Supplementary Information for

ORIGINAL ARTICLE

Development of the triazole-fused pyrimidine derivatives as highly potent and reversible inhibitors of histone lysine specific demethylase 1 (LSD1/KDM1A)

Zhonghua Li[a,c,d,†], Lina Ding[a,c,d,†], Zhongrui Li[a,c,d,†], Zhizheng Wang[a,c,d], Fengzhi Suo[a,c,d], Dandan Shen[a,c,d], Taoqian Zhao[a,c,d], Xudong Sun[a,c,d], Junwei Wang[a,c,d], Ying Liu[a,c,d], Liying Ma[a,c,d], Bing Zhao[a,c,d], Pengfei Geng[a,c,d], Bin Yu[a,b,c,d,*], Yichao Zheng[a,c,d,*], Hongmin Liu[a,c,d,*]

[a]*School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China*

[b]*State key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210023, China*

[c]*Co-Innovation Center of Henan Province for New Drug R&D and Preclinical Safety, Zhengzhou 450001, China*

[d]*Key Laboratory of Advanced Drug Preparation Technologies, Ministry of Education of China, Zhengzhou 450001, China*

*Corresponding authors.

E-mail addresses: zzuyubin@hotmail.com (Bin Yu); yichaozheng@zzu.edu.cn (Yichao Zheng); liuhm@zzu.edu.cn (Hongmin Liu).

[†]These authors made equal contributions to this work.

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1. CoMFA Model of LSD1 Inhibitors. To further understand the structure requirement of LSD1 inhibition, we performed a 3D-QSAR study based on our synthesized compounds that the bioactivities were determined using CoMFA method in Sybyl-X 2.0. All the studied compounds were aligned based on the docking conformation of compound **15u** and the result was shown in Fig. S1A. The partial least-squares (PLS) method was implemented to perform the CoMFA analyses, and the result was shown in Table S1. The CoMFA model had a leave-one-out cross-validated correlation coefficient q^2 of 0.641, an optimal number of components of 9, a non-cross-validated correlation coefficient r^2 of 0.987, a standard error of the estimate (SEE) of 0.108, an F value of 376.609, and a predictive correlation coefficient r^2_{pred} of 0.809, indicating that this model has a great predictive ability[1]. As shown in Fig. S1B and Table S2, the good linear relationships of experimental pIC_{50} and calculated pIC_{50} further indicated that the generated CoMFA model would be suitable for the activity prediction. Moreover, we could see that the residual of experimental pIC_{50} and calculated pIC_{50} of all test set compounds were smaller than 0.5 logarithmic unit. The contour map of the CoMFA model was shown in Fig. S1C. The green and yellow regions represent the steric bulky groups favorable and unfavorable for the bioactivity, respectively. The red and blue areas indicate that adding the negatively or positively partial-charged groups would be good for increasing the bioactivity, individually. As shown in Fig. S1C, there was a green contour near R^2 group connecting to the triazole ring, indicating that adding steric larger group may increase the bioactivity. For example, compounds bearing the steric phenyl group (R^2) had better binding affinity than other compounds with relatively smaller groups. A yellow area was near R^1 at position 2 of the pyrimidine ring, suggesting that bulky groups (R^1) were unfavorable for the bioactivity, and compounds containing the linear propargyl group (R^1) had better binding affinity than those with the phenyl group. Moreover, the red contour near the tetrazole ring implied that negatively charged group could increase the bioactivity. This could explain the importance of the tetrazole ring. Generally, the docking results and our CoMFA model could help us understand the binding modes and SARs of our synthesized compounds,

and would be useful for further inhibitor design.

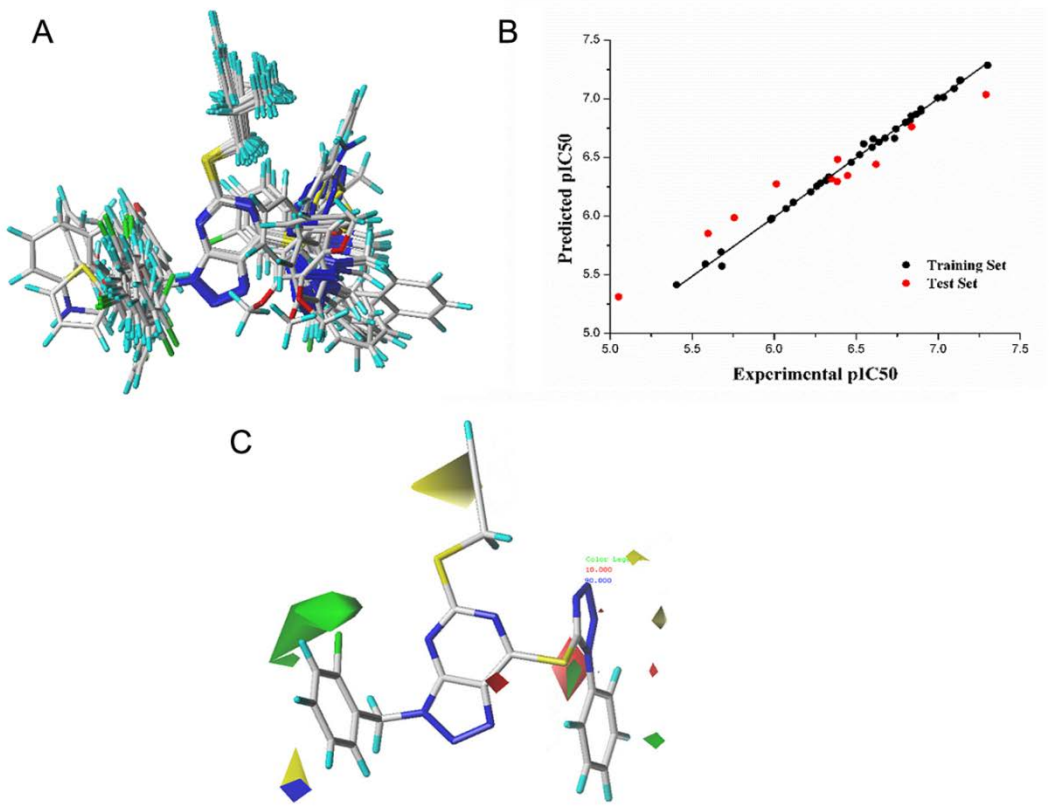
2. Table S1 Statistical results of the CoMFA model.

Parameter[a]	CoMFA model
q^2	0.641
ONC	9
r^2	0.987
SEE	0.108
F	376.609
r^2_{pred}	0.809
Steric contribution	0.466
Electrostatic contribution	0.534

[a]Abbreviations used: q^2, leave-one-out cross-validated correlation coefficient; ONC, optimal number of components; r^2, non-cross-validated correlation coefficient; SEE, standard error of the estimate; r^2_{pred}, a predictive correlation coefficient.

3. Table S2 Experimental pIC_{50}, calculated pIC_{50}, and their residuals of the studied compounds based on our CoMFA model.

Compd.	Exptl pIC_{50}	Calcd .pIC_{50}	Residual	Compd.	Exptl pIC_{50}	Calcd. pIC_{50}	Residual
Training set of compounds							
8a	5.405	5.414	0.009	**15l**	6.604	6.657	0.053
8b	5.580	5.592	0.012	**15m**	6.259	6.254	-0.005
8e	5.979	5.970	–0.009	**15p**	7.097	7.087	–0.010
8f	5.677	5.694	0.017	**15r**	6.742	6.744	0.002
8h	5.987	5.982	–0.005	**15s**	6.996	7.006	0.010
8j	6.223	6.207	–0.016	**15u**	7.310	7.286	–0.024
8k	6.072	6.064	–0.008	**15v**	7.131	7.154	0.023
15b	6.470	6.457	–0.013	**15w**	7.032	7.013	–0.019
15c	6.333	6.334	0.001	**15y**	6.867	6.869	0.002
15e	5.682	5.574	–0.108	**15z**	6.521	6.522	0.001
15f	6.597	6.587	–0.010	**15ab**	7.137	7.159	0.022
15g	6.836	6.854	0.018	**15ac**	6.638	6.631	–0.007
15h	6.676	6.664	–0.012	**15ad**	6.117	6.118	0.001
15i	6.801	6.798	–0.003	**15af**	6.316	6.304	–0.012
15j	6.545	6.616	0.071	**15ah**	6.830	6.816	–0.014
15k	6.733	6.663	–0.070	**15ai**	6.896	6.895	–0.001
Test set of compounds							
8c	5.051	5.312	0.261	**15t**	6.839	6.761	–0.078
8g	5.596	5.852	0.256	**15x**	7.260	7.036	–0.224
15a	6.347	6.318	–0.029	**15aa**	6.386	6.483	0.097
15d	6.384	6.294	–0.090	**15ae**	6.014	6.274	0.260
15n	6.447	6.346	–0.101	**15ag**	5.753	5.986	0.233
15q	6.622	6.441	–0.181				



4. Figure S1 (A) Structural alignment based on the conformation of the compound **15u**. (B) Plots of experimental versus predicted pIC_{50} values of compounds in both training and test sets for the CoMFA model. (C) CoMFA contour map with compound **15u**. Bulky group favored (contribution level of 90%) and disfavored (contribution level of 10%) areas are in green and yellow, respectively. Positively partial-charged favored (contribution level of 90%) and disfavored (contribution level of 10%) areas are in blue and red, respectively.

5. Table S3 Inhibitory effect of staurosporine on BTK and CDKs.

Kinase	IC_{50} (nmol/L)
BTK	100.4
CDK1	2.4
CDK2	1.0
CDK4	26.9
CDK6	132.9
CDK7	71.9
CDK9	16.7

6. Experimental section

6.1. 3D-QSAR Model Generation

The 3D-QSAR study was carried out by generating the CoMFA model of our developed 43 pyrimidine-triazole derivatives in Sybyl-X 2.0. All the compounds were randomly divided into a training set composed of 32 compounds and a test set containing another 11 ligands for the examination of the generated 3D-QSAR model. The conformation of each compound was taken from the result of our docking simulations and then structural superimposition was implemented based on the core ring of pyrimidine-triazole using the conformation of the compound **15u** as a template. The IC_{50} values of compounds in both training and test sets were converted to pIC_{50} ($-\log IC_{50}$) values as dependent variables in the CoMFA studies. All the aligned molecules were placed in a rectangular box and an sp^3-hybridized carbon probe atom with a van der Waal's radius of 1.52 Å as well as a charge of +1 was used for the calculation of the steric and electrostatic fields of CoMFA, and grid spacing was set to 2.0 Å. Steric and electrostatic contributions were truncated at 30 kcal/mol. The dielectric constant was applied with distance dependence. The partial least-squares (PLS) analyses were performed with the training set of compounds using leave-one-out(LOO) cross-validation while the optimum number of components set as 10. With the purpose of reducing the noise, the minimum column filtering σ value was set as 2.0 kcal/mol. The q^2 and ONC values were calculated and given by the software automatically. Subsequently, the non-cross-validated analyses were performed with the optimum number of components determined in the cross-validation to develop the final model. A series statistical results were obtained to confirm the reliability of our 3D-QSAR model. Then the CoMFA model was further tested by predicting the bioactivities of the compounds in the test set. Predictive ability of the model could also be evaluated by forecasting the activity of an external test set of molecules using the models derived from the training set. Predictive correlation coefficient (r^2_{pred}) was calculated by the following formula[1] (r^2_{pred} = (SD–PRESS)/SD), where SD was the sum of squared deviations between the biological activities of the test set molecules

and the meanactivity of the training set molecules, while PRESS was the sum of squared deviations between the observed

6.2. Spectrum data of compounds

6.2.1.

2-(5-(Propylthio)-7-(pyridin-2-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethan-1-ol ***(8b)***. Yellow sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68–8.69 (m, 1H), 7.80–7.82 (m, 2H), 7.38–7.42 (m, 1H), 4.71–4.74 (t, *J*=5.0 Hz, 2H), 4.16–4.18 (t, *J*=5.0 Hz, 2H), 2.84–2.87 (t, *J*=7.2 Hz, 2H), 1.52–1.61 (m, 2H), 0.90–0.93 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 163.7, 150.8, 150.0, 148.9, 137.3, 131.7, 131.4, 124.2, 60.7, 50.4, 33.4, 22.3, 13.3. HR-MS (ESI): Calcd. $C_{14}H_{16}N_6OS_2$, $[M+H]^+$: 349.0905, Found: 349.0902.

6.2.2.

2-(5-(Propylthio)-7-(pyrimidin-2-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)etha n-1-ol ***(8c)***. Pale yellow solid, m.p. 70–71 ^{o}C, yield 69%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, *J*=4.9 Hz, 2H), 7.58–7.60 (t, *J*=4.9 Hz, 1H), 4.97–5.00 (t, *J*=5.8 Hz, 1H), 4.62–4.65 (t, *J*=5.4 Hz, 2H), 3.91–3.95 (m, 2H), 3.00–3.04 (t, *J*=7.0 Hz, 2H), 1.58–1.67 (m, 2H), 0.91–0.95 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 165.2, 160.8, 159.5, 149.9, 132.7, 121.3, 59.2, 50.3, 33.1, 22.4, 13.6. HR-MS (ESI): Calcd. $C_{13}H_{15}N_7OS_2$, $[M+Na]^+$: 372.0677, Found: 372.0677.

6.2.3.

2-(5-(Propylthio)-7-(p-tolylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethan-1-ol ***(8d)***. Orange solid, m.p. 107–108 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.52 (d, *J*=8.4 Hz, 2H), 7.27–7.29 (d, *J*=8.0 Hz, 2H), 4.72–4.74 (t, *J*=4.8 Hz, 2H), 4.14–4.18 (m, 2H), 3.34–3.37 (t, *J*=6.6 Hz, 1H), 2.75–2.79 (t, *J*=7.2 Hz, 2H), 2.43 (s, 3H), 1.43–1.49 (m, 2H), 0.82–0.86 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 165.1, 148.7, 140.4, 136.0, 131.6, 130.2, 122.0, 60.8, 50.6, 33.4, 22.5, 21.4, 13.3. HR-MS (ESI): Calcd. $C_{16}H_{19}N_5OS_2$, $[M+Na]^+$: 384.0929, Found: 384.0931.

6.2.4.

*2-(7-((1,3,4-Thiadiazol-2-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethan-1-ol (**8e**).* White solid, m.p. 149–150 °C, yield 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 4.94–4.97 (t, J=6.0 Hz, 1H), 4.65–4.67 (t, J=5.4 Hz, 2H), 3.92–3.96 (m, 2H), 3.03–3.07 (t, J=7.2 Hz, 2H), 1.58–1.67 (m, 2H), 0.93–0.97 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 159.4, 158.0, 155.1, 149.6, 131.2, 59.3, 50.4, 33.1, 22.4, 13.6. HR-MS (ESI): Calcd. $C_{11}H_{13}N_7OS_3$, $[M+Na]^+$: 378.0241, Found: 378.0241.

6.2.5.

*2-(7-((4-Amino-1,2,3-thiadiazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethan-1-ol (**8f**).* Pale yellow solid, m.p. 163–164 °C, yield 79%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 2H), 4.90–4.93 (t, J=5.9 Hz, 1H), 4.63 (t, J=5.4 Hz, 2H), 3.90–3.94 (m, 2H), 3.03–3.07 (t, J=7.2 Hz, 2H), 1.58–1.67 (m, 2H), 0.94–0.97 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 168.9, 160.3, 149.1, 138.4, 130.8, 58.8, 49.8, 32.8, 22.1, 13.1. HR-MS (ESI): Calcd. $C_{11}H_{14}N_8OS_3$, $[M+H]^+$: 371.0531, Found: 371.0530.

6.2.6.

*2-(7-(Benzo[d]oxazol-2-ylthio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethan-1-ol (**8g**).* Pale yellow solid, m.p. 86–88 °C, yield 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92–7.94 (m, 1H), 7.85–7.88 (m, 1H), 7.56–7.60 (m, 1H), 7.50–7.54 (m, 1H), 4.95 (br, 1H), 4.61–4.63 (t, J=5.4 Hz, 2H), 3.89–3.92 (m, 2H), 2.76–2.79 (t, J=7.2 Hz, 2H), 1.33–1.42 (m, 2H), 0.67–0.71 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 160.0, 153.7, 152.8, 149.9, 141.8, 131.4, 127.5, 125.8, 120.9, 111.7, 59.2, 50.3, 33.1, 22.1, 13.2. HR-MS (ESI): Calcd. $C_{16}H_{16}N_6O_2S_2$, $[M+Na]^+$: 411.0674, Found: 411.0675.

6.2.7.

*2-(5-(Propylthio)-7-(thiazol-2-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-ethan-1-ol (**8h**).* White solid, m.p. 125–126 °C, yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J*=3.4 Hz, 1H), 7.68 (d, *J*=3.4 Hz, 1H), 4.74–4.77 (t, *J*=4.8 Hz, 2H), 4.17–4.21 (m, 2H), 2.96–3.00 (m, 3H), 1.62–1.71 (m, 2H), 0.98–1.02 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 160.7, 152.0, 149.2, 143.6, 131.0, 125.0, 60.0, 49.9, 33.3, 22.2, 13.4. HR-MS (ESI): Calcd. $C_{12}H_{14}N_6OS_3$, $[M+H]^+$: 355.0469, Found: 355.0458.

6.2.8.

*2-(7-((1-Methyl-1H-imidazol-2-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-3-yl)ethan-1-ol (**8i**).* Light yellow solid, m.p. 161–162 °C, yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*=1.2 Hz, 1H), 7.25 (d, *J*=1.3 Hz, 1H), 4.71–4.73 (t, *J*=5.0 Hz, 2H), 4.17 (m, 2H), 3.73 (s, 3H), 2.89–2.93 (m, 2H), 1.59–1.65 (m, 2H), 0.97–1.00 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 167.4, 154.2, 136.3, 136.1, 135.7, 130.0, 64.6, 54.5, 38.8, 38.2, 27.0, 18.1. HR-MS (ESI): Calcd. $C_{13}H_{17}N_7OS_2$, $[M+H]^+$: 352.1014, Found: 352.1002.

6.2.9.

*2-(7-((1-Methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-3-yl)ethan-1-ol (**8j**).* White solid, m.p. 102–103 °C, yield 71%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.93–4.96 (t, *J*=5.8 Hz, 1H), 4.62–4.65 (t, *J*=5.4 Hz, 2H), 4.12 (s, 3H), 3.89–3.93 (m, 2H), 2.85–2.88 (t, *J*=7.2 Hz, 2H), 1.48–1.57 (m, 2H), 0.90–0.94 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 158.7, 149.9, 145.9, 131.5, 59.2, 50.3, 35.2, 33.1, 22.4, 13.5. HR-MS (ESI): Calcd. $C_{11}H_{15}N_9OS_2$, $[M+Na]^+$: 376.0739, Found: 376.0741.

6.2.10.

*2-(7-(Benzo[d]thiazol-2-ylthio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethan-1-ol (**8k**).* White solid, m.p. 154–155 °C, yield 82%. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.23–8.25 (m, 1H), 8.10–8.12 (m, 1H), 7.55–7.63 (m, 2H), 4.95–4.98 (t, *J*=5.8 Hz, 1H), 4.64–4.67 (t, *J*=5.4 Hz, 2H), 3.92–3.96 (m, 2H), 2.95–2.99 (t, *J*=7.2 Hz, 2H), 1.48–1.57 (m, 2H), 0.77–0.80 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.4, 159.1, 155.2, 152.1, 149.5, 137.3, 131.1, 127.3, 126.7, 123.4, 122.6, 59.3, 50.4, 33.1, 22.3, 13.4. HR-MS (ESI): Calcd. $C_{16}H_{16}N_6OS_3$, $[M+Na]^+$: 427.0445, Found: 427.0445.

6.2.11.

*2-(2-(7-(Benzo[d]thiazol-2-ylthio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)ethoxy)ethan-1-ol (**8l**).* White solid, m.p. 114–115 ^{o}C, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.10 (m, 1H), 7.91–7.97 (m, 1H), 7.52–7.56 (m, 1H), 7.45–7.49 (m, 1H), 4.78–4.81 (t, *J*=5.2 Hz, 2H), 4.03–4.06 (t, *J*=5.2 Hz, 2H), 3.65 (m, 2H), 3.58–3.60 (t, *J*=4.2 Hz, 2H), 2.91–2.95 (t, *J*=7.4 Hz, 2H), 1.50–1.59 (m, 2H), 0.80–0.84 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 160.2, 155.2, 152.2, 149.2, 137.4, 131.1, 126.6, 126.0, 123.5, 121.3, 72.6, 68.7, 61.6, 46.9, 33.5, 22.2, 13.2. HR-MS (ESI): Calcd. $C_{18}H_{20}N_6O_2S_3$, $[M+H]^+$: 449.0888, Found: 449.0887.

6.2.12.

*3-(Furan-2-ylmethyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo-[4,5-d]pyrimidine (**15a**).* Pale yellow solid, m.p. 136–137 ^{o}C, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=1.9 Hz, 1H), 6.51 (d, *J*=3.3 Hz, 1H), 6.35 (m, 1H), 5.74 (s, 2H), 4.13 (s, 3H), 2.91–2.94 (t, *J*=7.2 Hz, 2H), 1.60–1.69 (m, 2H), 0.99–1.03 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 158.0, 149.2, 146.8, 145.0, 143.5, 131.1, 110.8, 110.5, 43.4, 34.8, 33.5, 22.1, 13.4. HR-MS (ESI): Calcd. $C_{14}H_{15}N_9OS_2$, $[M+Na]^+$: 412.0739, Found: 412.0738.

6.2.13.

*7-((1-Methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3-(2-(thiophen-2-yl)ethyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15b**).* White solid, m.p. 123–124 ^{o}C, yield 76%. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.14 (m, 1H), 6.87–6.89 (m, 1H), 6.76 (d, *J*=3.1 Hz, 1H), 4.83–4.86 (t, *J*=7.2 Hz, 2H), 4.14 (s, 3H), 3.55–3.59 (t, *J*=7.2 Hz, 2H), 2.87–2.91 (t, *J*=7.2 Hz, 2H), 1.59–1.65 (m, 2H), 0.99–1.02 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 157.9, 149.4, 145.1, 138.3, 131.0, 127.1, 126.1, 124.7, 48.4, 34.8, 33.5, 29.6, 22.2, 13.4. HR-MS (ESI): Calcd. $C_{15}H_{17}N_9S_3$, $[M+Na]^+$: 442.0667, Found: 442.0664.

6.2.14.

*3-Isobutyl-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15c**).* White solid, m.p. 91–92 ^{o}C, yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39–4.41 (d, *J*=7.2 Hz, 2H), 4.16 (s, 3H), 2.89–2.92 (t, *J*=7.2 Hz, 2H), 2.39–2.45 (m, 1H), 1.59–1.68 (m, 2H), 0.97–1.02 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 157.9, 149.6, 145.1, 131.0, 54.3, 34.8, 33.5, 29.1, 22.2, 20.0, 13.3. HR-MS (ESI): Calcd. $C_{13}H_{19}N_9S_2$, $[M+Na]^+$: 388.1103, Found: 388.1105.

6.2.15.

*3-Cyclopentyl-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15d**).* White solid, m.p. 93–95 ^{o}C, yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23–5.30 (m, 1H), 4.15 (s, 3H), 2.90–2.94 (t, *J*=7.2 Hz, 2H), 2.25–2.30 (m, 4H), 1.99–2.09 (m, 2H), 1.77–1.86 (m, 2H), 1.60–1.67 (m, 2H), 0.99–1.02 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 157.8, 148.9, 145.2, 131.5, 59.8, 34.8, 33.5, 32.5, 24.6, 22.2, 13.3. HR-MS (ESI): Calcd. $C_{14}H_{19}N_9S_2$, $[M+Na]^+$: 400.1103, Found: 400.1104.

6.2.16.

*4-(3-(7-((1-Methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)propyl)morpholine (**15e**).* Pale yellow oil, yield 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02–4.04 (t, *J*=4.9 Hz, 4H), 3.92 (s, 3H), 3.62–3.65 (t, *J*=5.8 Hz, 2H), 3.31–3.35 (t, *J*=7.0 Hz, 2H), 3.26 (br, 4H), 3.01–3.05 (t, *J*=7.2 Hz, 2H), 2.16–2.22 (m, 2H), 1.70–1.75 (m, 2H), 1.00–1.03 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6)

δ 166.5, 155.4, 152.6, 137.6, 120.0, 64.3, 54.7, 51.9, 38.4, 32.7, 32.1, 23.8, 22.6, 13.3. HR-MS (ESI): Calcd. $C_{16}H_{24}N_{10}OS_2$, $[M+H]^+$: 437.1654, Found: 437.1635.

6.2.17.

*3-(2-(1H-indol-3-yl)ethyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15f**).* Yellow solid, m.p. 131–132 ^oC, yield 75%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (br, 1H), 7.54 (d, *J*=7.9 Hz, 1H), 7.34 (d, *J*=8.2 Hz, 1H), 7.18–7.21 (m, 1H), 7.09–7.13 (m, 1H), 6.91 (d, *J*=2.4 Hz, 1H), 4.87–4.91 (t, *J*=7.3 Hz, 2H), 4.10 (s, 3H), 3.45–3.49 (t, *J*=7.2 Hz, 2H), 2.75–2.78 (t, *J*=7.2 Hz, 2H), 1.52–1.60 (m, 2H), 0.96–0.99 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 157.7, 149.4, 145.2, 136.2, 131.0, 127.0, 122.4, 122.3, 119.6, 118.1, 111.3, 110.9, 60.4, 47.7, 34.8, 33.4, 22.0, 13.4. HR-MS (ESI): Calcd. $C_{19}H_{20}N_{10}S_2$, $[M+Na]^+$: 475.1212, Found: 475.1210.

6.2.18.

*7-((1-Methyl-1H-tetrazol-5-yl)thio)-3-(3-phenylpropyl)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15g**).* Yellow semi-solid, yield 68%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.28 (m, 2H), 7.13–7.20 (m, 3H), 4.58–4.62 (t, *J*=7.0 Hz, 2H), 4.14 (s, 3H), 2.87–2.91 (t, *J*=7.2 Hz, 2H), 2.67–2.71 (t, *J*=7.4 Hz, 2H), 2.34–2.41 (m, 2H), 1.58–1.67 (m, 2H), 0.98–1.01 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 157.9, 149.4, 145.1, 139.9, 131.1, 128.5, 128.3, 126.3, 46.7, 34.8, 33.5, 32.7, 30.4, 22.2, 13.3. HR-MS (ESI): Calcd. $C_{18}H_{21}N_9S_2$, $[M+H]^+$: 428.1440, Found: 428.1428.

6.2.19.

*3-Benzyl-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15h**).* White solid, m.p. 114–115 ^oC, yield 82%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.46 (m, 2H), 7.34–7.39 (m, 3H), 5.75 (s, 2H), 4.14 (s, 3H), 2.92–2.95 (t, *J*=7.2 Hz, 2H), 1.60–1.67 (m, 2H), 1.01–1.04 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 158.0, 149.2, 145.1, 134.1, 131.2, 129.0, 128.9, 128.6, 51.0,

34.8, 33.5, 22.2, 13.4. HR-MS (ESI): Calcd. $C_{16}H_{17}N_9S_2$, $[M+Na]^+$: 422.0946, Found: 422.0945.

6.2.20.

*3-(2-Chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15i**).* White solid, m.p. 122–123 °C, yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.43 (m, 1H), 7.28–7.32 (m, 1H), 7.21–7.25 (m, 2H), 5.88 (s, 2H), 4.14 (s, 3H), 2.90–2.93 (t, J=7.4 Hz, 2H), 1.59–1.66 (m, 2H), 0.97–1.01 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 158.1, 149.4, 145.0, 133.7, 131.6, 131.0, 130.5, 130.2, 130.0, 127.3, 48.2, 34.8, 33.5, 22.1, 13.4. HR-MS (ESI): Calcd. $C_{16}H_{16}ClN_9S_2$, $[M+Na]^+$: 456.0556, Found: 456.0556.

6.2.21.

*3-(3-Chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15j**).* White solid, m.p. 97–98 °C, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43(m, 1H), 7.27–7.33 (m, 3H), 5.71 (s, 2H), 4.13 (s, 3H), 2.91–2.95 (t, J=7.4 Hz, 2H), 1.60–1.69 (m, 2H), 0.99–1.03 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 158.1, 149.1, 145.0, 135.8, 134.8, 131.2, 130.3, 129.1, 128.7, 126.7, 50.2, 34.9, 33.6, 22.1, 13.4. HR-MS (ESI): Calcd. $C_{16}H_{16}ClN_9S_2$, $[M+Na]^+$: 456.0556, Found: 456.0559.

6.2.22.

*3-(4-Chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4, 5-d]pyrimidine (**15k**).* White solid, m.p. 130–131 °C, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.39 (m, 2H), 7.31–7.33 (m, 2H), 5.70 (s, 2H), 4.12 (s, 3H), 2.88–2.92 (t, J=7.2 Hz, 2H), 1.59–1.65 (m, 2H), 0.99–1.03 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 158.1, 149.1, 144.9, 135.0, 132.4, 131.2, 130.0, 129.2, 50.2, 34.8, 33.5, 22.1, 13.4. HR-MS (ESI): Calcd. $C_{16}H_{16}ClN_9S_2$, $[M+Na]^+$: 456.0556, Found: 456.0555.

6.2.23.

*3-(4-Bromobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(propylthio)-3H-[1,2,3]triazolo[4, 5-d]pyrimidine (**15l**).* White solid, m.p. 133–134 ^{o}C, yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.50 (m, 2H), 7.30–7.33 (m, 2H), 5.68 (s, 2H), 4.12 (s, 3H), 2.88-2.92 (t, J=7.2 Hz, 2H), 1.59–1.65 (m, 2H), 0.99–1.02 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 158.1, 149.1, 145.0, 132.9, 132.2, 131.2, 130.3, 123.1, 50.3, 34.8, 33.6, 22.2, 13.4. HR-MS (ESI): Calcd. $C_{16}H_{16}BrN_9S_2$, $[M+Na]^+$: 500.0051, Found: 500.0052.

6.2.24.

*5-(Benzylthio)-3-(4-bromobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4, 5-d]pyrimidine (**15m**).* Pale yellow solid, m.p. 157–158 ^{o}C, yield 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54–7.56 (m, 2H), 7.24–7.33 (m, 7H), 5.85 (s, 2H), 4.27 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.4, 149.0, 144.9, 136.0, 132.9, 132.1, 131.1, 130.1, 128.6, 128.6, 127.5, 122.9, 50.1, 35.7, 34.8. HR-MS (ESI): Calcd. $C_{20}H_{16}BrN_9S_2$, $[M+K]^+$: 563.9791, Found: 563.9789.

6.2.25.

*5-(Benzylthio)-3-(4-chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15n**).* Pale yellow solid, m.p. 133–134 ^{o}C, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.33 (m, 9H), 5.70 (s, 2H), 4.24 (s, 2H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 158.5, 149.0, 144.9, 136.1, 134.9, 132.4, 131.3, 129.9, 129.3, 128.7, 127.6, 50.2, 35.8, 34.8. HR-MS (ESI): Calcd. $C_{20}H_{16}ClN_9S_2$, $[M+Na]^+$: 504.0556, Found: 504.0555.

6.2.26.

*5-(Benzylthio)-3-(2-chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4, 5-d]pyrimidine (**15o**).* Light yellow solid, m.p. 143–144 ^{o}C, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.44 (m, 1H), 7.29–7.32 (m, 3H), 7.20–7.24 (m, 4H), 7.15–7.17 (m, 1H), 5.89 (s, 2H), 4.23 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 170.7, 158.5, 149.4, 145.0, 136.2, 133.6, 131.6, 131.1, 130.2, 130.0, 128.8, 128.6, 127.5, 127.4, 48.2, 35.8, 34.8. HR-MS (ESI): Calcd. $C_{20}H_{16}ClN_9S_2$, $[M+Na]^+$: 504.0556, Found: 504.0558.

6.2.27.

*3-(2-Chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15p**).* White solid, m.p. 165–166 °C, yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51–7.53 (m, 1H), 7.34–7.43 (m, 3H), 5.91 (s, 2H), 4.10 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 158.6, 149.0, 145.4, 132.8, 131.9, 131.3, 130.8, 130.4, 129.6, 127.6, 47.9, 34.7, 13.9. HR-MS (ESI): Calcd. $C_{14}H_{12}ClN_9S_2$, $[M+Na]^+$: 428.0243, Found: 428.0243.

6.2.28.

*3-(2-Chlorobenzyl)-5-methyl-7-((1-methyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15q**).* Light yellow solid, m.p. 141–142 °C, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.44 (m, 1H), 7.27–7.32 (m, 1H), 7.21–7.25 (m, 1H), 7.12–7.15 (m, 1H), 5.93 (s, 2H), 4.16 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 158.3, 149.5, 145.3, 133.5, 131.8, 131.6, 130.1, 130.0, 129.9, 127.3, 48.1, 34.8, 26.1. HR-MS (ESI): Calcd. $C_{14}H_{12}ClN_9S$, $[M+H]^+$: 374.0703, Found: 374.0692.

6.2.29.

*3-(2-Chlorobenzyl)-7-((1-methyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15r**).* White solid, m.p. 166–168 °C, yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.43 (m, 1H), 7.29–7.33 (m, 1H), 7.24–7.27 (m, 2H), 5.99 (s, 2H), 4.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.3, 148.6, 145.0, 133.7, 133.1, 131.5, 130.4, 130.3, 130.0, 127.3, 48.5, 34.8. HR-MS (ESI): Calcd. $C_{13}H_{10}ClN_9S$, $[M+H]^+$: 360.0547, Found: 360.0533.

6.2.30.

3-Benzyl-7-((1-methyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1,2,3]triazol

*o[4, 5-d]pyrimidine (**15s**).* White solid, m.p. 138–139 °C, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.48 (m, 2H), 7.33–7.36 (m, 3H), 5.76 (s, 2H), 4.13 (s, 3H), 3.71 (d, *J*=2.8 Hz, 2H), 2.16–2.17 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.7, 149.0, 144.8, 133.9, 131.4, 129.0, 128.9, 128.8, 78.8, 71.0, 51.1, 34.9, 20.0. HR-MS (ESI): Calcd. $C_{16}H_{13}N_9S_2$, $[M+Na]^+$: 418.0633, Found: 418.0635.

6.2.31.

*3-Benzyl-7-((1-phenyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1,2,3]triazol o[4,5- d]pyrimidine (**15t**).* Yellow solid, m.p. 142–143 °C, yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.59 (m, 2H), 7.42–7.47 (m, 5H), 7.32–7.34 (m, 3H), 5.71 (s, 2H), 3.74 (d, *J*=2.4 Hz, 2H), 2.10 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 158.8, 148.9, 144.7, 133.8, 133.5, 131.3, 130.8, 129.6, 129.0, 128.9, 128.7, 124.9, 78.6, 71.0, 51.0, 20.1. HR-MS (ESI): Calcd. $C_{21}H_{15}N_9S_2$, $[M+Na]^+$: 480.0790, Found: 480.0788.

6.2.32.

*3-(2-Chlorobenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1, 2,3]triazolo[4,5-d]pyrimidine (**15u**).* Yellow solid, m.p. 157–158 °C, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.60 (m, 2H), 7.47–7.49 (m, 3H), 7.40–7.42 (m, 1H), 7.22–7.31 (m, 3H), 5.85 (s, 2H), 3.72 (d, *J*=2.4 Hz, 2H), 2.09–2.10 (t, *J*=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.9, 149.2, 144.7, 133.8, 133.6, 131.4, 131.1, 130.8, 130.7, 130.3, 130.0, 129.6, 127.3, 124.9, 78.5, 71.1, 48.3, 20.1. HR-MS (ESI): Calcd. $C_{21}H_{14}ClN_9S_2$, $[M+Na]^+$: 514.0400, Found: 514.0398.

6.2.33.

*3-(3-Chlorobenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1, 2,3]triazolo[4,5-d]pyrimidine (**15v**).* Orange solid, m.p. 121–122 °C, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.59 (m, 2H), 7.47–7.48 (m, 3H), 7.43(m, 1H), 7.28–7.34 (m, 3H), 5.67 (s, 2H), 3.74–3.76 (d, *J*=2.4 Hz, 2H), 2.12 (t, *J*=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 159.0, 148.9, 144.7, 135.6, 134.8, 133.6, 131.3,

130.8, 130.4, 129.6, 129.2, 128.8, 126.9, 124.9, 78.6, 71.1, 50.3, 20.1. HR-MS (ESI): Calcd. $C_{21}H_{14}ClN_9S_2$, $[M+Na]^+$: 514.0400, Found: 514.0398.

6.2.34.

*3-(4-Chlorobenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1, 2,3]triazolo[4,5-d]pyrimidine (**15w**).* Yellow solid, m.p. 136–137 °C, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.60 (m, 2H), 7.47–7.48 (m, 3H), 7.37–7.40 (m, 2H), 7.30–7.32 (m, 2H), 5.67 (s, 2H), 3.73 (d, J=2.4 Hz, 2H), 2.09–2.11 (t, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 159.0, 148.8, 144.6, 135.0, 133.6, 132.2, 131.3, 130.8, 130.2, 129.6, 129.2, 124.9, 78.7, 71.0, 50.3, 20.1. HR-MS (ESI): Calcd. $C_{21}H_{14}ClN_9S_2$, $[M+Na]^+$: 514.0400, Found: 514.0402.

6.2.35.

*3-(4-Isopropylbenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15x**).* Light yellow solid, m.p. 125–126 °C, yield 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68–7.71 (m, 2H), 7.54–7.56 (m, 3H), 7.34 (m, 2H), 7.22 (m, 2H), 5.74 (s, 2H), 3.91 (d, J=2.6 Hz, 2H), 3.18 (t, J=2.6 Hz, 1H), 2.81–2.88 (m, 1H), 1.15 (d, J=6.9 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 159.2, 148.6, 148.6, 145.7, 133.1, 132.1, 130.9, 130.8, 129.6, 128.5, 126.7, 125.0, 79.4, 73.4, 49.9, 33.1, 23.7, 19.4. HR-MS (ESI): Calcd. $C_{24}H_{21}ClN_9S_2$, $[M+Na]^+$: 522.1259, Found: 522.1259.

6.2.36.

*3-(4-Methoxybenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15y**).* Light red solid, m.p. 140–141 °C, yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.59 (m, 2H), 7.46–7.47 (m, 3H), 7.39–7.41 (m, 2H), 6.83–6.86 (m, 2H), 5.64 (s, 2H), 3.77 (s, 3H), 3.75 (d, J=2.8 Hz, 2H), 2.11–2.12 (t, J=2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 164.6, 163.4, 153.4, 138.2, 136.0, 135.5, 135.0, 134.3, 130.7, 129.6, 129.6, 119.0, 83.4, 75.8, 60.0, 55.3, 24.7. HR-MS (ESI): Calcd. $C_{22}H_{17}N_9OS_2$, $[M+H]^+$: 488.1076, Found: 488.1060.

6.2.37.

*5-(Benzylthio)-3-(4-chlorobenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15z**).* Light red solid, m.p. 98–100 ^{o}C, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.55 (m, 2H), 7.40–7.45 (m, 3H), 7.25–7.31 (m, 9H), 5.63 (s, 2H), 4.25 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.5, 148.8, 144.8, 136.2, 134.9, 133.5, 132.4, 131.2, 130.7, 129.9, 129.5, 129.2, 128.7, 128.6, 127.5, 124.9, 50.1, 35.8. HR-MS (ESI): Calcd. $C_{25}H_{18}ClN_9S_2$, $[M+K]^+$: 582.0452, Found: 582.0453.

6.2.38.

*5-(Benzylthio)-3-(4-bromobenzyl)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15aa**).* Yellow solid, m.p. 122–123 ^{o}C, yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.55 (m, 2H), 7.42–7.45 (m, 5H), 7.27–7.30 (m, 5H), 7.19–7.21 (m, 2H), 5.62 (s, 2H), 4.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.6, 148.9, 144.8, 136.2, 133.6, 132.9, 132.2, 131.2, 130.7, 130.2, 129.6, 128.7, 128.7, 127.6, 124.9, 123.1, 50.2, 35.8. HR-MS (ESI): Calcd. $C_{25}H_{18}BrN_9S_2$, $[M+Na]^+$: 610.0208, Found: 610.0206.

6.2.39.

*3-(2-Chlorobenzyl)-5-(methylthio)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15ab**).* Light yellow solid, m.p. 178–180 ^{o}C, yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66–7.71 (m, 2H), 7.56–7.58 (m, 3H), 7.49–7.52 (m, 1H), 7.32–7.42 (m, 3H), 5.86 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 158.7, 148.9, 145.8, 133.1, 132.8, 131.8, 131.3, 130.9, 130.5, 130.4, 129.7, 129.6, 127.5, 124.9, 48.0, 14.0. HR-MS (ESI): Calcd. $C_{19}H_{14}ClN_9S_2$, $[M+H]^+$: 468.0580, Found: 468.0567.

6.2.40.

3-(2-Chlorobenzyl)-5-((cyclopropylmethyl)thio)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-3

*H-[1,2, 3]triazolo[4,5-d]pyrimidine (**15ac**).* Light brown solid, m.p. 113–115 ^{o}C, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.62 (m, 2H), 7.49 (m, 3H), 7.40 (m, 1H), 7.27–7.31 (m, 1H), 7.22–7.25 (m, 2H), 5.83 (s, 2H), 2.91 (d, *J*=7.2 Hz, 2H), 1.00 (m, 1H), 0.58 (m, 2H), 0.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 158.1, 149.1, 144.9, 133.6, 133.4, 131.4, 130.7, 130.5, 130.1, 129.8, 129.5, 127.2, 124.8, 123.7, 48.1, 37.3, 9.9, 5.8. HR-MS (ESI): Calcd. $C_{22}H_{18}ClN_9S_2$, $[M+H]^+$: 508.0893, Found: 508.0921.

6.2.41.

*3-(2-Chlorobenzyl)-7-((1-(4-methoxyphenyl)-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15ad**).* Yellow solid, m.p. 121–123 ^{o}C, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.49 (m, 2H), 7.40–7.42 (m, 1H), 7.22–7.32 (m, 3H), 6.93–6.95 (m, 2H), 5.86 (s, 2H), 3.81 (s, 3H), 3.73 (d, *J*=2.7 Hz, 2H), 2.10 (t, *J*=2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 161.2, 159.0, 149.1, 144.8, 133.8, 131.5, 131.1, 130.7, 130.3, 130.0, 127.3, 126.4, 126.2, 114.7, 78.6, 71.1, 55.6, 48.3, 20.0. HR-MS (ESI): Calcd. $C_{22}H_{16}ClN_9OS_2$, $[M+Na]^+$: 544.0505, Found: 544.0507.

6.2.42.

*3-(2-Chlorobenzyl)-5-(prop-2-yn-1-ylthio)-7-((1-(3,4,5-trimethoxyphenyl)-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15ae**).* Yellow semi-solid, yield 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46–7.51 (m, 2H), 7.33–7.42 (m, 2H), 7.00 (m, 2H), 5.88 (s, 2H), 3.91 (d, *J*=2.6 Hz, 2H), 3.69 (s, 6H), 3.65 (s, 3H), 3.14–3.15 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 159.1, 152.9, 148.8, 145.9, 138.9, 132.8, 131.7, 131.5, 130.7, 130.4, 129.6, 128.4, 127.6, 103.3, 79.3, 73.4, 60.1, 56.2, 54.8, 48.0, 19.3. HR-MS (ESI): Calcd. $C_{24}H_{20}ClN_9O_3S_2$, $[M+Na]^+$: 604.0717, Found: 604.0715.

6.2.43.

*3-(2-Chlorobenzyl)-7-((1-(4-chlorophenyl)-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylth io)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15af**).* Light yellow semi-solid, yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74–7.77 (m, 2H), 7.64–7.68 (m, 2H), 7.45–7.52 (m, 2H), 7.33–7.42 (m, 2H), 5.88 (s, 2H), 3.86 (d, *J*=2.6 Hz, 2H), 3.13 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 159.2, 148.9, 145.8, 135.6, 132.8, 131.9, 131.7, 131.5, 130.7, 130.4, 130.0, 129.8, 129.6, 127.6, 126.8, 126.5, 79.2, 73.5, 48.0, 19.4. HR-MS (ESI): Calcd. $C_{21}H_{13}Cl_2N_9S_2$, $[M+Na]^+$: 548.0010, Found: 548.0012.

6.2.44.

*7-((1-(4-Bromophenyl)-1H-tetrazol-5-yl)thio)-3-(2-chlorobenzyl)-5-(prop-2-yn-1-ylthi o)-3H- [1,2,3]triazolo[4,5-d]pyrimidine (**15ag**).* White solid, m.p. 154–156 ^{o}C, yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78–7.81 (m, 2H), 7.68–7.71 (m, 2H), 7.45–7.52 (m, 2H), 7.33–7.42 (m, 2H), 5.88 (s, 2H), 3.86 (d, *J*=2.6 Hz, 2H), 3.13 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 159.2, 148.9, 145.8, 132.8, 132.8, 132.3, 131.8, 131.4, 130.8, 130.4, 129.6, 127.6, 127.0, 124.3, 79.2, 73.5, 48.0, 19.4. HR-MS (ESI): Calcd. $C_{21}H_{13}BrClN_9S_2$, $[M+Na]^+$: 591.9505, Found: 591.9506.

6.2.45.

*3-(2-Chlorobenzyl)-7-((1-(naphthalen-1-yl)-1H-tetrazol-5-yl)thio)-5-(prop-2-yn-1-ylt hio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15ah**).* White semi-solid, yield 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (m, 1H), 8.06 (m, 1H), 7.87 (m, 1H), 7.55–7.68 (m, 3H), 7.49 (m, 1H), 7.32–7.45 (m, 4H), 5.84 (s, 2H), 3.92 (d, *J*=2.5 Hz, 2H), 3.14 (t, *J*=2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 158.9, 148.7, 147.3, 133.4, 132.8, 131.8, 131.7, 131.5, 130.6, 130.4, 129.6, 128.7, 128.2, 128.1, 127.9, 127.5, 127.3, 125.8, 125.2, 121.9, 79.3, 73.5, 47.9, 19.4. HR-MS (ESI): Calcd. $C_{25}H_{16}ClN_9S_2$, $[M+Na]^+$: 564.0556, Found: 564.0558.

6.2.46.

3-(2-Chlorobenzyl)-5-(prop-2-yn-1-ylthio)-7-((1-(pyridin-3-yl)-1H-tetrazol-5-yl)thio)-

*3H-[1,2,3]triazolo[4,5-d]pyrimidine (**15ai**).* Yellow solid, m.p. 142–144 ^{o}C, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (m, 1H), 8.74 (m, 1H), 7.99–8.02 (m, 1H), 7.47–7.50 (m, 1H), 7.40–7.42 (m, 1H), 7.28–7.32 (m, 2H), 7.22–7.24 (m, 1H), 5.86 (s, 2H), 3.73 (d, *J*=2.7 Hz, 2H), 2.09 (t, *J*=2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.4, 151.8, 149.2, 145.4, 145.1, 133.8, 132.5, 131.3, 131.0, 130.8, 130.7, 130.3, 130.0, 127.3, 124.1, 78.4, 71.2, 48.4, 20.1. HR-MS (ESI): Calcd. $C_{20}H_{13}ClN_{10}S_2$, $[M+Na]^+$: 515.0352, Found: 515.0355.

6.2.47.

*2-(5-((3-(2-Chlorobenzyl)-5-(prop-2-yn-1-ylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)thio)-1H-tetrazol-1-yl)-N,N-dimethylethan-1-amine (**15aj**).* Yellow oil, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.43 (m, 1H), 7.27–7.32 (m, 2H), 7.22–7.26 (m, 1H), 5.89 (s, 2H), 4.49–4.52 (t, *J*=6.2 Hz, 2H), 3.70 (d, *J*=2.6 Hz, 2H), 2.81–2.84 (t, *J*=6.2 Hz, 2H), 2.22 (s, 6H), 2.12 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 159.6, 149.3, 145.4, 133.8, 131.5, 131.3, 130.6, 130.2, 130.0, 127.3, 78.7, 71.0, 58.1, 48.3, 46.7, 45.5, 20.0. HR-MS (ESI): Calcd. $C_{19}H_{19}ClN_{10}S_2$, $[M+Na]^+$: 509.0822, Found: 509.0823.

6.2.48.

*2-(5-(Benzylthio)-7-((1-phenyl-1H-tetrazol-5-yl)thio)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-3-yl)ethan-1-ol (**15ak**).* Yellow solid, m.p. 116–117 ^{o}C, yield 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66–7.70 (m, 2H), 7.55–7.57 (m, 3H), 7.39–7.41 (m, 2H), 7.22–7.32 (m, 3H), 4.92–4.94 (t, *J*=5.9 Hz, 1H), 4.61–4.64 (t, *J*=5.3 Hz, 2H), 4.32 (s, 2H), 3.86–3.90 (q, *J*=5.5 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 158.6, 149.2, 145.8, 137.0, 133.1, 130.9, 130.7, 129.6, 128.9, 128.4, 127.2, 125.0, 58.8, 49.9, 34.7. HR-MS (ESI): Calcd. $C_{20}H_{17}N_9OS_2$, $[M+Na]^+$: 486.0895, Found: 486.0896.

Reference

1. Verma J, Khedkar VM, Coutinho EC. 3D-QSAR in drug design—a review. *Curr Top Med Chem* 2010**;10**:95-115.

^{1}H & ^{13}C NMR spectra

Figure S2 ^{1}H NMR spectrum of compound **8a**.

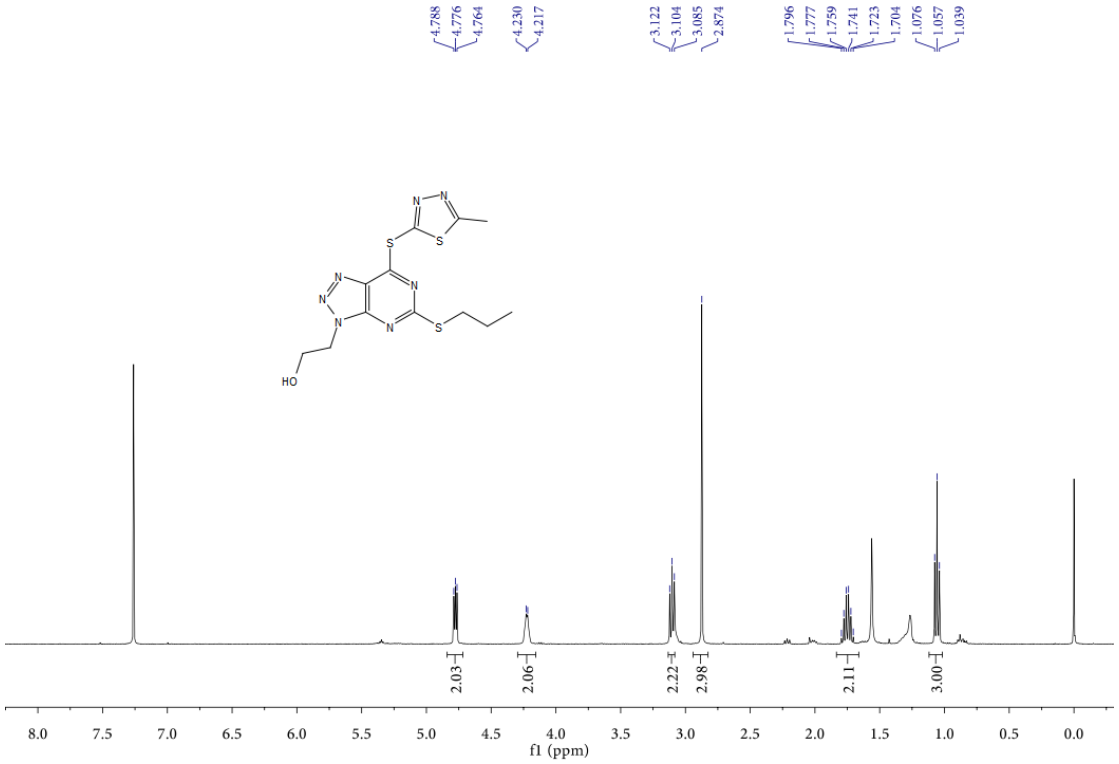


Figure S3 ^{13}C NMR spectrum of compound **8a**.

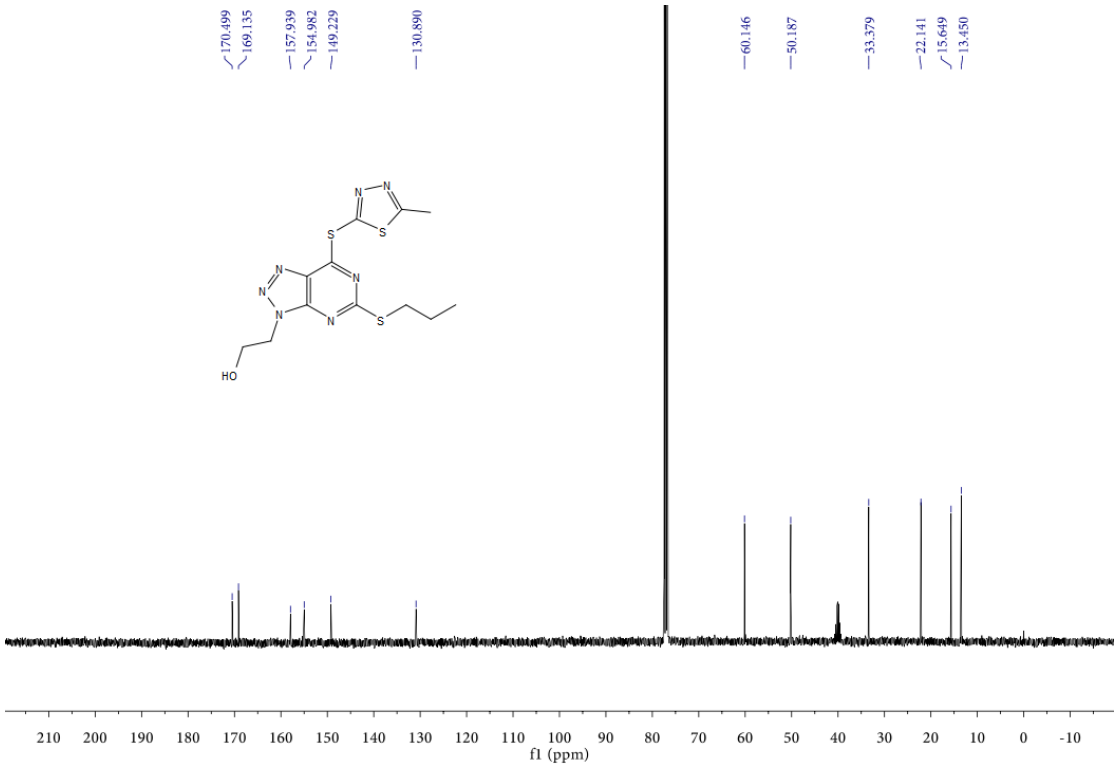


Figure S4 ^{1}H NMR spectrum of compound **8b**.

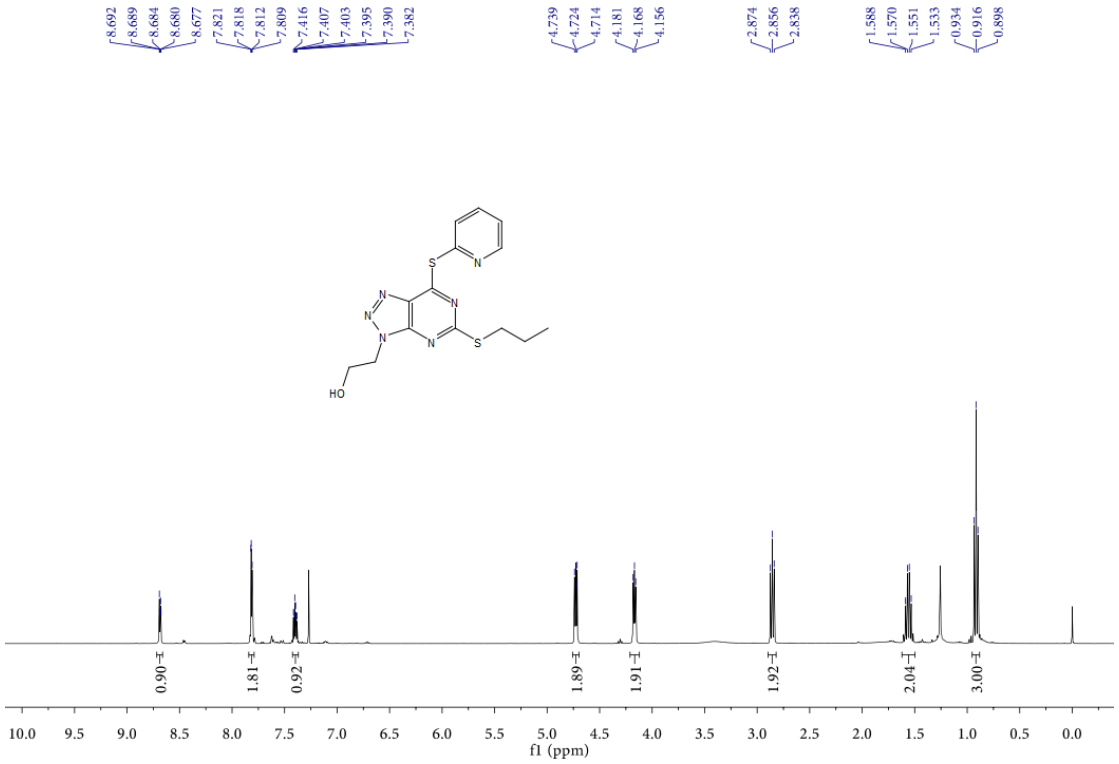


Figure S5 ^{13}C NMR spectrum of compound **8b**.

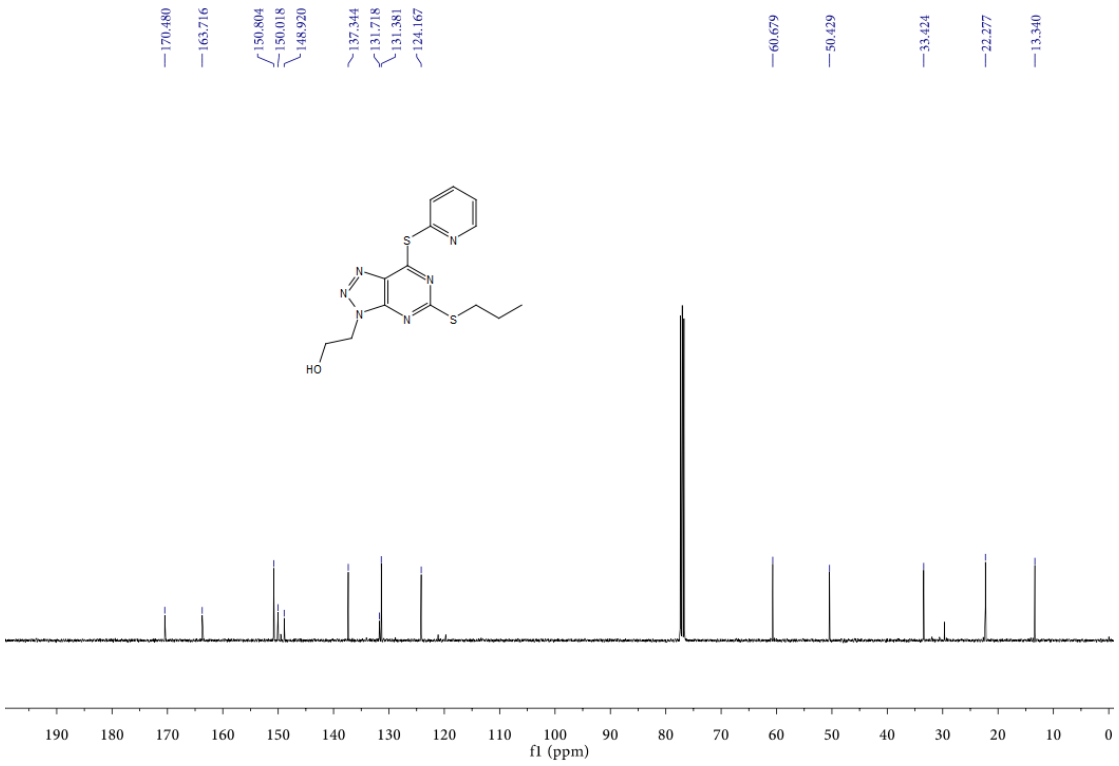


Figure S6 ^{1}H NMR spectrum of compound **8c**.

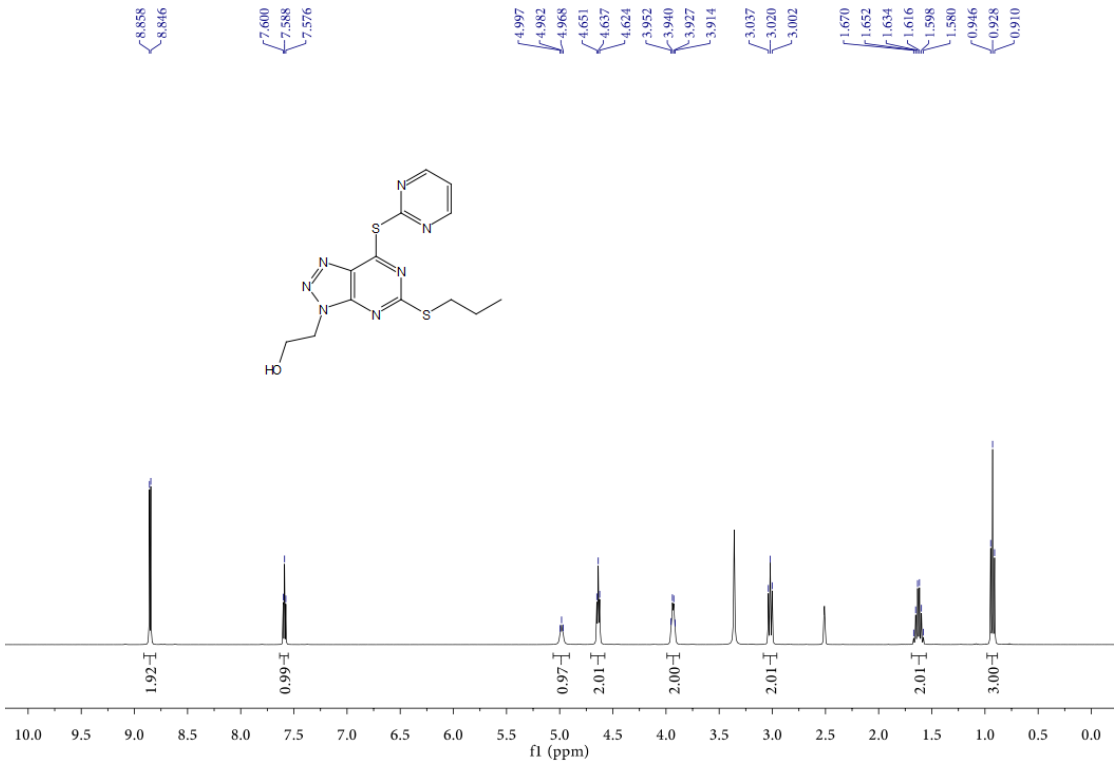


Figure S7 ^{13}C NMR spectrum of compound **8c**.

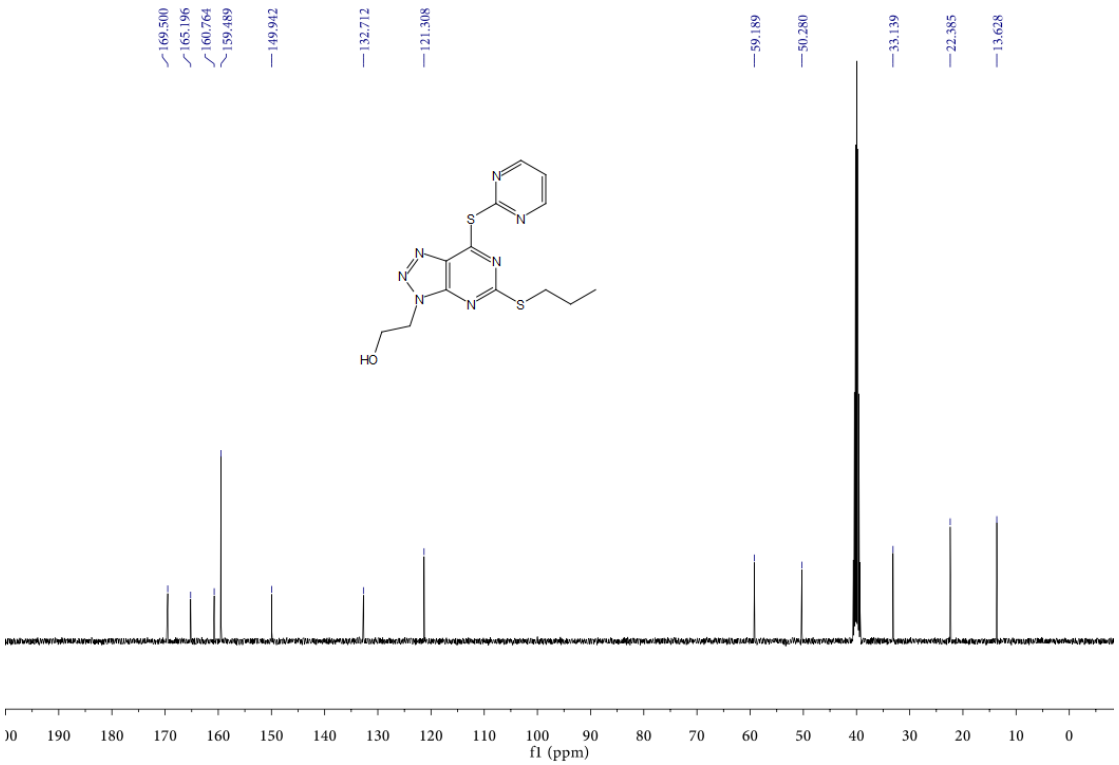


Figure S8 ^{1}H NMR spectrum of compound **8d**.

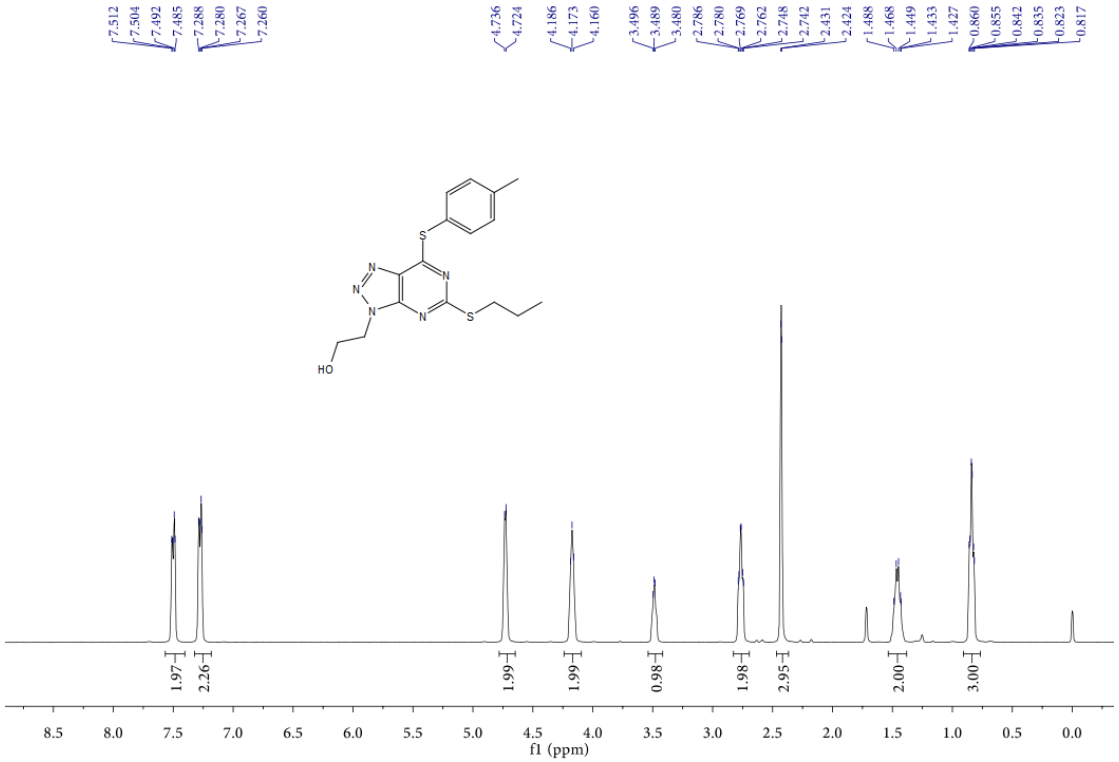


Figure S9 ^{13}C NMR spectrum of compound **8d**.

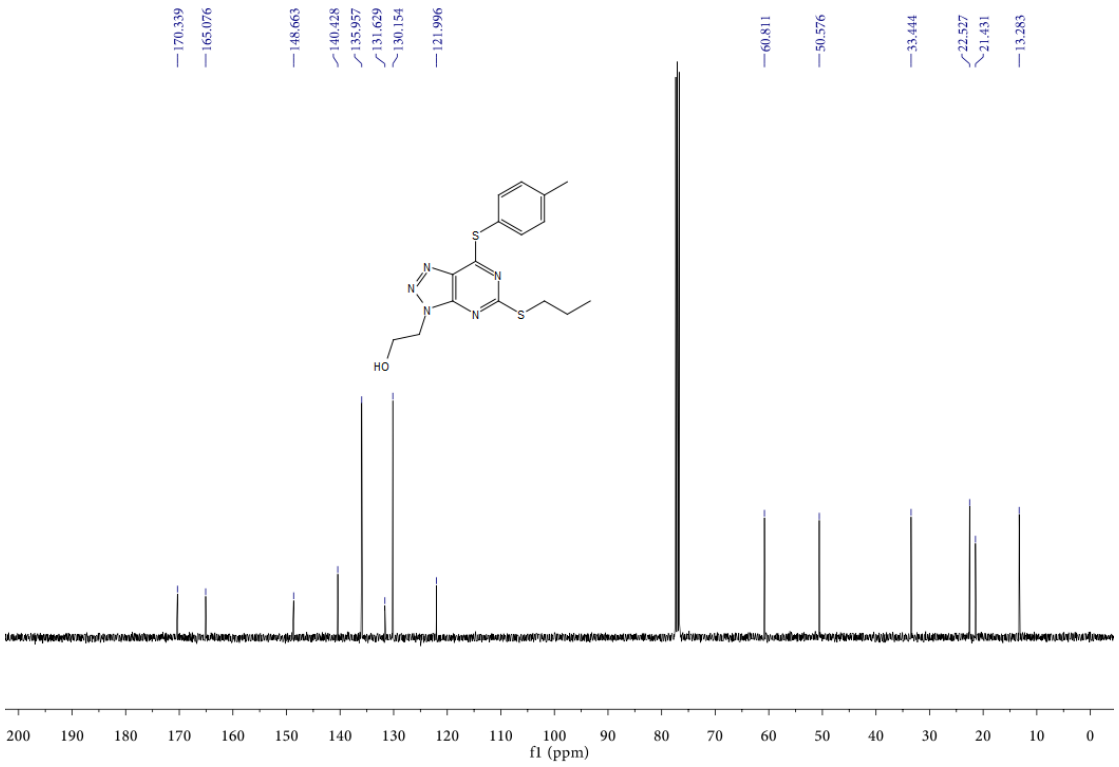


Figure S10 ^{1}H NMR spectrum of compound **8e**.

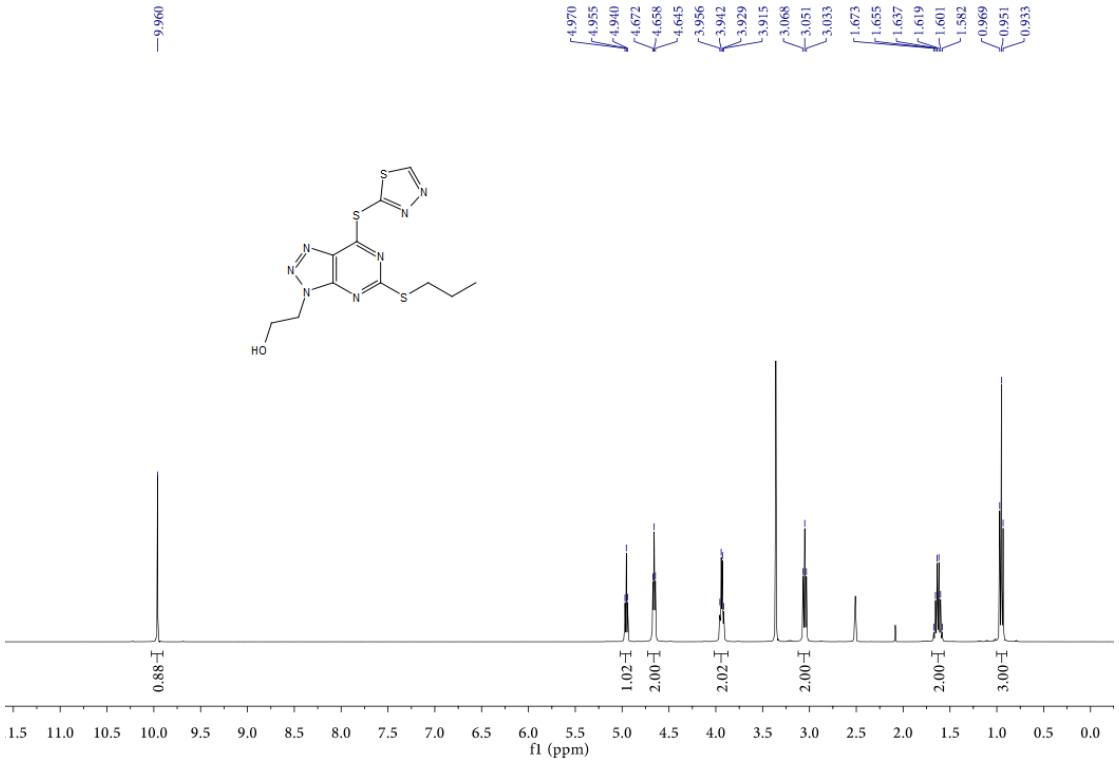


Figure S11 ^{13}C NMR spectrum of compound **8e**.

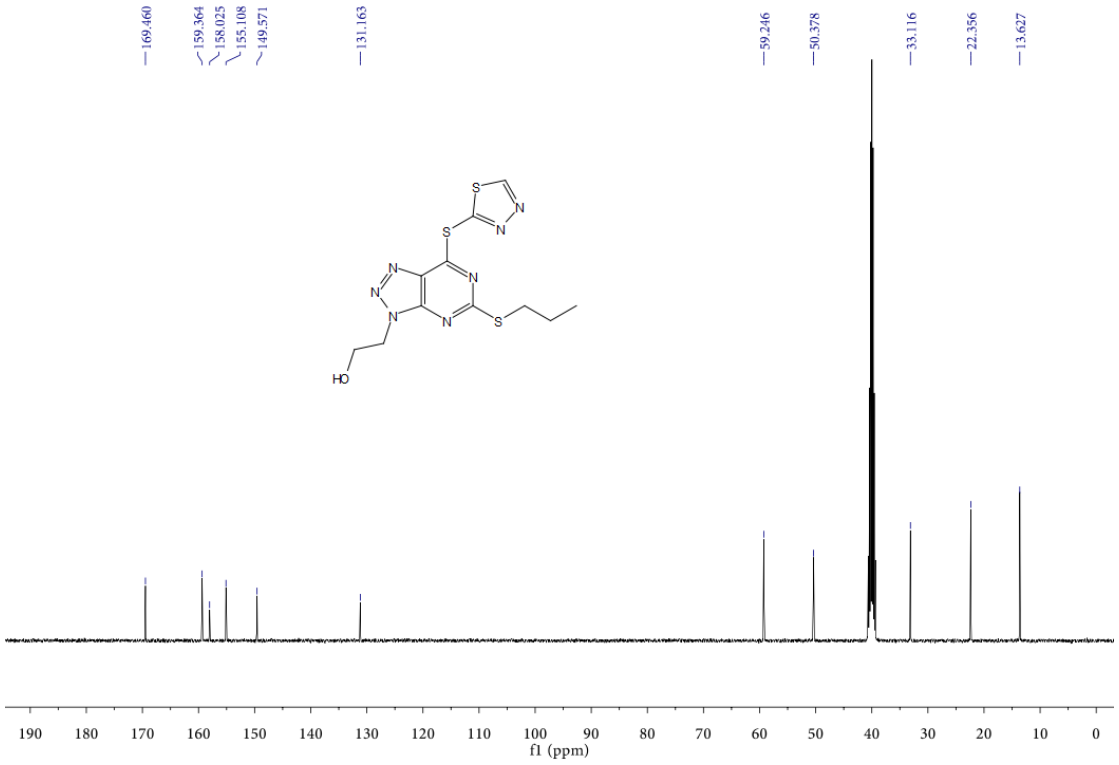


Figure S12 ^{1}H NMR spectrum of compound **8f**.

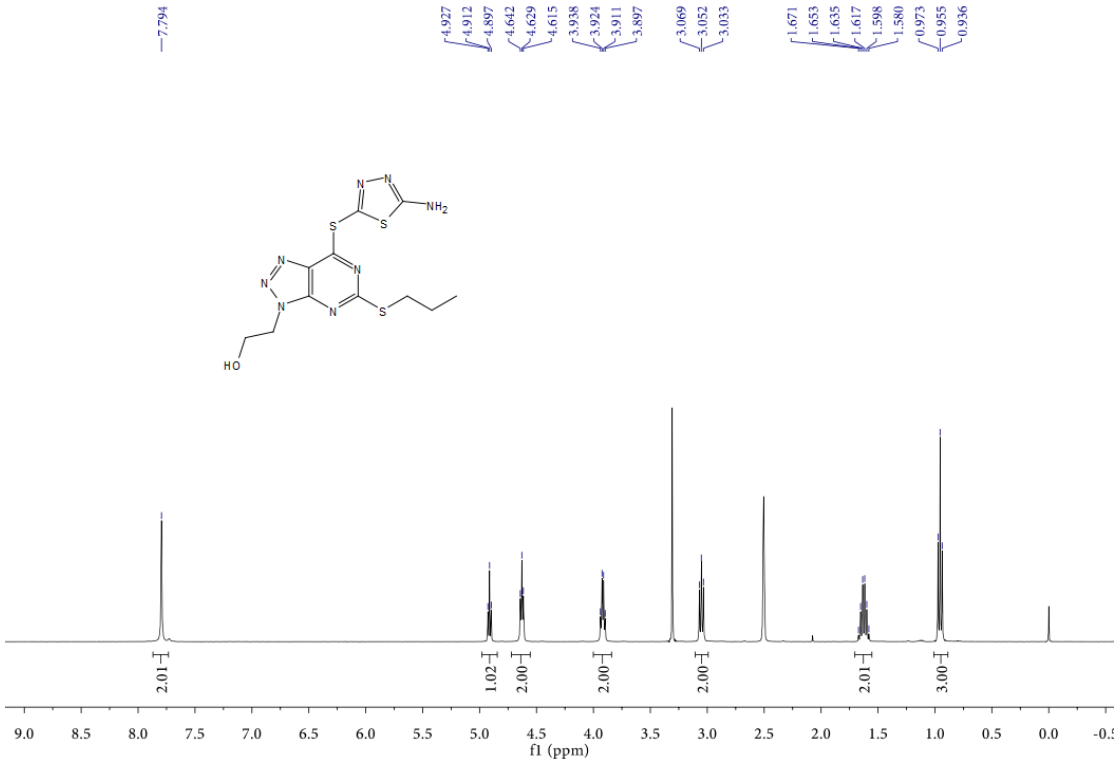


Figure S13 ^{13}C NMR spectrum of compound **8f**.

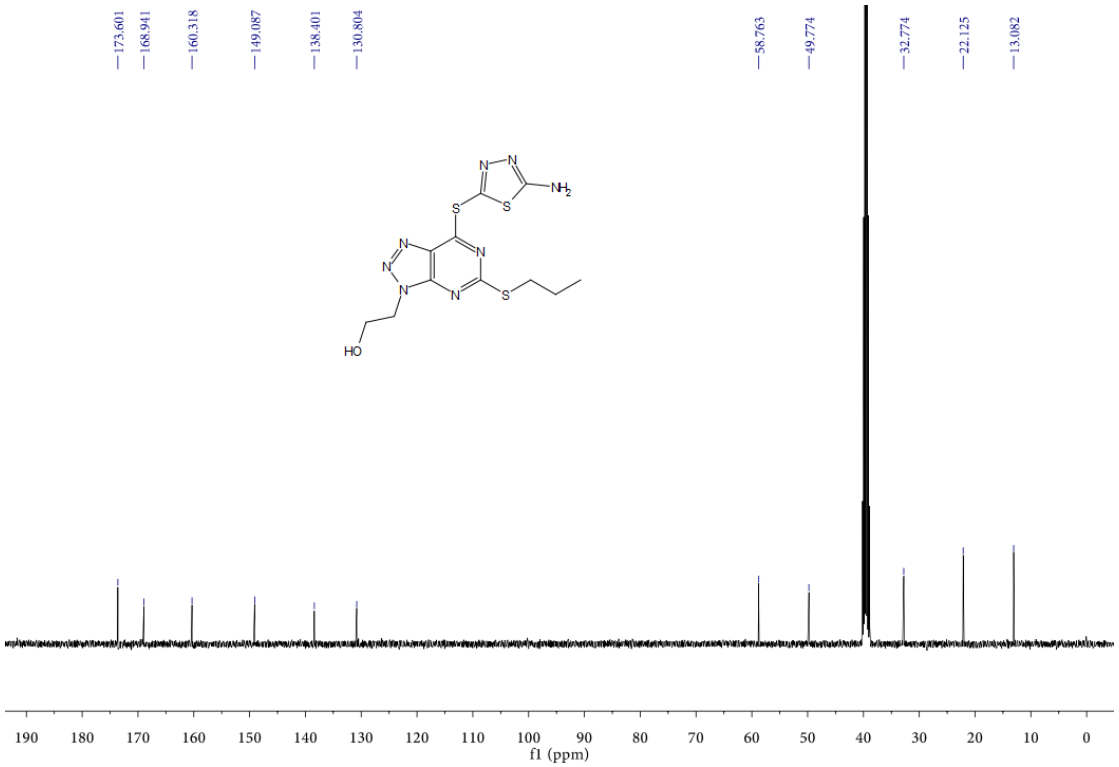


Figure S14 ^{1}H NMR spectrum of compound **8g**.

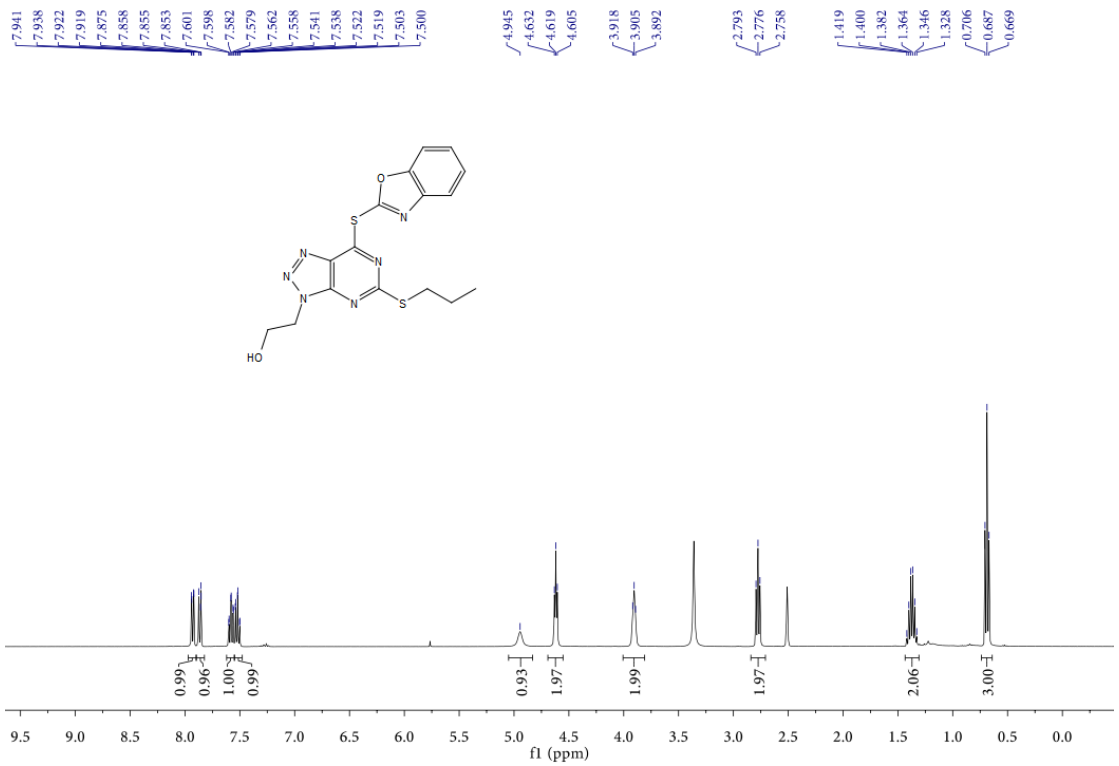


Figure S15 ^{13}C NMR spectrum of compound **8g**.

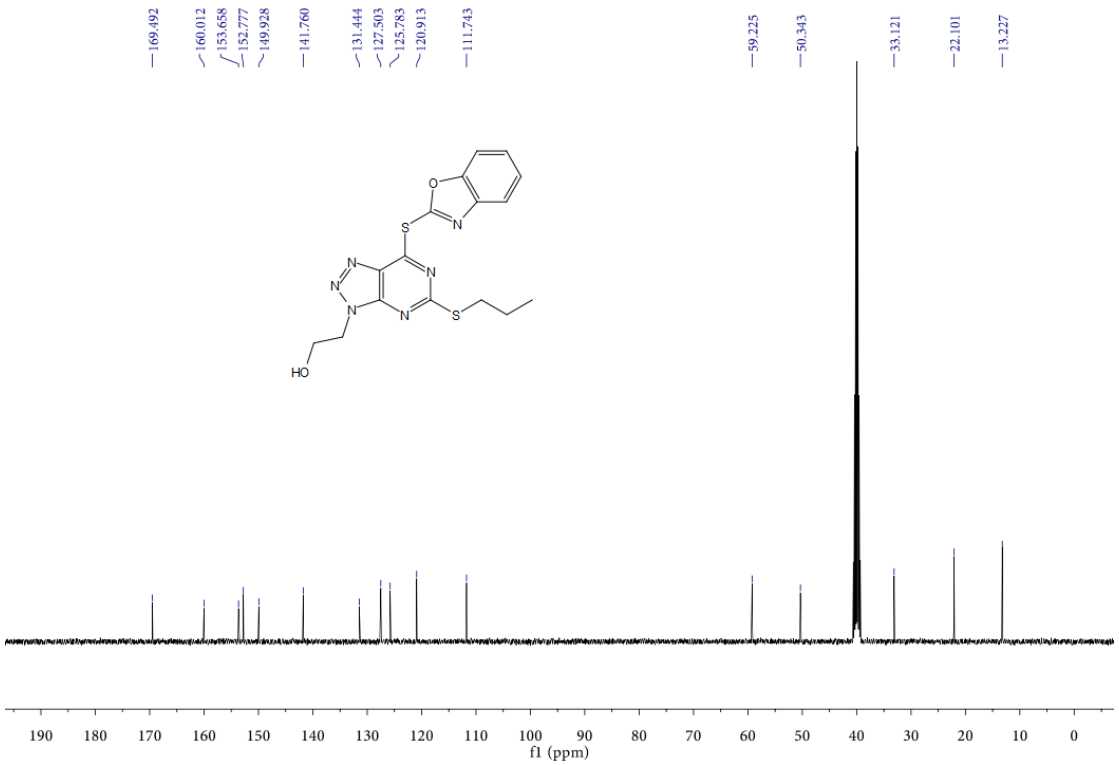


Figure S16 ^{1}H NMR spectrum of compound **8h**.

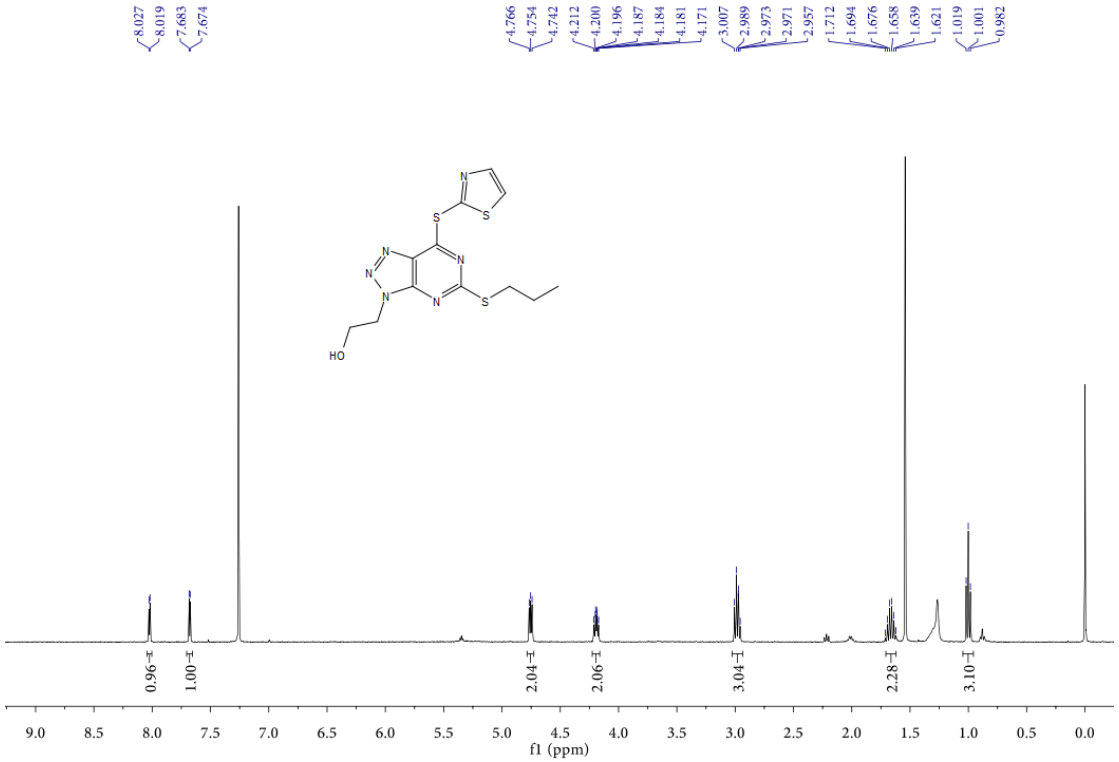


Figure S17 ^{13}C NMR spectrum of compound **8h**.

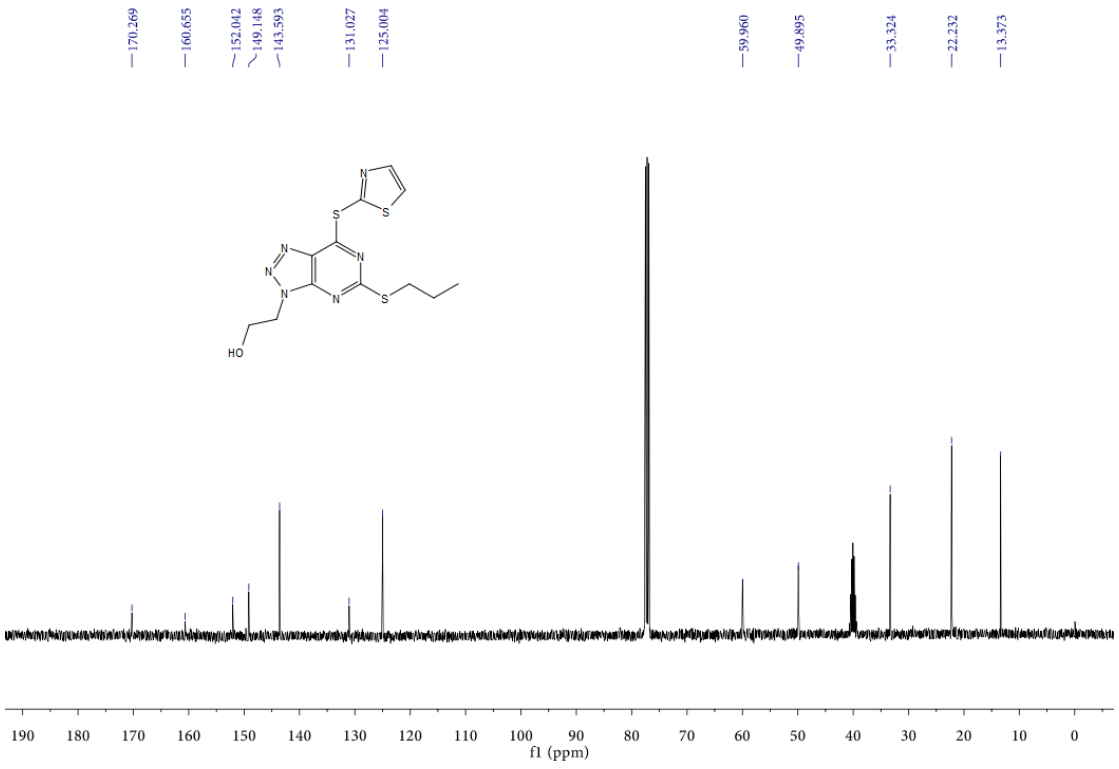


Figure S18 ^{1}H NMR spectrum of compound **8i**.

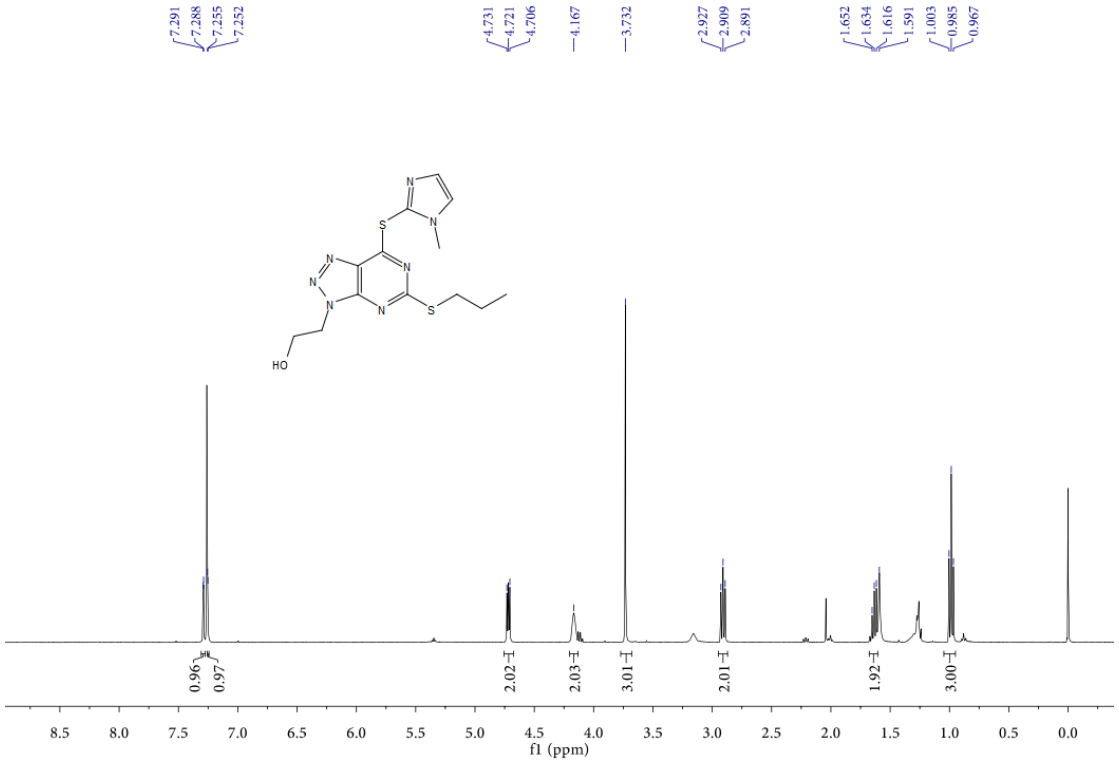


Figure S19 ^{13}C NMR spectrum of compound **8i**.

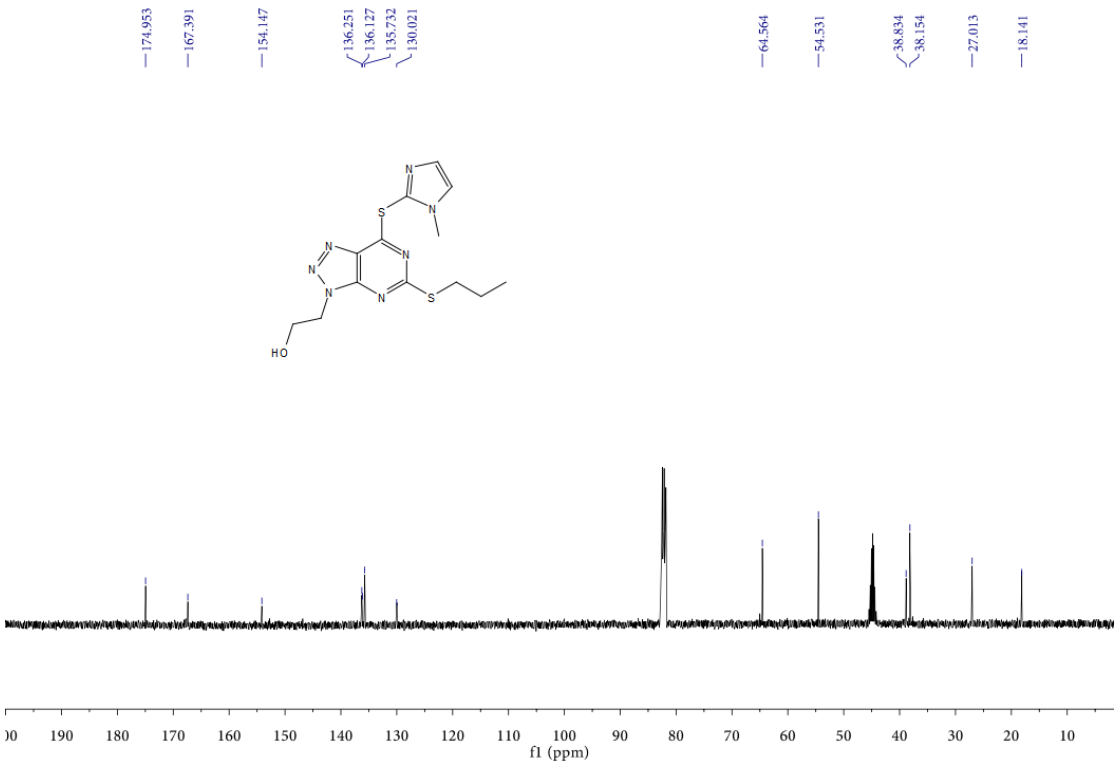


Figure S20 ^{1}H NMR spectrum of compound **8j**.

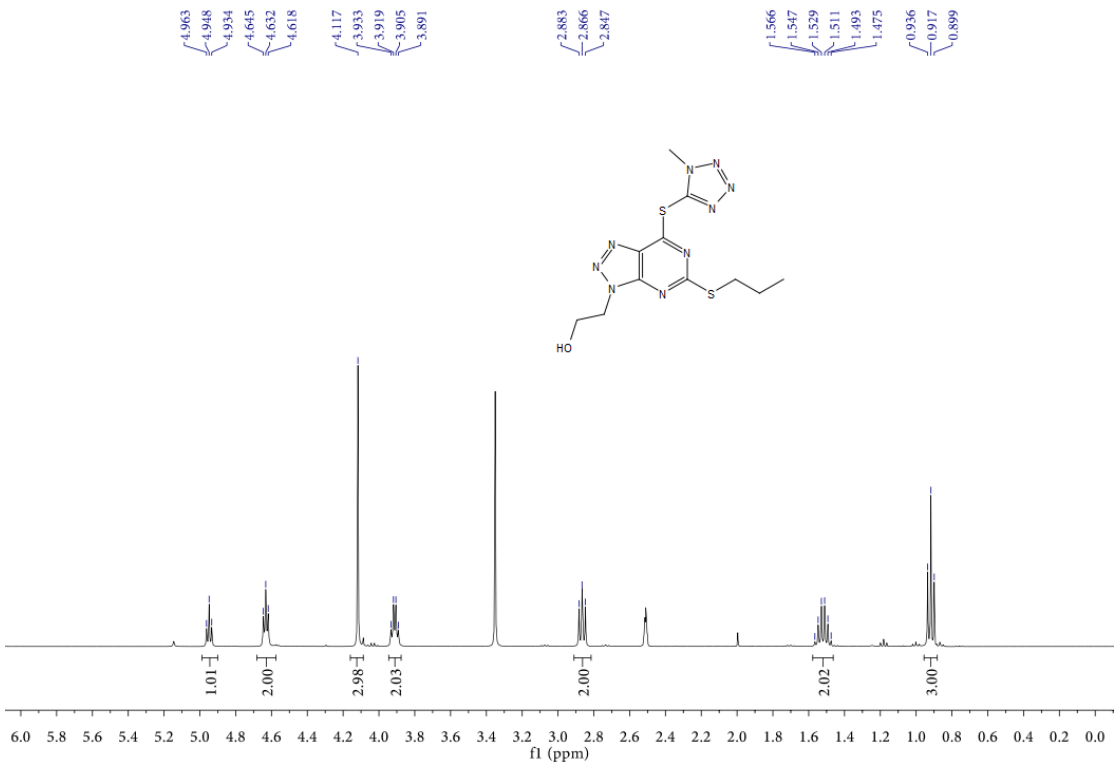


Figure S21 ^{13}C NMR spectrum of compound **8j**.

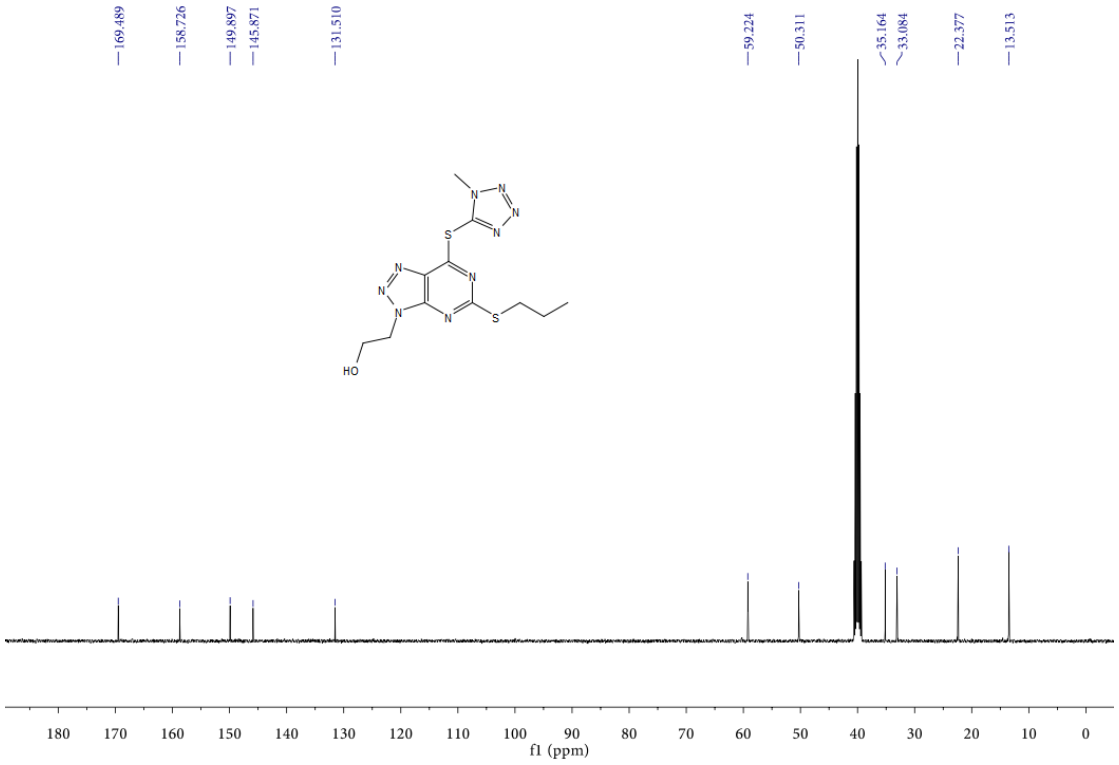


Figure S22 ^{1}H NMR spectrum of compound **8k**.

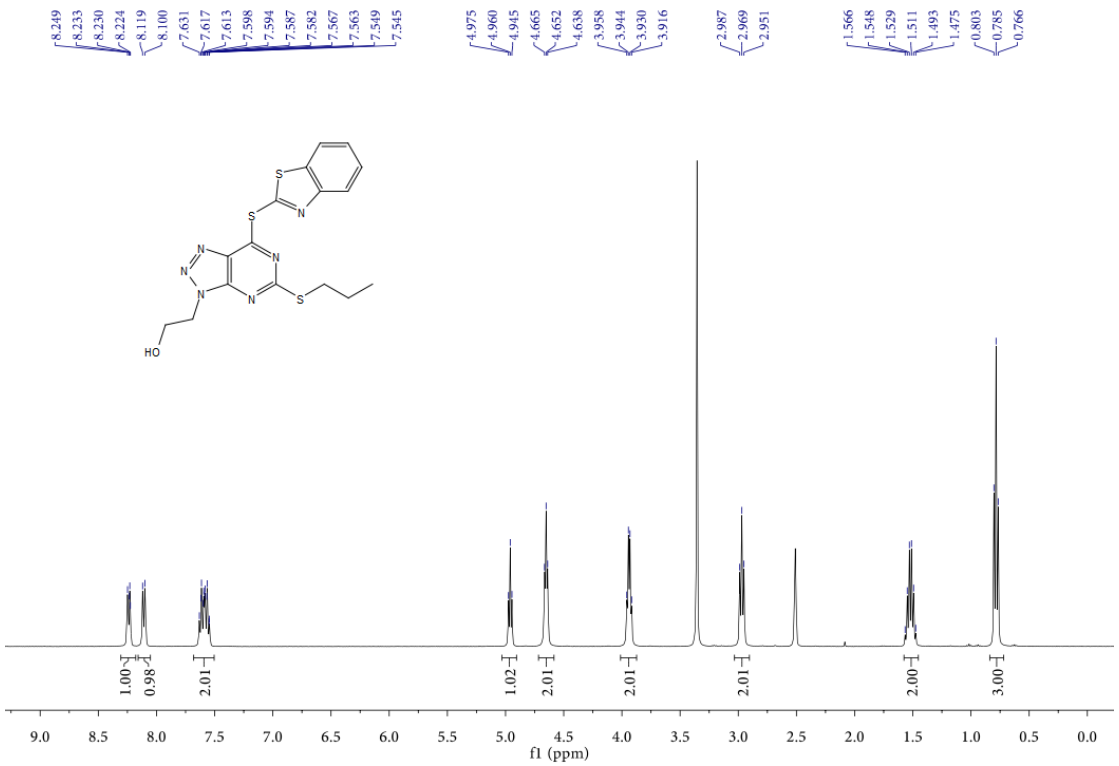


Figure S23 ^{13}C NMR spectrum of compound **8k**.

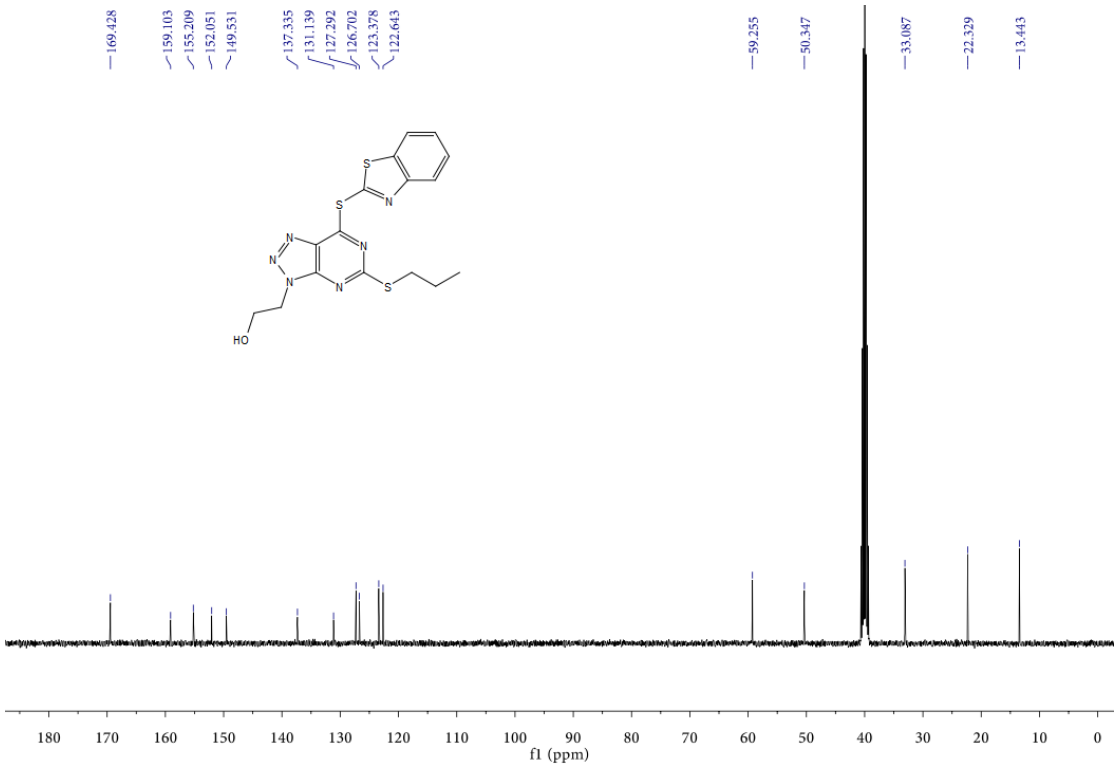


Figure S24 ^{1}H NMR spectrum of compound **9a**.

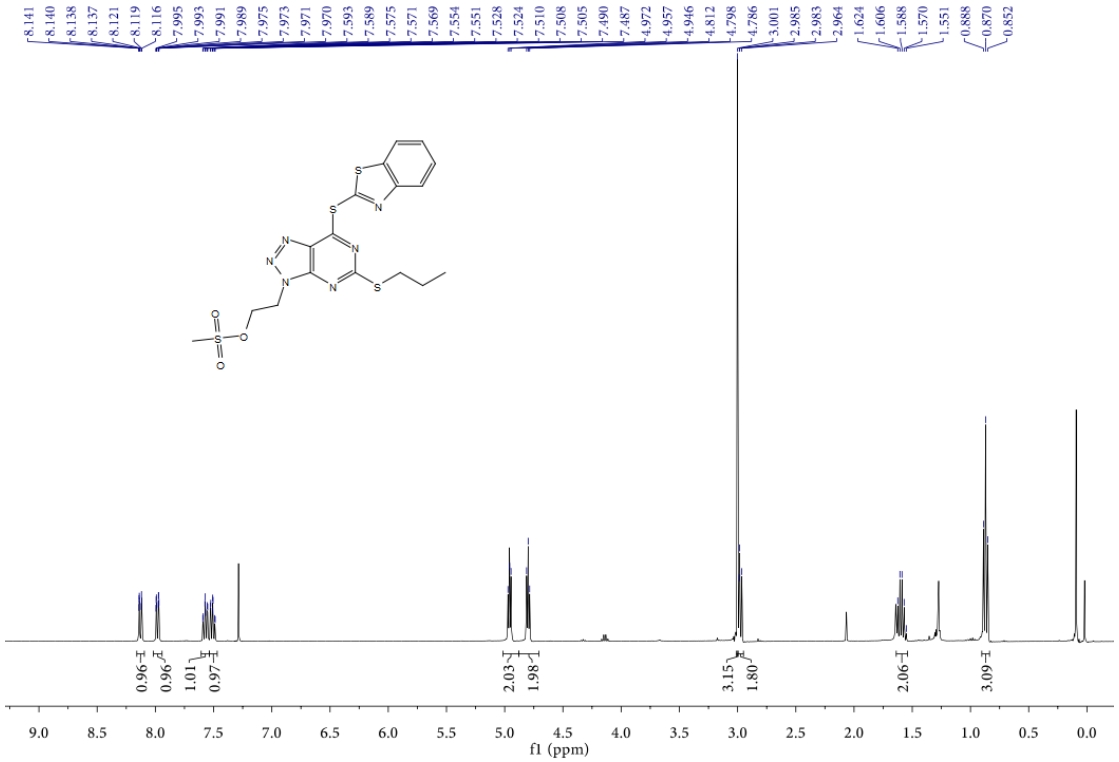


Figure S25 ^{13}C NMR spectrum of compound **9a**.

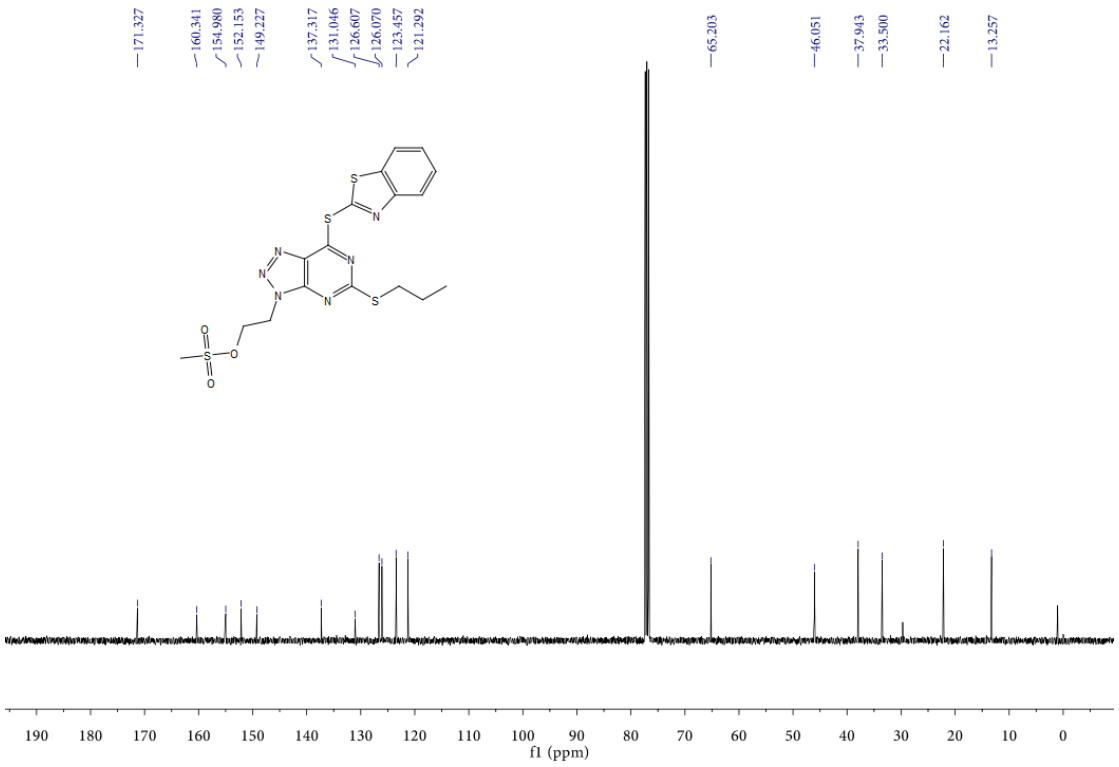


Figure S26 ^{1}H NMR spectrum of compound **9b**.

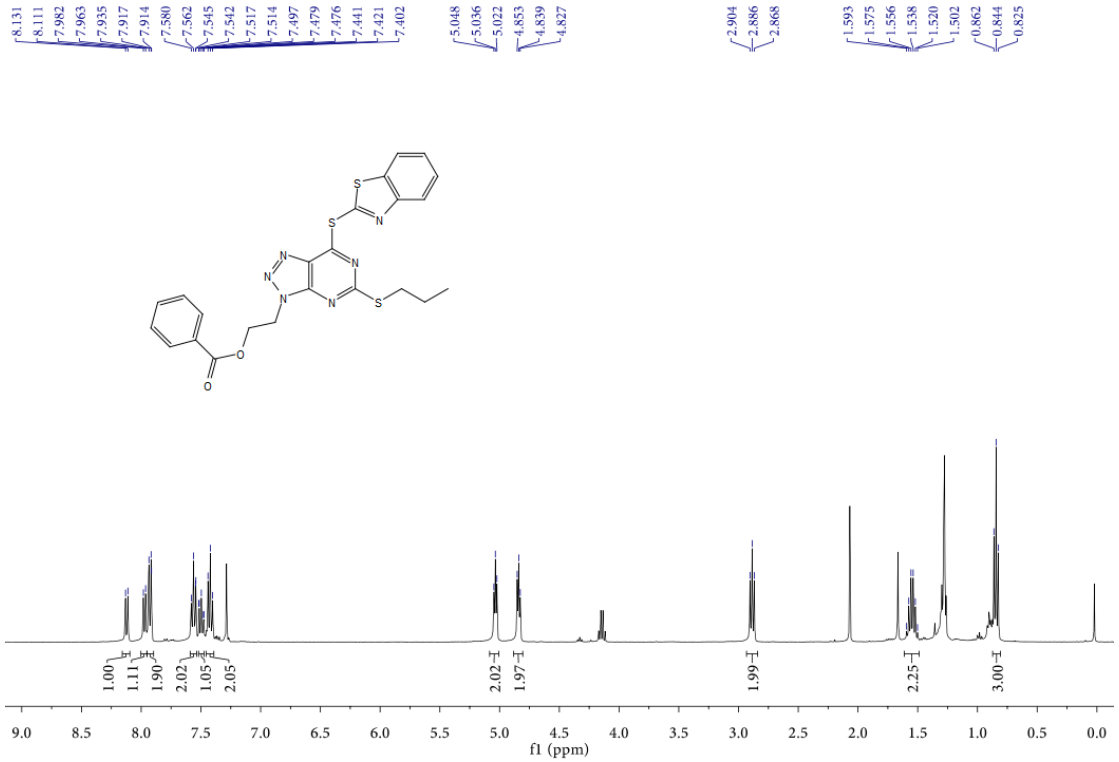


Figure S27 ^{13}C NMR spectrum of compound **9b**.

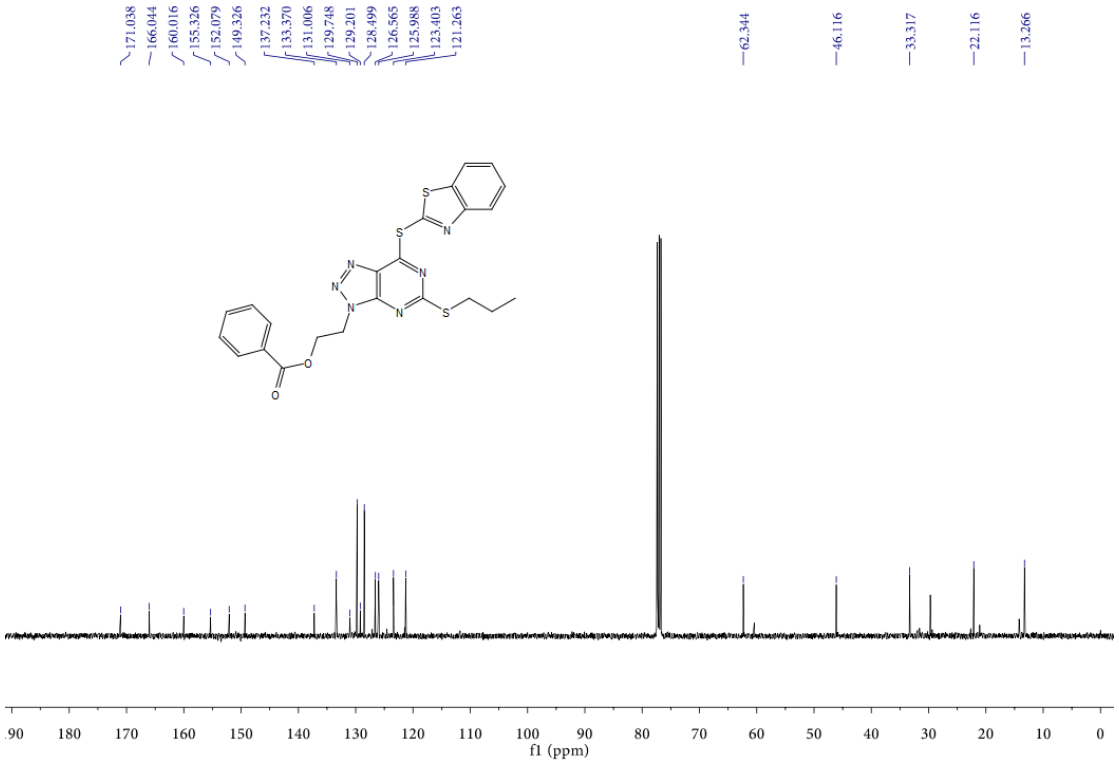


Figure S28 ^{1}H NMR spectrum of compound **8l**.

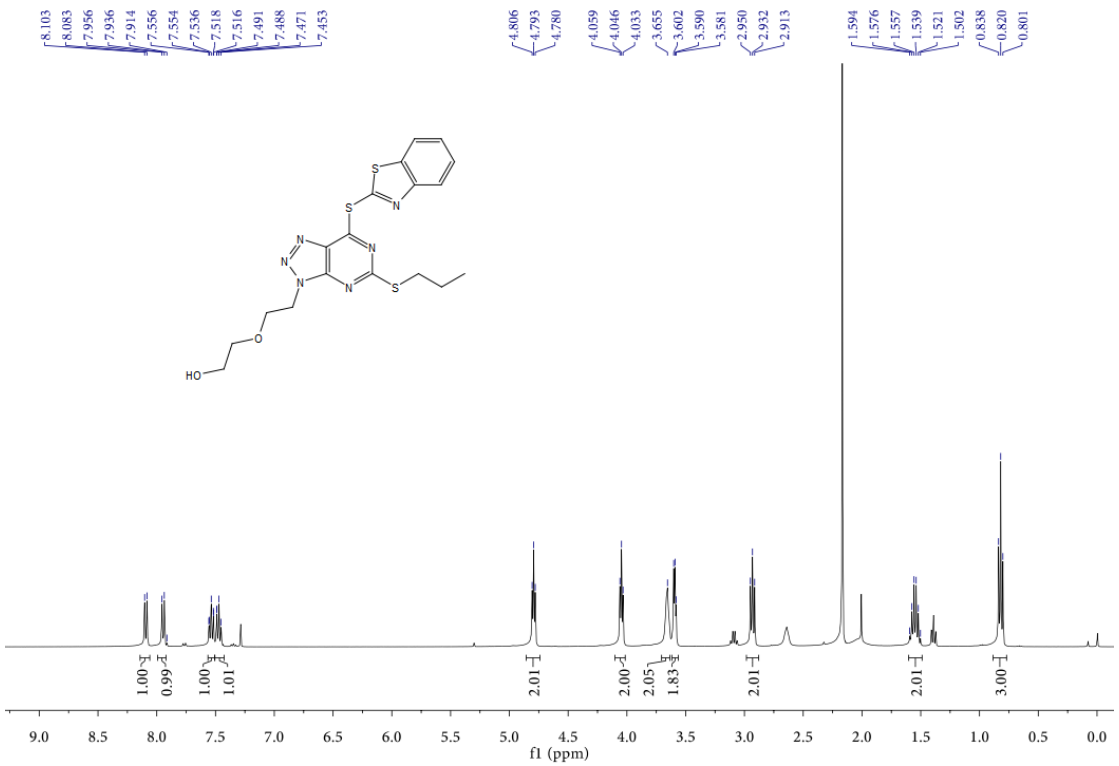


Figure S29 ^{13}C NMR spectrum of compound **8l**.

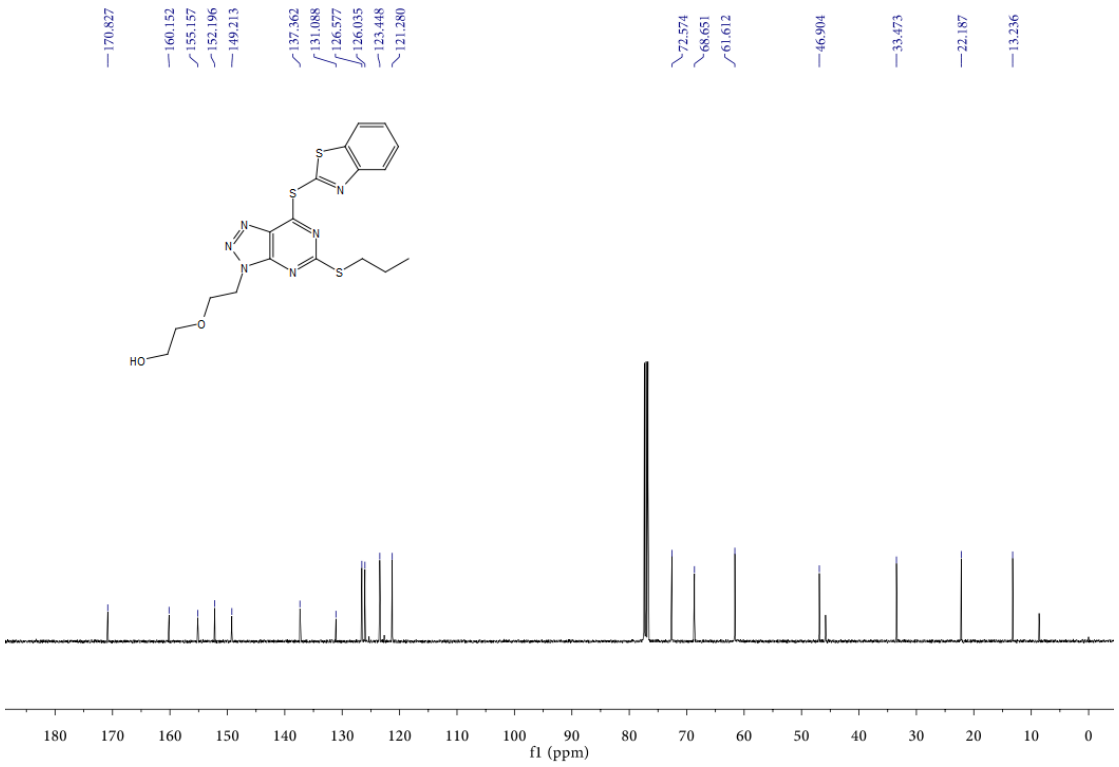


Figure S30 ^{1}H NMR spectrum of compound **11**.

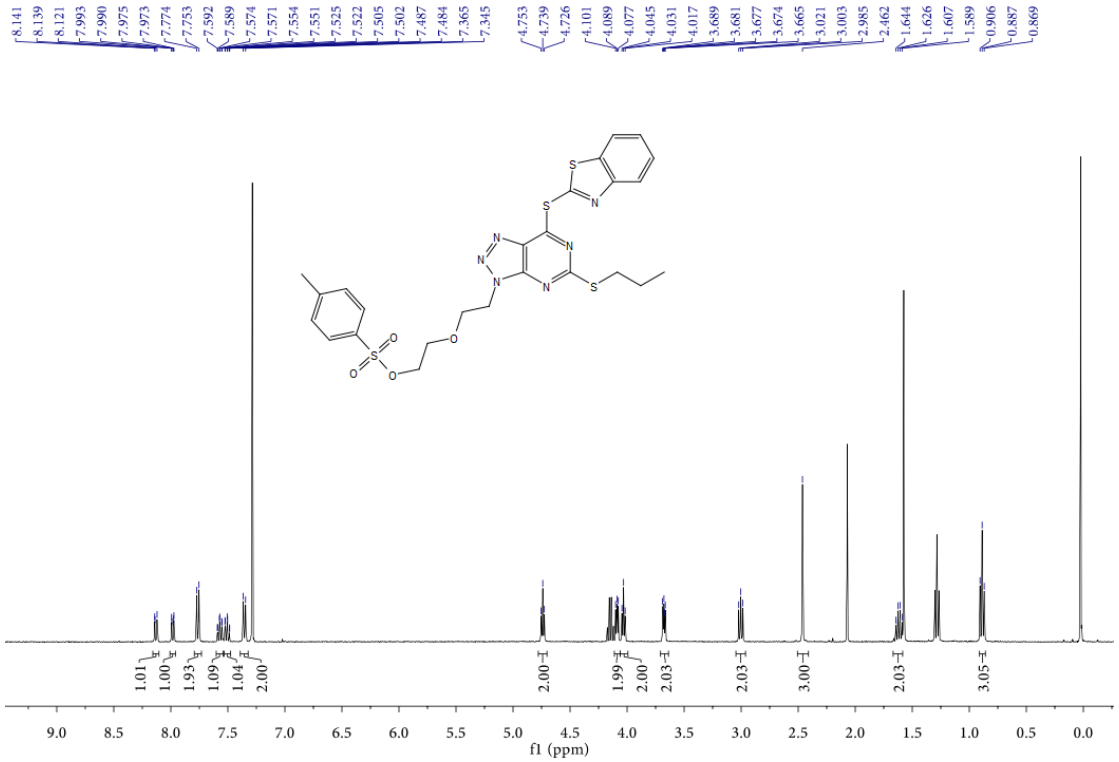


Figure S31 ^{13}C NMR spectrum of compound **11**.

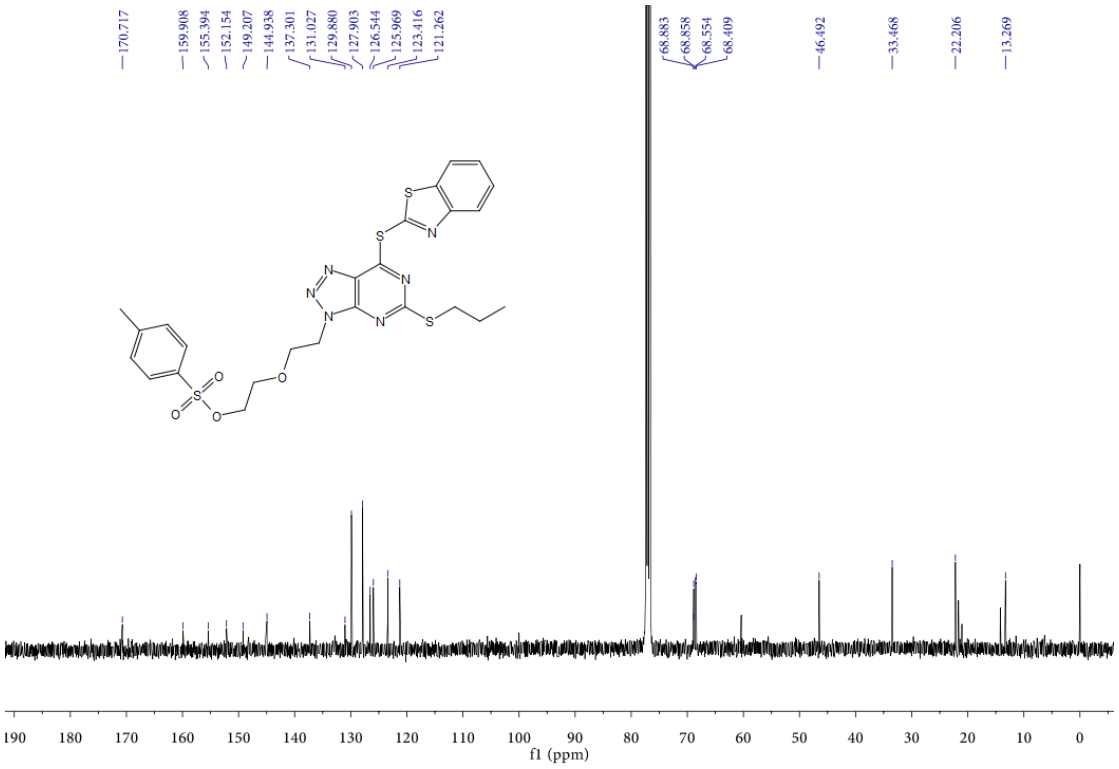


Figure S32 ^{1}H NMR spectrum of compound **15a**.

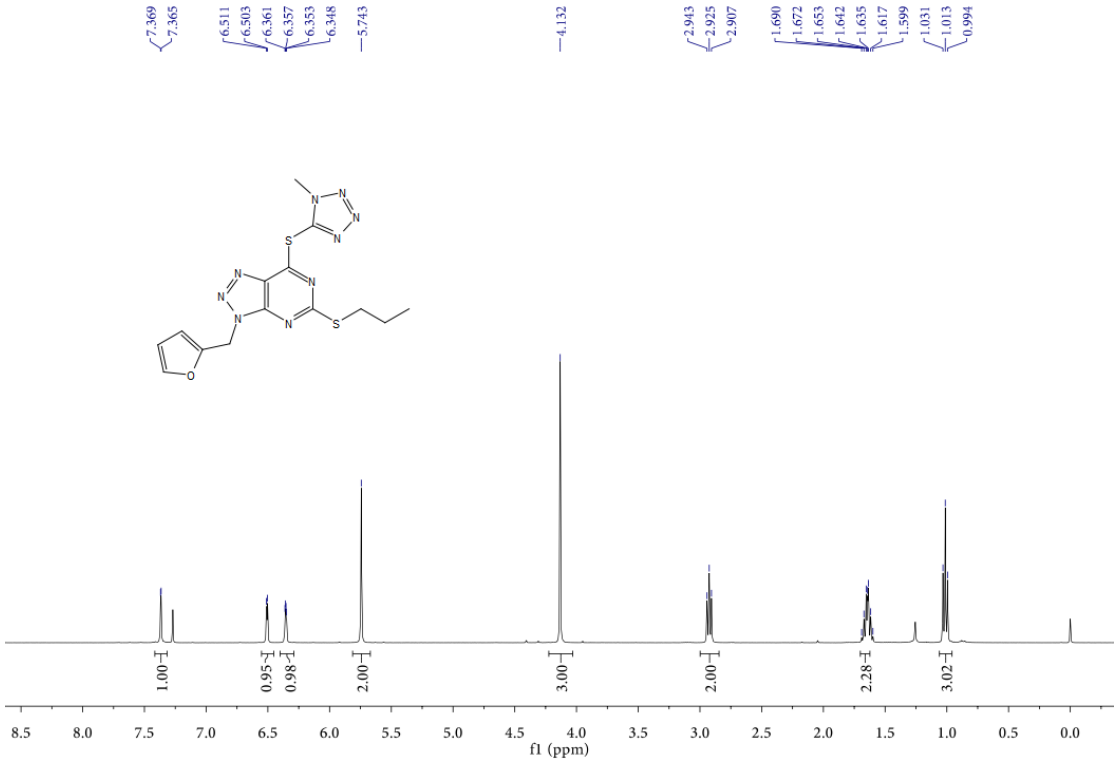


Figure S33 ^{13}C NMR spectrum of compound **15a**.

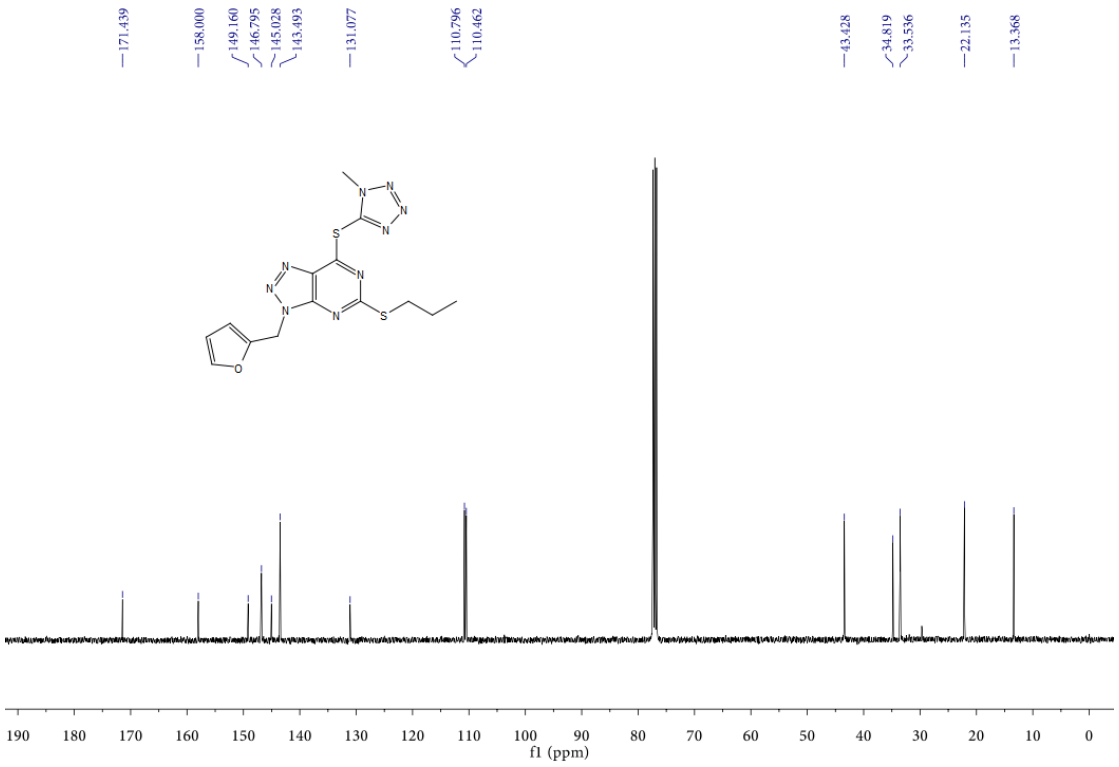


Figure S34 ^{1}H NMR spectrum of compound **15b**.

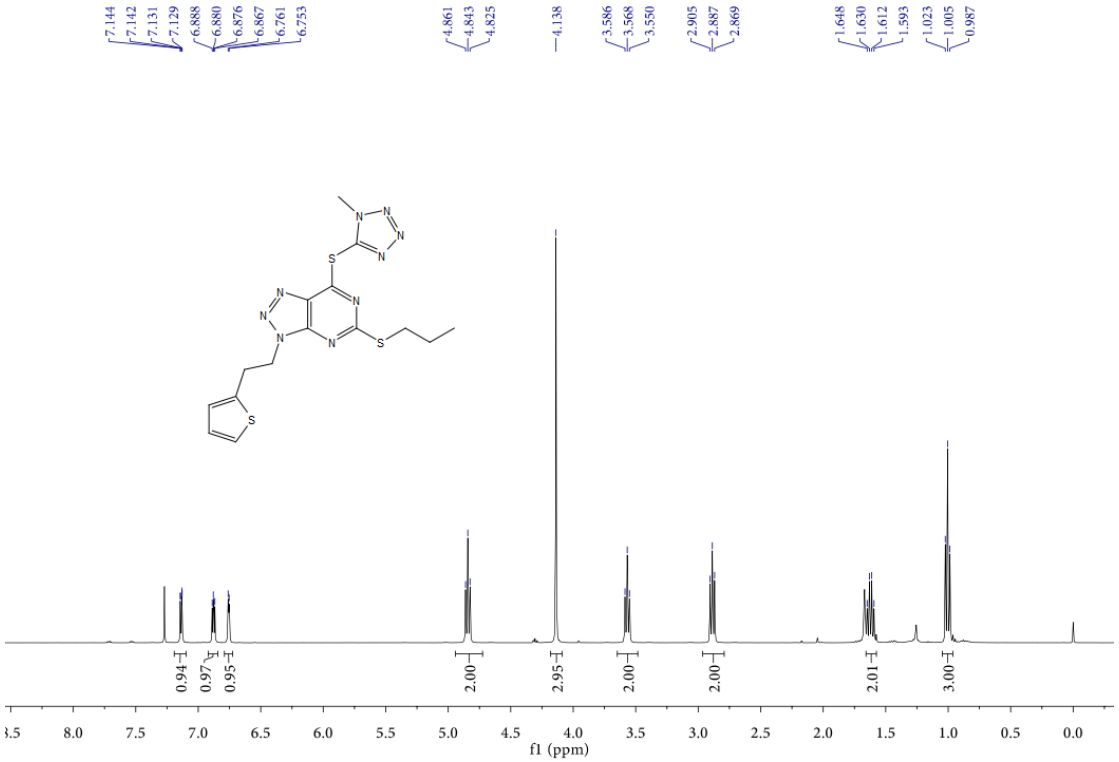


Figure S35 ^{13}C NMR spectrum of compound **15b**.

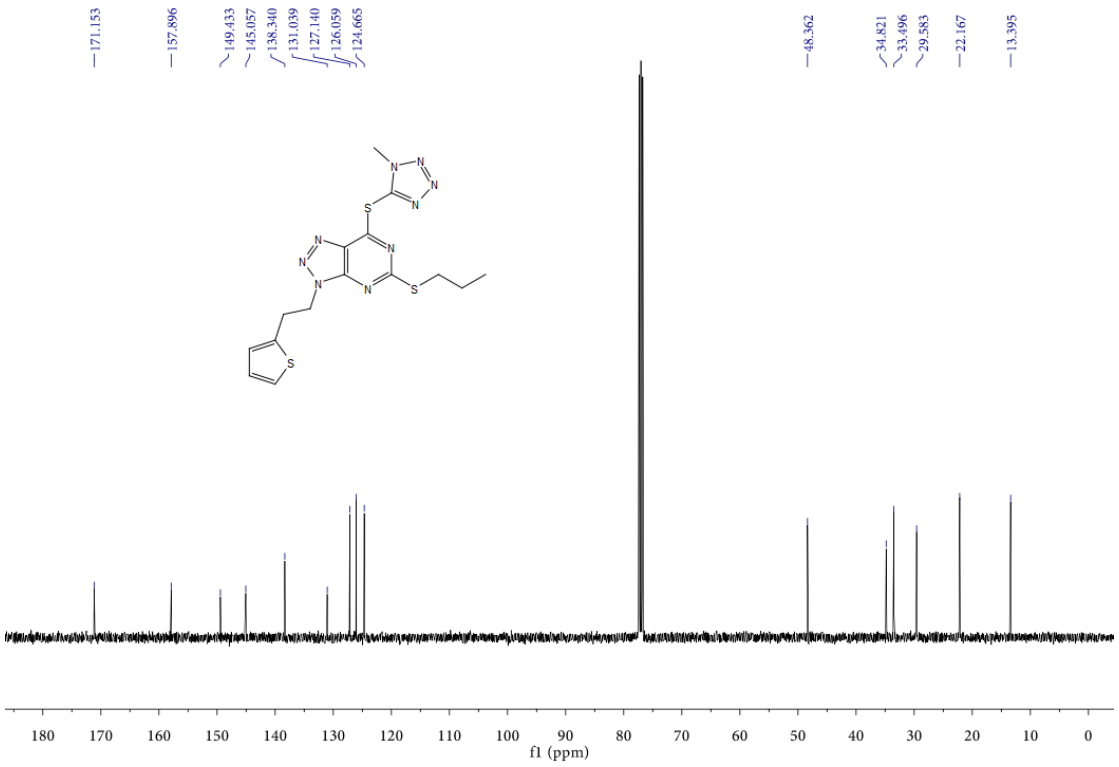


Figure S36 ^{1}H NMR spectrum of compound **15c**.

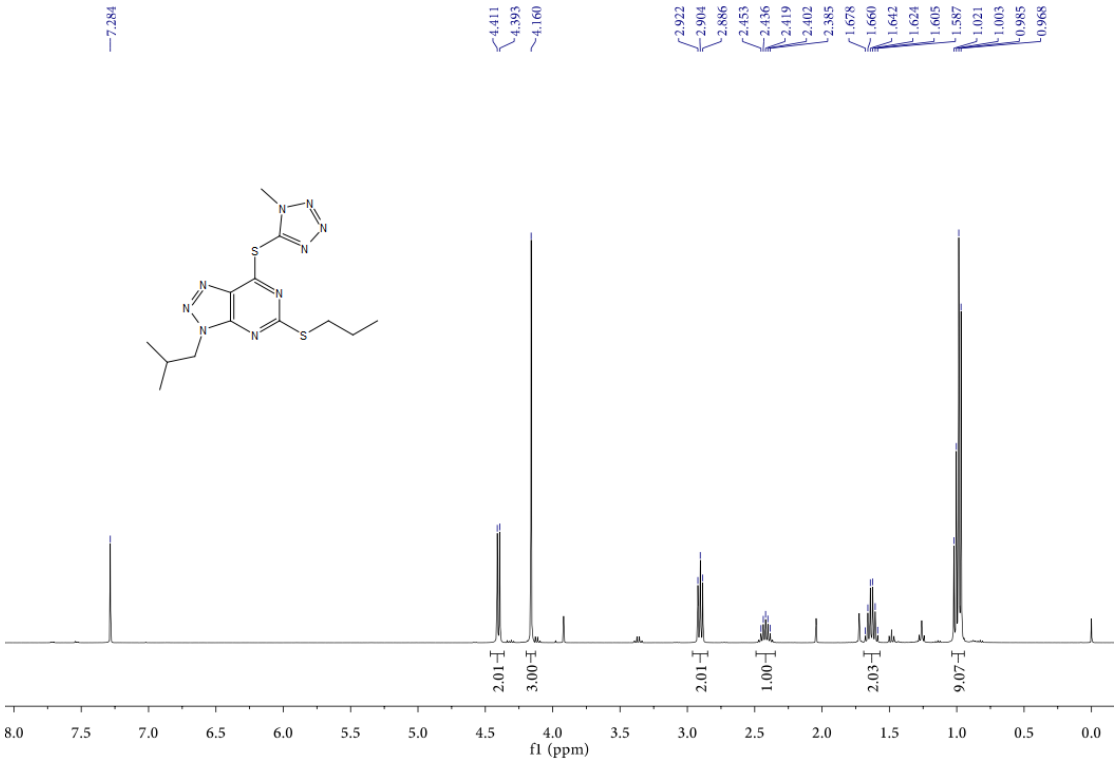


Figure S37 ^{13}C NMR spectrum of compound **15c**.

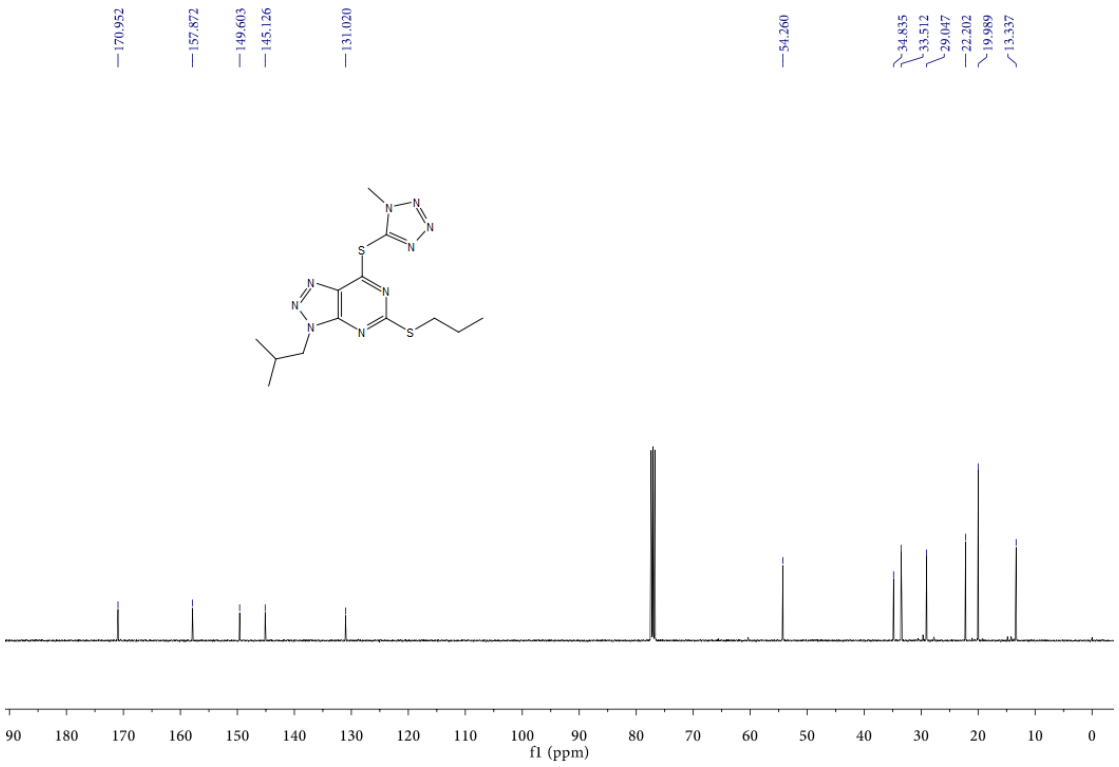


Figure S38 ^{1}H NMR spectrum of compound **15d**.

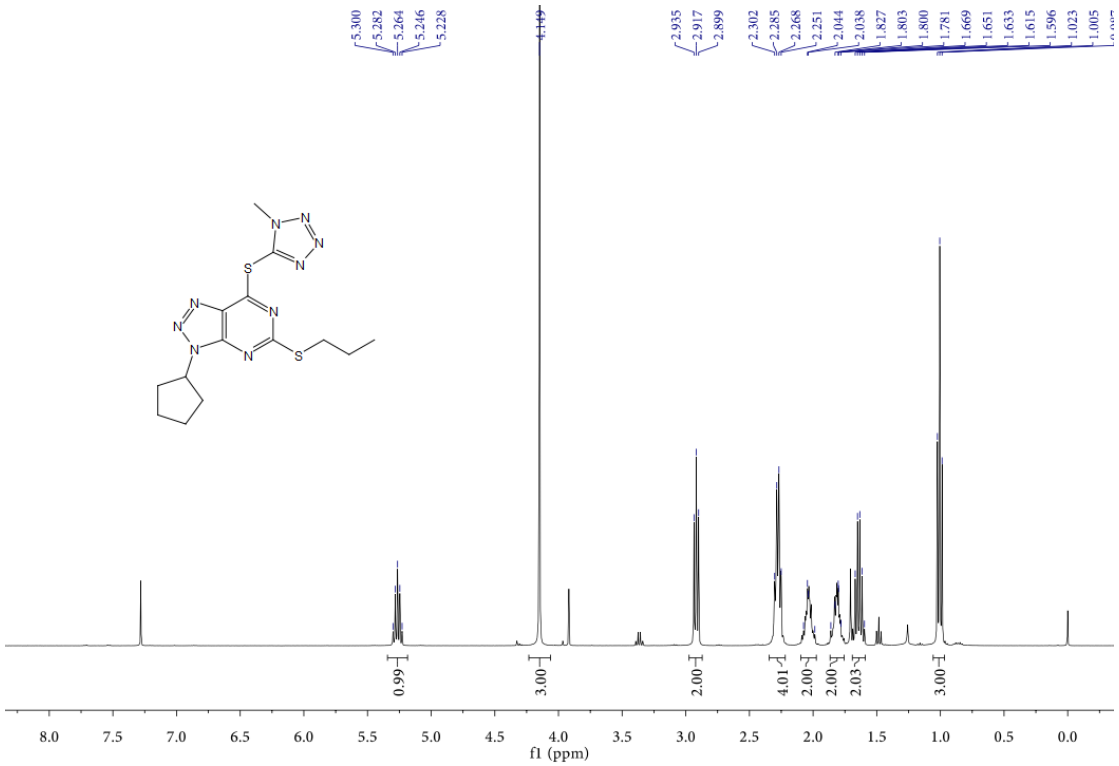


Figure S39 ^{13}C NMR spectrum of compound **15d**.

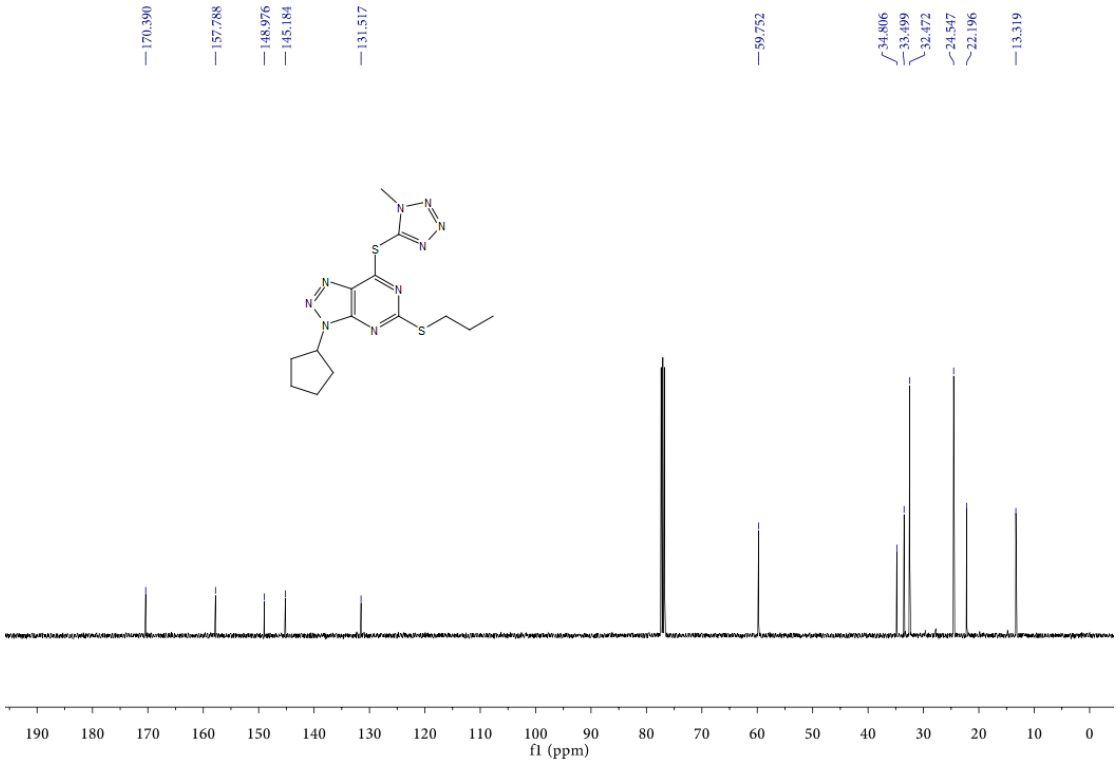


Figure S40 ^{1}H NMR spectrum of compound **15e**.

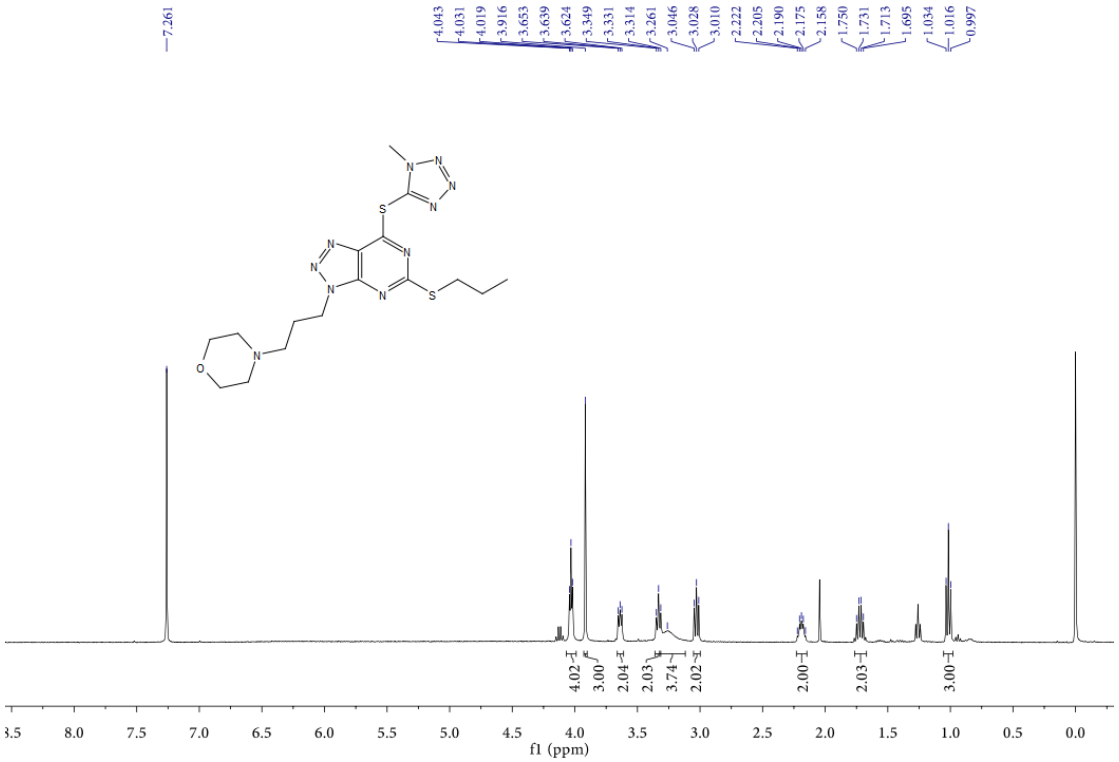


Figure S41 ^{13}C NMR spectrum of compound **15e**.

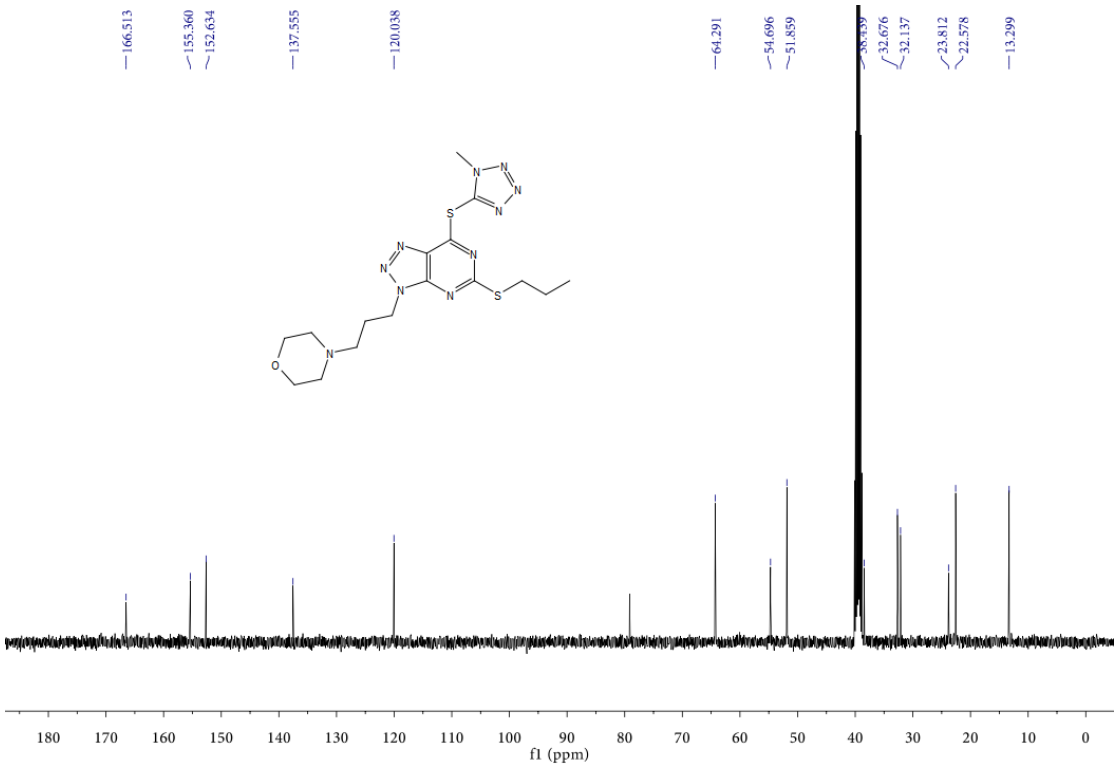


Figure S42 ^{1}H NMR spectrum of compound **15f**.

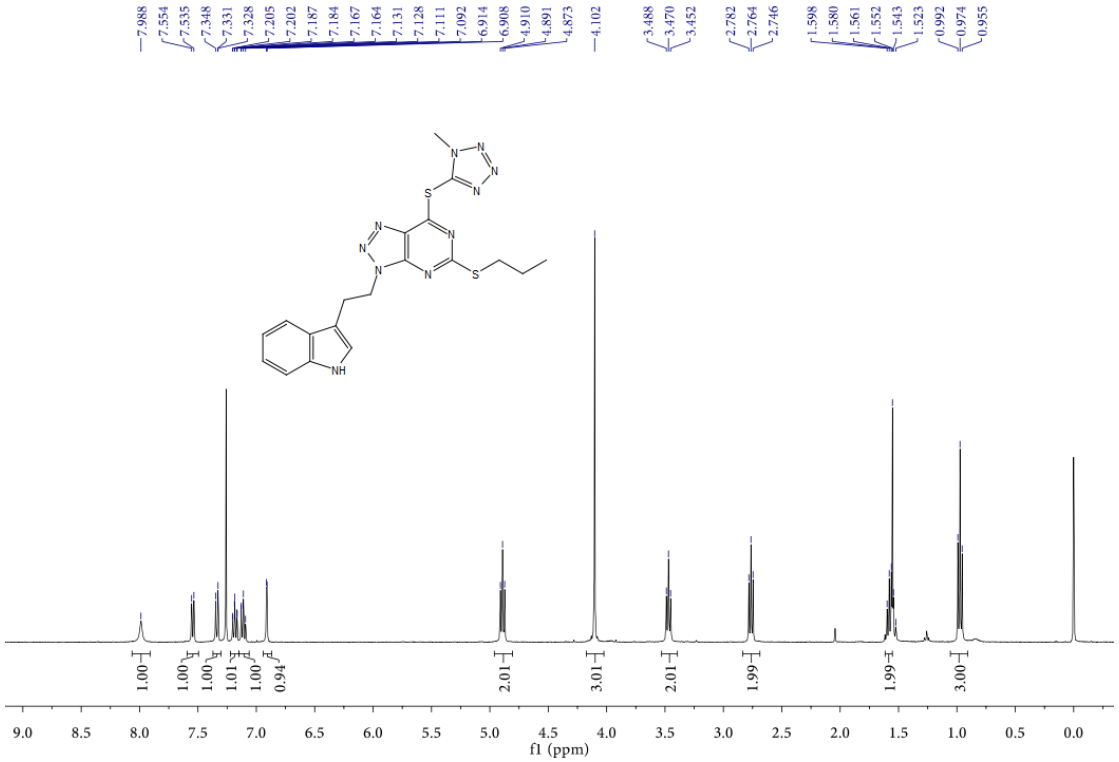


Figure S43 ^{13}C NMR spectrum of compound **15f**.

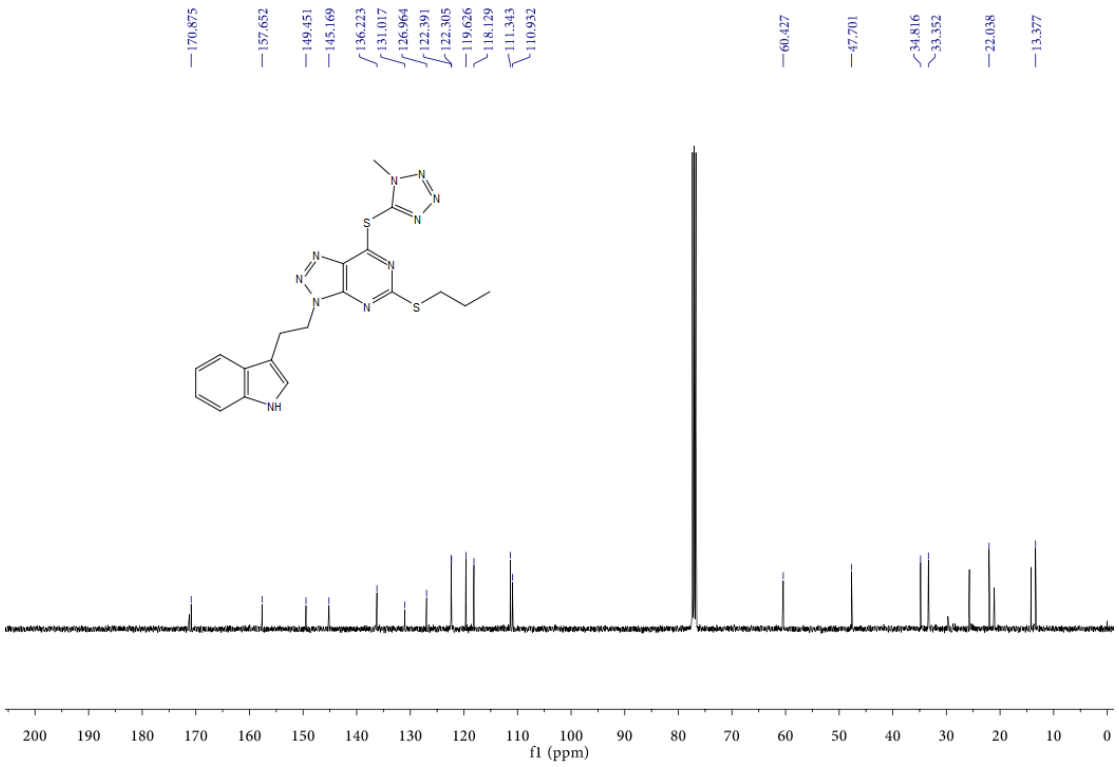


Figure S44 ^{1}H NMR spectrum of compound **15g**.

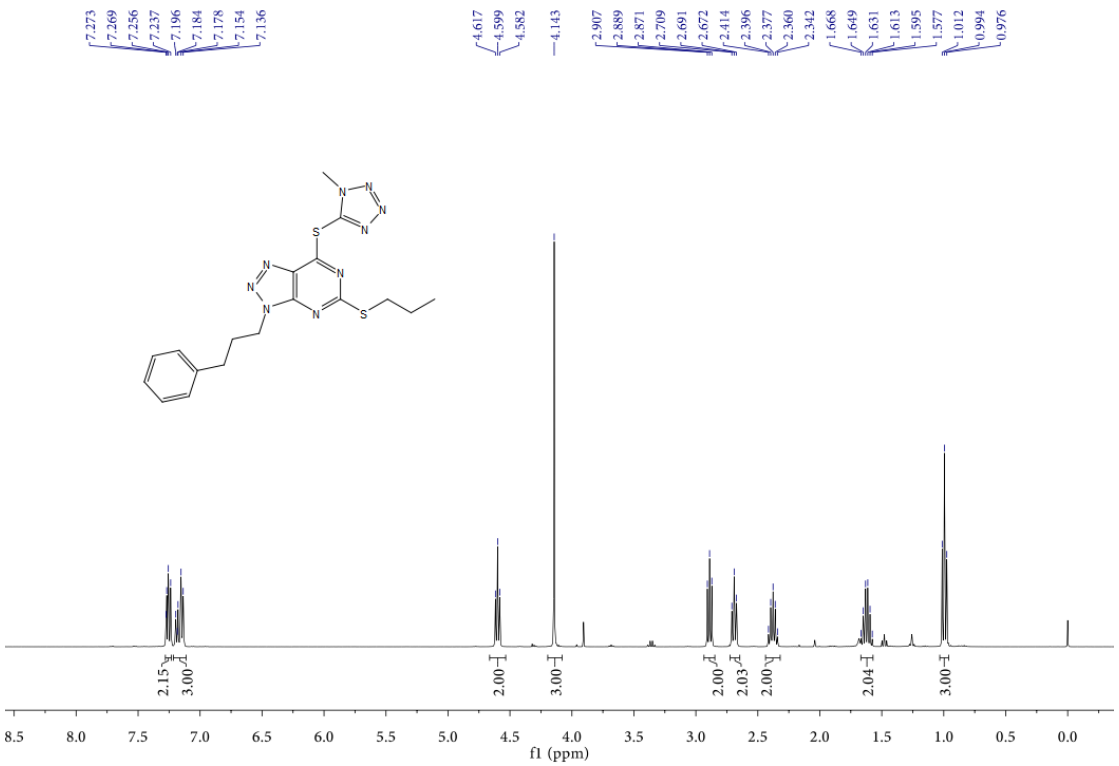


Figure S45 ^{13}C NMR spectrum of compound **15g**.

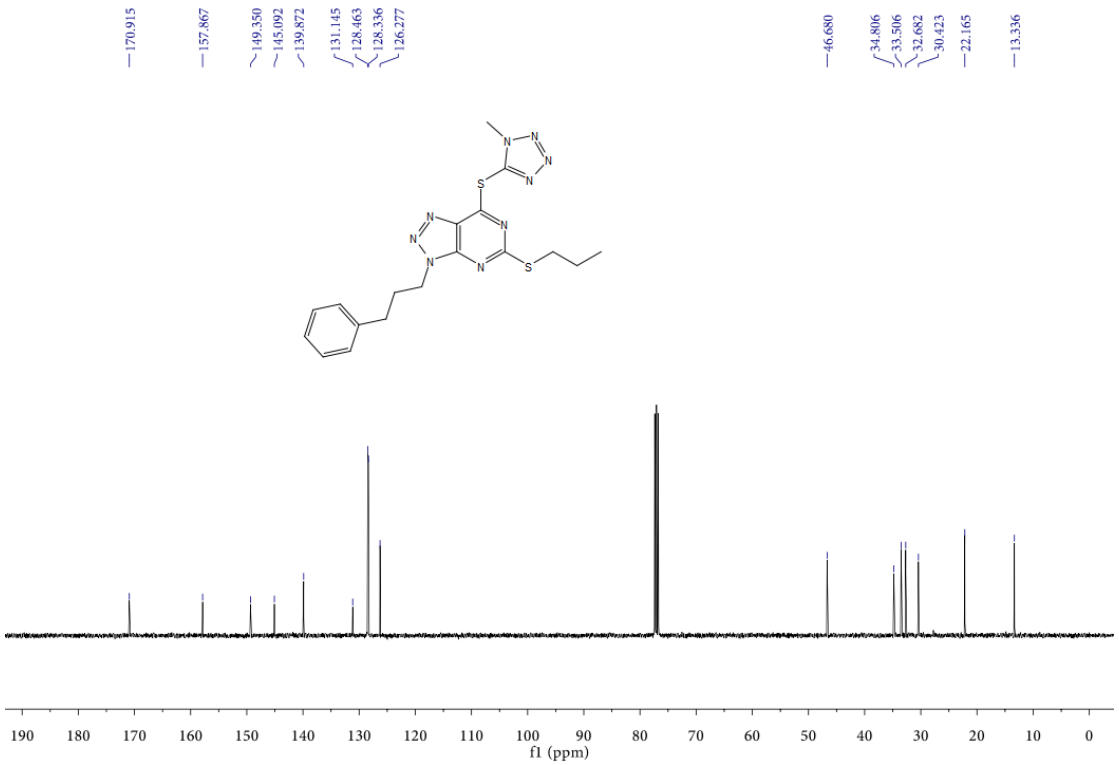


Figure S46 ^{1}H NMR spectrum of compound **15h**.

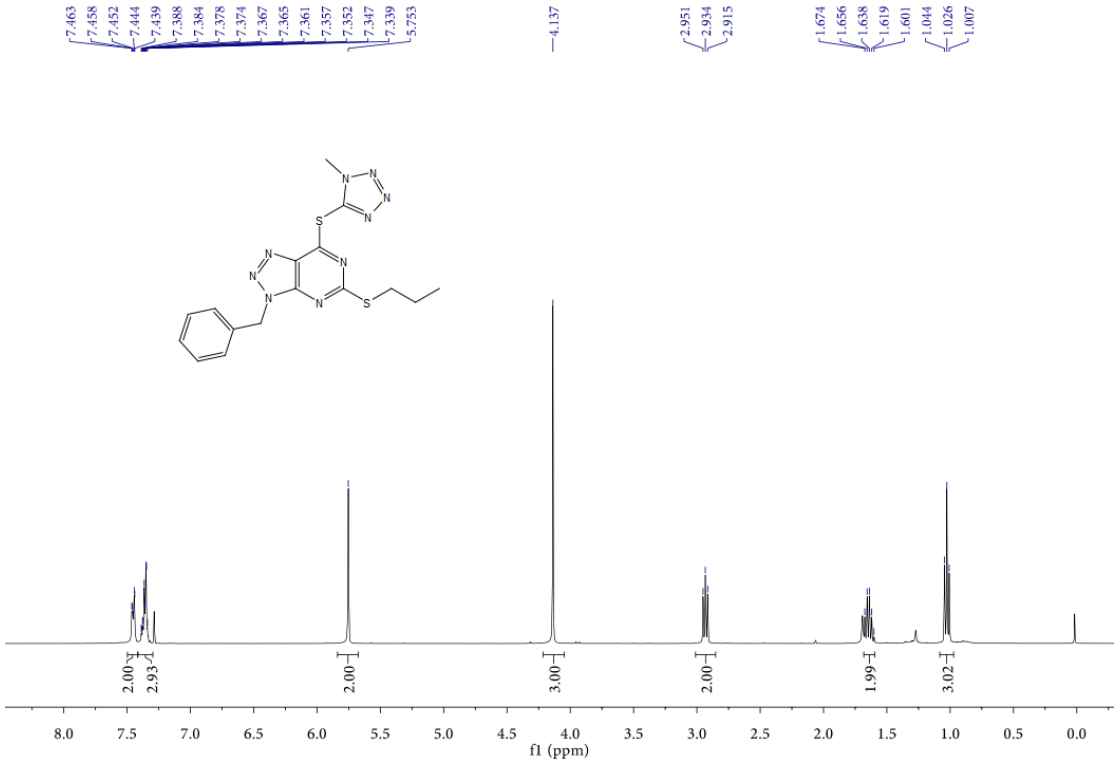


Figure S47 ^{13}C NMR spectrum of compound **15h**.

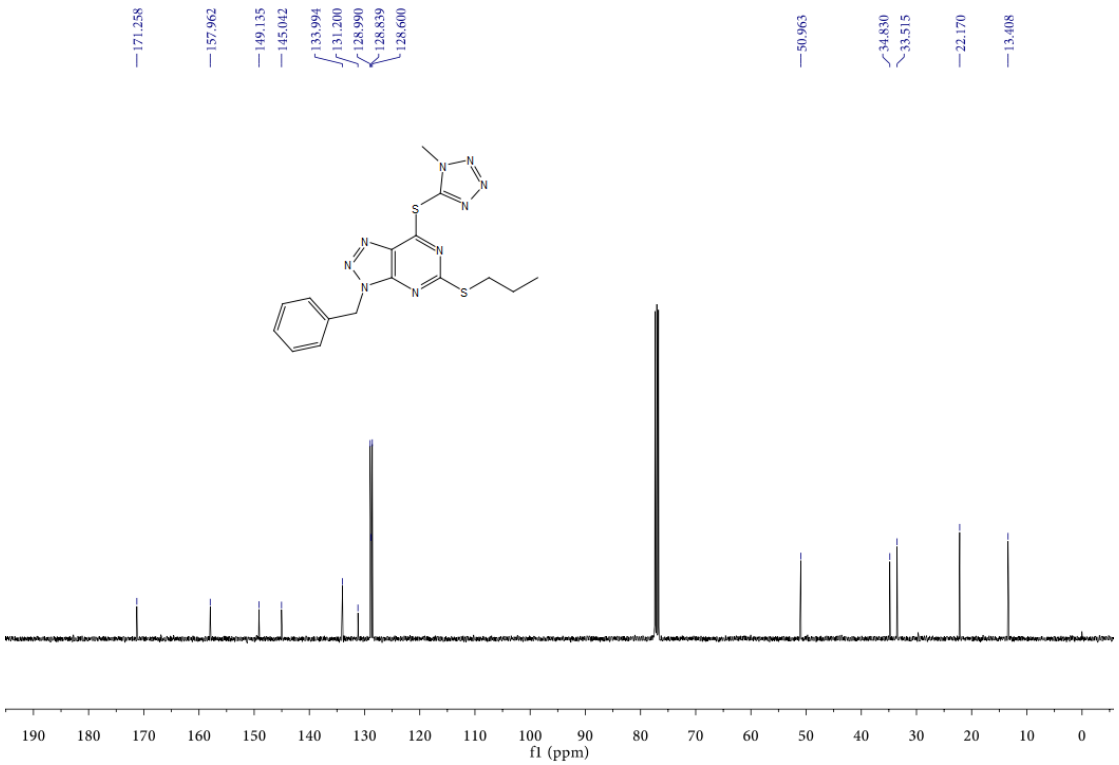


Figure S48 ^{1}H NMR spectrum of compound **15i**.

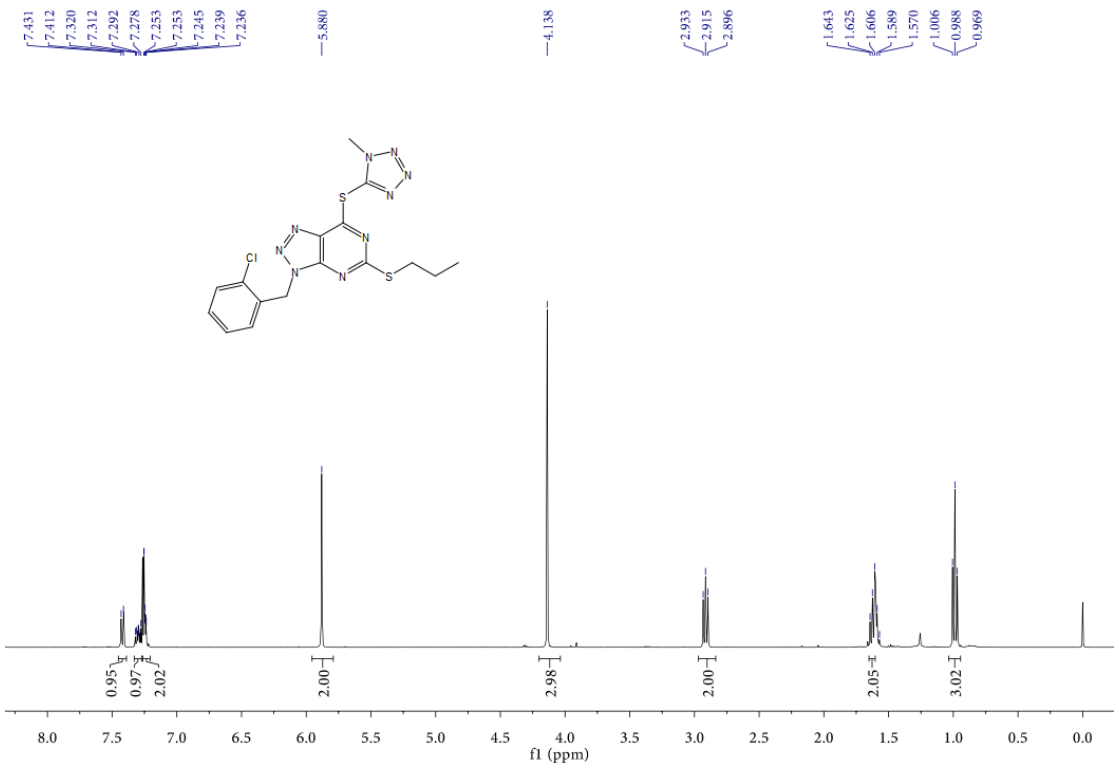


Figure S49 ^{13}C NMR spectrum of compound **15i**.

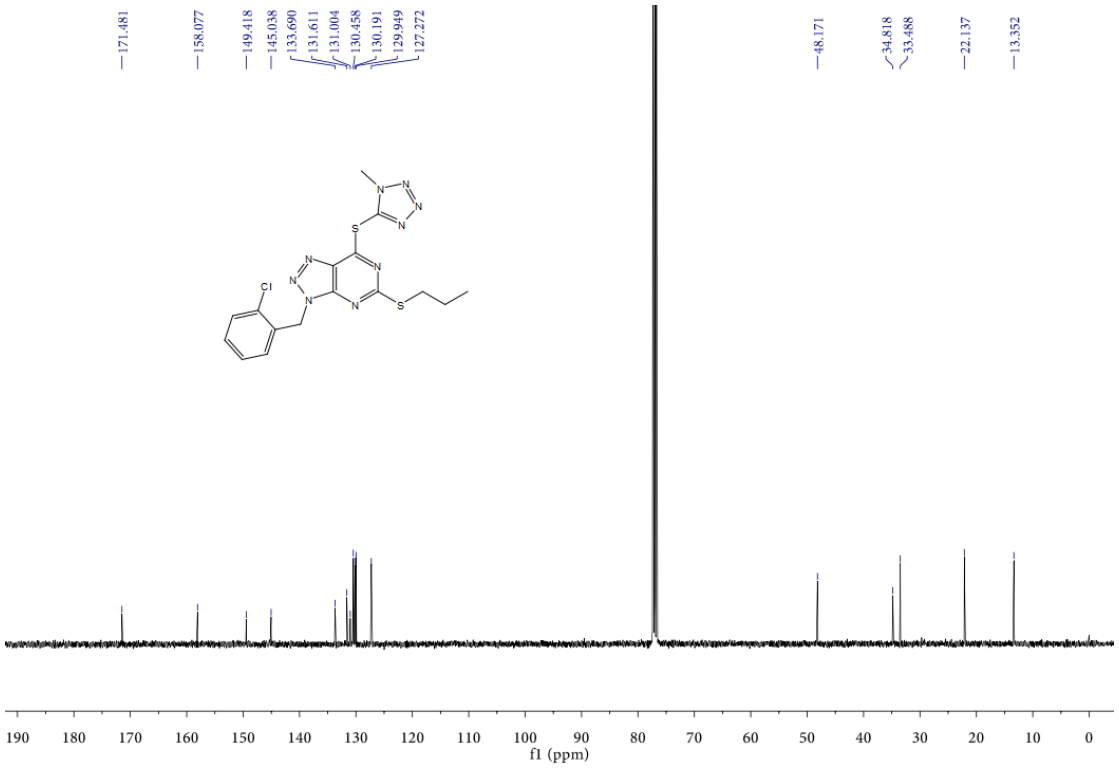


Figure S50 ^{1}H NMR spectrum of compound **15j**.

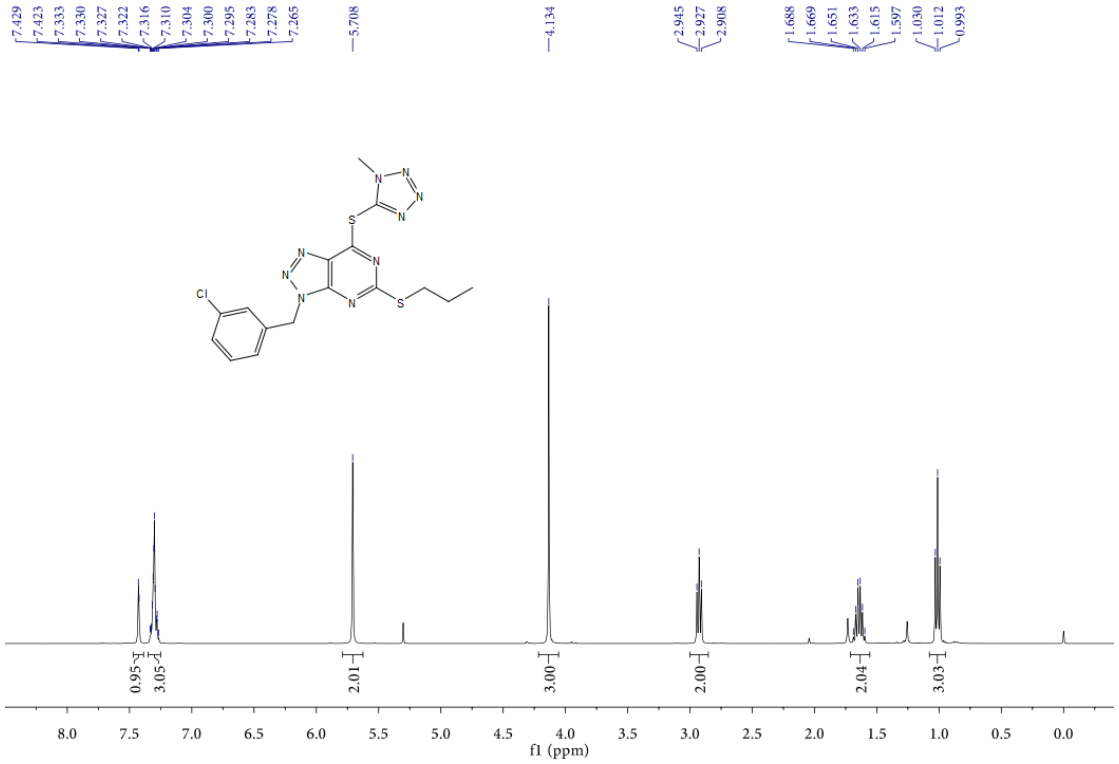


Figure S51 ^{13}C NMR spectrum of compound **15j**.

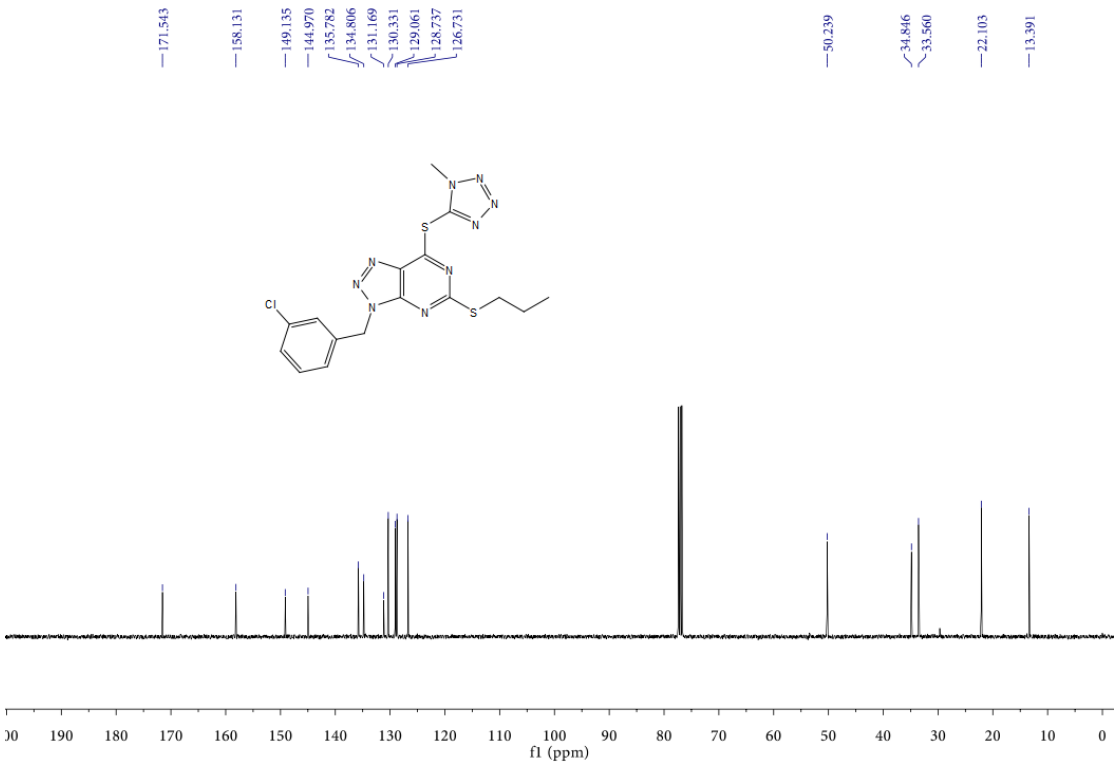


Figure S52 ^{1}H NMR spectrum of compound **15k**.

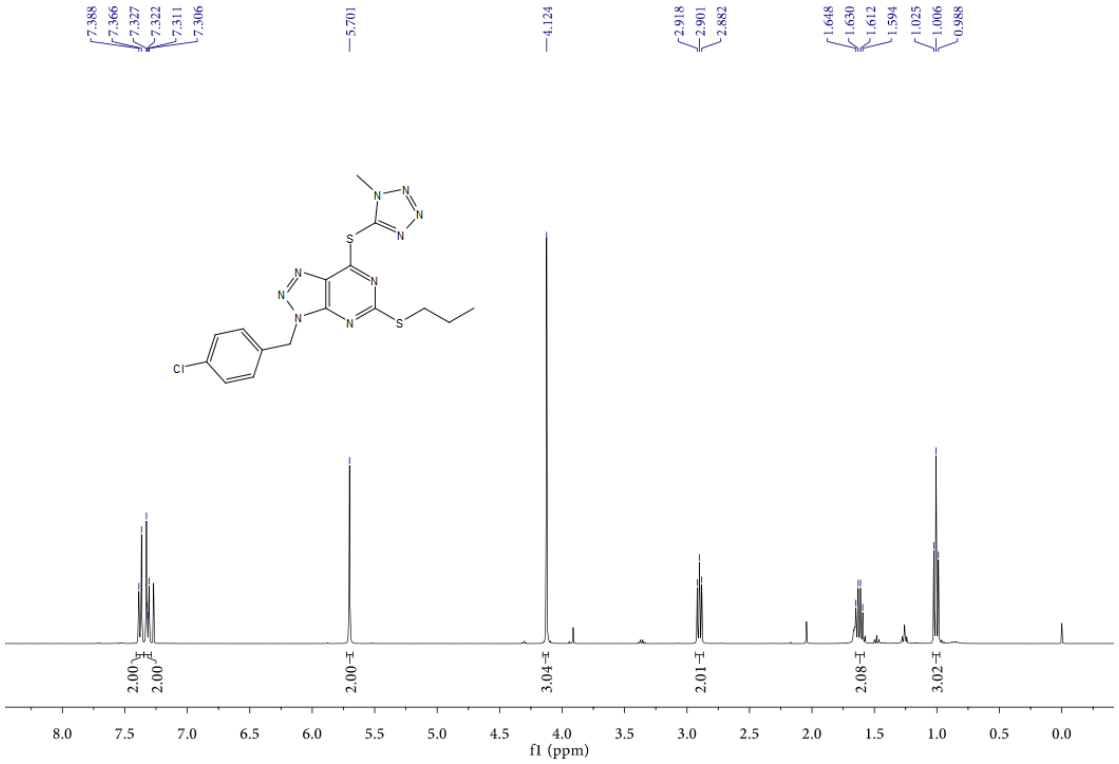


Figure S53 ^{13}C NMR spectrum of compound **15k**.

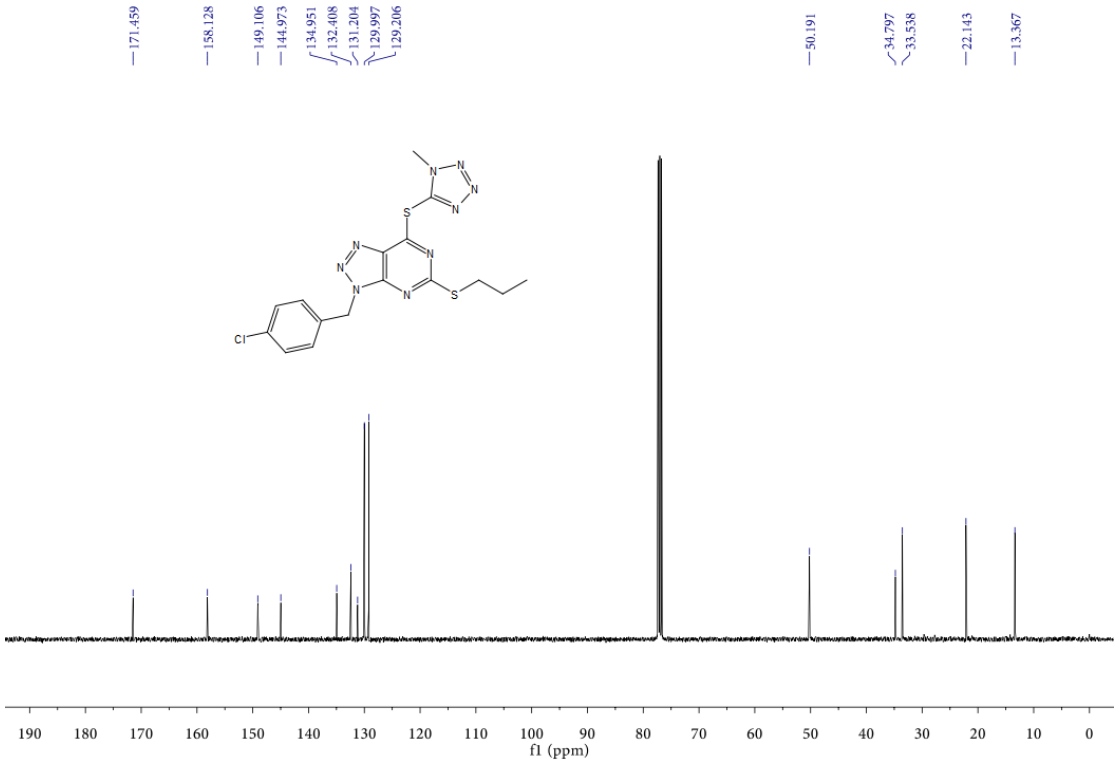


Figure S54 ^{1}H NMR spectrum of compound **15l**.

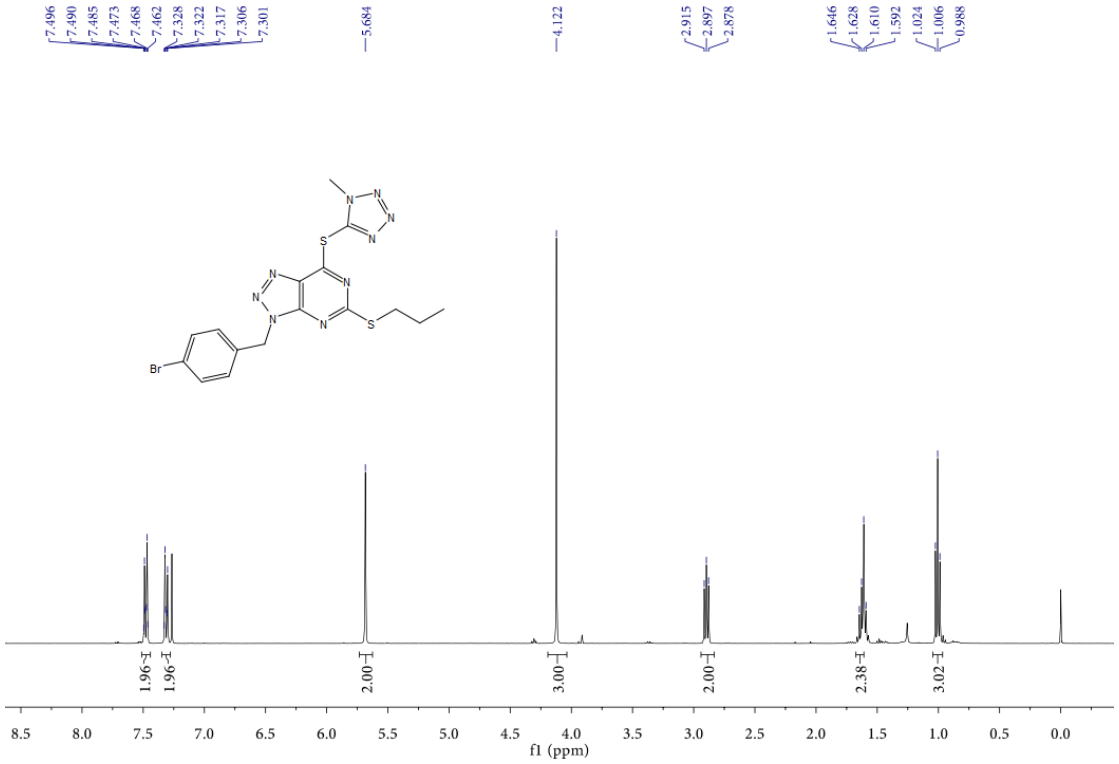


Figure S55 ^{13}C NMR spectrum of compound **15l**.

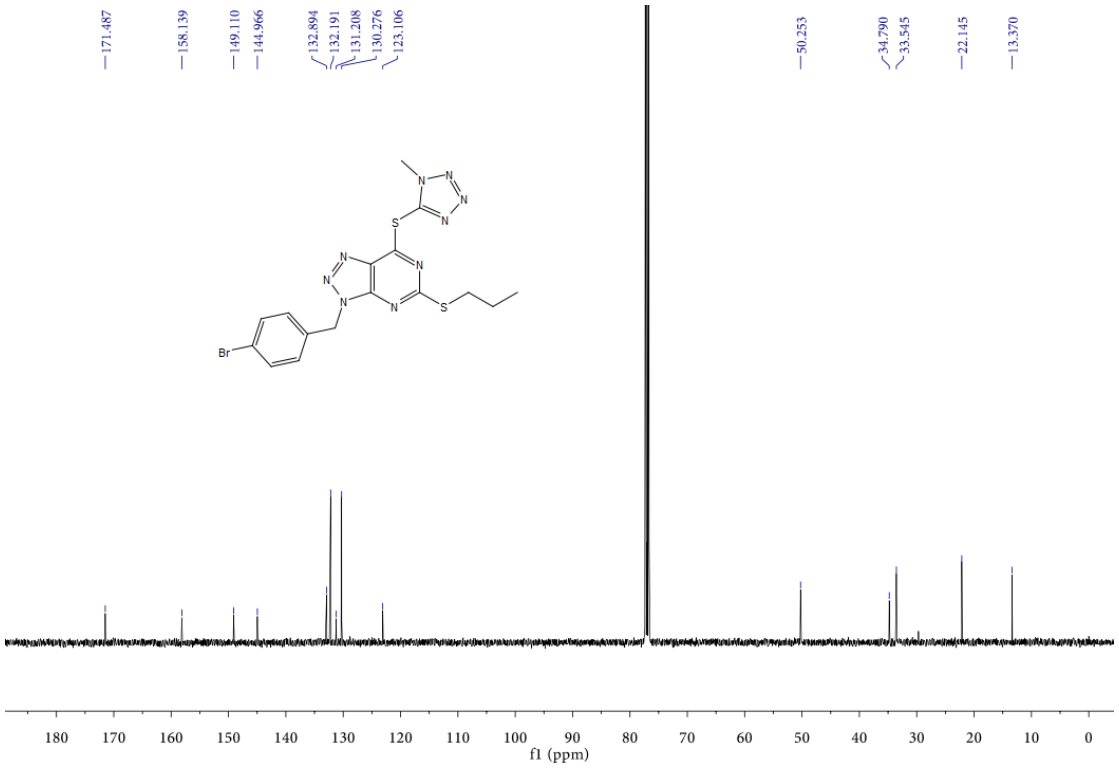


Figure S56 ^{1}H NMR spectrum of compound **15m**.

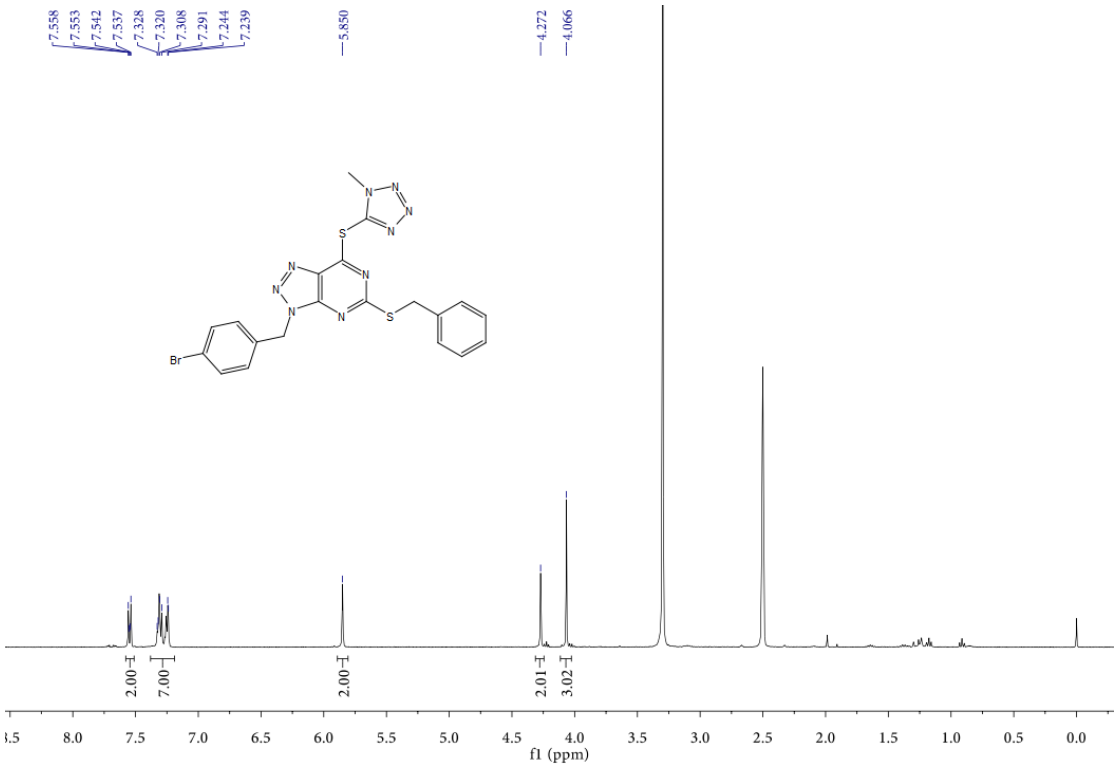


Figure S57 ^{13}C NMR spectrum of compound **15m**.

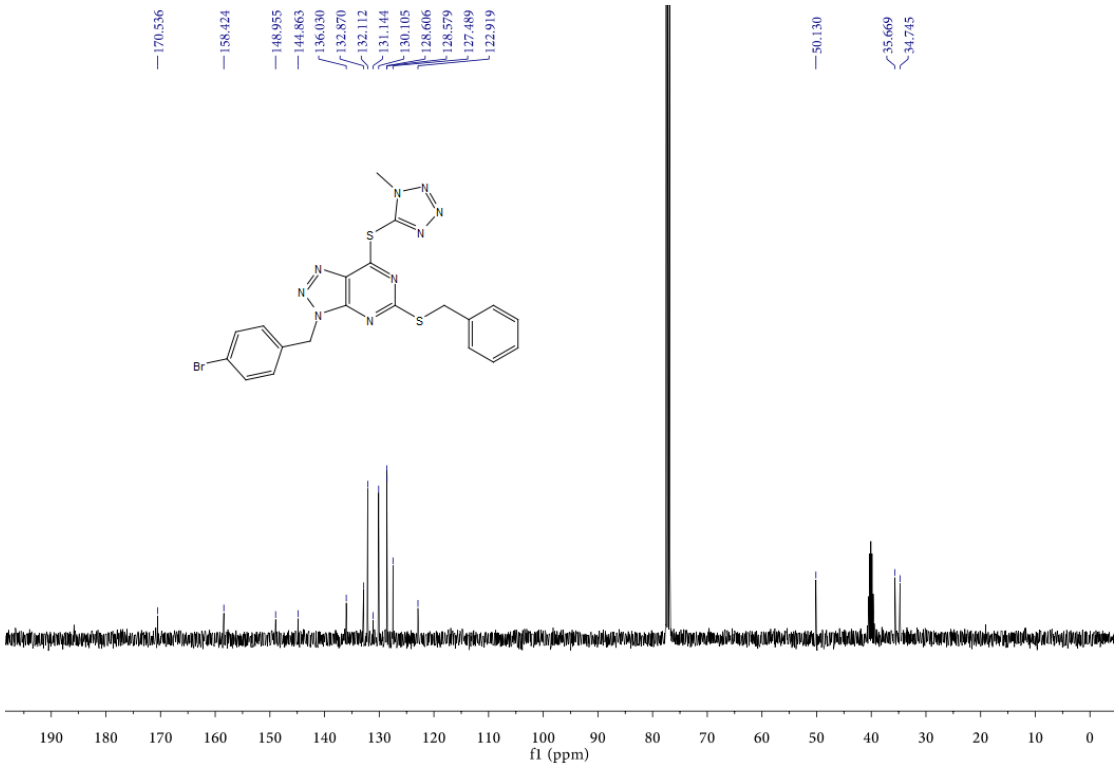


Figure S58 ^{1}H NMR spectrum of compound **15n**.

Figure S59 ^{13}C NMR spectrum of compound **15n**.

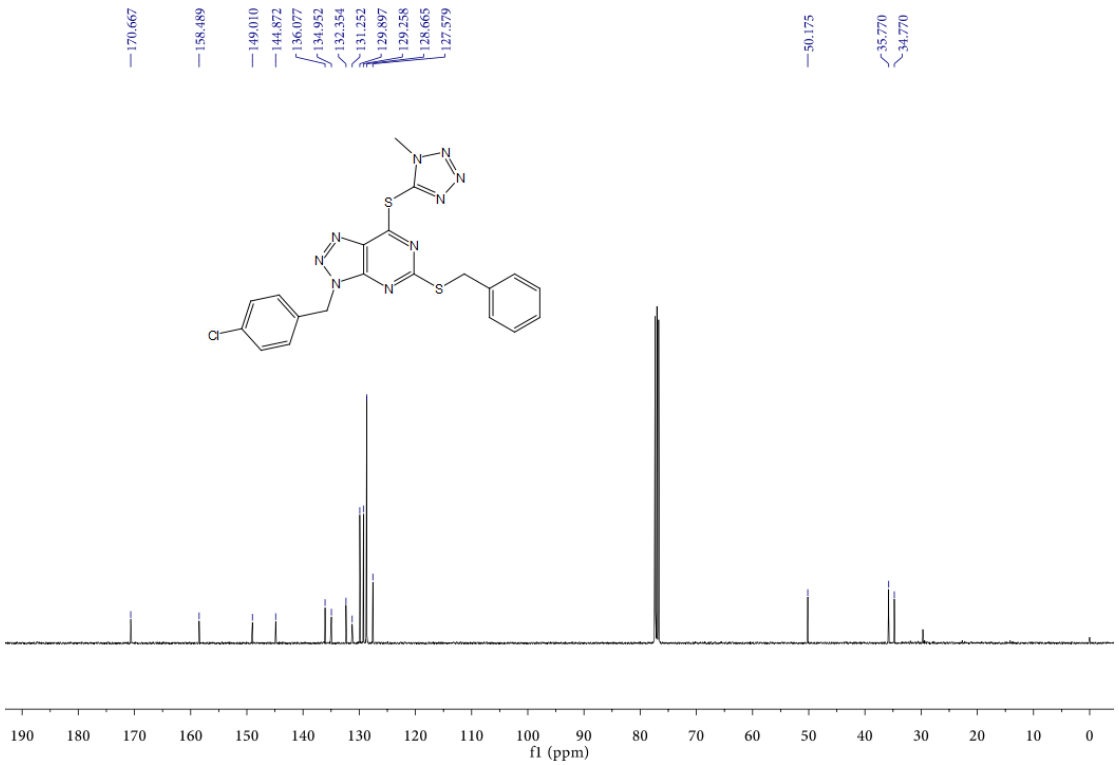


Figure S60 ^{1}H NMR spectrum of compound **15o**.

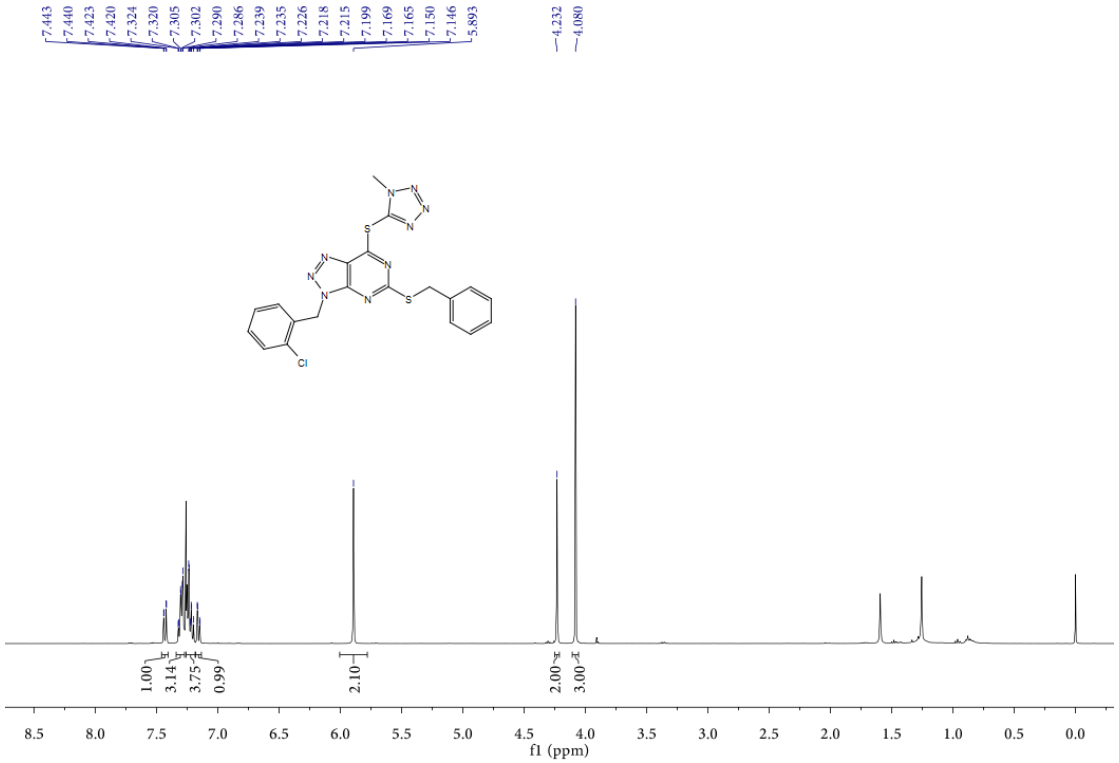


Figure S61 ^{13}C NMR spectrum of compound **15o**.

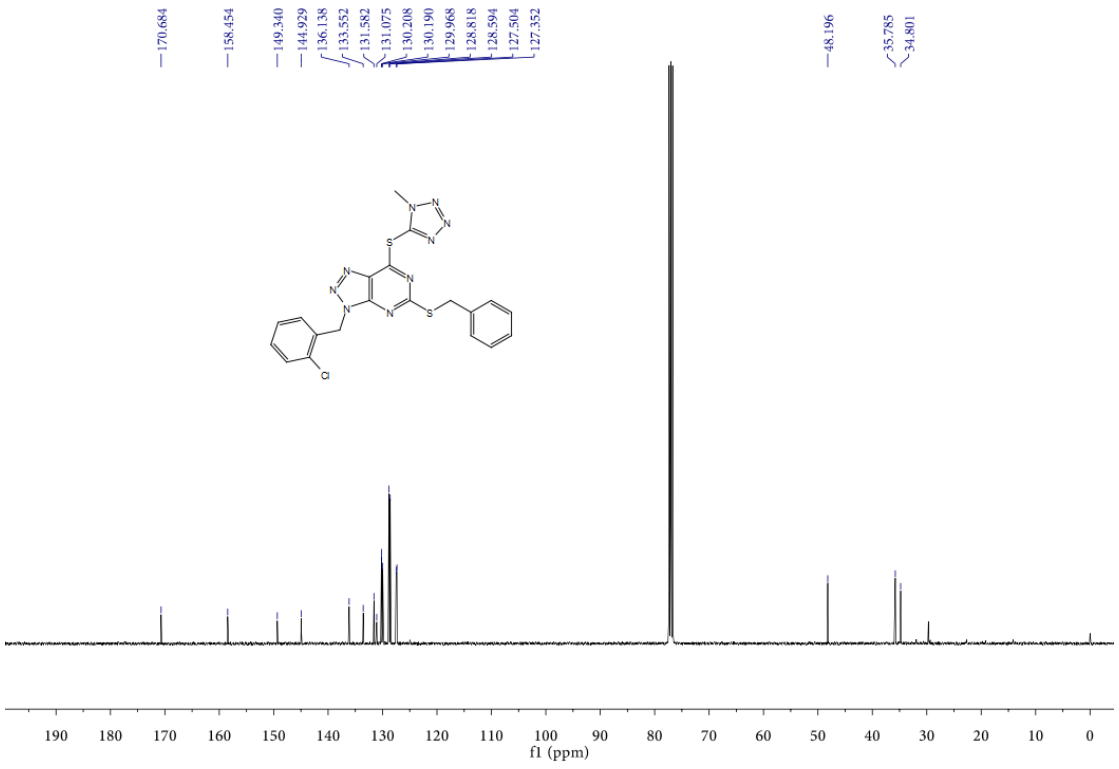


Figure S62 ^{1}H NMR spectrum of compound **15p**.

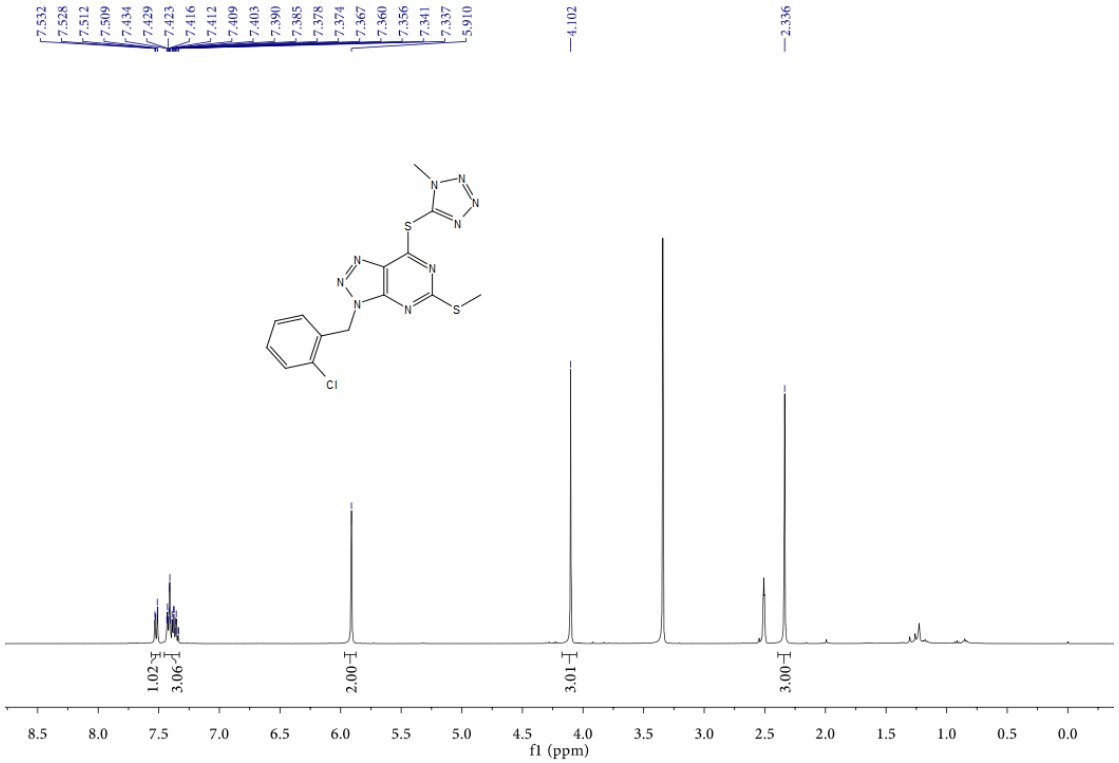


Figure S63 ^{13}C NMR spectrum of compound **15p**.

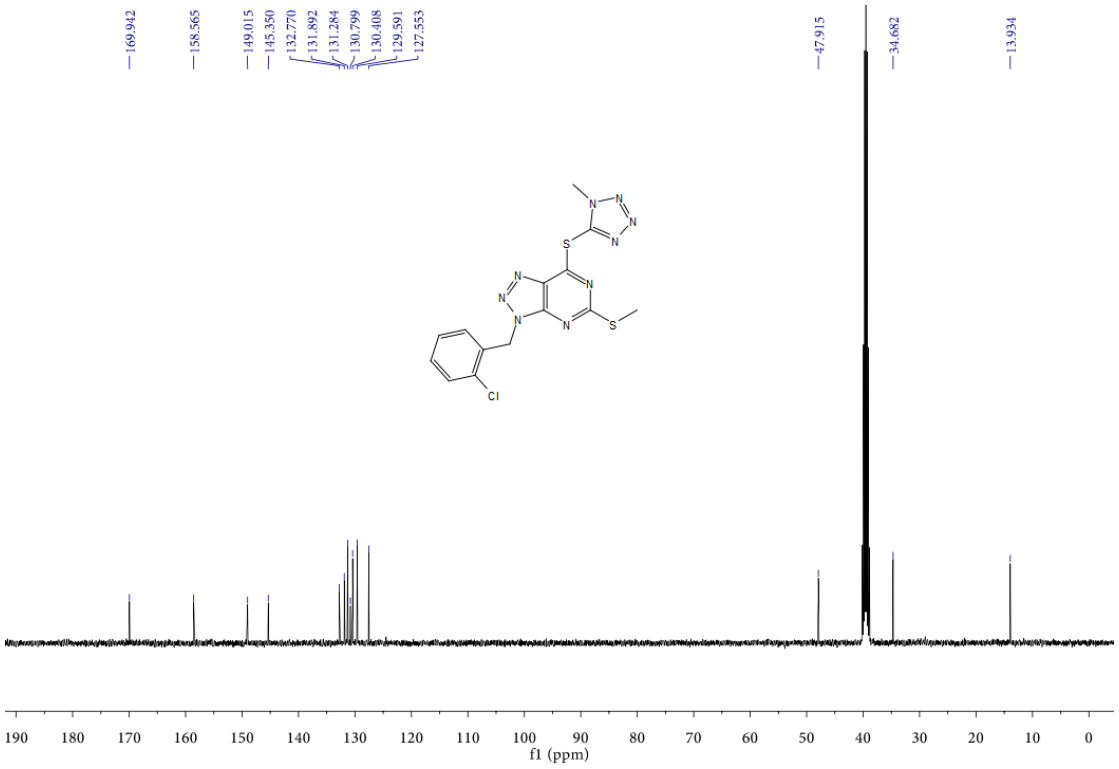


Figure S64 ^{1}H NMR spectrum of compound **15q**.

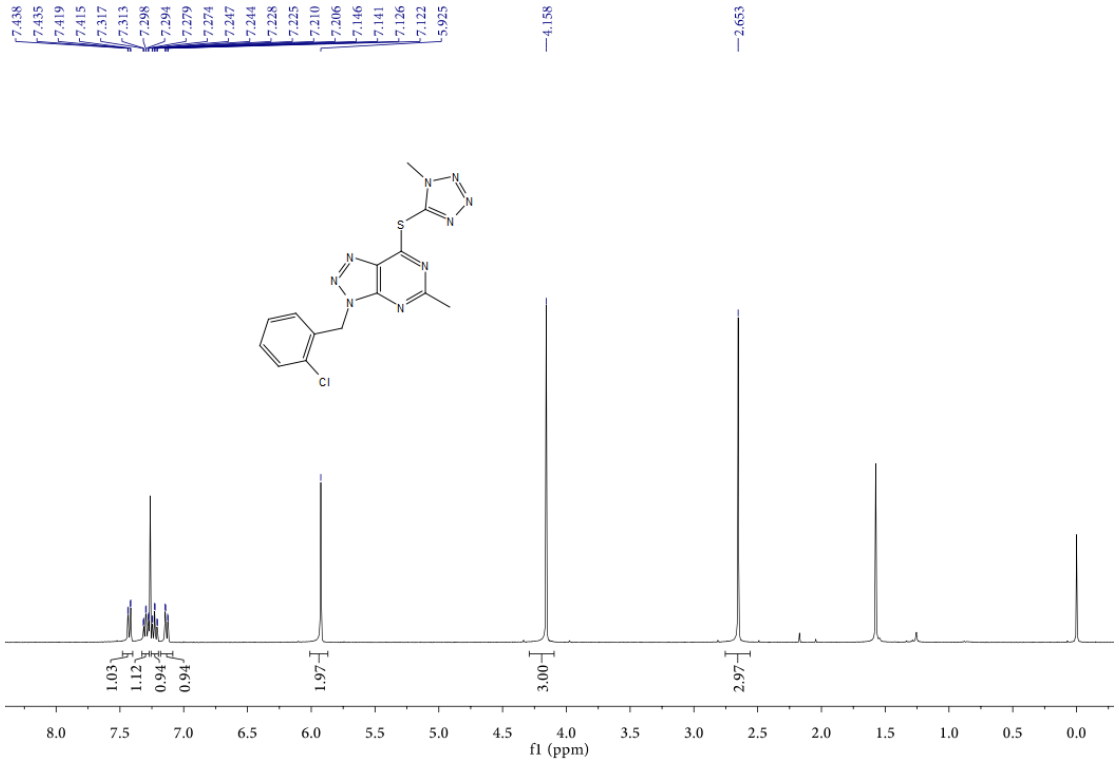


Figure S65 ^{13}C NMR spectrum of compound **15q**.

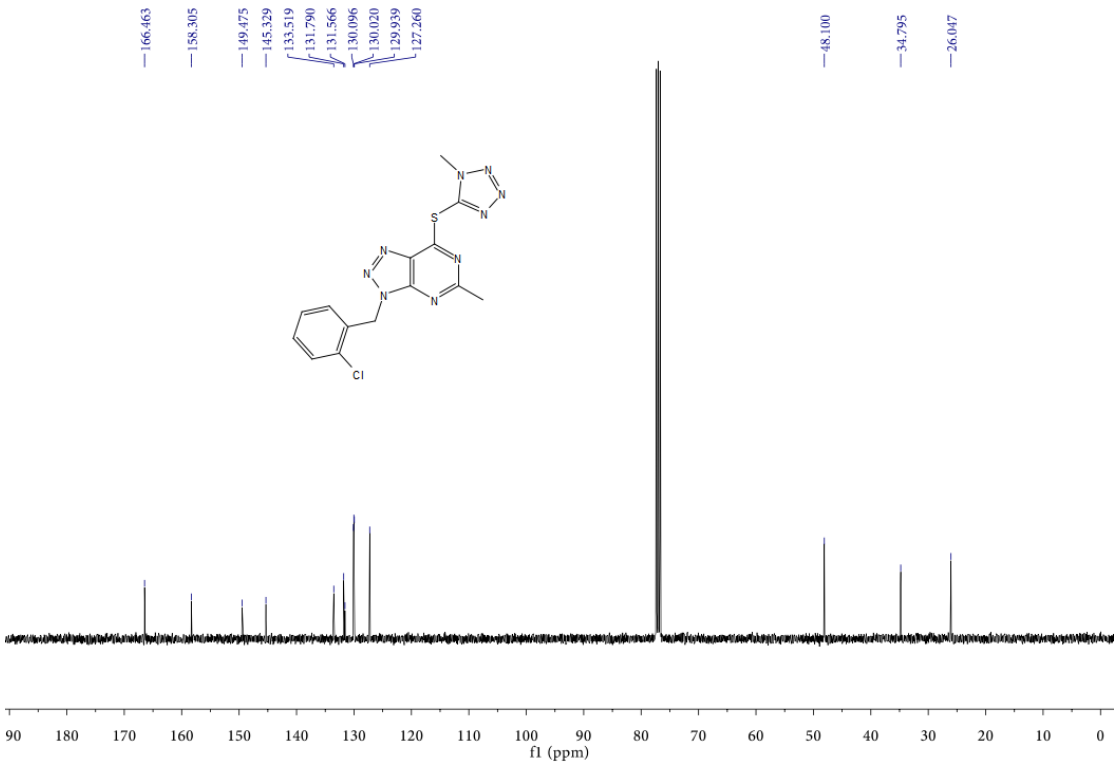


Figure S66 ^{1}H NMR spectrum of compound **15r**.

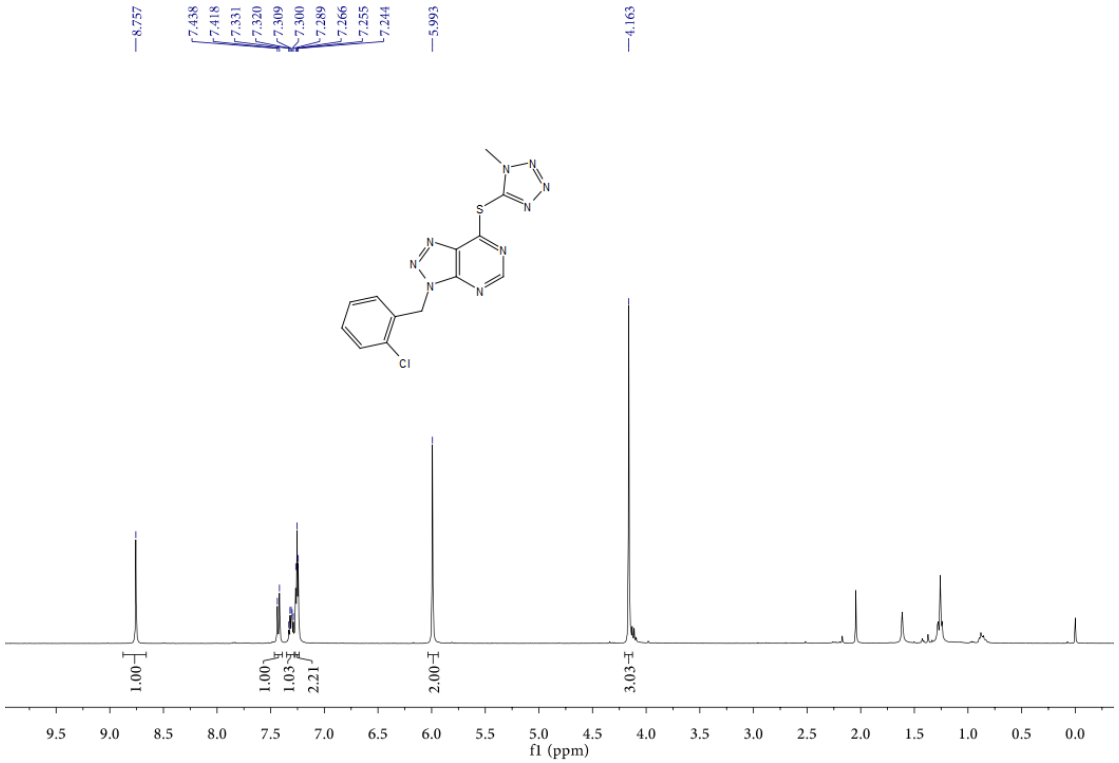


Figure S67 ^{13}C NMR spectrum of compound **15r**.

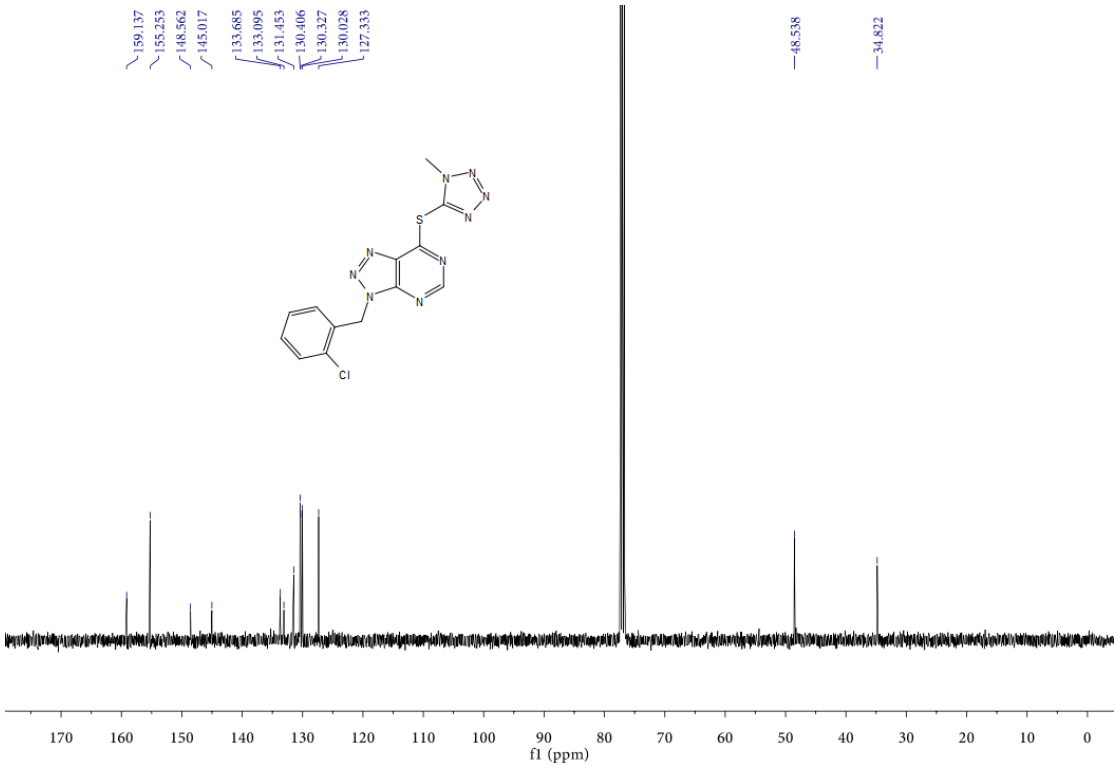


Figure S68 ^{1}H NMR spectrum of compound **15s**.

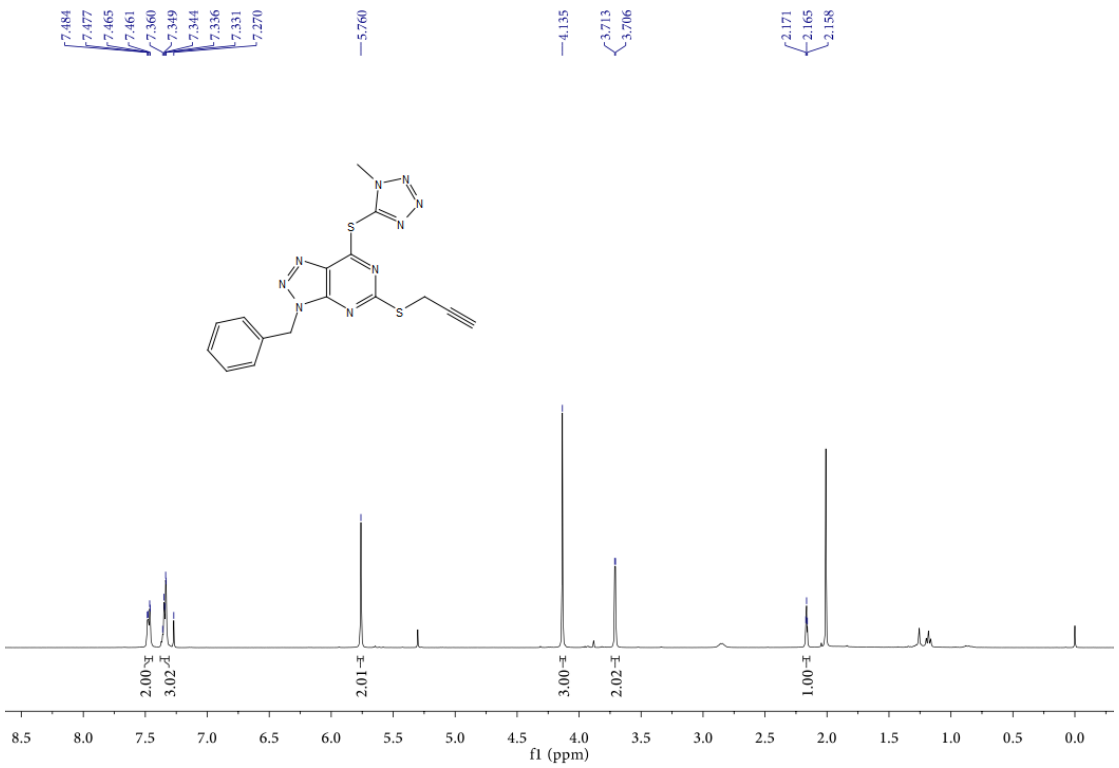


Figure S69 ^{13}C NMR spectrum of compound **15s**.

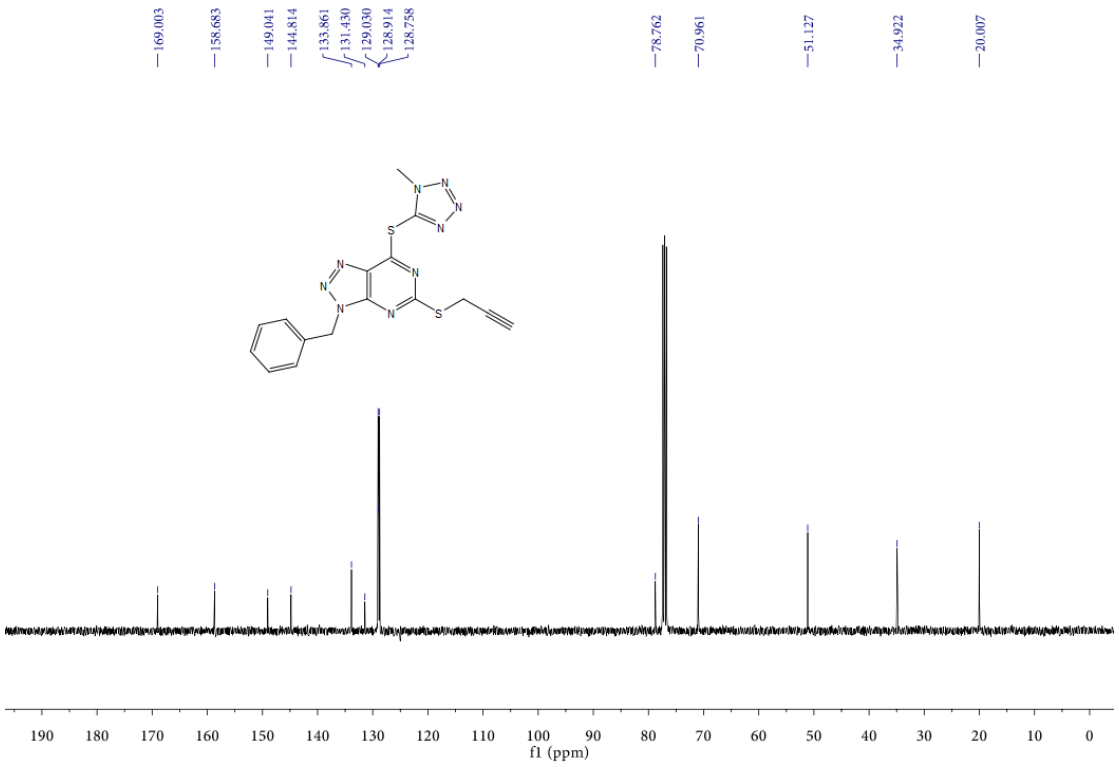


Figure S70 ^{1}H NMR spectrum of compound **17**.

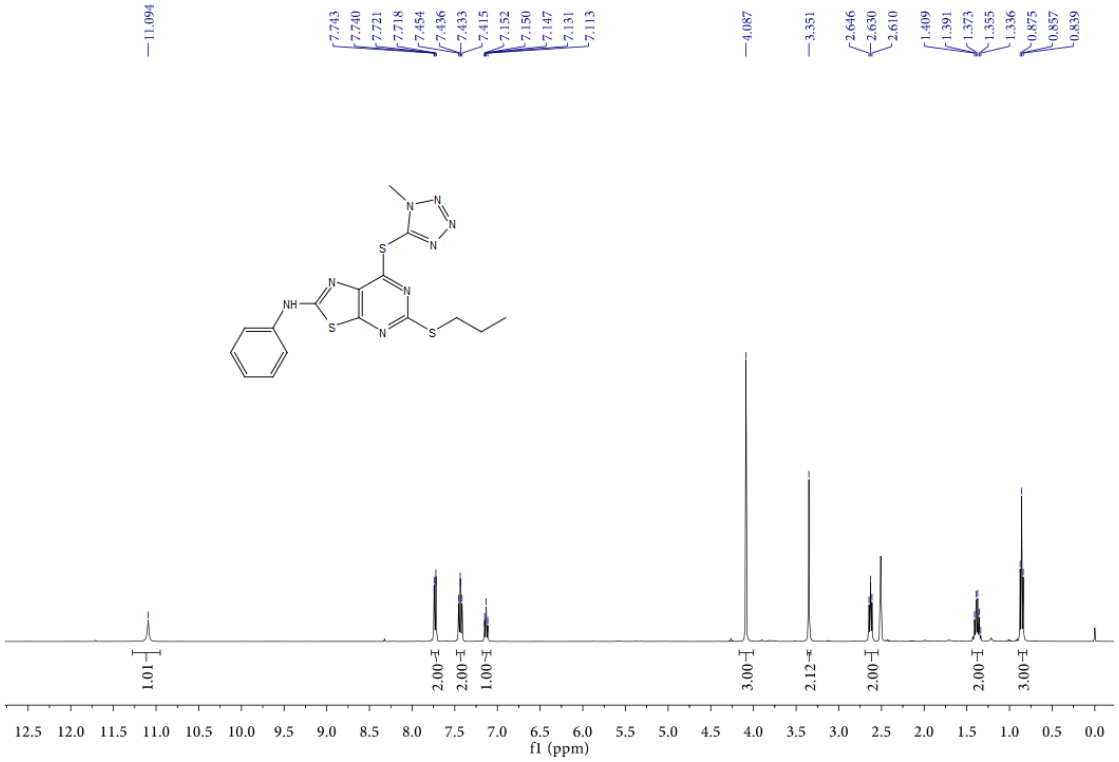


Figure S71 ^{13}C NMR spectrum of compound **17**.

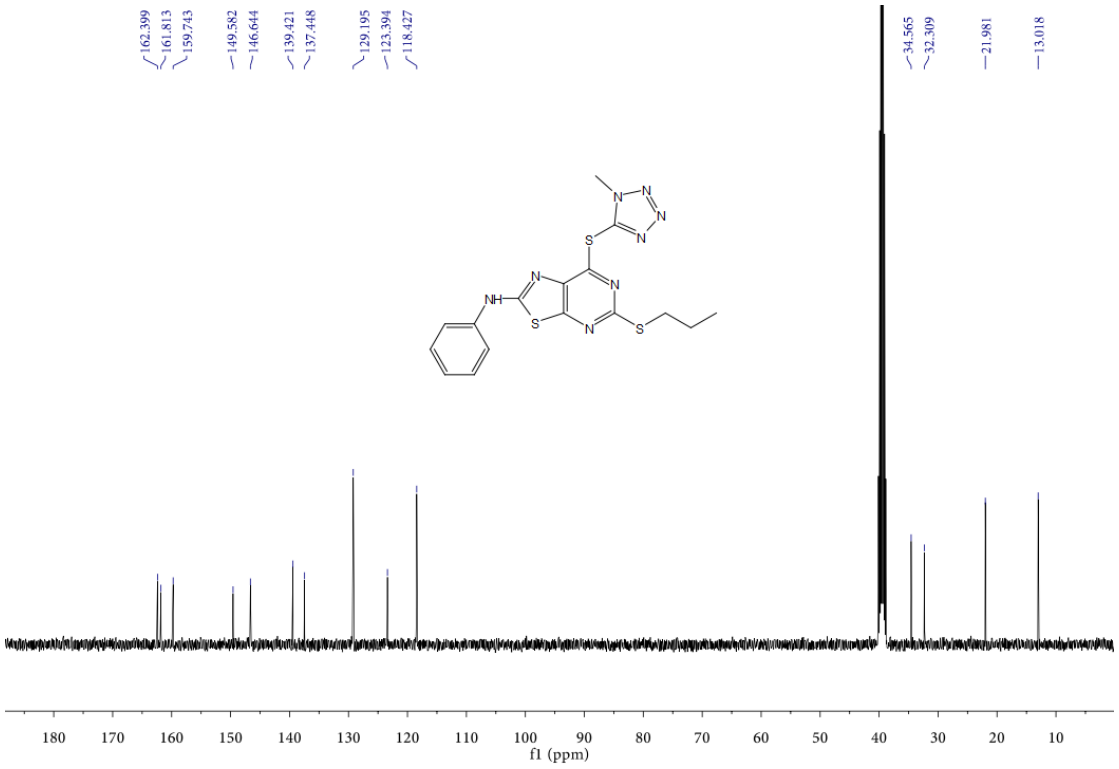


Figure S72 ^{1}H NMR spectrum of compound **19**.

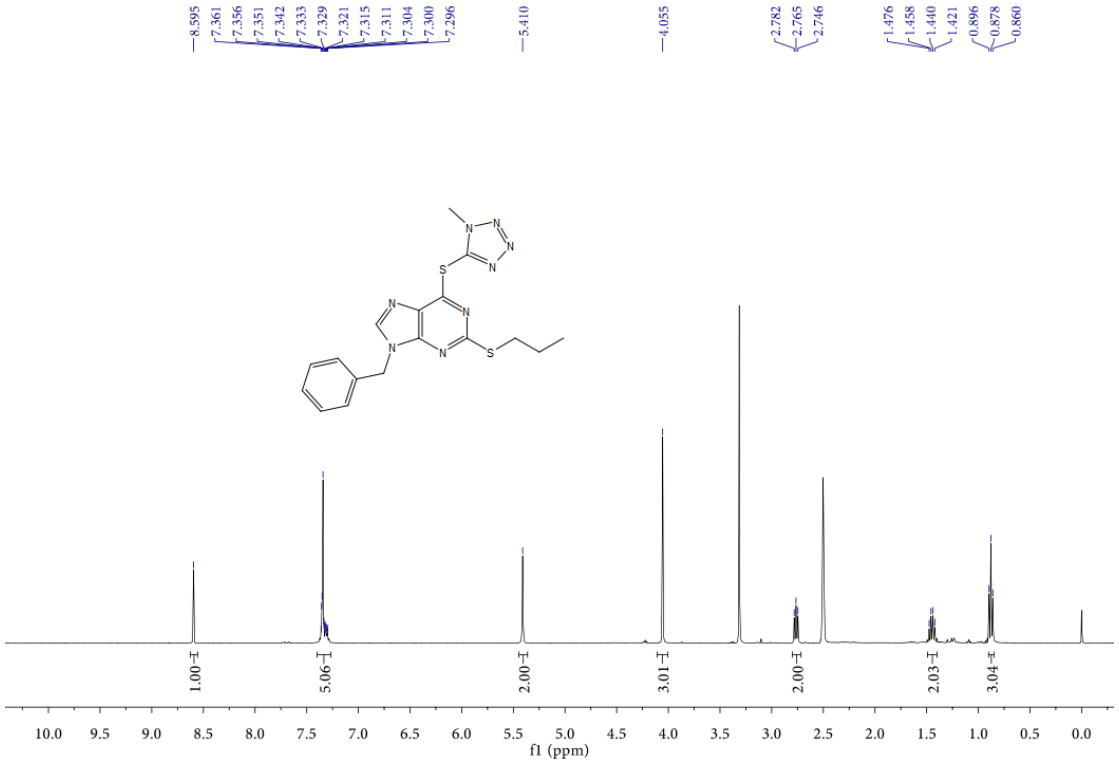


Figure S73 ^{13}C NMR spectrum of compound **19**.

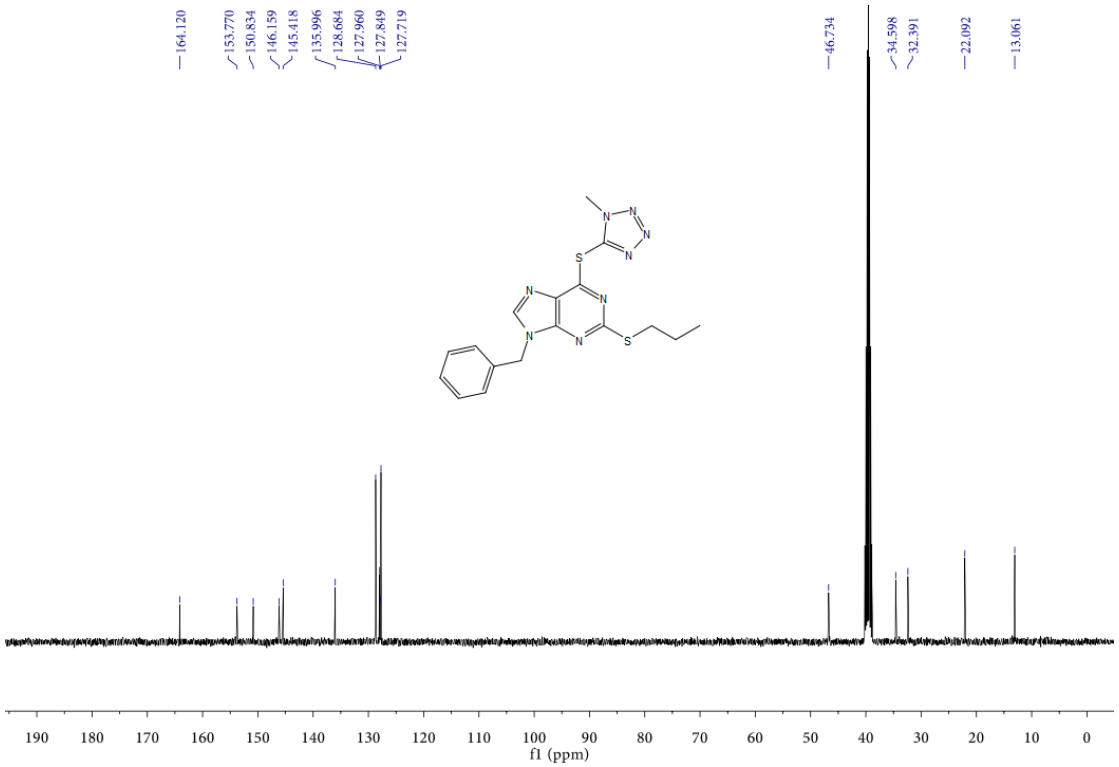


Figure S74 ^{1}H NMR spectrum of compound **15t**.

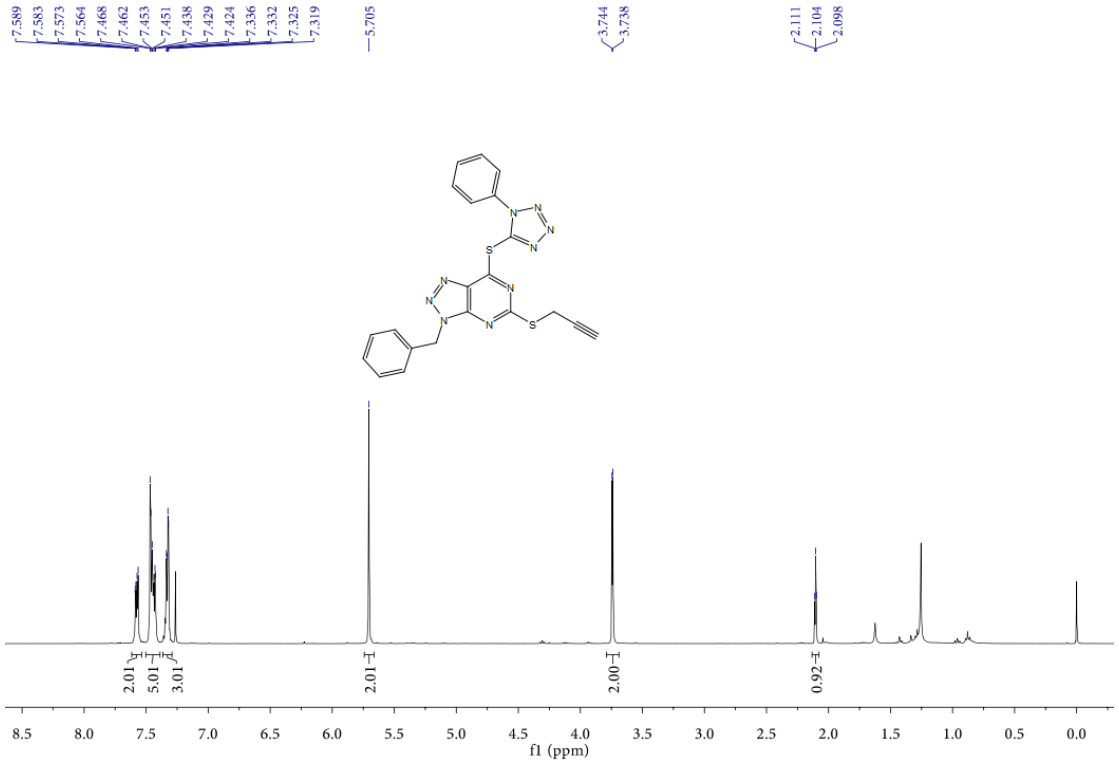


Figure S75 ^{13}C NMR spectrum of compound **15t**.

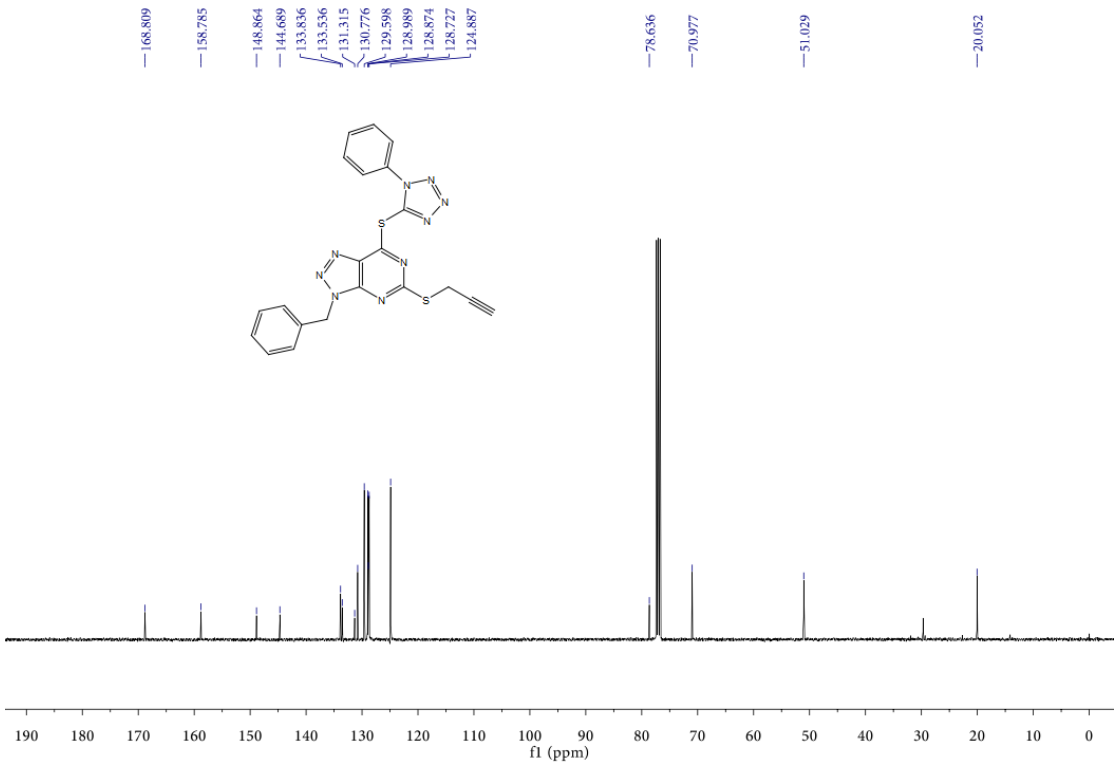


Figure S76 ^{1}H NMR spectrum of compound **15u**.

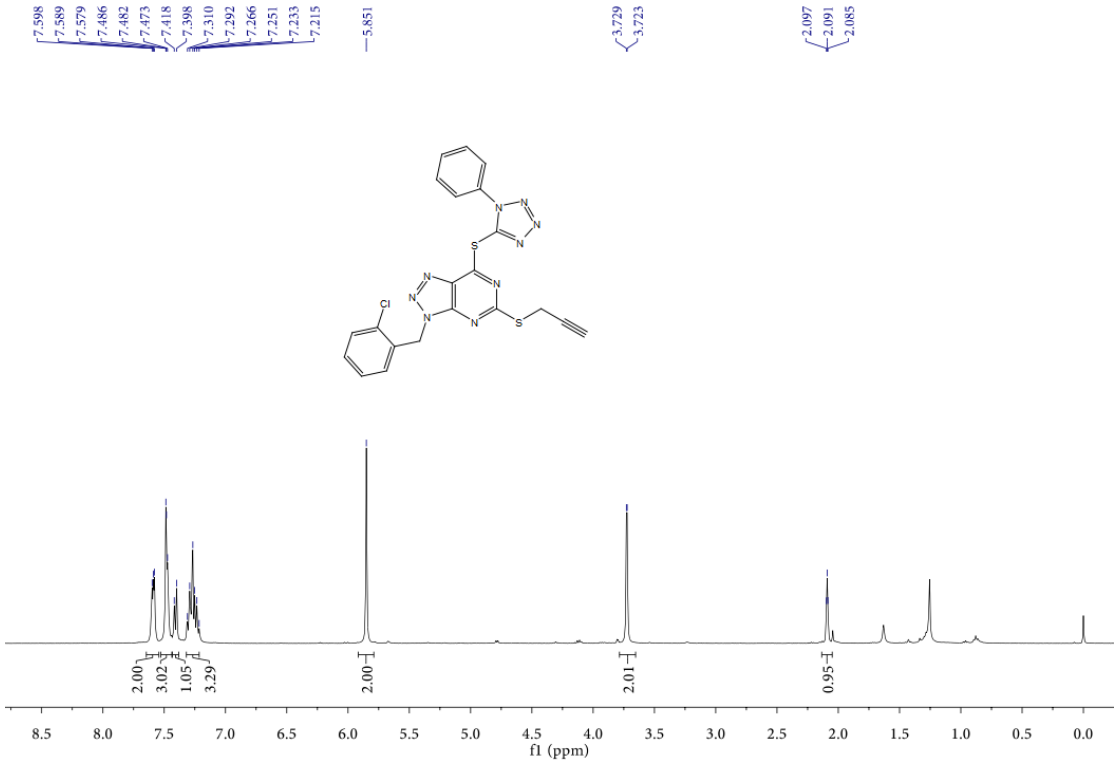


Figure S77 ^{13}C NMR spectrum of compound **15u**.

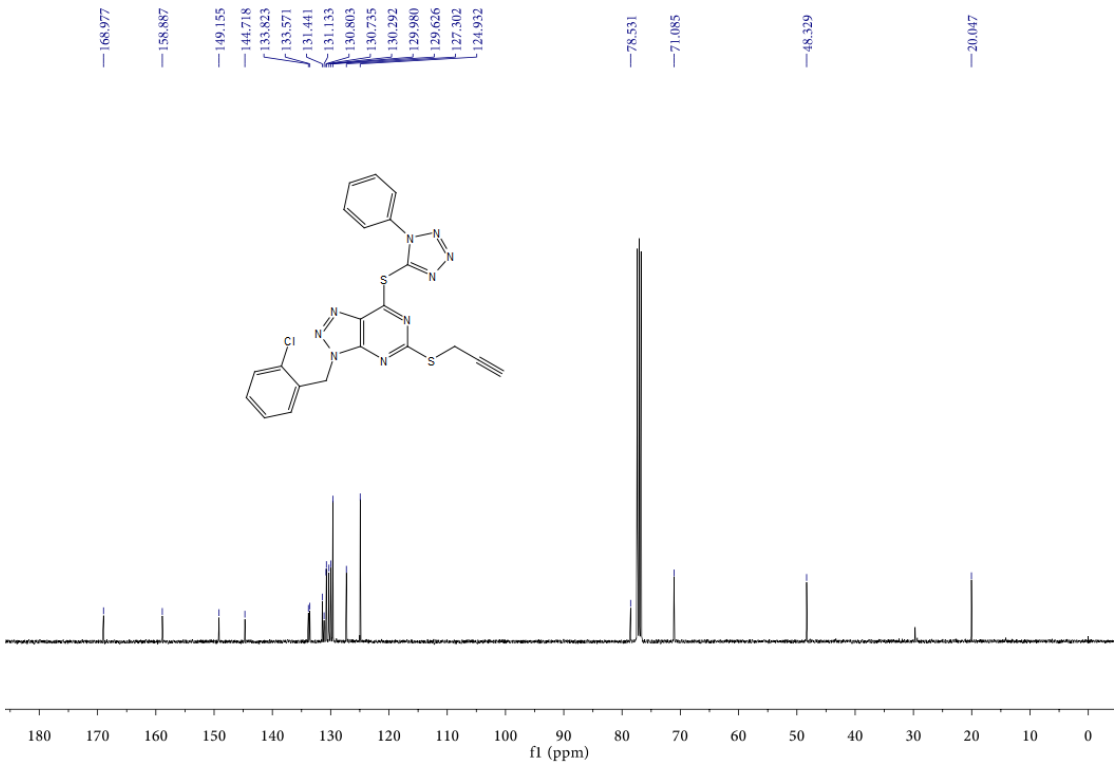


Figure S78 ^{1}H NMR spectrum of compound **15v**.

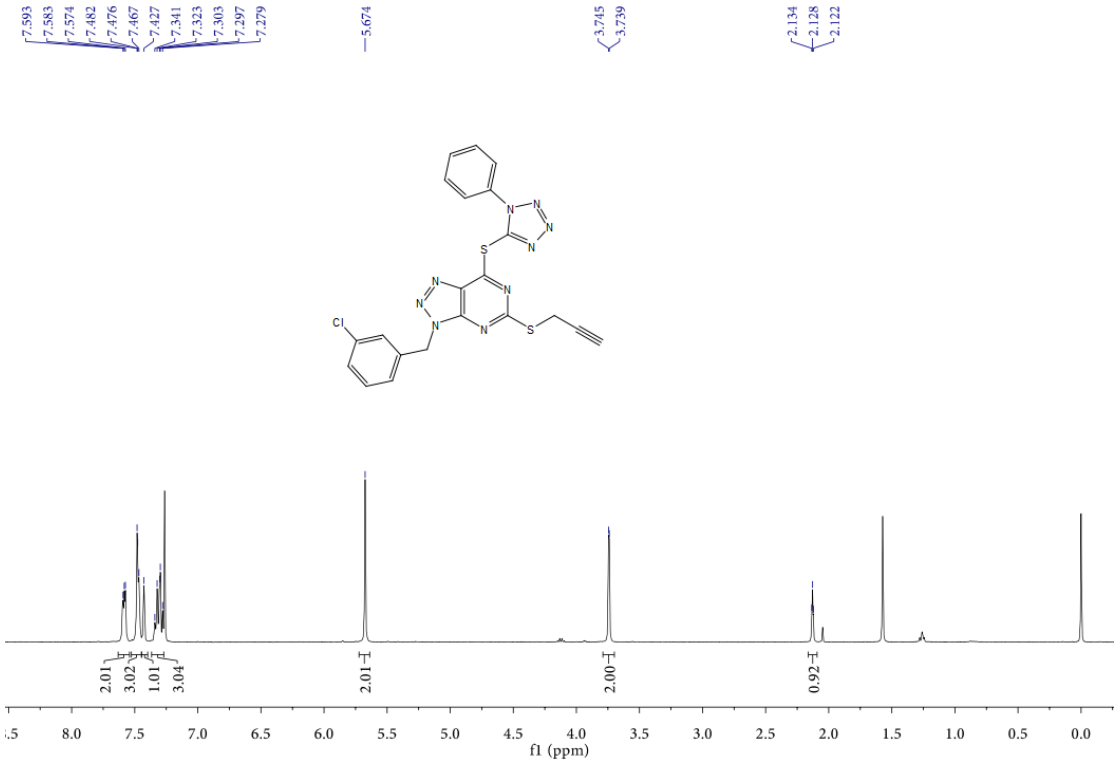


Figure S79 ^{13}C NMR spectrum of compound **15v**.

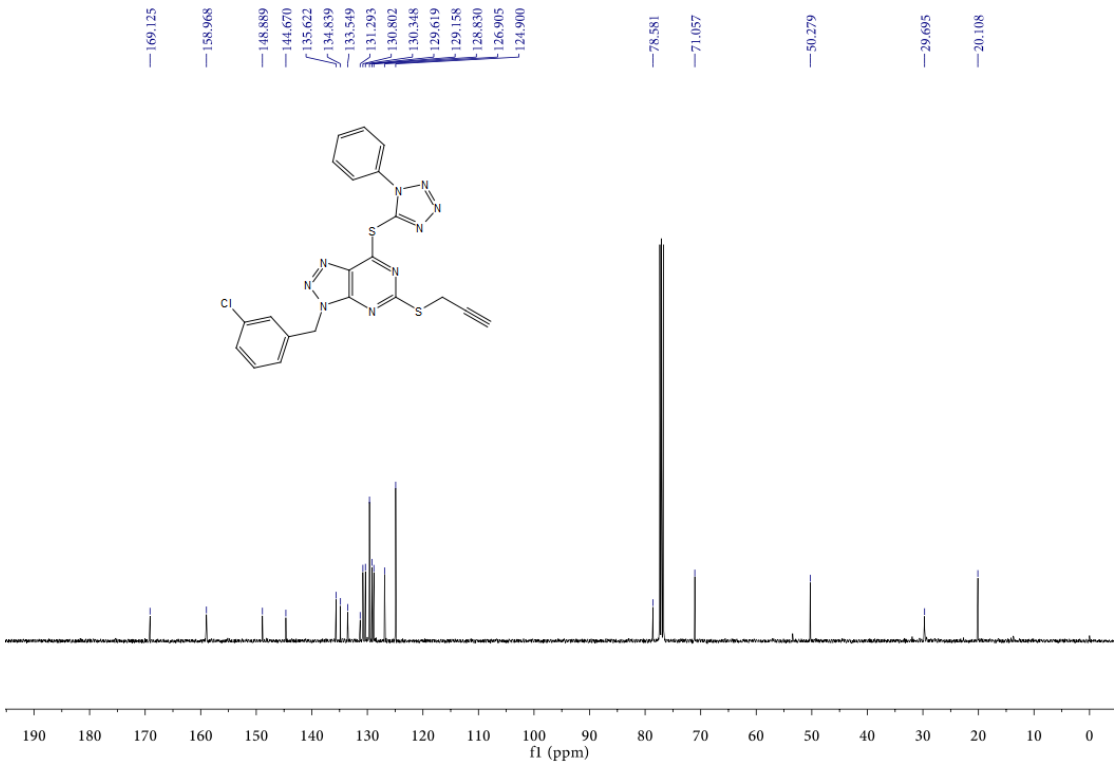


Figure S80 ^{1}H NMR spectrum of compound **15w**.

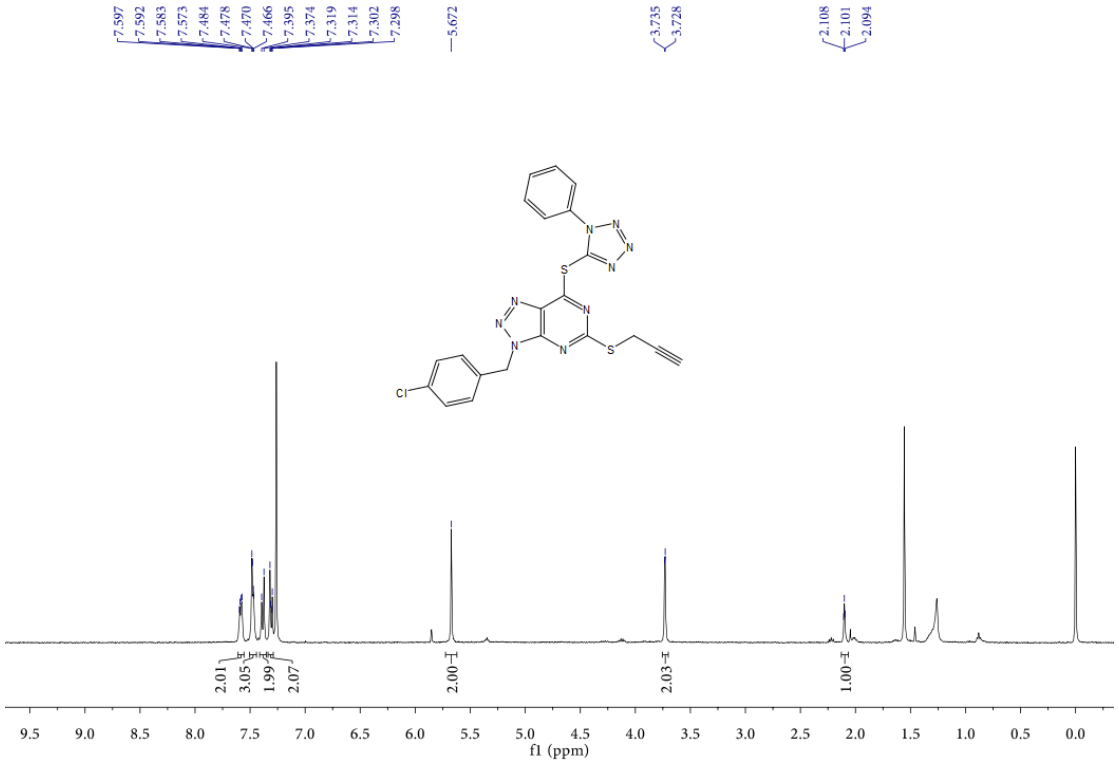


Figure S81 ^{13}C NMR spectrum of compound **15w**.

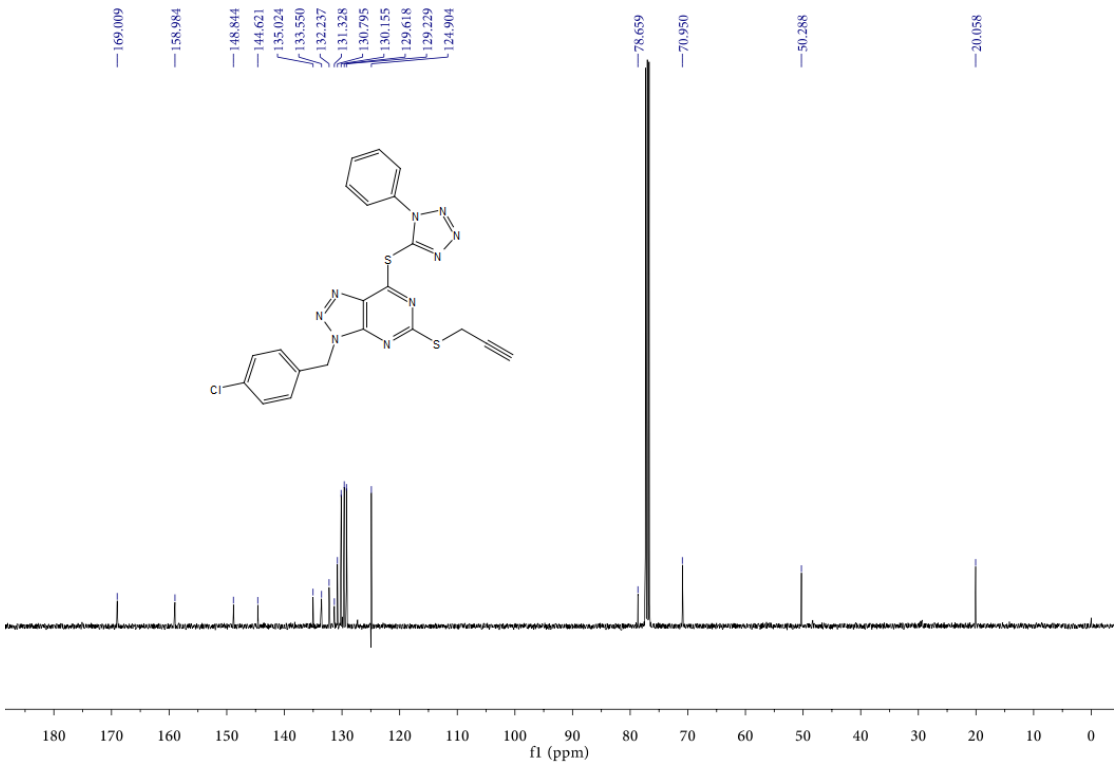


Figure S82 ^{1}H NMR spectrum of compound **15x**.

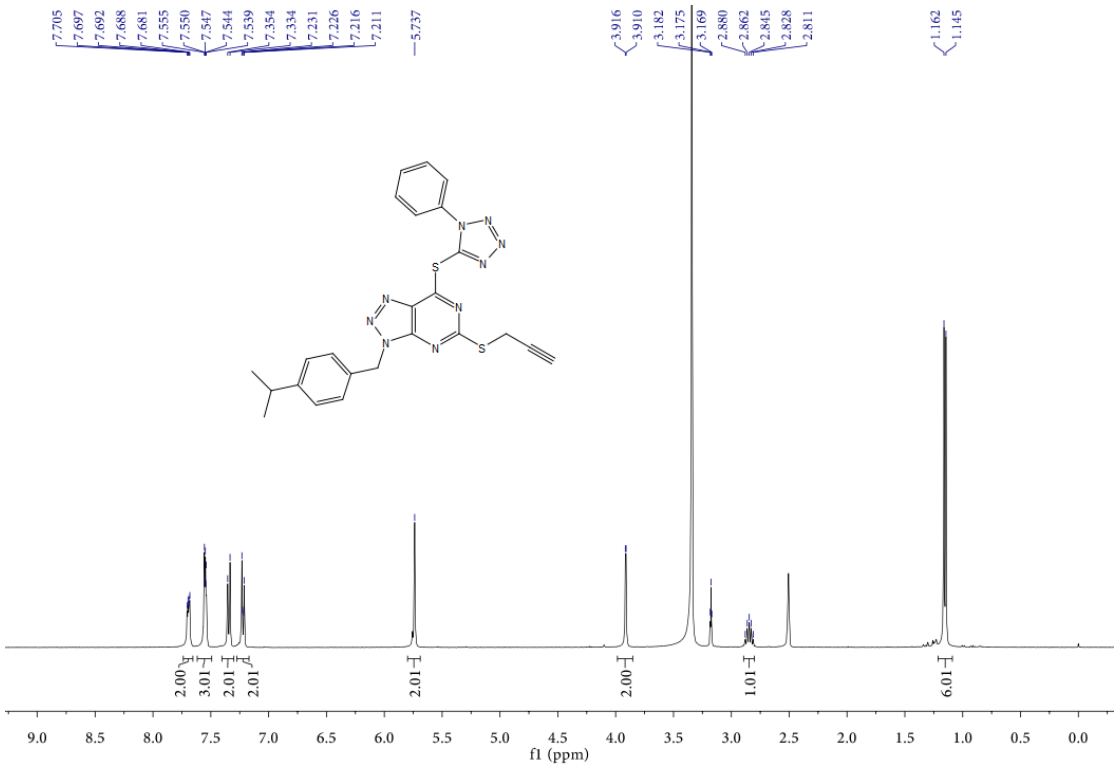


Figure S83 ^{13}C NMR spectrum of compound **15x**.

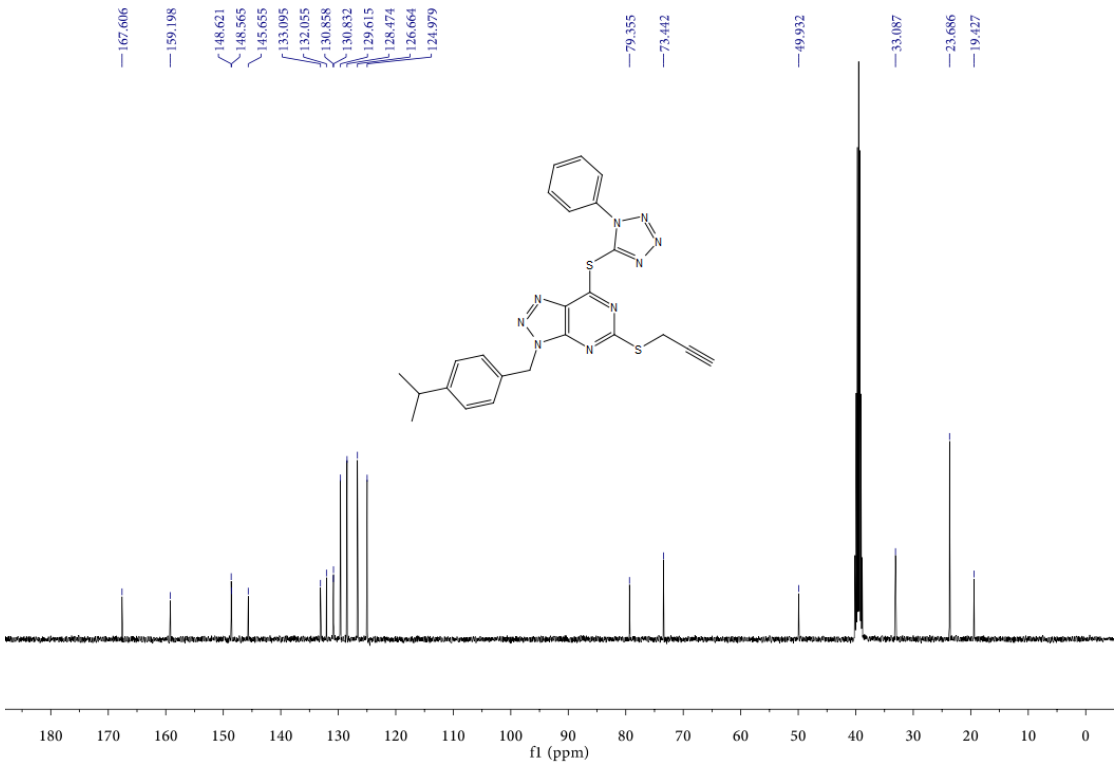


Figure S84 ^{1}H NMR spectrum of compound **15y**.

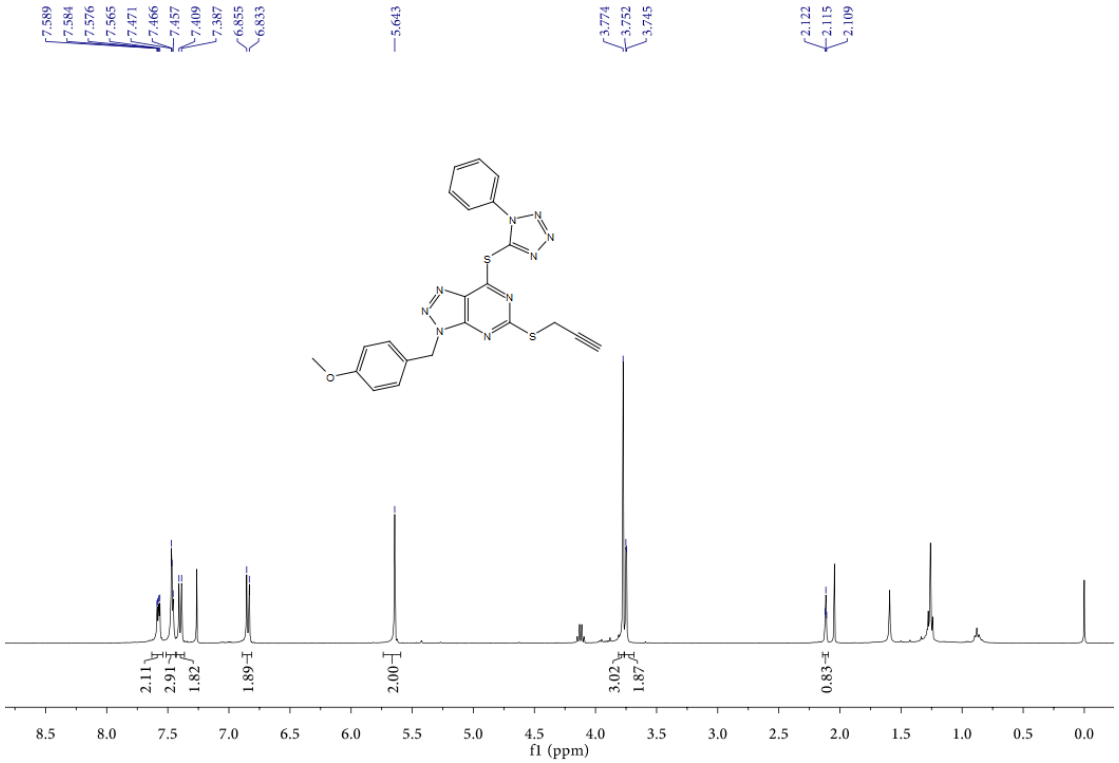


Figure S85 ^{13}C NMR spectrum of compound **15y**.

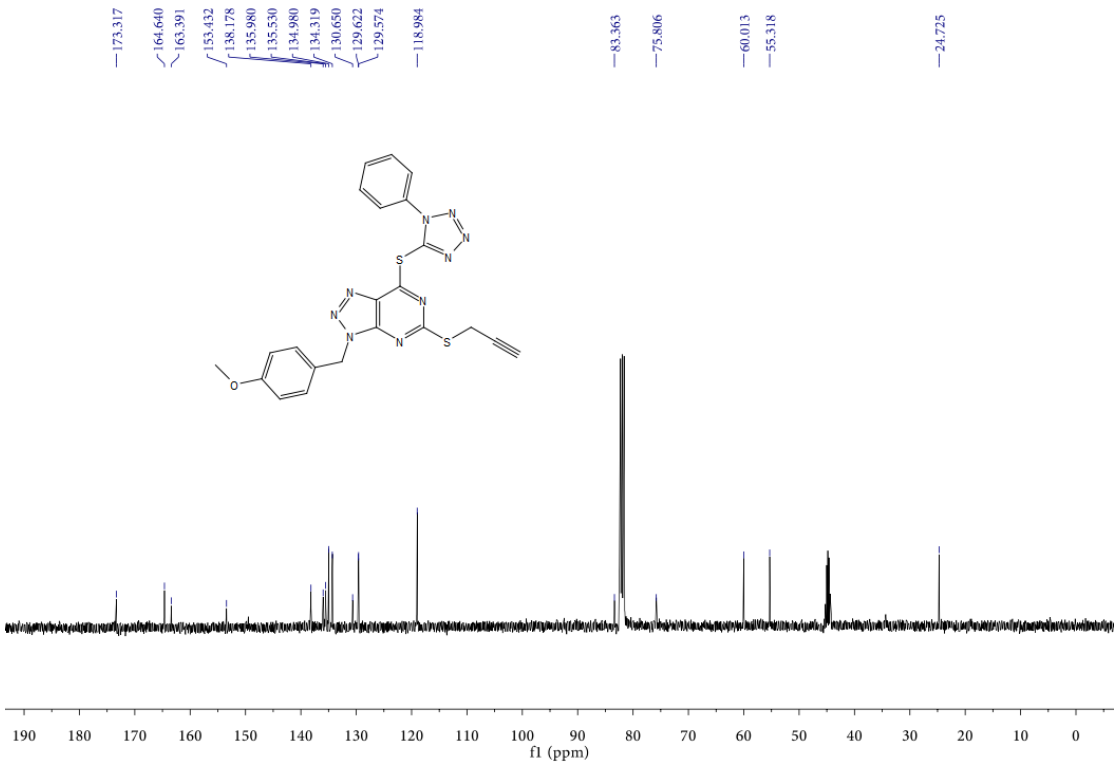


Figure S86 ^{1}H NMR spectrum of compound **15z**.

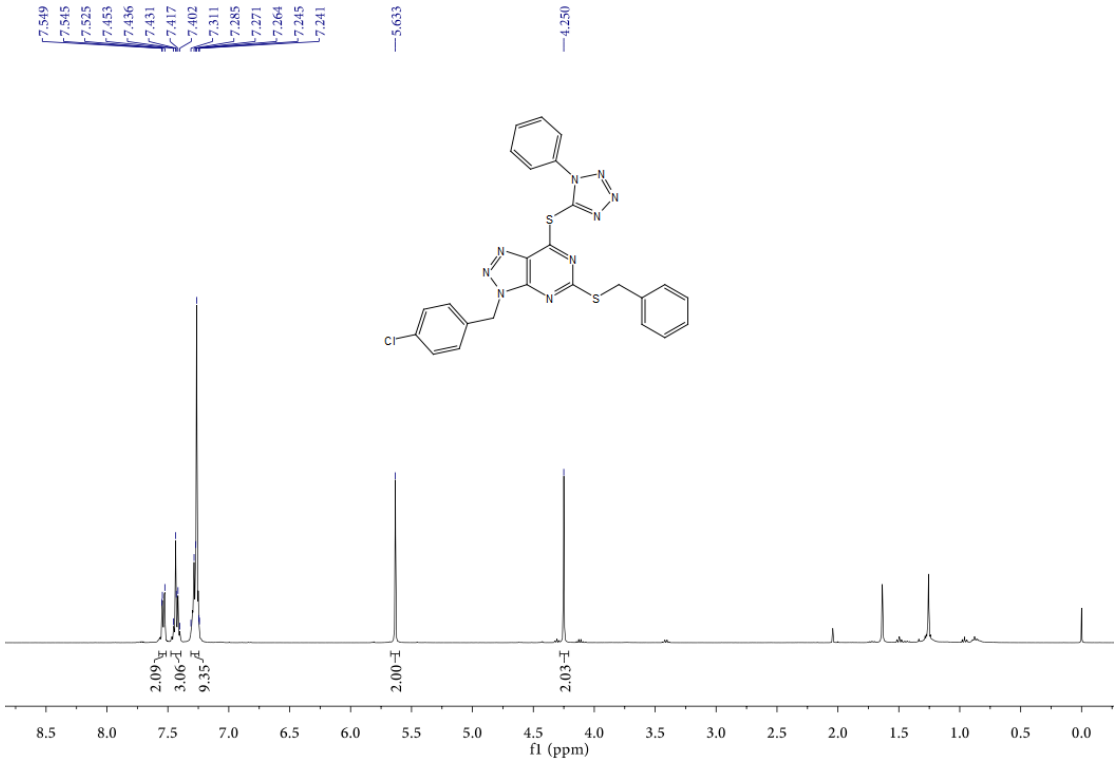


Figure S87 ^{13}C NMR spectrum of compound **15z**.

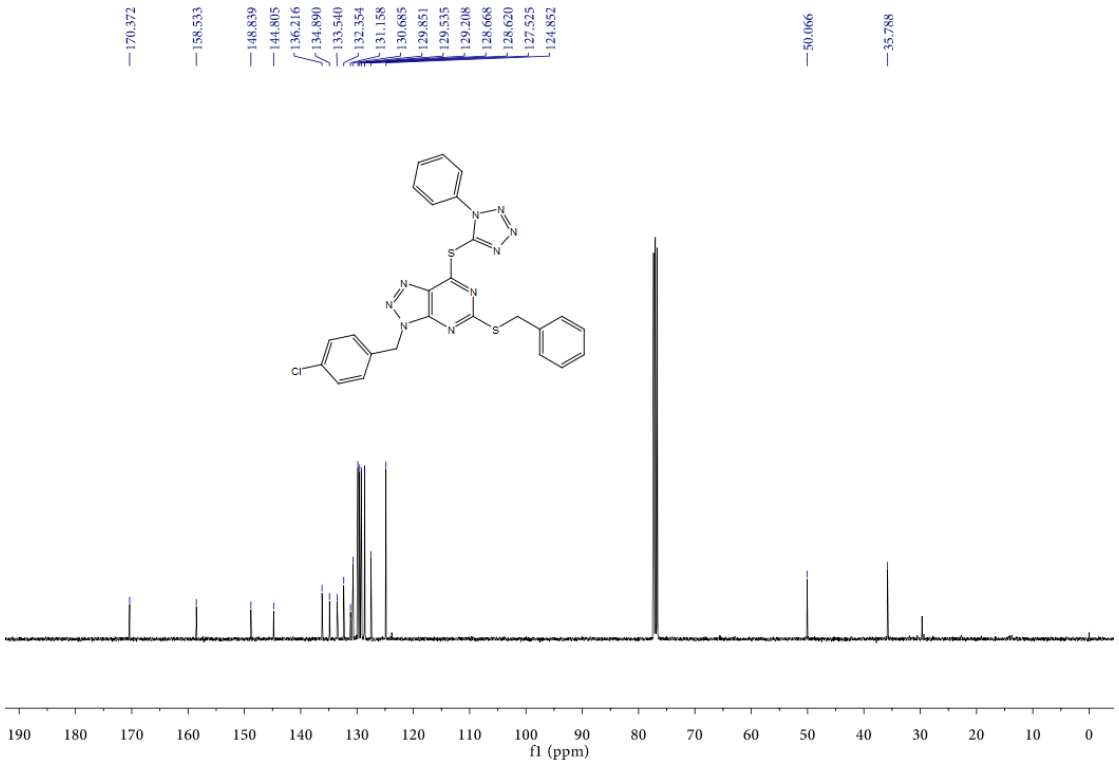


Figure S88 ^{1}H NMR spectrum of compound **15aa**.

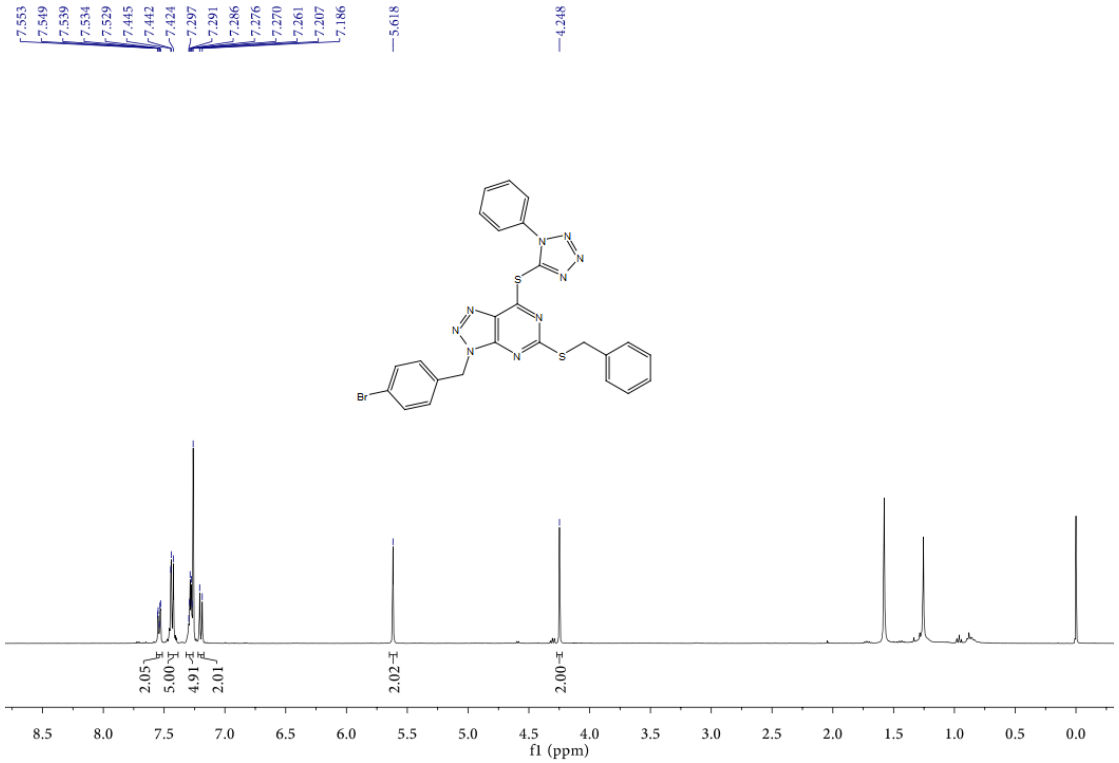


Figure S89 ^{13}C NMR spectrum of compound **15aa**.

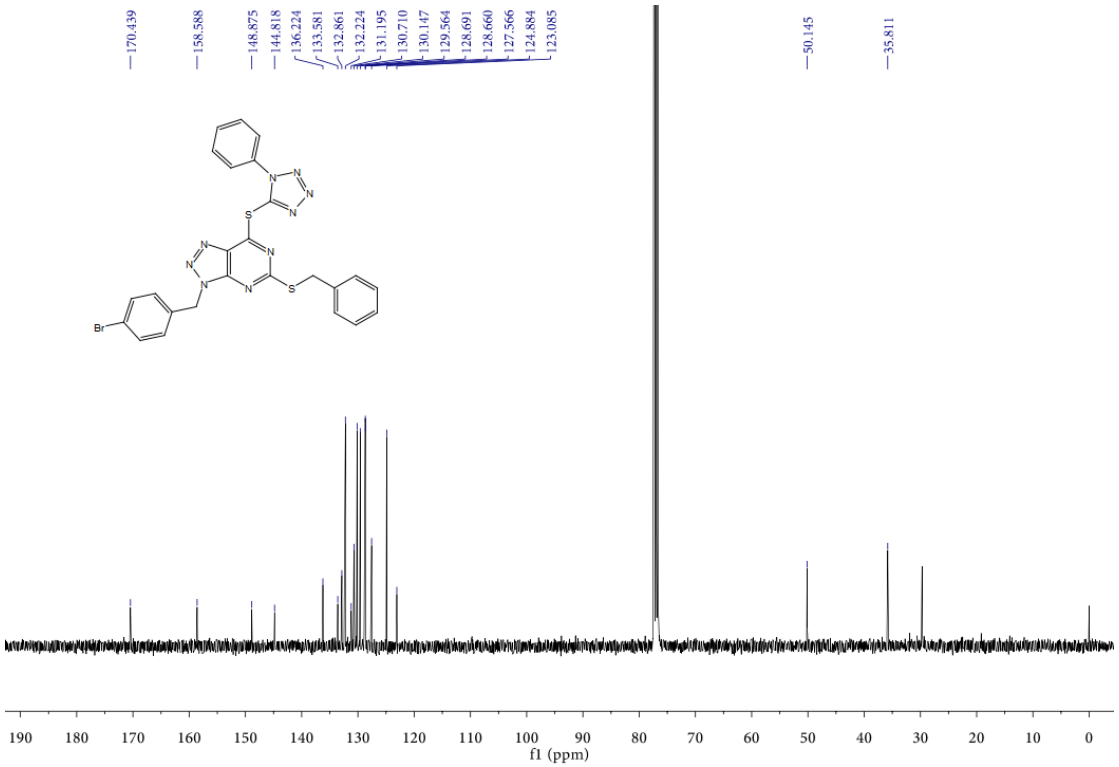


Figure S90 ^{1}H NMR spectrum of compound **15ab**.

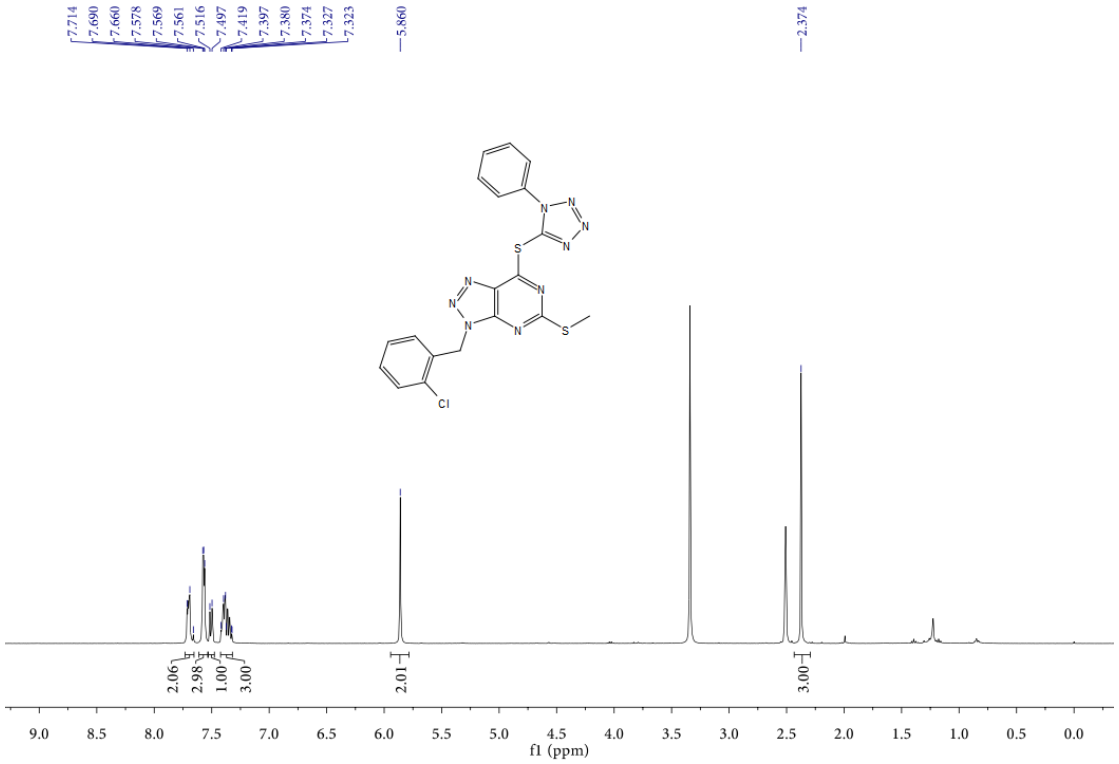


Figure S91 ^{13}C NMR spectrum of compound **15ab**.

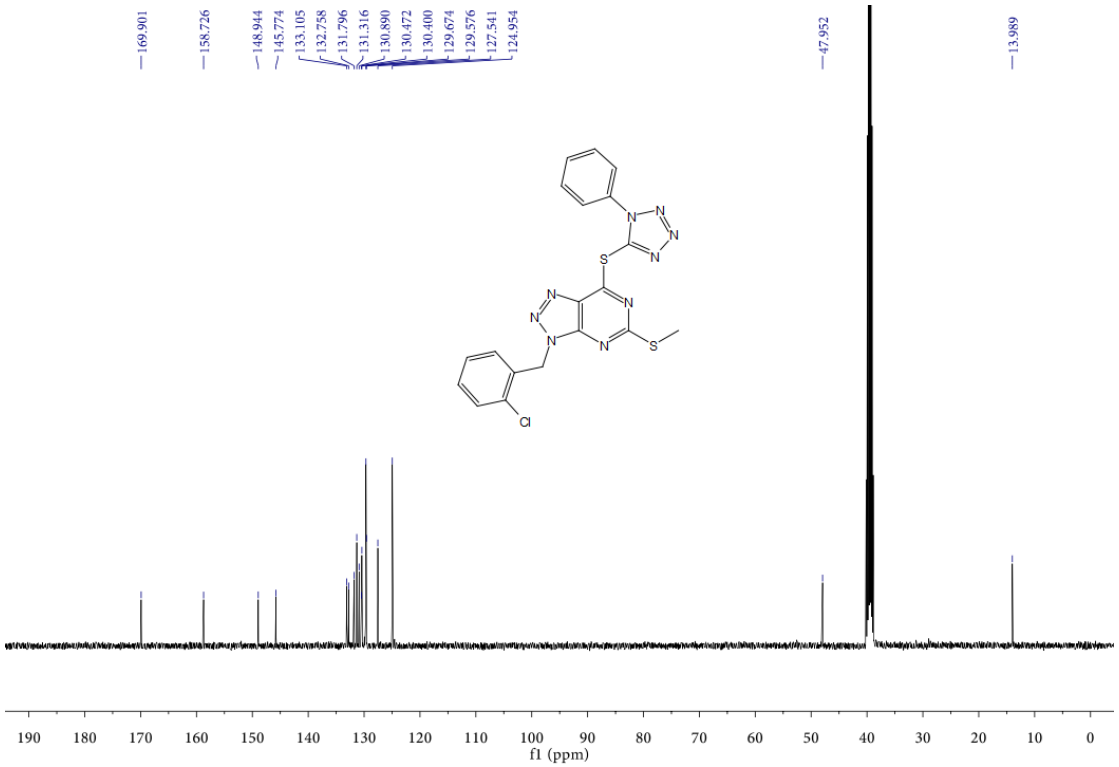


Figure S92 ^{1}H NMR spectrum of compound **15ac**.

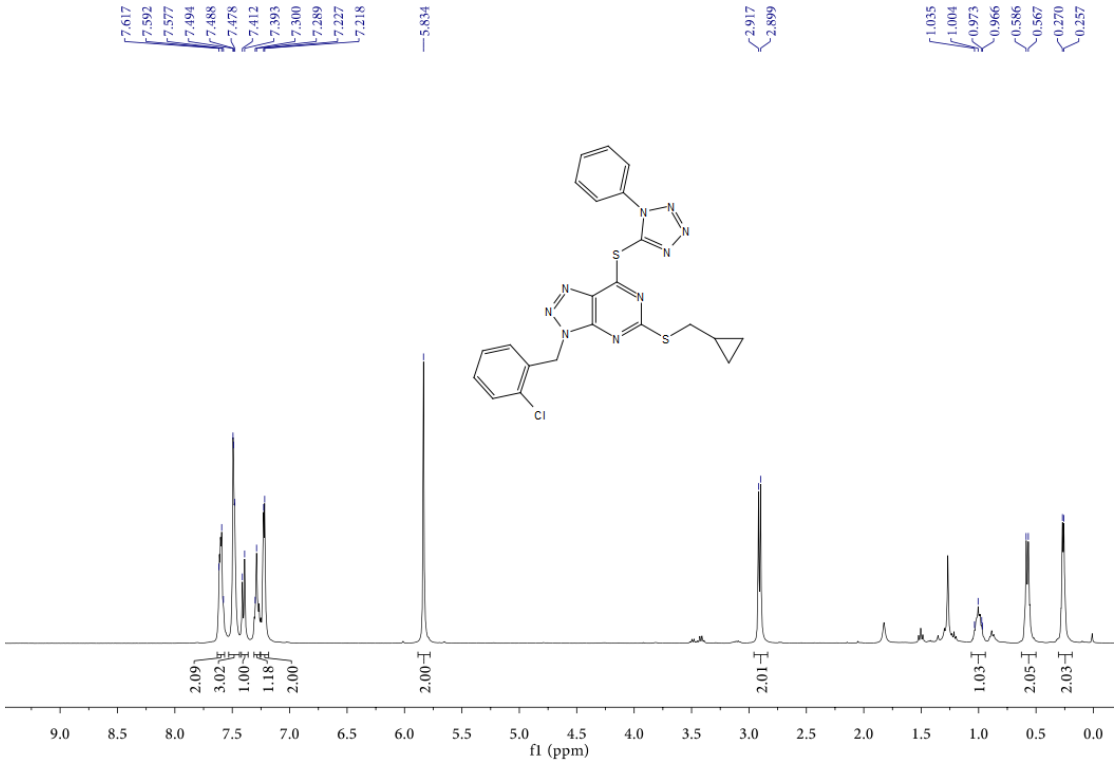


Figure S93 ^{13}C NMR spectrum of compound **15ac**.

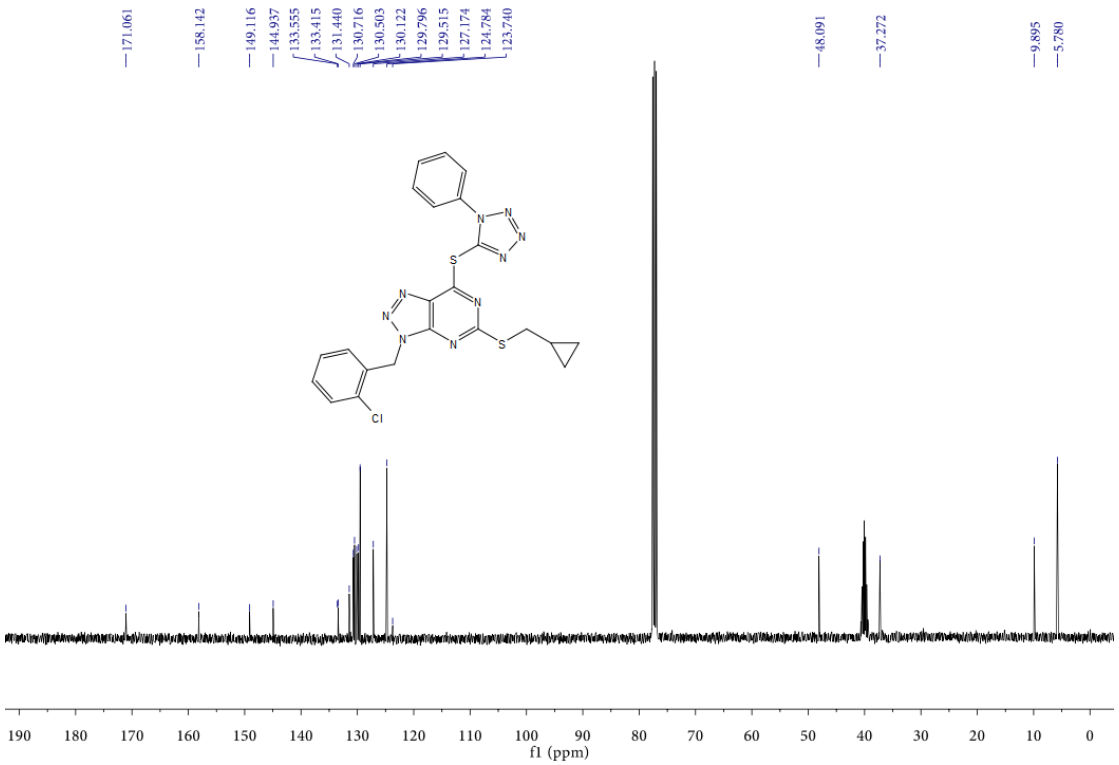


Figure S94 ^{1}H NMR spectrum of compound **15ad**.

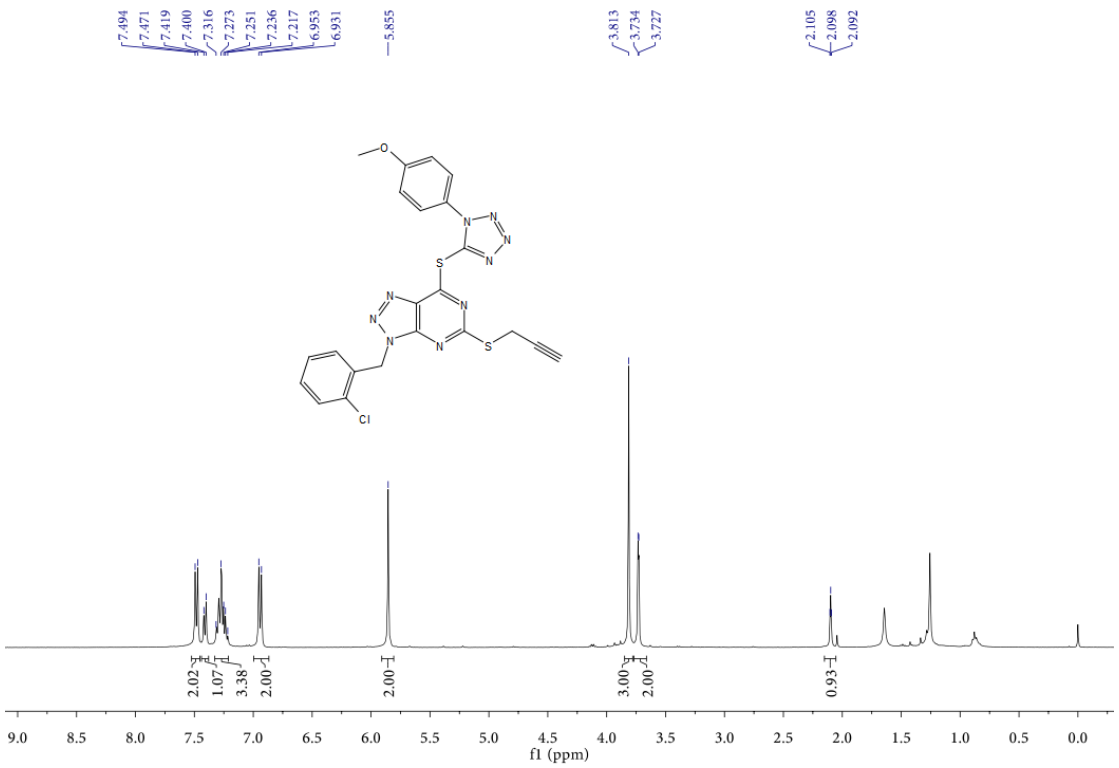


Figure S95 ^{13}C NMR spectrum of compound **15ad**.

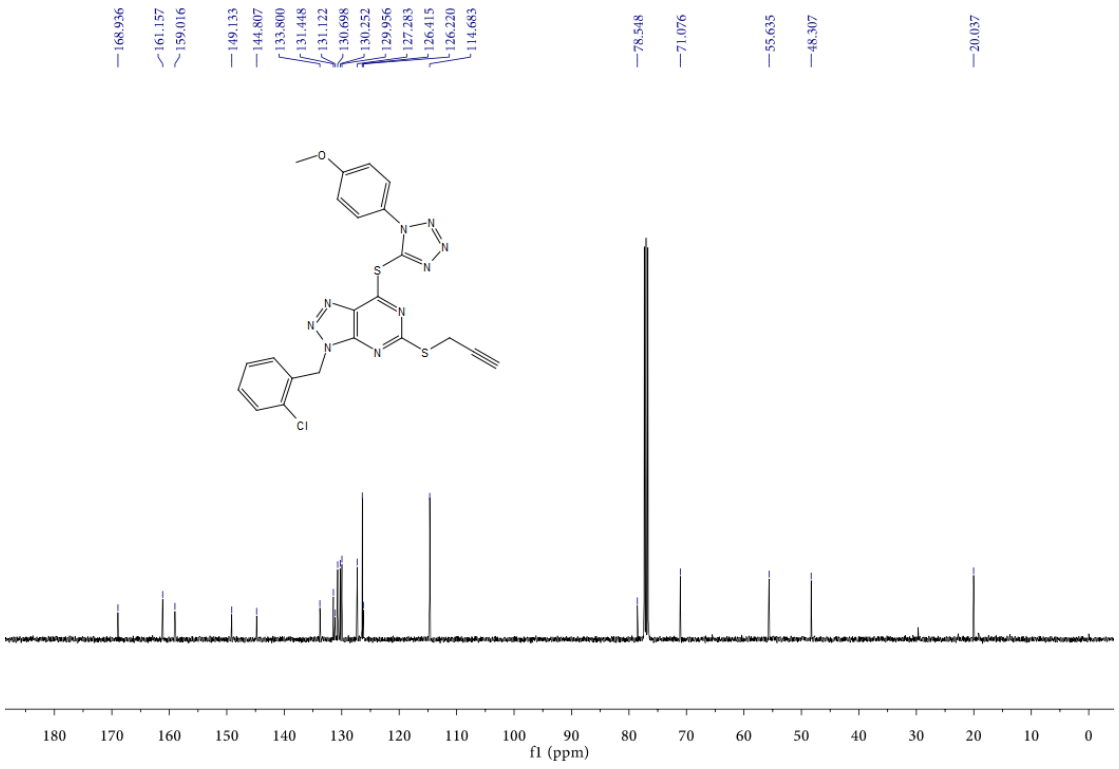


Figure S96 ^{1}H NMR spectrum of compound **15ae**.

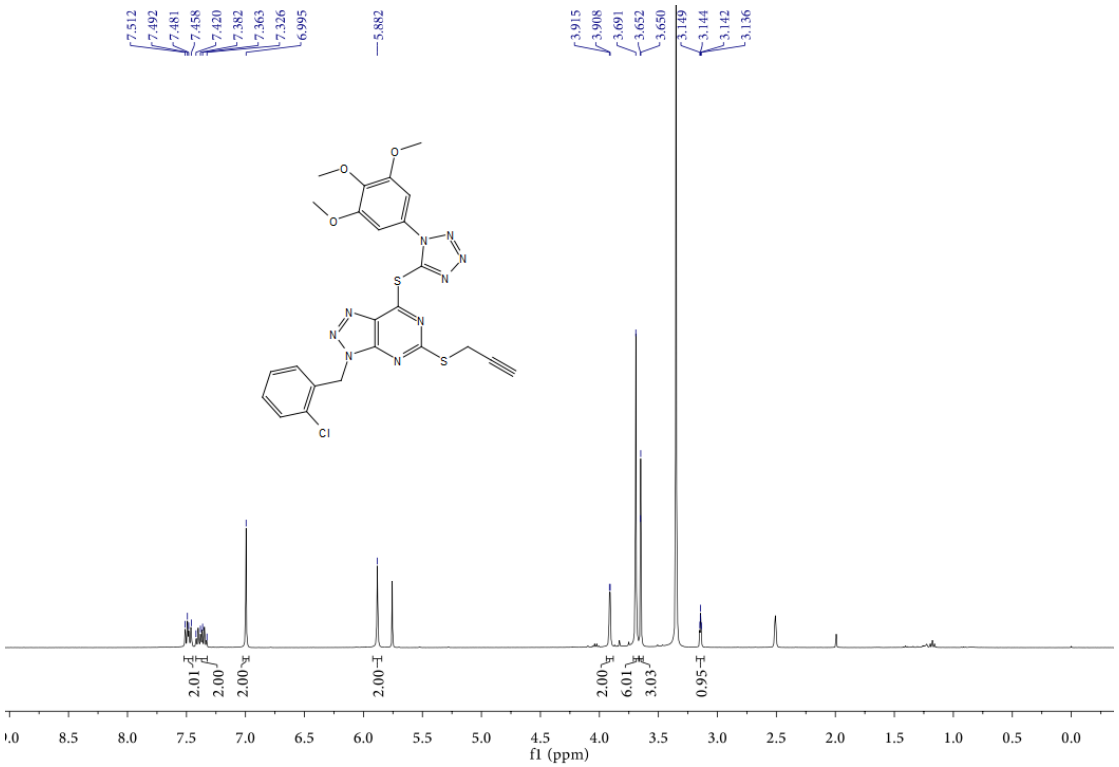


Figure S97 ^{13}C NMR spectrum of compound **15ae**.

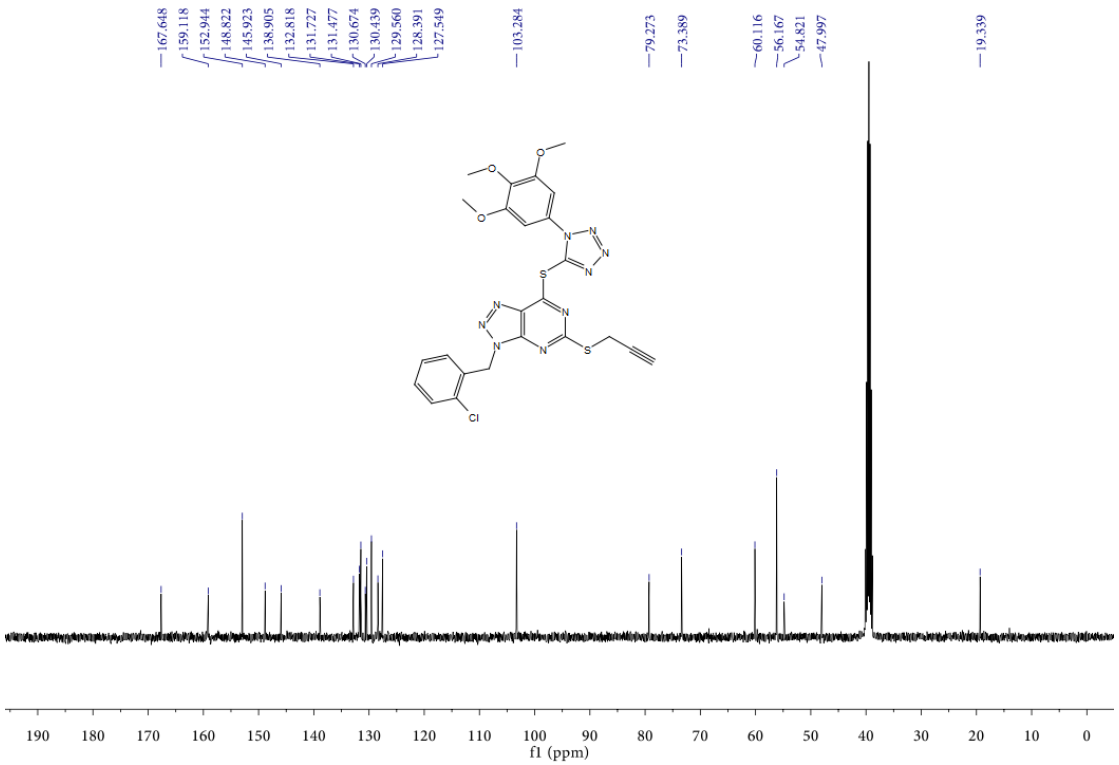


Figure S98 ^{1}H NMR spectrum of compound **15af**.

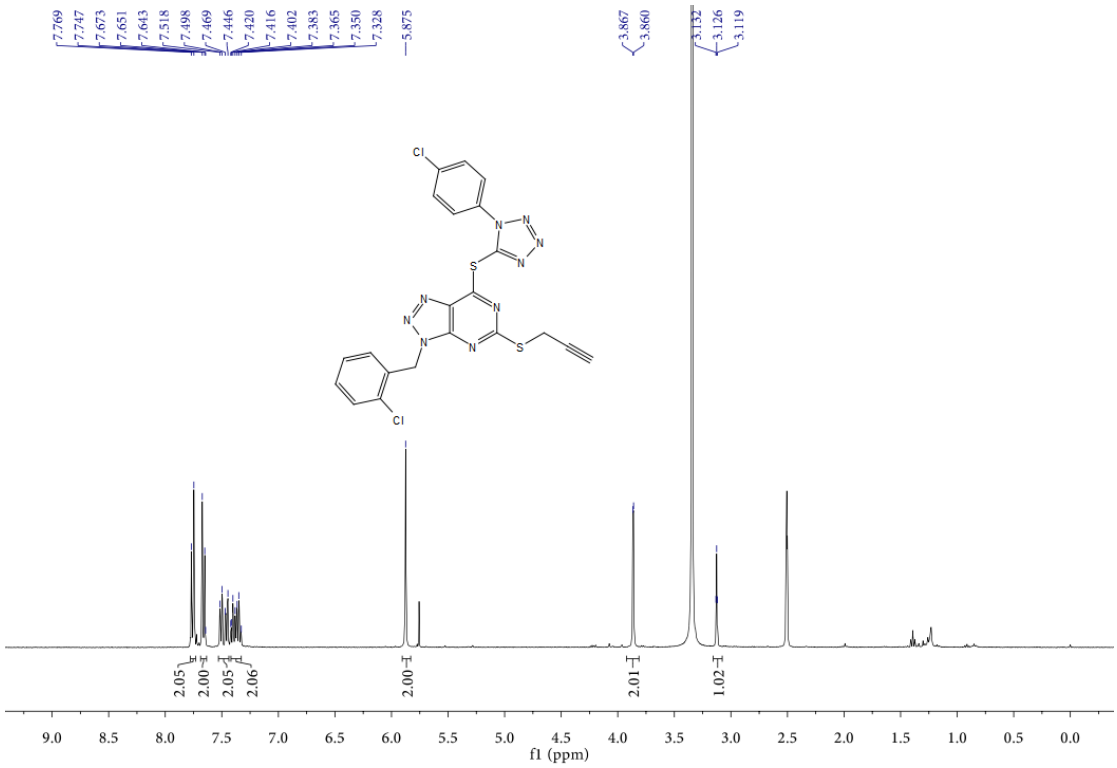


Figure S99 ^{13}C NMR spectrum of compound **15af**.

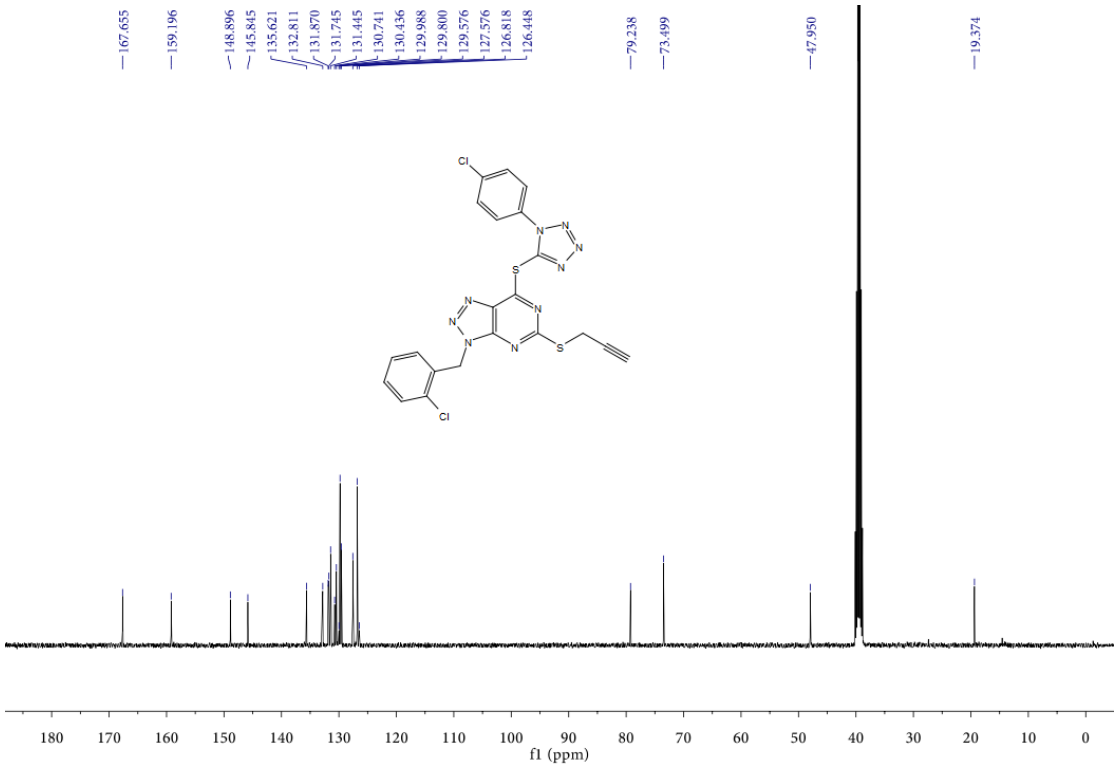


Figure S100 ^{1}H NMR spectrum of compound **15ag**.

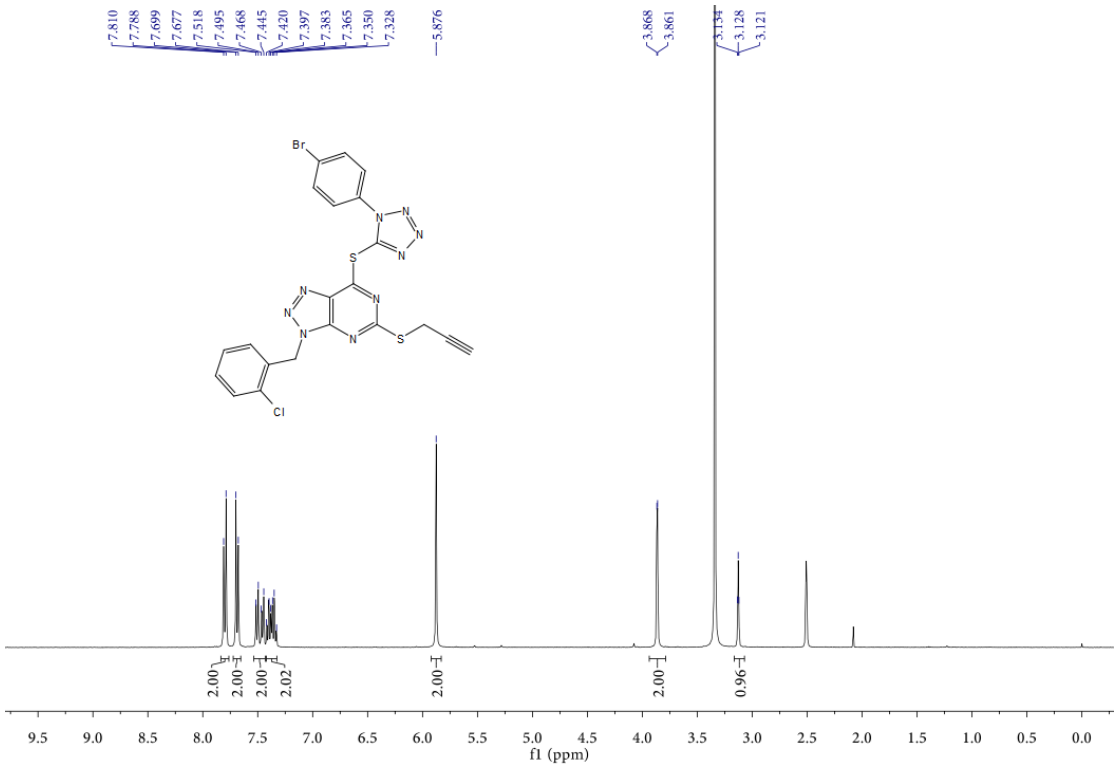


Figure S101 ^{13}C NMR spectrum of compound **15ag**.

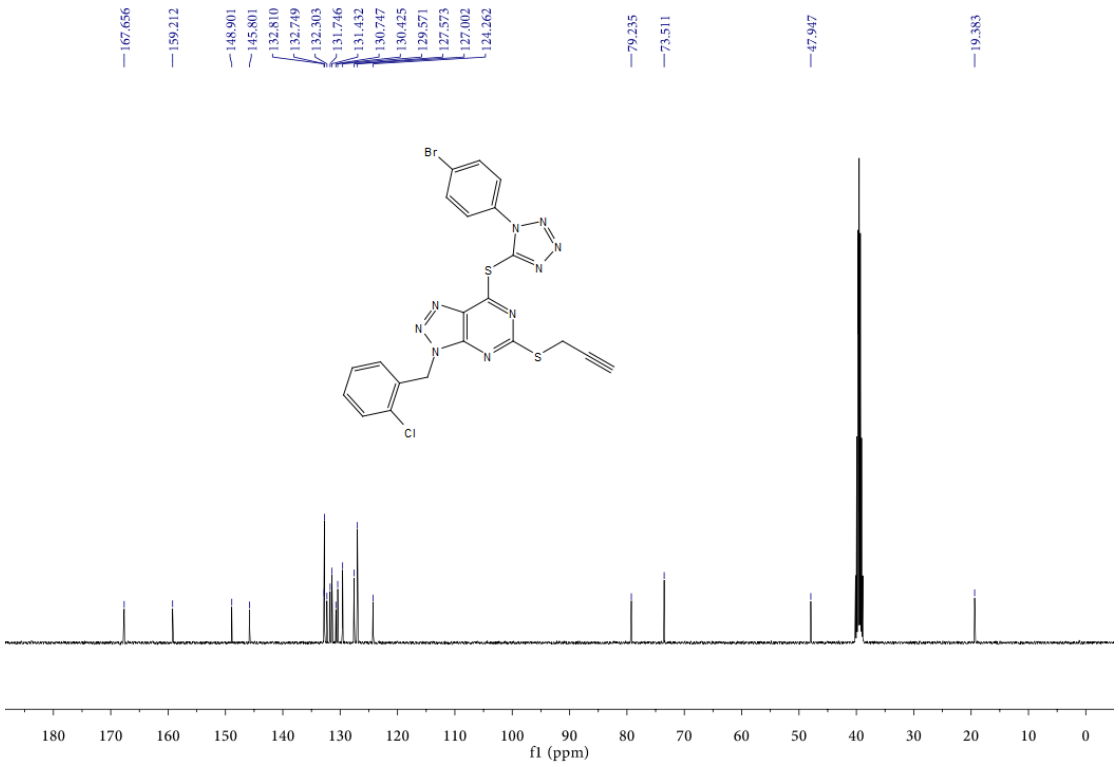


Figure S102 ^{1}H NMR spectrum of compound **15ah**.

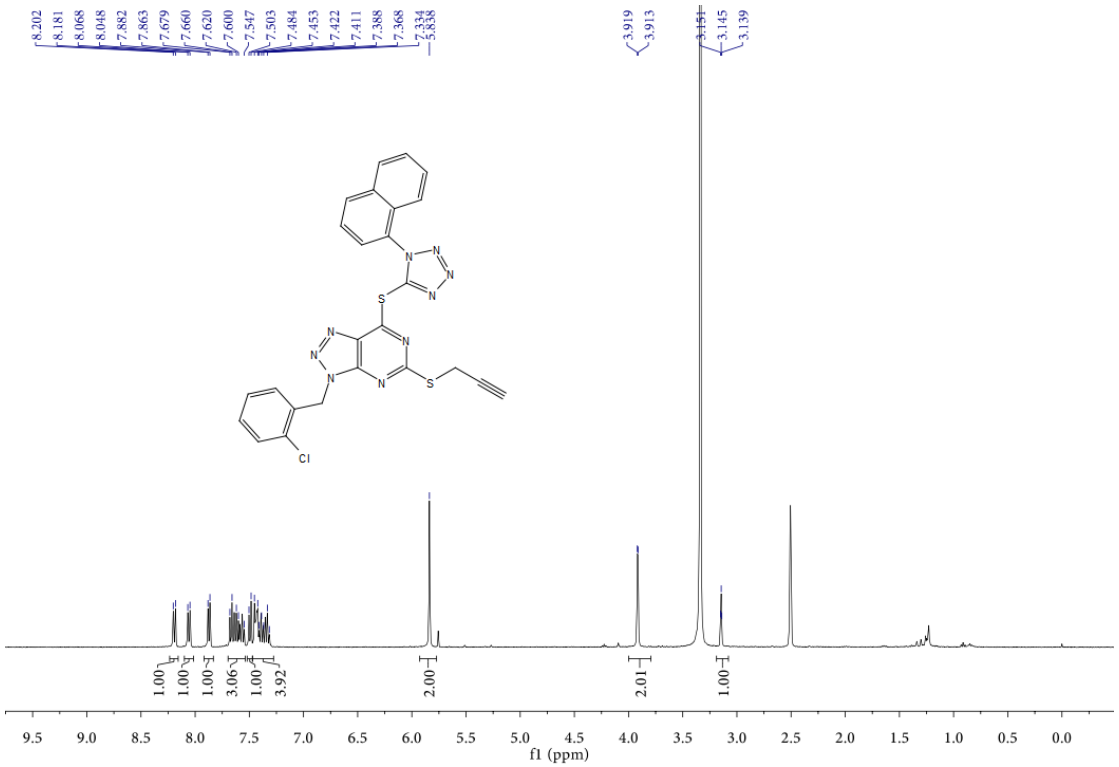


Figure S103 ^{13}C NMR spectrum of compound **15ah**.

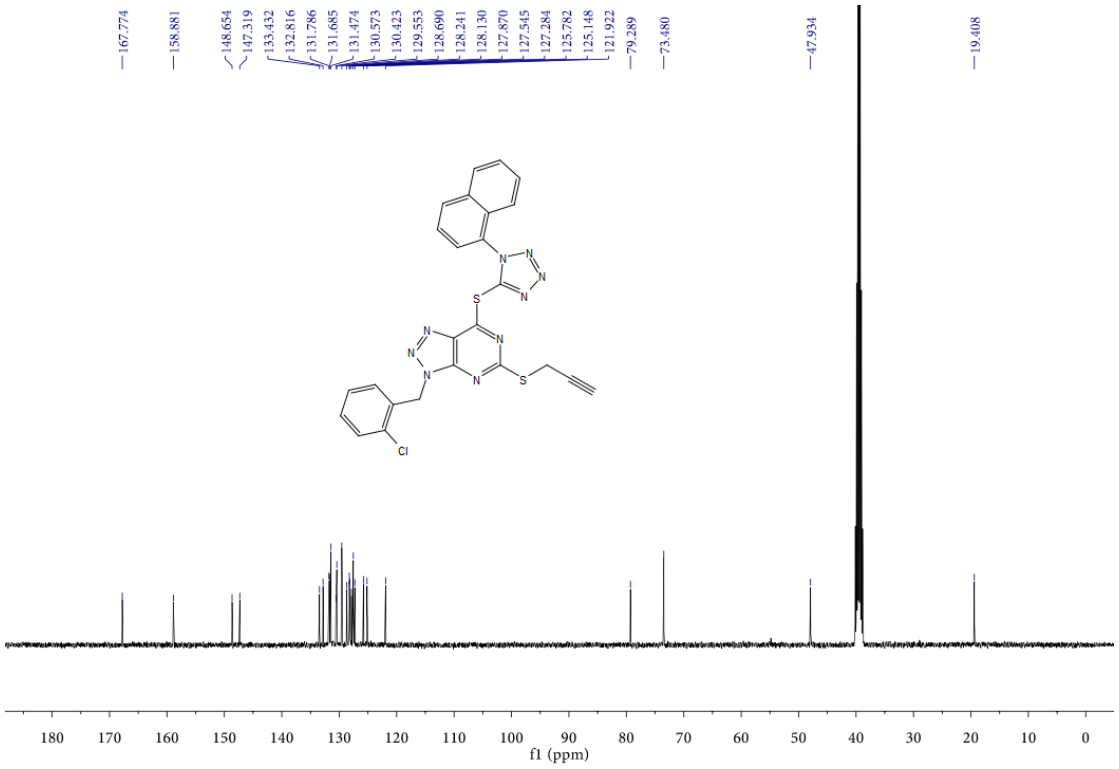


Figure S104 ^{1}H NMR spectrum of compound **15ai**.

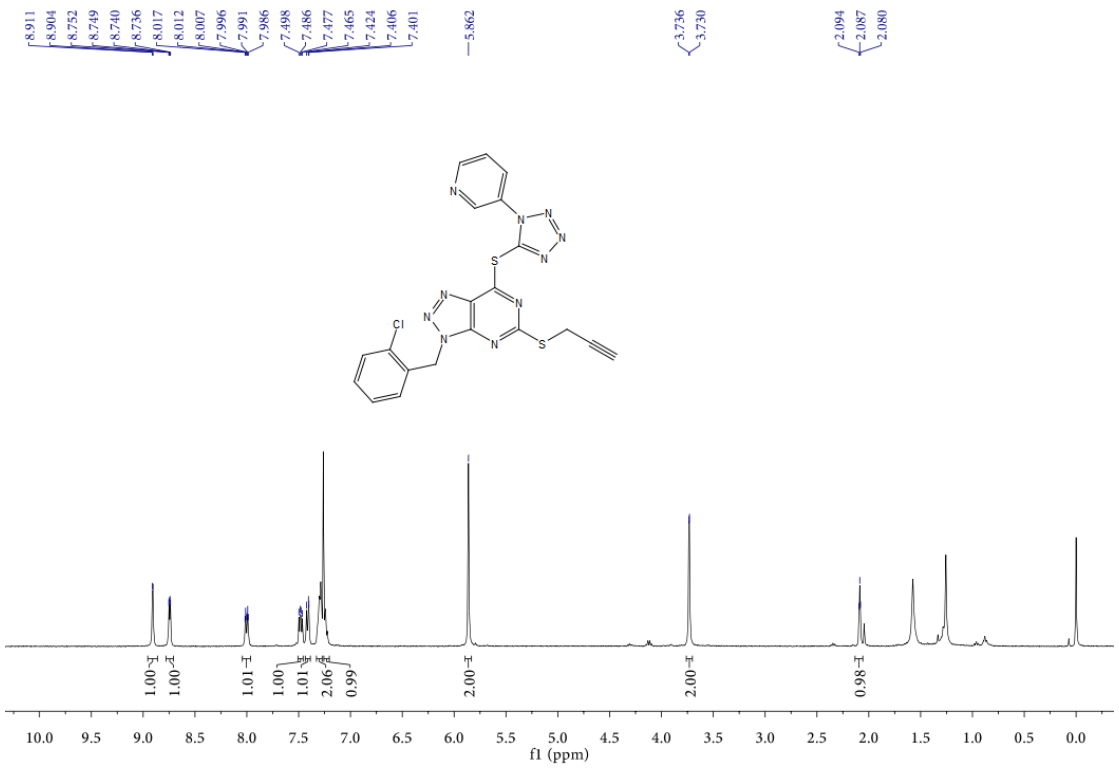


Figure S105 ^{13}C NMR spectrum of compound **15ai**.

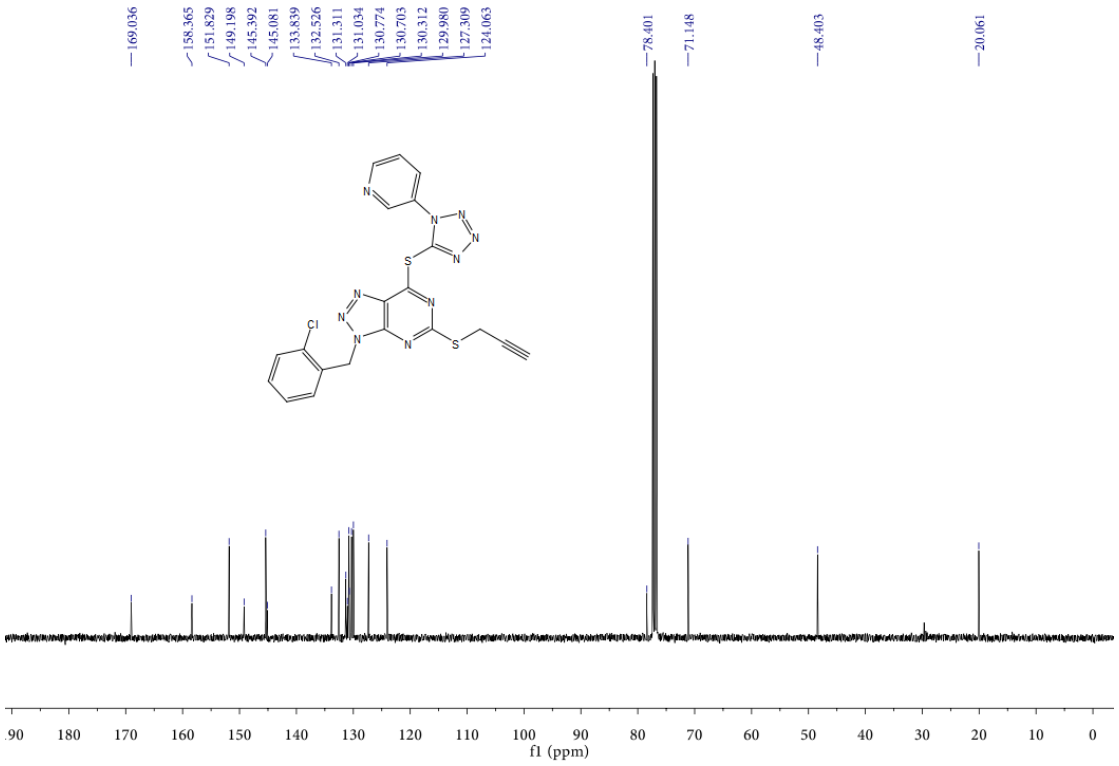


Figure S106 ^{1}H NMR spectrum of compound **15aj**.

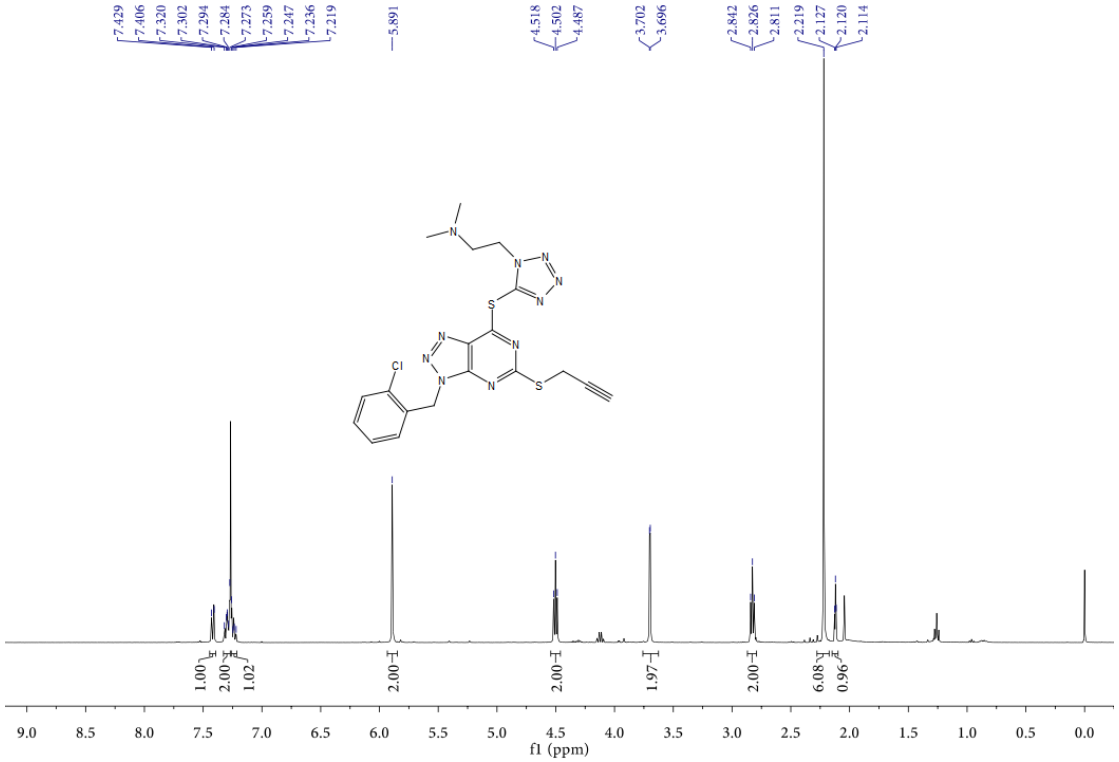


Figure S107 ^{13}C NMR spectrum of compound **15aj**.

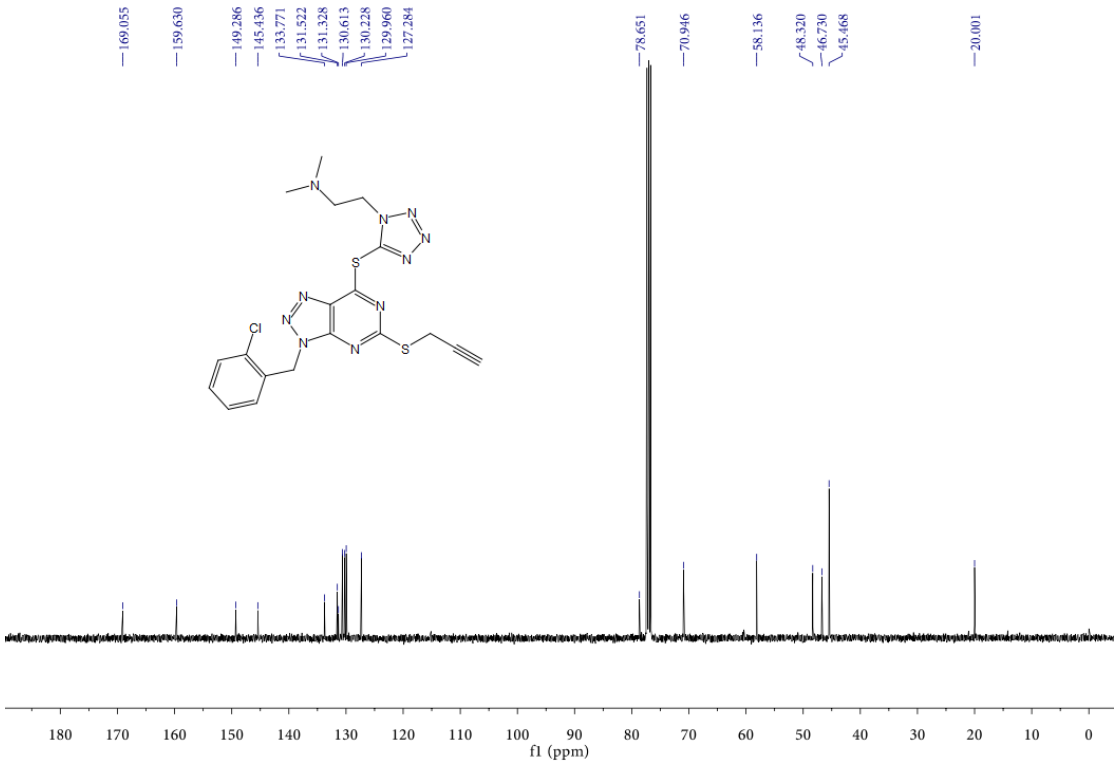


Figure S108 ^{1}H NMR spectrum of compound **15ak**.

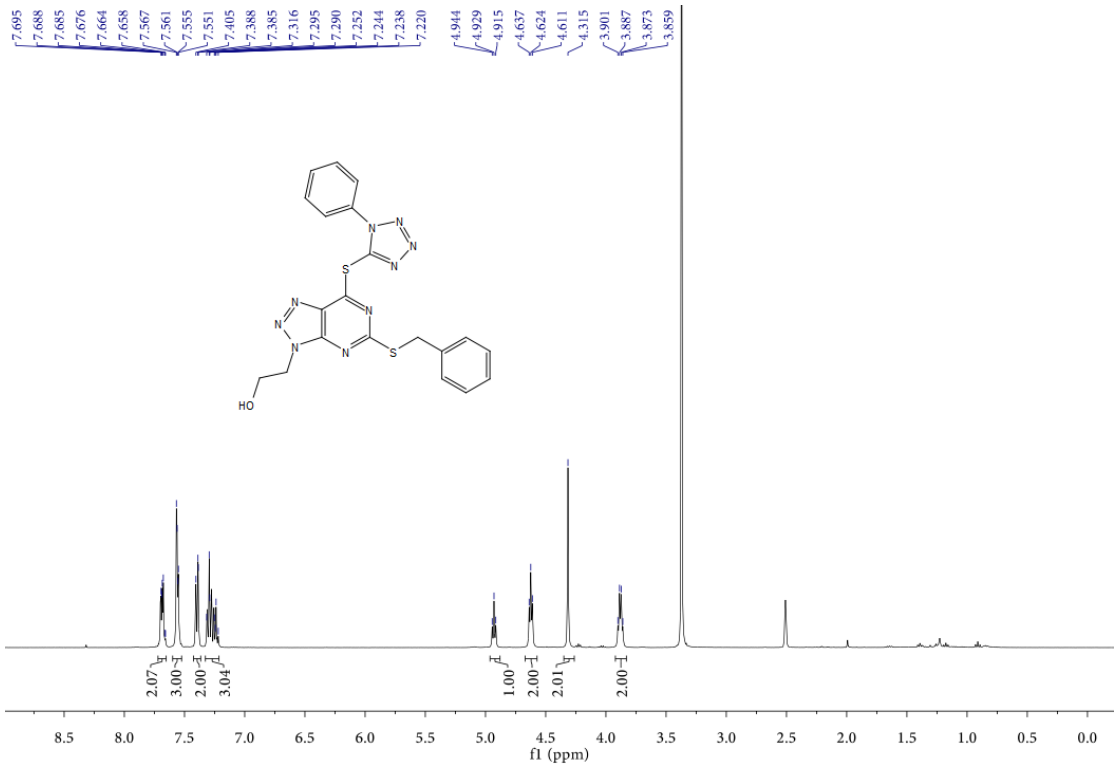


Figure S109 ^{13}C NMR spectrum of compound **15ak**.

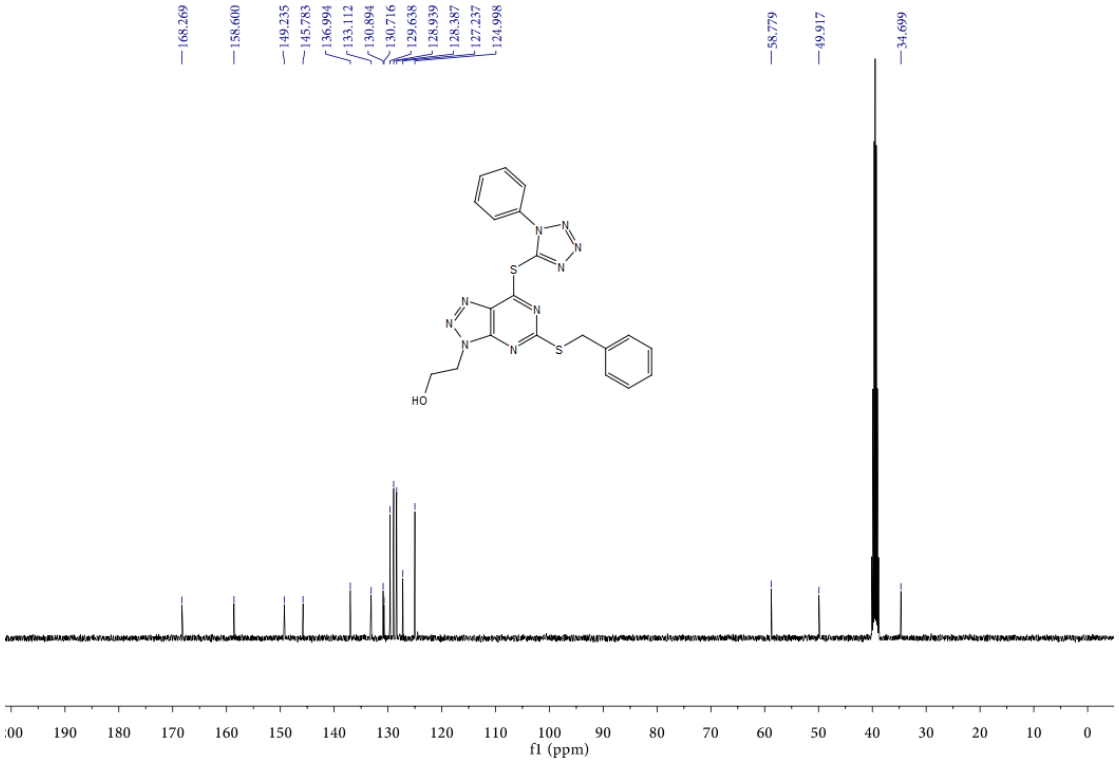


Figure S110 ^{1}H NMR spectrum of compound **22b**.

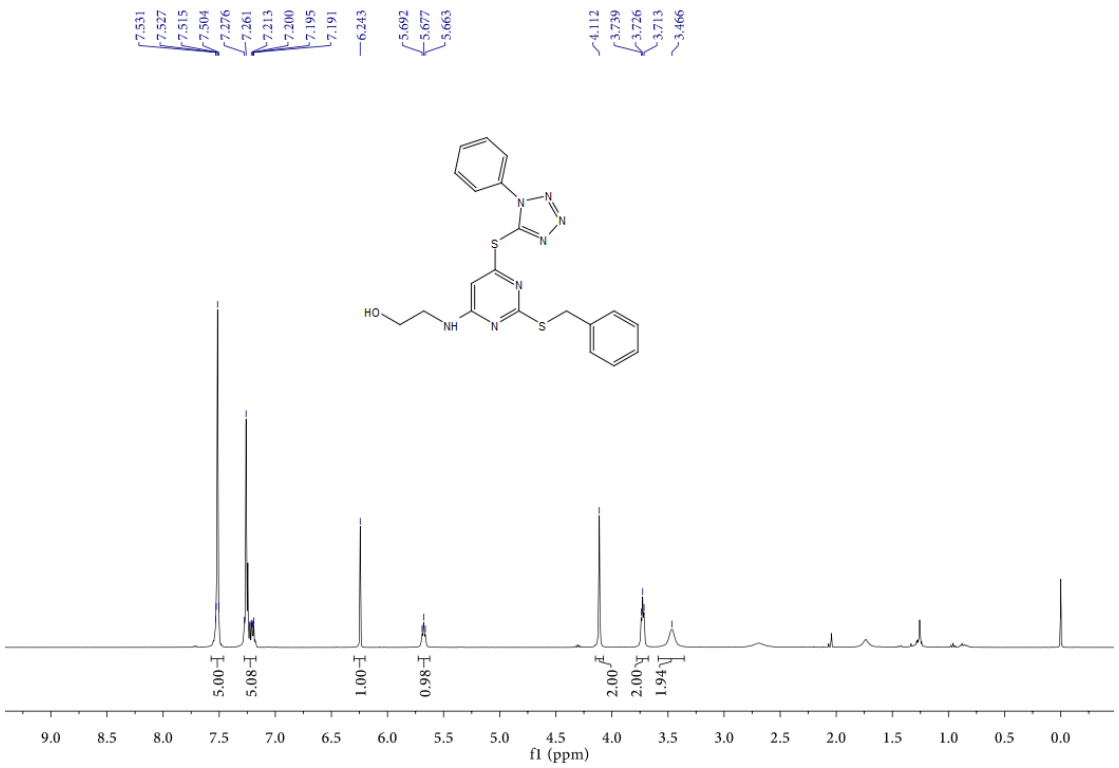


Figure S111 ^{13}C NMR spectrum of compound **22b**.

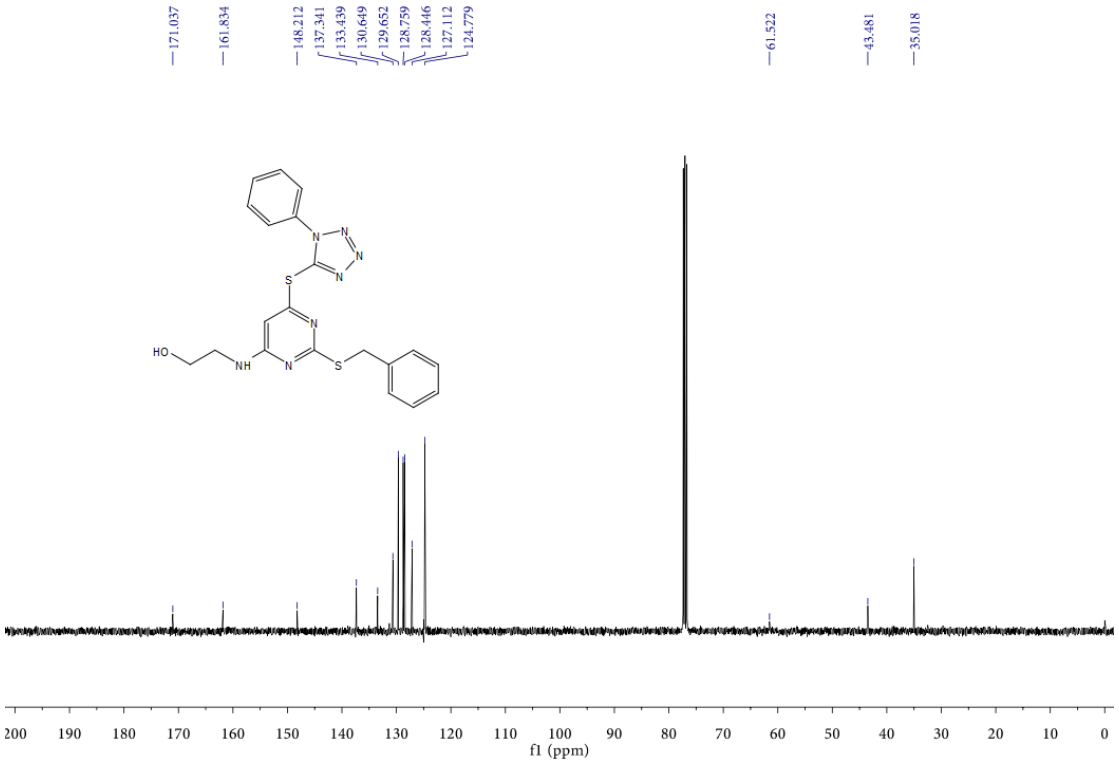


Figure S112 ^{1}H NMR spectrum of compound **23**.

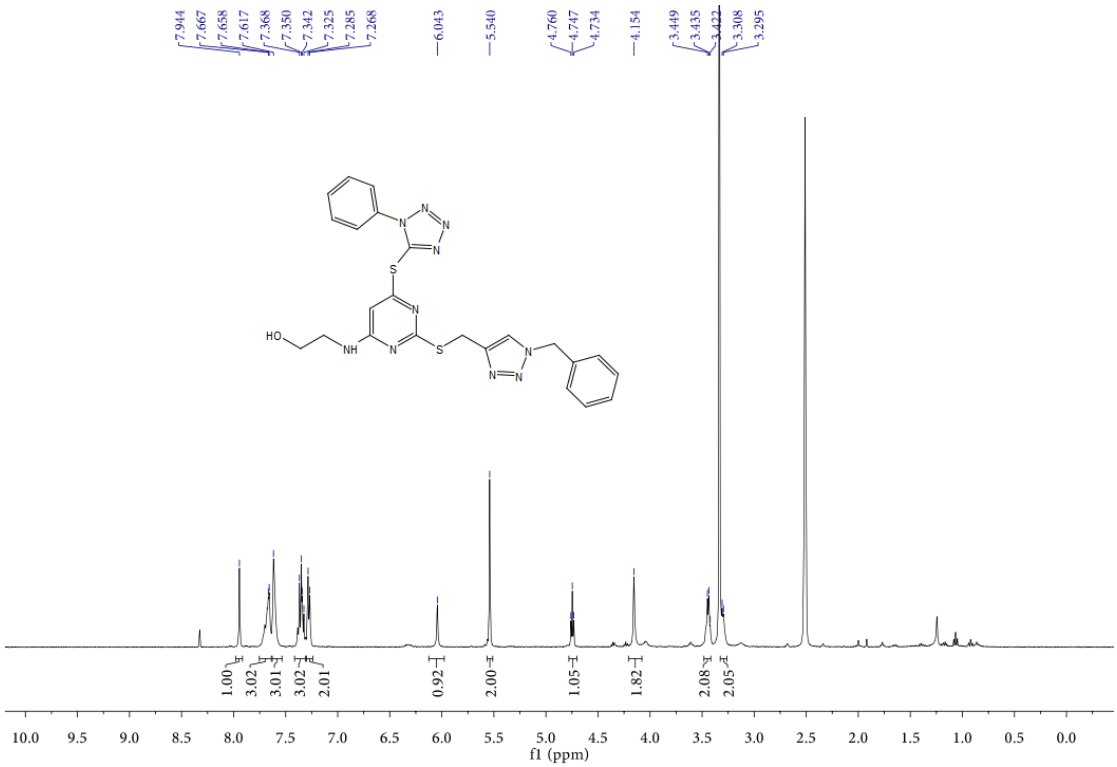


Figure S113 ^{13}C NMR spectrum of compound **23**.