Indian Journal of Chemistry
Vol. 60B, March 2021, pp. 409-417

Synthesis, *in silico* pharmacokinetic analysis and anticancer activity evaluation of benzothiazole-triazole hybrids

Srishti Rawat[a], Diwan S Rawat[a] & Beena Negi*[b]

[a] Department of Chemistry, University of Delhi, Delhi 110 007, India

[b] Gargi College, University of Delhi, Delhi 110 049, India

E-mail: beenanegi@gargi.du.ac.in

Received 27 July 2020; accepted (revised) 18 January 2021

Over the past decade, a variety of benzothiazole derivatives have been reported with promising anticancer activity. Benzothiazole and its analogues are capable of acting on a number of molecular targets and thus exerting their anticancer activity. To further develop benzothiazole derivatives as anticancer agents, we attempted to design and synthesize a library of benzothiazole-triazole derivatives. The synthesized hybrid compounds have been selected by National Cancer Institute, USA for the *in vitro* activity evaluation against 60 human cancer cell lines in a one dose screening panel. Most of the synthesized compounds showed 60-80% growth rate against renal cancer cell line UO-31.

Keywords: 2-Aminobenzothiazole, triazole, renal cancer, hybrid, click chemistry

Cancer is an uncontrolled and rapid growth of abnormal cells[1]. It is the second leading cause of death after cardiovascular diseases with one in every six deaths worldwide. As estimated by International Agency for Research on Cancer, in the year 2018 there were 18.1 million new cases around the world with 9.6 million cancer related deaths[2]. According to American Chemical Society by the year 2040, it is expected that 27.5 million new cancer cases and 16.3 million cancer deaths can occur globally[2,3].

The successful treatment of cancer is a huge challenge due to early diagnosis difficulties, drug side effects, drug resistance and the malignancy of tumor metastasis. Thus, there is always a search for development of new antitumor agents[4]. Generally cancer therapy targeting a single biological molecule is being used[4,5]. However, better efficacy can be obtained by using agents which can modulate more than one target as compared to single target drugs[5,6]. Multiple targets can be modulated by the combination of various drugs having different mechanisms or by using ligands which comprise of two or more pharmacophores in a single biological molecule (hybrid drugs)[6,7]. Thus, hybrid drugs are designed with improved affinity and efficacy as compared to the parent drugs.

Benzothiazoles are important class of heterocyclic compounds that have attracted great attention due to their antimicrobial[8], antileshmanial[9], antitumor[10], anti-viral[11], antimalarial[12] and CNS depressant activities[13]. The promising biological activity profile and synthetic accessibility has led to development of new benzothiazoles as potential chemotherapeutics. In recent years, 2-arylbenzothiazoles and 2-aminobenzothiazoles have both emerged as important pharmacophores in the development of anticancer agents[14]. Various modified benzothiazole derivatives are even reported for inhibition of topoisomerase II[15-18] (*e.g.* Figure 1a, 1b), β-glucoronidase[19] (*e.g.* Figure 1c), CYP1A1 of cytochrome P450 enzyme[20] (*e.g.* Figure 1d) and tyrosine kinase histone deacetylase[21] (*e.g.* Figure 1e) enzymes. While triazole is another important heterocyclic pharmacophore which notably has wide range of biological activities[22,23].

Using this hybrid approach and in-continuation of our work on the synthesis of biologically relevant molecules[24-27], a series of benzothiazole-triazole hybrids were designed, synthesized and their anticancer activity was explored against a panel of different cancer cell lines (Figure 2).

Result and Discussion

Chemistry

The synthesis of the designed set of hybrid compound was carried out as shown in Scheme I. Initially, commercially available 2-aminobenzothiazole (**1**) on reaction with chloroacetyl chloride in presence of K_2CO_3

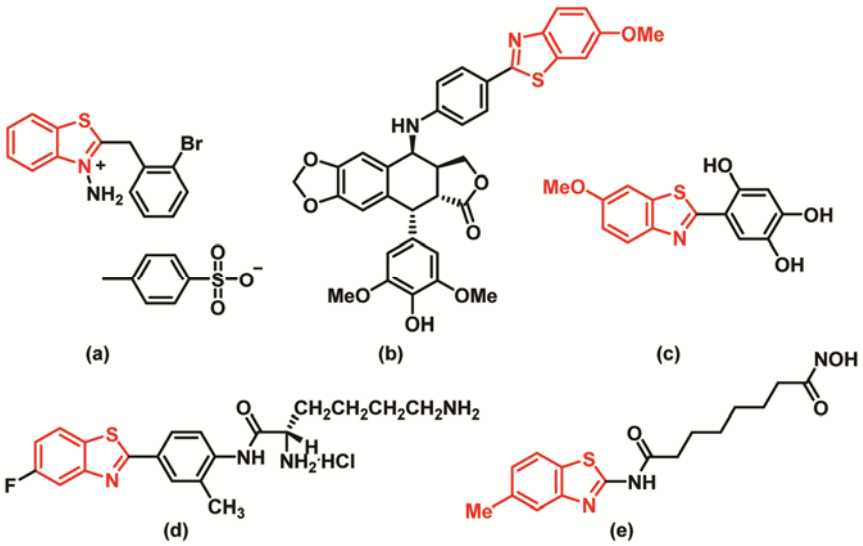


Figure 1 — Benzothiazole core in drugs and biologically active molecules

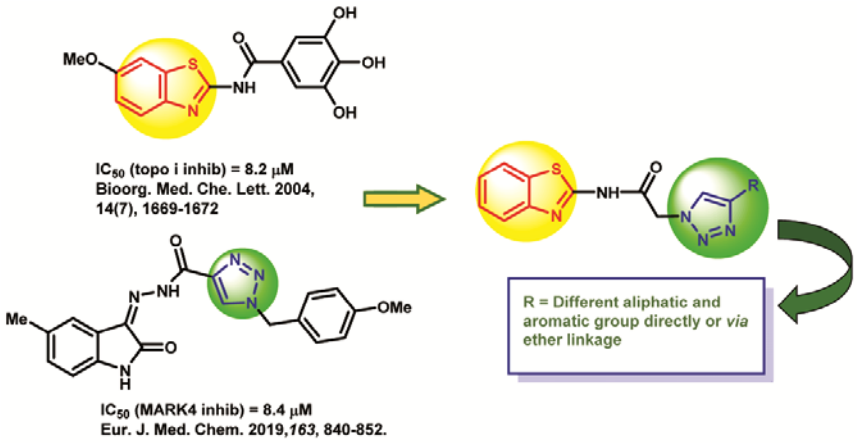
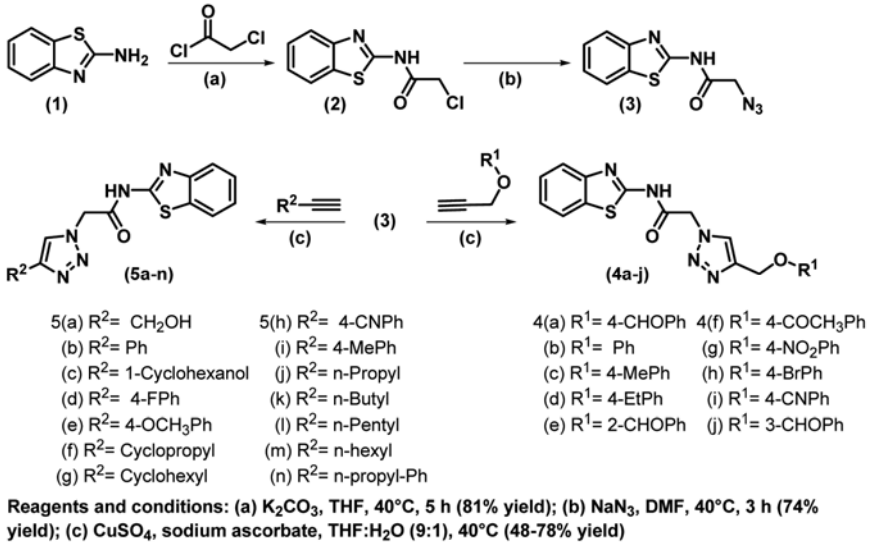


Figure 2 — Design of benzothiazole-triazole hybrids

resulted in the formation of intermediate **2**. The substitution of chloro group on intermediate **2** by azido (-N_3) using sodium azide resulted in the formation of intermediate 2-azido-*N*-benzothiazol-2-yl-acetamide (**3**) which on click reaction with various substituted alkynes resulted in the formation of desired benzothiazole-triazole hybrids **4a-j** and **5a-n**.

In silico prediction of pharmacokinetic properties:

In silico predictions of the pharmacokinetic properties of the designed hybrid molecules under study were explored using Qikprop v3.5[28]. The important parameters with inclusion of their permissible range are mentioned in Table **S2** and Table **S3** (supporting file). It was observed that the designed set of hybrid compound follows the Lipinski's rule of five, which is a preliminary criterion to test drug-likeness for a compound. For this, any compound which is orally active should not violate more than 4 Lipinski Rules[29]. In our designed set of compounds (**4a-j** and **5a-n**) as all hybrids successfully passed the Lipinski's rule, it indicates they have the potential to become orally active drug (in Table S2, supporting). *In silico* ADME predictions such as oral drug absorption (*i.e.* Percent Human Oral Absorption) was found in permissible range for all designed hybrids (in Table **S3**, supporting). The percentage values of most of the compound ranged between 80-96, while few of them showed 100% oral absorption (**4c, 4d, 5g, 5i** and **5n**). As reported earlier properties like molecular flexibilty affect oral bioavailability which is measured by the number of rotatable bonds (<15) in the compound[30]. The test set of compounds displayed rotatable bonds in the permissible range



Scheme I — Synthesis of benzothiazole-triazole hybrid

(*i.e.* < 15 rotatable bonds) (Table **S3,** supporting file). While other ADME parameters like Caco-2 cells permeability (QPPCaco) to measure intestinal drug absorption, QPlogKhsa for the prediction of human serum albumin binding both lied in the required range for all designed hybrids (Table **S3,** supporting file). Even the predicted values of brain/blood partition coefficient (QPlogBB), HERG-K+ channel inhibition (QPlogHERG) and the blood-brain barrier mimic MDCK cell permeability (QPPMDCK) all were found in permissible ranges (Table **S3,** supporting file). Overall, the molecules displayed good ADME properties.

Anti-cancer Activity

On the basis of pharmacokinetic profile, a series of 24 benzothiazole-triazole derivatives were synthesised. Initially the structure of the designed compounds was uploaded on the US-NCI-DTP website (NCI Developmental Therapeutic Program) and the 24 selected compounds were then screened against NCI 60 cell line panel from nine different tissues for *in vitro* cytotoxicity. The details of the methodology for screening of compounds against NCI cell line are provided at http://dtp.nci.nih.gov/branches/ btb/ivclsp. html. The *in-vitro* screening done by NCI is a two-step process which begins with assessment of compound against NCI 60 cell line at 10 μM concentration. Only the compounds which show growth inhibition of more than 60% are selected for five dose studies. The one dose data of the selected 24 compounds at a single-dose concentration of 10 μM, and the percentages of growth rate over tested cell lines were determined.

It can be seen from the data that most of the derivatives displayed weak growth inhibition against the mentioned cancer cell lines (Table **S1,** supporting file). Most of the compounds show 60-80% growth rate against renal cancer cell line UO-31 (Table I). Compounds **4a-4j** with benzene ring *via* ether linkage (Table I) showed 65 to 74 percent growth. Compound **4d** with *para* ethyl group showed maximum inhibition amongst the series **4a-4j** with 65% growth rate against UO-31 cell line. Replacement of ethyl group by methyl (**4c**) at *para* position resulted into decrease in inhibition. Amongst the CHO substituted derivatives compound **4j** with *meta* CHO showed lesser growth of renal cancer cell line than the *para* (**4a**) and *ortho* (**4e**), respectively. Derivative with nitro group at *para* position (**4g**) showed maximum growth rate and hence least active. Amongst the series **5a-5n** where various substituents are directly attached to triazole nucleus compound **5d** with fluoro group showed least growth rate and maximum inhibition against renal cancer cell line UO-31. Amongst the alkyl substituted derivatives increase in chain length from n-propyl (**5j**) to n-butyl (**5k**) and then n-pentyl (**5l**) leads to decrease in inhibition. However, the *n*-hexyl substituent (**5m**) led to an increase in inhibition. The cyclopropyl (**5f**) derivative was least active amongst the series.

Experimental Section

Melting points (m.p.) were determined using the EZ-Melt automated melting point apparatus (Stanford Research Systems) and are uncorrected. Nuclear magnetic resonance (NMR) spectral data for proton

Table I — Growth rate of compounds 4a-j and 5a-n against renal cancer cell line UO-31

S.No.	Entry	Growth Percent	S.No.	Entry	Growth Percent
1	4a	67.66	13	5c	76.52
2	4b	72.64	14	5d	60.63
3	4c	70.56	15	5e	71.10
4	4d	65.42	16	5f	78.40
5	4e	73.14	17	5g	76.30
6	4f	70.06	18	5h	66.75
7	4g	74.23	19	5i	67.01
8	4h	69.14	20	5j	65.95
9	4i	73.35	21	5k	67.06
10	4j	67.09	22	5l	70.22
11	5a	72.11	23	5m	62.14
12	5b	63.90	24	5n	62.89

NMR (^{1}H NMR) at 400 MHz and carbon NMR (^{13}C NMR) at 100 MHz were recorded using a Jeol ECX Spectrospin. All chemical shifts were referenced to tetramethylsilane (TMS) as internal standard reference. The shifts were reported in ppm (*i.e.* parts per million) with delta scale (δ). Infrared spectral (IR) data were determined using Perkin-Elmer FT-IR spectrophotometer. Agilent Accurate-Mass Q-TOF-MS mass spectrometer instrument was used to record mass of the compound.

Commercial reagents and analytical grade solvents used for the reaction were directly used without purification. The chemicals and solvents used were purchased from Alfa Aesar, Sigma Aldrich, TCI Chemicals and Spectrochem. Reaction progress was monitored on thin layer chromatography sheets *i.e.* (TLC) of Merck Kiesel 60 F254 of 0.2 mm sheets. Spot of intermediates and final compounds monitored on TLC were visualized on UV-lamp, iodine stain or ninhydrin stain. The final compounds were pure (>90%) enough for biological studies as per their NMR data.

Synthesis and Characterization of Compounds

Synthesis of *N*-benzothiazol-2-yl-2-chloro-acetamide[31], 2: To a solution of 2-aminobenzothiazole (5g, 33.28 mmol) in THF (50 mL) added K_2CO_3 (5g, 9.2 mmol) at 0°C followed by addition of chloroacetyl chloride (3.18 mL, 1.2 mmol). The reaction mixture was allowed to stir for 5 h at RT and the completion of reaction was monitored by TLC. After completion of reaction THF was removed followed by addition of water and the obtained white solid was filtered, dried and then used directly for the next step. Off-White solid. Yield: 81%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.78 (dd, *J* = 4.4 Hz, 8.1 Hz, 2H), 7.41 (t, *J* = 8.11Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 4.25 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.79, 157.49, 147.71, 131.95, 126.71, 124.67, 121.65, 121.12, 42.19.

Synthesis of 2-azido-*N*-benzothiazol-2-yl-acetamide[32,33], 3: To a solution of compound **2** (4 g, 17.149 mmol) in DMF (20 mL) added NaN_3 **(**2.23 g, 34.30 mmol) at 40°C and reaction was kept for 3 h. Completion of reaction was monitored by TLC. Ice was added to above reaction mixture and obtained solid was filtered and washed with cold water and dried overnight. White solid. Yield: 74%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H*)*, 7.46 (t, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 4.27 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.34, 157.95, 148.90, 131.97, 126.77, 124.30, 122.32, 121.17, 51.30.

Synthesis of compound 4 or 5: To a solution of compound **3** (200 mg, 1eq) in THF:H_2O (9:1) was added sodium ascorbate (0.02 eq) and $CuSO_4$ (0.01 eq) followed by alkyne (1.2 eq). After completion of the reaction as monitored by TLC, THF was evaporated using rotary-evaporator and the obtained product was extracted using ethyl acetate and purified by column chromatography.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((4-formylphenoxy) methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4a**: Yield: 76%. Solid. m.p.232-234°C. IR ($CHCl_3$): 3422, 3298, 3150, 2919, 2853, 2220, 1733, 1710, 1604, 1556, 1508, 1458, 1442, 1418, 1382, 1318, 1295, 1272, 1251, 1177, 1118, 1147, 1089, 1051, 1026, 863, 839, 810, 780, 757, 724, 692, 663, 633, 561, 549, 482, 463 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.88 (s, 1H), 8.35 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 6.9 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H),

5.57 (s, 2H), 5.33 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 192.28, 163.36, 142.55, 132.39, 130.38, 127.31, 126.88, 124.66, 122.38, 121.24, 115.74, 61.72, 52.10; ESI-HRMS: *m/z* Calcd for [($C_{19}H_{15}N_5O_3S$)+H]$^+$: 394.0974 (M+H)$^+$. Obsd: 394.0957(M+H)$^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4b**: Yield: 64%; solid; m.p.255-257°C. IR ($CHCl_3$): 3417, 2920, 2852, 1694, 1612, 1495, 1462, 1442, 1382, 1272, 1239, 1220, 1194, 1172, 1118, 1081, 1064, 1011, 980, 872, 822, 749, 686, 669, 639, 564, 480, 461 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.30 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 8.24 Hz, 1H), 7.29-7.34 (m, 3H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 5.56 (s, 2H), 5.17 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.30, 158.56, 157.88, 148.99, 143.22, 132.00, 130.07, 126.92, 126.84, 124.39, 122.40, 121.38, 115.12, 61.31, 52.16. ESI-HRMS: *m/z* Calcd for [($C_{18}H_{15}N_5O_2S$)+H]$^+$: 366.1025(M+H)$^+$. Obsd: 366.1031 (M+H)$^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((4-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4c**: Yield: 70%; solid; m.p.268-270°C. IR ($CHCl_3$): 3408, 292, 1698, 1611, 1576, 1511,1463, 1442, 1342, 1272, 1241, 1179, 1063, 1041, 1016, 864, 808, 751, 723, 506 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.86 (brs, 1H), 8.25 (s, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.53 (s, 2H), 5.10 (s, 2H), 2.20 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.40, 158.01, 156.51, 148.93, 143.31, 132.00, 130.38, 130.04, 126.78, 124.37, 122.38, 121.26, 115.04, 61.52, 52.21, 20.62; ESI-HRMS: *m/z* Calcd for [($C_{19}H_{17}N_5O_2S$)+H]$^+$: 380.1181(M+H)$^+$, observed: 380.1163 (M+H)$^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((4-ethylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4d**: Yield: 73%; solid; m.p.242-244°C. IR ($CHCl_3$): 3429, 2922, 1695, 1610, 1575, 1511, 1443, 1382, 1271, 1237, 1064, 1013, 865, 824, 755, 471 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.29 (s, 1H), 7.99 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.453 (t, *J* = 6.87, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.55 (s, 2H), 5.14 (s, 2H), 2.53 (q, *J* = 7.8Hz, 2H), 1.14 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.36, 157.96, 156.68, 149.01, 143.41, 136.59, 132.01, 129.20, 126.80, 124.37, 122.38, 121.29, 115.03, 61.51, 52.21, 27.84, 16.46. ESI-HRMS: *m/z* Calcd for [($C_{20}H_{19}N_5O_2S$)+H]$^+$: 394.1338 (M+H)$^+$, observed: 394.1349 (M+H)$^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((2-formylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4e**: Yield: 71%; solid; m.p.243-245°C. IR ($CHCl_3$): 3233, 2921, 1682, 1597, 1555, 1486, 1451, 1356, 1290, 1270, 1240, 1219, 1190, 1045, 979, 848, 809, 756, 693, 491 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.35 (s, 1H), 8.39-8.40 (m, 1H), 7.97-7.99 (m, 1H), 7.76-7.78 (m, 1H), 7.66-7.71 (m, 2H), 7.42-7.49 (m, 2H), 7.29-7.34 (m, 1H), 7.09-7.13 (m, 1H), 5.56 (s, 2H), 5.39 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 189.67, 166.32, 160.95, 157.96, 148.99, 142.87, 137.06, 131.99, 128.23, 127.00, 126.82, 125.01, 124.38, 122.40, 121.70, 121.28, 114.74, 62.66, 52.25. ESI-HRMS: *m/z* Calcd for [($C_{19}H_{15}N_5O_3S$)+H]$^+$: 394.0974 (M+H)$^+$. Obsd: 394.0978 (M+H)$^+$.

2-(4-((4-Acetylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(benzo[d]thiazol-2-yl)acetamide, 4f: Yield: 56%; solid; m.p.258-260°C. IR ($CHCl_3$): 3299, 3147, 2919, 2849, 1716, 1609,1541, 1519, 1497, 1454, 1412, 1342, 1295, 1262, 1224, 1167, 1141, 1110, 1063, 1041, 1025, 979, 865, 839, 762, 748, 728, 684, 655, 562, 531, 515, 493, 478, 431 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.34 (s, 1H), 7.99 (d, *J* = 6.9 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.45 (s, 1H), 7.33 (d, *J* = 6.9 Hz, 1H), 7.17 (d, *J* = 8.7Hz, 2H), 5.57 (s, 2H), 5.30 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 196.89, 166.39, 162.41, 158.01, 148.92, 142.68, 131.97, 131.02, 130.66, 127.15, 126.82, 124.38, 122.39, 121.26, 115.06, 61.77, 52.25, 26.96. ESI-HRMS: *m/z* Calcd for [($C_{20}H_{17}N_5O_3S$)+H]$^+$: 408.1130 (M+H)$^+$,observed: 408.1119(M+H)$^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((4-nitrophenoxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide 4g**: Yield: 71%; solid; m.p.256-258°C. IR ($CHCl_3$): 3220, 3147, 2923, 2853, 1735, 1705, 1658, 1600, 1559, 1511, 1460, 1442, 1421, 1380, 1358, 1318, 1293, 1277, 1250, 1182, 1148, 1080, 1048, 1024, 1004, 963, 864, 832, 806, 747, 727, 671, 632, 579, 540, 499, 485, 408 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.36 (s, 1H), 8.23 (d, *J* = 9.2 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.31 (m, 3H), 5.57 (s, 2H), 5.37 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.36, 163.84, 158.02, 148.84, 142.24, 141.58, 131.96, 127.35, 126.83, 126.4, 124.41, 122.37, 121.23, 115.85, 62.36, 52.26; ESI-HRMS: *m/z* Calcd for [($C_{18}H_{14}N_6O_4S$)+H]$^+$: 411.0875 (M+H)$^+$. Obsd: 411.0887 (M+H)$^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((4-bromophenoxy) methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4h**: Yield: 71%; solid; m.p.257-259°C. IR ($CHCl_3$): 3433, 2922, 1696, 1610, 1574, 1488, 1463, 1442, 1411, 1343, 1273, 1235, 1174, 1063, 1041, 1010, 978, 863, 815, 754, 725, 640, 616, 500 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.30 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.43-7.48 (m, 3H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 2H), 5.55 (s, 2H), 5.18 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.40, 158.15, 148.95, 142.87, 132.69, 131.99, 127.00, 126.80, 124.35, 122.37, 121.23, 117.56, 112.82, 62.00, 52.41. ESI-HRMS: *m/z* Calcd for $[(C_{18}H_{14}BrN_5O_2S)+H]^+$: 444.0130 $(M+H)^+$. Obsd: 444.0119 $(M+H)^+$, 446.0099 $(MH+2)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((4-cyanophenoxy) methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4i**: Yield: 78%; solid; m.p.267-269°C. IR ($CHCl_3$): 3416, 2921, 2853, 1695, 1606, 1459, 1441, 1382, 1304, 1273, 1243, 1163, 1064, 1012, 866, 824, 755, 726, 637, 609, 481 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.34 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 3H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 5.57 (s, 2H), 5.31 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.37, 162.03, 158.02, 148.89, 142.42, 134.74, 131.98, 127.25, 126.81, 124.37, 122.37, 121.24, 119.64, 116.34, 103.71, 61.93, 52.27; ESI-HRMS: *m/z* Calcd for $[(C_{19}H_{14}N_6O_2S)+H]^+$: 391.0977 $(M+H)^+$. Obsd: 391.0980 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-((3-formylphenoxy) methyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 4j**: Yield: 73%; solid; m.p.222-224°C. IR ($CHCl_3$): 3430, 2921, 2870, 1699, 1608, 1533, 1480, 1444, 1383, 1364, 1287, 1270, 1062, 839, 751,725, 677, 562 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 9.99 (s, 1H), 8.34 (s, 1H), 7.98-8.00 (m, 1H), 7.77-7.79 (m, 1H), 7.54-7.58 (m, 3H), 7.40-7.45 (m, 2H), 7.32-7.33 (m, 1H), 5.58 (s, 2H), 5.29 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 193.43, 166.41, 159.12, 158.07, 148.88, 142.86, 138.20, 131.99, 130.96, 127.05, 126.80, 124.36, 123.19, 122.37, 122.09, 121.24, 114.71, 61.81, 52.26; ESI-HRMS: *m/z* Calcd for $[(C_{19}H_{15}N_5O_3S)+H]^+$: 394.0974 $(M+H)^+$. Obsd: 394.0981 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 5a**: Yield: 69%; solid; m.p.222-224°C. IR($CHCl_3$): 3284, 3151, 2848, 1687, 1608, 1571, 1490, 1440, 1298, 1271, 1228, 1197, 1141, 1020, 968, 875, 813, 754, 729, 688, 572 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.03 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 5.51 (s, 2H), 5.24 (brs, 1H), 4.55 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (DMSO-d_6,100 MHz): δ 166.47, 158.02, 148.96, 148.53, 131.97, 126.82, 125.03, 124.70, 124.36, 122.38, 121.24, 55.54, 52.06; ESI-HRMS: for $[C_{12}H_{11}N_5O_2S)+H]^+$: 290.0712 $(M+H)^+$. Obsd: 290.0709$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5b**[32]: Yield: 66%; solid; m.p.248-250°C. IR ($CHCl_3$): 3432, 2923, 2854, 1721, 1645, 1601, 1541, 1463, 1441, 1381, 1349, 1294, 1272, 1233, 1177, 1131, 1078, 1048, 1020, 971, 883, 808, 770, 754, 732, 710, 693, 609, 557, 507, 494, 477, 456, 429 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.63 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.43-7.48 (m, 3H), 7.29-7.36 (m, 2H), 5.59 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 166.43, 158.09, 148.86, 146.90, 131.99, 131.14, 129.48, 128.47, 126.81, 125.72, 124.36, 123.67, 122.38, 121.23, 52.38; ESI-HRMS: *m/z* Calcd for $[(C_{17}H_{13}N_5OS)+H]^+$: 336.0919 $(M+H)^+$. Obsd: 336.0899 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(1-hydroxycyclohexyl) -1*H*-1,2,3-triazol-1-yl)acetamide, 5c**: Yield: 73%; solid; m.p.206-208°C. IR ($CHCl_3$): 3262, 3067, 2931, 2853, 1698, 1604, 1566, 1443, 1409, 1382, 1347, 1294, 1270, 1232, 1180, 1159, 1129, 1071, 1058, 1035, 1017, 980, 895, 879, 848, 833, 808, 795, 755, 722, 695, 661, 567, 522 486, 432, 408 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.00 (d, *J* = 7.8 Hz, 1H), 7.97 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 5.50 (s, 2H), 4.95 (s, 1H), 1.89 (t, *J* = 10.1 Hz, 2H), 1.67-1.74 (m, 4H), 1.52-1.57 (m, 1H), 1.43-1.46 (m, 2H), 1.23-1.34 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.44, 157.94, 156.40, 149.02, 132.01, 126.80, 124.350, 123.25, 122.37, 121.30, 68.55, 52.03, 38.36, 25.78, 22.17; ESI-HRMS: *m/z* Calcd for $[(C_{17}H_{19}N_5O_2S)+H]^+$: 358.1338 $(M+H)^+$. Obsd: 358.1332 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 5d**[33]: Yield: 72%; solid; m.p.255-257°C. IR($CHCl_3$): 3205, 3073, 2993, 1711, 1598, 1557, 1496, 1456, 1443, 1427, 1376, 1349, 1278, 1264, 1227, 1181, 1156, 1095, 1074, 1033, 985, 872, 838, 817, 795, 758, 725, 679, 656, 601, 570, 539, 517, 478, 432 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.63 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.90-7.94 (m, 2H), 7.7 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* =

7.8 Hz, 1H), 7.28-7.34 (m, 3H), 5.60 (s, 2H); ^{13}C NMR (DMSO-d_6,100 MHz): δ 166.36, 163.56, 161.13, 148.79, 146.05, 131.96, 127.80, 127.72, 126.84, 124.40, 123.58, 122.41, 121.33, 116.54, 116.33, 52.11; ESI-HRMS: *m/z* Calcd for $[(C_{17}H_{12}FN_5OS)+H]^+$: 354.0825 $(M+H)^+$. Obsd:354.0817$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 5e**[33]: Yield: 76%; m.p.242-244°C. IR ($CHCl_3$): 3431, 3084, 2922, 1725, 1596, 1556, 1542, 1457, 1442, 1411, 1373, 1273, 1249, 1175, 1085, 1050, 1025, 973, 886, 832, 816, 795, 754, 607, 562, 530, 478 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.53 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 3H), 7.46 (t, *J* = 7.3Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 2H), 5.58 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.48, 159.60, 158.07, 148.91, 146.89, 132.01, 127.11, 126.81, 124.38, 123.72, 122.69, 122.37, 121.24, 114.88, 55.65, 52.33; ESI-HRMS: Calcd for $[(C_{18}H_{15}N_5O_2S)+H]^+$: 366.1025$(M+H)^+$. Obsd: 366.1011 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5f**: Yield: 68%; solid; m.p.230-232°C. IR ($CHCl_3$): 3134, 3084, 2916, 1713, 1604, 1558, 1481, 1443, 1411, 1375, 1334, 1311, 1292, 1270, 1219, 1186, 1141, 1063, 1017, 979, 901, 871, 810, 748, 717, 671, 614, 570, 540, 515, 431 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.89 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.4 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 6.9 Hz, 1H), 5.46 (s, 2H), 1.93-1.99 (m, 1H), 0.88-0.92 (m, 2H), 0.71-0.75 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.47, 158.02, 149.49, 148.79, 131.91, 126.84, 124.40, 123.09, 122.34, 121.21, 52.02, 8.18, 6.98; ESI-HRMS: *m/z* Calcd for $[(C_{14}H_{13}N_5OS)+H]^+$: 300.0919 $(M+H)^+$, Observed Mass: 300.0902$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-cyclohexyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5g**: Yield: 69%; solid; m.p.222-224°C. IR ($CHCl_3$): 3627, 3408, 2922, 1721, 1602, 1559, 1536, 1498, 1442, 1364, 1272, 1229, 1180, 1156, 1081, 1049, 975, 830, 755, 601, 477 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.98 (d, *J* = 7.8, 1H), 7.89 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 5.46 (s, 2H), 2.66-2.70 (m, 1H), 1.95-1.97 (m, 2H), 1.65-1.74 (m, 2H), 1.31-1.43 (m, 4H), 1.22-1.24 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.52, 158.01, 152.62, 148.90, 131.98, 126.79, 124.34, 122.81, 122.35, 121.24, 52.03, 35.12, 33.06, 26.14; ESI-HRMS: *m/z* Calcd for $[(C_{17}H_{19}N_5OS)+H]^+$: 342.1389 $(M+H)^+$. Obsd: 342.1394$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(4-cyanophenyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 5h**[33]: Yield: 50%; solid; m.p.246-248°C. IR ($CHCl_3$): 3369, 3142, 2920, 2852, 2220, 1683, 1647, 1602, 1564, 1490, 1448, 1392, 1352, 1298, 1269, 1184, 1070, 1037, 1014, 972, 875, 844, 800, 771, 678, 623, 576, 547 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.84 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 7.8Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 5.64 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.25, 158.05, 148.89, 145.34, 135.57, 133.60, 131.97, 126.84, 125.39, 124.41, 122.42, 121.27, 119.36, 110.74, 52.50; ESI-HRMS: *m/z* Calcd for $[(C_{18}H_{12}N_6OS)+H]^+$: 361.0872 $(M+H)^+$. Obsd:361.0877 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 5i**: Yield: 73%; solid; m.p.263-265°C. IR ($CHCl_3$): 3626, 3403, 3154, 3047, 2922, 2853, 1852, 1806, 1729, 1652, 1597, 1548, 1497, 1445, 1413, 1381, 1342, 1294, 1271, 1234, 1209, 1173, 1132, 1071, 1048, 987, 971, 879, 804, 766, 648, 556, 539, 489, 471, 408 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.57 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.75-7.79 (m, 3H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.3Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 5.58 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.20, 157.83, 148.65 146.79, 137.66, 131.74, 129.85, 128.07, 126.64, 125.45, 124.21, 123.03, 122.15, 121.03, 52.08, 21.15; ESI-HRMS: *m/z* Calcd for $[(C_{18}H_{15}N_5OS)+H]^+$: 350.1076 $(M+H)^+$. Obsd: 350.1071$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-propyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5j**: Yield: 51%; solid; m.p.208-210°C. IR ($CHCl_3$): 3435, 2922, 1681, 1605, 1568, 1442, 1427, 1381, 1266, 1219, 1143, 1055, 978, 872, 795, 747, 725, 663, 570, 481 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.80 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J*=7.8 Hz, 1H), 5.36 (s, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 1.47-1.56 (m, 2H), 0.81 (t, *J* =7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.52, 158.00, 149.00, 147.24, 131.97, 126.80, 124.34, 124.15, 122.37, 121.24, 52.00, 27.54, 22.80, 14.16; ESI-HRMS: *m/z* Calcd for $[(C_{14}H_{15}N_5OS)+H]^+$: 302.1076 $(M+H)^+$. Obsd: 302.1084$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5k**: Yield: 54%; solid; m.p.199-201°C. IR ($CHCl_3$): 3409, 3133, 3005, 2953,

2925, 2854, 1689, 1606, 1567, 1459, 1442, 1427, 1381, 1287, 1267, 1199, 1142, 1086, 1055, 1034, 981, 956, 874, 831, 817, 749, 725, 689, 663, 618, 569, 480, 429 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.90 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.3Hz, 1H), 7.31 (d, *J* = 7.3Hz, 1H), 5.47 (s, 2H), 2.64 (d, *J* = 7.8 Hz, 2H), 1.55-1.62 (m, 2H), 1.28-1.38 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.48, 157.93, 148.97, 147.40, 131.97, 126.82, 124.36, 124.11, 122.38, 121.28, 51.97, 31.64, 25.14, 22.21, 14.25; ESI-HRMS: *m/z* Calcd for $[(C_{15}H_{17}N_5OS)+H]^+$: 316.1232 $(M+H)^+$. Obsd: 316.1238$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5l**: Yield: 48%; solid; m.p.203-205°C. IR ($CHCl_3$): 3182, 3147, 3066, 2991, 2924, 2860, 1680, 1602, 1558, 1463, 1435, 1361, 1292, 1261, 1193, 1143, 1087, 1053, 1022, 974, 927, 871, 812, 788, 750, 723, 661, 569, 538, 514 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.96 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.75 (d, *J*= 8.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 5.45 (s, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.54-1.61 (m, 2H), 1.25-1.30 (m, 4H), 0.84 (t, *J* = 6.9 Hz, 3H); ESI-HRMS: *m/z* Calcd for $[(C_{16}H_{19}N_5OS)+H]^+$: 330.1389 $(M+H)^+$. Obsd: 330.1372 $(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-hexyl-1*H*-1,2,3-triazol-1-yl)acetamide, 5m**: Yield: 50%; solid; m.p.204-206°C. IR ($CHCl_3$): 3432, 3126, 3062, 2923, 2853, 1726, 1595, 1556, 1536, 1457, 1442 1405, 1363, 1273, 1226, 1211, 1172, 1057, 977, 886, 824, 754, 729, 562, 478 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J*= 8.2 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 5.35 (s, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 1.44-1.49 (m, 2H), 1.09-1.15 (m, 6H), 0.73 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ =166.16, 157.67, 148.50, 147.15, 131.58, 126.50, 124.06, 123.79, 122.02, 120.88, 51.64, 31.19, 29.08, 28.42, 25.10, 22.21, 14.10; ESI-HRMS: *m/z* Calcd for $[(C_{17}H_{21}N_5OS)+H]^+$: 344.1545 $(M+H)^+$. Obsd: 344.1549$(M+H)^+$.

***N*-(Benzo[d]thiazol-2-yl)-2-(4-(4-propylphenyl)-1*H*-1,2,3-triazol-1-yl)acetamide, 5n**: Yield: 62%; solid; m.p.249-251°C. IR ($CHCl_3$): 3912**,** 3883, 3775, 3719, 3659, 3430, 2923, 2854, 1853, 1721, 1597, 1557, 1535, 1443, 1381, 1272, 1233, 1176, 1079, 1049, 977, 884, 813, 748, 725, 561, 471, 433, 414 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.47 (s, 1H), 7.89 (d, *J* = 7.79 Hz, 1H), 7.67-7.69 (m, 3H), 7.35 (t, *J*=7.8 Hz, 1H), 7.22 (t, *J*=7.3 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 5.49 (s, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 1.46-1.54 (m, 2H), 0.80 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.45, 158.11, 148.93, 146.98, 142.48, 132.01, 129.43, 128.66, 126.81, 125.67, 124.36, 123.27, 122.40, 121.24, 52.34, 37.52, 24.51, 14.15; ESI-HRMS: *m/z* Calcd for $[(C_{20}H_{19}N_5OS)+H]^+$: 378.1389 $(M+H)^+$. Obsd: 378.1381$(M+H)^+$.

Conclusion

Herein we report the design, synthesis and one dose anticancer activity (selected by NCI) of 24 benzothiazole-triazole hybrids. All of the synthesized compounds showed growth percent in the range of 60-80% for UO-31 renal cancer cell line (data obtained from NCI). As the designed series even follow *in silco* pharmacokinetic parameters, hence these compounds can result in design and development of potent leads.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgement

The authors are thankful to USIC-CIF, University of Delhi, Delhi for analytical data. SR is thankful to CSIR for awarding CSIR-JRF and CSIR-SRF fellowship and BN is thankful to BSR UGC for Start UP grant letter No F.30-358/2017(BSR). The authors are thankful to National Cancer Institute (NCI) for initial screening of compounds.

References

1 Boyle P & Levin B, World Cancer Report 2008, *International Agency for Research on Cancer* (IARC) Lyon (2008).
2 Bray F; Ferlay J, Soerjomataram I, Siegel R L, Torre L A & Jemal A, *Cancer J Clin*, 68 (2018) 394.
3 Cantley L C, Dalton W S, DuBois R N, Finn O J, Futreal P A, Golub T R, Hait W N, Lozano G, Maris J M, Nelson W G, Sawyers C L, Schreiber S L, Spitz M R & Steeq P S, *Clin Cancer Res*,18 (2012) S1-S100.
4 Sawyers C, *Nature*, 432 (2004) 294.
5 Bode A M & Dong Z G, *Nat Rev Cancer*, 9 (2009) 508.
6 Gediya L K & Njar V C, *Expert Opin Drug Dis*, 4 (2009) 1099.
7 Morphy R, Kay C & Rankovic Z, 9 (2004) 641.
8 Bondock S, Fadaly W & Metwally M A, *Eur J Med Chem*, 45 (2010) 3692.
9 Delmas F, Avellaneda A, Di Giorgio C, Robin M, De Clercq E, Timon-David P & Galy J P, *Eur J Med Chem*, 39 (2004) 685.
10 Hong S, Kim J, Yun S M, Lee H, Park Y, Hong S S & Hong S, *J Med Chem*, 56 (2013) 3531.
11 Ke S, Wei Y, Yang Z, Wang K, Liang Y & Shi L, *Bioorg Med Chem Lett*, 23 (2013) 5131.

12 Sarkar S, Siddiqui A A, Saha S J, De R, Mazumder S, Banerjee C, Iqbal M S, Nag S, Adhikari S & Bandyopadhyay U, *Antimicrob Agents Chemother*, 60 (2016) 4217.
13 Gagoria J, Verma P K & Khatkar A, *Cent Nerv Syst Agents Med Chem*, 15 (2015) 11.
14 Dubey R, Shrivastava P K, Basniwal P K, Bhattacharya S, Moorthy N & Narayana S, *Mini Rev Med Chem*, 6 (2006) 633.
15 Kaplan-Ozen C, Tekiner-Gulbas B, Foto E, Yildiz I, Diril N, Aki E & Yalcin I, *Med Chem Res*, 22 (2013) 5798.
16 Keri R S, Patil M R, Patil S A & Budagumpi S A, *Eur J Med Chem*, 89 (2015) 207.
17 Aki-Yalcin E, Ertan-Bolelli T, Taskin-Tok T, Ozturk O, Ataei S, Ozen C, Yildiz I & Yalcin I, *SAR QSAR Environ Res*, 25 (2014) 637.
18 Kamal A, Kumar B A, Suresh P, Shankaraiah N & Kumar M S, *Bioorg Med Chem Lett*, 21 (2011) 350.
19 Khan K M, Rahim F, Halim S A, Taha M, Khan M, Perveen S, Mesaik M A & ChoudharyM I, *Bioorg Med Chem*, 19 (2011) 4286.
20 O'Brien S E, Browne H L, Bradshaw T D, Westwell A D, Stevens M F & Laughton C A, *Org Biomol Chem*, 1 (2003) 493.
21 Oanh D T K, Van Hai H, Park S H, Kim H J, Han B W, Kim H S, Hong J T, Han S B & Nam N H, *Bioorg Med Chem Lett*, 21 (2011) 7509.
22 Kharb R, Sharma P C & Yar M S, *J Enzyme Inhib Med Chem*, 26(1) (2011) 1.
23 Kumar S S & Kavitha H P, *Min Rev Org Chem*, 10(1) (2013) 40.
24 Manohar S, Pepe A, Gerena C E V, Zayas B, Malhotra S V & Rawat D S, *RSC Adv*, 4 (2014) 7062.
25 Thakur A, Manohar S, Gerena C E V, Zayas B, Kumar V, Malhotra S V & Rawat D S, *Med Chem Commun*, 5 (2014) 576.
26 Kandi S K, Manohar S, Gerena C E V, Zayas B, Malhotra S V & Rawat D S, *New J Chem*, 39 (2015) 224.
27 Anthwal A, Singh K, Rawat M S M, Tyagi A K, Aggarwal B B & Rawat D S, *RSC Adv*, 4 (2014) 28756.
28 QikProp, version 3.5, Schrodinger, LLC, New York, NY (2012).
29 QikProp User Manual Copyright © 2013 Schrödinger, LLC.
30 Lu J J, Crimin K, Goodwin J T, Crivori P, Orrenius C, Xing L, Tandler P J, Vidmar T J, Amore B M, Wilson A G & Stouten P F, *J Med Chem*, 47 (2004) 6104.
31 Pedgaonkar GS, Sridevi JP, Jeankumar VU, Saxena S, Devi PB, Renuka J, Yogeeswari P & Sriram D. *Eur J Med Chem*, *8*6 (2014) 613.
32 Rezki N, *Molecules*, 21 (2016) 505.
33 Zhao C, Huang D, Li R, Xu Y, Su S, Gu Q & Xu J. *J Med Chem*, 62 (2019) 5885.