Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Design, synthesis and biological evaluation of novel benzthiazole and triazole analogs as inhibitors of falcipain, cysteine protease of malaria parasite Plasmodium falciparum.

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Figure S1 and S2, ^{1}H and ^{13}CNMR spectra of synthesized compounds

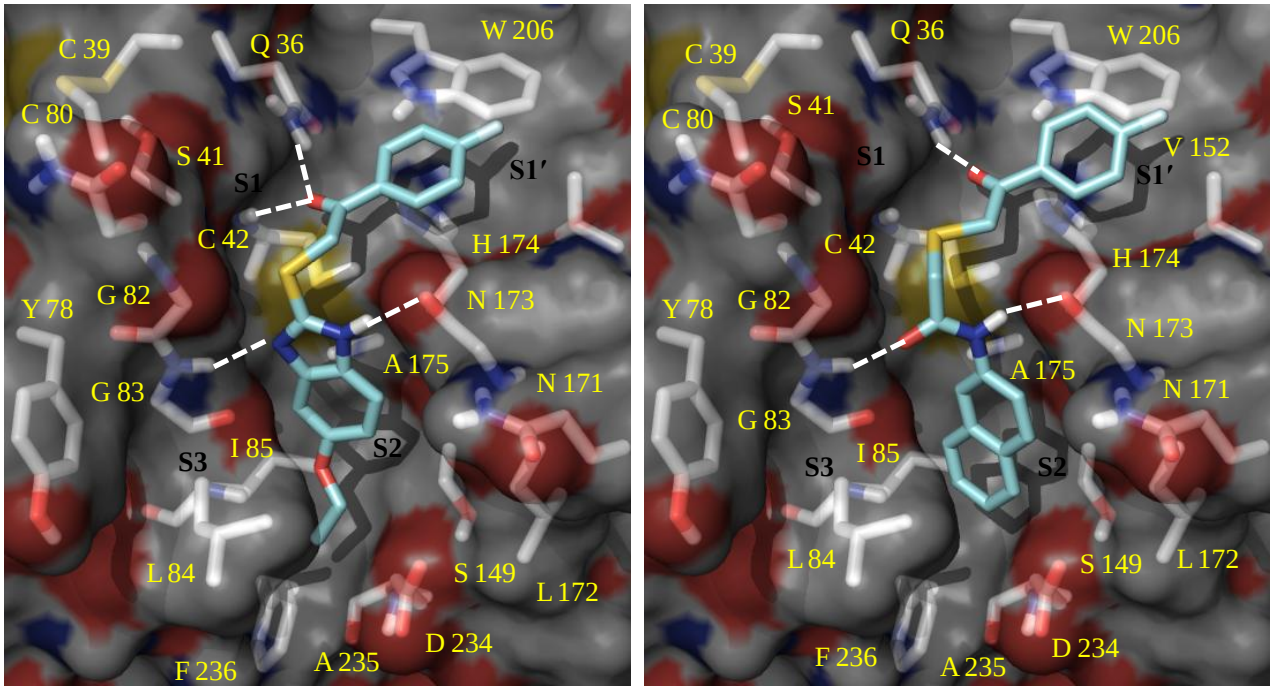

Figure S1. Docking pose of representative compounds from benzimidazole (**3**) and thioacetamide (**7**) series.

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FP-2     LINNAFEDMIELGGICP---DGDYPYVSDAPNLCNIDRCTEKYGIKNYLS 130
FP-3     YITNAFDDMIDLGGLCS---QDDYPYVSNLPETCNLKRCNERYTIKSYVS 139
CAT_K    YMTNAFQYVQKNRGIDS---EDAYPYVGQE-ESCMYNPTGKAAKCRGYRE 113
CAT_L1   LMDYAFQYVQDNGGLDS---EESYPYEATE-ESCKYNPKYSVANDTGFVD 112
CAT_B    YPAEAWNFWTRKGLVSGGLYESHVGCRPYSIPPCEHHVNGSRPPCTGEGD 150

FP-2     VPD-----------------------------NKLKEALRFLGPISISV 150
FP-3     IPD-----------------------------DKFKEALRYLGPISISI 159
CAT_K    IPEG---------------------------NEKALKRAVARVGPVSVAI 136
CAT_L1   IPK----------------------------QEKALMKAVATVGPISVAI 134
CAT_B    TPKCSKICEPGYSPTYKQDKHYGYNSYSVSNSEKDIMAEIYKNGPVEGAF 200

FP-2     YYYIIKNSWGQQWGERGFINIETDESGLMRKCGLGTDAFIPLIE------ 241
FP-3     YYYIIKNSWGSDWGEGGYINLETDENGYKKTCSIGTEAYVPLLE------ 250
CAT_K    KHWIIKNSWGENWGNKGYILMARNKN---NACGIANLASFPKM------- 216
CAT_L1   KYWLVKNSWGEEWGMGGYVKMAKDRR---NHCGIASAASYPTV------- 218
CAT_B    PYWLVANSWNTDWGDNGFFKILRGQD----HCGIESEVVAGIPRTDQYWE 284
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Figure S2. Multiple sequence alignment of FPs with homologous cysteine proteases performed using Clustal 2.0.12. Only interested portion of alignment is shown here (See ref[19] for full alignment). Sequence information is from SWISS-PROT (accession numbers *(m/z)*: Q9NAW2, Q9NB39, P43235, P07711 and P07858). The conserved residues are shown in green. The amino acid residues of S2 pocket differing between FPs and mammalian cysteine proteases are highlighted in red

^{1}H and ^{13}C spectra of intermediates and final compounds were recorded on Bruker 500MHz, 400MHz, or Bruker 400MHz Ultra Shield and the analyses conducted in CDCl3, MeOD, or DMSO-d6.

2-((6-aminobenzo[d]thiazol-2-yl)thio)-1-phenylethanone (16)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06 (d, *J* = 6.84 Hz, 2H), 7.64 - 7.78 (m, 1H), 7.58 (d, *J* = 6.41 Hz, 2H), 7.43 (d, *J* = 8.55 Hz, 1H), 6.99 (br. s., 1H), 6.69 (d, *J* = 7.27 Hz, 1H), 5.34 (br. s., 2H), 5.03 (br. s., 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 193.2, 157.4, 146.6, 144.1, 136.6, 135.4, 133.7, 128.8, 128.4, 121.5, 114.4, 103.9, 40.9; HRMS *(m/z)*: [M +H] calcd for $C_{15}H_{13}N_2OS_2$ 301.0469, found 301.0448

2-((6-aminobenzo[d]thiazol-2-yl)thio)-1-(naphthalen-2-yl)ethanone (17)

^{1}H NMR (500 MHz, DMSO-d6) d 8.83 (br. s., 1H), 8.11 - 8.42 (m, 2H), 8.04 (br. s., 2H), 7.58 - 7.78 (m, 2H), 7.44 (br. s., 1H), 7.01 (br. s., 1H), 6.70 (br. s., 1H), 5.27 - 5.47 (m, 2H), 5.17 (br. s., 2H); 13C NMR (126 MHz, DMSO-d6) d 193.0, 157.3, 146.5, 144.0, 136.5, 135.1, 132.5, 131.9, 130.5, 129.5, 128.8, 128.3, 127.6, 126.9, 123.6, 121.3, 114.2, 103.7
HRMS *(m/z)*: [M + H] calcd for $C_{19}H_{15}N_2OS_2$ 351.0626, found 351.0626

ethyl 2-((6-aminobenzo[d]thiazol-2-yl)thio)acetate (18)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (dd, *J* = 3.14, 8.41 Hz, 1H), 7.00 (br. s., 1H), 6.66 - 6.86 (m, 1H), 5.36 (br. s., 2H), 4.16 - 4.29 (m, 2H), 4.13 (dd, *J* = 3.01, 7.03 Hz, 2H), 1.09 - 1.30 (m, 3H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 146.7, 144.1, 136.6, 135.9, 121.6, 114.4, 103.9, 61.2, 34.8, 14.0; HRMS *(m/z)*: [M + H] calcd for $C_{11}H_{13}N_2O_2S_2$ 269.0418, found 269.0389

2-((6-aminobenzo[d]thiazol-2-yl)thio)-*N*-(*p*-tolyl)acetamide (19)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (br. s., 1H), 7.42 - 7.66 (m, 2H), 7.10 (br. s., 2H), 6.74 (br. s., 1H), 5.34 (br. s., 2H), 4.24 (br. s., 2H), 2.14 - 2.39 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 157.8, 146.7, 144.3, 136.7, 136.3, 132.6, 129.2, 121.6, 119.3, 114.5, 104.0, 37.9, 20.5; HRMS *(m/z)*: [M + H] calcd for $C_{16}H_{16}N_3OS_2$ 330.0735, found 330.0700

2-nitro-*N*-(2-((2-oxo-2-phenylethyl)thio)benzo[d]thiazol-6-yl)benzenesulfonamide (20)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.07 (d, *J* = 7.28 Hz, 2H), 7.87 (d, *J* = 7.78 Hz, 1H), 7.76 - 7.80 (m, 1H), 7.67 - 7.72 (m, 2H), 7.62 - 7.67 (m, 2H), 7.55 - 7.59 (m, 1H), 7.50 - 7.55 (m, 2H), 7.35 (s, 1H), 7.17 (dd, *J* = 2.13, 8.66 Hz, 1H), 4.93 (s, 2H); ^{13}C NMR (126 MHz, CHLOROFORM-d) δ 193.8, 166.9, 150.6, 148.4, 136.3, 135.8, 135.5, 134.7, 133.6, 133.3, 131.6, 130.8, 129.7, 129.1, 125.2, 122.1, 121.6, 115.2, 41.3; HRMS *(m/z)*: [M - H] calcd for $C_{21}H_{14}N_3O_5S_3$ 484.0095, found 484.0066

_N_-(2-((2-oxo-2-phenylethyl)thio)benzo[d]thiazol-6-yl)-4-(trifluoromethoxy)benzene sulfonamide (21)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.06 - 8.12 (m, 2H), 7.77 (d, *J* = 8.78 Hz, 2H), 7.62 - 7.67 (m, 2H), 7.58 (d, *J* = 2.01 Hz, 1H), 7.50 - 7.56 (m, 2H), 7.25 (s, 1H), 6.99 (dd, *J* = 2.26, 8.53 Hz, 1H), 6.64 (br. s., 1H), 4.94 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.8, 179.1, 165.4, 151.1, 149.7, 138.1, 135.7, 135.3, 133.9, 133.8, 129.3, 128.9, 128.4, 121.5, 121.4, 120.2, 113.8, 40.9; HRMS *(m/z)*: [M-H] calcd for $C_{22}H_{13}F_3N_2O_4S_3$ 523.0067, found 523.9977

_N_-(2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)-4-(trifluoromethoxy)benzenesulfonamide (22)

^{1}H NMR (400 MHz, DMSO-d6) d 8.86 (br. s., 1H), 8.16 (br. s., 2H), 7.99 - 8.12 (m, 2H), 7.86 (br. s., 1H), 7.60 - 7.81 (m, 3H), 7.27 (br. s., 1H), 5.29 (br. s., 2H), 4.56 (d, J = 9.54 Hz, 2H), 4.13 (br. s., 1H), 1.27 (br. s., 3H), 0.86 (br. s., 2H); ^{13}C NMR (126 MHz, CHLOROFORM-d) δ 192.7, 165.2, 149.7, 135.8, 135.3, 133.7, 132.7, 132.1, 130.7, 129.7, 129.0, 128.5, 127.7, 127.1, 123.7, 121.5, 120.2, 113.3, 41.0; HRMS *(m/z)*: calcd for $C_{21}H_{14}F_3N_2O_3S_3$ 495.0041, found 495.0118

_N_-(2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)acetamide (23)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.65 (s, 1H), 8.27 (br. s., 1H), 8.10 (dd, *J* = 1.71, 8.55 Hz, 1H), 7.99 (d, *J* = 7.69 Hz, 1H), 7.93 (dd, *J* = 8.33, 17.31 Hz, 2H), 7.72 (d, *J* = 8.55 Hz, 1H), 7.65 (t, *J* = 7.05 Hz, 1H), 7.59 (t, *J* = 7.05 Hz, 1H), 7.34 (br. s., 1H), 7.20 - 7.26 (m, 1H), 5.07 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 192.9, 181.9, 168.4, 163.8, 136.2, 135.4, 135.3, 132.7, 132.1, 130.7, 129.7, 129.0, 128.5, 127.7, 127.1, 123.7, 121.0, 118.4, 111.1, 79.2, 41.0, 24.0; HRMS *(m/z)*: [M + Na] calcd for $C_{21}H_{16}N_2NaO_2S_2$ 415.0550, found 415.0566

_N_-(2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)quinoline-8-sulfonamide (24)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.15 - 9.22 (m, 1H), 8.58 (s, 1H), 8.55 (br. s., 1H), 8.32 (br. s., 1H), 8.30 (d, *J* = 2.35 Hz, 1H), 8.00 - 8.07 (m, 2H), 7.96 (d, *J* = 8.02 Hz, 1H), 7.86 - 7.94 (m, 2H), 7.64 (dt, *J* = 4.18, 8.27 Hz, 2H), 7.53 - 7.60 (m, 2H), 7.50 - 7.53 (m, 1H), 7.48 (d, *J* = 8.80 Hz, 1H), 6.92 (dd, *J* = 1.96, 8.61 Hz, 1H), 4.99 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 192.7,

164.6, 151.5, 149.1, 142.7, 137.0, 135.4, 135.2, 135.0, 134.6, 134.3, 132.6, 132.2, 132.1, 130.7, 129.6, 129.0, 128.4, 128.4, 127.7, 127.1, 125.6, 123.7, 122.6, 121.1, 119.6, 112.5, 41.0; HRMS (*m*/z): [M + Na] calcd for $C_{28}H_{19}N_3O_3S_3Na$, 564.0486; found, 564.0499

4-fluoro-*N*-(2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)benzene sulfonamide (25)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.63 (s, 1H), 8.08 (s, 1H), 7.99 (d, *J* = 8.12 Hz, 1H), 7.92 (dd, *J* = 8.33, 16.03 Hz, 2H), 7.75 (dd, *J* = 4.92, 8.76 Hz, 2H), 7.58 - 7.69 (m, 3H), 7.55 (d, *J* = 1.71 Hz, 1H), 7.09 (t, *J* = 8.55 Hz, 1H), 6.98 - 7.04 (m, 1H), 5.05 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 192.7, 165.3, 149.6, 135.7, 135.2, 134.1, 132.6, 132.1, 130.7, 129.7, 129.7, 129.0, 128.5, 128.4, 127.7, 127.1, 127.0, 123.7, 121.4, 120.2, 116.5, 116.3, 113.6, 40.9; HRMS *(m*/z): [M + Na] calcd for $C_{25}H_{17}FN_2O_3S_3Na$, 531.0283; found, 531.0308

ethyl 2-((6-(2,2,2-trifluoroethylsulfonamido)benzo[d]thiazol-2-yl)thio)acetate (26)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.74 (d, *J* = 8.55 Hz, 1H), 7.69 (s, 1H), 7.40 (br. s., 1H), 7.22 (dd, *J* = 2.14, 8.55 Hz, 1H), 4.28 (d, *J* = 7.27 Hz, 4H), 4.16 (s, 2H), 3.80 (d, *J* = 8.98 Hz, 2H), 1.32 (t, *J* = 7.05 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.0, 164.8, 149.7, 135.9, 133.7, 123.4, 121.7, 120.3, 113.4, 61.4, 52.5, 34.7, 14.0; HRMS *(m/z)*: [M + H] calcd for $C_{13}H_{14}$ $F_3N_2O_4S_3$ 415.0068, found 415.0059

ethyl 2-((6-(4-fluorophenylsulfonamido)benzo[d]thiazol-2-yl)thio)acetate (27)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.72 - 7.81 (m, 2H), 7.63 (d, *J* = 8.61 Hz, 1H), 7.56 (s, 1H), 7.17 (br. s., 1H), 7.10 (t, *J* = 8.51 Hz, 2H), 7.01 (dd, *J* = 1.96, 8.61 Hz, 1H), 4.26 (q, *J* = 7.17 Hz, 2H), 1.30 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.0, 165.3, 164.8, 163.3, 149.5, 135.8, 135.6, 134.2, 129.8, 129.7, 121.5, 120.2, 116.5, 116.3, 113.6, 61.3, 34.7, 13.9; HRMS *(m/z)*: [M +H] calcd for $C_{17}H_{16}FN_2O_4S_3$ 427.0256 found 427.02562

ethyl 2-((6-(2-nitrophenylsulfonamido)benzo[d]thiazol-2-yl)thio)acetate (28)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.85 - 7.93 (m, *J* = 7.69 Hz, 1H), 7.80 (d, *J* = 7.69 Hz, 1H), 7.71 (br. s., 2H), 7.54 - 7.61 (m, 1H), 7.38 (br. s., 1H), 7.29 (s, 1H), 7.16 - 7.23 (m, *J* = 8.12 Hz, 1H), 4.23 - 4.31 (m, 2H), 4.16 (s, 2H), 1.31 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 165.3, 149.8, 147.9, 135.8, 134.7, 133.3, 132.6, 131.2, 130.1, 124.6, 121.6, 120.6, 114.2, 61.4, 34.7, 14.0; HRMS *(m/z)*: [M + Na] calcd for $C_{17}H_{15}N_3NaO_6S_3$ 476.0021, found 476.0068

ethyl 2-((6-(quinoline-7-sulfonamido)benzo[d]thiazol-2-yl)thio)acetate (29)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 9.20 (d, *J* = 4.27 Hz, 1H), 8.58 (br. s., 1H), 8.33 (t, *J* = 6.62 Hz, 2H), 8.04 (d, *J* = 8.12 Hz, 1H), 7.65 (dd, *J* = 4.27, 8.55 Hz, 1H), 7.55 - 7.61 (m, 2H), 7.53 (d, *J* = 8.55 Hz, 1H), 6.93 (dd, *J* = 1.92, 8.76 Hz, 1H), 4.21 (q, *J* = 7.12 Hz, 2H), 4.09 (s, 2H), 1.26 (t, *J* = 7.05 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.9, 164.1, 151.5, 149.0, 142.7, 136.9, 135.4, 135.0, 134.7, 134.3, 132.2, 128.3, 125.6, 122.6, 121.2, 119.6, 112.6, 61.3, 34.6, 13.9; HRMS *(m/z)*: [M+H] calcd for $C_{20}H_{18}N_3O_4S_3$ 460.0459, found 460.0483

***N*-(*p*-tolyl)-2-((6-(2,2,2-trifluoroethylsulfonamido)benzo[d]thiazol-2-yl)thio) acetamide (30)**

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 - 10.34 (m, 1H), 9.77 (br. s., 1H), 7.69 - 7.75 (m, 1H), 7.40 - 7.46 (m, 1H), 7.32 - 7.37 (m, 2H), 7.31 (br. s., 1H), 7.01 (d, *J* = 8.12 Hz, 2H), 4.09 (br. s., 2H), 3.72 - 3.89 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.2, 164.6, 149.7, 143.7, 135.7, 133.3, 132.4, 128.8, 121.2, 119.8, 119.1, 112.9, 37.5, 20.3; HRMS *(m/z)*: [M - H] calcd for $C_{18}H_{15}F_3N_3O_3S_3$ 474.0306, found 474.0145

2-((6-acetamidobenzo[d]thiazol-2-yl)thio)-*N*-(*p*-tolyl)acetamide (31)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (br. s., 1H), 9.67 (br. s., 1H), 8.28 (s, 1H), 7.66 (d, *J* = 8.98 Hz, 1H), 7.48 - 7.54 (m, 1H), 7.39 - 7.44 (m, 1H), 7.35 (d, *J* = 8.12 Hz, 2H), 7.00 (d, *J* = 8.12 Hz, 2H), 4.08 (br. s., 2H), 2.21 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.5, 165.0, 164.1, 148.5, 136.3, 135.4, 132.6, 129.2, 121.0, 119.2, 118.5, 111.2, 37.8, 24.0, 20.4; HRMS *(m/z)*: [M + H] calcd for $C_{18}H_{18}N_3O_2S_2$ 372.0840, found 372.0797

2-((6-(quinoline-7-sulfonamido)benzo[d]thiazol-2-yl)thio)-*N*-(*p*-tolyl)acetamide (32)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 9.59 (br. s., 1H), 9.22 (d, *J* = 2.99 Hz, 1H), 8.69 (br. s., 1H), 8.35 (dd, *J* = 8.12, 9.83 Hz, 2H), 8.06 (d, *J* = 7.69 Hz, 1H), 7.68 (dd, *J* = 4.06, 8.33 Hz, 1H), 7.64 (d, *J* = 8.55 Hz, 1H), 7.60 (d, *J* = 7.69 Hz, 1H), 7.56 - 7.59 (m, 1H), 7.33 (d, *J* = 8.12 Hz, 2H), 7.29 (s, 1H), 7.07 (d, *J* = 8.12 Hz, 2H), 3.99 (s, 2H), 2.26 - 2.36 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.8, 151.5, 149.2, 142.7, 137.0, 136.2, 135.4, 135.0, 134.6, 134.3, 132.5, 132.2, 129.2, 128.4, 125.6, 122.6, 121.1, 119.6, 119.2, 112.6, 52.9, 37.7, 20.4; HRMS (m/z): [M + Na] calcd for $C_{25}H_{20}N_4O_3S_3Na$, 543.0595; found 543.0584

2-((6-(4-fluorophenylsulfonamido)benzo[d]thiazol-2-yl)thio)-*N*-(*p*-tolyl)acetamide (33)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 9.55 (br. s., 1H), 7.78 (dd, *J* = 5.77, 8.33 Hz, 3H), 7.62 (d, *J* = 1.71 Hz, 1H), 7.36 (d, *J* = 8.55 Hz, 2H), 7.08 - 7.17 (m, 4H), 6.78 (br. s., 1H), 4.06 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 165.4, 163.5, 150.1, 136.7, 136.2, 136.0, 134.6, 133.0, 130.2, 129.6, 121.9, 120.7, 119.7, 117.0, 116.8, 114.1, 63.8, 38.2, 20.8; HRMS *(m/z)*: [M + H] calcd for $C_{22}H_{19}FN_3O_3S_3$ 488.0573, found 488.0602

***N*-(*p*-tolyl)-2-((6-(4-(trifluoromethoxy)phenylsulfonamido)benzo[d]thiazol-2-yl)thio) acetamide (34)**

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.60 (br. s., 1H), 7.80 (dd, *J* = 2.35, 8.80 Hz, 2H), 7.64 (d, *J* = 1.96 Hz, 1H), 7.36 (d, *J* = 8.22 Hz, 2H), 7.28 (br. s., 1H), 7.14 (d, *J* = 1.76 Hz, 1H), 7.10 (d, *J* = 8.41 Hz, 2H), 6.81 (br. s., 1H), 4.06 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.9, 151.0, 149.6, 136.2, 136.0, 135.8, 134.5, 132.6, 129.3, 129.2, 121.4, 120.4, 119.2, 113.7, 63.2, 37.7, 20.4; HRMS *(m/z)*: [M +H] calcd for $C_{23}H_{19}F_3N_3O_4S_3$ 553.0412, found 553.0545

***(R)*-tert-butyl (3-methyl-1-oxo-1-((2-((2-oxo-2-(*p*-tolylamino)ethyl)thio)benzo [d]thiazol-6-yl)amino)butan-2-yl)Carbamate (35)**

^{1}H NMR (400 MHz, CHLOROFORM-d), δ 9.81 (s, 1H), 9.36 (br. s., 1H), 8.13 (br. s., 1H), 7.56 (d, *J* = 7.78 Hz, 1H), 7.36 - 7.43 (m, *J* = 8.28 Hz, 2H), 7.14 (d, *J* = 8.03 Hz, 1H), 7.04 - 7.11 (m, *J* = 8.03 Hz, 2H), 5.54 (d, *J* = 8.03 Hz, 1H), 4.24 (t, *J* = 6.65 Hz, 1H), 3.90 - 4.09 (m, 2H), 2.26 (s, 3H), 2.14 (d, *J* = 19.07 Hz, 1H), 1.50 (s, 9H), 1.08 (d, *J* = 5.77 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.11, 166.42, 165.92, 156.85, 148.23, 135.84, 135.51, 135.19, 133.92, 129.49, 120.47, 119.64, 118.59, 111.58, 80.55, 77.38, 77.07, 76.75, 61.14, 37.44, 30.91, 28.44, 20.86, 19.33, 18.64.

***(R)*-tert-butyl (2-oxo-2-((2-((2-oxo-2-(*p*-tolylamino)ethyl)thio)benzo[d]thiazol-6-yl)amino)-1-phenylethyl)carbamate (36)**

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (br. s., 0H), 9.88 (br. s., 1H), 8.19 - 8.32 (m, 1H), 7.65 (d, *J* = 8.78 Hz, 1H), 7.38 - 7.48 (m, 3H), 7.34 (d, *J* = 8.53 Hz, 3H), 7.23 - 7.29 (m, 2H), 7.21 (d, *J* = 6.53 Hz, 1H), 6.99 (d, *J* = 8.53 Hz, 2H), 6.20 (br. s., 1H), 5.43 (br. s., 1H), 4.06 (s, 3H), 3.42 (br. s., 1H), 2.93 - 2.99 (m, 1H), 2.20 (s, 3H), 1.36 (br. s., 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.1, 164.5, 148.2, 137.7, 135.3, 135.1, 135.0, 132.8, 128.6, 128.0, 127.3, 126.4, 120.2, 118.9, 118.8, 118.4, 111.3, 37.0, 27.6, 20.1

***(R)*-tert-butyl (3-methyl-1-((2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)amino)-1-oxobutan-2-yl)carbamate (37)**

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.90 (br. s., 1H), 8.61 (s, 1H), 8.16 (br. s., 1H), 8.06 (d, *J* = 8.53 Hz, 1H), 7.96 (d, *J* = 8.03 Hz, 1H), 7.88 (t, *J* = 8.66 Hz, 2H), 7.59 - 7.65 (m, 1H), 7.56 (d, *J* = 7.53 Hz, 2H), 7.15 (d, *J* = 7.28 Hz, 1H), 5.37 (d, *J* = 7.78 Hz, 1H), 5.05 (d, *J* = 2.26 Hz, 2H), 4.16 (br. s., 1H), 2.19 (br. s., 1H), 1.47 (s, 9H), 1.05 (t, *J* = 5.77 Hz, 6H); ^{13}C NMR (101 MHz, CHLOROFORM-d) δ 193.0, 170.7, 156.6, 149.4, 135.8, 134.5, 132.8, 132.4, 130.6, 129.7, 128.9, 128.7, 127.8, 127.0, 123.9, 121.1, 118.4, 111.8, 77.3, 77.2, 77.0, 76.7, 71.5, 41.2, 30.7, 28.4, 19.4

(*R*)-tert-butyl (2-((2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)amino)-2-oxo-1-phenylethyl)carbamate (38)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.63 (s, 1H), 8.27 (br. s., 1H), 8.14 (br. s., 1H), 8.09 (d, *J* = 8.28 Hz, 1H), 7.99 (d, *J* = 8.03 Hz, 1H), 7.90 (d, *J* = 8.53 Hz, 1H), 7.93 (d, *J* = 8.78 Hz, 1H), 7.63 (d, *J* = 8.03 Hz, 2H), 7.55 - 7.61 (m, 1H), 7.48 (d, *J* = 7.03 Hz, 2H), 7.37 (d, *J* = 7.78 Hz, 3H), 7.15 (d, *J* = 8.53 Hz, 1H), 5.77 (br. s., 1H), 5.42 (br. s., 1H), 5.06 (s, 2H), 1.45 (s, 9H)

(*R*)-2-amino-3-methyl-N-(2-((2-oxo-2-(*p*-tolylamino)ethyl)thio)benzo[d]thiazol-6-yl) butanamide hydrochloride (39)

^{1}H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 7.77 (d, *J* = 8.78 Hz, 1H), 7.61 (d, *J* = 8.53 Hz, 1H), 7.44 (d, *J* = 8.03 Hz, 2H), 7.09 (d, *J* = 8.03 Hz, 2H), 4.32 (s, 2H), 3.97 (br. s., 1H), 2.27 (s, 3H), 1.13 (dd, *J* = 6.78, 12.80 Hz, 6H); ^{13}C NMR (101 MHz, MeOD) δ 167.8, 166.8, 166.2, 147.6, 135.5, 135.1, 134.0, 129.0, 120.2, 119.9, 119.5, 112.3, 60.9, 59.0, 37.6, 30.4, 19.6, 17.7, 16.6; HRMS *(m/z)*: [M + Na] calcd for $C_{21}H_{24}N_4O_2S_2$ Na 451.5601, found 451.1238

(*R*)-2-amino-N-(2-((2-oxo-2-(*p*-tolylamino)ethyl)thio)benzo[d]thiazol-6-yl)-2-phenyl acetamide hydrochloride (40)

^{1}H NMR (400 MHz, MeOD) δ 8.26 - 8.37 (m, 1H), 7.69 (d, *J* = 8.78 Hz, 1H), 7.65 - 7.67 (m, 1H), 7.64 (br. s., 1H), 7.51 (d, *J* = 1.76 Hz, 4H), 7.42 (d, *J* = 8.28 Hz, 2H), 7.09 (d, *J* = 8.03 Hz, 2H), 5.24 (s, 1H), 4.27 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 168.8, 167.8, 167.4, 149.5, 137.0, 136.8, 136.7, 135.5, 134.2, 131.4, 130.7, 130.5, 129.6, 121.8, 121.8, 120.7, 113.6, 58.6, 38.9, 21.1; HRMS *(m/z)*: [M + Na] calcd for $C_{24}H_{22}N_4ClO_2S_2Na$ 521.0298, found 521.0345

(*R*)-3-methyl-1-((2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)amino)-1-oxobutan-2-aminium chloride (41)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (br. s., 1H), 8.86 (s, 1H), 8.48 (br. s., 2H), 8.42 (s, 1H), 8.15 (d, *J* = 8.03 Hz, 1H), 7.98 - 8.09 (m, 3H), 7.60 - 7.76 (m, 3H), 5.23 - 5.36 (m, 2H), 3.99 (br. s., 1H), 2.15 - 2.33 (m, 1H), 1.01 (d, *J* = 6.53 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.9, 167.0, 164.7, 149.0, 135.5, 135.3, 135.1, 132.7, 132.1, 130.8, 129.7, 129.0, 128.5, 127.8, 127.2, 123.7,

121.2, 118.9, 111.9, 66.4, 58.0, 41.1, 30.0, 18.5, 18.0; HRMS *(m/z)*: [M + Na] calcd for $C_{24}H_{24}N_3ClO_2S_2Na$ 508.0311, found 508.0896

_(R)_-2-((2-((2-(naphthalen-2-yl)-2-oxoethyl)thio)benzo[d]thiazol-6-yl)amino)-2-oxo-1-phenylethanaminium chloride (42)

^{1}H NMR (400 MHz, DMSO-d6) d 11.50 (br. s., 1H), 8.93 (br. s., 3H), 8.86 (br. s., 1H), 8.37 (s, 1H), 8.16 (d, J = 7.78 Hz, 1H), 7.98 - 8.09 (m, 3H), 7.67 - 7.79 (m, 5H), 7.59 - 7.67 (m, 2H), 7.45 (d, J = 7.53 Hz, 3H), 5.28 (s, 2H); 13C NMR (101 MHz, DMSO-d6) d 192.8, 166.1, 149.1, 145.5, 135.5, 135.3, 135.0, 133.7, 132.6, 132.1, 130.7, 129.7, 129.3, 129.0, 128.9, 128.5, 127.9, 127.8, 127.2, 123.7, 121.2, 118.7, 111.8, 66.4, 41.0; HRMS *(m/z)*: [M + Na] calcd for $C_{27}H_{22}N_3O_2S_2Na$ 507.6017, found 507.1051

2-chloro-_N_-(5-methylisoxazol-3-yl)acetamide (44)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (br. s., 1H), 5.66 (s, 1H), 3.34 (s, 2H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.3, 165.3, 158.0, 96.5, 43.2, 12.4

2-azido-_N_-(5-methylisoxazol-3-yl)acetamide (45)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.46 (br. s., 1H), 6.73 (s, 1H), 4.16 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-d) δ 170.4, 165.1, 136.4, 96.3, 52.6, 12.7

_N_-(5-methylisoxazol-3-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetamide (**46**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.86 (d, J = 7.43 Hz, 2H), 7.46 (t, J = 7.53 Hz, 2H), 7.29 - 7.39 (m, 1H), 6.58 (br. s., 1H), 5.41 (br. s., 2H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.0, 157.6, 146.2, 130.6, 128.9, 127.9, 125.1, 123.0, 96.1, 51.9, 12.1; HRMS (m/z): [M + Na] calcd for $C_{14}H_{13}N_5O_2Na$, 306.0967; found, 306.0960

N-(5-methylisoxazol-3-yl)-2-(4-(naphthalen-1-yl)-1H-1,2,3-triazol-1-yl)acetamide (47)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 11.52 (br. s., 1H), 8.60 (s, 1H), 8.47 (d, J = 4.27 Hz, 1H), 7.94 - 8.12 (m, 2H), 7.73 - 7.85 (m, 1H), 7.52 - 7.72 (m, 3H), 6.63 (br. s., 1H), 5.51 (s, 2H), 3.31 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.0, 157.6, 145.3, 133.5, 130.2, 128.5, 128.5, 127.8, 126.8, 126.6, 126.1, 125.7, 125.6, 125.2, 96.2, 51.9, 12.1; HRMS (m/z): [M + Na] calcd for $C_{18}H_{15}N_5O_2Na$, 356.1123; found, 356.1126

N-(5-methylisoxazol-3-yl)-2-(4-(4-phenoxyphenyl)-1H-1,2,3-triazol-1-yl)acetamide (**48**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (br. s., 1H), 8.53 (s, 1H), 7.87 (d, J = 8.28 Hz, 2H), 7.42 (t, J = 7.53 Hz, 2H), 7.17 (t, J = 7.28 Hz, 1H), 7.08 (t, J = 7.78 Hz, 4H), 6.59 (br. s., 1H), 5.43 (br. s., 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.0, 157.6, 156.4,156.4, 145.8, 130.1, 126.9, 126.0, 123.7, 122.7, 118.9, 118.8, 96.1, 51.9, 12.1; HRMS (m/z): [M + Na] calcd for $C_{20}H_{17}N_5O_3Na$, 398.1229; found, 398.1237

N-(5-methylisoxazol-3-yl)-2-(4-(pyridin-3-yl)-1H-1,2,3-triazol-1-yl)acetamide (**49**)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.51 (br. s., 1H), 9.08 (br. s., 1H), 8.72 (s, 1H), 8.56 (br. s., 1H), 8.24 (d, J = 8.12 Hz, 1H), 7.50 (dd, J = 5.13, 6.84 Hz, 1H), 6.59 (s, 1H), 5.47 (s, 2H), 2.26 - 2.46 (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.0, 164.6, 157.6, 148.9, 146.4, 143.5, 132.4, 124.0, 123.8, 96.1, 52.0, 12.1; HRMS (m/z): [M + Na] calcd for $C_{13}H_{12}N_6O_2Na$, 307.0919; found, 307.0931

2-(4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)acetamide (**50**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (br. s., 1H), 9.55 (s, 1H), 8.50 (s, 1H), 7.21 - 7.46 (m, 3H), 6.70 - 6.87 (m, 1H), 6.59 (br. s., 1H), 5.41 (br. s., 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.0, 164.7, 157.8, 157.6, 146.3, 131.8, 130.0, 123.0, 116.1, 115.0, 111.9, 96.2, 51.9, 12.1; HRMS (m/z): [M + Na] calcd for $C_{15}H_{13}N_5O_3Na$, 322.0916; found, 322.0937

2-(4-(4-formylphenyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)acetamide (**51**)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.52 (br. s., 1H), 10.02 (s, 1H), 8.78 (s, 1H), 8.11 (d, J = 7.27 Hz, 2H), 8.00 (d, J = 7.27 Hz, 2H), 6.59 (br. s., 1H), 5.47 (br. s., 2H), 2.38 (br. s., 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.7, 173.7, 149.6, 137.3, 136.2, 130.3, 125.5, 124.6, 118.1, 96.1, 52.0, 38.7, 37.5, 12.1 HRMS (m/z): [M + Na] calcd for $C_{15}H_{13}N_5O_3Na$, 334.0916; found, 334.0938

2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)acetamide (**52**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (br. s., 1H), 8.56 (s, 1H), 7.90 (dd, J = 5.65, 8.16 Hz, 2H), 7.29 (t, J = 8.66 Hz, 2H), 6.58 (s, 1H), 5.42 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.0, 157.6, 145.4, 127.2, 127.1, 123.0, 120.0, 116.0, 115.8, 96.1, 51.9, 12.1 HRMS (m/z): [M + Na] calcd for $C_{14}H_{12}FN_5O_2Na$, 324.0873; found, 324.0882

2-(4-(6-methoxynaphthalen-2-yl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)acetamide (**53**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (br. s., 1H), 8.63 (s, 1H), 8.35 (s, 1H), 7.93 - 7.99 (m, J = 8.53 Hz, 1H), 7.89 (d, J = 8.53 Hz, 1H), 7.34 (s, 1H), 7.17 - 7.23 (m, 1H), 6.60 (s, 1H), 5.46 (s, 2H), 3.89 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.0, 157.5, 146.5, 133.9, 129.6, 129.3, 128.7, 128.6, 127.4, 125.9, 124.1, 123.5, 122.9, 119.4, 119.1, 106.0, 96.2, 55.2, 12.1; HRMS (m/z): [M + Na] calcd for $C_{19}H_{17}N_5O_3Na$, 386.1229; found, 386.1218

N-(5-methylisoxazol-3-yl)-2-(4-(4-pentylphenyl)-1H-1,2,3-triazol-1-yl)acetamide (**54**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (br. s., 1H), 8.51 (s, 1H), 7.75 (d, J = 7.78 Hz, 2H), 7.27 (d, J = 8.03 Hz, 2H), 6.59 (s, 1H), 5.41 (s, 2H), 2.59 (t, J = 7.65 Hz, 2H), 2.38 (s, 3H), 1.52 - 1.65 (m, 2H), 1.28 - 1.37 (m, 4H), 0.86 (t, J = 6.78 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.0, 164.8, 157.6, 146.3, 142.2, 128.8, 128.1, 125.1, 122.7, 96.2, 51.9, 34.9, 30.9, 30.5, 22.0, 13.9, 12.1; HRMS (m/z): [M + Na] calcd for $C_{19}H_{23}N_5O_2Na$, 376.1749; found, 376.1756

N-(5-methylisoxazol-3-yl)-2-(4-(m-tolyl)-1H-1,2,3-triazol-1-yl)acetamide (**55**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (br. s., 1H), 8.01 (s, 1H), 7.60 (s, 1H), 7.50 - 7.57 (m, J = 7.53 Hz, 1H), 7.47 (s, 1H), 7.22 (t, J = 7.53 Hz, 1H), 7.01 - 7.11 (m, J = 7.78 Hz, 1H), 6.52 (s, 1H), 5.26 (s, 2H), 2.83 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-d) δ 168.9, 157.2, 137.6, 135.7, 129.8, 128.1, 128.0, 125.6, 122.1, 121.1, 95.7, 62.9, 20.7, 11.9; HRMS (m/z): [M + Na] calcd for $C_{15}H_{15}N_5O_2Na$, 320.1123; found, 320.1141

N-(5-methylisoxazol-3-yl)-2-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)acetamide (**56**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (br. s., 1H), 8.24 (s, 1H), 7.31 (t, J = 7.91 Hz, 2H), 7.05 (d, J = 8.28 Hz, 2H), 6.95 (t, J = 7.28 Hz, 1H), 6.58 (s, 1H), 5.40 (s, 2H), 5.17 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.0, 164.7, 158.1, 157.6, 142.6, 129.5, 126.2, 120.8, 114.6, 96.1, 60.9, 51.8, 12.1; HRMS (m/z): [M + Na] calcd for $C_{15}H_{15}N_5O_3Na$, 336.1073; found, 336.1091

2-(4-(3-chloropropyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)acetamide (**57**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (br. s., 1H), 7.91 (s, 1H), 6.57 (br. s., 1H), 5.32 (s, 2H), 3.63 - 3.88 (m, 2H), 2.78 (t, J = 6.78 Hz, 2H), 2.37 (s, 3H), 2.00 - 2.13 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.9, 164.8, 157.6, 145.4, 123.8, 96.1, 51.7, 44.6, 31.8, 22.2, 12.1; HRMS (*m*/z): [M + Na] calcd for $C_{11}H_{14}ClN_5O_2Na$, 306.0734; found, 306.0705