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Article

Thiol-epoxy Click Chemistry: The Synthesis of Vicinal Amino Alcohols Containing 1,2,4-Triazole Ring

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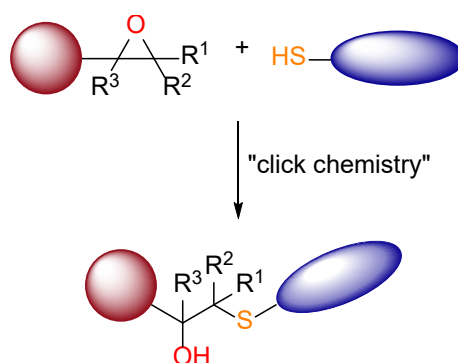
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Abstract: As examples of “Click Chemistry”, the reaction of 1-(oxiran-2-ylmethyl)piperidine with several 1,2,4-triazoles derivatives was studied. According to as a result, the reaction shows that the oxirane ring opens regiospecifically, according to Krasusky’s rule, without using a catalyst. The basic nitrogen present in 1-(oxiran-2-ylmethyl)piperidine has a catalytic (anchimer) effect.

Keywords: click chemistry; thiol-epoxy reaction; bis-1,2,4-triazole; vicinal amino alcohols; Krasusky rule

1. Introduction

The thiol-epoxy reaction is a “click” reaction that has drawn intensive attention in recent years due to its outstanding advantages, such as fast reaction rate, high selectivity, mild reaction conditions, and wide range of applications [1,2]. The thiol-epoxy reaction is used in the synthesis of polymers, materials with programmed properties, biologically active compounds, etc. [1–22].



Scheme 1. “Click chemistry”: thiol-epoxy reaction.

The reaction becomes particularly significant when oxiranes containing an amino group in the vicinal position react with thiols leading to a formation of vicinal amino alcohols with thioether bridge.

A number of vicinal amino alcohols are currently employed in medical applications, with some of these compounds functioning as β -adrenergic blocking agents, demonstrating targeted effects in inhibiting the stimulation of β -adrenergic receptor systems [23–26]. Figure 1 shows derivatives of vicinal amino alcohols that are used in medicine.

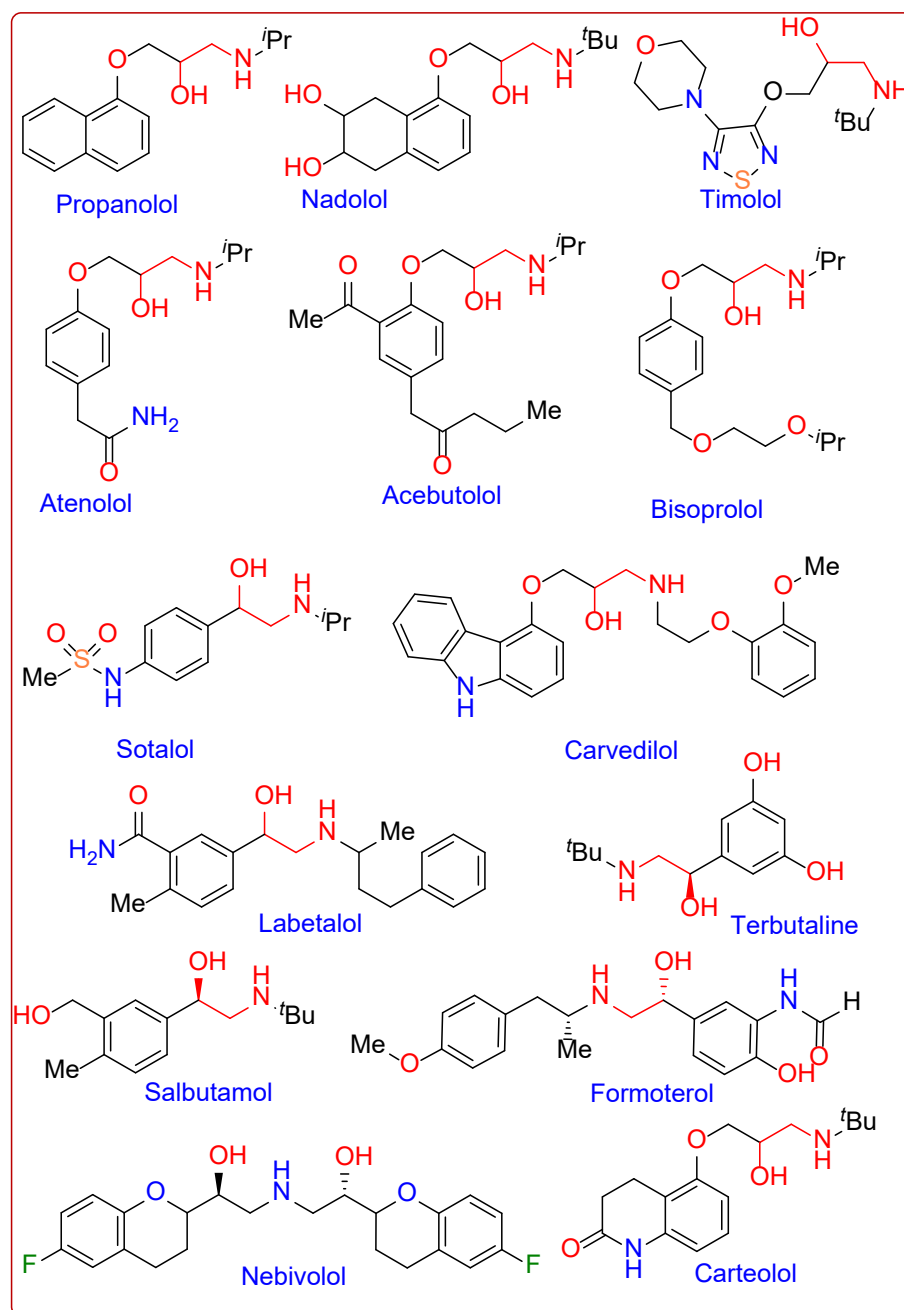


Figure 1. Derivatives of vicinal amino alcohols used in medical practice (β -adrenergic blocking agents).

Salbutamol and propranolol are on the World Health Organization List of Essential Medicines [27] and represent the most important examples of therapeutic agents bearing this structural feature.

In addition to their high relevance in drug discovery [28–30], *N*-substituted vicinal amino alcohols are important building blocks in the preparation of added value chemicals [31,32] and ligands for catalysis [33,34].

Previously we have studied the reaction of epoxides of various structures with *S*-, *N*-, and *O*-nucleophiles, resulting in the synthesis of vicinal amino alcohols, lactones, and other compounds (Figure 2) [35–41].

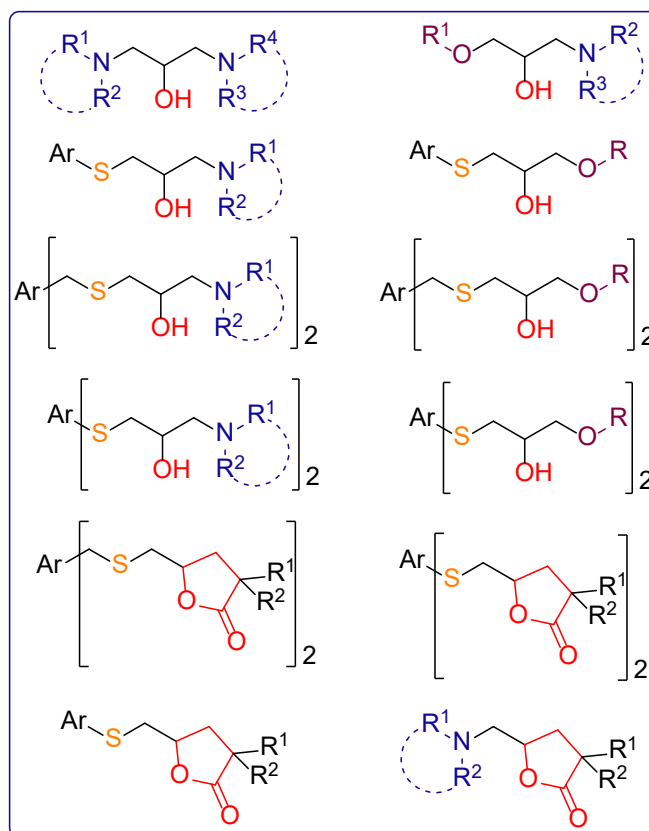


Figure 2. Vicinal amino alcohols, lactones, and other compounds synthesized by our team.

Similarly, derivatives of 5,4-disubstituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones hold potential interest for developing novel bioactive compounds. This is because certain derivatives of 1,2,4-triazoles are recognized as bioactive compounds and are extensively used in medicine (Figure 3) [42–51].

Our previous studies have shown that the alkylation of 5,4-disubstituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones depends on the nature of the alkylating electrophile. In particular, alkylation with alkyl halides leads to *S*-alkylation, and in the case of activated conjugated systems, *N*-alkylation. The arylation reaction with arylhalides proceeds in systems utilizing Ullmann-type under Cu(0) catalysis conditions leads to *S*-arylation (Scheme 2) [52–58].

Given this prospect, it becomes intriguing to investigate the direction in which the alkylation reaction proceeds in epoxaid-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones systems. With this objective in mind, this study aims to explore the alkylation potential of 5,4-disubstituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones under “Click Chemistry” conditions.

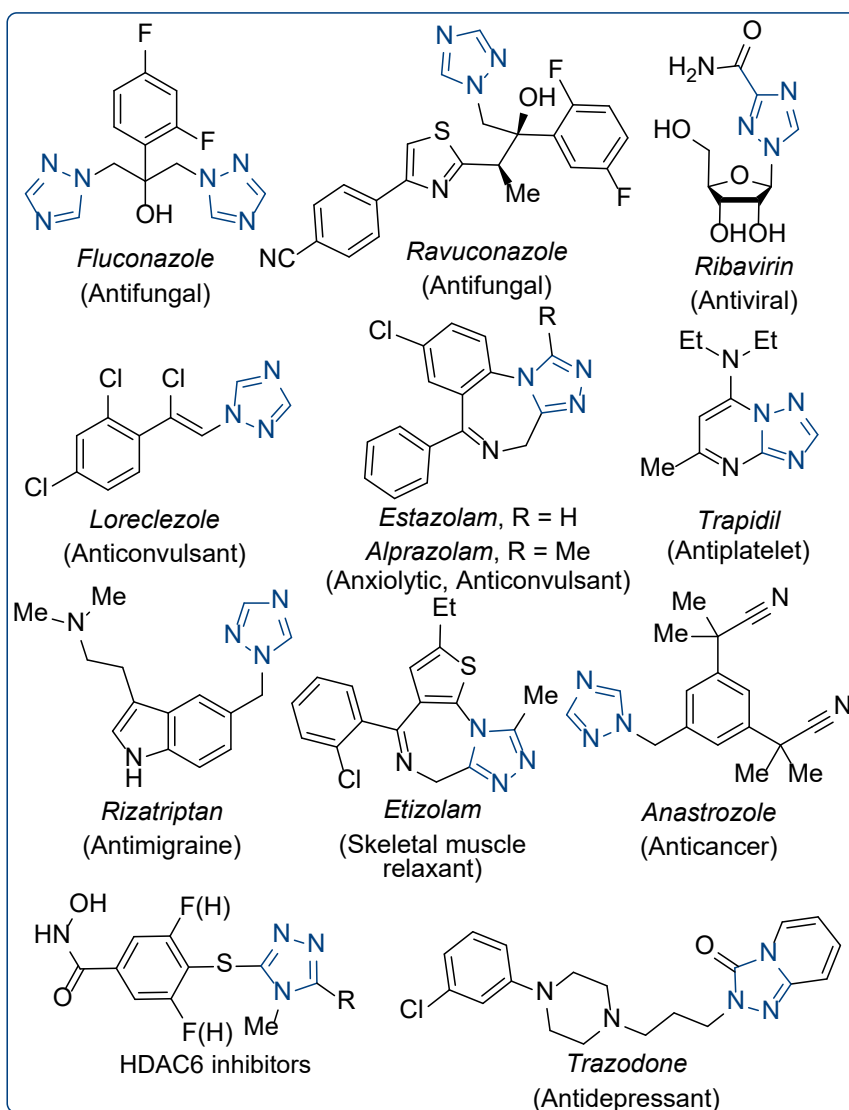
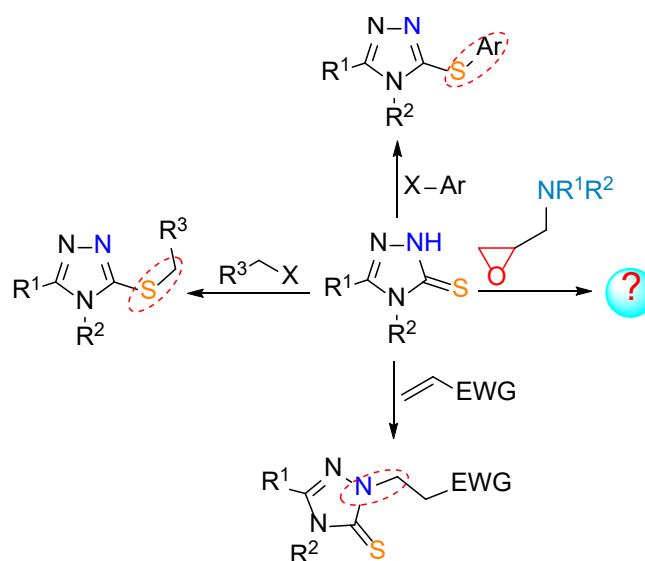


Figure 3. Drugs with 1,2,4-triazole backbone used in clinical practice.



Scheme 2. Reaction 5,4-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones with electrophilic agents.

2. Materials and Methods

^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 MHz or on Bruker Avance Neo 400 MHz spectrometer in DMSO/ CCl_4 mixture (1:3) or DMSO- d_6 . Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of solvents, for instance, DMSO- d_6 (2.5 for ^1H NMR and 39.5 for ^{13}C NMR) as internal references. The coupling constants (J) are given in Hertz. ESI-MS spectra were measured with a Waters Xevo G3 QToF Mass Spectrometer. Spectroscopic measurements were performed on a Nicolet IS 50 FTIR spectrometer (Thermo Scientific Fisher, USA) coupled with an ATR accessory. TLC analysis was performed on "Silufol UV-254" plates. All reagents were of reagent grade and were used as such or distilled prior to use. Starting 1,2,4-triazoles were prepared as previously reported (**1a**, **1k**, **1m-o**, **1r** [56]; **1f** [58]; **1g** – CAS 21358-12-3; **1j** – CAS: 93378-58-6; **1v** [52]; **1h**, **1i** [57]; **1e** [59]; **1q** [60]; **1u** [61]). Melting points were determined on "SMP-10".

4-propyl-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (1b). Yield 84%, white solid, m.p. 135 °C. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 13.77 (s, 1H, NH), 7.63 (dd, J = 5.1, 1.1 Hz, 1H_{thph}), 7.52 (dd, J = 3.7, 1.1 Hz, 1H_{thph}), 7.18 (dd, J = 5.1, 3.7 Hz, 1H_{thph}), 4.19 – 4.03 (m, 2H, NCH_2), 1.84 – 1.67 (m, 2H, CH_2CH_3), 0.97 (t, J = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 167.4 (C=S), 145.2 (C=N), 128.4 (CH=), 127.8 (CH=), 127.5 (CH=), 126.8, 45.1 (NCH_2), 21.1 (CH_2), 10.6 (CH_3). IR_{vmax} = 3094.23; 3083.14; 3062.41; 3006.96; 2959.23; 2927.41; 2911.50; 2869.56; 2819.42; 2793.38; 2757.71; 2723.00; 2683.46; 2583.66; 2573.54; 1792.03; 1719.23; 1648.36; 1623.29; 1571.22; 1544.22; 1515.29; 1480.10; 1458.89; 1443.46; 1432.85; 1400.55; 1372.59; 1352.82; 1323.89; 1299.79; 1282.91; 1253.02; 1230.36; 1217.83; 1204.81; 1145.03; 1102.60; 1085.73; 1070.78; 1060.17; 1035.10; 1014.37; 950.73; 942.06; 895.29; 867.81; 853.83; 846.11; 824.42; 779.58; 758.85; 750.17; 742.46; 727.51; 705.34; 694.73; 668.70; 660.50; 654.71; 577.09; 567.93; 493.21; 434.39; 423.30 cm^{-1} . HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_9\text{H}_{12}\text{N}_3\text{S}^+$ 226.0473; Found 226.0473.

5-(4-bromophenyl)-4-cyclohexyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (1c). Yield 89%, white solid, m.p. 198 °C. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 13.72 (s, 1H, NH), 7.74 – 7.58 (m, 2H_{arom}), 7.46 – 7.35 (m, 2H_{arom}), 4.39 – 4.17 (m, 1H, NCH), 2.38 – 1.91 (m, 2H, Cy), 1.86 – 1.67 (m, 4H, Cy), 1.67 – 1.53 (m, 1H, Cy), 1.37 – 1.19 (m, 2H, Cy), 1.16 – 0.99 (m, 1H, Cy). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 166.5 (C=S), 149.8 (C=N), 131.4 (2^*CH=), 131.1 (2^*CH=), 126.1, 124.3, 56.8 (NCH), 29.5 (2^*CH_2), 25.4 (2^*CH_2), 24.4 (CH_2). IR_{vmax} = 3090.85; 3068.67; 3058.55; 3025.28; 2979.96; 2931.27; 2894.15; 2863.29; 2853.65; 2824.24; 2778.92; 2746.62; 2688.77; 1600.15; 1574.59; 1544.22; 1500.35; 1473.83; 1450.21; 1442.01; 1408.75; 1382.71; 1340.28; 1307.02; 1289.18; 1281.47; 1255.91; 1241.93; 1188.42; 1150.81; 1140.69; 1116.10; 1096.82; 1084.76; 1066.44; 1057.28; 1009.55; 995.57; 970.50; 942.06; 925.18; 895.77; 854.79; 832.13; 818.63; 793.08; 782.48; 759.33; 728.00; 718.84; 706.30; 670.14; 666.29; 629.16; 604.09; 539.01; 508.63; 484.05; 461.39; 451.74; 432.46; 420.41; 413.66 cm^{-1} . HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{17}^{79}\text{BrN}_3\text{S}^+$ 338.0327; Found 338.0327.

5-(4-bromophenyl)-4-phenethyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (1d). Yield 81%, white solid, m.p. 178 °C. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 13.83 (s, 1H, NH), 7.61 – 7.54 (m, 2H_{arom}), 7.31 – 7.25 (m, 2H_{arom}), 7.20 – 7.11 (m, 3H_{arom}), 7.04 – 6.98 (m, 2H_{arom}), 4.27 – 4.17 (m, 2H, NCH_2), 3.06 – 2.98 (m, 2H, CH_2Ph). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 167.1 (C=S), 149.9 (C=N), 136.9, 131.4 (2^*CH=), 129.9 (2^*CH), 128.4 (2^*CH=), 128.0 (2^*CH=), 126.1, 125.0, 124.0, 45.0 (NCH_2), 33.1 (CH_2). IR_{vmax} = 3119.78; 3084.10; 3041.67; 3029.62; 2983.82; 2953.45; 2936.57; 2908.13; 2867.63; 2840.63; 2770.24; 1604.48; 1558.20; 1503.24; 1473.35; 1442.98; 1404.41; 1392.84; 1372.10; 1352.34; 1332.57; 1321.96; 1274.72; 1199.99; 1188.90; 1177.33; 1139.24; 1104.05; 1077.53; 1061.14; 1031.25; 1023.05; 1010.03; 967.61; 944.47; 925.18; 900.11; 836.47; 828.76; 776.69; 761.74; 754.03; 748.25; 731.37; 719.32; 698.59; 674.96; 658.57; 622.89; 600.72; 555.40; 538.04; 492.72; 454.64; 444.99; 417.03; 403.53 cm^{-1} . HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{15}^{79}\text{BrN}_3\text{S}^+$ 360.0170; Found 360.0170.

4-allyl-5-(2-iodophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (1l). Yield 88%, white solid, m.p. 145 °C. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 13.84 (s, 1H, NH), 7.96 (dd, J = 8.0, 1.1 Hz, 1H_{arom}), 7.50 (td, J = 7.5, 1.1 Hz, 1H_{arom}), 7.41 (dd, J = 7.7, 1.8 Hz, 1H_{arom}), 7.28 (td, J = 7.7, 1.7 Hz, 1H_{arom}), 5.69 (ddt, J = 16.1, 10.3, 5.7 Hz, 1H, CH=), 5.01 (dd, J = 10.3, 1.4 Hz, 1H^a, $=\text{CH}_2$), 4.80 (dt, J = 17.1, 1.6 Hz, 1H^b, $=\text{CH}_2$), 4.42 (dt, J = 6.0, 1.6 Hz, 2H, NCH_2). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 166.7 (C=S), 151.3 (C=N),

138.8 (CH=), 131.8 (CH=), 131.5 (CH=), 130.5 (CH=), 130.4, 127.8 (CH=), 117.9 (=CH₂), 98.9 (=Cl), 45.7 (NCH₂). IR_ν_{max} = 3083.14; 3057.58; 3037.34; 2967.43; 2922.59; 2909.57; 2849.79; 2835.81; 2754.33; 2649.71; 1643.54; 1624.25; 1596.29; 1561.09; 1527.83; 1497.94; 1458.89; 1441.53; 1425.14; 1394.76; 1353.78; 1330.64; 1292.55; 1262.18; 1249.65; 1197.10; 1158.53; 1147.44; 1099.23; 1076.57; 1018.23; 993.16; 981.59; 948.81; 914.09; 870.70; 779.10; 754.03; 728.00; 719.80; 708.71; 664.84; 641.22; 617.59; 602.16; 576.13; 525.99; 484.53; 465.24; 444.03; 420.89; 404.50 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₁H₁₁IN₃S⁺ 343.9718; Found 343.9726.

4-phenyl-5-(*m*-tolyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (1t). Yield 90%, white solid, m.p. 245 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 13.94 (s, 1H, NH), 7.52 – 7.43 (m, 3H_{arom}), 7.30 – 7.23 (m, 2H_{arom}), 7.18 – 7.07 (m, 3H_{arom}), 6.99 – 6.92 (m, 1H_{arom}), 2.25 (s, 3H, CH₃). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 168.5 (C=S), 149.7 (C=N), 137.4, 134.5, 130.3, 128.7 (CH=), 128.7 (2CH=), 128.3 (CH=), 128.2 (2*CH=), 127.7 (CH=), 125.6, 124.7 (CH=), 20.7 (CH₃). IR_ν_{max} = 3107.24; 3084.58; 3057.58; 3031.07; 2995.39; 2927.90; 2823.28; 2770.24; 2752.40; 1591.47; 1550.97; 1496.49; 1488.29; 1459.37; 1437.67; 1402.48; 1382.71; 1334.50; 1313.29; 1285.32; 1273.75; 1243.38; 1208.18; 1174.92; 1129.60; 1098.26; 1083.32; 1073.67; 1037.03; 1003.28; 977.25; 918.91; 885.17; 851.42; 796.94; 772.83; 737.16; 717.39; 700.52; 691.84; 668.70; 660.02; 620.97; 613.73; 545.27; 524.54; 513.94; 481.15; 442.10; 427.16 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₅H₁₄N₃S⁺ 268.0909; Found 268.0931.

Dimethyl 2,2'-(((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl)) diacetate (**ac**).

Method A: 0.48 g (21 mmol) of sodium was dissolved in 25 ml of methanol, then 4.16 g (21 mmol) of (2,5-dimethyl-1,4-phenylene)dimethanethiol was added and the mixture was stirred at r.t. for 30min. Then 1.09 g (10 mmol, 0.95 ml) of ethyl chloroformate and 25 ml of methanol were added to the mixture and refluxed for 4h. Resulting mixture was left overnight, and the precipitate was filtered and washed with water and dried. Yield 84%.

Method B: 0.48 g (21 mmol) sodium was dissolved in 25 ml of methanol, then 2.22 g (21 mmol, 1.88 ml) methyl 2-mercaptoacetate was added and the mixture was stirred at r.t. for 30min. Then 2.03 g (10 mmol) of 1,4-bis(chloromethyl)-2,5-dimethylbenzene and 25 ml of methanol were added to the mixture and refluxed for 4h. Resulting mixture was left overnight, and the precipitate was filtered and washed with water and dried. Yield 89%. White solid, m.p. 100 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 6.99 (s, 2H_{arom}), 3.75 (s, 4H, CH₂CO), 3.69 (s, 6H, OCH₃), 3.11 (s, 4H, SCH₂Ar), 2.32 (s, 6H, ArCH₃). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 169.5 (2*C=O), 133.4 (2*C), 133.3 (2*C), 131.8 (2*CH=), 51.4 (2*OCH₃), 33.4 (2*SCH₂), 31.8 (2*SCH₂), 17.9 (2*CH₃). IR_ν_{max} = 3427.85; 3032.51; 3004.07; 2972.73; 2950.07; 2918.25; 2894.15; 2862.33; 2727.33; 1723.09; 1680.18; 1505.65; 1436.23; 1427.55; 1408.75; 1392.84; 1371.62; 1290.63; 1214.93; 1144.06; 1113.21; 1038.00; 1004.73; 936.75; 907.83; 866.85; 828.28; 795.49; 718.84; 700.03; 595.41; 579.99; 466.21; 424.26 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₆H₂₃O₄S₂⁺ 343.1038; Found 343.1048.

2,2'-(((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl))di(acetohydrazide) (ad). The mixture of 3.42 g dimethyl 2,2'-(((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl)) diacetate and 8 ml hydrazine hydrate in 10 ml of ethanol was stirred for 1h at r.t., then refluxed for 3h. Resulting mixture was left overnight, and the precipitate was filtered and washed with ethanol and water and dried. Yield 95%, white solid, m.p. 179 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 9.07 (br.s., 2H, NH), 7.03 (s, 2H_{arom}), 4.11 (br.s., 4H, NH₂), 3.77 (s, 4H, CH₂CO), 2.96 (s, 4H, SCH₂Ar), 2.30 (s, 6H, ArCH₃). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 168.3 (2*C=O), 134.0 (2*C), 133.3 (2*C), 131.7 (2*CH), 33.6 (2*SCH₂), 32.1 (2*SCH₂), 18.0 (2*CH₃). IR_ν_{max} = 3329.98; 3307.32; 3255.25; 3206.56; 3140.99; 3015.64; 2991.05; 2963.57; 2953.45; 2933.68; 2914.40; 2847.38; 1654.14; 1622.81; 1501.31; 1458.40; 1433.82; 1396.21; 1376.93; 1325.34; 1296.41; 1240.00; 1217.83; 1178.78; 1127.19; 1117.06; 1034.14; 986.89; 920.36; 889.02; 853.83; 801.76; 780.06; 706.30; 696.18; 659.05; 582.88; 536.60; 463.31 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₄H₂₃N₄O₄S₂⁺ 343.1263; Found 343.1263.

2,2'-(2,2'-(((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl))bis(acetyl))bis(*N*-phenylhydrazine-1-carbothioamide) (ae). The mixture of 1.026 g (3 mmol) 2,2'-(((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl))di(acetohydrazide) and 0.81 g (6 mmol) phenyl isothiocyanate in 5 ml ethanol was stirred at r.t for 1h, then was refluxed for 2h. The resulting mixture

was left overnight, and the precipitate was filtered and washed with ethanol and dried. Yield 91%, white solid, m.p. 210 °C. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 10.03 (br.s., 2H, NH), 9.68 – 9.32 (m, 4H, NH), 7.55 (d, J = 8.0 Hz, 4H_{arom}), 7.29 (t, J = 7.8 Hz, 4H_{arom}), 7.15 – 7.02 (m, 4H_{arom}), 3.83 (s, 4H, CH_2CO), 3.14 (s, 4H, SCH_2Ar), 2.33 (s, 6H, CH_3). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) 180.3(2* C), 138.9 (2* C), 133.8 (2* C), 133.3 (2* CH), 131.8 (2* $\text{CH}=\text{}$), 127.6 (4* $\text{CH}=\text{}$), 124.1 (br, 6* CH), 33.5 (2* SCH_2), 32.3 (2* SCH_2), 18.1 (2* CH_3). IR_{Vmax} = 3303.46; 3222.47; 3165.58; 3066.74; 3004.55; 2970.32; 2923.07; 2861.36; 1680.18; 1654.14; 1623.77; 1604.97; 1560.13; 1535.54; 1499.38; 1476.72; 1445.87; 1419.83; 1363.43; 1327.75; 1314.25; 1294.00; 1254.95; 1238.56; 1222.17; 1204.81; 1194.20; 1164.31; 1156.12; 1141.65; 1081.87; 1032.21; 996.54; 970.02; 928.56; 906.86; 897.22; 876.01; 837.92; 797.42; 752.58; 747.28; 731.37; 710.64; 690.87; 574.20; 502.85; 464.76 cm^{-1} . HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_6\text{O}_2\text{S}_4^+$ 613.1548; Found 613.1545.

5,5'-((((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl))bis(methylene))bis(4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione) (**1w**). The mixture of 1.23 g (2 mmol) 2,2'-(2,2'-(((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl))bis(acetyl))bis(N-phenylhydrazine-1-carbothioamide) and 0.35 g (6 mmol) KOH in 5 ml of water was refluxed for 4h. The resulting mixture was acidified with 6M HCl, the precipitate was filtered and washed with water and dried. Yield 88%, white solid, m.p. 270 °C. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 13.72 (s, 2H, NH), 7.57 – 7.46 (m, 6H_{arom}), 7.37 – 7.29 (m, 4H_{arom}), 6.91 (s, 2H_{arom}), 3.62 (s, 4H, CH_2CNN), 3.42 (s, 4H, SCH_2Ar), 2.21 (s, 6H, CH_3). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 168.2 (2* $\text{C}=\text{S}$), 148.6 (2* $\text{C}=\text{N}$), 133.4 (2* C), 133.2 (2* C), 133.2 (2* C), 131.6 (2* $\text{CH}=\text{}$), 128.9 (2* $\text{CH}=\text{}$), 128.7 (4* $\text{CH}=\text{}$), 128.0 (4* $\text{CH}=\text{}$), 32.8 (2* SCH_2), 24.6 (2* SCH_2), 17.9 (2* CH_3). IR_{Vmax} = 3103.22; 3036.47; 2929.45; 1591.22; 1567.16; 1497.84; 1491.49; 1454.25; 1416.03; 1397.99; 1332.63; 1276.56; 1232.78; 1164.59; 1091.60; 1069.42; 1038.22; 1013.86; 921.36; 888.32; 843.82; 801.25; 785.33; 758.73; 742.69; 709.13; 692.17; 672.19; 613.42; 553.44; 503.60; 456.57 cm^{-1} . HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_6\text{S}_4^+$ 577.1337; Found 577.1335.

General procedure of syntheses 1-((4,5-disubstituted-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ols. Mixture of the corresponding triazole (2 mmol) and 1-(oxiran-2-ylmethyl)piperidine (2.2 mmol, 310 mg) was stirred in 50 °C 4 hours. Then the mixture was cooled down to r.t. and purified with flash chromatography (eluent: C_6H_6 :MeOH:Et₃N 50:1:1).

1-((5-isobutyl-4-propyl-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3a**). Yield 68%, yellow oil. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 4.74 (br.s., 1H, OH), 3.90 – 3.80 (m, 1H, CHOH), 3.80 – 3.72 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 3.30 (dd, J = 13.2, 4.2 Hz, 1H^a, SCH_2), 3.08 (dd, J = 13.2, 6.7 Hz, 1H^b, SCH_2), 2.49 (d, J = 7.1 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.46 – 2.33 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 2.31 (dd, J = 6.4, 1.8 Hz, 2H, NCH_2CH), 2.16 – 2.05 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.72 – 1.61 (m, 2H), 1.56 – 1.44 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 1.42 – 1.30 (m, 2H, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 0.97 (d, J = 6.7 Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 0.91 (t, J = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 153.6 ($\text{SC}=\text{N}$), 149.3 ($\text{C}=\text{N}$), 66.8 (OCH), 63.3 (NCH_2), 54.6 (2* NCH_2), 44.4 (NCH_2), 38.2 (SCH_2), 33.2 (CH_2), 26.5 (CH), 25.5 (2* CH_2), 23.8 (CH_2), 22.8 (CH_2), 22.1 (2* CH_3), 10.6 (CH_3). IR_{Vmax} = 3258.63; 2931.75; 2871.01; 2853.17; 2796.28; 2757.23; 1514.33; 1465.15; 1442.49; 1428.03; 1398.14; 1383.68; 1366.80; 1351.86; 1342.21; 1300.75; 1280.02; 1244.83; 1225.06; 1202.40; 1168.17; 1156.60; 1116.58; 1088.62; 1039.93; 995.09; 962.79; 924.70; 898.18; 862.02; 804.17; 787.78; 745.83; 688.46; 656.16; 614.22; 592.52; 555.88; 514.90; 476.81; 469.58; 444.51; 430.05; 423.78; 416.07; 408.35 cm^{-1} . HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{33}\text{N}_4\text{OS}^+$ 341.2375; Found 341.2388.

1-(piperidin-1-yl)-3-((4-propyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-yl)thio)propan-2-ol (**3b**). Yield 85%, yellow oil. ^1H NMR (400 MHz, DMSO/ CCl_4 -1/3) δ 7.58 (dd, J = 5.1, 1.2 Hz, 1H_{thph}), 7.45 (dd, J = 3.7, 1.2 Hz, 1H_{thph}), 7.16 (ddd, J = 5.0, 3.6, 1.2 Hz, 1H_{thph}), 4.70 (br.s., 1H, OH), 4.06 (dd, J = 8.6, 6.8 Hz, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 4.00 – 3.87 (m, 1H, CHOH), 3.44 (dd, J = 13.2, 4.2 Hz, 1H^a, SCH_2), 3.27 – 3.14 (m, 1H^b, SCH_2), 2.42 (br.t., J = 5.1 Hz, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 2.37 (dd, J = 6.4, 1.2 Hz, 2H, NCH_2CHOH), 1.82 – 1.69 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 1.59 – 1.49 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 1.46 – 1.36 (m, 2H, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 0.95 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO/ CCl_4 -1/3) δ 151.4 ($\text{SC}=\text{N}$), 149.0 ($\text{C}=\text{N}$), 128.0, 127.6 ($\text{CH}=\text{}$), 127.3 ($\text{CH}=\text{}$), 126.6 ($\text{CH}=\text{}$), 66.6 (OCH), 63.4 (NCH_2), 54.6 (2* NCH_2), 45.6 (NCH_2), 38.4 (SCH_2), 25.6 (2* CH_2), 23.9 (CH_2), 22.6 (CH_2), 10.5 (CH_3). IR_{Vmax} = 3297.68; 3100.01; 3078.32; 2931.27; 2876.31; 2851.72; 2797.24; 2757.23; 1652.70; 1565.43; 1467.56; 1458.89; 1432.37; 1416.94;

1386.57; 1366.32; 1351.86; 1334.98; 1300.75; 1278.09; 1250.13; 1232.77; 1209.63; 1155.63; 1141.17; 1115.62; 1086.21; 1039.44; 994.61; 962.30; 943.02; 896.74; 850.45; 787.30; 710.64; 648.93; 582.88; 543.83; 505.74; 490.79; 478.26; 461.39; 444.03; 420.89 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₇H₂₇N₄OS₂⁺ 367.1626; Found 367.1648.

1-((5-(4-bromophenyl)-4-cyclohexyl-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3c**). Yield 87%, white solid, m.p. 109 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.70 – 7.55 (m, 2H_{arom}), 7.46 – 7.33 (m, 2H_{arom}), 4.73 (br.s., 1H, OH), 4.02 – 3.85 (m, 2H, 1H CHOH, 1H NCH), 3.47 (dd, J = 13.2, 4.3 Hz, 1H^a, SCH₂), 3.25 (dd, J = 13.2, 6.7 Hz, 1H^b, SCH₂), 2.42 (br.t., J = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.36 (dd, J = 6.4, 1.5 Hz, 2H, NCH₂CHOH), 2.19 – 2.02 (m, 2H, Cy), 1.89 – 1.74 (m, 4H, Cy), 1.68 – 1.58 (m, 1H, Cy), 1.57 – 1.47 (m, 4H, N(CH₂CH₂)₂CH₂), 1.43 – 1.34 (m, 2H, N(CH₂CH₂)₂CH₂), 1.33 – 1.09 (m, 3H, Cy). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.8 (SC=N), 150.1 (C=N), 131.4 (2*CH), 130.7 (2*CH), 126.8, 123.5, 66.6 (OCH), 63.5 (NCH₂), 56.2 (NCH), 54.6 (2*NCH₂), 38.3 (SCH₂), 30.6 (2*CH₂), 25.6 (2*CH₂), 25.2 (2*CH₂), 24.3 (CH₂), 23.9 (CH₂). IR_{Vmax} = 3185.83; 3062.41; 3036.37; 2931.27; 2856.54; 2796.76; 2781.81; 2757.71; 2745.17; 2694.07; 2668.52; 1595.81; 1567.36; 1465.15; 1440.08; 1410.67; 1389.94; 1362.46; 1345.11; 1288.70; 1272.79; 1258.32; 1213.49; 1200.95; 1183.60; 1157.56; 1146.47; 1129.12; 1105.01; 1061.62; 1041.37; 1025.94; 1010.52; 999.43; 971.47; 947.84; 928.07; 900.59; 892.88; 870.22; 855.28; 837.92; 823.46; 788.74; 764.64; 751.62; 731.37; 712.57; 690.39; 626.27; 592.52; 561.18; 530.81; 515.38; 483.08; 456.56; 443.07; 433.90; 421.37; 405.94 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₂H₃₂BrN₄OS⁺ 479.1480; Found 479.1489.

1-((5-(4-bromophenyl)-4-phenethyl-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3d**). Yield 78%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.62 – 7.54 (m, 2H_{arom}), 7.35 – 7.31 (m, 2H_{arom}), 7.21 – 7.14 (m, 3H_{arom}), 6.97 – 6.91 (m, 2H_{arom}), 4.73 (br.s., 1H, OH), 4.21 (t, J = 7.4 Hz, 2H, NCH₂CH₂Ph), 4.00 – 3.90 (m, 1H, CHOH), 3.45 (dd, J = 13.2, 4.2 Hz, 1H^a, SCH₂), 3.21 (dd, J = 13.1, 6.9 Hz, 1H^b, SCH₂), 2.93 (t, J = 7.4 Hz, 2H, CH₂Ph), 2.44 (br.t., J = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.39 (dd, J = 6.5, 1.5 Hz, 2H, NCH₂CHOH), 1.61 – 1.50 (m, 4H, N(CH₂CH₂)₂CH₂), 1.48 – 1.38 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.5 (SC=N), 151.3 (C=N), 136.2, 131.3 (2*CH=), 129.8 (2*CH=), 128.3 (2*CH=), 128.1 (2*CH=), 126.3 (CH=), 126.2, 123.3, 66.6 (OCH), 63.4 (NCH₂), 54.6 (2*NCH₂), 45.3 (NCH₂), 38.4 (SCH₂), 35.0 (CH₂Ph), 25.5 (2*CH₂), 23.8 (CH₂). IR_{Vmax} = 3282.73; 3086.51; 3062.89; 3027.21; 3001.18; 2931.75; 2851.72; 2797.72; 2757.23; 1599.18; 1567.36; 1496.49; 1454.55; 1432.37; 1385.60; 1353.78; 1334.02; 1300.75; 1276.16; 1240.97; 1206.74; 1177.33; 1155.63; 1115.14; 1091.99; 1067.89; 1039.44; 1007.14; 995.57; 970.98; 931.45; 891.43; 860.58; 827.79; 786.81; 764.64; 750.17; 728.48; 720.28; 698.10; 678.82; 625.79; 577.58; 549.13; 522.61; 496.10; 477.30; 452.71; 438.24; 430.53; 425.71; 419.44; 410.28 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₄H₃₀BrN₄OS⁺ 501.1324; Found 501.1328.

1-((4-phenethyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3e**). Yield 92%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.58 (dd, J = 5.1, 1.1 Hz, 1H_{arom}), 7.36 (dd, J = 3.7, 1.1 Hz, 1H_{arom}), 7.28 – 7.14 (m, 4H_{arom}), 7.12 – 7.06 (m, 2H_{arom}), 4.68 (br.s., 1H, OH), 4.38 – 4.21 (m, 2H, CH₂CH₂Ph), 3.98 – 3.85 (m, 1H, CHOH), 3.40 (dd, J = 13.2, 4.2 Hz, 1H^a, SCH₂), 3.16 (dd, J = 13.2, 6.8 Hz, 1H^b, SCH₂), 3.01 (t, J = 7.8 Hz, 2H, CH₂Ph), 2.43 (br.t., J = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.37 (dd, J = 6.3, 0.9 Hz, 2H, NCH₂CHOH), 1.60 – 1.50 (m, 4H, N(CH₂CH₂)₂CH₂), 1.46 – 1.37 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 151.4, 149.0, 136.2, 128.3 (2*CH=), 128.2 (2*CH=), 127.7 (CH=), 127.3 (CH=), 126.9 (CH=), 126.4 (CH=), 66.6 (OCH), 63.4 (NCH₂), 54.6 (NCH₂), 45.4 (NCH₂), 38.6 (SCH₂), 35.1 (CH₂Ph), 25.5 (2*CH₂), 23.8 (CH₂). IR_{Vmax} = 3302.98; 3102.90; 3085.55; 3064.82; 3026.73; 3001.66; 2931.27; 2851.24; 2797.24; 2757.71; 1603.52; 1583.75; 1565.43; 1496.49; 1474.31; 1454.06; 1431.40; 1416.94; 1386.57; 1354.27; 1333.05; 1301.23; 1276.65; 1255.43; 1240.49; 1224.58; 1210.60; 1175.88; 1155.63; 1115.14; 1086.21; 1039.93; 994.61; 961.82; 942.54; 906.86; 891.92; 850.94; 808.51; 786.81; 764.15; 748.73; 697.14; 648.93; 643.14; 620.48; 571.31; 539.49; 495.13; 478.74; 429.57; 420.41; 407.39 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₂H₂₉N₄OS₂⁺ 429.1783; Found 429.1796.

1-((4-phenyl-5-(m-tolyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3f**). Yield 83%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 5.88 (ddt, J = 17.2, 10.1, 4.9 Hz, 1H, CH=), 5.20 (dq, J = 10.4, 1.5 Hz, 1H^a, =CH₂), 4.92 (dq, J = 17.1, 1.6 Hz, 1H^b, =CH₂), 4.71 (br.s., 1H, OH), 4.53 (dt, J = 5.0,

1.9 Hz, 2H, NCH₂ in Allyl), 3.92 – 3.80 (m, 1H, CHOH), 3.29 (dd, *J* = 13.2, 4.2 Hz, 1H^a, SCH₂), 3.07 (dd, *J* = 13.2, 6.8 Hz, 1H^b, SCH₂), 2.60 (t, *J* = 7.5 Hz, 2H, CH₂CH₂CH₃), 2.40 (br.t, *J* = 5.2 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.37 – 2.27 (m, 2H, NCH₂CHOH), 1.82 – 1.69 (m, 2H, CH₂CH₂CH₃), 1.58 – 1.47 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.35 (m, 2H, N(CH₂CH₂)₂CH₂), 1.01 (t, *J* = 7.4 Hz, 3H, CH₃). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 154.4 (SC=N), 149.5 (C=N), 131.7 (CH=CH₂), 116.6 (=CH₂), 66.7 (OCH), 63.3 (NCH₂), 54.5 (2*NCH₂), 45.0 (NCH₂), 38.5 (SCH₂), 26.2 (CH₂), 25.5 (2*CH₂), 23.8 (CH₂), 19.7 (CH₂), 13.4 (CH₃). IR_ν_{max} = 3245.61; 3086.03; 2931.75; 2873.42; 2852.69; 2796.28; 2757.23; 1645.46; 1518.67; 1460.81; 1441.05; 1431.40; 1411.16; 1399.58; 1375.48; 1352.34; 1332.09; 1300.27; 1279.54; 1255.91; 1242.41; 1215.90; 1196.13; 1156.12; 1116.10; 1088.62; 1039.93; 994.12; 962.79; 915.06; 891.92; 862.02; 812.85; 786.81; 739.08; 685.09; 664.36; 615.18; 553.47; 478.74; 462.83; 442.58; 420.89; 411.25 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₁₆H₂₉N₄OS⁺ 325.2062; Found 325.2083.

1-((4-allyl-5-benzyl-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3g**). Yield 68%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.31 – 7.15 (m, 5H_{arom}), 5.62 (ddt, *J* = 17.2, 10.3, 5.2 Hz, 1H, CH=), 5.09 (dt, *J* = 10.4, 1.3 Hz, 1H^a, =CH₂), 4.87 (m, 2H, 1H, OH, 1H^b, =CH₂), 4.41 (dt, *J* = 5.3, 1.7 Hz, 2H, NCH₂ in Allyl), 4.09 (s, 2H, PhCH₂), 3.95 – 3.82 (m, 1H, CHOH), 3.31 (dd, *J* = 13.2, 4.3 Hz, 1H^a, SCH₂), 3.10 (dd, *J* = 13.2, 6.7 Hz, 1H^b, SCH₂), 2.57 – 2.31 (m, 6H, NCH₂), 1.62 – 1.47 (m, 4H, N(CH₂CH₂)₂CH₂), 1.47 – 1.37 (m, 2H N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.3 (SC=N), 150.4 (C=N), 135.4, 131.0 (CH=CH₂), 128.1 (2*CH), 128.1 (2*CH), 126.3 (CH=), 117.2 (=CH₂), 66.5 (OCH), 63.1 (NCH₂), 54.4 (2*NCH₂), 45.3 (NCH₂), 38.4 (SCH₂), 30.6 (CH₂Ph), 25.3 (2*CH₂), 23.6 (CH₂). IR_ν_{max} = 3257.66; 3086.03; 3063.37; 3029.14; 2931.75; 2851.72; 2796.28; 2758.67; 1644.98; 1603.52; 1517.70; 1495.53; 1463.71; 1452.62; 1440.56; 1420.32; 1392.84; 1374.03; 1352.82; 1329.20; 1300.75; 1278.57; 1242.90; 1203.36; 1155.63; 1115.62; 1087.66; 1075.60; 1039.44; 993.64; 962.30; 928.07; 915.54; 862.02; 787.30; 751.62; 725.59; 695.69; 680.75; 616.15; 572.75; 553.95; 493.69; 478.74; 445.96; 425.23; 402.09 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₀H₂₉N₄OS⁺ 373.2062; Found 373.2090.

1-((4-allyl-5-((4-chloro-2-methylphenoxy)methyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3h**). Yield 93%, colorless oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.17 – 7.05 (m, 3H_{arom}), 5.89 (ddt, *J* = 17.0, 10.4, 5.2 Hz, 1H, CH=), 5.24 – 5.15 (m, 3H, 1H^a, =CH₂, 2H OCH₂), 5.00 (dq, *J* = 17.1, 1.4 Hz, 1H^b, =CH₂), 4.80 – 4.55 (m, 3H, 2H NCH₂ in Allyl, 1H OH), 3.96 – 3.85 (m, 1H, CHOH), 3.39 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.16 (dd, *J* = 13.1, 6.9 Hz, 1H^b, SCH₂), 2.42 (br.t., *J* = 5.1 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.38 – 2.34 (m, 2H, NCH₂CHOH) 2.16 (s, 3H, CH₃), 1.58 – 1.50 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.38 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 154.1 (SC=N), 152.0, 150.6, 131.2 (CH=CH₂), 129.8 (CH=), 127.8, 126.0 (CH=), 125.0, 117.5 (=CH₂), 112.6 (CH=), 66.5 (OCH), 63.3 (NCH₂), 60.1 (OCH₂), 54.5 (2*NCH₂), 45.7 (NCH₂), 38.3 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂), 15.7 (CH₃). IR_ν_{max} = 3299.13; 3085.55; 2932.72; 2852.69; 2797.72; 2758.19; 1645.46; 1597.73; 1489.74; 1467.08; 1440.08; 1418.87; 1396.21; 1330.16; 1295.93; 1276.65; 1239.52; 1225.06; 1186.49; 1154.67; 1133.46; 1088.62; 1071.26; 1039.44; 1013.89; 994.12; 962.79; 930.49; 919.88; 877.93; 838.40; 803.69; 786.81; 746.80; 687.98; 654.23; 641.22; 590.11; 554.43; 513.94; 481.63; 468.14; 460.90; 441.14; 404.50 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₁H₃₀ClN₄O₂S⁺ 437.1778; Found 437.1794.

1-((4-allyl-5-((2,4-dichlorophenoxy)methyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3i**). Yield 68%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.38 – 7.32 (m, 2H_{arom}), 7.26 (dd, *J* = 8.9, 2.6 Hz, 1H_{arom}), 5.93 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1H, CH=), 5.31 (s, 2H, OCH₂), 5.21 (dq, *J* = 10.3, 1.3 Hz, 1H^a, =CH₂), 5.07 (dq, *J* = 17.0, 1.5 Hz, 1H^b, =CH₂), 4.79 – 4.57 (m, 3H, 1H OH, 2H NCH₂ in Allyl), 3.96 – 3.85 (m, 1H, CHOH), 3.39 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.16 (dd, *J* = 13.1, 6.8 Hz, 1H^b, SCH₂), 2.41 (br.t., 4H, N(CH₂CH₂)₂CH₂), 2.35 (d, *J* = 6.4 Hz, 2H, NCH₂CHOH), 1.57 – 1.50 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.37 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 152.2, 151.6, 150.0, 131.0 (CH=CH₂), 129.1 (CH=), 127.4 (CH=), 125.6, 122.7, 117.9 (=CH₂), 115.1 (CH=), 66.5 (OCH), 63.3 (NCH₂), 60.9 (OCH₂), 54.6 (2*NCH₂), 45.9 (NCH₂), 38.3 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_ν_{max} = 3248.02; 3081.69; 3029.14; 2934.16; 2886.43; 2853.65; 2796.28; 2757.71; 1642.57; 1587.13; 1575.08; 1528.31; 1481.06; 1469.49; 1455.51; 1441.53; 1418.39; 1390.42; 1355.23; 1329.20; 1284.84; 1266.04; 1244.83; 1232.77; 1203.85; 1154.19; 1115.14; 1105.01; 1092.96; 1059.69; 1040.89; 1006.18; 995.09; 962.79; 932.90; 914.58; 890.95; 863.47; 833.58; 815.74; 802.72; 785.85; 722.69; 698.10; 687.02; 651.34; 641.70; 593.00;

555.40; 507.67; 490.79; 486.46; 467.65; 440.65; 421.85; 409.80 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₀H₂₇Cl₂N₄O₂S⁺ 457.1232; Found 457.1252.

1-((4-phenethyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3j**). Yield 87%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.52 – 7.46 (m, 2H_{arom}), 7.28 (d, J = 7.9 Hz, 2H_{arom}), 5.95 (ddt, J = 17.2, 10.5, 4.6 Hz, 1H, CH=), 5.31 – 5.18 (m, 1H^a, =CH₂), 5.00 – 4.88 (m, 1H^b, =CH₂), 4.71 (br.s., 1H, OH), 4.60 (dt, J = 4.3, 1.9 Hz, 2H, NCH₂ in Allyl), 3.98 – 3.87 (m, 1H, CHOH), 3.41 (dd, J = 13.2, 4.3 Hz, 1H^a, SCH₂), 3.18 (dd, J = 13.2, 6.8 Hz, 1H^b, SCH₂), 2.47 – 2.38 (m, 7H, 4H, N(CH₂CH₂)₂CH₂, 3H CH₃), 2.37 (dd, J = 6.4, 2.1 Hz, 2H, NCH₂CHOH), 1.60 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.37 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 154.5 (SC=N), 151.3 (C=N), 139.0, 131.8 (CH=CH₂), 128.9 (2*CH=), 127.7 (2*CH=), 124.1, 117.0 (=CH₂), 66.6 (OCH), 63.4 (NCH₂), 54.6 (2*NCH₂), 46.1 (NCH₂), 38.4 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂), 20.8 (CH₃). IR_{Vmax} = 3275.50; 3085.07; 3025.76; 2931.27; 2852.20; 2796.28; 2757.23; 1645.46; 1617.02; 1574.11; 1478.65; 1452.62; 1431.40; 1386.09; 1352.82; 1330.64; 1300.75; 1279.54; 1256.40; 1201.43; 1186.01; 1155.63; 1114.65; 1087.66; 1039.44; 1021.61; 993.64; 983.52; 962.79; 916.50; 891.92; 861.54; 821.53; 786.81; 762.23; 727.03; 685.09; 639.77; 626.75; 579.50; 552.99; 530.81; 491.28; 438.73; 430.53; 414.14; 405.94 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₀H₂₉N₄O₂S⁺ 373.2062; Found 373.2068.

1-((4-allyl-5-(2-bromophenyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3k**). Yield 81%, colorless oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.72 – 7.67 (m, 1H_{arom}), 7.49 – 7.37 (m, 3H_{arom}), 5.69 (ddt, J = 17.2, 10.4, 5.3 Hz, 1H, CH=), 5.07 (dt, J = 10.2, 1.3 Hz, 1H^a, =CH₂), 4.83 (dq, J = 17.0, 1.5 Hz, 1H^b, =CH₂), 4.69 (br.s., 1H, OH), 4.43 – 4.30 (m, 2H, NCH₂ in Allyl), 3.96 – 3.86 (m, 1H, CHOH), 3.38 (dd, J = 13.1, 4.4 Hz, 1H^a, SCH₂), 3.17 (dd, J = 13.1, 6.8 Hz, 1H^b, SCH₂), 2.51 – 2.28 (m, 6H, NCH₂), 1.58 – 1.48 (m, 4H, N(CH₂CH₂)₂CH₂), 1.44 – 1.34 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.2 (SC=N), 150.8 (C=N), 132.4 (CH=), 132.2 (CH=), 131.6 (CH=CH₂), 130.9 (CH=), 128.7, 127.2 (CH=), 123.3, 117.6 (=CH₂), 66.5 (OCH), 63.3 (NCH₂), 54.5 (2*NCH₂), 45.9 (NCH₂), 38.5 (SCH₂), 25.4 (2*CH₂), 23.8 (CH₂). IR_{Vmax} = 3295.75; 3085.07; 3064.33; 3019.02; 2931.27; 2851.24; 2798.21; 2758.19; 2701.30; 1644.98; 1597.25; 1563.99; 1528.31; 1446.83; 1428.99; 1387.05; 1352.34; 1328.23; 1301.23; 1276.65; 1245.79; 1203.85; 1156.12; 1115.14; 1087.66; 1040.41; 1026.91; 993.64; 981.59; 962.30; 916.02; 891.92; 862.02; 768.98; 725.59; 712.57; 684.12; 647.96; 587.70; 567.45; 552.51; 511.04; 471.03; 451.26; 422.82; 403.53 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₉H₂₆BrN₄O₂S⁺ 437.1011; Found 437.1019.

1-((4-allyl-5-(2-iodophenyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3l**). Yield 72%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.98 (dd, J = 8.0, 1.1 Hz, 1H_{arom}), 7.51 (td, J = 7.5, 1.2 Hz, 1H_{arom}), 7.39 (dd, J = 7.6, 1.7 Hz, 1H_{arom}), 7.28 (td, J = 7.7, 1.8 Hz, 2H_{arom}), 5.73 (ddt, J = 17.1, 10.5, 5.3 Hz, 1H, CH=), 5.12 (dq, J = 10.4, 1.3 Hz, 1H^a, =CH₂), 4.88 (dq, J = 17.0, 1.5 Hz, 1H^b, =CH₂), 4.69 (br.s., 1H, OH), 4.46 – 4.29 (m, 2H, NCH₂ in Allyl), 3.99 – 3.86 (m, 1H, CHOH), 3.42 (dd, J = 13.1, 4.4 Hz, 1H^a, SCH₂), 3.20 (dd, J = 13.1, 6.8 Hz, 1H^b, SCH₂), 2.43 (br.t., J = 4.8 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.38 (dd, J = 6.4, 2.1 Hz, 2H, NCH₂CHOH), 1.60 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.47 – 1.37 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 155.3 (SC=N), 150.8 (C=N), 138.7 (CH=), 132.7, 131.4 (CH=CH₂), 131.3 (CH=), 130.9 (CH=), 127.5 (CH=), 117.7 (=CH₂), 99.1 (=CI), 66.6 (OCH), 63.4 (NCH₂), 54.6 (2*NCH₂), 46.0 (NCH₂), 38.6 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_{Vmax} = 3293.34; 3085.55; 3058.55; 3033.48; 2983.34; 2930.79; 2850.76; 2796.28; 2757.71; 1644.98; 1590.50; 1559.65; 1525.42; 1441.53; 1428.03; 1386.57; 1351.86; 1328.23; 1300.75; 1272.79; 1245.79; 1203.36; 1155.63; 1115.14; 1087.66; 1039.44; 1016.78; 993.64; 980.63; 962.30; 916.02; 891.43; 861.54; 768.98; 720.76; 705.82; 679.78; 640.73; 587.22; 553.47; 509.12; 468.62; 459.94; 444.03; 421.85; 418.00 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₉H₂₆IN₄O₂S⁺ 485.0872; Found 485.0896.

1-((4-allyl-5-(2-nitrophenyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3m**). Yield 89%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 8.25 – 8.14 (m, 1H_{arom}), 7.91 – 7.76 (m, 2H_{arom}), 7.70 – 7.59 (m, 1H_{arom}), 5.77 (ddt, J = 17.1, 10.5, 5.4 Hz, 1H, CH=), 5.14 (dt, J = 10.3, 1.3 Hz, 1H^a, =CH₂), 4.97 (dq, J = 17.1, 1.5 Hz, 1H^b, =CH₂), 4.68 (br.s., 1H, OH), 4.52 – 4.37 (m, 2H, NCH₂ in Allyl), 3.98 – 3.86 (m, 1H, CHOH), 3.44 (dd, J = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.20 (dd, J = 13.1, 6.9 Hz, 1H^b, SCH₂), 2.43 (br.t., J = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.41 – 2.33 (m, 2H, NCH₂CHOH), 1.62 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.47 – 1.38 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 151.3,

150.8, 148.4, 133.1 (CH=), 132.2 (CH=), 131.3 (CH=CH), 131.0 (CH=), 124.4 (CH=), 121.9, 117.8 (=CH₂), 66.5 (OCH), 63.4 (NCH₂), 54.6 (2*NCH₂), 46.1 (NCH₂), 38.6 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_ν_{max} = 3293.34; 3084.58; 2932.72; 2852.20; 2799.17; 2758.67; 1644.98; 1617.50; 1575.08; 1527.83; 1452.14; 1441.05; 1432.37; 1419.83; 1388.50; 1344.14; 1301.23; 1278.57; 1253.50; 1203.85; 1155.63; 1115.14; 1087.66; 1070.78; 1039.44; 993.16; 983.04; 962.79; 930.00; 891.43; 852.86; 786.33; 751.14; 728.00; 716.91; 697.14; 652.30; 589.63; 559.26; 534.19; 511.04; 479.22; 459.94; 442.10; 423.30; 576.13; 525.99; 484.53; 465.24; 444.03; 420.89; 404.50 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₉H₂₆N₅O₃S⁺ 404.1756; Found 404.1772.

1-((4-allyl-5-(furan-2-yl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3n**). Yield 91%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.70 (d, *J* = 1.8 Hz, 1H_{fur}), 6.95 (d, *J* = 3.5 Hz, 1H_{fur}), 6.59 (dd, *J* = 3.5, 1.9 Hz, 1H_{fur}), 5.94 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H, CH=), 5.26 – 5.13 (m, 1H^a, =CH₂), 5.00 (dd, *J* = 17.2, 2.2 Hz, 1H^b, =CH₂), 4.81 (dt, *J* = 5.2, 1.8 Hz, 2H, NCH₂ in Allyl), 4.67 (br.s., 1H, OH), 3.97 – 3.85 (m, 1H, CHOH), 3.40 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.17 (dd, *J* = 13.1, 6.9 Hz, 1H^b, SCH₂), 2.42 (br.t., *J* = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.36 (dd, *J* = 6.3, 1.5 Hz, 2H, NCH₂CHOH), 1.58 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.44 – 1.36 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 151.2 (SC=N), 146.5 (C=N), 143.5 (CH=), 141.7, 131.5 (CH=CH), 117.2 (=CH₂), 111.2 (CH=), 110.8 (CH=), 66.5 (OCH), 63.3 (NCH₂), 54.6 (2*NCH₂), 46.4 (NCH₂), 38.6 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_ν_{max} = 3293.34; 3148.22; 3121.22; 3088.92; 2983.34; 2932.23; 2852.20; 2797.72; 2758.67; 2697.44; 1645.46; 1612.20; 1515.29; 1466.60; 1440.56; 1428.51; 1420.80; 1378.85; 1352.82; 1331.61; 1301.23; 1278.57; 1257.84; 1224.09; 1205.77; 1158.04; 1115.14; 1087.66; 1070.30; 1039.44; 1015.82; 993.16; 962.30; 915.54; 902.04; 885.17; 862.02; 821.53; 785.37; 742.94; 712.09; 684.12; 648.45; 592.52; 546.24; 496.58; 475.85; 444.03; 429.08; 413.66; 403.53 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₇H₂₅N₄O₂S⁺ 349.1698; Found 349.1708.

1-((4-allyl-5-(5-bromofuran-2-yl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3o**). Yield 80%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.01 – 6.92 (m, 1H_{fur}), 6.64 – 6.55 (m, 1H_{fur}), 5.94 (ddt, *J* = 17.3, 10.3, 5.1 Hz, 1H, CH=), 5.28 – 5.18 (m, 1H^a, =CH₂), 5.09 – 4.98 (m, 1H^b, =CH₂), 4.83 – 4.72 (m, 2H, NCH₂ in Allyl), 4.61 (br.s., 1H, OH), 3.96 – 3.83 (m, 1H, CHOH), 3.41 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.17 (dd, *J* = 13.1, 6.8 Hz, 1H^b, SCH₂), 2.41 (br.t., *J* = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.35 (d, *J* = 6.4 Hz, 2H, NCH₂CHOH), 1.59 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.46 – 1.36 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 151.6 (SC=N), 145.6 (C=N), 143.6, 131.2 (CH=CH), 122.9, 117.5 (=CH₂), 113.2 (2*CH=), 66.5 (OCH), 63.3 (NCH₂), 54.6 (2*NCH₂), 46.4 (NCH₂), 38.6 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_ν_{max} = 3308.77; 3140.03; 3120.74; 3087.96; 2984.30; 2932.23; 2851.72; 2796.28; 2757.23; 1645.46; 1613.64; 1514.81; 1465.63; 1441.05; 1426.58; 1420.32; 1378.85; 1353.30; 1331.12; 1301.23; 1278.09; 1256.40; 1205.29; 1155.63; 1114.65; 1091.99; 1039.44; 1012.45; 993.64; 962.30; 928.56; 892.40; 861.54; 786.33; 762.71; 709.19; 684.61; 649.41; 587.70; 548.65; 534.67; 510.08; 477.30; 459.94; 433.90; 414.14; 408.83; 403.0594 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₇H₂₄⁷⁹BrN₄O₂S⁺ 427.0803; Found 427.0818.

1-((4-allyl-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3p**). Yield 80%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 8.80 (d, *J* = 2.2 Hz, 1H_{pyr}), 8.66 (dd, *J* = 4.9, 1.7 Hz, 1H_{pyr}), 8.01 (dt, *J* = 8.0, 2.0 Hz, 1H_{pyr}), 7.48 (dd, *J* = 7.9, 4.8 Hz, 1H_{pyr}), 6.04 – 5.89 (m, 1H, CH=), 5.27 (dd, *J* = 10.5, 2.0 Hz, 1H^a, =CH₂), 4.94 (dd, *J* = 17.2, 2.1 Hz, 1H^b, =CH₂), 4.81 – 4.47 (m, 3H, 1H OH, 2H NCH₂ in Allyl), 3.99 – 3.86 (m, 1H, CHOH), 3.44 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.20 (dd, *J* = 13.1, 6.9 Hz, 1H^b, SCH₂), 2.43 (br.t., *J* = 5.0 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.37 (dd, *J* = 6.4, 1.5 Hz, 2H, NCH₂CHOH), 1.59 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.46 – 1.36 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 152.3, 152.1, 150.1 (CH=N), 148.1 (CH=N), 135.0 (CH=), 131.7 (CH=CH), 123.2, 123.1 (CH=), 117.1 (=CH₂), 66.6 (OCH), 63.4 (NCH₂), 54.6 (2*NCH₂), 46.3 (NCH₂), 38.5 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_ν_{max} = 3291.41; 3086.03; 3072.05; 3035.41; 2982.37; 2931.75; 2851.72; 2796.76; 2759.64; 1644.98; 1598.70; 1571.22; 1513.85; 1453.10; 1432.37; 1412.60; 1386.09; 1352.34; 1328.71; 1301.23; 1278.57; 1257.84; 1241.45; 1201.43; 1191.79; 1155.63; 1115.14; 1088.14; 1039.44; 1024.98; 994.12; 981.59; 962.79; 918.43; 891.43; 861.54; 812.37; 786.33; 764.64; 709.19; 687.02; 651.34; 620.00; 590.11; 551.54; 505.26; 479.22; 437.76; 424.26 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₈H₂₆N₅OS⁺ 360.1858; Found 360.1876.

1-((4-allyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3q**). Yield 89%, m.p. 86 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 8.77 – 8.60 (m, 2H_{pyr}), 7.71 – 7.52 (m, 2H_{pyr}), 5.99 (ddt, *J* = 17.2, 10.5, 4.5 Hz, 1H, CH=), 5.34 – 5.23 (m, 1H^a, =CH₂), 5.01 – 4.90 (m, 1H^b, =CH₂), 4.79 – 4.58 (m, 3H, 2H NCH₂ in Allyl, 1H OH), 3.99 – 3.86 (m, 1H, CHOH), 3.45 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.20 (dd, *J* = 13.1, 6.9 Hz, 1H^b, SCH₂), 2.49 – 2.25 (m, 6H, NCH₂), 1.60 – 1.47 (m, 4H, N(CH₂CH₂)₂CH₂), 1.46 – 1.36 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.0, 152.3, 149.8 (2*CH=N), 134.1, 131.6 (CH=CH₂), 121.4 (2*CH=), 117.2 (=CH₂), 66.5 (OCH), 63.4 (NCH₂), 54.6 (2*NCH₂), 46.4 (NCH₂), 38.4 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂). IR_ν_{max} = 3190.17; 3084.58; 3045.53; 2985.75; 2969.84; 2929.34; 2917.29; 2849.79; 2806.40; 2774.58; 2755.30; 2730.71; 2669.48; 2552.81; 2519.54; 1644.50; 1604.97; 1557.24; 1515.29; 1451.65; 1428.03; 1411.16; 1379.34; 1367.28; 1326.30; 1312.32; 1301.72; 1284.36; 1255.91; 1235.67; 1221.68; 1201.43; 1186.01; 1154.19; 1116.10; 1087.17; 1066.44; 1049.57; 1039.44; 1016.30; 998.46; 988.82; 962.30; 925.66; 870.70; 857.69; 825.87; 790.19; 762.23; 728.48; 705.82; 699.07; 658.57; 582.88; 574.68; 557.81; 536.11; 511.04; 478.74; 457.53; 447.89; 422.82; 408.35; 403.53 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₁₈H₂₆N₅O⁺ 360.1858; Found 360.1862.

1-((4-phenyl-5-propyl-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3r**). Yield 63%, colorless oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.58 – 7.45 (m, 3H_{arom}), 7.36 – 7.28 (m, 2H_{arom}), 4.63 (br.s., 1H, OH), 3.91 – 3.77 (m, 1H, CH), 3.28 (dd, *J* = 13.2, 4.4 Hz, 1H^a, SCH₂), 3.04 (dd, *J* = 13.2, 6.7 Hz, 1H^b, SCH₂), 2.49 – 2.44 (m, 2H, CH₂CH₂CH₃), 2.38 (br.t., *J* = 5.2 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.29 (dd, *J* = 6.7, 2.4 Hz, 2H, NCH₂CHOH), 1.62 – 1.53 (m, 2H, CH₂CH₂CH₃), 1.53 – 1.45 (m, 4H, N(CH₂CH₂)₂CH₂), 1.41 – 1.32 (m, 2H, N(CH₂CH₂)₂CH₂), 0.87 (t, *J* = 7.4 Hz, 3H, CH₃). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 154.5 (SC=N), 150.3 (C=N), 133.2 (=CH), 129.3 (2*CH=), 129.2, 126.9 (2*CH=), 66.5 (OCH), 63.3 (NCH₂), 54.5 (2*NCH₂), 37.4 (SCH₂), 26.4 (CH₂), 25.4 (2*CH₂), 23.7 (CH₂), 19.7 (CH₂), 13.3 (CH₃). IR_ν_{max} = 3281.77; 3062.89; 2931.27; 2872.45; 2851.72; 2796.76; 2757.71; 1597.25; 1589.06; 1521.56; 1498.42; 1441.53; 1431.40; 1396.69; 1351.86; 1327.75; 1300.27; 1276.16; 1156.12; 1116.10; 1087.66; 1074.64; 1039.44; 1009.07; 994.61; 962.79; 891.43; 862.02; 808.99; 785.85; 770.90; 742.46; 696.18; 614.22; 602.65; 562.63; 499.95; 480.19; 470.55; 445.48; 419.92; 411.73; 405.94 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₁₉H₂₉N₄O⁺ 361.2062; Found 361.2073.

1-((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3s**). Yield 83%, white solid, m.p. 97 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.59 – 7.45 (m, 3H_{arom}), 7.37 – 7.24 (m, 7H_{arom}), 4.68 (br.s., 1H, OH), 4.01 – 3.87 (m, 1H, CHOH), 3.43 (dd, *J* = 13.1, 4.4 Hz, 1H^a, SCH₂), 3.18 (dd, *J* = 13.2, 6.8 Hz, 1H^b, SCH₂), 2.44 (br.t., *J* = 5.4 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.39 – 2.31 (m, 2H, NCH₂CHOH), 1.61 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.46 – 1.36 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.6, 152.4, 134.0, 129.3 (2*CH=), 128.9 (CH=), 127.9 (2*CH=), 127.4 (2*CH=), 127.1 (2*CH=), 126.6, 66.4 (OCH), 63.3 (NCH₂), 54.5 (2*NCH₂), 37.4 (SCH₂), 25.4 (2*CH₂), 23.7 (CH₂). IR_ν_{max} = 3450.51; 3104.35; 3085.55; 3049.87; 3012.27; 2934.16; 2918.25; 2855.10; 2787.12; 2757.71; 2736.01; 2696.96; 2647.79; 1596.29; 1497.94; 1473.35; 1457.44; 1445.87; 1425.62; 1377.89; 1356.68; 1330.16; 1304.61; 1282.91; 1271.82; 1257.36; 1246.27; 1214.45; 1176.85; 1153.71; 1118.99; 1095.85; 1073.19; 1043.30; 1032.21; 1006.66; 995.09; 970.98; 922.29; 906.38; 889.02; 861.54; 849.49; 834.06; 808.99; 791.64; 771.87; 729.92; 710.16; 694.25; 620.00; 614.22; 602.65; 584.33; 558.29; 514.42; 504.29; 482.12; 465.72; 425.71; 406.42 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₂H₂₇N₄O⁺ 395.1906; Found 395.1912.

1-((4-phenyl-5-(*m*-tolyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3t**). Yield 90%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.57 – 7.46 (m, 3H_{arom}), 7.33 – 7.29 (m, 3H_{arom}), 7.14 – 7.08 (m, 2H_{arom}), 7.04 – 6.99 (m, 1H_{arom}), 4.63 (br.s., 1H, OH), 4.01 – 3.87 (m, 1H, CHOH), 3.43 (dd, *J* = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.18 (dd, *J* = 13.1, 6.8 Hz, 1H^b, SCH₂), 2.42 (br.t., 4H, N(CH₂CH₂)₂CH₂), 2.37 – 2.31 (m, 2H, NCH₂CHOH), 2.28 (s, 3H, CH₃), 1.59 – 1.49 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.36 (m, 2H, N(CH₂CH₂)₂CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.6, 152.2, 137.2, 134.0, 129.6 (CH=), 129.3 (2*CH=), 129.1 (CH=), 128.2 (CH=), 127.7 (2*CH=), 126.4, 124.4 (CH=), 66.5 (OCH), 63.4 (NCH₂), 54.5 (2*NCH₂), 37.5 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂), 20.8 (CH₃). IR_ν_{max} = 3303.95; 3060.48; 3036.37; 2931.27; 2851.24; 2797.24; 2757.23; 1607.86; 1595.81; 1497.45; 1485.40; 1465.15; 1453.10; 1432.37; 1375.96; 1324.37; 1303.16; 1268.45; 1242.90; 1210.11; 1156.12; 1116.10; 1088.14; 1073.19; 1038.96; 1009.55; 994.61; 962.79; 911.20; 887.09; 861.06; 849.97; 788.26; 768.49; 717.87; 692.32; 680.75; 667.73; 608.43; 545.27; 525.03;

502.85; 481.15; 442.10; 429.57; 418.96; 410.28 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₃H₂₉N₄OS⁺ 409.2062; Found 409.2082.

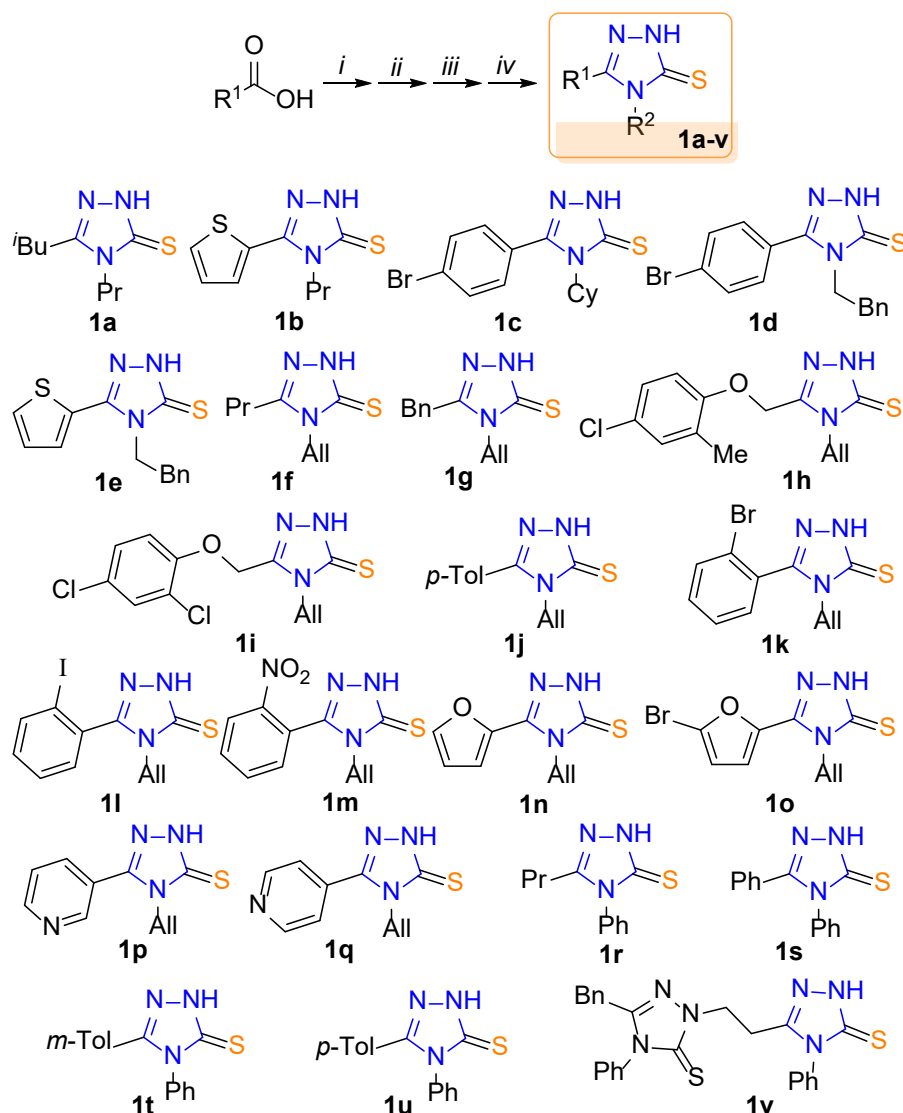
1-((4-phenyl-5-(p-tolyl)-4H-1,2,4-triazol-3-yl)thio)-3-(piperidin-1-yl)propan-2-ol (**3u**). Yield 85%, white solid, m.p. 115 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.56 – 7.46 (m, 3H_{arom}), 7.34 – 7.26 (m, 2H_{arom}), 7.26 – 7.18 (m, 2H_{arom}), 7.11 – 7.03 (m, 2H_{arom}), 4.60 (br.s., 1H, OH), 3.98 – 3.85 (m, 1H, CHOH), 3.41 (dd, J = 13.1, 4.3 Hz, 1H^a, SCH₂), 3.16 (dd, J = 13.1, 6.8 Hz, 1H^b, SCH₂), 2.41 (br.t., J = 5.3 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.36 – 2.25 (m, 5H, 2H NCH₂CH, 3H CH₃), 1.59 – 1.47 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.36 (m, 2H, N(CH₂CH₂)2CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 153.6, 152.1, 138.6, 134.1, 129.3 (2*CH=), 129.1 (CH=), 128.5 (2*CH=), 127.4 (2*CH=), 127.1 (2*CH=), 123.7, 66.5 (OCH), 63.4 (NCH₂), 54.5 (2*NCH₂), 37.4 (SCH₂), 25.5 (2*CH₂), 23.8 (CH₂), 20.7 (CH₃). IR_{vmax} = 3410.01; 3099.53; 3069.64; 3048.91; 2932.23; 2920.18; 2858.47; 2803.51; 2759.64; 2665.14; 1613.64; 1593.40; 1494.56; 1479.62; 1430.44; 1403.92; 1374.51; 1356.68; 1335.95; 1322.93; 1305.09; 1284.36; 1264.11; 1243.38; 1227.95; 1205.77; 1185.53; 1158.04; 1152.26; 1120.92; 1106.94; 1081.39; 1062.10; 1039.93; 1020.64; 1012.45; 1005.70; 992.20; 970.02; 947.84; 917.47; 890.95; 867.81; 847.08; 822.97; 798.87; 782.48; 769.46; 748.73; 725.59; 708.23; 694.25; 645.55; 633.50; 612.77; 583.84; 552.51; 525.51; 514.90; 498.51; 484.05; 478.74; 444.03; 424.26; 406.91 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₂₃H₂₉N₄OS⁺ 409.2062; Found 409.2062.

5-benzyl-2-(2-(5-((2-hydroxy-3-(piperidin-1-yl)propyl)thio)-4-phenyl-4H-1,2,4-triazol-3-yl)ethyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (**3v**). Yield 68%, yellow oil. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.61 – 7.52 (m, 3H_{arom}), 7.48 – 7.40 (m, 5H_{arom}), 7.21 – 7.09 (m, 5H_{arom}), 6.93 – 6.85 (m, 2H_{arom}), 4.62 (br.s., 1H, OH), 4.44 (t, J = 7.3 Hz, 2H, NNCH₂), 3.92 – 3.86 (m, 1H, CHOH), 3.83 (s, 2H, CH₂Ph), 3.34 (dd, J = 13.2, 4.3 Hz, 1H^a, SCH₂), 3.16 – 3.06 (m, 3H, 1H^b, SCH₂, 2H NNCH₂CH₂), 2.39 (br.t., J = 5.1 Hz, 4H, N(CH₂CH₂)₂CH₂), 2.31 (d, J = 6.4 Hz, 2H, NCH₂CHOH), 1.57 – 1.47 (m, 4H, N(CH₂CH₂)₂CH₂), 1.45 – 1.36 (m, 2H, N(CH₂CH₂)2CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 167.4, 151.5, 151.0, 149.3, 133.7, 133.6, 132.9, 129.4, 129.3, 128.9, 128.7, 128.2, 127.9, 127.7, 127.0, 126.4, 66.5 (OCH), 63.4 (NCH₂), 54.5 (2*NCH₂), 45.5 (NCH₂), 37.6 (SCH₂), 31.2 (CH₂), 25.5 (2*CH₂), 23.8 (CH₂), 23.3 (CH). IR_{vmax} = 3363.73; 3088.44; 3062.89; 3033.00; 2932.72; 2851.72; 2799.17; 2757.71; 1596.77; 1567.84; 1522.52; 1497.45; 1478.17; 1454.55; 1442.01; 1415.01; 1344.62; 1333.53; 1295.45; 1256.88; 1213.97; 1155.63; 1115.62; 1072.71; 1038.00; 1016.30; 995.09; 962.79; 918.91; 890.95; 862.02; 767.53; 722.69; 694.25; 679.30; 638.80; 614.22; 566.00; 533.22; 503.81; 477.30; 458.01; 436.80; 418.96 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₃₃H₃₈N₇O₂S⁺ 612.2579; Found 612.2579.

3,3'-((((2,5-dimethyl-1,4-phenylene)bis(methylene))bis(sulfanediyl))bis(methylene))bis(4-phenyl-4H-1,2,4-triazole-5,3-diyl))bis(sulfanediyl))bis(1-(piperidin-1-yl)propan-2-ol) (**3w**). Yield 73%, white solid, m.p. 186 °C. ¹H NMR (400 MHz, DMSO/CCl₄ -1/3) δ 7.59 – 7.46 (m, 6H_{arom}), 7.39 – 7.28 (m, 4H_{arom}), 7.00 (s, 2H_{arom}), 4.58 (br.s., 2H, OH), 3.94 – 3.83 (m, 2H, CHOH), 3.65 (s, 4H, CH₂CNN), 3.53 (s, 4H, SCH₂Ar), 3.38 (dd, J = 13.1, 4.3 Hz, 2H^a, SCH₂CHOH), 3.12 (dd, J = 13.1, 6.8 Hz, 2H^b, SCH₂CHOH), 2.40 (br.t., J = 5.3 Hz, 8H, N(CH₂CH₂)₂CH₂), 2.32 (d, J = 6.4 Hz, 4H, NCH₂CHOH), 2.22 (s, 6H, CH₃), 1.61 – 1.46 (m, 8H, N(CH₂CH₂)₂CH₂), 1.46 – 1.32 (m, 4H, N(CH₂CH₂)2CH₂). ¹³C NMR (101 MHz, DMSO/CCl₄ -1/3) δ 152.3 (2*N=CCH₂), 151.5 (2*N=CS), 133.7 (2*C=CCH₃), 133.2 (2*C=CCH₂), 132.7 (2*NC=CH), 131.7 (2*CH=CCH₃), 129.5 (2*CH=), 129.3 (4*CH=), 126.9 (4*CH=CN), 66.4 (2*OCH), 63.5 (2*NCH₂CH), 54.5 (4*NCH₂), 37.6 (2*SCH₂CH), 32.6 (2*SCH₂(C₆H₅)), 25.4 (4*NCH₂), 24.0 (2*SCH₂(C₂N₃)), 23.8 (2*CH₂), 17.9 (2*CH₃). IR_{vmax} = 3447.62; 3070.12; 3055.17; 2960.68; 2948.63; 2920.66; 2851.72; 2803.03; 2759.15; 2735.53; 1496.49; 1445.39; 1435.26; 1409.23; 1403.44; 1388.01; 1374.03; 1354.75; 1325.82; 1321.00; 1303.16; 1279.06; 1253.02; 1238.56; 1222.65; 1171.54; 1151.78; 1116.10; 1090.07; 1069.82; 1044.75; 1028.84; 1007.62; 991.23; 964.23; 923.25; 916.02; 891.43; 859.61; 843.22; 833.58; 797.42; 781.03; 748.25; 702.93; 689.43; 663.87; 615.66; 582.40; 554.92; 486.94; 462.35; 426.19 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ Calcd for C₄₄H₅₉N₈O₂S₄⁺ 859.3644; Found 859.3639.

3. Results and Discussion

Initially, the starting triazoles with different substituents at the 4th and 5th positions (Scheme 3) were synthesized from the corresponding acids using the procedure described in the literature [52,56].

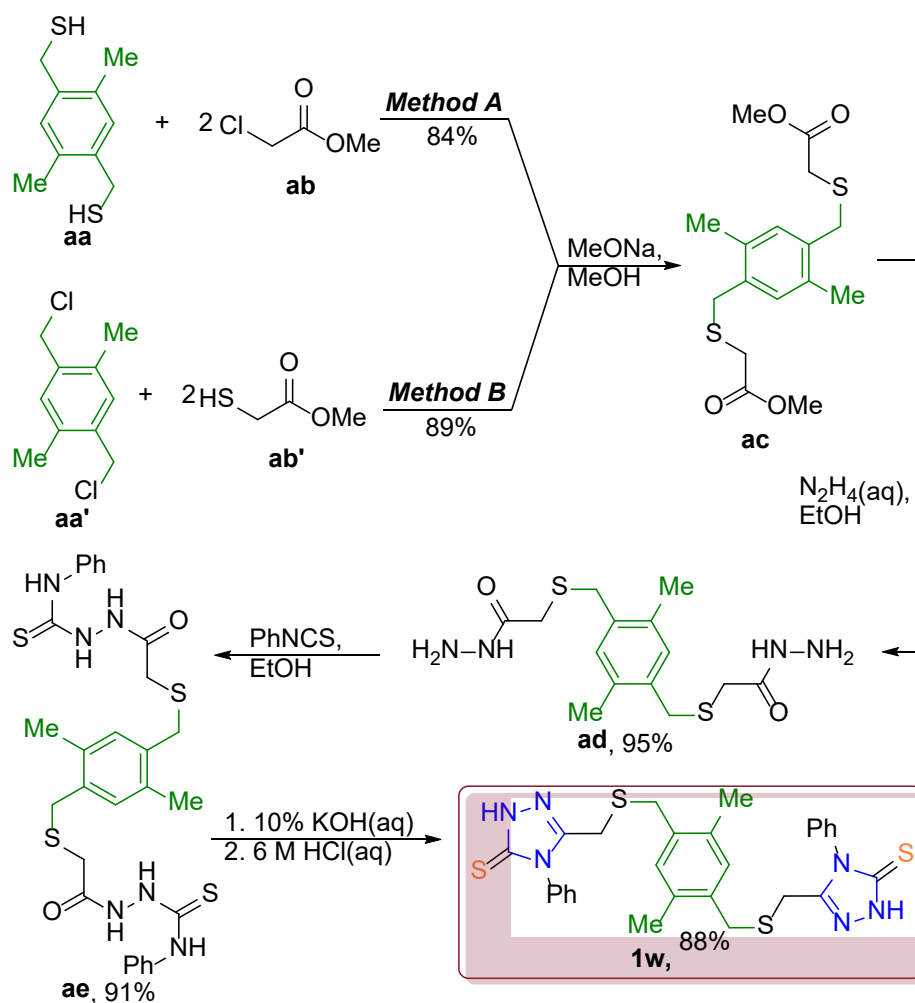


Scheme 3. The synthesis of starting 5,4-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones **1a-v**. Reagents and conditions: *i* – EtOH/MeOH, H^+ reflux; *ii* – $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH, r.t. 1 h and reflux 4 h; *iii* – R_2NCS , EtOH, reflux 4 h; *iv* – 10% sol. KOH(aq) 3 eq., reflux 5 h.

Bis-1,2,4-triazole **1w** was synthesized according to the Scheme 4.

The starting bis-ester ac was synthesized using two methods. Method A involved the use of (2,5-dimethyl-1,4-phenylene)dimethanethiol (**aa**) and methyl 2-chloroacetate (**ab**), whereas Method B utilized 1,4-bis(chloromethyl)-2,5-dimethylbenzene (**aa'**) and methyl 2-mercaptoacetate (**ab'**). In both cases, the reactions were carried out under the same conditions in a methanol medium in the presence of sodium methylate. The bis-ester ac was obtained in almost the same quantitative yields. The synthesized ester was subjected to hydrazinolysis using excess aq. hydrazine in an ethanol medium. To construct the 1,2,4-triazole ring, the synthesized hydrazide (**ad**) was reacted with phenylisothiocyanate to give the corresponding bis(thiosemicarbazide) (**ae**).

For the cyclization of bis(thiosemicarbazide) (**ae**), the classic base cyclization using a 10% potassium hydroxide solution was utilized under heating conditions, which resulted in obtaining bis-1,2,4-triazole-3-thione **1w** in relatively high yields.

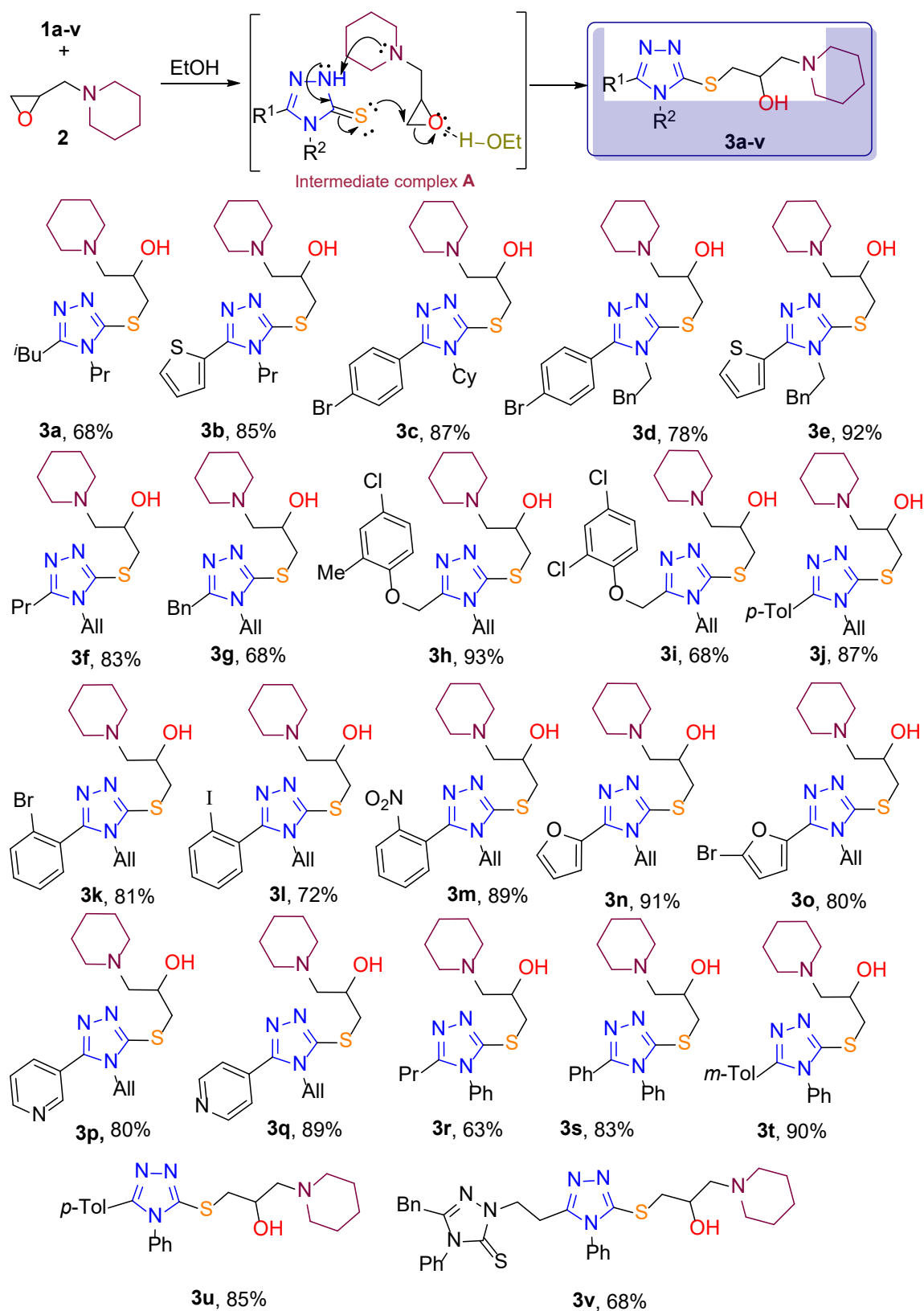


Scheme 4. The synthesis of starting bis-1,2,4-triazole-3-thione **1w**.

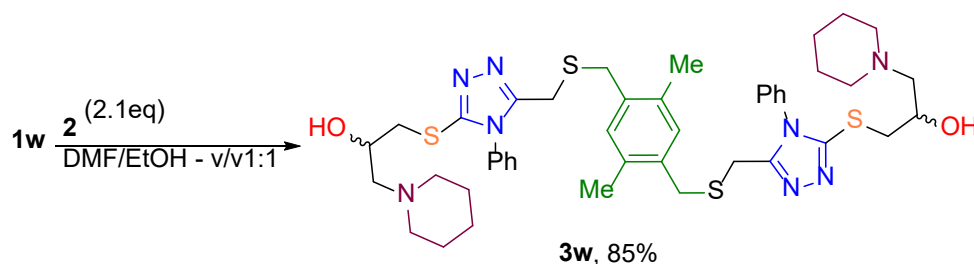
The reaction of the triazoles **1a-v** with 1-(oxiran-2-ylmethyl)piperidine (**2**), which was synthesized according to the method of the article [35], was studied (Scheme 5).

The reaction proceeds without the use of basic catalysts because the nitrogen of the piperidine ring in compound **2** has an anchimeric effect, that is, it plays the role of basic catalysis.

The solvent also plays an important role here; ethanol forms a hydrogen bond with the epoxide ring by polarizing the C-O bond [62–64]. In our opinion, intermediate complex A is formed during this reaction, which facilitates the course of the reaction. According to the Krasusky rule, the reaction proceeds regiospecifically and produces secondary alcohols. This is evidenced by the presence of the signal of the CH group at 3.8–4.0 ppm in the ^1H NMR spectra.



Scheme 5. The synthesis of vicinal amino alcohols containing 1,2,4-triazole ring **3a-v**. The reaction of the synthesized bis-1,2,4-triazole **1w** with oxirane **2** was also investigated, and as a result the corresponding bis-vicinal amino alcohol **3w** was obtained in good yields (Scheme 6).



Scheme 6. The synthesis of bis-vicinal amino alcohol **3w**.

The structure of the compound **3w** was confirmed by several 2D NMR spectra (HSQC, HMBC, NOESY). Interestingly, although the compound has two chiral carbons, there is only one set of signals present in both ^1H and ^{13}C NMR spectra. As it is known, NMR spectroscopy in achiral solvents cannot distinguish between enantiomers, thus there should be at least two chiral centers in the molecule to produce two different diastereomers with their corresponding spectra. However, the chiral centers being located far apart from each other, the symmetry and the conformational flexibility of the molecule can further reduce the number of different stereoisomers, which can be observed by NMR spectroscopy. In case of the compound **3w**, using conventional NMR techniques it is impossible to determine if we observe the signals of meso isomer (*R,S* and *S,R*), the set of enantiomers (*R,R*) and (*S,S*) or even a set of stereoisomers with averaged signals.

5. Conclusions

The reaction of 1-(oxiran-2-ylmethyl)piperidine with 5,4-disubstituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones can be used as an option for “click chemistry” because that it meets all requirements. The reaction is regiospecifically and produces secondary alcohols was obtained in good yields. The reaction proceeds with the nucleophilic attack of the sulfur atom of 5,4-disubstituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thione, which is facilitated by the basic nitrogen present in 1-(oxiran-2-ylmethyl)piperidine, which has a catalytic (anchimer) effect. NMR techniques of the mixture of diastereomers resulting from bis-1,2,4-triazole reaction it is impossible to determine if we observe the signals of meso isomer (*R,S* and *S,R*), the set of enantiomers (*R,R*) and (*S,S*) or even a set of stereoisomers with averaged signals. This may be due to chiral centers being far apart.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Copies of ^1H and ^{13}C NMR spectra of all compounds.

Author Contributions: Investigation, A.V.P., A.A.S. and A.M.D.; Validation, K.S.A., M.A.S. and T.V.G.; Reviewing, V.G.N.; Conceptualization, A.S.G. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest, either of a financial or personal nature

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