefitinib (IC_{50} = 0.08 µM). (Çot et al, 2022).



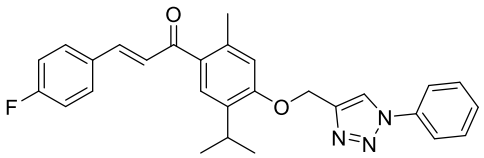
1



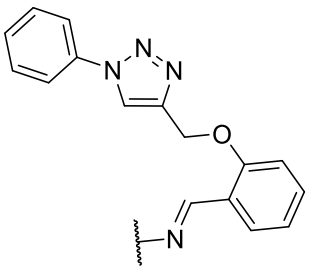
2

Also, a series of novel 1,2,3-triazole-chalcone hybrid compounds were designed and synthesized using thymol as the starting material. The *in vitro* anticancer potential of these compounds was tested against four human cancer cell lines: fibrosarcoma (HT-1080), lung adenocarcinoma (A-299), and breast adenocarcinoma (MCF-7 and MDA-MB-231). Most of the 1,2,3-triazole-chalcone hybrids exhibited promising growth inhibition, with IC_{50} values ranging from 4.36 to 50 μM. Notably, compound **3** demonstrated strong antiproliferative activity against HT-1080 cells, with an IC_{50} value of 4.36 μM (Ashok et al., 2020).

Moreover, a novel series of 1,2,3-triazole and Schiff base hybrids were synthesized and assessed for their anticancer activity against human prostate cancer (PC3) and melanoma (A375) cell lines, as well as normal human fetal lung fibroblast (MRC-5) cells. The compounds exhibited significant cytotoxicity against the cancer cell lines. Among the tested compounds, **4a** and **4b** demonstrated excellent activity in inhibiting cancer cell growth, with IC_{50} values ranging from 21.86 and 45.00 µg/mL, while showing low toxicity toward the healthy MRC-5 cells, with IC_{50} values between 86.40 and 93.07 µg/mL (Dheer et al., 2020).

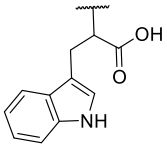


3

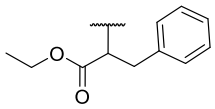


4a, b

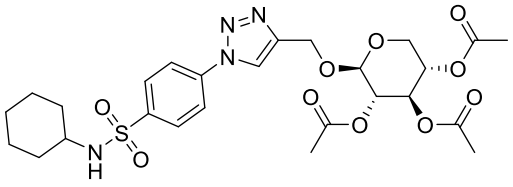
4a:



4b:

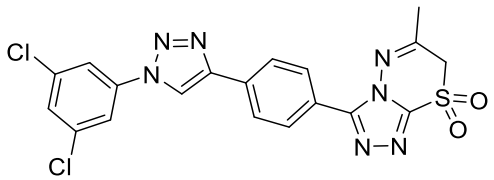


Novel derivatives of sulfonamide-triazole-glycoside hybrids were designed, synthesized, and evaluated for their anticancer activity. The sulfonamide hybrid **5** exhibited promising efficacy against HepG-2 and MCF-7 cell lines, with IC_{50} values of 8.39 μM against HepG-2 and 21.15 μM against MCF-7, outperforming doxorubicin (IC_{50} = 13.76 and 17.44 μM for HepG-2 and MCF-7, respectively). To investigate the possible mechanisms of action, the inhibitory effects of compound **30** on VEGFR-2 and the human carbonic anhydrase isoforms (CA) IX and CA XII were assessed. Compound **30** showed notable potency, with IC_{50} values of 0.38 μM for VEGFR-2, 40 nM for CA IX, and 3.2 nM for CA XII, compared to sorafenib (IC_{50} = 0.43 μM for VEGFR-2 inhibition) and SLC-0111 (IC_{50} = 53 nM and 4.80 nM for CA IX and CA XII inhibition, respectively) (Wang et al., 2020).



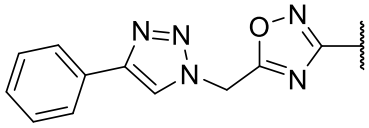
5

Additionally, the *in vitro* anticancer activity of a novel series of 1,2,3-triazole hybrids was assessed using three human breast cancer cell lines: MCF-7, MDA-MB-231, and MDA-MB-415. Notably, hybrid **6** exhibited remarkable activity against MCF-7 and MDA-MB-231 cell lines, with IC_{50} values of 4.10 and 6.98 μM, respectively, and demonstrated comparable efficacy against the MDA-MB-415 cell line (IC_{50} = 5.32 μM). These results were in comparison to the standard drug erlotinib, which showed IC_{50} values of 4.13, 8.06, and 4.02 μM, respectively. Moreover, this compound demonstrated significant potency in the *in vitro* EGFR inhibition assay, with an IC_{50} value of 0.31 μM, outperforming erlotinib (IC_{50} = 0.42 μM) (Fu et al., 2019).

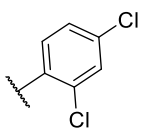


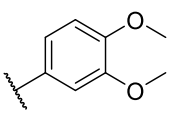
6

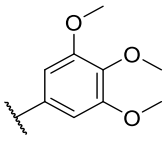
A novel series of 1,2,3-triazole-1,2,4-oxadiazole hybrid compounds **7a-c** was designed evaluated for their dual inhibition of EGFR and VEGFR-2. *In vitro* analysis revealed that compounds **7a-c** inhibited EGFR with IC_{50} values of 89, 82, and 76 nM, respectively, in comparison to erlotinib (IC_{50} = 80 nM). Additionally, they inhibited VEGFR-2 with IC_{50} values of 4.70, 3.80, and 2.40 nM, respectively, compared to sorafenib (IC_{50} = 0.17 nM). Evaluation of their apoptotic potential showed that compounds **7a-c** promote apoptosis by activating caspase-3, caspase-8, and Bax, while downregulating the anti-apoptotic protein Bcl-2. (Vala et al., 2024).



7a-c

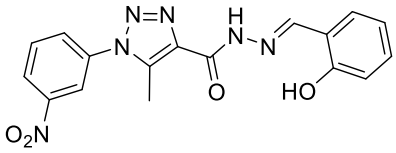
7a: 

7b: 

7c: 

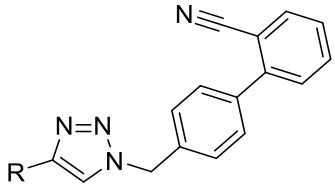
As well, a novel library of triazole-linked

hydrazones was designed, synthesized, and tested for their inhibitory activity against carbonic anhydrase II (CA II). The *in vitro* evaluation revealed substantial inhibitory effects on CA II, with IC_{50} values ranging from 9.10 to 48.26 µM, with compound **8** identified as the most potent inhibitor. Kinetic studies on compound **8** demonstrated a concentration-dependent inhibition, with a Ki value of 7.24 µM (Othman et al., 2022).



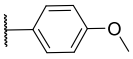
8

A novel series of brain-penetrant bioactive 1,2,3-triazole derivatives with anticancer properties was designed and synthesized. Analogues 9a and 9b exhibited promising anticancer activity against lung cancer cell lines (A299 and SW1323), with IC_{50} values of 5.32 and 4.43 μM, respectively. Moreover, analogue 9b demonstrated broad-spectrum anti-growth activity across multiple cancer types, with IC_{50} values ranging from 2.36 to 5.20 μM (Othman et al., 2022).



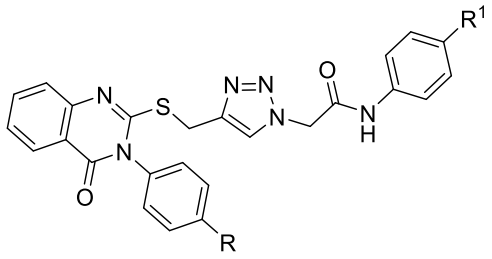
9a, b

39a: R= 

9b: R= 

A series of quinazolone-1,2,3-triazole hybrids were designed and synthesized as multi-target inhibitors of EGFR, VEGFR-2, and Topoisomerase (Topo) II. The synthesized hybrids were evaluated for their anticancer activity, and *in vitro* testing revealed that compounds **10a-c** exhibited the most potent activity against four different cancer cell lines HeLa, HepG-2, MCF-7, and HCT-116 demonstrating low micromolar IC_{50} values while showing good selectivity towards the normal cell line WI-38. The three compounds were further assessed for their inhibitory effects on EGFR, VEGFR-2, and Topo II.

Compound **10b** demonstrated moderate EGFR inhibition (IC_{50} = 0.10 μM) compared to erlotinib (IC_{50} = 0.05 µM), potent VEGFR-2 inhibition (IC_{50} = 0.07 µM) compared to sorafenib (IC_{50} = 0.03 µM), and stronger Topo II inhibition (IC_{50} = 19.74 µM) compared to etoposide (IC_{50} = 34.19 µM), being approximately 1.7 times more potent. Compounds **35a** and **35c** showed strong Topo II inhibitory activity, with IC_{50} values of 31.02 µM and 31.31 µM, respectively, in comparison to etoposide (Sun et al., 2022).



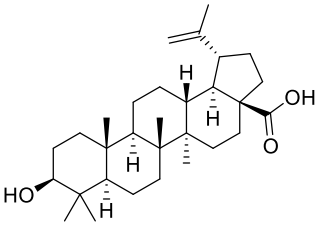
10a-c

10a: R= H, R^1= NO_2
10b: R= H, R^1= CH_3
10c: R= Cl, R^1= Br

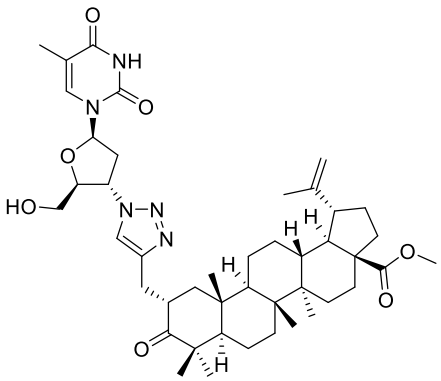
Further, nucleoside derivatives conjugated with a 1,2,3-triazole moiety were synthesized to improve

low toxicity (TC_{50} > 100 μM). In terms of water solubility, compound **11** exhibited approximately

the antitumor potency. Among these compounds, **11** demonstrated broad-spectrum antitumor activity across several tumor cell lines, including SMMC-7721 (IC_{50} = 5.02 μM), KYSE-150 (IC_{50} = 5.68 μM), and SW370 (IC_{50} = 4.36 μM), while exhibiting 40 times higher solubility (1.98 µg/mL) compared to betulinic acid (<0.05 μg/mL). In SMMC-7721 cells, compound **36** was found to induce both autophagy and apoptosis in a dose-dependent manner (Şenol et al., 2023).

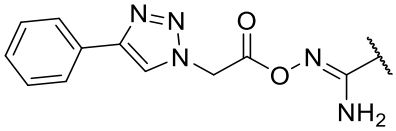


Betulinic acid

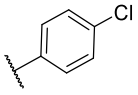


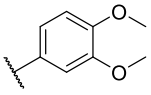
11

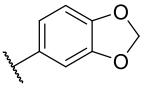
In addition, a novel series of substituted 1,2,3-triazoles was designed, synthesized, and evaluated for their antiproliferative activity against four different cancer cell lines. Compounds **12a-c** exhibited the most potent activity, with average GI_{50} values of 34, 31, and 36 nM, respectively, in comparison to erlotinib (GI_{50} = 33 nM). The most potent compounds **12a-c** were further assessed for their efficacy as EGFR inhibitors. The results revealed that these compounds inhibited EGFR with IC_{50} values of 87, 83, and 91 nM, respectively, when compared to erlotinib (IC_{50} = 80 nM). Additionally, the compounds were tested for their inhibitory activity against VEGFR-2, showing IC_{50} values of 2.90, 1.80, and 2.40 nM, respectively, compared to sorafenib (IC_{50} = 0.17 nM) (Abbas et al., 2024).



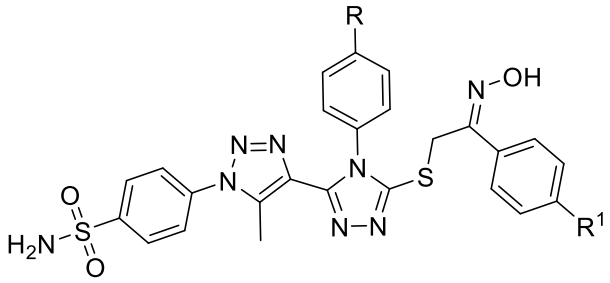
12a-c

12a: 

12b: 

12c: 

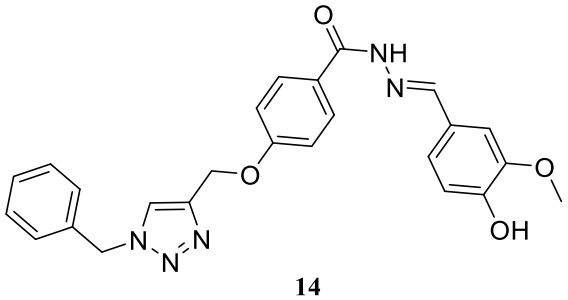
A novel series of 1,2,3-triazole-1,2,4-triazole hybrids derivatives was synthesized with the aim of developing hybrid molecules possessing anticancer activities. Compounds **13a-d** inhibited breast cancer cells (MCF-7) proliferation with IC_{50} values between 9 and 16 µM, outperforming tamoxifen (IC_{50} = 27.90 µM), and demonstrated potent activity against hepatocellular carcinoma (HEP-3B) with IC_{50} values of 4.50 to 14 µM, compared to sorafenib (IC_{50} = 3.52 µM). In NSCLC (A299), compounds **13a-d** exhibited excellent inhibitory activity with IC_{50} values between 3 and 4.51 µM, compared to 5-FU (IC_{50} = 6 µM). Additionally, **13a-d** compounds inhibited aromatase (IC_{50} = 22.40, 23.20, 22.70, and 30.30 µM), EGFR (IC_{50} = 0.11, 0.21, 0.17, and 0.07 µM), and B-$RAF^{(V350E)}$ (IC_{50} = 0.09, 0.06, 0.07, and 0.05 µM), showing promising multifaceted anticancer potential (Ashour et al., 2020).



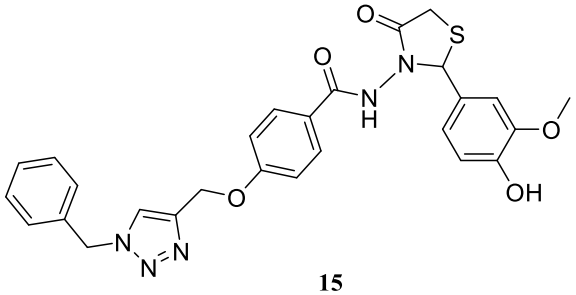
13a-d

13a: R= H, R^1= OCH_3
13b: R= H, R^1= Br
13c: R= H, R^1= CH_3
13d: R= OCH_3, R^1= CH_3

In 2023, a series of novel 1,2,3-triazole hybrid compounds were synthesized and evaluated for their anti-cancer activity against MCF-7 breast cancer cells and MCF-10A normal breast tissue cells. The *in vitro* results revealed that compounds **14** and **15** exhibited the highest selectivity and potency against breast cancer cells. Specifically, the IC_{50} values of compounds **14** and **15** against MCF-7 cells were 8.48 µM and 4.38 µM, respectively. In contrast, the IC_{50} values for these compounds against MCF-10A cells were significantly higher, at 114.80 µM and 170.35 µM, respectively. When compared to the reference drug doxorubicin, compounds **14** and **15** demonstrated superior selectivity, with selectivity indices of 13.50 and 39, respectively, compared to doxorubicin. Furthermore, compound **15** showed notable anti-cancer activity at lower doses while remaining safe for normal cells at higher concentrations (El Azab et al., 2021).

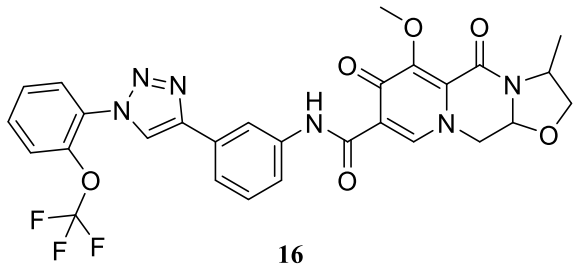


14



15

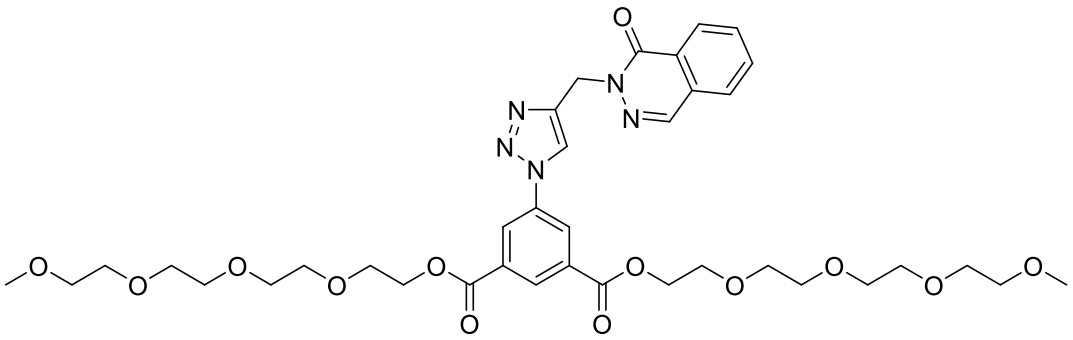
Further, a series of novel 1,2,3-triazole hybrids derived from cabotegravir analogues were designed and synthesized. These compounds were subjected to preliminary biological testing to evaluate their anticancer activities against NSCLC. The results demonstrated that several of these compounds exhibited promising antitumor effects against H435 cells, although their efficacy was reduced against H1299 cells. Notably, compound **16** was identified as the most potent, with an IC_{50} value of 6.06 μM. Furthermore, compound **16** significantly induced apoptosis and triggered the generation of reactive oxygen species (ROS) (Ashram et al., 2023).



16

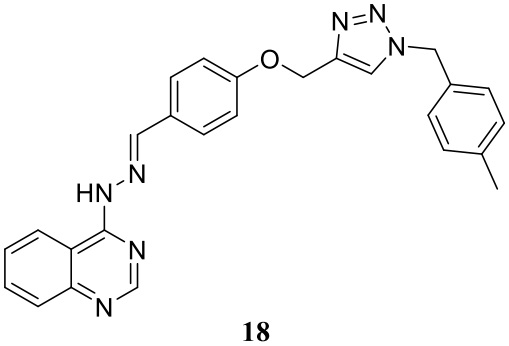
As well, a series of novel 1,2,3-triazole-phthalazone the tested cell lines. Among these compounds,

hybrids were synthesized and evaluated for their antiproliferative activity against four cancer cell lines: colorectal cancer, hepatoblastoma, prostate cancer, and breast adenocarcinoma, as well as the normal WI38 cell line. The antiproliferative assays demonstrated strong anticancer activity and selectivity, with a selectivity index (SI) of 3.35 for compound **17** was further assessed for its inhibitory effect on VEGFR-2, revealing potent activity with an IC_{50} value of 0.12 µM, comparable to sorafenib (IC_{50} = 0.12 µM). Additionally, compound **17** altered the cell cycle distribution in MCF-7 cells, increasing the proportion of cells in the S phase by 1.37-fold (Gholampour et al., 2019).



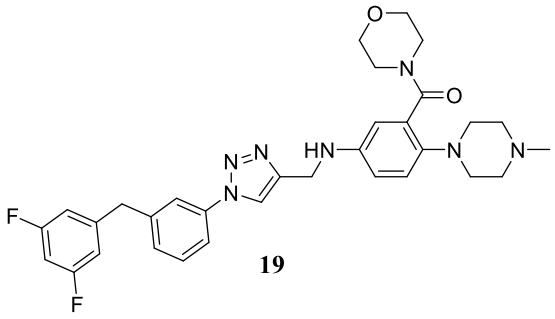
17

Also, a new series of quinazoline derivatives incorporating a 1,2,3-triazole moiety was designed and synthesized as targeted anticancer agents. These compounds were evaluated for their antiproliferative activity against six cancer cell lines of diverse origins, including MET-dependent AsPC-1, EBC-1, and MKN-45 cells, as well as Mia-Paca-2, HT-29, and K312 cells. Compound **18**, featuring a *p*-methyl benzyl group on the triazole ring, exhibited significant antiproliferative effects across all tested cell lines, with particularly strong inhibitory activity against MET-positive cells, displaying IC_{50} values as low as 6.10 μM. Furthermore, it demonstrated the highest MET inhibitory activity among the compounds tested (Mortazavi et al., 2023).



18

Besides, a series of triazole derivatives were designed and synthesized as dual regulators of ALK/TRK. These compounds were evaluated for their antiproliferative activity through MTT assays. The results demonstrated significant cytotoxicity, with IC_{50} values below 10 μM across colon cancer (KM12), non-small cell lung cancer (H2228), and non-Hodgkin's lymphoma (KARPAS299) cell lines. Among these, compound **19** was identified as the most promising candidate in enzymatic screening, exhibiting IC_{50} values of 1.90 *n*M for tropomyosin receptor kinase A (TRKA), 7.12 nM for anaplastic lymphoma kinase (ALK), and 65.22 nM for the mutant ALK^{L1196M}. Furthermore, compound **19** effectively inhibited KM12 cell migration and colony formation in a dose-dependent manner (Raghavender et al., 2020).

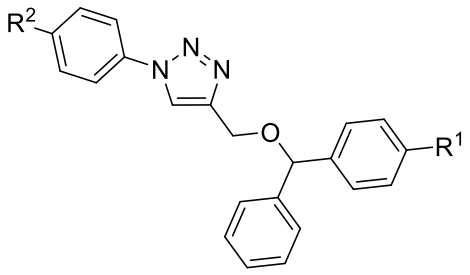


19

Also, a series of novel structures incorporating the designed, synthesized, and tested for their growth inhibition activity against a panel of sixty cancer

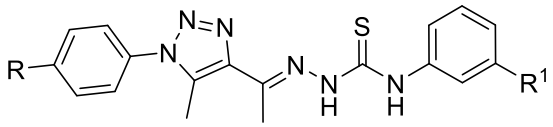
1,2,3-triazole moiety were synthesized, and their antioxidant and *in vitro* anticancer activities were evaluated. The results demonstrated that these new hybrids exhibited strong antioxidant and anticancer properties in line with standard benchmarks. Specifically, compounds **20a-d** (IC_{50} = 1.87, 12.50, 7.22, and 8.04 μg/mL, respectively) showed superior anticancer activity compared to the standard drug 5-Fu (IC_{50} = 40.89 μg/mL) (Abdelgawad et al., 2023).

A series of 1,2,3-triazoles conjugated with semicarbazone and thiosemicarbazone were cell lines at the National Cancer Institute (NCI). Thiosemicarbazones **21a-c** exhibited the most potent activity across nearly all tested cancer cell lines particularly HL-35 and SR. Additionally, these compounds inhibited VEGFR-2 with IC_{50} values of 0.13, 0.41, and 0.07 µM, respectively, compared to 0.05 µM for sorafenib. Further mechanistic studies on compound **21a** revealed its potential to induce both early and late-stage apoptosis, increase the Bax/Bcl2 ratio, activate caspase-3 and caspase-9, and cause cell cycle arrest in HL-35 cells at the G2/M and G0-G1 phases (Mahmoud et al., 2022).



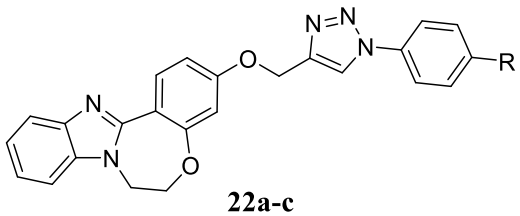
20a: R^1= Cl, R^2= OCH_3
20b: R^1= OCH_3, R^2= CH_3
20c: R^1= OCH_3, R^2= OCH_3
20d: R^1= OCH_3, R^2= Cl

20a-c



21a: R= Br, R^1= H
21b: R= F, R^1= H
21c: R= NO_2, R^{21}= Cl

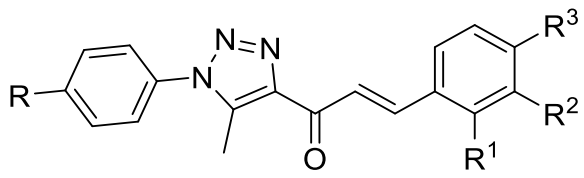
Too, a series of novel 1,2,3-triazole-benzoxazepine derivatives were synthesized and evaluated for their anticancer properties against prostate cancer cells (PC3), breast cancer cells (MCF-7), and leukemia cells (HL35). Most of the synthesized compounds exhibited moderate to good cytotoxicity against tested cancer cell lines, especially **22a-c**, showed excellent anticancer properties with submicromolar IC_{50} values ranging from 6 to 18 μM (Mahmoud et al., 2023).



22a-c

22a: R= Cl, **22b**: R= Br, **22c**: R= I

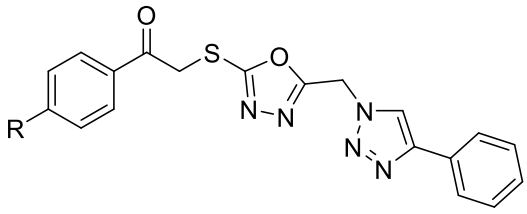
A new series of 1,2,3-triazole-chalcone hybrids was designed as potential therapeutic agents for leukemia. The synthesized compounds were evaluated for their cytotoxicity against a panel of 35 cancer cell lines at the NCI. Compounds **23a-c** exhibited significant growth inhibition, particularly against leukemia cell lines, including RPMI-8226 (% of growth inhibition values in the range of 10.53 to 20.94). Further *in vitro* mechanistic studies were conducted on compounds **23a-c** to assess their effects on the cell cycle, poly [ADP-ribose] polymerase 1 (PARP-1) activity, and specific apoptotic and antiapoptotic markers in RPMI-8226 cells (Mahmoud et al., 2024).



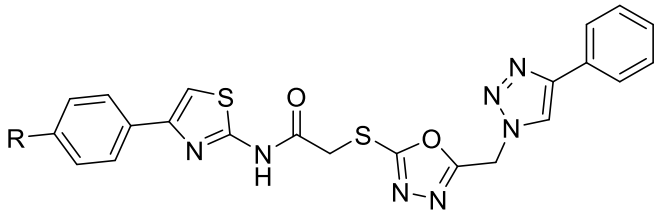
23a-c

23a: R= Br, R^1= H, R^2= OCH_3, R^3= OCH_3
23b: R= Br, R^1= H, R^2= NO_2, R^3= H
23c: R= F, R^1= OCH_3, R^2= H, R^3= H

Besides, a series of 1,2,3-triazole-1,3,4-oxadiazole hybrids were designed and synthesized. Their antiproliferative activity was assessed against pancreatic cancer (Panc-1), breast cancer (MCF-7), colon cancer (HT-29), and epithelial cancer (A-299) cell lines. Results indicated that the most potent compounds, **24a**, **24b**, and **25a–e**, effectively inhibited cancer cell growth (GI_{50} = 0.23–2.00 µM), with activity comparable to that of erlotinib (GI_{50} = 0.06 µM). Additionally, compound **25d** elevated Bax levels by 40-fold relative to doxorubicin, while decreasing Bcl-2 expression by 6.3-fold (Fatima et al., 2024).

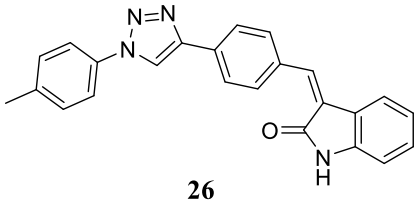


24a, b
24a: R= Cl; **49b**: R= Br



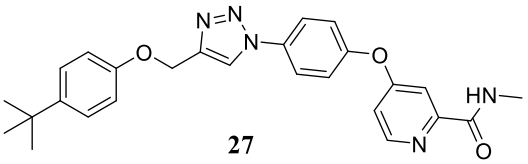
25a-e
25a: R= H; **50b**: R= Cl; **50c**: R= CH_3; **50d**: R= OCH_3

In 2021, a series of novel indole-2-one derivatives incorporating 1,2,3-triazole scaffolds were synthesized for the first time and evaluated for their inhibitory activity against VEGFR-2. Among them, compound 26 (IC_{50} = 26.38 nM) demonstrated the most potent kinase inhibition compared to sunitinib (IC_{50} = 83.20 nM). Additionally, compound **26** exhibited strong inhibitory effects on colon cancer cells (HT-29) and gastric adenocarcinoma cells (MKN-45). *In vivo* studies using a zebrafish model with VEGFR-2 labeling confirmed that compound **26** had superior anti-angiogenic activity relative to sunitinib (Rezki et al., 2020).



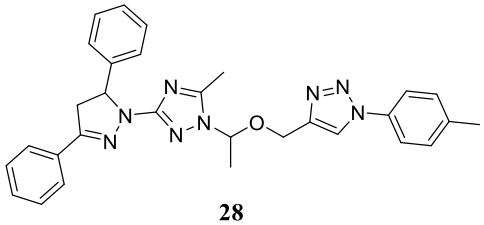
26

As to add, a series of sorafenib analogues containing a 1,2,3-triazole moiety, where the aryl urea group of sorafenib was substituted with a 1,2,3-triazole ring linked to a substituted phenoxy fragment, were designed and synthesized. The cytotoxicity of these compounds was tested against human hepatocellular carcinoma (HCC) cell lines, HepG2 and Huh7. Among them, compound **52** demonstrated significant inhibitory activity against Huh7 cells, with an IC_{50} of 5.67 µM. Furthermore, compound **27** showed minimal cytotoxicity against the human embryonal lung fibroblast cell line MRC-5 (IC_{50} > 100 µM), indicating a highly selective cytotoxic profile (SI > 17.6) against Huh7 cells, which is notably superior to that of sorafenib (SI = 6.73) (Nawareg et al., 2025).



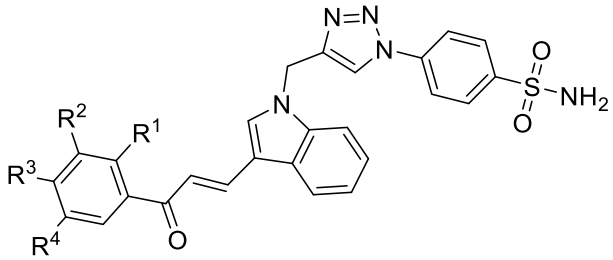
27

A novel series of hybrids containing a 1,2,3-triazole moiety were designed, synthesized, and evaluated for their potential antitumor effects *in vitro* against the human liver cancer cell line (HepG-2), human colon cancer cell line (HCT-116), and human breast adenocarcinoma cell line (MCF-7). Among the compounds tested, conjugate **28** exhibited the highest cytotoxic activity against HepG-2, HCT-116, and MCF-7 cells, with IC_{50} values of 12.22, 14.16, and 14.64 µM, respectively. These results were comparable to the standard drug doxorubicin, which showed IC_{50} values of 11.21, 12.46, and 13.45 µM for the same cell lines (Li et al., 2020).



28

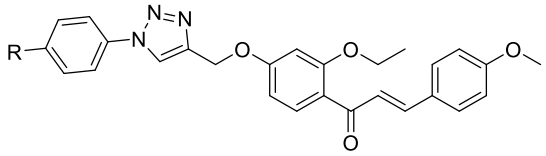
A novel series of benzenesulfonamide-1,2,3-triazole conjugates has been synthesized and evaluated for their inhibitory activity against a panel of CAs. Most of the newly synthesized compounds demonstrated notable inhibition constants in the nanomolar range, with some derivatives exhibiting greater potency than the standard drug acetazolamide against the CA I isoform. Among these, compounds **29a** (18.8 *n*M), **29f** (38.3 *n*M), and **29b** (50.4 *n*M) were 13, 6, and 5 times more potent than acetazolamide against CA I, respectively. Additionally, compounds **29c**, **29d**, and **29e** effectively inhibited the CA XII isoform, with inhibition constants (KIs) ranging from 10 to 41.9 *n*M. Several other compounds also showed activity against CA II and CA IX isoforms, with KIs below 100 *n*M (Singh et al., 2020).



29a-f

29a: R^1= H, R^2= H, R^3= Br, R^4= H
29b: R^1= H, R^2= H, R^3= CH_3, R^4= H
29c: R^1= H, R^2= Br, R^3= H, R^4= H
29d: R^1= H, R^2= CF_3, R^3= H, R^4= CF_3
29e: R^1= Br, R^2= H, R^3= H, R^4= H
29f: R^1= H, R^2= OCH_3, R^3= OCH_3, R^4= OCH_3

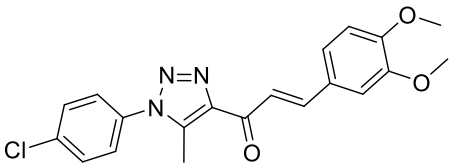
A novel series of 1,2,3-triazole-chalcone hybrids was synthesized and their anticancer potency was tested using MTT assay against human alveolar adenocarcinoma (A299). Compound **30a, b** demonstrated potent activity with IC_{50} = 37.51 and 75.41 μM, respectively being compared with the standard drug doxorubicin whose IC_{50} = 39.86 μM (Telukuntla et al., 2024).



30a, b

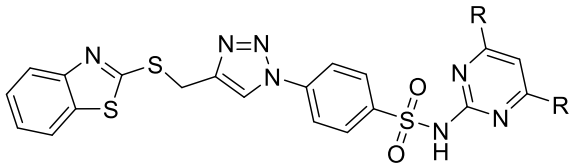
30a: R= Cl, **30b**: R= F

Conjugates of 1,2,3-triazole with chalcone linker were synthesized and screened for *in vitro* antiproliferative activity. All the conjugates exhibited promising proliferative activity against a panel of 35 human cancer cell lines (NCI) especially derivative **31** which displayed greater cytotoxic activity with IC_{50} values of 0.24 and 0.26 μM against the breast (MC-F7) and colon (HCT-116) cancer cell lines, respectively. Also, further studies revealed that **31** induced apoptosis *via* aggregation of RPMI-8226 cells in a dose-dependent manner and cell cycle arrest at the G2/M phase (Wang et al., 2024).



31

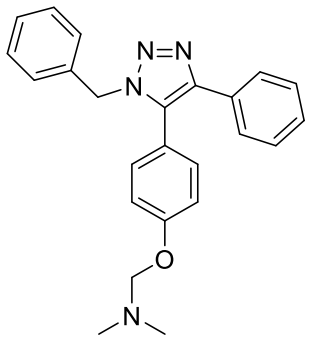
A series of benzothiazole derivatives linked to a 1,2,3-triazole moiety were synthesized and evaluated for their cytotoxic activity against a panel of cancer cell lines. The newly synthesized compounds exhibited a broad range of IC_{50} values, with some showing potent activity compared to the reference drug. The most promising compounds were further assessed based on the hypothesis that they could mimic quinazoline-based EGFR inhibitors and evaluated for their inhibitory activity against the EGFR tyrosine kinase (TK) enzyme. The results indicated that compounds **32a** and **32b** demonstrated more potent activity against EGFR compared to erlotinib (IC_{50} = 103 and 104 nM vs. 67.6 nM). Additionally, compounds **32a** and **32b** were tested in an HepG2 cancer model, where they effectively inhibited tumor growth, strongly induced cancer cell apoptosis, and suppressed cell cycle progression, ultimately leading to DNA fragmentation (Yan et al., 2019).



32a b

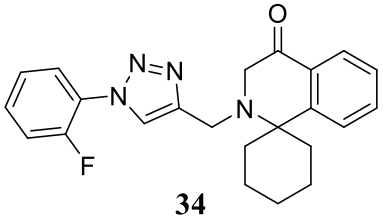
32a: R= H, **32b**: R=CH_3

A series of 1,2,3-triazole derivatives were synthesized and evaluated for their cytotoxicity against breast cancer cell lines. The biological results demonstrated that most of the compounds exhibited comparable anti-proliferative activity to tamoxifen in both estrogen receptor-positive (ER+) MCF-7 and estrogen receptor-negative (ER-) MDA-MB-231 breast cancer cell lines. Among the synthesized compounds, **33** had IC_{50} values greater than 30 μM in FR-2 (normal) cells. Additionally, compound **33** was found to induce higher reactive oxygen species (ROS) generation, along with a decrease in mitochondrial membrane potential. Furthermore, molecular docking studies, in comparison to tamoxifen, were performed to investigate the interaction of compound **33** with the estrogen receptor alpha (ER-α), suggesting its potential mechanism of action in cancer treatment (Fadaly et al., 2023).



33

A novel series of erythrina derivatives incorporating a 1,2,3-triazole moiety were designed, synthesized, and evaluated for their anticancer activity. The results revealed that compound **34** exhibited the most potent anti-proliferative activity against human alveolar adenocarcinoma (A299) cells when compared to five other cancer cell lines. In addition, compound **34** demonstrated significantly superior *in vitro* enzyme inhibitory activity against PARP-1 than the reference drug, rucaparib. Notably, the selectivity index of compound **34** was also higher than that of rucaparib for lung cancer cells. Flow cytometry analysis revealed that compound **34** induced apoptosis in A299 cells through the mitochondrial pathway. (Vanaparthi et al., 2020).

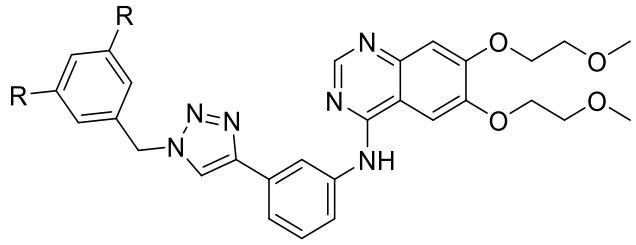


34

A novel series of erlotinib derivatives incorporating a 1,2,3-triazole ring were synthesized by conjugating erlotinib with various azide compounds. The newly synthesized compounds were evaluated for their anticancer activity, and the results demonstrated strong antiproliferative effects against a range of NSCLC cell lines, including PC-9, H435, H1975, and A299. Two of the most potent compounds, **35a** and **b**, were found to be more effective than erlotinib in all NSCLC cell lines, with the exception of PC-9. These compounds significantly induced apoptosis and cell cycle arrest in both PC-9 and H435 cells. (Belay et al., 2024).

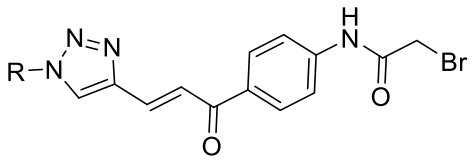
A new series of 1,2,3-triazole-linked chalcone acetamide derivatives were synthesized and assessed for their cytotoxic activity against four human cancer cell lines: human cervical cancer (HeLa), human alveolar adenocarcinoma (A299), human breast adenocarcinoma (MCF-7), and human brain cancer (SKNSH). Among the synthesized compounds, compound **36c** demonstrated significant anti-proliferative activity with IC_{50} values of 7.41 μM for HeLa, 8.68 μM for SKNSH, and 9.76 μM for MCF-7. Additionally, compounds **36a** and **36b** exhibited promising anti-proliferative effects across the four cancer cell lines, with IC_{50} values ranging from 7.95 to 11.37 μM. (Palakhachane et al., 2021)

A series of novel 1,2,3-triazole-pyrazole derivatives were synthesized and evaluated for their potential antiproliferative activity against two cancer cell lines: nerve cells (C6) and human breast cancer cells (MCF-7). Compounds **37** and **38** exhibited highly potent activity against the C6 cell line, with IC_{50} values of 0.09 and 0.10 μM, respectively, outperforming cisplatin (IC_{50} = 0.12 μM). Similarly, these compounds also demonstrated strong antiproliferative activity against the MCF-7 cell line, with IC_{50} values of 0.11 μM for both, in contrast to cisplatin (IC_{50} = 0.35 μM). (El Hamaky et al., 2024).



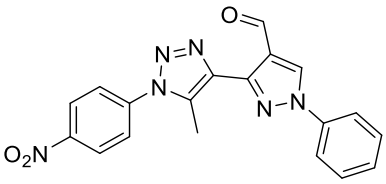
35a: R= Br
35b: R= CH_3

35a, b

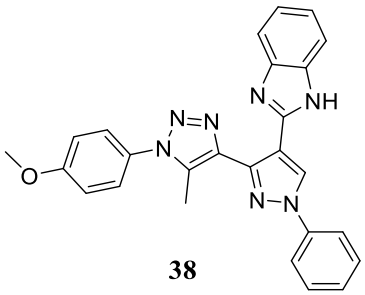


36a: R= 4-Br-C_6H_4
36b: R= n-C_8H_{17}
36c: R= n-$C_{12}H_{25}$

36a-c

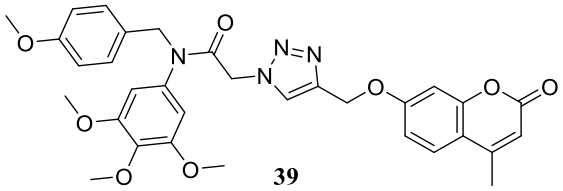


37



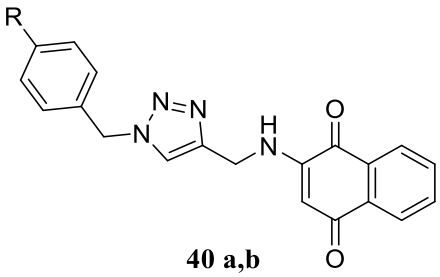
38

A series of 1,2,3-triazole-linked trimethoxyphenyl scaffolds were synthesized and evaluated for antiproliferative activity against prostate (PC3), liver (HepG2), and gastric (MGC803) cancer cell lines. Among the synthesized hybrids, compound **39**, which contained a coumarin moiety, demonstrated notable antiproliferative activity, with an IC_{50} value of 0.13 μM against the MGC803 cell line, outperforming the standard drug colchicine (IC_{50} = 0.27 μM). Also, compound **39** effectively inhibited MGC803 cell growth and colony formation, induced cell cycle arrest at the G2/M phase (Laamari et al., 2025).



39

A series of novel 1,4-naphthoquinone-1,2,3-triazole hybrids were synthesized and evaluated for their anticancer activity. The compounds were tested against human breast adenocarcinoma (MCF-7), human colorectal adenocarcinoma (HT-29), and human acute lymphoblastic leukemia (MOLT-4) cell lines. Among the tested compounds, derivatives **40a** and **b** demonstrated strong cytotoxic potential across all cancer cell lines. Notably, compound **40b** showed the highest cytotoxicity, with IC_{50} values ranging from 6.80 to 10.40 μM. Flow cytometric analysis revealed that both compounds **65a** and **65b** caused cell cycle arrest at the G0/G1 phase. (Cao et al., 2023).



40 a,b

40a: R= CH_3
40b: R= CF_3

References:

Abbas, H.A.S, E.S. Nossier, M.A. El-Manawaty, M.N. El-Bayaa, New sulfonamide-based glycosides incorporated 1,2,3-triazole as cytotoxic agents through VEGFR-2 and carbonic anhydrase inhibitory activity, Sci. Rep. 14 (2024) 13028. https://doi.org/10.1038/s41598-024-62864-9.

Abdelgawad, M.A., S.N.A. Bukhari, A. Musa, M. Elmowafy, A.A. Nayl, A.H. El-Ghorab, M. Sadek Abdel-Bakky, H.A. Omar, N. Hadal Alotaibi, H.M. Hassan, M.M. Ghoneim, R.B. Bakr, Phthalazone tethered 1,2,3-triazole conjugates: In silico molecular docking studies, synthesis, in vitro antiproliferative, and kinase inhibitory activities, Bioorg. Chem. 133 (2023) 106404. https://doi.org/https://doi.org/10.1016/j.bioorg.2023.106404.

Ashok, D. M. Ram Reddy, N. Nagaraju, R. Dharavath, K. Ramakrishna, S. Gundu, P. Shravani, M. Sarasija, Microwave-assisted synthesis and in vitro antiproliferative activity of some novel 1,2,3-triazole-based pyrazole aldehydes and their benzimidazole derivatives, Med. Chem. Res. 29 (2020) 699–706. https://doi.org/10.1007/s00044-020-02515-6.

Ashour, H.F., L.A. Abou-zeid, M.A.-A. El-Sayed, K.B. Selim, 1,2,3-Triazole-Chalcone hybrids: Synthesis, in vitro cytotoxic activity and mechanistic investigation of apoptosis induction in multiple myeloma RPMI-8226, Eur. J. Med. Chem. 189 (2020) 112062. https://doi.org/10.1016/j.ejmech.2020.112062.

Ashram, M., A.Y. Habashneh, S. Bardaweel, M.O. Taha, A Click Synthesis, Molecular Docking and Biological Evaluation of 1,2,3-triazoles-benzoxazepine hybrid as potential anticancer agents, Med. Chem. Res. 32 (2023) 271–287. https://doi.org/10.1007/s00044-022-03001-x.

Belay, Y., A. Muller, F.S. Mokoena, A.S. Adeyinka, L.R. Motadi, A.K. Oyebamiji, 1,2,3-triazole and chiral Schiff base hybrids as potential anticancer agents: DFT, molecular docking and ADME studies, Sci. Rep. 14 (2024) 6951. https://doi.org/10.1038/s41598-024-57689-5.

Cao, Z., J. Zhang, M. Guo, B. Shao, X. Wei, S. Li, P. Wang, X. Zhai, Discovery of novel phenyl triazole analogs as TRK/ALK dual inhibitors with prospective antitumor effects, Bioorg. Chem. 136 (2023) 106563. https://doi.org/https://doi.org/10.1016/j.bioorg.2023.106563.

Çot, A. F. Betül Özgeriş, İ. Şahin, M. Çeşme, S. Onur, F. Tümer, Synthesis, characterization, antioxidant and anticancer activity of new hybrid structures based on diarylmethanol and 1,2,3-triazole, J. Mol. Struct. 1269 (2022) 133763. https://doi.org/https://doi.org/10.1016/j.molstruc.2022.133763.

Dheer, D. C. Behera, D. Singh, M. Abdullaha, G. Chashoo, S.B. Bharate, P.N. Gupta, R. Shankar, Design, synthesis and comparative analysis of triphenyl-1,2,3-triazoles as anti-proliferative agents, Eur. J. Med. Chem. 207 (2020) 112813. https://doi.org/10.1016/j.ejmech.2020.112813.

El Azab, I.H., H.S. El-Sheshtawy, R.B. Bakr, N.A.A. Elkanzi, New 1,2,3-triazole-containing hybrids as antitumor candidates: design, click reaction synthesis, DFT calculations, and molecular docking study, Molecules 26 (2021) 708. https://doi.org/10.3390/molecules26030708.

El Hamaky, N.F.M., A. Hamdi, W.A. Bayoumi, A.A. Elgazar, M.N.A. Nasr, Novel quinazolin-2-yl 1,2,3-triazole hybrids as promising multi-target anticancer agents: Design, synthesis, and molecular docking study, Bioorg. Chem. 148 (2024) 107437. https://doi.org/https://doi.org/10.1016/j.bioorg.2024.107437.

Fadaly, W.A.A., M.T.M. Nemr, T.H. Zidan, F.E.A. Mohamed, M.M. Abdelhakeem, N.N. Abu Jayab, H.A. Omar, K.R.A. Abdellatif, New 1,2,3-triazole/1,2,4-triazole hybrids linked to oxime moiety as nitric oxide donor selective COX-2, aromatase, B-RAFV600E and EGFR inhibitors celecoxib analogs: design, synthesis, anti-inflammatory/anti-proliferative activities, apoptosis and molecular modeling study, J. Enzyme Inhib. Med. Chem. 38 (2023) 2290461. https://doi.org/10.1080/14756366.2023.2290461.

Fatima, N., A. Saeed, S. Ullah, S.A. Halim, A. Khan, M. Yaseen, A. Mumtaz, M.Z. Hashmi, H.R. El-Seedi, J. Uddin, A. Al-Harrasi, Synthesis of novel 1,2,3-triazole-tethered N-acyl hydrazones as a new class of carbonic anhydrase II inhibitors: In

vitro and in silico potentials, Bioorg. Chem. 153 (2024) 107822. https://doi.org/https://doi.org/10.1016/j.bioorg.2024.107822.

Fu, D.J., P. Li, B.W. Wu, X.X. Cui, C. Bin Zhao, S.Y. Zhang, Molecular diversity of trimethoxyphenyl-1,2,3-triazole hybrids as novel colchicine site tubulin polymerization inhibitors, Eur. J. Med. Chem. 165 (2019) 309–322. https://doi.org/10.1016/j.ejmech.2019.01.033.

Gholampour, M., S. Ranjbar, N. Edraki, M. Mohabbati, O. Firuzi, M. Khoshneviszadeh, Click chemistry assisted synthesis of novel aminonaphthoquinone-1,2,3-triazole hybrids and investigation of their cytotoxicity and cancer cell cycle alterations, Bioorg. Chem. 88 (2019) 102967. https://doi.org/10.1016/j.bioorg.2019.102967.

Guo, Y., D. Sang, B. Guo, D. Wang, X. Xu, H. Wang, C. Hou, L. Mao, F. Li, S. Li, Synthesis and biological evaluation of novel 1,2,3-triazole hybrids of cabotegravir: identification of potent antitumor activity against lung cancer, Front. Pharmacol. 14 (2023) 1265245. https://doi.org/10.3389/fphar.2023.1265245.

Laamari, Y., M. Fawzi, A. Oubella, S.H. Alotaibi, F.M. Alotaibi, T. Rohand, L. Van Meervelt, H. Morjani, M.Y. Ait Itto, A. Auhmani, Semisynthesis of novel chalcone hybrid compounds linked by 1,2,3-triazole and evaluation of their cytotoxic effects, J. Mol. Struct. 1319 (2025) 139648. https://doi.org/https://doi.org/10.1016/j.molstruc.2024.139648.

Li, S. X. yang Li, T. jian Zhang, J. Zhu, W. han Xue, X. hua Qian, F. hao Meng, Design, synthesis and biological evaluation of erythrina derivatives bearing a 1,2,3-triazole moiety as PARP-1 inhibitors, Bioorg. Chem. 96 (2020) 103575. https://doi.org/10.1016/j.bioorg.2020.103575.

Mahmoud, M.A. A.F. Mohammed, O.I.A. Salem, H.A.M. Gomaa, B.G.M. Youssif, New 1,3,4-oxadiazoles linked with the 1,2,3-triazole moiety as antiproliferative agents targeting the EGFR tyrosine kinase, Arch. Pharm. 355 (2022) e2200009. https://doi.org/10.1002/ardp.202200009.

Mahmoud, M.A. A.F. Mohammed, O.I.A. Salem, S.M. Rabea, B.G.M. Youssif, Design, synthesis, and antiproliferative properties of new 1,2,3-triazole-carboximidamide derivatives as dual EGFR/VEGFR-2 inhibitors, J. Mol. Struct. 1282 (2023) 135165. https://doi.org/https://doi.org/10.1016/j.molstruc.2023.135165.

Mahmoud, M.A., A.F. Mohammed, O.I.A. Salem, T.M. Almutairi, S. Bräse, B.G.M. Youssif, Design, synthesis, and apoptotic antiproliferative action of new 1,2,3-triazole/1,2,4-oxadiazole hybrids as dual EGFR/VEGFR-2 inhibitors, J. Enzyme Inhib. Med. Chem. 39 (2024) 2305856. https://doi.org/10.1080/14756366.2024.2305856.

Mortazavi, M., M. Eskandari, F. Moosavi, T. Damghani, M. Khoshneviszadeh, S. Pirhadi, L. Saso, N. Edraki, O. Firuzi, Novel quinazoline 1,2,3 triazole hybrids with anticancer and MET kinase targeting properties, Sci. Rep. 13 (2023) 1–17. https://doi.org/10.1038/s41598-023-41283-2.

Nawareg, N.A., A.S.A. Yassen, E.M. Husseiny, M.A.A. El-Sayed, H.A. Elshihawy, Exploring 1,2,3-triazole-Schiff's base hybrids as innovative EGFR inhibitors for the treatment of breast cancer: In vitro and in silico study, Bioorg. Chem. 155 (2025) 108106. https://doi.org/https://doi.org/10.1016/j.bioorg.2024.108106.

Othman, E.M., E.A. Fayed, E.M. Husseiny, H.S. Abulkhair, Apoptosis induction, PARP-1 inhibition, and cell cycle analysis of leukemia cancer cells treated with novel synthetic 1,2,3-triazole-chalcone conjugates, Bioorg. Chem. 123 (2022) 105762. https://doi.org/https://doi.org/10.1016/j.bioorg.2022.105762.

Othman, E.M., E.A. Fayed, E.M. Husseiny, H.S. Abulkhair, The effect of novel synthetic semicarbazone- and thiosemicarbazone-linked 1,2,3-triazoles on the apoptotic markers, VEGFR-2, and cell cycle of myeloid leukemia, Bioorg. Chem. 127 (2022) 105968. https://doi.org/https://doi.org/10.1016/j.bioorg.2022.105968.

Palakhachane, S., Y. Ketkaew, N. Chuaypen, J. Sirirak, Synthesis of sorafenib analogues incorporating a 1, 2,3-triazole ring and cytotoxicity towards hepatocellular carcinoma cell lines,

Bioorg. Chem. 112 (2021) 104831. https://doi.org/10.1016/j.bioorg.2021.104831.

Raghavender, M. A.K. Kumar, V. Sunitha, T. Vishnu, P. Jalapathi, Synthesis and cytotoxicity of chalcone based 1,2,3-triazole derivatives, Russ. J. Gen. Chem. 90 (2020) 697–702. https://doi.org/10.1134/S1070363220040210.

Rezki, N., M.A. Almehmadi, S. Ihmaid, A.M. Shehata, A.M. Omar, H.E.A. Ahmed, M.R. Aouad, Novel scaffold hopping of potent benzothiazole and isatin analogues linked to 1,2,3-triazole fragment that mimic quinazoline epidermal growth factor receptor inhibitors: Synthesis, antitumor and mechanistic analyses, Bioorg. Chem. 103 (2020) 104133. https://doi.org/10.1016/j.bioorg.2020.104133.

Şenol, H. A.G. Ağgül, S. Atasoy, N.U. Güzeldemirci, Synthesis, characterization, molecular docking and in vitro anti-cancer activity studies of new and highly selective 1,2,3-triazole substituted 4-hydroxybenzohyrdazide derivatives, J. Mol. Struct. 1283 (2023) 135247. https://doi.org/https://doi.org/10.1016/j.molstruc.2023.135247.

Singh, P., B. Swain, P.S. Thacker, D.K. Sigalapalli, P. Purnachander Yadav, A. Angeli, C.T. Supuran, M. Arifuddin, Synthesis and carbonic anhydrase inhibition studies of sulfonamide based indole-1,2,3-triazole chalcone hybrids, Bioorg. Chem. 99 (2020) 103839. https://doi.org/10.1016/j.bioorg.2020.103839.

Sun, G., L. Mao, W. Deng, S. Xu, J. Zhao, J. Yang, Discovery of a series of derivatives with potent anti-tumor activities against non-small cell lung cancer, Chem. Biol. Drug Des. 101 (2022) 749–759. https://doi.org/10.3389/fchem.2021.789030.

Telukuntla, P. M. Chandrakanth, P.G. Amrutha, N.M. Thomas, R. Gondru, K.R. Valluru, J. Banothu, 1,2,3-Triazole-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine hybrids: A switch for improvement of antibreast cancer activity targeting epidermal growth factor receptor, Tetrahedron Lett. 146 (2024) 155180. https://doi.org/https://doi.org/10.1016/j.tetlet.2024.155180.

Vala, D.P. A. Dunne Miller, A. Atmasidha, M.P. Parmar, C.D. Patel, D.B. Upadhyay, S.S. Bhalodiya, A. González-Bakker, A.N. Khan, J. Nogales, J.M. Padrón, S. Banerjee, H.M. Patel, Click-chemistry mediated synthesis of OTBN-1,2,3-Triazole derivatives exhibiting STK33 inhibition with diverse anti-cancer activities, Bioorg. Chem. 149 (2024) 107485. https://doi.org/https://doi.org/10.1016/j.bioorg.2024.107485.

Vanaparthi, S, R. Bantu, N. Jain, S. Janardhan, L. Nagarapu, Synthesis and anti-proliferative activity of a novel 1,2,3-triazole tethered chalcone acetamide derivatives, Bioorg. Med. Chem. Lett. 30 (2020) 127304. https://doi.org/10.1016/j.bmcl.2020.127304.

Wang, D. K. Liu, X. Li, G. Lu, W. Xue, X. Qian, K.M. O, F. Meng, Design, synthesis, and in vitro and in vivo anti-angiogenesis study of a novel vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor based on 1,2,3-triazole scaffold, Eur. J. Med. Chem. 211 (2020) 113083. https://doi.org/10.1016/j.ejmech.2020.113083.

Wang, Q. F. Ma, J. Wang, H. Xu, K. Li, Y.-Y. Cheng, X. Chen, S. Qu, T. Wei, X. Hao, M. Kong, C. Xie, W. Wang, Y. Wang, L.S. Jeong, Antitumor activity and transcriptome sequencing (RNA-seq) analyses of hepatocellular carcinoma cells in response to exposure triterpene-nucleoside conjugates, Eur. J. Med. Chem. 276 (2024) 116635. https://doi.org/https://doi.org/10.1016/j.ejmech.2024.116635.

Yan, W., C. Xiangyu, L. Ya, W. Yu, X. Feng, An orally antitumor chalcone hybrid inhibited HepG2 cells growth and migration as the tubulin binding agent, Invest. New Drugs 37 (2019) 784–790. https://doi.org/10.1007/s10637-019-00737-z.