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Synthesis and biological evaluation of triazole and isoxazole tagged Benzothiazole/Benzoxazole derivatives as potent cytotoxic agents

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Table 1: FACS Analysis for HeLa cells

Compounds	HeLa			
	G0 (%)	G1(%)	S/G2(%)	G2/M(%)
Control	3.50	73.63	5.34	17.57
TAK-165	4.47	68.44	6.50	20.58
GW-610	3.67	70.13	5.71	20.52
8a	22.49	57.29	2.75	17.47
8f	5.37	70.92	6.90	16.81
13c	12.60	71.45	2.38	13.57
13g	42.56	42.94	1.93	12.55
13h	17.92	59.88	7.36	14.81
13j	21.15	52.77	2.84	23.24

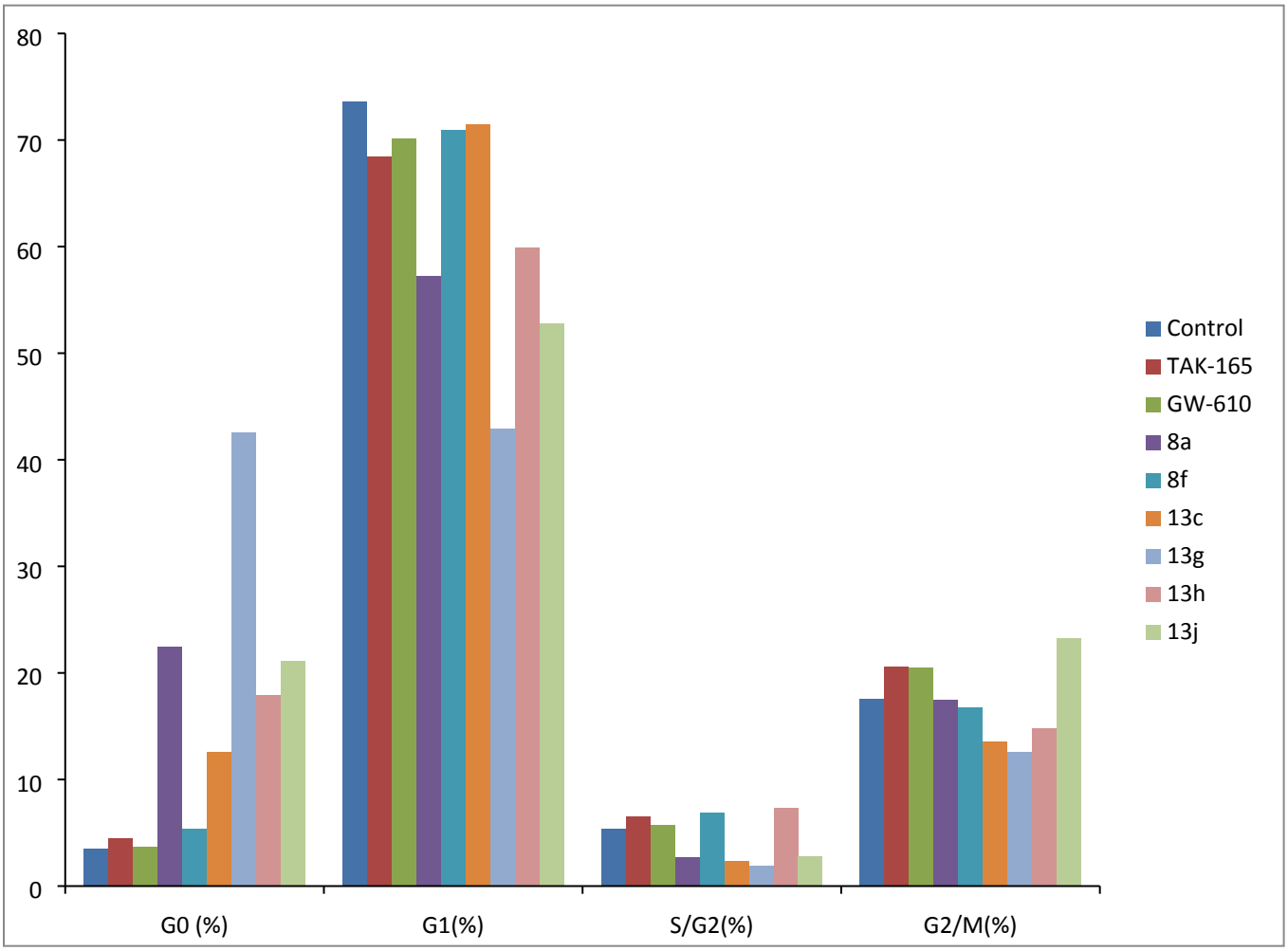

Fig. 1- Graphical presentation of cell cycle distribution after chemical treatment on HeLa cells.

Table 2: FACS Analysis for A549 cells

Compounds	A549			
	G0(%)	G1(%)	S/G2(%)	G2/M(%)
Control	1.04	70.35	5.54	23.03
TAK-165	1.14	75.71	4.42	18.74
GW-610	1.15	76.46	4.56	17.83
8a	9.46	67.84	4.57	18.13
8d	4.93	85.50	1.96	7.61
8f	19.98	59.19	4.76	16.07
13d	2.64	78.55	4.42	14.38
13g	49.43	39.78	1.72	9.07
13j	26.66	56.37	3.72	13.25

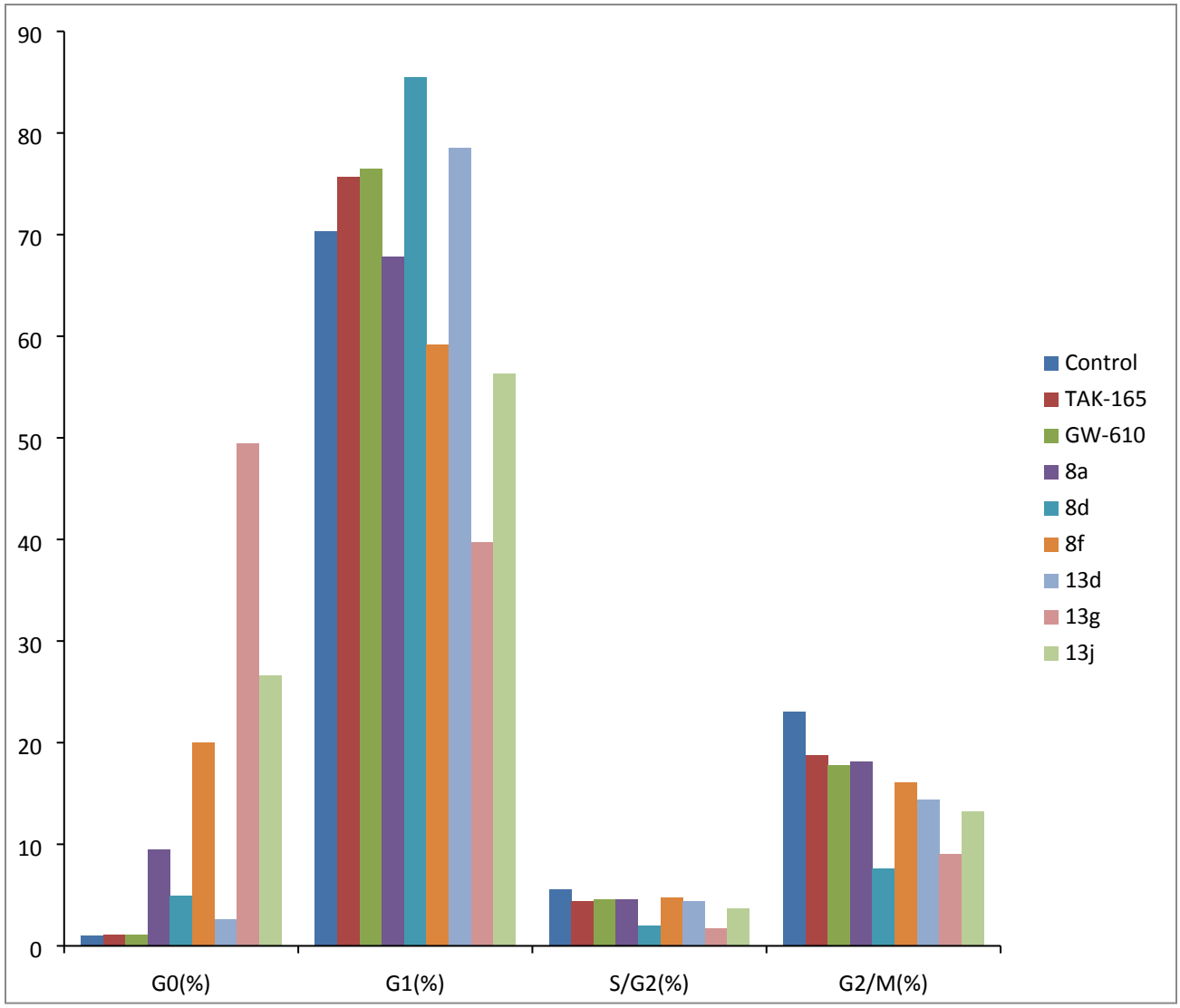

Fig. 2 Cell cycle distribution pattern of A549 cells after chemical treatment on A549 cells.

Table 3: The IC_{50} values and SI index

S. No.	IC_{50} in HeLa	SI in HeLa	IC_{50} in A549	SI in A549
8a	1.57	6.04	2.41	3.93
8f	2.38	7.95	2.026	9.34
13c	2.40	14.63	4.8	7.31
13g	1.76	27.32	2.59	18.57
13h	2.0	14.95	3.155	9.47
13j	1.7	10.1	2.29	7.49
TAK165	1.86	6.20	2.04	5.73
GW160	2.25	31.90	2.47	29.06

Chemistry

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) 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. ^{1}H and ^{13}C spectra were recorded Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield 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.

Experimental section

All solvents were distilled prior to use. Dry reactions were conducted under a nitrogen atmosphere. Melting points were measured with a Fischer–Johns melting point apparatus and are uncorrected. IR spectra were recorded as neat liquids or KBr pellets and absorptions are reported in cm_1. 1H NMR spectra were recorded on 300 (Bruker) and 500 MHz (Varian) spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Coupling constants J are expressed in Hertz. High-resolution mass spectra were obtained by using ESI-QTOF mass spectrometry. All the experiments were monitored by analytical thin layer chromatography (TLC) performed on silica gel GF254 pre-coated plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with PMA and charring on a hot plate. Silica gel finer than 200 mesh was used for column chromatography.

General Procedure for Oxime Chlorination (3).

To a solution of 4-hydroxybenzaldoxime (30.8 mmol) in $CHCl_3$ (29 mL) was added pyridine (3.07 mmol). The temperature was raised to 40 °C and *N*-chloro succinimide (33.9 mmol) was added to the resulting solution. Stirring was continued at this temperature for 3 h before the reaction mixture was diluted by CH_2Cl_2 (200mL). The organic layer was washed by water (2 X

100 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford hydoxyiminoyl chloride **3**(5.05 g, 95%, >95% purity) a slight yellow powder.

General Procedure for Isoxazole synthesis (4):

To a solution of propargyl benzothiazole **2** (4 mmol) and 4-hydroxybenzohydroximoyl chloride **3** (4mmol) in ethyl acetate (20ml) was added $NaHCO_3$ (20 mmol), the mixture was heated at 100 ^{0}C, for 1-2 hrs, cooled at room temperature, solvent was removed *invacuo*. The product was extracted into dichloromethane (3 X 20 ml) the combined organic layer was washed with water (2 X 20 ml) and brine solution (2 X 20 ml), dried over $Na_2SO_4$and the solvent removed in vacuo to yield the desired isoxazole derivative **4**.

General procedure for 1,2,3-Triazole synthesis:(6a-c, 8a-g and 13a-j)

The propargylated isoxazole linked benzothiazole derivatives **5**, **7**, **12** (0.27 mmol) was dissolved in dry THF (5 ml) and catalytic amount of CuI was added. Then various azides (0.27 mmol) in dry THF were slowly added at room temperature under nitrogen atmosphere and continued stirring for 24 hrs. 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 61-85% isolated yield.

tert-butylbenzo[d]thiazol-2-yl((3-(4-((1-(2-oxo-2-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-ylamino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)isoxazol-5-yl)methyl)carbamate (**6a**)

white solid; Yield = 68 %; mp = 168-170 ^{0}C, IR (KBr): ν_{max} 3154, 2986, 1660,1565, 1516, 1441, 1369, 1256, 1183,685, 641 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 1.59 (s, 9H, BOC), 5.22 (s, 2H, -COCH$_2$), 5.32 (s, 2H, -N-CH$_2$), 5.56 (s, 2H, -O-CH$_2$), 6.55-6.74 (m, 1H, Isoxazole), 7.00-7.45 (m, 4H, Ar-H), 7.57-7.90 (m, 4H, Ar-H), 8.19 (s, 1H, Triazole), 9.85 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 29.9, 44.1, 50.9, 60.8, 82.4, 98.5, 114.2, 118.1, 120.2, 121.1, 123.6, 124.1, 127.9, 132.9, 146.5, 147.2, 151.5, 152.3, 156.3, 162.2, 162.9, 163.3, 166.9 ppm; MS (ESI) *m/z* 714 [M+H]$^+$; Anal. Calcd. for $C_{30}H_{26}F_3N_9O_5S_2$, C 50.49, H 3.67, N 17.66% . Found C 50.46 H 3.64, N 17.65%.

N-(benzo[d]thiazol-2-yl)-N-((3-(4-((1-(2-(2,4-difluorophenylamino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)isoxazol-5-yl)methyl)-3,3-dimethylbutanamide (**6b**)

white solid; Yield = 64 %; mp = 184-186 ºC, IR (KBr): ν_{max} 3140, 2959, 1576, 1552, 1524, 1446, 1369, 1265, 1190, 828, 750, 696, 606 cm^{-1}; ^{1}H NMR (DMSO, 500 MHz): δ = 1.60 (s, 9H, BOC), 5.21 (s, 2H, -COCH$_2$), 5.36 (s, 2H, -N-CH$_2$), 5.56 (s, 2H, -O-CH$_2$), 6.51-6.65 (m, 1H, Isoxazole), 6.79-7.43 (m, 6H, Ar-H), 7.56-7.89 (m, 4H, Ar-H), 7.97-8.17 (m, 2H), 10.15 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO, 75 MHz): δ = 30.3, 44.3, 51.4, 61.1, 83.5, 99.1, 107.3, 113.6, 116.3 118.3, 119.6, 121.8, 124.1, 125.4, 126.8, 131.9, 145.8, 148.9, 150.1, 152.1, 154.2, 156.4, 162.6, 163.1, 165.1, 167.2 ppm; MS (ESI) *m/z* 674 [M+H]$^+$; Anal. Calcd. for $C_{33}H_{29}F_2N_7O_5S$, C 58.83, H 4.34, N 14.55% . Found C 58.80 H 4.32, N 14.54%.

N-(benzo[d]thiazol-2-yl)-N-((3-(4-((1-(2-(cyclohexyl amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methoxy) phenyl)isoxazol-5-yl)methyl)-3,3-dimethylbutanamide (**6c**)

white solid; Yield = 72 %; mp = 172-174 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 500 MHz): δ = 1.08-1.40 (m, 6H, Cyclohexane), 1.59 (s, 9H, BOC), 1.66-1.89 (m, 4H, Cyclohexane), 3.50-3.66 (m, 1H, Cyclohexane), 5.01 (s, 2H, -COCH$_2$), 5.19 (s, 2H, -N-CH$_2$), 5.55 (s, 2H, -O-CH$_2$), 6.60 (s, 1H, Isoxazole), 7.01-7.17 (m, 1H, Ar-H), 7.21-7.44 (m, 2H, Ar-H), 7.59-7.88 (m, 4H, Ar-H), 7.98-8.14 (m, 2H, Ar-H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 26.6, 28.4, 30.4, 34.5, 44.1, 51.4, 53.5, 59.7, 82.6, 99.3, 117.5 118.1, 120.2, 123.0, 126.2, 131.1, 145.3, 150.1, 156.5, 162.5, 164.4, 167.7 ppm; MS (ESI) *m/z* 644 [M+H]$^+$; Anal. Calcd. for $C_{33}H_{37}N_7O_5S$, C 61.57, H 5.79, N 15.23% . Found C 61.55 H 5.76, N 15.22%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol -3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-(trifluoromethoxy)benzyl)acetamide (**8a**)

white solid; Yield = 78 %; mp = 185-187 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 4.34 - 4.41 (m, 2H, Benzylic-CH_2), 4.78 (s, 2H, -NH-CH_2), 5.11(s, 2H, -$COCH_2$), 5.28 (s, 2H, -O-CH_2), 6.58 (s, 1H, Isoxazole), 6.97-7.04 (m, 1H, Ar-H), 7.09-7.25 (m, 4H, Ar-H), 7.27-7.35 (m, 2H, Ar-H), 7.44-7.56 (m, 3H, Ar-H), 7.57-7.64 (m, 2H, Ar-H), 7.76 (s, 1H, Triazole), 8.08 (s, 1H, NH), 8.60 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 40.1, 44.2, 50.0, 60.5, 98.4, 112.5, 113.3, 116.7, 119.0, 119.5, 120.5, 123.7, 124.4, 124.8, 126.2, 127.4, 128.9, 136.1, 140.0, 145.7, 150.2, 153.0, 158.8, 163.7, 164.0, 168.8 ppm; MS (ESI) *m/z* 636 $[M+H]^+$; Anal. Calcd. for $C_{30}H_{24}F_3N_7O_4S$, C 56.69, H 3.81, N 15.43% . Found C 56.67 H 3.79, N 15.42%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol -3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(6-fluorobenzo[d]thiazol-2-yl)acetamide (**8b**)

white solid; Yield = 61 %; mp = 172-174 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 4.82 (s, 2H, -NH-CH_2), 5.35 (s, 2H, -$COCH_2$), 5.53 (s, 2H, -O-CH_2), 6.74 (s, 1H, Isoxazole), 7.02-7.12 (m, 1H, Ar-H), 7.14-7.28 (m, 2H, Ar-H), 7.32-7.39 (m, 1H, Ar-H), 7.43-7.50 (m, 1H, Ar-H), 7.56-7.65 (m, 2H, Ar-H),7.68-7.78 (m, 2H, Ar-H), 7.81-7.96 (m, 2H, Ar-H), 8.22 (s, 1H, Triazole), 8.43 (s, 1H, NH), 12.85 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 45.9, 51.4, 62.1, 99.8, 107.3 (d, J = 27.5 Hz), 113.8 (d, J = 25.8 Hz), 118.2, 120.3, 120.7, 121.0, 121.3, 122.2 (d, J = 18.7 Hz), 123.8, 125.1, 125.9, 127.7, 133.3, 137.4, 138.2, 142.8, 144.7, 145.7, 150.1, 156.9, 155.7 (d, J = 276.7 Hz), 160.2, 162.0, 165.0, 170.7 ppm; MS (ESI) *m/z* 613 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{21}FN_8O_3S_2$, C 56.85, H 3.45, N 18.29% . Found C 56.82 H 3.44, N 18.28%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol -3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide (**8c**)

white solid; Yield = 85%; mp = 220-222 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.77 (s, 3H, OCH_3), 4.82 (s, 2H, -NH-CH_2), 5.26 (s, 2H, -$COCH_2$), 5.33 (s, 2H, -O-CH_2), 6.61 (s, 1H, Isoxazole), 6.77-6.90 (m, 2H, Ar-H), 7.02-7.14 (m, 1H, Ar-H), 7.20-7.34 (m, 2H, Ar-H), 7.44-7.75 (m, 6H, Ar-H), 7.81 (s, 1H, Triazole), 8.06 (s, 1H, Ar-H), 8.13 (s, 1H, NH), 10.07 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 50.8, 53.5, 59.8, 60.8, 98.5, 112.2, 112.6, 113.4, 117.0, 119.0, 119.3, 119.7, 120.8, 121.0, 123.9, 124.4, 124. 9, 126.5, 129.8, 132.7, 142.8, 150.6, 152.6, 153.2, 154.1, 159.0, 161.7, 168.9 ppm; MS (ESI) *m/z* 568 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{25}N_7O_4S$, C 61.36, H 4.44, N 17.27% . Found C 61.35 H 4.42, N 17.26%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol -3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-(trifluoromethyl)phenyl)acetamide (**8d**)

white solid; Yield = 79 %; mp = 178-180 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 4.79 (s, 2H, -NH-CH_2), 5.30 (s, 2H, -$COCH_2$), 5.33 (s, 2H, -O-CH_2), 6.69 (s, 1H, Isoxazole), 6.99-7.07 (m, 1H, Ar-H), 7.18-7.24 (m, 1H, Ar-H), 7.27-7.35 (m, 2H, Ar-H), 7.40-7.48 (m, 2H, Ar-H), 7.54 (d, J = 7.76 Hz, 1H, Ar-H), 7.64-7.84 (m, 4H, Ar-H), 8.00 (s, 1H, Ar-H), 8.13 (s, 1H, Triazole), 8.37 (s, 1H, NH), 10.69 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 45.5, 52.2, 62.2, 100.0, 113.9, 115.7, 118.3, 120.0, 120.5, 121.2, 122.5, 125.3, 125.9, 126.3, 127.9, 129.4, 138.7, 142.1, 151.8, 154.6, 157.7, 160.4, 163.1, 164.2, 166.0, 170.3 ppm; MS (ESI) *m/*z 606 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{22}F_3N_7O_3S$, C 57.52, H 3.66, N 16.19% . Found C 57.50 H 3.63, N 16.17%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol -3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-chloro-4-fluorophenyl)acetamide (**8e**)

white solid; Yield = 83 %; mp = 206-208 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 4.82 (s, 2H, -NH-CH_2), 5.31 (s, 2H, -$COCH_2$), 5.33 (s, 2H, -O-CH_2), 6.68 (s, 1H, Isoxazole), 7.02-7.17 (m, 3H, Ar-H), 7.20-7.34 (m, 2H, Ar-H), 7.40-7.52 (m, 2H, Ar-H), 7.54-7.61 (m, 2H, Ar-H), 7.64-7.72 (m, 1H, Ar-H), 7.79-7.90 (m, 2H, Ar-H), 8.12 (s, 1H, Triazole), 8.35 (s, 1H, NH), 10.53 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 45.6, 52.1, 62.0, 100.2, 114.4, 115.1, 117.0, 117.2, 118.4, 119.4 (d, J = 14.8 Hz), 120.6, 121.2 (d, J = 22.5 Hz), 122.0 (d, J = 6.6 Hz), 125.5, 126.6, 127.9, 130.5, 135.5, 141.7, 152.0, 154.6, 153.3 (d, J= 244.2 Hz), 160.5, 164.5, 165.7, 170.7 ppm; MS (ESI) *m/z* 591 $[M+H]^+$; Anal. Calcd. for $C_{28}H_{21}ClFN_7O_3S$, C 57.00, H 3.59, N 16.62% . Found C 56.96 H 3.57, N 16.60%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol-3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-(trifluoromethylthio)phenyl)acetamide (**8f**)

white solid; Yield = 80 %; mp = 188-190 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 4.82 (s, 2H, -NH-CH_2), 5.24 (s, 2H, -$COCH_2$), 5.33 (s, 2H, -O-CH_2), 6.66 (s, 1H, Isoxazole), 6.94-7.11 (m, 2H, Ar-H), 7.18-7.33 (m, 2H, Ar-H), 7.42-7.86 (m, 8H, Ar-H), 8.11 (s, 1H, Triazole), 8.28 (s, 1H, NH), 10.61 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 46.5, 50.7, 60.7, 98.4, 112.5, 113.4, 115.4, 116.8, 118.4, 119.0, 119.6, 123.8, 124.5, 124.8, 126.3, 129.0, 135.4, 137.0, 139.6, 140.3, 150.4, 151.5, 153.1, 158.9, 162.8, 164.1, 168.9 ppm; MS (ESI) *m/z* 638 $[M+H]^+$;

Anal. Calcd. for $C_{29}H_{22}F_3N_7O_3S_2$, C 54.62, H 3.48, N 15.38% . Found C 54.62 H 3.48, N 15.38%.

2-(4-((4-(5-((benzo[d]thiazol-2-ylamino)methyl)isoxazol-3-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluoro phenyl)acetamide (**8g**)

white solid; Yield = 85 %; mp = 198-200 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 4.81 (s, 2H, -NH-CH_2), 5.36 (s, 4H, -$COCH_2$ and -O-CH_2), 6.88 (s, 1H, Isoxazole), 7.02-7.35 (m, 4H, Ar-H), 7.40-8.00 (m, 7H, Ar-H), 8.04-8.19 (m, 1H, Ar-H), 8.31 (s, 1H, Triazole), 8.67 (s, 1H, NH), 10.58 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 44.5, 51.1, 61.0, 99.2, 113.4, 114.4 (d, J = 22.5 Hz), 117.4, 120.0 (d, J = 9.3 Hz), 120.3, 120.9, 124.5, 125.6, 126.8, 128.0, 133.6, 138.7, 151.4, 153.6, 155.5, 155.8 (d, J = 254.1 Hz), 159.4, 162.9, 166.2, 169.6 ppm; MS (ESI) *m/z* 556 $[M+H]^+$; Anal. Calcd. for $C_{28}H_{22}FN_7O_3S$, C 60.53, H 3.99, N 17.65% . Found C 60.51 H 3.97, N 17.64%.

2-(4-((4-(5-((2-(benzo[d]thiazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-(trifluoromethyl)phenyl)acetamide (**13a**)

white solid; Yield = 76 %; mp = 144-146 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.92 (s, 3H, -OCH_3), 5.20 (s, 2H, -$COCH_2$), 5.36 (s, 2H, -O-CH_2), 5.44 (s, 2H, BT-O-CH_2), 6.70 (s, 1H, Isoxazole), 7.08-7.33 (m, 4H, Ar-H), 7.36-7.55 (m, 6H, Ar-H), 7.60-7.67 (m, 1H, Ar-H), 7.78-7.97 (m, 3H, Ar-H), 8.08-8.14 (m, 1H, Ar-H), 8.19-8.30 (m, 1H, Ar-H), 8.51-8.58 (m, 1H, Ar-H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 52.1, 55.5, 61.2, 65.5, 102.8, 109.7, 113.3, 113.8, 115.2, 119.6, 120.0, 121.0, 121.7, 122.0, 122.4, 122.7, 124.9, 125.7, 126.2, 126.4, 129.0, 126.1 (q, J = 290.5 Hz), 129.1 (q, J = 31.3 Hz), 130.1, 132.2, 135.3, 139.0, 142.1, 149.2, 151.4, 155.1, 161.8, 164.8, 167.3, 167.9 ppm; MS (ESI) *m/z* 713 $[M+H]^+$; Anal. Calcd. for $C_{36}H_{27}F_3N_6O_5S$, C 60.67, H 3.82, N 11.79% . Found C 60.65 H 3.80, N 11.78%.

2-(4-((4-(5-((2-(benzo[d]thiazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-(trifluoromethyl)phenyl)acetamide (**13b**)

white solid; Yield = 79 %; mp = 198-200 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.91 (s, 3H, -OCH_3), 5.21 (s, 2H, -$COCH_2$), 5.35 (s, 2H, -O-CH_2), 5.45 (s, 2H, BT-O-CH_2), 6.71 (s, 1H, Isoxazole), 7.05-7.70 (m, 12H, Ar-H), 7.76-8.01 (m, 2H, Ar-H), 8.04-8.16 (m, 1H, Ar-H), 8.45-8.62 (m, 2H, Ar-H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 52.1, 55.5, 61.2, 65.5, 102.8, 109.7, 113.8, 115.2, 119.6, 120.0, 121.7, 122.0, 122.4, 122.7, 125.0, 126.2, 126.0 (q, J = 291.1 Hz),

129.1 (q, J =31.3 Hz), 130.0, 130.1, 132.2, 135.3, 139.0, 142.4, 149.2, 151.4, 155.1, 161.8, 164.8, 167.3, 167.9 ppm; MS (ESI) *m/z* 713 $[M+H]^+$; Anal. Calcd. for $C_{36}H_{27}F_3N_6O_5S$, C 60.67, H 3.82, N 11.79% . Found C 60.66 H 3.81, N 11.77%.

2-(4-((4-(5-((2-(benzo[d]thiazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(furan-2-ylmethyl)acetamide (**13c**)

white solid; Yield = 70 %; mp = 172-174 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.91 (s, 3H, -OCH_3), 4.41 (s, 2H, Furan-CH_2), 5.10 (s, 2H, -$COCH_2$), 5.25 (s, 2H, -O-CH_2), 5.48 (s, 2H, BT-O-CH_2), 6.15-6.41(m, 4H, Ar-H), 6.78-6.88 (m, 1H, Ar-H), 7.09-7.59 (m, 7H, Ar-H), 7.89-8.21 (m, 3H, Ar-H), 8.37-8.61 (m, 2H, Ar-H)ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 35.5, 51.3, 55.3, 61.0, 65.5, 102.5, 107.0, 110.1, 113.3, 119.5, 121.3, 121.7, 122.2, 124.5, 125.8, 126.9, 131.8, 135.3, 141.8, 149.1, 151.2, 154.9, 160.7, 161.7, 164.9, 166.9, 167.5 ppm; MS (ESI) *m/z* 649 $[M+H]^+$; Anal. Calcd. for $C_{34}H_{28}N_6O_6S$, C 62.95, H 4.35, N 12.96% . Found C 62.94 H 4.32, N 12.95%.

2-(4-((4-(5-((2-(benzo[d]thiazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)acetamide (**13d**)

white solid; Yield = 80 %; mp = 158-160 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.92 (s, 3H, -OCH_3), 5.32 (s, 2H, -$COCH_2$), 5.42 (s, 2H, -O-CH_2), 5.55 (s, 2H, BT-O-CH_2), 6.91 (s, 1H, Isoxazole), 7.12-7.45 (m, 6H, Ar-H), 7.55-7.72 (m, 3H, Ar-H), 7.75-7.83 (m, 1H, Ar-H), 8.07 (s, 1H, Triazole), 8.18-8.28 (m, 1H, Ar-H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 52.1, 55.5, 61.8, 65.5, 102.8, 109.7, 113.3, 113.8, 115.2, 119.6, 120.0, 121.0, 121.7, 121.6, 122.4, 122.7, 124.9, 126.2, 125.7, 126.4, 128.9 (q, J = 31.3 Hz), 130.1, 132.2, 135.3, 139.0, 142.1, 149.2, 151.4, 155.1, 161.8, 164.8, 167.3, 167.9 ppm; MS (ESI) *m/z* 721 $[M+H]^+$; Anal. Calcd. for $C_{32}H_{23}F_3N_8O_5S_2$, C 53.33, H 3.22, N 15.55% . Found C 53.29 H 3.20, N 15.53%.

2-(4-((4-(5-((2-(benzo[d]thiazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide (**13e**)

white solid; Yield = 81 %; mp = 140-142 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.76 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 5.17 (s, 2H, -$COCH_2$), 5.36 (s, 2H, -O-CH_2), 5.45 (s, 2H, BT-O-CH_2), 6.72 (s, 1H, Isoxazole), 6.79-6.87 (m, 2H, Ar-H), 7.07-7.29 (m, 5H, Ar-H), 7.30-7.42 (m, 3H, Ar-H), 7.43-7.54 (m, 2H, Ar-H), 7.86-8.15 (m, 4H, Ar-H), 8.55 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 51.6, 53.6, 54.7, 61.1, 65.3, 101.9, 108.3, 112.2, 113.0, 113.7,

116.9, 119.6, 120.7, 121.7, 122.0, 123.1, 125.9, 126.8, 127.0, 132.7, 135.6, 141.9, 149.0, 151.3, 155.9, 161.7, 164.7, 166.8, 167.5 ppm; MS (ESI) *m/z* 675 $[M+H]^+$; Anal. Calcd. for $C_{36}H_{30}F_3N_6O_6S$, C 64.08, H 4.48, N 12.46% . Found C 64.05 H 4.46, N 12.45%.

2-(4-((4-(5-((2-(benzo[d]thiazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl)acetamide (**13f**)

white solid; Yield = 71 %; mp = 178-180 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.83 (s, 3H, -OCH_3), 5.17 (s, 2H, -$COCH_2$), 5.24 (s, 2H, -O-CH_2), 5.41 (s, 2H, BT-O-CH_2), 6.74 (s, 1H, Isoxazole), 6.85-7.01 (m, 2H, Ar-H), 7.06-7.64 (m, 11H, Ar-H), 7.80-8.08 (m, 2H, Ar-H), 8.46 (s, 1H, Ar-H), 10.15 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 52.3, 55.6, 61.3, 65.3, 101.7, 109.5, 113.7, 114.1 (d, J = 22.7 Hz), 116.3, 119.4, 120.0, 121.0 (d, J = 13.3 Hz), 122.4, 122.8, 124.1, 125.8, 130.8, 132.3, 134.9, 138.1, 141.2, 149.2, 151.3, 156.1, 154.5 (d, J = 246.3 Hz), 161.1, 164.8, 167.1, 167.9 ppm; MS (ESI) *m/z* 663 $[M+H]^+$; Anal. Calcd. for $C_{35}H_{27}FN_6O_5S$, C 63.43, H 4.11, N 12.68% . Found C 63.41 H 4.09, N 12.65%.

2-(4-((4-(5-((2-(benzo[d]oxazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(furan-2-ylmethyl)acetamide (**13g**)

white solid; Yield = 72 %; mp = 156-158 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.90 (s, 3H, -OCH_3), 4.41 (s, 2H, Furan-CH_2), 5.10 (s, 2H, -$COCH_2$), 5.30 (s, 2H, -O-CH_2), 5.42 (s, 2H, BT-O-CH_2), 6.17-6.39(m, 4H, Ar-H), 7.13-7.48 (m, 6H, Ar-H), 7.51-7.67 (m, 2H, Ar-H), 7.77-7.84 (m, 1H, Ar-H), 7.96 (s, 1H, Triazole), 8.13-8.23 (m, 1H, Ar-H), 8.49 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 35.5, 51.3, 55.3, 62.0, 65.5, 101.7, 106.3, 107.1, 109.5, 110.2, 110.4, 113.2, 114.6, 116.3, 119.0, 119.4, 119.5, 121.7, 124.3, 125.0, 126.0, 130.9, 132.9, 141.2, 141.9, 144.5, 148.1, 150.0, 155.0, 156.1, 161.4, 165.0, 168.0, 168.5 ppm; MS (ESI) *m/z* 633 $[M+H]^+$; Anal. Calcd. for $C_{34}H_{28}N_6O_7$, C 64.55, H 4.46, N 13.28% . Found C 64.52 H 4.43, N 13.25%.

2-(4-((4-(5-((2-(benzo[d]oxazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2,4-difluorophenyl)acetamide (**13h**)

white solid; Yield = 63 %; mp = 152-154 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.83 (s, 3H, -OCH_3), 5.21 (s, 2H, -$COCH_2$), 5.26 (s, 2H, -O-CH_2), 5.33 (s, 2H, BT-O-CH_2), 6.68-6.88 (s, 3H, Ar-H), 7.00-7.37 (m, 7H, Ar-H), 7.38-7.59 (m, 2H, Ar-H), 7.66-7.79 (m, 1H, Ar-H), 7.84-8.03 (m, 2H, Ar-H), 8.05-8.15 (m, 1H, Ar-H), 9.82 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75

MHz): δ = 51.7, 55.2, 55.9, 62.0, 101.5, 103.6 (t, J = 25.8 Hz), 109.3 (d, J = 20.3 Hz), 110.2, 110.6 (d, J = 22.5 Hz), 113.2, 114.5, 116.3, 119.3, 121.2, 121.6, 124.1, 124.4, 124.8, 125.9, 128.0, 130.8, 132.6, 141.1, 144.4, 148.9, 149.9, 152.0 (d, J = 253.0 Hz), 154.8, 156.0, 158.7 (d, J = 252.5 Hz), 161.3, 164.3, 167.8, 168.4 ppm; MS (ESI) *m/z* 665 $[M+H]^+$; Anal. Calcd. for $C_{35}H_{26}F_2N_6O_6$, C 63.25, H 3.94, N 12.64% . Found C 63.23 H 3.92, N 12.63%.

2-(4-((4-(5-((2-(benzo[d]oxazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)acetamide (**13i**)

white solid; Yield = 73 %; mp = 146-148 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.91 (s, 3H, -OCH_3), 5.33 (s, 2H, -$COCH_2$), 5.44 (s, 2H, -O-CH_2), 5.54 (s, 2H, BT-O-CH_2), 6.90 (s, 1H, Isoxazole), 7.14-7.47 (m, 6H, Ar-H), 7.53-7.69 (m, 3H, Ar-H), 7.76-7.85 (m, 1H, Ar-H), 8.07 (s, 1H, Triazole), 8.14-8.24 (m, 1H, Ar-H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 51.3, 55.2, 55.9, 62.1, 101.3, 109.4, 110.0, 111.2, 113.3, 114.4, 116.4, 119.3, 119.6, 121.0, 121.6, 124.0, 124.7, 128.0, 130.7, 132.5, 139.0, 141.1, 148.8, 149.1, 156.0, 161.2, 166.0, 167.7, 170.9, 175.4 ppm; MS (ESI) *m/z* 705 $[M+H]^+$; Anal. Calcd. for $C_{32}H_{23}F_3N_8O_6S$, C 54.54, H 3.29, N 15.90% . Found C 54.53 H 3.27, N 15.89%.

2-(4-((4-(5-((2-(benzo[d]oxazol-2-yl)phenoxy)methyl)isoxazol-3-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl)acetamide (**13j**)

white solid; Yield = 76 %; mp = 170-172 ^{0}C, IR (KBr): ν_{max} 3170, 3027, 1568, 1522, 1488, 1441, 1365, 1262, 1189, 1088, 1014, 755, 653 cm^{-1}; ^{1}H NMR (DMSO, 300 MHz): δ = 3.91 (s, 3H, -OCH_3), 5.27 (s, 2H, -$COCH_2$), 5.32 (s, 2H, -O-CH_2), 5.44 (s, 2H, BT-O-CH_2), 6.89 (s, 1H, Isoxazole), 6.95-7.06 (m, 2H, Ar-H), 7.15-7.44 (m, 5H, Ar-H), 7.53-7.68 (m, 6H, Ar-H), 7.76-7.85 (m, 1H, Ar-H), 8.04 (s, 1H, Triazole), 8.15-8.22 (m, 1H, Ar-H), 10.29 (s, 1H, NH) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 52.0, 55.2, 62.0, 65.5, 101.5, 109.5, 110.2, 113.3, 114.5, 114.9 (d, J = 22.5 Hz), 116.4, 119.3, 120.7 (d. J = 7.7 Hz), 121.6, 124.1, 124.8, 125.8, 130.8, 132.6, 134.3, 141.1, 148.9, 149.1, 156.0, 158.1 (d, J = 241.5 Hz), 161.3, 163.5, 167.8, 173.0 ppm; MS (ESI) *m/z* 647 $[M+H]^+$; Anal. Calcd. for $C_{35}H_{27}FN_6O_6$, C 65.01, H 4.21, N 13.00% . Found C 65.00 H 4.18, N 12.98%.