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Copper Fluorapatite assisted synthesis of new 1,2,3-triazoles bearing benzothiazolyl moiety and their antibacterial and anticancer activities

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Abstract:

A series of new 2-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] thiazoles and 2-(4-((4-(benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-t**) has been synthesized via Copper Fluorapatite (CuFAP) catalysed click reaction. The compounds (**5a-t**) were synthesized using freshly prepared 2-aryl-4-hydroxybenzothiazole (**1**) as a starting material. 2-Aryl-4-hydroxybenzothiazole (**1**) was condensed with propargyl bromide (**2**) in *N,N*-dimethylformamide in the presence of potassium carbonate to obtain a key intermediate, benzothiazolyl phenoxymethylalkyne (**3**). This alkyne (**3**) was then separately subjected following click chemistry with freshly prepared aryl/benzyl azides and substituted 2-azido-*N*-phenylacetamides (**4a-t**) in presence of Copper fluorapatite (CuFAP) and triethyl amine and obtained better to excellent yields of the titled compounds (**5a-t**). All the newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS analyses. All the synthesized compounds were found to be effective against human breast carcinoma (MCF-7) cells. Among them, compounds **5e**, **5h**, **5j**, **5o** and **5p** were found to be strong inhibitors for the growth of MCF-7 cells with IC_{50} values 10.14, 9.84, 10.06, 10.13 and 9.19 µg/mL, respectively. In addition, compounds **5a, 5c, 5d, 5e, 5f, 5k, 5n, 5o** and **5q** have shown activity against the multidrug resistant pathogenic strain of *E.coli* with MIC values 7.99, 8.44, 8.11, 8.06, 8.54, 9.40, 8.02, 9.25 and 10.62 µg/mL, respectively.

Keywords

Copper Fluorapatite, 1,2,3-Triazole, 2-Arylbenzothiazole, Click Chemistry, Anticancer Activity, Antibacterial Activity, ADME Prediction.

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1. Introduction

1,2,3-triazoles are five membered *N*-heterocyclic compounds and are featured in a large number of bioactive molecules and medicinal chemistry.[1] Among the various 1,2,3-triazoles, 1,4-disubstituted-1,2,3-triazole derivatives have been found to have broad spectrum applications in different areas such as bioconjugations, polymers, pesticides, supramolecular chemistry, pharmaceuticals and surface sciences.[2-5] Triazoles act as effective surrogates in bioactive molecules because they are capable to exhibit hydrogen bonding, dipole-dipole moments and π-stacking interactions.[6] They are also used as a linkers and show bioisosteric effects on peptide linkage, aromatic rings, imidazoles and double bonds.[7,8] These aforementioned features of triazoles are found to be responsible for their therapeutic significance in medicinal chemistry as they bind with biological targets with high affinity and have improved solubility.[9]

Literature survey revealed that, 1,4-disubstituted-1,2,3-triazole derivatives are endowed with numerous therapeutic activities such as antifungal,[10] antibacterial,[11] antitubercular,[12] antidiabetic,[13] anticancer,[14] anti-HIV,[15] antileishmanial[16] and antiviral.[17] In recent years, triazole has been gaining special attention in the drug discovery because the drugs bearing 1,2,3-triazole scaffold viz tazobactum, cephalosporin and cetatrizine are clinically used against bacterial infections.[18] While triazole bearing medicaments like fluconazole, itraconazole, voriconazole and ketoconazole are widely used as antifungal agents.[19]

Benzothiazole is a privileged fused heteroatomic compound containing sulphur and nitrogen as heteroatoms. Benzothiazoles are emerged as key scaffolds for new drugs discovery because of their inherent affinity for diverse biological receptors.[20] Benzothiazole and its derivatives offer high degree of structural diversity that has proven their usefulness for searching new therapeutic leads.[21] Benzothiazole containing compounds are gaining immense importance due to the broad spectrum of pharmacological activities such as antimicrobial,[22] anticancer,[23] antitubercular,[24] antifungal,[25] antidiabetic,[26] antiinflammtory[27] and antiviral.[28]

Physical, metabolic, chemical and genetic conditions are mainly responsible for the growth of the malignant cells. Breast cancers are the malignancies in mammary gland cells in women.[29] Several factors make women at high risk of the breast cancer.[30] The use of various therapies like radiations, surgical removal and chemotherapeutic drugs can reduce invasive breast cancer. However due to harmful side effects of the radio/chemotherapy the

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patients are found to remain traumatized.[31,32] The search for target-specific and less side-effect cancer therapy is still undergoing. Owing to the therapeutic significance of benzothiazoles and 1,2,3-triazoles, in recent years a library of thiazole/benzothiazole derivatives conjugated with 1,2,3-triazole (**Fig. 1**) has been synthesized and the conjugates are found to possess antibacterial and anticancer activities. Benzothiazole based 1,2,3-triazole **1** has displayed potent anticancer activity against Colo-205 and A549 cells.[33] Whereas thiazole substituted 1,2,3-triazole **2** has exhibited potent anticancer activity against leukemia K-562 and SK-MEL-5 cell lines.[34] Recently reported thiazoles/benzothiazoles coupled with 1,2,3-triazole **3-4** have been reported for their antibacterial and antitubercular activities.[35-36]

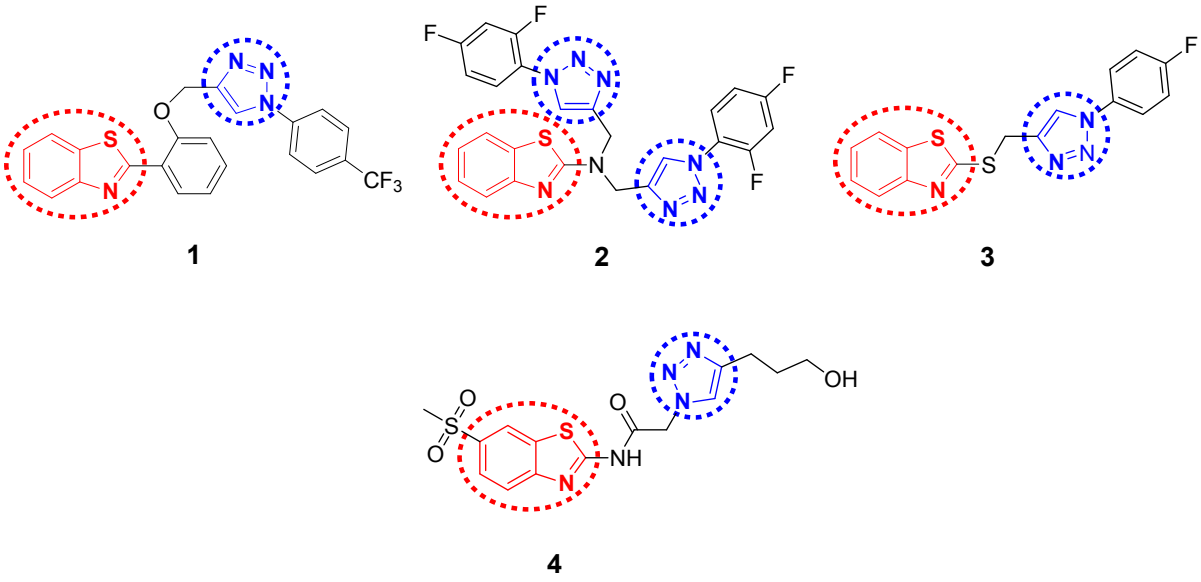

Figure 1. 1,2,3-Triazoles containing bioactive molecules

Literature reveals that triazoles possessing benzothiazolyl scaffold have displayed remarkable anticancer and antibacterial activities. It has been also revealed that triazoles possessing 4-benzothiazolyl phenoxymethyl moiety has not been reported. Keeping this in view and in a search of better anticancer and antibacterial new therapeutics here it has been thought worthwhile to design and synthesize the titled compounds, 2-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazoles and 2-(4-((4-(benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-t**) by developing a convenient and novel synthetic protocol from readily available 2-aryl-4-hydroxy benzothiazole.

In view of the wide applications of 1,2,3-triazoles, there is an extensive interest in developing novel synthetic methods for their constructions. The conventional way to synthesize 1,2,3-triazoles is by following Huisgen 1,3-dipolar cycloaddition of alkynes with

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organic azides.[37] This cycloaddition normally requires high temperature and long reaction time and affords a mixture of 1,4 and 1,5-regioisomers. To overcome the above difficulties, most popular "click chemistry approach", for the synthesis of exclusively 1,2,3-triazoles has been developed by Sharpless and co-workers[38] and independently by Meldal and co-workers.[39] Copper-catalyzed alkyne-azide cycloaddition (CuAAC) has been become a classical protocol for getting 1,4-disubstituted 1,2,3-triazoles as a sole regioisomer. Numerous successful examples have been reported in the literature for the preparation of 1,2,3-triazoles using $CuSO_4.5H_2O$ and sodium ascorbate,[40] copper nanoparticles,[41] copper oxide nanoparticles,[42] copper supported on graphene oxide,[43] cellulose supported copper nanoparticles,[44] copper nanoparticles supported on silica coated maghemite,[45] copper nanoparticles supported on charcoal[46] and copper ferrite nanoparticles.[47]

It is also revealed from literature that, apatites are emerging as accelerators for carrying various value added transformations.[48] Apatites are found in nature or derived from minerals. Hydroxy calcium apatites and fluoro calcium apatites are most commonly used apatites having general formula, $Ca_{10}(PO_4)_6X_2$ (X=OH,F).[49] These are found to be well explored as catalysts for rapidly conducting various organic transformations.[50] Since last few decades, copper hydroxyapatite and copper fluorapatite (CuFAP) have been introduced as stable and safer heterogeneous catalysts for carrying condensations/cyclocondensations and various other organic transformations such as- O-aryloxime ethers,[51] N-arylation,[52] and C-N bond formation.[53] CuFAP has ability to adsorb organic, organometallic molecules and salts on their surface.[54]

Literature survey also revealed that existing synthetic protocols, used for obtaining 1,2,3-triazoles by carrying cycloaddition of alkynes and azides are having one or other kind of limitations. Continuous efforts are found to be directed for performing the cycloaddition efficiently by incorporating safer and suitable recyclable catalysts, replacing $CuSO_4/Cu(OAc)_2$ and reducing agent. Considering the significance of Ca/Cu apatites as recyclable catalysts, recently Cu (II) hydroxyapatite has been applied not only for carrying O-arylation or N-arylation but also for accelerating the rate of cycloaddition of azides and alkyne for getting 1,2,3-triazoles.[55] It has also been observed that the use of CuFAP has not been attempted in carrying the cycloaddition under discussion. CuFAP is most stable and having more advantage as a catalyst than that of copper hydroxyapatite.[56] Keeping the above observations in mind here first time strategy has been adopted to incorporate CuFAP in catalysing cycloaddition of azides and new alkyne for obtaining high yields of 1,2,3-triazoles (**5a-t**).

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2. Results and Discussion

2.1 Chemistry

The desired compounds, new 2-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl) benzo[d]thiazoles and 2-(4-((4-(benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-phenylacetamides (**5a-t**) have been synthesized starting from freshly prepared 2-aryl-4-hydroxybenzothiazole (**1**). 2-Aryl-4-hydroxybenzothiazole (**1**) was allowed to interact with propargyl bromide (**2**) in DMF in the presence of K_2CO_3 at room temperature for 2h to obtain a key intermediate, benzothiazolyl phenoxymethyl alkyne (**3**). Then cycloaddition of this intermediate, benzothiazolyl phenoxymethyl alkyne (**3**) was separately carried with various azides **(4a-t**) in the presence of CuFAP and triethyl amine and obtained the desired products, 2-(4-((1-phenyl/benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazoles and 2-(4-((4-(benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamides (**5a-t**), respectively with better to excellent yields.

All the newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS techniques. The IR spectrum of compound (**5a**) indicates the formation of product as it shows a characteristic absorption peaks at 1466 and 1400 cm^{-1} which correspond to the N-N and N=N stretching, respectively. The ^{1}H NMR spectrum of compound (**5a**) displays peaks, a singlet at δ 5.40 ppm, due to the OCH_2 and a multiplet in the region 7.13 to 8.10 ppm due to the merged signals of triazolyl ring-H and 13 aromatic-H. The presence of three characteristics carbon signals are observed at 62.31, 115.41 and 167.80 ppm in ^{13}C NMR spectrum of compound (**5a**). The signal of carbon at 62.31 ppm due to the OCH_2 group whereas carbon signals at 115.41 and 167.80 ppm due to the triazolyl ring carbon and thiazolyl ring carbon, respectively, confirming the presence of a 1,2,3-triazole ring in (**5a**). The HRMS spectrum further strengthen the structure assigned to (**5a**) as 2-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole, showing $[M+H]^+$ ion peak at m/z 385.1132 for its molecular formula $C_{22}H_{16}N_4OS$. Experimental procedures and spectra of 1,2,3-triazoles (**5a-t**) and intermediates are given in **supplementary data**. The synthetic sequence is depicted in **Scheme 1.**

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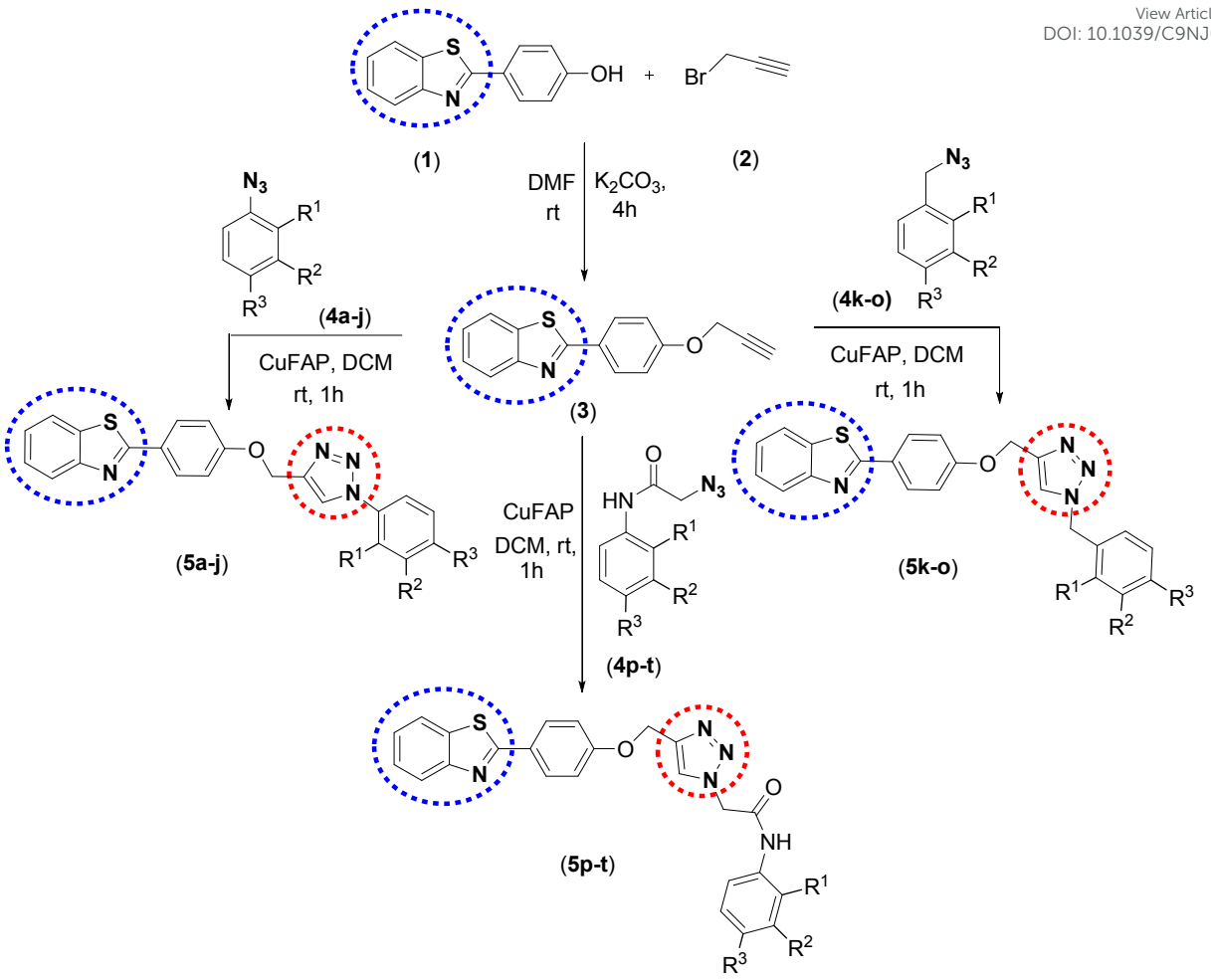

5a=R^1=H, R^2=H, R^3=H
5b=R^1=Cl, R^2=H, R^3=H
5c=R^1=H, R^2=Cl, R^3=H
5d=R^1=H, R^2=H, R^3=Cl
5e=R^1=Br, R^2=H, R^3=H
5f=R^1=H, R^2=Br, R^3=H
5g=R^1=OCH_3, R^2=H, R^3=H
5h=R^1=H, R^2=H, R^3=OCH_3
5i=R^1=F, R^2=H, R^3=F
5j=R^1=CH_3, R^2=CH_3, R^3=CH_3
5k=R^1=H, R^2=H, R^3=H
5l=R^1=H, R^2=H, R^3=F
5m=R^1=Cl, R^2=**H**, R^3=H
5n=R^1=H, R^2=Cl, R^3=H
5o=R^1=H, R^2=H, R^3=Br
5p=R^1=H, R^2=H, R^3=H
5q=R^1=H, R^2=Cl, R^3=**H**
5r=R^1=H, R^2=H R^3=Cl
5s=R^1=H, R^2=CH_3, R^3=H
5t=R^1=H, R^2=H, R^3=CH_3

Scheme 1. Synthetic route for 1,2,3-triazole coupled benzo[d]thiazole derivatives **(5a-t).**

In the present work freshly prepared azides (**4a-t**) have been cyclo added on freshly prepared alkyne (**3**) using CuFAP as reusable catalyst. Attempts were made to provide right reaction conditions for the cycloaddition. In search of right conditions, the model reaction has been performed by varying amount of CuFAP catalyst, media and bases. Here we performed cyclocondensation of a new benzothiazolyl phenoxy methyl alkyne (**3**) with phenyl azide (**4a**) as a model reaction in the presence of CuFAP and triethylamine at room temperature to obtain **5a**. This model reaction was performed under identical condition in different solvents. The screening results of the model reaction run in different solvents at rt in the presence of CuFAP are recorded in **Table 1, entry 1-12.** Among the screened solvents, DCM was found to be the best solvent to afford product **5a.**

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To optimise the amount of CuFAP, required to carry the model cycloaddition, we attempted the cycloaddition in DCM by varying amounts of CuFAP from 25 mg to 100 mg using alkyne (**3**) (0.0004 mol), phenyl azide (**4a**) (0.0004 mol) and triethyl amine (0.0004 mol). It was observed that high yield of 2-(4-((1-aryl-1H-1,2,3-triazol-4-yl)methoxy)phenyl) benzo[d]thiazole (**5a**) was obtained, when the model reaction was performed in the presence of 50 mg catalyst using 0.0004 mole initial concentration of each of the reactant (**Table 2, entry 1-4**). The cyclocondensation was found to be completed within 1h giving 94 % yield of 1,2,3-triazole (**5a**). Therefore, 50 mg of CuFAP catalyst was selected as the optimal quantity for the reaction (**Table 2**). To investigate the role of the CuFAP, the cycloaddition was performed under identical conditions in the absence of CuFAP and observed that reaction did not proceed even when constantly stirred at rt for more than 30 h. This observation clearly indicated that here CuFAP has played key role in accelerating the rate of the cycloaddition.

Table 1. Screening of reaction media for the synthesis of compound **5a.**[a]

Entry	Solvents	Time (h)	Yields[b] (%)
1	DCM	1h	94
2	DMF	1h	92
3	DMSO	1h	70
4	Isopropanol	1h	52
5	MeOH	1h	68
6	PEG-400	1h	48
7	$CHCl_3$	1h	72
8	1,4-Dioxane	1h	31
9	THF	1h	18
10	EtOH	1h	37
11	Toluene	1h	24
12	CH_3CN	1h	42

[a]**Reaction Conditions:** Alkyne (**3**) (0.0004 mol), phenylazide (**4a**) (0.0004 mol), triethyl amine (0.0004 mol), solvent (5 ml), CuFAP (50 mg), at room temperature, [b]Isolated yields.

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Table 2. Optimization of amount of CuFAP as catalyst, required for the cycloaddition[a]

Entry	Catalyst concentration	Compound (Yield %[b])
1	25 mg	65
2	50 mg	94
3	75 mg	~94
4	100 mg	~94

[a]**Reaction Conditions:** Alkyne (**3**) (0.0004 mol), phenylazide (**4a**) (0.0004 mol), triethyl amine (0.0004 mol), solvent (5 ml) at room temperature, [b] Isolated yields.

The model reaction was performed under identical conditions as above by varying organic and inorganic bases, keeping their initial concentration same. The results were recorded in **Table 3** and noted that model reaction gave highest yield of reaction product **5a,** when run in the presence of triethyl amine than the other bases. Keeping all the above observations in mind, the model reaction was performed under optimised conditions i.e. using 0.0004 mol of initial concentration of each reactant and base, triethyl amine and carrying reaction in DCM (10 ml) in the presence of 50 mg of CuFAP with stirring for 1h at rt and obtained 94% yield of **5a**. Using the above optimised conditions, various titled reaction products **(5a-t)** have been synthesized with better to excellent yields, starting from respective azides (**4a-t**) and alkyne (**3**).

Table 3. Screening of the bases

Entry	Base	Time (h)	Yield (%)
1	Triethyl amine	1h	94
2	Dimethylamine	1h	74
3	*N,N*-diisopropylamine	1h	91
4	DABCO	1h	61
5	DBU	1h	76
6	K_2CO_3	1h	34
7	CS_2CO_3	1h	67
8	Without base	1h	Trace

[a]**Reaction Conditions:** Alkyne (**3**) (0.0004 mol), phenylazide (**4a**) (0.0004 mol), DCM (5 ml), CuFAP (50 mg), Bases (0.0004 mol) at room temperature, [b] Isolated yields.

Owing to the environmental concern the development of heterogeneous recyclable catalyst are in high demands in worldwide. Hence the having established efficiency of the CuFAP catalyzed 1,3 dipolar cycloaddition reactions, then we investigated the recyclability

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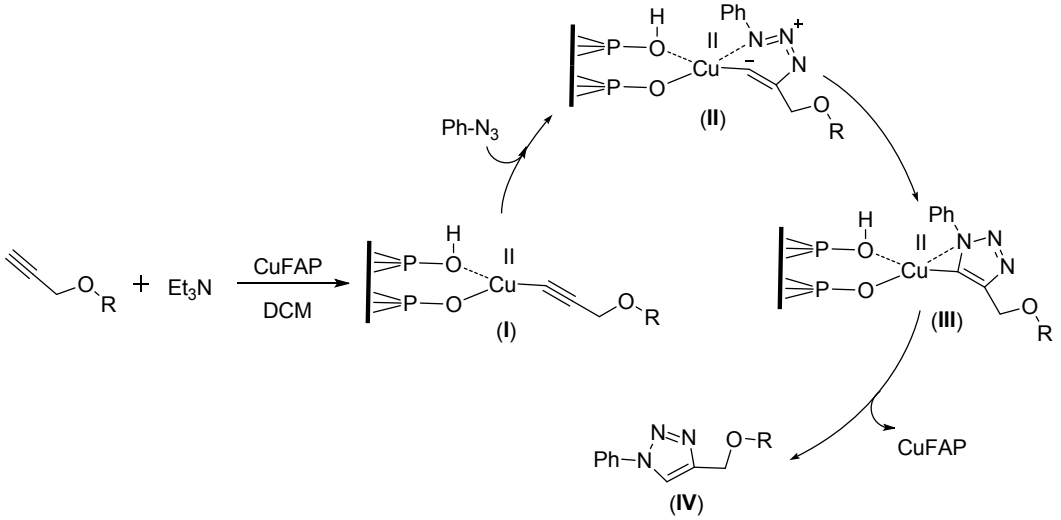
and reusability of catalyst for the synthesis of triazoles (**5a-t**) from alkyne (**3**) with phenylazide (**4a**) under standard reaction condition, and results are shown in **Table 4**. The Copper fluorapatite catalyst can be used to next turn without loss of significant activity. This cycloaddition proceeded very smoothly and afforded the titled triazoles (**5a-t**) with excellent yield. (**Table 4**, entries 2-5).

Table 4. Recoverability and reusability of CuFAP catalyst.[a]

Entry	Run	(Yield%[b])
1	Fresh	95
2	Run-1	94
3	Run-2	94
4	Run-3	90
5	Run-4	90

[a]**Reaction Conditions:** Alkyne (**3**) (0.0004 mol), phenylazide (**4a**) (0.0004 mol), DCM (5 ml), CuFAP (50 mg), Et_3N (0.0004 mol) at room temperature, [b] Isolated yields

On the basis of the above presented experimental results and the previous literature reports on the CuFAP catalyst,[57] a probable reaction mechanism indicating the role of CuFAP in rate acceleration of 1,3 dipolar cycloaddition, leading to triazoles has been presented in **Scheme 2**. Initially, the triethyl amine abstracts the proton from alkyne, and insitu generated nucleophile then reacts with CuFAP catalyst to generate the intermediate complex (I). The corresponding complex (I) undergoes addition on phenyl azide to form intermediate complex (II), which is subsequently interconverted to give complex (III). The unstable complex (III) rapidly breaks, forming stable 1,2,3-triazole (IV) and CuFAP, catalyst in its original form.



Scheme 2. Plausible reaction mechanism of 1,3 dipolar cycloaddition reaction over CuFAP catalyst for the synthesis of 1,2,3-triazoles **(5a-t).**

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2.2 Biological Evaluation

2.2.1 Analysis of the antiproliferative action of compounds on human breast cancer cells

The anticancer potential of the synthesized compounds (**5a-t**) was evaluated *in vitro* against Human breast cancer (MCF-7) cells. The effect of the compounds on the MCF-7 cells growth was observed. The MCF-7 cells were exposed to the compounds for 24 h with concentration ranges from 9 µg/mL to 120 µg/mL. The Paclitaxel was used as standard reference anticancer drug. It is evident from **Table 5** that the most of synthesized compounds have shown excellent action as anticancer compounds compared to standard drug, Paclitaxel. Among the newly synthesized compounds **5b**, **5c**, **5e**, **5h**, **5j**, **5m**, **5n**, **5o**, **5p**, **5q**, **5r**, **5s** and **5t** were found to be more effective for inhibition of growth of the MCF-7 cells (**Fig. 2**). The compound **5p** have phenyl acetamido moiety shown promising anticancer action on MCF-7 cells (IC_{50} 9.19 µg/ml). The compound **5h** with 4-methoxy substituted benzene ring has also displayed notable inhibitory activity with IC_{50} 9.84 µg/mL. The compounds **5j** and **5e** have 2,4-difluoro and 2-bromo substituted benzene ring, respectively found effective against MCF-7 cells with IC_{50} 10.06 and 10.14 ug/mL. In addition to this, compounds **5b** (IC_{50}=18.9), **5c** (IC_{50}=12.39), **5m** (IC_{50}=12.91), **5n** (IC_{50}=12.59), **5o** (IC_{50}=10.14), **5q** (IC_{50}=12), **5r** (IC_{50}=11.04), **5s** (IC_{50}=13.07) and **5t** (IC_{50}=14.4) were found to be strong inhibitors for the growth of MCF-7 cells (**Fig. 2**). The compounds with phenyl acetamido ring and 4-methoxy substituted benzene ring are inducing death in MCF-7 cells. Benzothiazoles act via competing with ATP for binding at the catalytic domain of tyrosine kinase. These compounds may act into the hydrophobic pockets of EGFR tyrosine kinase.[58]

Table 5. The IC_{50} values of compounds (**5a-t**)

Compounds	IC_{50} ($ug.mL^{-1}$)
5a	57.4
5b	18.9
5c	12.39
5d	120.7
5e	10.14
5f	27.78
5g	Na
5h	9.84
5i	40.45

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5j	10.06
5k	20.51
5l	30.26
5m	12.91
5n	12.59
5o	10.14
5p	9.19
5q	12
5r	11.04
5s	13.07
5t	14.4

IC_{50}= Concentrations of drug that decrease viability of the cell by 50 % compared to untreated control cell. The values are the mean of IC_{50} of triplicate experiment.

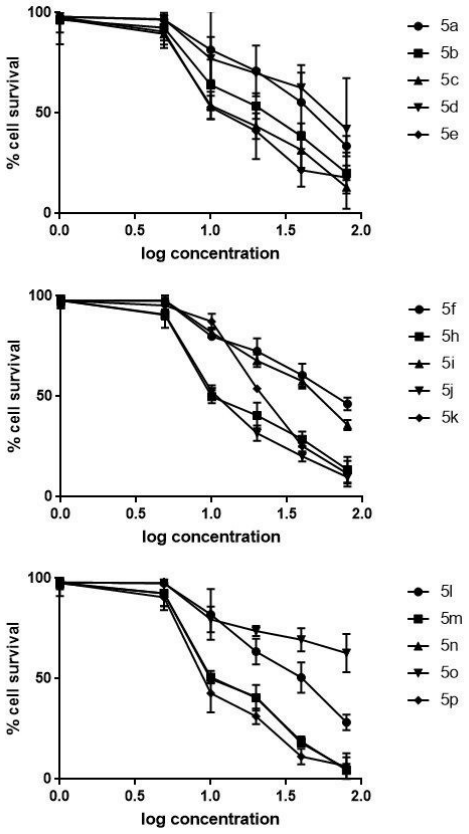

Figure 2. Antiproliferative action of 1,2,3-triazoles (**5a-t**) on Human Breast cancer cells (MCF-7 cells).

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2.2.2 Antimicrobial action of 1,2,3-triazoles (5a-t)

To determine the antimicrobial activity of each compound, antibacterial assay was performed. The pathogenic bacterial cultures were exposed to the compounds (concentration 0 to 50 microgram/mL). All the newly synthesized compounds (**5a-t**) were screened for their antimicrobial activity against multidrug resistant pathogenic strains of *E.coli*. We found that, nine compounds viz. **5a, 5c, 5d, 5e, 5f, 5k, 5n, 5o** and **5q** were found to display potent activity against multidrug resistant pathogenic strain of *E.coli* as compared to the standard reference drug, Tetracyclin. Compound **5a** bearing phenyl ring was found to be the most potent with MIC 7.99 µg/mL. The compound **5n** with 3-chloro benzyl moiety has shown potent activity with MIC 8.02 µg/mL. The compounds **5e** (MIC 8.06), **5d** (MIC 8.11), **5c** (MIC 8.44) and **5f** (MIC 8.54) were having 2-bromo, 3-chloro, 4-chloro, 3-bromo substituents on phenyl, respectively. Other compounds **5k, 5o** and **5q** have displayed potential activity with MIC 9.40, 9.25, 10.62 µg/mL, respectively (**Fig. 3**). Similarly, the compounds **5r, 5s** and **5t** were also found to be active against the *E.coli* **(Fig. 3)**.

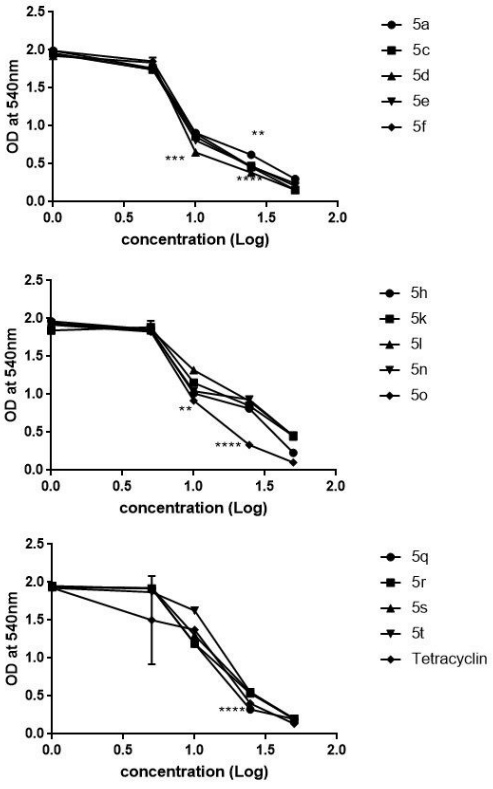

Figure 3. Inhibition of growth of multidrug resistant *Escherichia coli* by using 1,2,3-triazoles **(5a-t).**

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2.2.3 In silico ADME prediction:

Good efficacy and an acceptable ADME (absorption, distribution, metabolism and excretion) profile are the most important properties of any successful drug. ADME properties prediction is one of the widely known pharmacokinetic parameter for the prediction of the oral bioavailability of any drug. Therefore, here we predicted the in *silico* ADME properties of newly synthesized compounds (**5a-t**) and results are incorporated in **Table 6**.

Table 6. Pharmacokinetic parameters for in *silico* ADME prediction of 1,2,3-triazoles (**5a-t**).

Entry	% ABS[a]	TPSA[b] (A^2)	n-RO TB[c]	MV[d]	MW[e]	miLog[f]	n-ON[g]	n-OH NH[h]	Lipinski violations[i]	Drug likeness model score
Rule	-	-	-	-	<500	≤ 5	<10	<5	≤ 1	-
5a	90.77	52.84	5	331.66	384.46	5.37	5	0	1	-0.30
5b	90.77	52.84	5	345.19	418.91	6.21	5	0	1	-0.13
5c	90.77	52.84	5	345.19	418.91	6.24	5	0	1	-0.19
5d	90.77	52.84	5	345.19	418.91	6.05	5	0	1	-0.02
5e	90.77	52.84	5	349.54	463.36	6.34	5	0	1	-0.43
5f	90.77	52.84	5	349.54	463.36	6.37	5	0	1	-0.47
5g	87.58	62.08	6	357.20	414.49	5.59	6	0	1	-0.39
5h	87.58	62.08	6	357.20	414.49	5.43	6	0	1	-0.41
5i	90.77	52.84	5	341.52	420.44	5.84	5	0	1	-0.47
5j	90.77	52.84	5	381.34	426.55	7.00	5	0	1	-0.11
5k	90.77	52.84	6	348.46	398.49	5.69	5	0	1	0.10
5l	90.77	52.84	6	353.39	416.48	5.85	5	0	1	0.43
5m	90.77	52.84	6	362.00	432.94	6.32	5	0	1	0.27
5n	90.77	52.84	6	362.00	432.94	6.37	5	0	1	0.57
5o	90.77	52.84	6	366.34	477.39	6.50	5	0	1	0.24
5p	80.73	81.94	7	393.38	475.96	5.53	7	1	1	0.96
5q	80.73	81.94	7	393.38	475.96	5.55	7	1	1	0.67
5r	80.73	81.94	7	393.38	475.96	5.58	7	1	1	0.04
5s	80.73	81.94	7	396.41	455.54	5.30	7	1	1	0.75
5t	80.73	81.94	7	396.41	455.54	5.35	7	1	1	0.50

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[a]Percentage Absorption; [b]Topographical polar surface area; [c]Number of rotatable bonds; [d]Molecular volume; [e]Molecular Weight; [f]Lipophilicity; [g]No. of hydrogen bond acceptors; [h]No. of hydrogen bond acceptors; [i]Number of violations.

In this study, we calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (mi LogP), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five[59] of all the newly synthesized compounds using Molinspiration online property calculation toolkit.[60] A compound is considered to be an orally active drug as well as obeys the Lipinski's rule of five if there is only one violation is observed out of the following four criteria's: miLog P (octanol-water partition coefficient) ≤5, molecular weight ≤500, number of hydrogen bond acceptors ≤10 and number of hydrogen bond donors ≤5. Other than this absorption (% ABS) of all the derivatives of the series was calculated by formula,

$$\% \text{ ABS} = 109-(0.345 \times \text{TPSA}).$$[61]

In addition to this, the drug-likeness model score (a collective property of physico-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) of each and every compound was computed by MolSoft software.[62]

It was observed from **Table 6** that most of the predictions were found to be within the acceptable range. All the synthesized compounds exhibited very good % ABS ranging from 80.73 to 90.77 %. Drug likeness score was also calculated in order to achieve biological activity of compound. Most of the compounds from the synthesized series show positive drug likeness score. All the results show that the compounds possess average to good potential for the development as orally active drug molecule.

3. Conclusion

A series of new 1,2,3-triazoles bearing benzothiazolyl moiety were synthesized from 1,3-dipolar cycloaddition reaction of alkyne **3** and various azides (**4a-t**) using Copper Fluorapatite (CuFAP) as a catalyst. All the synthesized compounds were evaluated for their *in vitro* antiproliferative activity against human breast carcinoma cells MCF-7. Most of the compounds were found to be effective against human breast carcinoma cells MCF-7. Compounds **5e**, **5h**, **5j**, **5o** and **5p** were found as promising anticancer compounds against MCF-7 cells with IC_{50} values 10.14, 9.84, 10.06, 10.13 and 9.19 μg/mL, respectively. Whereas compounds **5a, 5c, 5d, 5e, 5f, 5k, 5n, 5o** and **5q** were found antimicrobial against

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the multidrug resistant pathogenic strain of *E.coli* with MIC values 7.99, 8.44, 8.11, 8.06, 8.54, 9.40, 8.02, 9.25 and 10.62 µg/mL, respectively.

4. Experimental Section

4.1. General

All reagents and solvents were obtained from commercial suppliers and used without further purification. The Copper fluroapatite were prepared according to reported procedures[53] and prepared catalyst was tested by one example with standard reaction condition of published paper. All the various azides were synthesized from the reported procedures.[63] Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (GF 254) using UV light to visualize the course of the reactions. ^{1}H NMR spectra and ^{13}C NMR spectra were respectively recorded at 300 MHz and 100 MHz spectrometer using $CDCl_3$ and DMSO-d_6 as solvent at room temperature. Chemical shifts (δ) are reported in ppm with TMS as internal standard. Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. Routine monitoring of reaction was performed by TLC using 0.25 mm E. Merck precoated silica gel TLC plates (60 F254).

4.1.1 Synthesis of Benzothiazolylphenoxy methyl alkyne (3)

A mixture of 4-(benzo[d]thiazol-2-yl)phenol (**1**) (0.0044 mol, 1 gm) and propargyl bromide (0.0048 mol, 0.52 gm) (**2**) was dissolved in DMF (10 ml) and to this solution K_2CO_3 (0.0088 mol, 1.22 gm) was added. The reaction mass was stirred at room temperature for 2h. The progress of the reaction was monitored by TLC. After 2 h, the reaction mass was poured on ice cold water. The off white solid obtained was filtered, washed with water and crystallized from ethanol.

Yield: 74 %, M.P.: 122-124 ^{o}C; Off White Solid; IR (KBr) ν cm^{-1}: 3274 (Aromatic C-H stretching), 2127 (C≡C stretching), 1601 (C=C stretching), 1241 (C-O stretching); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 2.57 (s, 1H, Alkynyl-CH), 4.77 (s, 2H, OCH_2), 7.06-8.08 (m, 8H, merged peaks, Ar-H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 55.78, 75.93, 77.86, 115.17, 121.42, 122.80, 124.78, 126.13, 127.15, 128.97, 134.78, 154.08, 159.62, 167.49; HRMS (ESI)$^+$ calcd. for $C_{16}H_{11}NOS$ $[M+H]^+$: 266.0595; found 266.0630.

4.1.2 General procedure for the synthesis of compounds (5a-t)

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Benzothiazolyl phenoxymethyl alkyne (**3**) (0.0004 mol, 0.1 gm) and various azides (**4a-t**) (0.0004 mol, 0.047 gm) were dissolved in DCM (5 ml). To this stirred solution CuFAP (50 mg) and triethyl amine (0.0004 mol, 0.056 ml) were added and stirring was continued at rt. The progress of the reaction was monitored by TLC. After stirring for 1h, reaction mixture was diluted with 10 ml DCM followed by filtration to recover the catalyst. The filtrate was concentrated in vacuo to get the crude product, which was further purified by crystallization to obtain 1,2,3-triazole product.

4.1.2.1 2-(4-((1-Phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5a)

Yield: 94 %, M.P.: 168-171 ^{o}C; White Solid; IR (KBr) ν cm^{-1}: 3273 (Aromatic C-H stretching), 1599 (C=C stretching) 1466 (N-N stretching), 1400 cm^{-1} (N=N stretching); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 5.40 (s, 2H, CH_2), 7.13-8.10 (m, 14H, merged signals, 13 Ar-H and triazolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 62.31, 115.41, 120.82, 121.28, 121.72, 123.08, 125.07, 126.43, 127.29, 129.15, 129.40, 129.99, 135.09, 137.12, 154.39, 160.62, 167.80; HRMS (ESI)$^{+}$ calcd. for $C_{22}H_{16}N_4OS$ [M+H]$^{+}$: 385.1038; found 385.1132.

4.1.2.2 2-(4-((1-(2-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5b)

Yield: 86 %, M.P.: 166-168 ^{o}C; White Solid; IR (KBr) ν cm^{-1}: 3124 (Aromatic C-H stretching), 1593 (C=C stretching), 1481 (N-N stretching), 1420 (N=N stretching); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 5.36 (s, 2H, OCH_2), 7.09-8.06 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 62.17, 115.31, 118.69, 121.00, 121.06, 121.69, 123.04, 125.06, 127.29, 129.18, 129.37, 131.04, 135.02, 135.81, 137.85, 144.89, 154.30, 157.32, 160.45, 167.71; HRMS (ESI)$^{+}$ calcd. for $C_{22}H_{16}ClN_4OS$ [M+H]$^{+}$: 419.0689 and found 419.0745.

4.1.2.3 2-(4-((1-(3-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5c)

Yield: 88 %, M.P.: 146-148 ^{o}C; White Solid; IR (KBr) ν cm^{-1}: 3097 (Aromatic C-H stretching), 1594 (C=C stretching), 1481 (N-N stretching), 1399 (N=N stretching); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 5.39 (s, 2H, OCH_2), 7.11-8.07 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 62.38, 115.47, 120.89, 121.80, 123.15,125.15, 126.50, 127.35, 129.23, 129.47, 130.06, 134.51, 134.70, 135.16, 135.30,

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135.61, 135.80, 137.00, 137.19, 144.80, 154.45, 160.68; HRMS (ESI)$^+$ calcd. for $C_{22}H_{16}ClN_4OS$ $[M+H]^+$: 419.0689; found 419.0740.

4.1.2.4 2-(4-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5d)

Yield: 94 %, M.P.: 202-205 ^oC; White Solid; IR (KBr) ν cm^{-1}: 3056 (Aromatic C-H stretching), 1596 (C=C stretching), 1480 (N-N stretching), 1420 (N=N stretching); ^1H NMR (300 MHz, DMSO-d_6) δ ppm = 5.40 (s, 2H, OCH_2), 7.28 9.07 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm = 61.97, 116.28, 122.61, 122.96, 123.23, 123.89, 125.88, 126.67, 127.27, 129.63, 130.62, 133.80, 134.97, 136.06, 144.36, 154.37, 161.15, 167.66; HRMS (ESI)$^+$ calcd. for $C_{22}H_{16}ClN_4OS$ $[M+H]^+$: 419.0689 and found 419.0739.

4.1.2.5 2-(4-((1-(2-Bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5e)

Yield: 87 %, M.P.: 133-136 ^oC; White Solid; IR (KBr) ν cm^{-1}: 3042 (Aromatic C-H stretching), 1600 (C=C stretching), 1476 (N-N stretching), 1431 (N=N stretching); ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.41 (s, 2H, OCH_2), 7.12-8.09 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 62.02, 115.21, 118.51, 121.47, 122.81, 124.82, 124.95, 126.28, 127.00, 128.16, 128.47, 129.12, 131.26, 133.88, 134.80, 136.33, 137.40, 160.36, 164.64, 167.57; HRMS (ESI)$^+$ calcd. for $C_{22}H_{16}BrN_4OS$ $[M+H]^+$: 463.0183 and found 463.0770.

4.1.2.6 2-(4-((1-(3-Bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5f)

Yield: 85 %, M.P.: 173-175 ^oC; White Solid; IR (KBr) ν cm^{-1}: 2914 (Aromatic C-H stretching), 1599 (C=C stretching), 1485 (N-N stretching), 1418 (N=N stretching); ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.40 (s, 2H, OCH_2), 7.14-8.10 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 62.04, 115.18, 119.07, 120.96, 121.55, 122.90, 123.38, 123.70, 124.92, 126.27, 127.17, 129.23, 131.33, 131.99, 134.70, 134.86, 137.80, 153.71, 154.17, 160.30; HRMS (ESI)$^+$ calcd. for $C_{22}H_{16}BrN_4OS$ $[M+H]^+$: 463.0183 and found 463.0214.

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4.1.2.7 2-(4-((1-(2-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] thiazole (5g)

Yield: 93 %, M.P.: 169-172 ^{o}C; White Solid; IR (KBr) ν cm^{-1}: 2913 (Aromatic C-H stretching), 1595 (C=C stretching), 1469 (N-N stretching), 1422 (N=N stretching); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 3.90 (s, 3H, OCH_3), 5.39 (s, 2H, OCH_2), 7.08-8.22 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 55.91, 62.09, 112.16, 115.21, 117.92, 121.19, 121.45, 122.78, 124.79, 125.41, 125.81, 126.15, 126.84, 129.08, 130.18, 131.53, 134.78, 151.01, 153.90, 160.51, 167.71; HRMS (ESI)$^{+}$ calcd. for $C_{23}H_{19}N_4O_2S$ $[M+H]^{+}$: 415.1184 and found 415.1243.

4.1.2.8 2-(4-((1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] thiazole (5h)

Yield: 91 %, M.P.: 184-186 ^{o}C; White solid; IR (KBr) ν cm^{-1}: 3135 (Aromatic C-H stretching), 2880 (Aromatic C-H stretching), 1597 (C=C stretching), 1478 (N-N stretching), 1444 (N=N stretching); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm = 3.74 (s, 3H, OCH_3), 5.35 (s, 2H, OCH_2), 6.91-8.33 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 55.21, 61.30, 114.08, 115.57, 120.89, 122.26, 122.54, 125.23, 126.62, 128.96, 131.48, 134.29, 142.11, 153.69, 156.91, 160.61, 163.67, 167.10; HRMS (ESI)$^{+}$ calcd. for $C_{23}H_{18}N_4O_2S$ $[M+H]^{+}$: 415.1184; found 415.1216.

4.1.2.9 2-(4-((1-(2,4-Difluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] thiazole (5i)

Yield: 93 %, M.P.: 158-161 ^{o}C; White Solid; IR (KBr) ν cm^{-1}: 3084 (Aromatic C-H stretching), 1603 (C=C stretching), 1466 (N-N stretching), 1445 (N=N stretching); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 5.31 (s, 2H, OCH_2), 7.01-8.08 (m, 12H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 61.96, 115.11, 118.49, 120.79, 120.86, 121.49, 122.83, 124.65, 126.20, 127.09, 128.97, 129.17, 130.83, 134.81, 135.60, 137.66, 144.69, 154.10, 157.32, 160.24, 167.51; LCMS (ESI)$^{+}$ calcd. for $C_{22}H_{15}F_2N_4OS$ $[M+H]^{+}$: 421.09 and found 421.09.

4.1.2.10 2-(4-((1-Mesityl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5j)

Yield: 89 %, M.P.: 145-147 ^{o}C; White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 1.94 (s, 6H, 2xCH_3), 2.33 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 6.91- 8.06 (m, 11H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 16.80, 20.41, 61.21, 115.50, 122.00,

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122.30, 124.27, 124.97, 125.71, 126.35, 128.12, 128.66, 133.07, 134.06, 134.25, 139.40, 142.18, 153.45, 160.31, 166.80; HRMS (ESI)$^+$ calcd. for $C_{25}H_{23}N_4OS$ $[M+H]^+$: 427.1548 and found 427.1582.

4.1.2.11 2-(4-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d]thiazole (5k)

Yield: 94 %, M.P.: 199-201 ^oC; White solid; ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.27 (s, 2H, OCH_2), 5.33 (s, 2H, N-CH_2), 7.06-8.06 (m, 14H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 52.22, 61.29, 115.48, 119.20, 122.17,122.47, 123.75, 125.10, 125.80, 126.48, 128.85, 128.88, 134.24, 138.37, 142.05, 153.65, 160.55, 164.12, 166.96; HRMS (ESI)$^+$ calcd. for $C_{23}H_{19}N_4OS$ $[M+H]^+$: 399.1235 and found 399.1281.

4.1.2.12 2-(4-((1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl) benzo[d] thiazole (5l)

Yield: 95 %, M.P.: 161-164 ^oC; White solid; ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.25 (s, 2H, OCH_2), 5.50 (s, 2H, N-CH_2), 7.01-8.03 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 53.75, 62.37, 115.40, 116.30, 116.52, 121.74, 122.78, 123.09, 125.09, 126.45, 127.25, 129.36, 130.19, 130.27, 130.44, 135.09, 154.41, 160.63, 164.36, 167.82; HRMS (ESI)$^+$ calcd. for $C_{23}H_{18}FN_4OS$ $[M+H]^+$: 417.1141 and found 417.1200.

4.1.2.13 2-(4-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] thiazole (5m)

Yield: 89 %, M.P.: 144-146 ^oC; White solid; ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.28 (s, 2H, OCH_2), 5.69 (s, 2H, N-CH_2), 7.06-8.06 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 51.29, 62.29, 115.37, 121.68, 123.01, 123.37, 125.02, 126.38, 127.12, 127.79, 129.29, 130.12, 132.39, 133.69, 135.03, 154.34, 160.61, 167.79; HRMS (ESI)$^+$ calcd. for $C_{23}H_{18}ClN_4OS$ $[M+H]^+$: 433.0812 and found 433.0893.

4.1.2.14 2-(4-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl) benzo[d] thiazole (5n)

Yield: 88 %, M.P.: 158-161 ^oC; White solid; ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.26 (s, 2H, OCH_2), 5.69 (s, 2H, N-CH_2), 7.07-8.06 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 51.74, 62.36, 115.42, 121.72, 123.07, 123.34, 125.06,

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126.42, 127.19, 127.84, 129.33, 130.17, 130.55, 130.63, 132.43, 133.74, 135.07, 154.38, 160.65, 167.84; HRMS (ESI)$^+$ calcd. for $C_{23}H_{18}ClN_4OS$ $[M+H]^+$: 433.0812 and found 433.0893.

4.1.2.15 2-(4-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] thiazole (5o)

Yield: 87 %, M.P.: 191-194 ^oC; White solid; ^1H NMR (300 MHz, $CDCl_3$) δ ppm = 5.26 (s, 2H, OCH_2), 5.48 (s, 2H, N-CH_2), 7.04-8.03 (m, 13H, merged signals, Ar-H and triazolyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 53.82, 62.37,115.43, 121.75, 122.86,123.11, 123.30, 125.10, 126.46, 127.27, 129.38, 129.93, 132.59, 133.60, 135.10, 154.41, 160.61, 167.82; HRMS (ESI)$^+$ calcd. for $C_{23}H_{18}BrN_4OS$ $[M+H]^+$: 477.0340 and found 477.0390.

4.1.2.16 2-(4-((4-(Benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-phenyl acetamide (5p)

Yield: 94 %, M.P.: 233-235 ^oC; White solid; ^1H NMR (300 MHz, DMSO-d_6) δ ppm = 5.31 (s, 2H, CH_2), 5.38 (s, 2H, OCH_2), 7.09-8.31 (m, 14H, merged signals, Ar-H and triazolyl-H), 10.48 (s, 1H, amido-NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm = 52.22, 61.29, 115.48, 119.20, 122.17, 122.47, 123.75, 125.10, 125.80, 126.48, 128.85, 128.88, 134.24, 138.37, 142.05, 153.65, 160.55, 164.12, 166.96; HRMS (ESI)$^+$ calcd. for $C_{24}H_{20}N_5O_2S$ $[M+H]^+$: 442.1293 and found 442.1340.

4.1.2.17 2-(4-((4-(Benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-(3-chlorophenyl)acetamide (5q)

Yield: 88 %, M.P.: 209-211 ^oC; White solid; ^1H NMR (300 MHz, DMSO-d_6) δ ppm = 5.34 (s, 2H, CH_2), 5.43 (s, 2H, OCH_2), 7.17-8.35 (m, 13H, merged signals, Ar-H and triazolyl-H), 10.74 (s, 1H, amido-NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm = 52.60, 61.66, 115.89, 118.02,119.11, 122.61, 122.89, 123.92, 125.53, 126.19, 126.91, 129.26, 131.06, 133.58, 134.64, 140.19, 142.48, 154.06, 160.96, 165.04, 167.37; HRMS (ESI)$^+$ calcd. for $C_{24}H_{19}ClN_5O_2S$ $[M+H]^+$: 476.0903 and found 476.0938.

4.1.2.18 2-(4-((4-(Benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-(4-chlorophenyl)acetamide (5r)

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Yield: 92 %, M.P.: 220-222 °C; White solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm = 5.31 (s, 2H, CH_2), 5.38 (s, 2H, OCH_2), 7.24-8.32 (m, 13H, merged signals, Ar-H and triazolyl-H), 10.65 (s, 1H, amido-NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm = 52.72, 61.78, 116.01, 121.28, 122.74, 123.04, 126.31, 126.44, 127.04, 127.67, 127.67, 129.37, 132.09, 134.77, 137.86, 142.60, 154.17, 161.07, 164.89, 167.50; HRMS (ESI)$^+$calcd. for $C_{24}H_{19}ClN_5O_2S$ $[M+H]^+$: 476.0903 and found 476.0935.

4.1.2.19 2-(4-((4-(Benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-(m-tolyl)acetamide (5s)

Yield: 87 %, M.P.: 204-206 °C; White solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm = 2.30 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 5.38 (s, 2H, OCH_2) 6.91-8.38 (m, 13H, merged signals, Ar-H and triazolyl-H), 10.46 (s, 1H, amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 21.89, 52.76, 61.80, 116.03, 116.91, 120.27, 122.76, 123.04, 125.01, 125.68, 126.32, 127.06, 129.49, 129.41, 134.78, 136.67, 136.85, 138.30, 142.56, 154.19, 161.10, 164.62, 167.52; HRMS (ESI)$^+$ calcd. for $C_{25}H_{22}N_5O_2S$ $[M+H]^+$: 456.1450 and found 456.1481.

4.1.2.20 2-(4-((4-(Benzo[d]thiazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-*N*-(p-tolyl)acetamide (5t)

Yield: 92 %, M.P.: 240-243 °C; White solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm = 2.28 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 5.37 (s, 2H, OCH_2), 7.14-8.34 (m, 13H, merged signals, Ar-H and triazolyl-H), 10.45 (s, 1H, amido-NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm = 20.80, 52.55, 61.62, 115.85, 119.55, 122.58, 122.86, 125.50, 126.14, 126.88, 129.23, 129.65, 133.10, 134.61, 136.24, 138.87, 142.38, 154.01, 160.92, 164.25, 167.34; HRMS (ESI)$^+$ calcd. for $C_{25}H_{22}N_5O_2S$ $[M+H]^+$: 456.1450 and found 456.1482.

4.2. Biological

4.2.1 Cell culture growth conditions

The breast cancer cells MCF-7 procured from cell repository, NCCS, Pune (India). The MCF-7 cells were maintained in Glutamax DMEM, (Life technologies Inc. USA); containing 10% v/v heat-inactivated FBS (Life technologies Inc. USA) and 0.01 mg/mL Insulin. The cells when achieved 70%-85% confluence at 37 °C and 5% CO_2 incubator were passaged in a sub cultivation ratio 1:3 to 1:5. The confluent cells were trypsinised with 1X

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Trypsin-EDTA solution (Life technologies Inc. USA), counted and aliquoted at the desired density for growth assays.

4.2.2 Determinations of IC_{50}

A serial dilution of newly synthesized compounds (**5a-t**) was prepared in DMSO. The compounds were added into the 24 h grown MCF-7 cells in RPMI 1640 with FBS (10 % v/v). The seeding density for cell line were $>5\times10^3$ cell per well/200 mL of medium. The cell lines were incubated for 24 h. The IC_{50} was determined by using EIA scan at 490 nm. The inhibitory concentration (Ic_{50}) was determined by addition of the compound in 24 h grown cells. It explains the MIC of compounds determined by using the MTT formation of compounds.

4.2.3 CellTiter 96 aqueous one solution cell proliferation assay

Assays are performed by adding a small amount of MTT reagent directly to culture wells, incubating for 2h and recording absorbance at 490 nm with a 96-well plate reader. The quantity of formazan product was measured at 490 nm absorbance which directly proportional to the number of living cells in culture. The cells were exposed to compounds at secondary density >5000 cell /100 mL /well in 24 well plates. 20 µL of MTT Reagent was added into each well of the 96-well assay plate containing the cells with compounds in 100 µL of culture medium. The plate incubated at 37°C for 2 h in a humidified, 5 % (w/v) CO_2 atmosphere. The absorbance recorded at 490 nm using a 96-well plate reader.

4.2.4 Antimicrobial activity determination

To determine the antimicrobial activities of each compound, the disk diffusion method was utilized.[64] Using cultures of *E. coli* strains; bacterial species were cultured on nutrient agar media. Inoculums suspension (100 CFU per microliter) was prepared from microorganism in broth media, nutrient broth inoculated with bacterial species was incubated for 24 h at 37 °C. After incubation, the culture tubes were exposed to the compounds at different concentrations zero to 50 microgram/mL. The optical density was observed at 540 nm after 24 h. The dose dependent growth was analysed by using GraphPad Prism 7.

Conflict of Interest

The authors declare no conflict of interest.

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A Table of Contents Entry

Copper Fluorapatite assisted synthesis of new 1,2,3-triazoles bearing benzothiazolyl moiety and their antibacterial and anticancer activities

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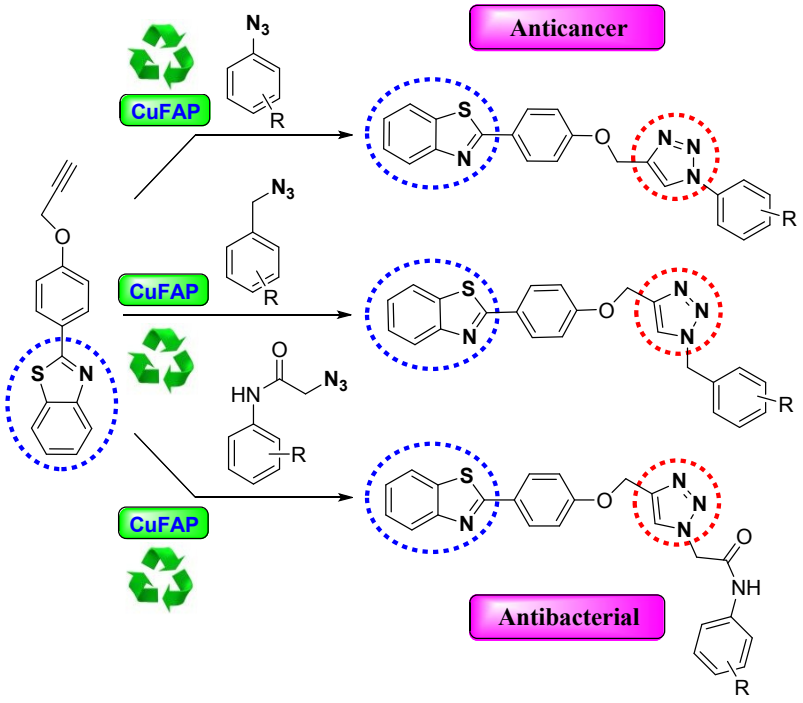

New 1,2,3-triazoles with benzothiazolyl scaffold have been first time synthesized using Copper Fluorapatite as a catalyst and their antibacterial and anticancer activities are reported.

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