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Synthesis of novel fluoro 1,2,3-triazole tagged amino bis(benzothiazole) derivatives, their antimicrobial and anticancer activity

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Abstract A new series of fluoro 1,2,3-triazole tagged amino bis (benzothiazole) derivatives **8**, **9** were prepared starting from 2-amino benzothiazole in four steps via amination, cyclization, alkylation followed by reaction with various azides under sharpless conditions through click chemistry approach. All newly synthesized compounds were screened for their antimicrobial and cytotoxic activity against four human cancer cell lines (U937, THP-1, Colo205, and A549), and promising compounds have been identified.

Keywords Amino bis (benzothiazole) ·
2-amino benzothiazole · Sharpless conditions ·
Antibacterial activity · Antifungal activity ·
Anticancer activity

Introduction

Fluorinated organic molecules often exhibit remarkable physical and biological properties which originate from C–F bond and with a wide range of applications, notably as

refrigerants (Sekiya and Misaki, 2000), pharmaceuticals (Rowley *et al.*, 2001; Isanbor and OHagan, 2006), agrochemicals (Hewitt and Silvester, 1988), polymers (Dear and Gilbert, 1974), blowing agents (Takada *et al.*, 1999), lubricants, artificial blood substitutes (Maichiodi *et al.*, 1998), etc. The introduction of fluorine into a specific position of bioactive compounds such as pharmaceutical or agrochemical may remarkably reduce the toxicity, improve the pharmacokinetics of the compounds, and improve the overall efficiency. Around 20 % of all licensed pharmaceutical products over the last 50 years contain a fluorine atom. In the recent past, it was found that fluorine is a substitute of distinctive qualities and one of the most lipophilic functional groups known provides an extremely useful way of making a molecule more easily delivered to the active site in the body. Since there are very few naturally occurring fluorine-containing compounds, and being a great demand for fluorinated chemicals all over the world, it is necessary to synthesize fluorinated organic compounds.

The presence of the benzothiazole nucleus of compounds aimed at evaluating new products that possess interesting biological activity. The 2-substituted benzothiazole has emerged in its usage as a core structure in the diversified therapeutic application. The structure–activity relationship studies interestingly reveal that change in the structure of substituent at C-2 position enhances the biological activities. Among those, 2-substituted benzothiazole derivatives with fluorine have received considerable attention due to their potential bioactivities (Ge *et al.*, 2007). Most of the benzothiazole derivatives were reported for their diversified activity viz., anti-tumor, anti-tubercular, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antifungal, a topical carbonic anhydrase inhibitor, and an anti-hypoxic (Hutchinson *et al.*, 2003; Yoshida *et al.*, 2005; Latrofa *et al.*, 2005;

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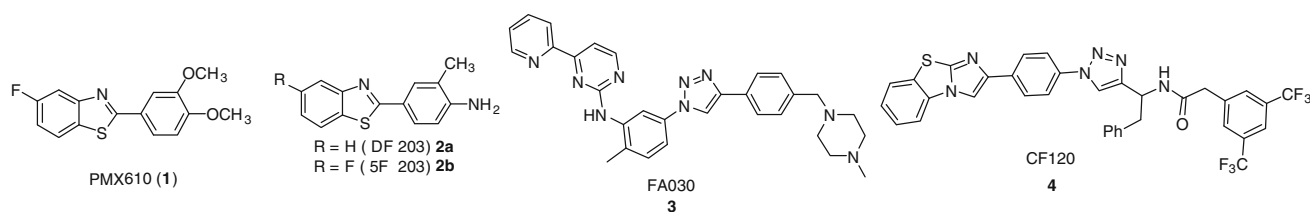


Fig. 1 Structure of fluorinated benzothiazole and triazoles derivatives

Caryolle and Loiseau 1990). Some of the structurally related benzothiazoles such as 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610) (Mortimer *et al.*, 2006; Aiello *et al.*, 2008) **1** (Fig. 1), 2-(4-amino-3-methylphenyl) benzothiazole (DF 203), and the 2-(4-amino-3-methylphenyl)-5-fluoro benzothiazole (5F 203) (Loaiza-Perez *et al.*, 2002; Trapani *et al.*, 2003; Leong *et al.*, 2004) (**2a** and **2b** of Fig. 1) have been reported to possess potent in vitro anti-tumor properties in human cancer cell lines, particularly against colon, non-small cell lung, and breast cancer lines of the National Cancer Institute (NCI) 60 human cancer cell line screen. Especially interesting are bis-benzothiazole derivatives which exhibit their importance in amyloid-imaging (Wu *et al.*, 2007), vulcanization accelerators (Monsanto 1968), and starting materials for various pharmaceutical industries (Papenfus and Theodor, 1983; Bondock *et al.*, 2009). *N*-Heterocyclic compounds such as [1,2,3]-triazoles may display biological activities, and there are several examples in the literature including antibacterial (Genin *et al.*, 2000), antifungal (Nilkanth *et al.*, 2009), antiallergic (Buckle and Rockell, 1982; Buckle *et al.*, 1983, 1986), anti-HIV (Alvarez *et al.*, 1994), anticonvulsant (Kelley *et al.*, 1995), β -lactamase inhibitory (Micetich *et al.*, 1987), and selective β_3 adrenergic receptor agonism (Brockunier *et al.*, 2000).

It is quite evident that the favorable properties of 1,2,3-triazole ring-like moderate dipole character, hydrogen bonding capability, rigidity, and stability under in vivo conditions are responsible for their enhanced biological activities. In recent years, several attempts were made for modifying the triazole nucleus to improve their biological activity. Modifications on the triazole nucleus have resulted in a large number of compounds having diverse pharmacological activities. Among them, triazole derivatives such as (phenyl)pyrimidine-2-amine scaffold **3** which have importance for their in vitro potential use as inhibitor of breakpoint cluster region (Bcr)-Abel-son kinase (Abl) (Arioli *et al.*, 2011; Peruzzotti *et al.*, 2013). Similarly, fluorinated triazole such as Triflorcas analog, having 1,2,3-triazole as a linkage of imidazo[2,1-b]benzothiazole-2-ylphenyl and phenyl-*N*-phenetyl acetamide moieties **4**, inhibits the HGF-induced

scattering of MDCK (epithelial cells) and in vitro tumorigenesis of H1437 (non-small-cell lung cancer) and GTL-16 (human gastric carcinoma) (Colombo *et al.*, 2012). In continuation of our efforts on the design of novel anticancer and antibacterial agents and keeping in mind the medicinal importance of benzothiazole moiety (Kumbhare and Nagragu 2011; Kumbhare *et al.*, 2011;2012), we have synthesized some new derivatives of novel fluoro 1,2,3-triazole tagged amino bis(benzothiazole) molecules and evaluated for antimicrobial and anticancer properties. Representatives of some biologically important fluorinated triazole compounds have been illustrated in Fig. 1.

Results and discussion

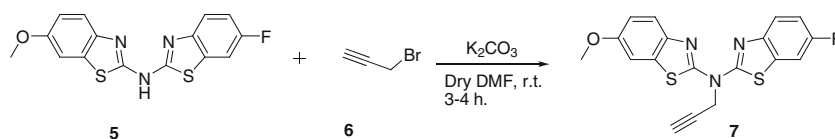
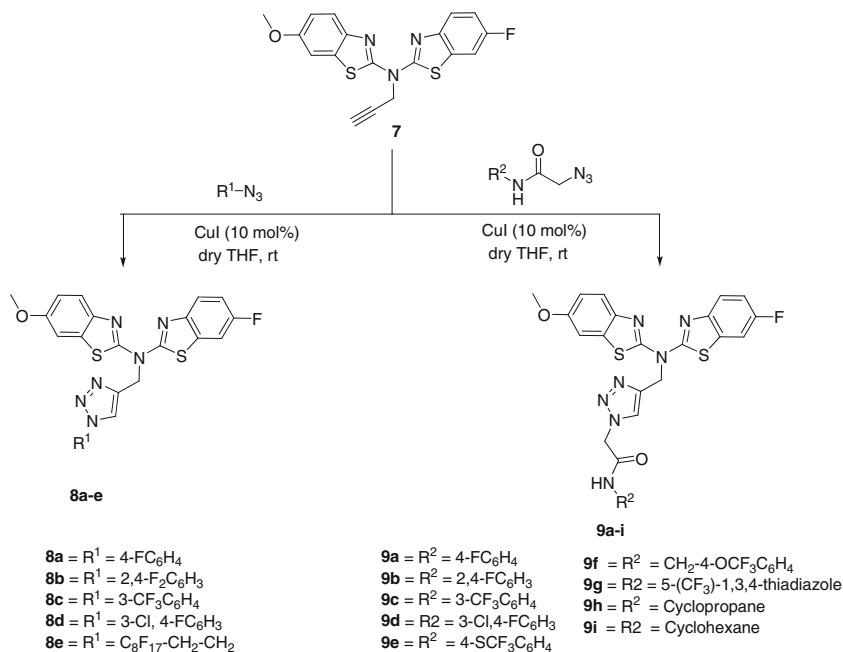
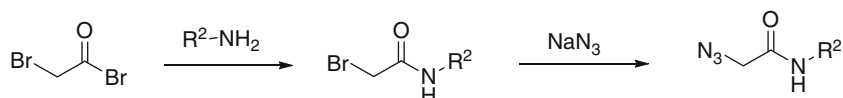
Chemistry

We first synthesized the compound **5** as our previous reported method (Kumbhare *et al.*, 2012). Compound **5** was further reacted with propargyl bromide in *N,N*-dimethyl formamide using potassium carbonate as a base resulted in the formation of *N*-propargylated 6-fluoro-*N*-6-methoxy-*N*-bis-benzothiazole **7**. The sequence of reactions outlined in Scheme 1.

Compound **7** was reacted with various fluorinated aromatic, aliphatic azides in THF, using Cu (I)-catalysed [3+2] azide-alkyne cycloaddition reaction through click chemistry under Sharpless conditions (Tornøe *et al.*, 2002; Himo *et al.*, 2005), as a result an exclusive formation of 1,4-disubstituted-1,2,3-triazole tagged amino bis(benzothiazole) derivatives **8**, **9** are formed. The details of reaction outlined in Scheme 2.

The azide-containing building blocks were synthesized in a one-pot procedure Scheme 3 in which different amines were reacted with the bromoacetyl bromide in *N,N*-dimethyl formamide followed by S_N2 reaction with sodium azide to generate the corresponding azides.

Several new triazole tagged bis-benzothiazole derivatives **8a–e** and **9a–i** were synthesized and screened for antimicrobial and anticancer activities.

Scheme 1 Synthesis of *N*-propargylated amino bis (benzothiazole)**Scheme 2** Synthesis of 1,2,3-triazole tagged amino bis(benzothiazole) derivatives**Scheme 3** Synthesis of azide-tagged diversity elements

Pharmacology

Antibacterial activity

The minimum inhibitory concentrations (MIC) of various synthetic compounds were screened against three representative gram-positive microorganisms, viz. *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 96); and gram-negative organisms, viz. *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741), and *Klebsiella pneumoniae* (MTCC 618). The assays were performed by broth dilution techniques according to the National Committee for Clinical Laboratory (2000) standards. Standard antibacterial agents such as penicillin and streptomycin were also screened under identical conditions for comparison. The minimum inhibitory concentration (MIC) values are presented in Table 1.

These results clearly indicate that compounds **8a–e** and **9a–i** displayed significant activity with a high degree of variation. The results demonstrated that the compounds **8e** and **9g** showed substantial activity against all the bacterial

strains. Moderate activity was shown by the compounds **8c**, **9c**, and **9f** against the entire tested organism. Compounds **8d**, **9a**, **9b**, **9d**, and **9e** showed some activity against few bacterial strains. Compounds **9h** and **9i** were showed similar activity against all tested strains except for *K. pneumoniae*. The compounds **8a** and **8b** have not been shown any notable activity compared to other compounds.

Antifungal activity

In vitro antifungal activity of the newly synthesized compounds were studied against the fungal strains, *Candida albicans* (MTCC 227), *Candida rugosa* (NCIM 3462), *Saccharomyces cerevisiae* (MTCC 36), *Rhizopus oryzae* (MTCC 262), and *Aspergillus niger* (MTCC 282) by Agar Well Diffusion Method (2). The ready-made Potato Dextrose Agar (PDA) medium (Hi-media, 39 g) was suspended in distilled water (1,000 ml) and heated to boil until it dissolved completely; the medium and Petri dishes were autoclaved at pressure of 15 lb/inc (Linday 1962) for

Table 1 Antibacterial activity of compounds **8a–e** and **9a–i**

| Compd code | MIC (μ M) | | | | | |
|---------------------------|--------------------|------------------|-----------------------|----------------|----------------------|----------------------|
| | <i>B. subtilis</i> | <i>S. aureus</i> | <i>S. epidermidis</i> | <i>E. coli</i> | <i>P. aeruginosa</i> | <i>K. pneumoniae</i> |
| 8a | 148.22 | 74.11 | 296.44 | 74.11 | 296.44 | 148.22 |
| 8b | 71.56 | 286.26 | 143.13 | 286.26 | 71.56 | 286.26 |
| 8c | 67.45 | 134.89 | 33.723 | 67.45 | 134.89 | 16.85 |
| 8d | 277.26 | 34.66 | 138.633 | 69.32 | 17.32 | 34.66 |
| 8e | 5.454 | 2.73 | 5.4543 | 10.92 | 2.73 | 10.92 |
| 9a | 66.61 | 16.64 | 133.213 | 33.30 | 33.30 | 16.64 |
| 9b | 8.05 | 129.09 | 32.273 | 16.12 | 129.08 | 32.27 |
| 9c | 15.28 | 30.58 | 61.173 | 30.58 | 122.35 | 15.28 |
| 9d | 31.35 | 15.67 | 15.673 | 31.35 | 15.67 | 7.83 |
| 9e | 14.53 | 29.07 | 58.14 | 29.07 | 58.14 | 14.53 |
| 9f | 29.16 | 14.57 | 14.57 | 58.32 | 29.16 | 14.57 |
| 9g | 15.09 | 3.77 | 3.768 | 15.08 | 7.54 | 15.09 |
| 9h | 36.84 | 18.41 | 18.41 | 73.67 | 36.84 | 147.35 |
| 9i | 34.03 | 17.01 | 17.01 | 68.06 | 34.03 | 272.23 |
| ^a Penicillin | 4.67 | 4.67 | 9.35 | 37.38 | 37.38 | 18.69 |
| ^a Streptomycin | 10.75 | 10.75 | 5.37 | 10.75 | 2.68 | 5.37 |

MIC values are given in (μ M) = Minimum inhibitory concentration, i.e. the lowest concentration of drug which completely inhibit bacterial growth

^a Penicillin and Streptomycin with 98 % purity were used as positive control drugs

Table 2 Antifungal activity of compounds **8a–e** and **9a–i**

| Zone of Inhibition (mm) | | | | | | | | | | |
|----------------------------|------------------|-------------|-----------------|-------------|------------------|-------------|--------------------|-------------|----------------------|-------------|
| Compd code | <i>R. oryzae</i> | | <i>A. niger</i> | | <i>C. rugosa</i> | | <i>C. albicans</i> | | <i>S. cerevisiae</i> | |
| | 10 μ M | 300 μ M | 10 μ M | 300 μ M | 10 μ M | 300 μ M | 10 μ M | 300 μ M | 10 μ M | 300 μ M |
| 8a | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8b | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 6 | 0 | 0 |
| 8c | 7 | 10 | 8 | 12 | 6 | 8 | 6 | 9 | 0 | 6 |
| 8d | 0 | 0 | 6 | 9 | 0 | 6 | 0 | 0 | 0 | 6 |
| 8e | 16 | 20 | 14 | 19 | 14 | 19 | 16 | 20 | 14 | 20 |
| 9a | 9 | 14 | 11 | 16 | 0 | 0 | 9 | 14 | 10 | 14 |
| 9b | 10 | 14 | 10 | 14 | 0 | 0 | 9 | 12 | 9 | 14 |
| 9c | 11 | 16 | 0 | 6 | 10 | 14 | 9 | 14 | 13 | 16 |
| 9d | 13 | 16 | 0 | 6 | 10 | 14 | 13 | 16 | 11 | 16 |
| 9e | 14 | 20 | 13 | 19 | 11 | 16 | 10 | 14 | 9 | 14 |
| 9f | 11 | 16 | 13 | 16 | 13 | 19 | 9 | 12 | 10 | 14 |
| 9g | 14 | 20 | 16 | 21 | 13 | 19 | 16 | 21 | 14 | 19 |
| 9h | 9 | 14 | 10 | 14 | 0 | 6 | 9 | 14 | 13 | 16 |
| 9i | 13 | 19 | 14 | 20 | 11 | 16 | 10 | 14 | 13 | 16 |
| ^a Ampotericin B | 24 | | 25 | | 22 | | 23.5 | | 22 | |

MIC values are given in (μ g/ml) = Minimum inhibitory concentration, i.e. the lowest concentration of drug which completely inhibit fungal growth

^a Ampotericin B, 80 % was used as a positive control drug

20 min. Agar well bioassay was employed for testing antifungal activity, and the results are shown in Table 2.

The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber. When the medium in the plates solidified, 0.5 ml of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO, and different concentrations were made. After inoculation, wells were scooped out with 6 mm sterile cork borer, and the lids of the dishes were replaced. To each well, different concentrations of test solutions were added. Controls were maintained. The treated and the controls were kept at 27 °C for 48 h. Inhibition zones were measured, and the diameter was calculated in millimeter (mm). Three to four replicates were maintained for each treatment.

The antifungal screening data of compounds **8a–8e** and **9a–9i** revealed that the entire tested compounds showed moderate to good antifungal activities against the tested fungal strains. The compounds **8e** and **9g** showed better antifungal activity against all fungal strains. The compounds **8c**, **9c**, **9d**, **9e**, and **9f** displayed antifungal activity except on *A. niger*. Compounds **9a**, **9b**, **9h**, and **9i** exhibited almost similar activity. The compounds **8a**, **8b**, and **8d** show no activity against all tested strains.

Cytotoxic activity

The fluoro 1,2,3-triazole tagged amino bis-(benzothiazole) derivatives were evaluated by MTT assay (Mosmann, 1983) to investigate their antiproliferative/cytotoxic activities in four different types of human cancer cell lines such

as leukemia (U937, THP-1), colon and lung cancer cell lines (Colo205 and A549, respectively). It is evident from the results that these derivatives are not active on Colo205 and A549 cell lines at 200 µM concentration. However, partial derivatives (3 out of 14) exhibited antiproliferative activity.

Against U937, the highest activity ($IC_{50} = 61.99 \mu M$) is observed in **9b** followed by **9a** and **9h** with IC_{50} values of 93.76 and 191.39 µM, respectively. Nonetheless, only one derivative **9a** exhibited activity ($IC_{50} = 108.97 \mu M$) against THP1 cell line (Table 3). Remaining other derivatives are not active at 200 µM concentration. The differential activity of active derivatives among the cell lines may be due to the structure–activity relationship of the molecules.

Conclusion

A series of novel 1,2,3-triazole tagged amino bis(benzothiazole) derivatives **8** and **9** have been synthesized through a facile strategy and screened for antimicrobial and anti-cancer (cytotoxic) activity. The results of antibacterial screening reveal that compounds **8e** and **9g** showed good inhibition toward all the bacteria and fungi tested. Comparison with the IC_{50} values of positive control (Etoposide) indicated that the U937 cells are more sensitive than the other three (THP1, Colo205, and A549) cell lines. The order of sensitivity of human cancer cell lines toward fluoro triazole tagged bis-(benzothiazole) derivatives is U937 > THP-1. Among the derivatives, **9a** has exhibited a good cytotoxic activity against the U937 and THP-1 cell

Table 3 In vitro Cytotoxicity of fluoro 1,2,3-triazole tagged amino bis (benzothiazole) derivatives against U937, THP-1, COLO205, and A549 human cancer cells by MTT assay

| Compounds | ^a IC_{50} (µM) | | | |
|------------------------|-----------------------------|--------------|-------------|--------------|
| | U937 | THP1 | Colo205 | A549 |
| 9a | 93.76 ± 0.26 | 108.97 ± 3.3 | – | – |
| 9b | 61.99 ± 2.68 | – | – | – |
| 9h | 191.39 ± 2.42 | – | – | – |
| ^b Etoposide | 10.43 ± 2.02 | 3.67 ± 0.25 | 0.42 ± 0.22 | 18.19 ± 2.14 |

The values represent the mean ± SE of three individual observations

Exponentially growing cells were treated with different concentrations of benzothiazole derivatives for 48 h and cell growth inhibition was analyzed through MTT assay

^a IC_{50} is defined as the concentration, which results in a 50 % decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis

^b Etoposide, 98 % was employed as positive control. Among the derivatives eleven compounds (**8a**, **8b**, **8c**, **8d**, **8e**, **9c**, **9d**, **9e**, **9f**, **9g**, and **9i**) did not possess any cytotoxic activity at 200 µM concentration against four human cancer cell lines were used

Calculated the IC_{50} value by plotting, logarithm-transformed concentration–response versus percent growth inhibition, and fitted the data with a straight line. IC_{50} value is then estimated using the formula of fitted line, i.e., $Y_{scale}(50) = A + B \times X_{scale}(X)$. [A = intercept; B = slope]. $IC_{50} = \text{antilogarithm of } 50 - A/B$

lines. However, most of the derivatives are comparatively less potent than the commercially available drug molecule; nevertheless, slight structural modification of these active derivatives may yield as prospective anticancer drugs. Based on the present results, it is warranted that these derivatives to be further evaluated on other cancer cell lines.

Experimental

Materials and methods

All chemicals and reagents were purchased from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA), or Spectrochem Pvt. Ltd (Mumbai, India) with 80–98 % purity and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^1H , ^{13}C , and ^{19}F spectra were recorded Bruker UX-NMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm down field from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected. The purities of all of the compounds (>95 %) used for biological screening were determined by analytical HPLC (SPD-M20A, make: Shimadzu) using an ODS column eluted with a gradient mixture of acetonitrile–water.

General procedures

Preparation of N-propargyl-6-fluoro-N-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine (7)

6-fluoro-*N*-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine **5** (3.0 mmol) was dissolved in dry *N,N*-dimethyl formamide (10 ml), and K_2CO_3 (6.0 mmol) was added and the reaction mixture was stirred for 15 min at room temperature. The propargyl bromide **6** (3.6 mmol) was slowly added drop wise to the above mixture over a period of 15 min and continued stirring for 4 h. The reaction was quenched with water and extracted with EtOAc (3×20 ml). The combined extracts were washed with water (3×25 ml) and brine (20 ml). The organic layer was dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. Purification by silica gel chromatography

(5 % ethyl acetate in hexane) gave the desired product in 95 % isolated yield.

Synthesis of azide-tagged diversity elements

Commercially available amines (20 mmol) were dissolved in dry DMF (40 ml) under nitrogen. To this solution, Et_3N (20 mmol) was added and bromoacetyl bromide (20 mmol) via syringe at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min and then at room temperature for another 2 h. Next, solid NaN_3 (30 mmol) was added, and the reaction mixture was stirred overnight. The mixture was poured into water (100 ml) and extracted with EtOAc (3×100 ml). The combined extracts were washed with water (3×50 ml) and brine (50 ml). The organic layer was dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. Silica gel flash chromatography (10 % ethyl acetate in hexane) gave the desired azide product in 70–90 % isolated yield.

Synthesis of triazole derivatives of 6-fluoro-N-(6-methoxybenzo[d]thiazol-2-yl) benzo[d]thiazol-2-amine (8 and 9)

The propargylated 6-fluoro-*N*-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine **7** (0.27 mmol) was dissolved in dry THF (5 ml), and catalytic amount of CuI was added. Then, azides (0.27 mmol) in dry THF were slowly added at room temperature under nitrogen atmosphere and continued stirring for 24 h. The solvent was removed under reduced pressure; the residue was diluted with distilled water and extracted with EtOAc (3×15 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to get the product. The crude product was purified by column chromatography gave the desired product 85–96 % isolated yield.

6-fluoro-*N*-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine (**8a**) Yield 85 %; m.p. 158–160 °C. IR (KBr, ν_{max} cm^{-1}): 2,932, 1,515, 1,458, 1,263, 1,237, 1,046, 838, 805; ^1H NMR (CDCl_3 , 300 MHz): δ 3.95 (s, 3H, $-\text{OCH}_3$), 5.75 (s, 2H, $-\text{NCH}_2$), 7.02 (d, 1H, $J = 8.687$ Hz), 7.08–7.33 (m, 4H, Ar-H), 7.41–7.51 (m, 1H, Ar-H), 7.58–7.86 (m, 4H, Ar-H), 8.03 (s, 1H, Triazole-H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 47.24 ($\text{N}-\text{CH}_2$), 57.08 (OCH_3), 104.38, 107.45, 109.48, 111.25 ($\text{CH}-\text{Triazole}$), 114.85, 116.61, 116.70, 118.84, 119.92, 121.46, 122.61, 129.67, 131.14, 133.03, 133.30, 146.13, 152.38, 156.53, 160.43 (d, $J = 251.60$ Hz, $\text{BT}-\text{C}-\text{F}$), 161.864 (d, $J = 247.04$ Hz, $\text{Ph}-\text{C}-\text{F}$); ^{19}F NMR (CDCl_3 , 400 MHz): δ -112.01 to -112.43 (m, 1F), -118.17 to -118.89 (m, 1F); ESI-MS: 507 ($\text{M}+1$) $^+$; Anal. calcd. For $\text{C}_{24}\text{H}_{16}\text{F}_2\text{N}_6\text{O}_2$: C 56.91, H 3.18, N 16.59 %. Found: C 56.95, H 3.17, N 16.60 %.

N-((1-(2,4-difluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6-fluoro-*N*-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine (**8b**) Yield 89 %; m.p. 214–216 °C. IR (KBr, ν_{\max} cm⁻¹): 2,933, 1,536, 1,462, 1,328, 1,269, 1,254, 1,051, 842, 809; ¹H NMR (CDCl₃, 300 MHz): δ 3.89 (s, 3H, -OCH₃), 5.71 (s, 2H, -NCH₂), 6.89–7.03 (m, 4H, Ar-H), 7.10 (dt, 1H, *J* = 8.545 and 1.709 Hz, -Ar-H), 7.41 (s, 1H, Ar-H), 7.66 (d, 1H, *J* = 8.545 Hz, Ar-H), 7.71–7.83 (m, 2H, Ar-H), 8.13 (s, 1H, Triazole-H); ¹³C NMR (CDCl₃, 75 MHz): δ 47.35 (N-CH₂), 57.62 (OCH₃), 107.65 (CH-Triazole), 109.42, 110.51 (t, *J* = 25.31 Hz, F-CH-F), 112.10, 115.10, 120.35, 124.10, 126.15, 127.35, 130.00, 131.18, 137.32, 147.10, 152.13, 156.23, 157.47 (d, *J* = 254.10 Hz, BT-C-F), 158.56 (d, *J* = 245.25 Hz, Ph-4C-F), 160.22 (d, *J* = 248.23 Hz, Ph-2C-F); ¹⁹F NMR (CDCl₃, 400 MHz): δ -106.83 to -106.95 (m, 1F), -117.58 to -117.69 (m, 1F), -118.48 (q, 1F, *J* = 9.426 Hz); ESI-MS: 525 (M+1)⁺; Anal. calcd. For C₂₄H₁₅F₃N₆OS₂: C 54.95, H 2.88, N 16.02 %. Found: C 55.00, H 2.86, N 16.03 %.

6-fluoro-*N*-(6-methoxybenzo[d]thiazol-2-yl)-*N*-((1-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzo[d]thiazol-2-amine (**8c**) Yield 83 %; m.p. 150–152 °C. IR (KBr, ν_{\max} cm⁻¹): 2,933, 1,534, 1,460, 1,324, 1,256, 1,174, 1,127, 1,043, 850, 802; ¹H NMR (CDCl₃, 300 MHz): δ 3.85 (s, 3H, -OCH₃), 5.67 (s, 2H, -NCH₂), 6.84–6.97 (m, 1H, Ar-H), 6.99–7.12 (m, 1H, Ar-H), 7.14–7.29 (m, 1H, Ar-H), 7.35 (dt, 1H, *J* = 6.043 and 2.266 Hz, Ar-H), 7.46–7.83 (m, 5H, Ar-H), 7.87 (s, 1H, Ar-H), 8.07 (s, 1H, Triazole-H); ¹³C NMR (CDCl₃, 75 MHz): δ 47.15 (N-CH₂), 57.05 (OCH₃), 107.33, 109.50, 111.26 (CH-Triazole), 112.31, 114.86, 117.60, 119.95, 121.46, 123.16 (q, *J* = 273.37 Hz, -CF₃), 123.68, 125.46, 130.43, 130.55, 132.3, 133.21, 133.32, 145.15, 146.23, 152.60, 156.54, 157.32 (d, *J* = 251.60 Hz, BT-C-F); ¹⁹F NMR (CDCl₃, 400 MHz): δ -63.35 (s, 3F), -118.15 to -118.57 (m, 1F); ESI-MS: 557 (M+1)⁺; Anal. Calcd. For C₂₅H₁₆F₄N₆OS₂: C 53.95, H 2.90, N 15.10 %. Found: C 53.99, H 2.92, N 15.11 %.

N-((1-(3-chloro-4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6-fluoro-*N*-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine (**8d**) Yield 88 %; m.p. 217–219 °C. IR (KBr, ν_{\max} cm⁻¹): 2,930, 1,511, 1,457, 1,259, 1,050, 852, 804; ¹H NMR (CDCl₃, 300 MHz): δ 3.95 (s, 3H, -OCH₃), 5.77 (s, 2H, -NCH₂), 7.08–7.25 (m, 2H, Ar-H), 7.37–7.45 (m, 1H, Ar-H), 7.50–7.90 (m, 4H, Ar-H), 7.98 (s, 1H, Ar-H), 8.03–8.09 (m, 1H, Ar-H), 8.69 (s, 1H, Triazole-H); ¹³C NMR (CDCl₃, 75 MHz): δ 47.35 (N-CH₂), 57.07 (OCH₃), 107.25, 109.52, 111.35 (CH-Triazole), 112.41, 115.15, 118.43, 119.52, 120.01, 120.13, 125.56, 131.50, 132.90, 133.51, 142.31, 146.53, 153.52 (d, *J* = 245.60 Hz, Ph-C-

F), 156.92, 158.10 (d, *J* = 247.15 Hz, BT-C-F), 169.93; ¹⁹F NMR (CDCl₃, 400 MHz): δ -114.63 (s, 1F), -117.56 to -118.85 (m, 1F); ESI-MS: 542 (M+1)⁺; Anal. Calcd. For C₂₄H₁₅ClF₂N₆OS₂: C 53.28, H 2.79, N 15.53 %. Found: C 53.27, H 2.81, N 15.55 %.

6-fluoro-*N*-((1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-hepta-decafluorodecyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]thiazol-2-amine (**8e**) Yield 90 %; m.p. 164–166 °C. IR (KBr, ν_{\max} cm⁻¹): 2,938, 1,538, 1,503, 1,462, 1,205, 1,146, 1,052, 809, 651; ¹H NMR (CDCl₃+DMSO, 300 MHz): δ 2.72–2.86 (m, 2H, -CH₂-CF₂), 3.96 (s, 3H, -OCH₃), 4.59 (t, 2H, *J* = 7.919 Hz, -CH₂-), 5.69 (s, 2H, -NCH₂), 7.02–7.08 (m, 1H, Ar-H), 7.13–7.19 (m, 1H, Ar-H), 7.44–7.50 (m, 1H, Ar-H), 7.68–7.77 (m, 3H, Ar-H), 7.78–7.83 (m, 1H, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 31.68 (N-CH₂-CH₂), 42.43 (N-CH₂-CH₂), 47.12 (N-CH₂), 57.06 (OCH₃), 107.23, 109.12, 113.92 (CH-Triazole), 112.63, 114.76, 116.94, 119.10, 120.00, 122.10, 122.93, 124.31, 125.03, 125.87, 126.10, 127.93, 132.76, 133.32, 133.67, 145.93, 150.71, 157.10, 158.14 (d, *J* = 249.32 Hz, BT-C-F); ¹⁹F NMR (CDCl₃+DMSO, 400 MHz): δ -81.23 (t, 3F, *J* = 9.844 Hz), -114.43 to -114.69 (m, 2F), -118.24 to -118.68 (m, 1F), -121.95 to -122.55 (m, 6F), -123.20 (s, 2F, br), -123.89 (s, 2F, br), -126.58 (t, 2F, *J* = 12.305 Hz); ESI-MS: 859 (M+1)⁺; Anal. Calcd. For C₂₈H₁₆F₁₈N₆OS₂: C 39.17, H 1.88, N 9.79 %. Found: C 39.19, H 1.07, N 9.81 %.

2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl)acetamide (**9a**) Yield 92 %; m.p. 248–250 °C. IR (KBr, ν_{\max} cm⁻¹): 3,335, 2,941, 1,677, 1,536, 1,506, 1,460, 1,262, 1,221, 1,053, 837, 503; ¹H NMR (CDCl₃+DMSO, 300 MHz): δ 3.97 (s, 3H, -OCH₃), 5.20 (s, 2H, -CH₂-CO), 5.72 (s, 2H, -NCH₂), 6.89–7.24 (m, 4H, Ar-H), 7.48–7.62 (m, 3H, Ar-H), 7.64–7.85 (m, 3H, Ar-H), 8.05 (s, 1H, Triazole-H), 10.28 (s, 1H, NH); ¹³C NMR (CDCl₃, 75 MHz): δ 46.70 (N-CH₂), 52.02 (N-CH₂-C=O), 56.47 (OCH₃), 107.34, 111.00, 113.53 (CH-Triazole), 114.35, 115.43, 119.23, 120.00, 122.20, 125.22, 129.08, 130.07, 132.63, 138.52, 154.20 (d, *J* = 247.60 Hz, Ph-C-F), 158.06 (d, *J* = 246.50 Hz, BT-C-F), 160.33, 163.95 (C=O); ¹⁹F NMR (CDCl₃+DMSO, 400 MHz): δ -117.55 to -118.19 (m, 2F); ESI-MS: 564 (M+1)⁺; Anal. Calcd. For C₂₆H₁₉F₂N₇O₂S₂: C 55.41, H 3.40, N 17.40 %. Found: C 55.45, H 3.38, N 17.41 %.

N-(2,4-difluorophenyl)-2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**9b**) Yield 95 %; m.p. 213–215 °C. IR (KBr, ν_{\max} cm⁻¹): 3,263, 2,931, 1,677,

1,536, 1,460, 1,261, 1,229, 1,051, 849, 809; ^1H NMR ($\text{CDCl}_3 + \text{DMSO}$, 300 MHz): δ 3.97 (s, 3H, $-\text{OCH}_3$), 5.32 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.72 (s, 2H, $-\text{NCH}_2$), 6.77–6.96 (m, 2H, Ar-H), 6.99–7.24 (m, 2H, Ar-H), 7.53 (dd, 1H, $J = 8.120$ and 2.077 Hz, Ar-H), 7.62 (s, 1H, Ar-H), 7.67–7.86 (m, 2H, Ar-H), 7.91–8.05 (m, 1H, Ar-H), 8.12 (s, 1H, Triazole-H), 10.09 (s, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 46.50 ($\text{N}-\text{CH}_2$), 52.31 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 57.00 (OCH_3), 106.82 (t, $J = 26.35$ Hz, $\text{Ph}-\text{F}-\text{CH}-\text{F}$), 107.50, 111.14, 111.32, 113.92 ($\text{CH}-\text{Triazole}$), 114.61, 119.82, 120.32, 121.93, 125.31, 126.33, 130.34, 132.65, 149.53 (d, $J = 245.35$ Hz, $\text{Ph}-2\text{C}-\text{F}$), 157.63 (d, $J = 253.10$ Hz, $\text{BT}-\text{C}-\text{F}$), 160.31 (d, $J = 248.40$ Hz, $\text{Ph}-4\text{C}-\text{F}$), 163.15 ($\text{C}=\text{O}$); ^{19}F NMR ($\text{CDCl}_3 + \text{DMSO}$, 400 MHz): δ -113.98 to -114.13 (m, 1F), -117.54 to -118.83 (m, 1F), -121.17 (s, 1F, br.); ESI-MS: 582 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{26}\text{H}_{18}\text{F}_3\text{N}_7\text{O}_2\text{S}_2$: C 53.69, H 3.12, N 16.86 %. Found: C 53.72, H 3.09, N 16.87 %.

2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-trifluoromethyl)phenyl)acetamide (9c) Yield 91 %; m.p. 194–196 °C. IR (KBr, ν_{max} cm^{-1}): 3,264, 2,924, 1,683, 1,532, 1,457, 1,329, 1,259, 1,167, 1,120, 1,056, 851, 799; ^1H NMR ($\text{CDCl}_3 + \text{DMSO}$, 300 MHz): δ 3.94 (s, 3H, $-\text{OCH}_3$), 5.23 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.69 (s, 2H, $-\text{NCH}_2$), 6.88–7.25 (m, 2H, Ar-H), 7.29 (d, 1H, $J = 8.120$ Hz, Ar-H), 7.35–7.48 (m, 2H, Ar-H), 7.54 (d, 1H, $J = 7.743$ Hz, Ar-H), 7.60–7.85 (m, 3H, Ar-H), 7.94 (s, 1H, Ar-H), 8.07 (s, 1H, Triazole-H), 10.55 (s, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 46.41 ($\text{N}-\text{CH}_2$), 52.53 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 56.15 (OCH_3), 107.65, 111.45, 113.15 ($\text{CH}-\text{Triazole}$), 114.81, 117.93, 119.20, 120.00, 122.21, 121.34, 122.95 (q, $J = 252.32$ Hz, $-\text{CF}_3$), 127.30, 129.31, 131.63, 132.23, 134.32, 142.93, 157.63 (d, $J = 248.95$ Hz, $\text{BT}-\text{C}-\text{F}$), 160.70, 163.66 ($\text{C}=\text{O}$); ^{19}F NMR ($\text{CDCl}_3 + \text{DMSO}$, 400 MHz): δ -62.29 (s, 3F), -117.68 to -118.91 (m, 1F); ESI-MS: 614 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{27}\text{H}_{19}\text{F}_4\text{N}_7\text{O}_2\text{S}_2$: C 52.85, H 3.12, N 15.98 %. Found: C 52.89, H 3.10, N 15.96 %.

N-(3-chloro-4-fluorophenyl)-2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (9d) Yield 89 %; m.p. 224–226 °C. IR (KBr, ν_{max} cm^{-1}): 3,261, 2,924, 1,681, 1,537, 1,502, 1,460, 1,264, 1,228, 1,054, 854, 818; ^1H NMR ($\text{CDCl}_3 + \text{DMSO}$, 300 MHz): δ 3.85 (s, 3H, OCH_3), 5.21 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.71 (s, 2H, $-\text{NCH}_2$), 6.92–7.30 (m, 3H, Ar-H), 7.33–7.48 (m, 2H, Ar-H), 7.58–7.87 (m, 3H, Ar-H), 7.94 (s, 1H, Ar-H), 8.06 (s, 1H, Triazole-H), 10.45 (s, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 46.33 ($\text{N}-\text{CH}_2$), 52.43 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 56.71 (OCH_3), 107.75, 111.92, 114.10 ($\text{CH}-\text{Triazole}$), 114.93, 117.93, 119.40,

119.96, 121.10, 122.54, 124.11, 127.32, 131.65, 133.57, 141.24, 154.00 (d, $\nu_{246.93}$ Hz, $\text{Ph}-4\text{C}-\text{F}$), 157.15, 159.31 (d, $\nu_{251.90}$ Hz, $\text{BT}-\text{C}-\text{F}$), 165.34 ($\text{C}=\text{O}$); ^{19}F NMR ($\text{CDCl}_3 + \text{DMSO}$, 400 MHz): δ -117.70 to -118.93 (m, 1F), -120.77 (s, 1F); ESI-MS: 599 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{26}\text{H}_{18}\text{ClF}_2\text{N}_7\text{O}_2\text{S}_2$: C 52.22, H 3.03, N 16.39 %. Found: C 52.21, H 3.04, N 16.37 %.

2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-trifluoromethylthio)phenyl)acetamide (9e) Yield 94 %; m.p. 183–185 °C. IR (KBr, ν_{max} cm^{-1}): 3,336, 2,936, 1,690, 1,599, 1,536, 1,460, 1,261, 1,117, 834, 514; ^1H NMR ($\text{CDCl}_3 + \text{DMSO}$, 300 MHz): δ 3.83 (s, 3H, $-\text{OCH}_3$), 5.21 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.66 (s, 2H, $-\text{NCH}_2$), 6.88–7.82 (m, 10H, Ar-H), 8.02 (s, 1H, Triazole-H), 10.48 (s, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 46.60 ($\text{N}-\text{CH}_2$), 52.21 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 56.41 (OCH_3), 106.85, 110.93, 111.84, 113.33 ($\text{CH}-\text{Triazole}$), 114.11, 114.82, 117.60, 119.70, 120.75, 124.84, 125.75, 126.46 (q, $J = 245.93$ Hz, SCF_3), 127.63, 129.74, 132.60, 136.56, 140.22, 143.30, 151.80, 155.76, 158.72, 159.94 (d, $J = 283.36$ Hz, $\text{BT}-\text{C}-\text{F}$), 161.55, 163.42 ($\text{C}=\text{O}$); ^{19}F NMR ($\text{CDCl}_3 + \text{DMSO}$, 400 MHz): δ -41.58 (s, 3F), -117.15 to -118.83 (m, 1F); ESI-MS: 646 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{27}\text{H}_{19}\text{F}_4\text{N}_7\text{O}_2\text{S}_3$: C 50.22, H 2.97, N 15.19 %. Found: C 50.23, H 2.94, N 15.23 %.

2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-trifluoromethoxy)benzyl)acetamide (9f) Yield 92 %; m.p. 221–223 °C. IR (KBr, ν_{max} cm^{-1}): 3,279, 2,931, 1,665, 1,535, 1,461, 1,265, 1,219, 1,163, 1,048, 804; ^1H NMR ($\text{CDCl}_3 + \text{DMSO}$, 300 MHz): δ 3.84 (s, 3H, $-\text{OCH}_3$), 4.32 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.07 (s, 2H, Ar- CH_2), 5.68 (s, 2H, $-\text{NCH}_2$), 6.91–7.44 (m, 7H, Ar-H), 7.46–7.86 (m, 3H, Ar-H), 8.05 (s, 1H, Triazole-H), 8.73 (s, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 42.15 ($\text{NH}-\text{CH}_2$), 46.72 ($\text{N}-\text{CH}_2$), 52.39 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 56.43 (OCH_3), 107.13, 111.35, 112.93 ($\text{CH}-\text{Triazole}$), 114.73, 118.34, 119.55, 120.84, 122.00 (q, $J = 247.73$ Hz, OCF_3), 126.94, 129.53, 132.44, 133.83, 134.22, 149.93, 157.13 (d, $J = 256.34$ Hz, $\text{BT}-\text{C}-\text{F}$), 160.00, 164.11 ($\text{C}=\text{O}$); ^{19}F NMR ($\text{CDCl}_3 + \text{DMSO}$, 400 MHz): δ -56.98 (s, 3F), -117.12 to -118.80 (m, 1F); ESI-MS: 644 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{28}\text{H}_{21}\text{F}_4\text{N}_7\text{O}_3\text{S}_2$: C 52.25, H 3.29, N 15.23 %. Found: C 52.28, H 3.27, N 15.24 %.

2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(5-trifluoromethyl)-1,3,4-thiadiazol-2-yl)acetamide (9g) Yield 96 %; m.p. 218–220 °C. IR (KBr, ν_{max} cm^{-1}): 3,158, 2,941, 1,710, 1,535, 1,461, 1,328, 1,304, 1,262, 1,194,

1,157, 1,041, 851, 806; ^1H NMR (CDCl_3 +DMSO, 300 MHz): δ 3.94 (s, 3H, $-\text{OCH}_3$), 5.48 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.69 (s, 2H, $-\text{NCH}_2$), 6.87–7.28 (m, 2H, Ar-H), 7.34 (s, 1H, Ar-H), 7.40–7.90 (m, 3H, Ar-H), 8.11 (s, 1H, Triazole-H), 13.65 (s, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 46.60 ($\text{N}-\text{CH}_2$), 51.21 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 56.30 (OCH_3), 107.14, 110.83, 113.63 ($\text{CH}-\text{Triazole}$), 114.23, 119.56, 120.76, 121.91 (q, $J = 273.33$ Hz, $-\text{CF}_3$), 125.93, 132.42, 137.75, 145.463, 151.82, 155.53, 158.20 (d, $J = 254.34$ Hz, $\text{BT}-\text{C}-\text{F}$), 160.17, 160.43, 165.00 ($\text{C}=\text{O}$); ^{19}F NMR (CDCl_3 +DMSO, 400 MHz): δ -58.86 (s, 3F), -117.58 to -118.75 (m, 1F); ESI-MS: 622 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{23}\text{H}_{15}\text{F}_4\text{N}_9\text{O}_2\text{S}_3$: C 44.44, H 2.43, N 20.28 %. Found: C 44.45, H 2.41, N 20.26 %.

N-cyclopropyl-2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**9h**) Yield 94 %; m.p. 193–195 °C. IR (KBr, ν_{max} cm^{-1}): 3,279, 2,931, 1,663, 1,536, 1,458, 1,264, 1,227, 1,052, 847, 805; ^1H NMR (CDCl_3 +DMSO, 300 MHz): δ 0.39–0.54 (m, 2H, $\text{Cyp}-\text{CH}_2$), 0.59–0.72 (m, 2H, $\text{Cyp}-\text{CH}_2$), 2.58–2.72 (m, 1H, $\text{Cyp}-\text{CH}$), 3.95 (s, 3H, $-\text{OCH}_3$), 4.91 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.66 (s, 2H, $-\text{NCH}_2$), 6.88–7.29 (m, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 7.53–8.06 (m, 3H, Ar-H), 8.26 (s, 1H, Triazole-H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 6.10 ($\text{Cyp}-\text{CH}_2-\text{CH}_2$), 22.42 ($\text{Cyp}-\text{CH}-\text{CH}_2$), 46.42 ($\text{N}-\text{CH}_2$), 52.31 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 56.53 (OCH_3), 107.23, 109.62, 111.60, 112.43 ($\text{CH}-\text{Triazole}$), 114.75, 119.10, 124.34, 131.21, 130.61, 133.12, 145.02, 151.93, 156.23, 157.53 (d, $J = 249.54$ Hz, $\text{BT}-\text{C}-\text{F}$), 163.92 ($\text{C}=\text{O}$); ^{19}F NMR (CDCl_3 +DMSO, 400 MHz): δ -117.71 to -119.05 (m, 1F); ESI-MS: 510 ($\text{M}+1$) $^+$; Anal. Calcd. For $\text{C}_{23}\text{H}_{20}\text{FN}_7\text{O}_2\text{S}_2$: C 54.21, H 3.96, N 19.24 %. Found: C 54.24, H 3.95, N 19.25 %.

N-cyclohexyl-2-(4-(((6-fluorobenzo[d]thiazol-2-yl)(6-methoxybenzo[d]thiazol-2-yl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**9i**) Yield 92 %; m.p. 180–182 °C. IR (KBr, ν_{max} cm^{-1}): 3,279, 2,926, 2,852, 1,658, 1,533, 1,458, 1,261, 1,049, 801; ^1H NMR (CDCl_3 +DMSO, 300 MHz): δ 1.04–1.40 (m, 5H, $\text{Cyh}-\text{H}$), 1.51–1.90 (m, 5H, $\text{Cyh}-\text{H}$), 3.47–3.66 (m, 1H, $\text{Cyh}-\text{CH}$), 3.95 (s, 3H, $-\text{OCH}_3$), 4.93 (s, 2H, $-\text{CH}_2-\text{CO}$), 5.66 (s, 2H, $-\text{NCH}_2$), 6.88–7.23 (m, 2H, Ar-H), 7.32 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.52–7.82 (m, 2H, Ar-H), 7.90–8.05 (m, 2H, Ar-H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 26.92 ($\text{Cyhx}-4-\text{CH}_2$), 28.50 ($\text{Cyhx}-3,5-\text{CH}_2$), 34.93 ($\text{Cyhx}-2,6-\text{CH}_2$), 46.35 ($\text{N}-\text{CH}_2$), 52.53 ($\text{N}-\text{CH}_2-\text{C}=\text{O}$), 54.63 ($\text{Cyhx}-1-\text{CH}$), 57.09 (OCH_3), 107.93, 109.45, 111.53, 112.63 ($\text{CH}-\text{Triazole}$), 114.90, 120.03, 124.33, 129.05, 130.53, 134.13, 147.00, 152.15, 157.16, 159.10 (d, $J = 254.10$ Hz, $\text{BT}-\text{C}-\text{F}$), 163.15 ($\text{C}=\text{O}$); ^{19}F NMR (CDCl_3 +DMSO, 400 MHz): δ -117.66 to -118.83 (m, 1F); ESI-MS: 552 ($\text{M}+1$) $^+$; Anal. Calcd. For

$\text{C}_{26}\text{H}_{26}\text{FN}_7\text{O}_2\text{S}_2$: C 56.61, H 4.75, N 17.77 %. Found: C 56.60, H 4.77, N 17.78 %.

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