SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY STUDY OF 1,2,3-TRIAZOLE DERIVATIVES BEARING TETRAHYDROQUINOLINE-2-ONE

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Abstract:
A series of 1,2,3-triazole derivatives bearing tetrahydroquinoline-2-one were planned and synthesized in an endeavour to develop potent biologically active moiety via click chemistry. An approach to demonstrate these compounds using 1,3-dipolar azide-alkyne cycloaddition reaction was made. 7-(prop-2-yn-1-yloxy)-3,4-dihydroquinolin-2(1H)-one **(7)** with various 2-azido-N-arylacetamide **(4a-4h)** derivatives were combined using CuACC catalyst to give desired target moiety. The final compounds structure were proved using various analytical techniques such as ^{1}H-NMR, Infrared spectroscopy and Mass spectrometry. The designed compounds were subjected to antimicrobial activity using agar well diffusion method and the activity was screened against gram-positive bacteria, gram-negative bacteria and fungi. The minimum inhibitory concentration (MIC) of the designed compounds were observed indicating **8e** and **8f** active against gram positive bacteria in comparison to standard drug ampicillin, whereas none of the synthesized compound has shown inhibitory effect against gram negative bacteria compared to standard drug streptomycin. Compound **8a** and **8e** exhibits potent to moderate activity as antifungal agent in comparison with antifungal agent nystatin.

Keywords: Tetrahydroquinoline-2-one, 1,2,3-triazole, CuAAC, Click-chemistry, antibacterial and antifungal activity.

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1. Introduction:

Since past many decades heterocycles have proved to be an important class of compounds due to its versatile nature in the world of pharmaceutical science. Among these heterocycles, nitrogen containing benzo-fused compounds have been great moieties behind the activity of various active drug molecules.

3,4-dihydroquinolin-2-one containing compounds shows excellent biological activity and are used in various drug molecules. 3,4-dihydroquinolin-2(2H)–one was successfully synthesized from methyl 2-(2-carboxyethyl) benzoic acid **[1].** This molecule is widely found in many naturally derived products. For example, quinolone derivatives are active inhibitors for tubulin polymerization and shows anti-proliferative activity against HeLa, HCT-116 and HCT-8 human cancer cell lines **[2]**. As reported by K. Singh and team, 2-aminoimidazole-3-quinolone hybrids exhibited good anticancer activity against human colon cancer cell lines **[3]**. 1-[3-[4(3-Chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone and its derivatives showcased excellent antidepressant activity**[4]**.

In the area of novel organic synthetic pathways, click chemistry **[5-6]** tool has emerged as an excellent and efficient method in organic synthesis, easing up the rapid synthesis of complex molecules. Coined by K. Barry Sharpless in 2001, the term "click chemistry" refers to a set of highly reliable and selective reactions that can be used for generating a wide range of compounds by combining various tiny molecules. This paper provides an intensive use of click chemistry for synthesis of pharmaceutically active compounds. It falls into the class of cycloaddition reaction. The Cu catalyzed reaction involves 1,3-dipolar cycloaddition of azides with terminal alkynes. The azides undergo Huigsen type [3+2] cycloaddition reaction **[7]** with alkynes to yield 1,2,3-triazoles, proving it to be a dynamic reaction taking place at normal conditions using wide range of functional groups. This reaction has gained popularity so fast over decades as it takes shorter span of time for completion.

The basic principle behind click chemistry is to use simple reactions that occur under mild conditions and produce less by-products. Overall, click chemistry has become an important tool in modern heterocyclic **[8]** synthesis, offering significant advantages in terms of efficiency and versatility. Its application in various industrial materials, agrochemicals has encouraged many researchers across scientific discipline, for the creation of new molecules, materials, and technologies. As reported by Nayak and group 1-(aryl)-4-(((5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)methoxy)-methyl)-1H-1,2,3-triazole derivatives exhibited great antibacterial activity against *Mycobacterium tuberculosis* and also the work by K. Ali and group showcases the inhibitory effect of 1,2,3-triazoles against *M. luteus, S. aureus, and E. coli*. Compounds possessing triazole ring has broad application as biologically active compounds and classified among antibacterial **[9-12]**, anti-inflammatory **[13-16]**, anticancer **[17-23]**, antitumor **[24]**, antiviral **[25-32]**, antioxidant **[33-37]** and antifungal **[38-41]** agents across the world. The synthesis of 1,2,3-triazoles as an active pharmacophore via Cu catalyzed reaction serves as a crucial method for synthesis of such active compounds. We synthesized various derivatives of 1,2,3-triazoles using 7-hydroxy-3,4-dihydroquinolin-2(1H)-one as backbone moiety due to its biological activity against various microorganisms.

2. Methods and Materials

The reagents for the synthesis were purchased from Sigma Aldrich, SRL and were used further without purification. Melting points were recorded using open capillaries and are uncorrected. The progress of reaction was monitored using thin layer chromatography on pre- coated Silica gel plates. Spots were visualized using UV light and iodine chamber. 400MHz Bruker Advance II was used to record ^{1}H-NMR of the compounds with DMSO-d^6 as solvent. Chemical shifts are expressed in δ ppm using TMS as internal standard. IR spectra of the compounds were recorded on FT-IR spectrophotometer. Mass spectra were recorded on Shimadzu GC-MS QP 2010.

3. Experimental Section

3.1 Preparation of 2-chloro-N-arylacetamide derivatives (3a-3h)

Different substituted anilines **(1a-1h)** (1 mmol) were dissolved in 30 ml acetone and potassium carbonate (1.5 mmol) was added. The resulting solution was stirred at 0-5 ^{0}C for 15-20 mins. Addition of 2-chloroacetylchloride **(2)** (1 mmol) solution was carried out in drop wise manner at 0-5 ^{0}C. The reaction was stirred at room temperature for 5-6 hrs. The progress of reaction was traced using TLC. The reaction mass was slowly added to ice shavings with continuous stirring after completion of reaction. The resultant product was filtered, dried and recrystallized using methanol.

3.2 Preparation of 2-azido-N-arylacetamide derivatives (4a-4h)

To a solution of 2-chloro-N-arylacetamide derivatives **(3a-3h)** (1 mmol) in dimethylformamide (DMF), sodium azide (NaN_3) (2 mmol) was added in round bottom flask. The resulting reaction mixture was stirred at room temperature for 24 hr. The completion of reaction was analyzed using TLC. The resultant reaction mixture was poured into crushed ice and the solid product was filtered and dried. The crystallization was done using methanol.

3.3 Preparation of 7-(prop-2-yn-1-yloxy)-3,4-dihydroquinolin-2(1H)-one (7)

A solution of 7-hydroxy-3,4-dihydroquinolin-2(1H)-one **(5)** (1 mmol) was prepared by dissolving it in acetone. To this solution, propargyl bromide **(6)** (1.5 mmol) was added drop wise. Further to maintain the pH of solution, potassium carbonate (K_2CO_3) (5 mmol) was added to the reaction mixture and was refluxed for 12-14 hours at 56 ^oC. The progress of reaction was monitored using TLC. After completion of reaction, it was poured into ice shavings and the product was filtered and dried. The product was recrystallized using methanol to give brown color crystals with yield: 72 %, M/z: 199.9, MP =158 ^0C

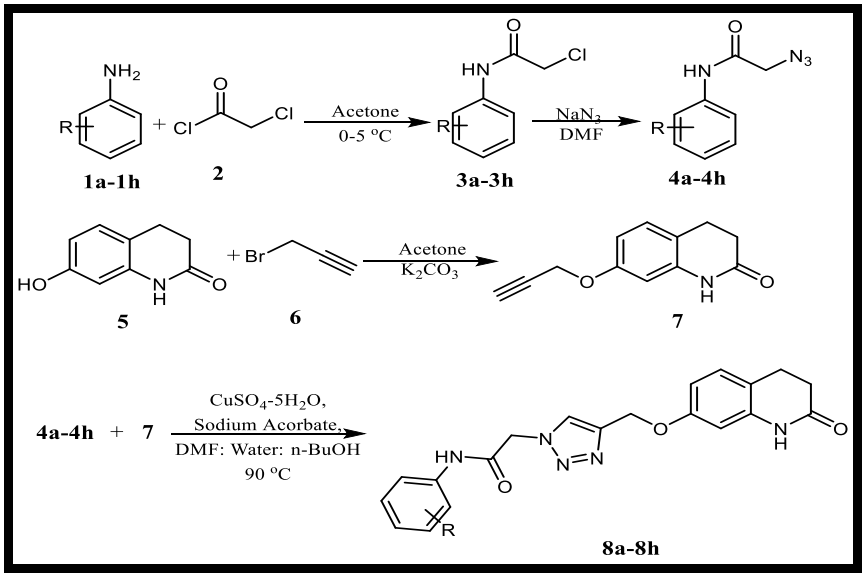
3.4 General method for preparation of 2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H- 2,3-triazol-4-yl)-N-Arylacetamide derivatives (8a-8h)

A round bottom flask containing mixture of solvents DMF: Water: n-Butanol (1:1:1), 7-(prop-2-yn-1-yloxy)-3,4-dihydroquinolin-2(1H)-one **(7)** (1 mmol) and 2-azido-N-arylacetamide derivatives **(4a-4h)** (1 mmol) were added at room temperature. Followed by addition of catalytic amount of ascorbic acid and $CuSO_4$-$5H_2O$. The reaction mixture was stirred at 80 ^oC for 8 hrs. After completion of reaction, which was monitored by TLC, the mixture was poured into crushed ice. The brown color solid mass was filtered, dried and recrystallized from ethanol.

Table-1: Physical data characteristics of 2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7yl)oxy)methyl)- 1H-2,3-triazol-4-yl)-N-Arylacetamide derivatives (8a-8h)

Compound Code	-R	Molecular Formula	Mol. weight (m/z)	M.P. (^oC)	Yield (%)
8a	4-H	C20H19N5O3	377.10	186-188	84
8b	4-CH_3	C21H21N5O3	391.10	190-192	49
8c	4-Cl	C20H18ClN5O3	411.20	234-236	51
8d	4-F	C20H18FN5O3	395.25	200-202	71
8e	3-NO_2	C20H18N6O5	423.10	248-250	66
8f	4-NO_2	C20H18N6O5	423.10	>320	51
8g	2-CH_3-5-NO_2	C21H20N6O5	436.20	268-270	74
8h	2,4-CH_3	C22H23N5O3	405.25	>320	81

4. Reaction Scheme



5. Spectral data analysis:

2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-Nphenylacetamide (8a) Dark brown solid, IR (KBr) cm^{-1}: 3463, 3282, 3146, 2956, 1686, 1625, 1599, 1559, 1446, 1394, 1385, 1268, 1062, 807. ^{1}H NMR (DMSO-d^6) δ ppm: 10.49 (s, 1H,-NH-amide), 10.03 (s, 1H,-NH-amide), 8.24(s, 1H, -C-H-triazole), 6.51-7.58 (m. 8H, ArH), 5.35 (s, 2H, O-CH_2-), 5.09 (s, 2H,-CO-CH_2-), 2.8-2.7(t, 2H, -CH_2-), 2.41-2.43(t,2H,-CH_2), MS: m/z; 377.10

(2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-N-(ptolyl)acetamide (8b): Dark brown solid, IR (KBr) cm^{-1}: 3475, 3256, 3138, 2955, 1683, 1666, 1599, 1517, 1438, 1387, 1229, 1063, 847, 814. ^{1}H NMR (DMSO-d^6) δ ppm: 10.39 (s, 1H,-NH-amide), 10.02 (s, 1H,-NH-amide), 8.23(s, 1H, -C-H-triazole), 6.52-7.47 (m. 7H, ArH), 5.32(s, 2H, O-CH_2-), 5.09(s, 2H,-CO-CH_2-) 2.76-2.78(t, 2H, -CH_2-),2.41-2.43(t,2H,-CH_2-),2.25-2.39(s,3H,-CH_3), MS: m/z; 391.2 **N-(4-chlorophenyl)-2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3triazol-4-yl)acetamide (8c):** Dark brown solid, IR (KBr) cm^{-1}: 3461, 3270, 3136, 2953, 1688, 1662, 1598, 1466, 1383, 1270, 1243, 1061, 853, 805. ^{1}H NMR (DMSO-d^6) δ ppm: 10.69 (s, 1H,-NH-amide), 10.02 (s, 1H,-NH-amide), 8.24(s, 1H, -C-H-triazole), 6.61-7. 77 (m. 7H, ArH), 5.36 (s, 2H, O-CH_2-), 5.10(s, 2H,-CO-CH_2-) ,2.78(t, 2H, -CH_2-),2.41-2.43(t,2H,-CH_2), MS: m/z; 411.20

N-(4-fluorophenyl)-2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3triazol-4-yl)acetamide (8d): Black solid, IR (KBr) cm^{-1}: 3464, 3284, 3162, 3098, 1686, **1623, 1598, 1589, 1487, 1438, 1385, 1228, 1190, 832, 807. ^{1}H NMR (DMSO-d^6) δ ppm: 10.55 (s, 1H,-NH-amide), 10.02 (s, 1H,-NH-amide), 8.24(s, 1H, -C-H-triazole), 6.52-7.59 (m.** 7H, Ar-H), 5.34 (s, 2H, O-CH_2-),5.09(s,2H,-CO-CH_2-) ,2.78(t, 2H, -CH_2-),2.41-2.43(t,2H,-CH_2),MS: m/z; 395.25

N-(3-nitrophenyl)-2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3triazol-4-yl)acetamide (8e): Light Black solid. ^{1}H NMR (DMSO-d^6) δ ppm: 11.0 (s, 1H,-NHamide), 10.02 (s, 1H,-NH-amide), 8.59 (s, 1H, -C-H-triazole), 6.52-8.26 (m. 7H, Ar-H), 5.41 (s, 2H, O-CH_2-), 5.10 (s,2H,-CO-CH_2-), 2.77-2.78 (t, 2H, -CH_2-), 2.41-2.43 (t,2H,-CH_2-), MS: m/z; 423.10

N-(4-nitrophenyl)-2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3triazol-4-yl)acetamide (8f) Dark brown solid, ^{1}H NMR (DMSO-d^6) δ ppm: 11.01 (s, 1H,-NHamide), 10.02 (s, 1H,-NH-amide), 8.25(s, 1H, -C-H-triazole), 6.52-7.82(m. 7H, ArH), 5.44(s, 2H, O-CH_2-),5.10(s,2H,-CO-CH_2-),2.78(t, 2H, -CH_2-),2.39(t,2H,-CH_2-), MS: m/z; 423.10

N-(2-methyl-5-nitrophenyl)-2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)acetamide (8g): Black solid, IR (KBr) cm^{-1}: 3260, 1676, 1626, 1597, 1550, 1518, 1408, 1389, 1345, 1105, 858, 741. ^{1}H NMR (DMSO-d^6) δ ppm: 10.09 (s, 1H, NH-amide), 10.02 (s, 1H,-NH-amide), 8.48(s, 1H, -C-H-triazole), 6.52-8.27 (m. 6H, ArH), 5.48(s, 2H, O-CH_2-), 5.10(s,2H,-CO-CH_2-),4.10-4.12(t,2H,-CH_2) 2.76-2.78(s, 3H,CH_3),3.15- 3.17(t, 2H-CH_2-)-2.43(t,2H,-CH_2-), MS: m/z; 436.20

N-(2,4-dimethylphenyl)-2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)acetamide (8h): Black solid, IR (KBr) cm^{-1}: 3258, 1670, 1626, 1595, 1543, 1519,1441, 1379, 1271, 1167, 1034, 853, 817, 685. ^{1}H NMR (DMSO-d^6) δ ppm: 10.02 (s, 1H,-NH-amide), 9.73 (s, 1H,-NH-amide), 8.23(s, 1H, -C-H-triazole), 6.52-7.28(m. 6H, ArH), 5.36(s, 2H, O-CH_2-),5.09(s, 2H, -CO-CH_2-),2.78-2.8(t, 2H-CH_2-),2.39-2.43(t,2H,-CH_2-),2.24(s,3H,-CH_3-),2.18(s,3H,-CH_3-) MS: m/z; 405.25

6. Result and Discussion:

6.1Chemistry:

Herein the synthesis of 2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3triazol-4-yl)-N-Arylacetamide **(8a-8h)** derivatives was depicted using four step reaction. Initially, in step-1 substituted anilines **(1a-1h)** were made to react with 2-chloroacetyl chloride **(2)** in the presence of potassium carbonate and acetone as reacting medium to yield 2-chloro arylacetamide derivatives **(3a-3h)**. In second step the formed product is subjected to react with sodium azide leading to formation of 2-azido-N-arylacetamide **(4a-4h)**. During step 3 the 7-(prop-2-yn-1-yloxy)-3,4-dihydroquinolin-2(1H)-one **(7)** synthesized by combining 7-hydroxy-3,4dihydroquinolin-2(1H)-one **(5)** and propargyl bromide **(6)** in acetone using potassium carbonate. In the final step 7-(ethynyloxy)-3,4-dihydroquinolin-2(1H)-one **(7)** and 2-azido-Narylacetamide derivatives **(4a-4h)** were condensed to give target molecule i.e. 2-(1-(((2-oxo1,2,3,4-tetrahydroquinolin-7-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-N-Arylacetamide derivatives **(8a-8h)**. The synthesized compounds were characterized by ^{1}H-NMR, FT-IR spectroscopy and mass spectroscopy. Further the synthesized derivatives were evaluated for antimicrobial activity against gram-positive, gram-negative bacteria and fungi.

6.2Antimicrobial Activity

The compounds of the present work were screened for the antibacterial and antifungal activity using 100 ppm concentration of ampicillin and nystatin respectively in DMF by cup and well method for gram-positive bacteria, fungi while 50 ppm concentration of streptomycin for gram-negative bacteria. The micro-organisms *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli* were used as bacterial strains and *Aspergillus niger* were used as fungal strains. The dilutions of the compounds were made 1000, 500, 250 (in ppm). The findings are displayed in Table 2.

Table-2: Anti-microbial activity study of 2-(1-(((2-oxo-1,2,3,4-tetrahydroquinolin-7yl)oxy)methyl)- 1H-2,3-triazol-4-yl)-N-Arylacetamide derivatives (8a-8h)

Compound	Antibacterial MIC (µg mL^{-1})				Antifungal MIC (µg mL^{-1})
	Bacillus subtilis	***Staphylococcus aureus***	***Escherichi a coli***	***Pseudomonas aeruginosa***	***Aspergillus Niger***
Ampicillin	100	100			
Streptomycin			50	50	
Nystatin					100
8a	1000	1000	1000	1000	**500**
8b	**500**	1000	1000	1000	1000
8c	**500**	1000	1000	1000	1000
8d	1000	1000	1000	1000	1000
8e	**250**	1000	1000	1000	**500**
8f	1000	**250**	1000	1000	1000
8g	**500**	1000	1000	1000	1000
8h	**500**	1000	1000	1000	1000

7. Conclusion:

The objective of the present research was to synthesize, characterize, and investigate antimicrobial and anti-fungal activities of some novel 7-hydroxy-3,4-dihydroquinolin-2(1H)one containing 1,2,3-triazole derivatives **(8a-8h)**. All the compounds were subjected to antimicrobial activity. Among the range of compounds **8a-8h**, it was analyzed that compounds **8e** and **8f** showcases potent activity and **8b, 8c, 8g, 8h** shows moderate activity against gram-positive bacteria. All the synthesized compounds are almost inactive against gram negative bacteria. In contrast, compounds **8a** and **8e** shows moderate antifungal activity.

8. References:

1. Dengiz, Ç., & Balci, M. (2013). New synthetic methodology for construction of the 3, 4dihydroquinolin-2-one skeleton. *Turkish Journal of Chemistry*, *37*(2), 220-227.
2. Gao, F., Zhang, X., Wang, T., & Xiao, J. (2019). Quinolone hybrids and their anti-cancer activities: An overview. *European journal of medicinal chemistry*, *165*, 59-79.
3. Singh, K., Verma, V., Yadav, K., Sreekanth, V., Kumar, D., Bajaj, A., & Kumar, V.
4. (2014). Design, regioselective synthesis and cytotoxic evaluation of 2-aminoimidazole–quinoline hybrids against cancer and primary endothelial cells. *European journal of medicinal chemistry*, *87*, 150-158.
5. Oshiro, Y., Sakurai, Y., Sato, S., Kurahashi, N., Tanaka, T., Kikuchi, T., & Nishi, T. (2000). 3, 4-Dihydro-2 (1 H)-quinolinone as a novel antidepressant drug: synthesis and pharmacology of 1-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl]-3, 4-dihydro-5methoxy-2 (1 H)-quinolinone and its derivatives. *Journal of medicinal chemistry*, *43*(2), 177-189.
6. Hou, J., Liu, X., Shen, J., Zhao, G., & Wang, P. G. (2012). The impact of click chemistry in medicinal chemistry. *Expert opinion on drug discovery*, *7*(6), 489-501.
7. Nulwala, H., Takizawa, K., Odukale, A., Khan, A., Thibault, R. J., Taft, B. R., & Hawker, C. J. (2009). Synthesis and characterization of isomeric vinyl-1, 2, 3-triazole materials by azide− alkyne click chemistry. *Macromolecules*, *42*(16), 6068-6074.
8. Agalave, S. G., Maujan, S. R., & Pore, V. S. (2011). Click chemistry: 1, 2, 3-triazoles as pharmacophores. *Chemistry–An Asian Journal*, *6*(10), 2696-2718.
9. Jampilek, J. (2019). Heterocycles in medicinal chemistry. *Molecules*, *24*(21), 3839.
10. Khedar, P., Pericherla, K., Singh, R. P., Jha, P. N., & Kumar, A. (2015). Click chemistry

inspired synthesis of piperazine-triazole derivatives and evaluation of their antimicrobial activities. *Medicinal Chemistry Research*, *24*, 3117-3126.

11. Thanh, N. D., Bich, V. T. N., Hien, P. T. T., Duyen, N. T. K., Mai, N. T., Dung, T. T., ... & Van, T. T. T. (2019). Efficient click chemistry towards novel 1H-1, 2, 3-triazoletethered 4H-chromene− d-glucose conjugates: Design, synthesis and evaluation of in vitro antibacterial, MRSA and antifungal activities. *European journal of medicinal chemistry*, *167*, 454-471.
12. Prasad, D., Aggarwal, N., Kumar, R., & Nath, M. (2012). Synthesis of novel heteroarenes based [1, 2, 3]-triazoles via click chemistry and their evaluation for antibacterial activity.
13. Nayak, N., Ramprasad, J., Dalimba, U., Yogeeswari, P., Sriram, D., Kumar, H. S., & Achur, R. (2016). Synthesis of new pyrazole-triazole hybrids by click reaction using a green solvent and evaluation of their antitubercular and antibacterial activity. *Research on Chemical Intermediates*, *42*, 3721-3741.
14. Boshra, A. N., Abdu-Allah, H. H., Mohammed, A. F., & Hayallah, A. M. (2020). Click chemistry synthesis, biological evaluation and docking study of some novel 2′hydroxychalcone-triazole hybrids as potent anti-inflammatory agents. *Bioorganic chemistry*, *95*, 103505.
15. Anandhan, R., Kannan, A., & Rajakumar, P. (2017). Synthesis and anti-inflammatory activity of triazole-based macrocyclic amides through click chemistry. *Synthetic Communications*, *47*(7), 671-679.
16. Ali, Y., Alam, M. S., Hamid, H., Husain, A., Bano, S., Dhulap, A.,& Haider, S. (2015). Design, synthesis and biological evaluation of piperic acid triazolyl derivatives as potent anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *92*, 490-500.
17. Ali, Y., Alam, M. S., Hamid, H., Husain, A., Bano, S., Dhulap, A., & Haider, S. (2015). Design, synthesis and biological evaluation of piperic acid triazolyl derivatives as potent anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *92*, 490-500.
18. Dar, M. A., Shrivastava, S., & Iqbal, P. F. (2015). Click chemistry and anticancer properties of 1, 2, 3-triazoles. *World J. Pharm. Res*, *4*, 1949-1975.
19. Hou, W., Luo, Z., Zhang, G., Cao, D., Li, D., Ruan, H.,& Xu, H. (2017). Click chemistry-based synthesis and anticancer activity evaluation of novel C-14 1, 2, 3triazole dehydroabietic acid hybrids. *European Journal of Medicinal Chemistry*, *138*, 1042-1052.
20. El Bourakadi, K., Mekhzoum, M. E. M., Saby, C., Morjani, H., Chakchak, H., Merghoub, N., & Bouhfid, R. (2020). Synthesis, characterization and in vitro anticancer activity of thiabendazole-derived 1, 2, 3-triazole derivatives. *New Journal of Chemistry*, *44*(28), 12099-12106.
21. El Malah, T., Nour, H. F., Nayl, A. A., Elkhashab, R. A., Abdel-Megeid, F. M., & Ali, M. M. (2016). Anticancer evaluation of tris (triazolyl) triazine derivatives generated via click chemistry. *Australian Journal of Chemistry*, *69*(8), 905-910.
22. Rani, A., Singh, G., Singh, A., Maqbool, U., Kaur, G., & Singh, J. (2020). CuAAC-ensembled 1, 2, 3-triazole-linked isosteres as pharmacophores in drug discovery. *RSC advances*, *10*(10), 5610-5635.
23. Chavan, P. V., Desai, U. V., Wadgaonkar, P. P., Tapase, S. R., Kodam, K. M., Choudhari, A., & Sarkar, D. (2019). Click chemistry based multicomponent approach in the synthesis of spirochromenocarbazole tethered 1, 2, 3-triazoles as potential anticancer agents. *Bioorganic Chemistry*, *85*, 475-486.
24. El Azab, I. H., El-Sheshtawy, H. S., Bakr, R. B., & Elkanzi, N. A. (2021). New 1, 2, 3triazole-containing hybrids as antitumor candidates: Design, click reaction synthesis, DFT calculations, and molecular docking study. *Molecules*, *26*(3), 708.
25. Li, J., Zheng, M., Tang, W., He, P. L., Zhu, W., Li, T., & Jiang, H. (2006). Syntheses of triazole-modified zanamivir analogues via click chemistry and anti-AIV activities. *Bioorganic & medicinal chemistry letters*, *16*(19), 5009-5013.
26. He, Y. W., Dong, C. Z., Zhao, J. Y., Ma, L. L., Li, Y. H., & Aisa, H. A. (2014). 1, 2, 3Triazole-containing derivatives of rupestonic acid: click-chemical synthesis and antiviral activities against influenza viruses. *European Journal of Medicinal Chemistry*, *76*, 245255.
27. El-Sayed, W. A., Khalaf, H. S., Mohamed, S. F., Hussien, H. A., Kutkat, O. M., & Amr, A. E. (2017). Synthesis and antiviral activity of 1, 2, 3-triazole glycosides based substituted pyridine via click cycloaddition. *Russian Journal of General Chemistry*, *87*, 2444-2453.
28. Vernekar, S. K. V., Qiu, L., Zacharias, J., Geraghty, R. J., & Wang, Z. (2014). Synthesis and antiviral evaluation of 4′-(1, 2, 3-triazol-

1-yl) thymidines. *MedChemComm*, *5*(5), 603-608.

29. Artyushin, O. I., Sharova, E. V., Vinogradova, N. M., Genkina, G. K., Moiseeva, A. A., Klemenkova, Z. S., ... & Brel, V. K. (2017). Synthesis of camphecene derivatives using click chemistry methodology and study of their antiviral activity. *Bioorganic & Medicinal Chemistry Letters*, *27*(10), 2181-2184.
30. El-Sayed, W. A., Khalaf, H. S., Mohamed, S. F., Hussien, H. A., Kutkat, O. M., & Amr, A. E. (2017). Synthesis and antiviral activity of 1, 2, 3-triazole glycosides based substituted pyridine via click cycloaddition. *Russian Journal of General Chemistry*, *87*, 2444-2453.
31. Seliem, I. A., Panda, S. S., Girgis, A. S., Moatasim, Y., Kandeil, A., Mostafa, A., & Al-Mahmoudy, A. M. (2021). New quinoline-triazole conjugates: Synthesis, and antiviral properties against SARS-CoV-2. *Bioorganic Chemistry*, *114*, 105117.
32. Gao, P., Sun, L., Zhou, J., Li, X., Zhan, P., & Liu, X. (2016). Discovery of novel anti HIV agents via Cu (I)-catalyzed azide-alkyne cycloaddition (CuAAC) click chemistrybased approach. *Expert Opinion on Drug Discovery*, *11*(9), 857-871.
33. El Malah, T., Nour, H. F., Nayl, A. A., Elkhashab, R. A., Abdel-Megeid, F. M., & Ali, M. M. (2016). Anticancer evaluation of tris (triazolyl) triazine derivatives generated via click chemistry. *Australian Journal of Chemistry*, *69*(8), 905-910.
34. Tan, W., Li, Q., Li, W., Dong, F., & Guo, Z. (2016). Synthesis and antioxidant property of novel 1, 2, 3-triazole-linked starch derivatives via 'click chemistry'. *International Journal of Biological Macromolecules*, *82*, 404-410.
35. Mohammed, J. H., & Aowda, S. A. (2020). Antioxidant activity of some triazoles synthesized by click chemistry. *European Journal of Molecular & Clinical Medicine*, *7*(08), 2020.
36. Chen, Y., Liu, X., Sun, X., Zhang, J., Mi, Y., Li, Q., & Guo, Z. (2020). Synthesis and antioxidant activity of cationic 1, 2, 3-Triazole functionalized starch derivatives. *Polymers*, *12*(1), 112.
37. Tan, W., Zhang, J., Zhao, X., Dong, F., Li, Q., & Guo, Z. (2018). Synthesis and antioxidant action of chitosan derivatives with amino-containing groups via azide-alkyne click reaction and N-methylation. *Carbohydrate polymers*, *199*, 583-592.
38. Wei, L., Sui, H., Zhang, J., & Guo, Z. (2021). Synthesis and antioxidant activity of the inulin derivative bearing 1, 2, 3-triazole and diphenyl phosphate. *International Journal of Biological Macromolecules*, *186*, 47-53.
39. Zou, Y., Zhao, Q., Liao, J., Hu, H., Yu, S., Chai, X., & Wu, Q. (2012). New triazole derivatives as antifungal agents: Synthesis via click reaction, in vitro evaluation and molecular docking studies. *Bioorganic & medicinal chemistry letters*, *22*(8), 2959-2962.
40. Xu, G., Zhao, J., Jiang, Y., Zhang, P., & Li, W. (2016). Design, synthesis and antifungal activity of novel indole derivatives linked with the 1, 2, 3-triazole moiety via the CuAAC click reaction. *Journal of Chemical Research*, *40*(5), 269-272.
41. Jiang, Y., Ren, B., Lv, X., Zhang, W., Li, W., & Xu, G. (2015). Design, synthesis and antifungal activity of novel phenol derivatives linked with 1, 2, 3-triazole moiety by the click reaction. *Journal of Chemical Research*, *39*(4), 243-246.
42. Tan, W., Zhang, J., Mi, Y., Dong, F., Li, Q., & Guo, Z. (2018). Synthesis, characterization, and evaluation of antifungal and antioxidant properties of cationic chitosan derivative via azide-alkyne click reaction. *International journal of biological macromolecules*, *120*, 318-324.