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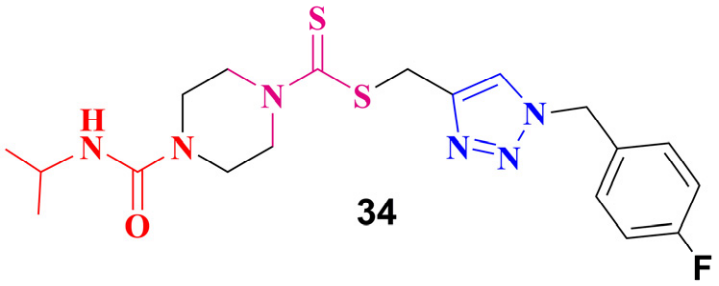

34

Novel 1,2,3-triazole-dithiocarbamate-urea hybrids **34** exhibited potent anticancer activity with IC_{50} values ranging from 0.76 to 13.55μM and was highly selective in its cytotoxicity activity.

Design, synthesis and antiproliferative activity studies of novel 1,2,3-triazole-dithiocarbamate-urea hybrids

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Abstract: A series of novel 1,2,3-triazole-dithiocarbamate-urea hybrids were designed, synthesized and their antiproliferative activities against four selected human cancer cell lines were evaluated. The results showed that a number of the hybrids exhibited potent activity in selected human cancer cell lines. Among them, compounds **27** and **34** showed broad spectrum anticancer activity with IC_{50} values ranging from 1.62 to 20.84μM and 0.76 to 13.55μM, respectively. Interestingly, compounds **27** and **34**, being very potent against MGC-803 cells, exhibited no significant cytotoxicity against normal human embryonic kidney cells at up to 55μM and 70μM, respectively. Evidences of cell cycle arrest and apoptosis induction were obtained for the most effective compounds **27** and **34** by means of flow cytometry and microscopic techniques.

Keywords: 1,2,3-triazole; dithiocarbamate; urea; hybrid; antiproliferative; apoptosis

1. Introduction

Cancer, being one of the leading causes of death globally, causes almost 8 million people death each year and poses a major socioeconomic hazard to humanity at large. Among all factors resulting in the ultimate failure of cancer treatment, drug resistance is a significant player [1]. Development of new molecules with novel mechanisms of action to fight cancer are urgently needed as most anticancer drugs are ineffective due to drug resistance. Molecular hybridization which covalently combines two or more drug pharmacophores into a single molecule is an effective tool to design highly active novel entities [2]. These merged pharmacophores may act on multiple therapeutic targets and offer the possibility of circumventing drug resistance. In addition, the hybrids may also minimize unwanted side effects and allow for synergic action [3]. The molecular hybridization approach has already been applied in developing novel antimalarial agents to overcome drug resistance [4].

1,2,3-Triazoles have been a fruitful source of inspiration for medicinal chemists for many years due to their synthetic accessibility by click chemistry as well as their numerous biological activities [5]. 1,2,3-Triazole is a versatile moiety found in a large variety of bioactive molecules, such as anti-fungal [6], anti-bacterial [7], anti-allergic [8], anti-HIV [9], anti-tubercular [10] and anti-inflammatory agents [11]. Recent research of 1,2,3-triazole's pharmacological effects became much more appealing and

promising for anticancer agents design. 1,2,3-Triazoles conjugated with a wide range of moieties were reported to exhibit potent anticancer activity [12]. N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl) arylamide was identified as a novel and proprietary small molecule scaffold for potential antitumor agents by M.J. Miller group, and compound **1** exhibited an IC_{50} of 46 nM against MCF-7 cancer cell line [13]. Compound **2,** a 1,2,3-triazol-naphthalimide hybrid, showed IC_{50} values of 0.348 and 0.258 μM against cell lines MCF-7 and SMMC-7721, respectively [14]. Carboxyamidotriazole (**3**) [15], a 1,2,3-triazole-containing anticancer agent, is now available in the market (Fig. 1).

Dithiocarbamates are considered privileged scaffolds in drug discovery with a wide array of biological activities. In the literature, dithiocarbamate derivatives have been described as anti-fungal [16], anti-bacterial [17], and carbonic anhydrase inhibitors [18]. In particular, their applications in the treatment of cancer have been explored [19]. Brassinin (**4**), a phytoalexin in cruciferous plants, has demonstrated cancer preventive activity [20]. Structural modifications of compound **4** led to the synthesis of sulforamate (**5**), which was found to exhibit antitumor activity both in vitro and in vivo [21]. Our group recently reported the synthesis of novel butenolide-containing dithiocarbamates (**6**), and several compounds exhibited good anticancer activities (Fig. 2) [22].

Urea-based compounds are largely present in nature and have received special attention due to their potent anticancer properties [23]. The urea derivatives, including ureas, arylureas, and thioureas, represent one of the most useful classes of anticancer agents, with a wide range of activities against various cancers [24] (Fig. 3).

In the course of our search for new anticancer agents, we recently reported the synthesis and biological activities of a series of 1,2,3-triazole-dithiocarbamate hybrids with general structure **10**, several compounds showed excellent broad spectrum anticancer activity [25]. The study of new hybrid systems in which 1,2,3-triazole, dithiocarbamate and urea are combined comprises an unexplored field of research. These findings have encouraged us to investigate the potential synergistic effect of 1,2,3-triazole, dithiocarbamate and urea scaffolds (Fig. 4). Herein, for the first time, the hybridization of these three pharmacophores into novel scaffold and their ability to inhibit four selected human tumor cell lines were reported.

2. Results and discussion

2.1. Chemistry

The general route for the synthesis of the target 1,2,3-triazole-dithiocarbamate-urea hybrids is depicted in Scheme 1. Commercially available tert-butyl piperazine-1-carboxylate **11** [26] was reacted with CS_2 and propargyl bromide in the presence of $Na_3PO_4{\cdot}12H_2O$ at room temperature to form compound **12**, which was subjected to click reaction with appropriately substituted benzyl azides to afford compounds **13-18** with good yields. The substituted benzyl azides were readily synthesized from the corresponding halides and sodium azide following literature procedures [27]. Compounds **13-18** were converted to compounds **19-24** by removing the protective group in a TFA/CH_2Cl_2 solution. Without further purification, compounds **19-24** were transformed into the corresponding urea derivatives **25-52** by treatment with triphosgene and various amines in one pot.

2.2. Evaluation of biological activity

2.2.1. Antiproliferative activity

All synthesized compounds were evaluated for their antiproliferative activity against four human cancer cell lines, MGC-803 (human gastric cancer cell line), MCF-7 (human breast cancer cell line), SMMC-7721(human hepatocellular carcinoma cell line), and EC-9706 (human esophageal cancer cell line) using MTT assay method [28] and compared with the well-known anticancer drug 5-fluorouracil.

As shown in Table 1, the antiproliferative activity of the tested compounds was generally more pronounced against MGC-803 and MCF-7 cells as compared with the other cell lines. With the MGC-803 and MCF-7 cell, compounds **26-28** and **33-35** were more potent than 5-fluorouracil in the single-digit micro molar range. Among them, the two most potent compounds were **27** and **34,** exhibiting IC_{50} values against the four tested human cancer cell lines ranging from 1.62 to 20.84μM and 0.76 to 13.55μM, respectively. With the exception of EC-9706, compounds **27** and **34** were more potent than 5-fluorouracil against three of the four cancer cell lines. Structure-activity relationship (SAR) analysis showed that the steric hindrance of substituents on the N-atom played a critical role for the antiproliferative activities. Compound **32**, bearing hydrogen atoms on the N-atom, demonstrated an IC_{50} of 9.33μM against MGC-803 which was significantly enhanced when the hydrogen atom was replaced by an ethyl group (compound **33,** IC_{50} = 2.17μM) or, even better, by an isopropyl group (compound **34,** IC_{50} = 0.76μM). However, changing the isopropyl group to bulkier benzyl group (compound **36**) led to a complete loss of activity with all four cell lines. The antiproliferative activities of the hybrids were also influenced by the substituents on the phenyl ring. The *p*-fluoro compound **34** proved to be nearly 10-fold more potent than fluorouracil in the case of MGC-803, while *p*-methoxy compound **47** and *m*, *p*, *m*-trimethoxy compound **51** showed almost no cytotoxicity against MGC-803. The replacement of *p*-fluoro atom (**34**) with *p*-chloro atom (**39**) or *p*-methyl group (**43**) was also detrimental to the anticancer activity.

Compounds **27** and **34** were further examined for possible cytotoxicity against normal human embryonic kidney cells (HEK293). As can be seen in Figure 5A, we found that compound **27**, being very potent against MGC-803 cells (1.62μM), exhibited no significant cytotoxicity against HEK293 cells at up to 55μM. Compound **34,** with an IC_{50} 0f 0.76μM against MGC-803 cells also exhibited no significant cytotoxicity against HEK293 cells at up to 70μM (Figure 5B). The result indicated that compounds **27** and **34** were highly selective in their cytotoxicity activity.

2.2.2. Apoptosis assay

Apoptosis is considered a major way that most of the anticancer drugs kill tumor cells. To test whether the inhibition of cell growth of the hybrids was related to cell apoptosis, MGC-803 cells were treated with compounds **27** or **34** at different concentrations (0, 0.25, 0.5, 1.0μmol/L) for 12 h, and changes in cell morphology were observed by fluorescence microscopy using Hoechst 33258 staining [29]. As shown in Figure 6A and 6B, compounds **27** and **34** altered cell morphology with respect to those of control cultures, and caused apoptosis characteristics including cellular nuclear shrinkage, chromatin condensation and nuclear fragmentation.

We also performed a biparametric cytofluorimetric analysis using propidium iodide (PI) and annexin-V-FITC to measure the apoptosis inducing activity of compound **34** in MGC-803 cells [30].

After treatment with compound **34** for 12 h at different concentrations (0, 0.25, 0.5, 1.0μmol/L), MGC-803 cells were labeled with the two dyes, and the resulting red (PI) and green (FITC) fluorescences were monitored by flow cytometry. As shown in Fig.6C, the apoptosis rates were significantly increased from 2.8% (DMSO control) to 31.4%. The results showed that compound **34** caused a significant induction of apoptotic cells in a concentration-dependent manner.

2.2.3. Cell cycle analysis

Because the anticancer efficacy of many current chemotherapeutic agents is correlated with their ability to arrest the cell cycle in cancer cells. To determine whether the high anticancer effects of the hybrids were caused by cell cycle accumulation at a certain phase, the effects of different concentrations (0, 0.25, 0.5, 1.0μmol/L) of compounds **27** and **34** on cell cycle progression were examined with MGC-803 cell line [31]. After treatment with compound **27** for 12 h, it was observed that the percentage of cells in G2/M phase were 18.14%, 21.86%, 50.35%, and 59.80%, respectively (Fig.7B), whereas after 24 h of exposure, the percentage of cells in G2/M phase were 15.21%, 32.93%, 68.71%, and 74.95%, respectively. After treatment with compound **34** for 12 h, the percentage of cells in G2/M phase were increased from 16.76% to 68.86%, whereas after 24 h of exposure, the percentage of cells in G2/M phase were increased from 16.04% to 79.02%. The results suggested that compounds **27** and **34** caused an obvious increase in cell numbers in the G2/M phase with a concomitant decrease of cells in the G1 and S phases in a concentration and time-dependent manner.

3. Conclusions

In conclusion, we have discovered that a number of 1,2,3-triazole-dithiocarbamate-urea hybrids displayed high activity against the proliferation of different human cancer cells in vitro. Two promising compounds **27** and **34** exhibited broad spectrum anticancer activity in vitro and were more potent than 5-fluorouracil against three human cancer cell lines. Moreover, compound **27** and **34** did not affect the normal cells (HEK-293) at up to 55μM and 70μM, respectively, despite being very potent against MGC-803 cells. The results of apoptosis assay and cell cycle analysis demonstrated that **27** and **34** could obviously inhibit the proliferation of MGC-803 cancer cells by inducing apoptosis and arresting the cell cycle at G2/M phase. Collectively, the potent anticancer activity, synthetic accessibility and high selectivity strongly encourage further optimization of **27** and **34** as leads to develop more potent anticancer agents.

4. Experimental section

4.1. General

Reagents and solvents were purchased from commercial sources and were used without further purification. Melting points were determined on an X-5 micromelting apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and 100MHz spectrometer respectively. IR spectra were recorded on a Nicolet iS10 infrared spectrometer. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-Tof Micro mass spectrometer.

4.2. Procedure for the synthesis of tert Butyl 4-((prop-2-ynylthio)carbonothioyl)piperazine-1-carboxylate compound **12**.

CS_2 (4.56g, 60mmol) was added drop wise to the solution of tert-butyl piperazine-1-carboxylate **11** (3.72g, 20mmol) and $Na_3PO_4{\cdot}12H_2O$ (4.56g, 12mmol) in acetone (80mL). The reaction mixture was stirred at room temperature for 0.5 h. Then propargyl bromide (2.32g, 22mmol) was added to the mixture, the reaction mixture was stirred at room temperature for another 0.5 h. Upon completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure, the residue was dissolved in EtOAc (80mL), washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compound **2** (5.56g, yield 92.2%). white solid. Mp: 87-88^{o}C. ^{1}H NMR (400 MHz, Acetone-d_6, δ, ppm): 4.28 (br, 2H), 4.14 (d, 2H, *J* = 2.7 Hz), 4.00 (br, 2H), 3.58 (br, 4H), 2.78 (t, 1H, *J* = 2.7 Hz), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 195.2, 154.4, 80.7, 78.2, 71.8, 28.4, 26.0; HRMS (ESI) calcd for $C_{13}H_{21}N_2O_2S_2$ $[M+H]^+$: 301.1044, found: 301.1046.

*4.3. General procedure for the synthesis of compounds***13-18**

In a round-bottom flask equipped with a magnetic stirred bar, **12** (1.51g, 5mmol), azide derivatives (5.5mmol), $CuSO_4{\cdot}5H_2O$ (62mg, 0.25mmol), sodium ascorbate (100mg, 0.5mmol), THF (20mL) and H_2O (20mL) were added. The resulting mixture was stirred at room temperature. The disappearance of compound **12** was monitored by TLC. Upon completion, water (40mL) was added and the reaction mixture was extracted with EtOAc (3×40mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was recrystallized from acetone to yield the pure product.

4.3.1.tert Butyl 4-(((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**13**): yield 79.0%. white solid. Mp: 109-110^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.66 (s, 1H), 7.09-7.38 (m, 4H), 5.55 (s, 2H), 4.69 (s, 2H), 4.29 (br, 2H), 3.91 (br, 3H), 3.54 (t, 4H, *J* = 5.1 Hz), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 161.7, 159.3, 154.4, 144.0, 130.9, 130.8, 130.5, 130.5, 124.8, 124.9, 123.0, 122.0, 121.8, 115.9, 115.7, 80.6, 47.7, 47.6, 31.8, 28.3; HRMS (ESI) calcd for $C_{20}H_{27}FN_5O_2S_2$ $[M+H]^+$: 452.1590, found: 452.1598.

4.3.2. tert Butyl 4-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**14**): yield 79.7%. white solid. Mp: 171-172^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.59 (s, 1H), 7.04-7.27 (m, 4H), 5.46 (s, 2H), 4.68 (s, 2H), 4.31 (br, 2H), 3.90 (br, 3H), 3.53 (s, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.40, 164.07, 161.60, 154.40, 130.49, 130.45, 129.96, 129.87, 116.20, 115.98, 80.66, 53.42, 31.78, 28.34; HRMS (ESI) calcd for $C_{20}H_{27}FN_5O_2S_2$ $[M+H]^+$: 452.1590, found: 452.1588.

4.3.3. tert Butyl 4-(((1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**15**): yield 85.5%. white solid. Mp: 177-178^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.59 (s, 1H), 7.35 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 5.45 (s, 2H), 4.68 (s, 2H), 4.29 (br, 2H), 3.90 (br, 2H), 3.54 (t, 4H, *J* = 5.2 Hz), 1.47(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ,

ppm):196.4, 154.4, 144.4, 134.8, 133.1, 129.4, 129.3, 122.8, 80.7, 53.4, 31.7, 28.4; HRMS (ESI) calcd for $C_{20}H_{27}ClN_5O_2S_2$ $[M+H]^+$: 468.1295, found: 468.1291.

4.3.4. tert Butyl 4-(((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-arboxylate (**16**): yield 81.9%. white solid. Mp: 182-183^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.55 (s, 1H), 7.16-7.21 (m, 4H), 5.43 (s, 2H), 4.67 (s, 2H), 4.29 (br, 2H), 3.91 (br, 2H), 3.54 (t, 4H, *J* = 5.2 Hz), 2.35 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.5, 154.4, 138.7, 131.6, 129.8, 128.1, 80.6, 54.0, 31.9, 28.4, 21.2; HRMS (ESI) calcd for $C_{21}H_{30}N_5O_2S_2$ $[M+H]^+$:448.1841, found: 448.1840.

4.3.5. tert Butyl 4-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**17**): yield 85.8%. white solid. Mp: 129-130^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.54 (s, 1H), 7.21(d, 2H, *J* = 8.7 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 5.41 (s, 2H), 4.67 (s, 2H), 4.29 (br, 2H), 3.90 (br, 2H), 3.80 (s, 3H), 3.51 (t, 4H, *J* = 5.2 Hz), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.5, 159.9, 154.4, 143.9, 129.6, 126.6, 122.5, 114.4, 80.6, 55.3, 53.7, 31.9, 28.4; HRMS (ESI) calcd for $C_{21}H_{30}N_5O_3S_2$ $[M+H]^+$: 464.1790, found: 464.1794.

4.3.6. tert Butyl 4-(((1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**18**): yield 83.4%. white solid. Mp: 134-135^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.63 (s, 1H), 6.48 (s, 2H), 5.41 (s, 2H), 4.70 (s, 2H), 4.30 (br, 2H), 3.91 (br, 2H), 3.85 (s, 3H), 3.84 (s, 6H), 3.55 (t, 4H, *J* = 5.2 Hz), 1.48 (s, 9H); HRMS (ESI) calcd for $C_{23}H_{34}N_5O_2S_2$ $[M+H]^+$: 524.2001, found: 524.2005.

4.4. General procedure for the synthesis of compounds **19-24**.

CF_3COOH (4.56g, 40mmol) was added to a solution of **13-18** (2mmol) in CH_2Cl_2 (20mL) at 0^{o}C. The reaction mixture was warmed to room temperature and stirred at the same temperature. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compounds **19-24**, which were used in the next reaction without further purification.

4.4.1. (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**19**): yield 96.7%. white solid. Mp: 93-94^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.67 (s, 1H), 7.09-7.36 (m, 4H), 5.55 (s, 2H), 4.69 (s, 2H), 4.30 (br, 2H), 3.93 (br, 2H), 2.96 (t, 4H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 195.8, 161.7, 159.3, 144.3, 130.9, 130.8, 130.5, 130.5, 124.8, 124.8, 123.0, 122.0, 121.9, 115.9, 115.7, 47.7, 47.6, 45.6, 31.8, 30.9; HRMS (ESI) calcd for $C_{15}H_{19}FN_5S_2$ $[M+H]^+$: 352.1066, found: 352.1064.

4.4.2. (1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**20**): yield 93.9%. white solid. Mp: 138-139^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.60 (s, 1H), 7.04-7.27 (m, 4H), 5.45 (s, 2H), 4.69 (s, 2H), 4.31 (br, 2H), 3.89 (br, 2H), 2.93 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.0, 164.0, 161.6, 144.3, 130.5, 130.4, 130.0, 129.9, 122.7, 116.2, 116.0,

53.4, 45.2, 31.8; HRMS (ESI) calcd for $C_{15}H_{19}FN_5S_2$ $[M+H]^+$: 352.1066, found: 352.1063.

4.4.3. (1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**21**): yield 95.1%. white solid. Mp: 79-80^oC; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.61 (s, 1H), 7.35 (d, 2H, *J* = 8.1 Hz), 7.20 (d, 2H, *J* = 8.1 Hz), 5.45 (s, 2H), 4.69 (s, 2H), 4.31 (br, 2H), 3.90 (br, 2H), 2.94 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 195.6, 144.5, 134.7, 133.2, 129.4, 129.3, 122.8, 53.4, 45.6, 31.7; HRMS (ESI) calcd for $C_{15}H_{19}ClN_5S_2$ $[M+H]^+$: 368.0770, found: 368.0767.

4.4.4. 1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**22**): yield 94.0%. white solid. Mp: 74-75^oC; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (s, 1H), 7.14-7.27 (m, 4H), 5.43 (s, 2H), 4.67 (s, 2H), 4.31 (br, 2H), 3.92 (br, 2H), 2.96 (br, 4H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 195.8, 138.6, 131.6, 129.7, 128.1, 122.7, 54.0, 31.8, 29.7, 21.2; HRMS (ESI) calcd for $C_{16}H_{22}N_5S_2$ $[M+H]^+$:348.1317, found: 348.1319.

4.4.5. (1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**23**): yield 92.7%. white solid. Mp: 95-96^oC; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.55 (s, 1H), 7.24 (d, 2H, *J* = 8.7 Hz), 6.91 (d, 2H, *J* = 8.7 Hz), 5.42 (s, 2H), 4.68 (s, 2H), 4.31 (br, 2H), 3.95 (br, 2H), 3.80 (s, 3H), 2.96 (t, 4H, *J* = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 195.8, 159.9, 144.1, 129.6, 126.6, 122.5, 114.5, 55.3, 53.7, 45.6, 31.8; HRMS (ESI) calcd for $C_{16}H_{22}N_5OS_2$ $[M+H]^+$:364.1266, found: 364.1263.

4.4.6. (1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**24**): yield 96.0%. white solid. Mp: 120-121^oC; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.64 (s, 1H), 6.47 (s, 2H), 5.40 (s, 2H), 4.69 (s, 2H), 4.30 (br, 2H), 3.91 (br, 2H), 3.83 (s, 3H), 3.82 (s, 6H), 2.93 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 195.6, 153.7, 144.4, 138.2, 130.2, 122.8, 105.2, 60.9, 56.2, 54.4, 45.7, 31.7; HRMS (ESI) calcd for $C_{18}H_{26}N_5O_3S_2$ $[M+H]^+$: 424.1477, found: 424.1472.

4.5. General procedure for the synthesis of compounds **25-52**.

To a solution of triphosgene (0.7mmol) in CH_2Cl_2 (10mL) under nitrogen, Et_3N (2.1mmol) was added drop wise, the reaction mixture was stirred at 0^oC for 20 minutes, then a solution of **19-24** (2mmol) in CH_2Cl_2 (10mL) were added drop wise to the mixture, the reaction mixture was stirred at room temperature for another 1 h, then various amines were added to the mixture, the mixture were allowed to stand at room temperature for 1 to 4 h. The reaction mixture was quenched by the addition of diluted HCl (1N, 50 mL), the organic layer was washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. The crude product were recrystallized from acetone to yield the pure product **25-53** as white solids.

4.5.1. (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate (**25**): yield 78.4%. white solid. Mp: 143-144^oC; ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.12 (s, 1H), 7.20-7.42 (m, 4H), 6.13 (br, 2H), 5.64 (s, 2H), 4.58 (s, 2H), 4.21 (br, 2H), 3.87 (br, 2H), 3.44 (t, 4H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 194.79, 161.77, 159.31, 158.23, 142.65, 131.26,

131.23, 131.19, 125.34, 125.30, 124.46, 123.35, 123.21, 116.20, 115.99, 47.33, 47.29, 43.00, 31.85; HRMS (ESI) calcd for $C_{16}H_{19}FN_6OS_2$ $[M+Na]^+$: 417.0943, found: 417.0943.

4.5.2.(1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethylcarbamoyl)piperazine-1-carbodithioate (**26**): yield 74.9%. white solid. Mp: 185-186^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.68 (s, 1H), 7.11-7.37 (m, 4H), 5.56 (s, 2H), 4.70 (s, 2H), 4.55 (br, 1H), 4.35 (br, 2H), 3.96 (br, 2H), 3.56 (t, 4H, *J* = 5.4 Hz), 3.31 (q, 2H, *J* = 7.1 Hz), 1.18 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.37, 161.73, 159.27, 157.24, 143.94, 130.95, 130.87, 130.53, 130.50, 124.84, 124.81, 123.02, 121.92, 121.78, 115.95, 115.74, 47.71, 47.67, 42.54, 35.83, 31.77, 15.52; HRMS (ESI) calcd for $C_{18}H_{23}FN_6NaOS_2$ $[M+Na]^+$: 445.1256, found: 445.1258.

4.5.3. (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate (**27**): yield 80.9%. white solid. Mp: 159-160^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.66 (s, 1H), 7.10-7.37 (m, 4H), 5.54 (s, 2H), 4.68 (s, 2H), 4.26 (br, 3H), 3.95-4.01 (m, 3H), 3.51 (s, 4H), 1.17 (d, 6H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.42, 161.73, 159.27, 156.56, 143.96, 130.94, 130.86, 130.54, 130.51, 124.85, 124.81, 123.01, 121.93, 121.79, 115.95, 115.74, 47.70, 47.66, 42.81, 31.76, 29.70, 23.42; HRMS (ESI) calcd for $C_{19}H_{26}FN_6OS_2$ $[M+H]^+$: 437.1594, found: 437.1592.

4.5.4 (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate (**28**): yield 83.7%. white solid. Mp: 144-145^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.68 (s, 1H), 7.09-7.38 (m, 4H), 5.55 (s, 2H), 4.68 (s, 2H), 4.34 (br, 2H), 3.95 (br, 2H), 3.36 (t, 4H, *J* = 4.8 Hz), 3.27 (q, 2H, *J* = 7.1 Hz), 2.84 (s, 3H), 1.18 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.37, 161.73, 159.27, 157.24, 143.94, 130.95, 130.87, 130.53, 130.50, 124.84, 124.81, 123.02, 121.92, 121.78, 115.95, 115.74, 53.5, 46.3, 44.8, 35.3, 31.7, 12.6; HRMS (ESI) calcd for $C_{19}H_{26}FN_6OS_2$ $[M+H]^+$: 437.1594, found: 437.1595.

4.5.5. (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(tert-butylcarbamoyl)piperazine-1-carbodithioate (**29**):yield 73.6%. white solid. Mp: 74-75^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.68 (s, 1H), 7.10-7.40 (m, 4H), 5.57 (s, 2H), 4.71 (s, 2H), 4.28 (br, 3H), 3.96 (br, 2H), 3.52 (t, 4H, *J* = 5.0 Hz), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.43, 161.73, 159.27, 156.35, 144.01, 130.93, 130.84, 130.54, 130.50, 124.84, 124.80, 122.97, 121.96, 121.81, 115.94, 115.73, 51.13, 47.68, 47.63, 31.77, 29.39; HRMS (ESI) calcd for $C_{20}H_{28}FN_6OS_2$ $[M+H]^+$: 451.1570, found: 451.1572.

4.5.6. (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(cyclohexylcarbamoyl)piperazine-1-carbodithioate (**30**): yield 71.7%. white solid. Mp: 124-125^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.70 (s, 1H), 7.10-7.40 (m, 4H), 5.57 (s, 2H), 4.72 (s, 2H), 4.37 (br, 3H), 3.97 (br, 2H), 3.63-3.71 (m, 1H), 3.55 (t, 4H, *J* = 5.1 Hz), 1.07-2.00 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.42, 161.74, 159.27, 156.49, 143.95, 130.96, 130.88, 130.55, 130.52, 124.85, 124.82, 123.05, 121.89, 121.75, 115.96, 115.75, 49.64, 47.75, 47.70, 33.93, 31.71, 29.70, 25.60, 25.04; HRMS (ESI) calcd for $C_{22}H_{29}FN_6NaOS_2$ $[M+Na]^+$: 499.1726, found: 499.1724.

4.5.7. (1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(benzylcarbamoyl)piperazine-1-carbodithioate (**31**): yield 75.5%. white solid. Mp: 131-132°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.65 (s, 1H), 7.08-7.37 (m, 9H), 5.54 (s, 2H), 4.81 (br, 1H), 4.67 (s, 2H), 4.43 (s, 2H), 4.32 (br, 2H), 3.94 (br, 2H), 3.56 (t, 4H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 161.7, 159.3, 157.2, 143.9, 139.1, 131.0, 130.9, 130.5, 130.5, 128.7, 127.8, 127.5, 124.9, 124.8, 123.0, 121.9, 121.8, 116.0, 115.8, 47.7, 47.7, 45.0, 42.7, 31.8; HRMS (ESI) calcd for $C_{23}H_{25}FN_6NaOS_2$ $[M+Na]^+$: 507.1413, found: 507.1416.

4.5.8. (1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate (**32**): yield 72.5%. white solid. Mp: 163-164°C; ^{1}H NMR (400 MHz, Acetone-d_6, δ, ppm): 7.98 (s, 1H), 7.13-7.46 (m, 4H), 5.61 (s, 2H), 5.54 (br, 1H), 4.62 (s, 2H), 4.30 (br, 2H), 3.98 (br, 2H), 3.57 (t, 4H, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 194.8, 163.6, 161.1, 158.2, 142.8, 132.8, 132.7, 130.8, 130.8, 124.2, 116.2, 116.0, 52.4, 43.0, 31.9; HRMS (ESI) calcd for $C_{16}H_{19}FN_6NaOS_2$ $[M+Na]^+$: 417.0943, found: 417.0946.

4.5.9.(1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethylcarbamoyl)piperazine-1-carbodithioate (**33**): yield 79.7%. white solid. Mp: 193-194°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.58 (s, 1H), 7.03-7.27 (m, 4H), 5.46 (s, 2H), 4.68 (s, 2H), 4.34 (br, 3H), 3.95 (br, 2H), 3.54 (t, 4H, *J* = 5.0 Hz), 3.32 (q, 2H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 164.1, 161.6, 157.2, 144.2, 130.4, 130.4, 130.0, 129.9, 122.7, 116.2, 116.0, 53.4, 42.6, 35.9, 31.7, 15.5; HRMS (ESI) calcd for $C_{18}H_{23}FN_6NaOS_2$ $[M+Na]^+$: 445.1256, found: 445.1255.

4.5.10. (1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate (**34**): yield 76.1%. white solid. Mp: 182-183°C; ^{1}H NMR (400 MHz, Acetone-d_6, δ, ppm): 7.98 (s, 1H), 7.13-7.46 (m, 4H), 5.69 (d, 1H, *J* = 6.6 Hz), 5.61 (s, 2H), 4.61 (s, 2H), 4.26 (br, 2H), 3.85-3.91 (m, 3H), 3.54 (t, 4H, *J* = 5.0 Hz), 1.12 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 164.1, 161.6, 156.6, 144.2, 130.5, 130.4, 130.0, 129.9, 122.7, 116.2, 116.0, 53.4, 42.8, 31.7, 23.4; HRMS (ESI) calcd for $C_{19}H_{25}FN_6NaOS_2$ $[M+Na]^+$: 459.1413, found: 459.1414.

4.5.11. (1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate (**35**): yield 81.4%. white solid. Mp: 85-86°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.61 (s, 1H), 7.05-7.28 (m, 4H), 5.47 (s, 2H), 4.70 (s, 2H), 4.34 (br, 2H), 3.95 (br, 2H), 3.35 (t, 4H, *J* = 4.8 Hz), 3.27 (q, 2H, *J* = 7.1 Hz), 2.85 (s, 3H), 1.18 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.2, 164.0, 163.9, 161.6, 130.5, 130.5, 130.0, 129.9, 122.7, 116.2, 116.0, 53.4, 46.2, 44.8, 35.3, 31.7, 12.6; HRMS (ESI) calcd for $C_{19}H_{26}FN_6OS_2$ $[M+H]^+$: 437.1594, found:437.1591.

4.5.12. (1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(cyclohexylcarbamoyl)piperazine-1-carbodithioate (**36**): yield 77.0%. white solid. Mp: 196-197°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.60 (s, 1H), 7.05-7.28 (m, 4H), 5.47 (s, 2H), 4.69 (s, 2H), 4.33 (br, 3H), 3.95 (br, 2H), 3.60-3.71 (m, 1H), 3.53 (s, 4H), 1.07-2.00 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 164.1, 161.6, 156.5, 144.2, 130.4, 130.4, 130.0, 129.9, 122.7, 116.2, 116.0, 53.4, 49.7, 33.9, 31.7, 29.7, 25.6, 25.0;

HRMS (ESI) calcd for $C_{22}H_{29}FN_6NaOS_2$ $[M+Na]^+$: 499.1726, found: 499.1725.

4.5.13. (1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-carbamoylpiperazine-1-carbodithioate (**37**): yield 82.3%. white solid. Mp: 97-98°C; ^{1}H NMR (400 MHz, Acetone-d_6, δ, ppm): 8.02 (s, 1H), 7.40-7.46 (m, 4H), 5.65 (s, 2H), 5.57 (br,1H), 4.65 (s, 2H), 4.32 (br, 2H), 3.99 (br, 2H), 3.59 (t, 4H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 194.8, 158.2, 142.8, 135.5, 133.3, 130.4, 129.2, 124.4, 52.4, 43.0, 31.9; HRMS (ESI) calcd for $C_{16}H_{19}ClN_6NaOS_2$ $[M+Na]^+$: 433.0648, found: 433.0646.

4.5.14. (1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate (**38**): yield 75.5%. white solid. Mp: 195-196°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.60 (s, 1H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 5.46 (s, 2H), 4.69 (s, 2H), 4.32 (br, 3H), 3.95 (br, 2H), 3.53 (s, 4H), 3.32 (q, 2H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.5, 157.2, 144.3, 134.8, 133.1, 129.4, 129.3, 122.9, 53.5, 42.6, 35.9, 31.7, 15.6; HRMS (ESI) calcd for $C_{18}H_{24}ClN_6OS_2$ $[M+H]^+$: 439.1142, found: 439.1144.

4.5.15. (1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate (**39**): yield 76.9%. white solid. Mp: 202-203°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.59 (s, 1H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 5.46 (s, 2H), 4.68 (s, 2H), 4.34 (br, 2H), 4.21 (d, 1H, *J* = 6.4 Hz), 3.93-4.01 (m, 3H), 3.53 (s, 4H), 1.17 (d, 6H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 156.6, 144.3, 134.8, 133.1, 129.4, 129.3, 122.8, 53.4, 42.8, 31.7, 23.4; HRMS (ESI) calcd for $C_{19}H_{26}ClN_6OS_2$ $[M+H]^+$: 453.1298, found: 453.1298.

4.5.16. (1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate (**40**): yield 81.0%. white solid. Mp: 112-113°C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.61 (s, 1H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 5.47 (s, 2H), 4.70 (s, 2H), 4.34 (br, 2H), 3.95 (br, 2H), 3.50 (t, 4H, *J* = 5.0 Hz), 3.27 (q, 2H, *J* = 7.1 Hz), 2.84 (s, 3H), 1.18 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.2, 163.9, 144.3, 134.7, 133.2, 129.4, 129.3, 122.8, 53.3, 50.9, 49.6, 46.2, 44.8, 35.3, 31.7, 12.6; HRMS (ESI) calcd for $C_{19}H_{26}ClN_6OS_2$ $[M+H]^+$: 453.1298, found: 453.1299.

4.5.17.(1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl4-carbamoylpiperazine-1-carbodithioate (**41**): Yield 72.9%. white solid. Mp:179-180°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.57 (s, 1H), 7.17-7.21 (m, 4H), 5.46 (s, 2H), 4.69 (s, 2H), 4.67 (br, 2H), 4.37 (br, 2H), 4.00 (br, 2H), 3.59 (t, 4H, *J* = 5.4 Hz), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 194.8, 158.2, 142.7, 138.0, 133.5, 129.8, 128.5, 124.1, 53.0, 43.0, 31.9, 21.2; HRMS (ESI) calcd for $C_{17}H_{22}N_6NaOS_2$ $[M+Na]^+$: 413.1194, found: 413.1192.

4.5.18. (1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate (**42**): yield 73.0%. white solid. Mp:123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (s, 1H), 7.15-7.19 (m, 4H), 5.45 (s, 2H), 4.68 (s, 2H), 4.35 (br, 3H), 3.92 (br, 2H), 3.53 (t, 4H, *J* = 5.1 Hz), 3.32 (q, 2H, *J* = 7.2 Hz), 2.35 (s, 3H), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ,

ppm): 196.5, 156.6, 138.7, 129.8, 128.1, 122.7, 53.8, 44.8, 35.9, 31.8, 21.3, 15.5; HRMS (ESI) calcd for $C_{19}H_{26}N_6NaOS_2$ $[M+Na]^+$: 441.1507, found: 441.1504.

4.5.19. (1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate (**43**): yield 83.1%. white solid. Mp: 198-199^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.55 (s, 1H), 7.15-7.19 (m, 4H), 5.44 (s, 2H), 4.67 (s, 2H), 4.33 (br, 2H), 4.21 (br, 1H), 3.92-3.97 (m, 3H), 3.52 (t, 4H, *J* = 5.3 Hz), 2.35 (s, 3H), 1.17 (d, 6H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.5, 156.6, 138.7, 129.8, 128.1, 122.7, 54.0, 42.8, 31.8, 23.4, 21.2; HRMS (ESI) calcd for $C_{20}H_{28}N_6NaOS_2$ $[M+Na]^+$: 455.1664, found: 455.1666.

*4.5.20. (1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-*carbodithioate (**44**): yield 73.7%. white solid. Mp: 110-111^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (s, 1H), 7.14-7.19 (m, 4H), 5.44 (s, 2H), 4.68 (s, 2H), 4.31 (br, 2H), 3.94 (br, 2H), 3.34 (t, 4H, *J* = 5.1 Hz), 3.26 (q, 2H, *J* = 7.1 Hz), 2.83 (s, 3H), 2.34 (s, 3H), 1.17 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.3, 163.9, 138.7, 131.6, 129.8, 128.1, 54.0, 46.1, 44.8, 35.4, 31.8, 21.2, 12.6; HRMS (ESI) calcd for $C_{20}H_{29}N_6OS_2$ $[M+H]^+$: 433.1844, found: 433.1843.

4.5.21.(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-carbamoylpiperazine-1-carbodithioate (**45**): yield 80.4%. white solid. Mp: 189-190^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.08 (s, 1H), 7.30 (d, 2H, *J* = 8.4 Hz), 6.94 (d, 2H, *J* = 8.4 Hz), 6.12 (s, 2H), 5.48 (s, 2H), 4.57 (s, 2H), 4.21 (br, 2H), 3.87 (br, 2H), 3.74 (s, 3H), 3.43 (t, 4H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 194.8, 159.6, 158.2, 142.6, 130.1, 128.4, 124.0, 114.6, 55.6, 52.8, 43.0, 31.9; HRMS (ESI) calcd for $C_{17}H_{22}N_6NaO_2S_2$ $[M+Na]^+$: 429.1143, found: 429.1142.

4.5.22.(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethylcarbamoyl)piperazine-1-carbodithioate (**46**): yield 71.9%. white solid. Mp: 179-180^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.54 (s, 1H), 7.23 (d, 2H, *J* = 8.6 Hz), 6.90 (d, 2H, *J* = 8.6 Hz), 5.41 (s, 2H), 4.67 (s, 2H), 4.35 (br, 3H), 3.94 (br, 2H), 3.81 (s, 3H), 3.54 (t, 4H, *J* = 5.3 Hz), 3.32 (q, 2H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.5, 159.9, 157.2, 143.8, 129.7, 126.5, 122.5, 114.5, 55.4, 53.8, 35.9, 31.8, 15.5; HRMS (ESI) calcd for $C_{19}H_{26}N_6NaO_2S_2$ $[M+Na]^+$: 457.1456, found: 457.1458.

4.5.23.(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate (**47**): yield 83.2%. white solid. Mp: 190-191^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (s, 1H), 7.25 (d, 2H, *J* = 8.6 Hz), 6.92 (d, 2H, *J* = 8.6 Hz), 5.44 (s, 2H), 4.69 (s, 2H), 4.36 (br, 2H), 4.23 (br, 1H), 3.92-4.03 (m, 3H), 3.83 (s, 3H), 3.54 (t, 4H, *J* = 5.1 Hz), 1.19 (d, 6H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.5, 159.9, 156.6, 143.8, 129.7, 126.5, 122.6, 114.5, 55.4, 53.8, 42.8, 31.8, 29.7, 23.4; HRMS (ESI) calcd for $C_{20}H_{28}N_6NaO_2S_2$ $[M+Na]^+$: 471.1613, found:471.1616.

4.5.24. (1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate (**48**): yield 87.0%. white solid. Mp: 82-83^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (s, 1H), 7.24 (d, 2H, *J* = 8.6 Hz), 6.91 (d, 2H, *J* = 8.6 Hz), 5.42 (s, 2H), 4.86 (s, 2H), 4.34 (br, 2H),

3.94 (br, 2H), 3.81(s, 3H), 3.34 (s, 4H), 3.27 (q, 2H, *J* = 7.1 Hz), 2.84 (s, 3H), 1.18 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.3, 163.9, 159.9, 143.9, 129.6, 126.6, 122.5, 114.5, 55.4, 53.7, 46.1, 44.8, 35.4, 31.8, 12.6; HRMS (ESI) calcd for $C_{20}H_{28}N_6NaO_2S_2$ $[M+Na]^+$: 471.1613, found: 471.1615.

*4.5.25. (1-(3,4,5-Trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-*carbodithioate (**49**): yield 79.4%. white solid. Mp: 142-143^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.62 (s, 1H), 6.48 (s, 2H), 5.41 (s, 2H), 4.94 (br, 2H), 4.68 (s, 2H), 4.33 (br, 2H), 3.97 (br, 2H), 3.83 (s, 3H), 3.82 (s, 6H), 3.57 (s, 4H) ; ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 194.8, 158.2, 153.4, 142.7, 137.7, 131.8, 124.3, 106.1, 60.4, 56.4, 53.5, 43.0, 31.9; HRMS (ESI) calcd for $C_{19}H_{27}N_6O_4S_2$ $[M+H]^+$: 467.1535, found: 467.1537.

4.5.26. (1-(3,4,5-Trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate (**50**): yield 81.7%. white solid. Mp: 154-155^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.62 (s, 1H), 6.48 (s, 2H), 5.41 (s, 2H), 4.69 (s, 2H), 4.50 (br, 1H), 4.34 (br, 2H), 3.95 (br, 2H), 3.84 (s, 3H), 3.83 (s, 6H), 3.52 (s, 4H), 3.31 (q, 2H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.3, 157.3, 153.7, 144.0, 138.2, 130.1, 122.9, 105.2, 60.9, 56.2, 54.4, 42.5, 35.8, 31.7, 15.5; HRMS (ESI) calcd for $C_{21}H_{31}N_6O_4S_2$ $[M+H]^+$: 495.1848, found: 495.1849.

4.5.27. (1-(3,4,5-Trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate (**51**): yield 73.5%. white solid. Mp: 170-171^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.61 (s, 1H), 6.47 (s, 2H), 5.40 (s, 2H), 4.69 (s, 2H), 4.33 (br, 3H), 3.93-4.02 (m, 3H), 3.84 (s, 3H), 3.83 (s, 6H), 3.51 (s, 4H), 1.17 (d, 6H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.4, 156.5, 153.7, 144.1, 138.3, 130.0, 122.9, 105.2, 60.9, 56.3, 54.5, 42.8, 31.7, 23.4; HRMS (ESI) calcd for $C_{22}H_{32}N_6NaO_4S_2$ $[M+Na]^+$: 531.1824, found: 531.1822.

*4.5.28.(1-(3,4,5-Trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethyl(methyl)carbamoyl)piperazin*e *-1-carbodithioate* (**52**): yield 86.2%. white solid. Mp:111-112^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.62 (s, 1H), 6.47 (s, 2H), 5.41 (s, 2H), 4.70 (s, 2H), 4.32 (br, 2H), 3.94 (br, 2H), 3.84 (s, 3H), 3.83 (s, 6H), 3.34 (t, 4H, *J* = 5.2 Hz), 3.25 (q, 2H, *J* = 7.1 Hz), 2.83 (s, 3H), 1.17 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 196.3, 163.9, 153.7, 144.2, 138.2, 130.1, 122.8, 105.2, 60.9, 56.2, 54.4, 46.2, 44.8, 35.3, 31.7, 12.6; HRMS (ESI) calcd for $C_{22}H_{33}N_6O_4S_2$ $[M+H]^+$: 509.2005, found: 509.2006.

4.6. Antiproliferative activity assays

Exponentially growing cells were seeded into 96-well plates at a concentration of 5×10^3 cells per well. After 24 h incubation at 37^{o}C, the culture medium was removed and replaced with fresh medium containing the candidate compounds in different concentrations. The cells were incubated for another 72 h. Afterwards, 20 μL of MTT solution (5mg/mL) was added to all wells and incubated for 4 h at 37^{o}C. Discarded the suspension and added 150 μL of dimethyl sulfoxide (DMSO) to each well and

shaked the plates to dissolve the dark blue crystals (formazan); the absorbance was measured using a microplate reader at a wavelength of 570 nm. Each concentration was analyzed in triplicate and the experiment was repeated three times. The average 50% inhibitory concentration (IC_{50}) was determined from the dose-response curves according to the inhibition ratio for each concentration.

4.7. Flow cytometric analysis of cell cycle distribution

For flow cytometric analysis of DNA content, 5×10^5 MGC-803 cells in exponential growth were treated with different concentrations of the test compounds for 12 or 24 h. After an incubation period, the cells were collected, centrifuged and fixed with icecold ethanol (70%). The cells were then treated with buffer containing RNAse A and 0.1% Triton X-100 and then stained with PI. Samples were analyzed on Accuri C6 flow cytometer (Becton, Dickinson). Data obtained from the flow cytometer was analysed using the FlowJo software (Tree Star, Inc., Ashland, OR, USA)

4.8. Morphologic analysis of cellular apoptosis.

MGC-803 cells were seeded in 24-well plates at a density of 8×10^3 cells/well, and incubated with **34** with different concentrations. After 12 h incubation, the cells were digested and collected. Then the cells were fixed and stained with DNA fluorochrome Hoechst 33258 for 20 min. After washing with phosphate buffered saline (PBS), the morphological features of apoptosis (including cellular nucleus shrinkage, chromatin condensation, intense fluorescence and nuclear fragmentation) were monitored by fluorescence microscopy (Nikon, Japan).

4.9. Flow cytometric analysis of cellular apoptosis

MGC-803 cells were plated in 6-well plates (5.0×10^4 cells/mL) and incubated at 37^0C for 12 h. Exponentially growing cells were then incubated for 12 h with complete medium (blank) or with the compound **34**. Cells were then harvested and the Annexin-V-FITC/PI apoptosis kit (Biovision) was used according to the manufacturer's instructions to detect apoptotic cells. Ten thousand events were collected for each sample and analyzed by Accuri C6 flow cytometer.

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Fig. 1. 1,2,3-Triazole derivatives with anticancer activity.

Fig. 2. Dithiocarbamate derivatives with anticancer activity.

Fig.3. Urea derivatives with anticancer activity.

Fig. 4. Structures of 1,2,3-triazole-dithiocarbamate-urea hybrids.

Fig.5. A**:** Selectivity of compound **27** towards MGC-803 cells over normal cells HEK293; B: Selectivity of compound **34** towards MGC-803 cells over normal cells HEK293

Fig.6. A: Effect of compound **27** on morphology of MGC-803 cells; B: Effect of compound **34** on morphology of MGC-803 cells; C: Representative flow cytometric histograms of apoptotic MGC-803 cells after 12 h treatment with **34** at different concentrations.

Fig.7. A: Effect of compound **27** on cell cycle in MGC-803 cells. a, b, c, d incubated for 12 h; e, f, g, h incubated for 24 h; B: Effect of compound **34** on cell cycle in MGC-803 cells. a, b, c, d incubated for 12 h; e, f, g, h incubated for 24 h.

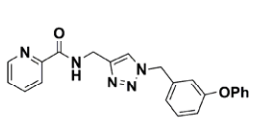
Scheme 1. Synthesis of the 1,2,3-triazole-dithiocarbamate-urea hybrids. Reagent and reaction conditions: (a) CS_2, $Na_3PO_4 \cdot 12H_2O$, propargyl bromide, acetone, rt; (b) BnN_3, $CuSO_4 \cdot 5H_2O$, Sodium ascorbate, THF-H_2O (1:1), rt; (c) CF_3COOH, CH_2Cl_2, rt; (d) BTC, Et_3N, R_4R_5NH, CH_2Cl_2, 0^oC-rt.

Table 1

Antiproliferative activity of 1,2,3-triazole-dithiocarbamate-urea hybrids

Com.	R_3	R_4R_5NH	IC_{50} (μM)[a]			
			MGC-803	MCF-7	SMMC-7721	EC-9706
25	*o*-F	NH_2	11.30±1.64	>128	>128	43.11±3.14
26	*o*-F	CH_3CH_2NH	2.83±0.18	5.76±1.21	>128	23.71±2.43
27	*o*-F	$(CH_3)_2CHNH$	1.62±0.12	1.86±0.41	7.13±0.36	20.84±2.19
28	*o*-F	$CH_3CH_2NCH_3$	5.86±2.19	7.21±0.46	19.65±2.44	15.55±1.67
29	*o*-F	$(CH_3)_3CNH$	40.7±2.25	18.80±1.37	>128	87.84±1.78
30	*o*-F	C_6H_6NH	36.51±2.60	84.96±3.37	>128	84.94±3.37
31	*o*-F	$PhCH_2$	13.27±1.67	38.10±2.53	>128	38.10±2.61
32	*p*-F	NH_2	9.33±1.04	22.05±2.38	>128	62.74±3.53
33	*p*-F	CH_3CH_2NH	2.17±0.22	3.66±0.51	44.36±2.21	27.79±2.53
34	*p*-F	$(CH_3)_2CHNH$	0.76±0.03	1.66±0.53	5.97±1.02	12.19±1.34
35	*p*-F	$CH_3CH_2NCH_3$	1.55±0.14	2.15±0.61	23.68±3.14	14.28±1.45
36	*p*-F	C_6H_6NH	>128	>128	>128	>128
37	*p*-Cl	NH_2	>128	>128	>128	>128
38	*p*-Cl	CH_3CH_2NH	35.35±2.72	>128	>128	>128
39	*p*-Cl	$(CH_3)_2CHNH$	19.87±1.07	>128	>128	25.60±2.35
40	*p*-Cl	$CH_3CH_2NCH_3$	4.32±0.64	14.73±1.82	38.23±2.73	17.68±1.99
41	*p*-CH_3	NH_2	29.85±2.73	>128	>128	>128
42	*p*-CH_3	CH_3CH_2NH	19.76±2.45	>128	>128	>128
43	*p*-CH_3	$(CH_3)_2CHNH$	16.55±1.97	4.63±0.70	>128	>128
44	*p*-CH_3	$CH_3CH_2NCH_3$	8.27±1.02	40.1±2.86	>128	70.59±3.43
45	*p*-OCH_3	NH_2	>128	>128	>128	>128
46	*p*-OCH_3	CH_3CH_2NH	>128	97.57±1.99	>128	>128
47	*p*-OCH_3	$(CH_3)_2CHNH$	99.23±3.68	19.58±2.10	>128	>128
48	*p*-OCH_3	$CH_3CH_2NCH_3$	87.89±3.79	21.41±1.01	>128	>128
49	*m,p, m*-triOCH_3	NH_2	>128	>128	>128	>128
50	*m,p, m*-triOCH_3	CH_3CH_2NH	101.3±3.52	>128	>128	>128
51	*m,p, m*-triOCH_3	$(CH_3)_2CHNH$	>128	>128	>128	>128
52	*m, p,m*-triOCH_3	$CH_3CH_2NCH_3$	85.73±3.23	68.47±3.03	>128	>128
5-Fu			7.14±1.26	7.33±0.54	26.71±2.66	0.32±0.25

[a] Antiproliferative activity was assayed by exposure for 72 hours to substances and expressed as concentration required to inhibit tumor cell proliferation by 50% (IC_{50}). Data are presented as the means ± SDs from the dose-response curves of three independent experiments.



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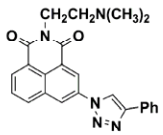

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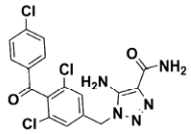

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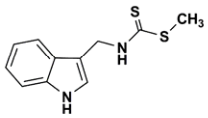

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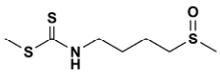

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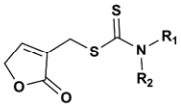

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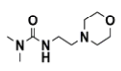

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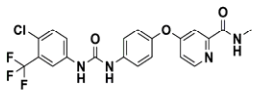

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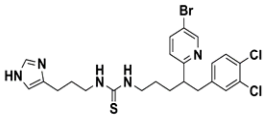

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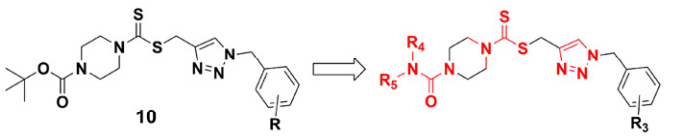
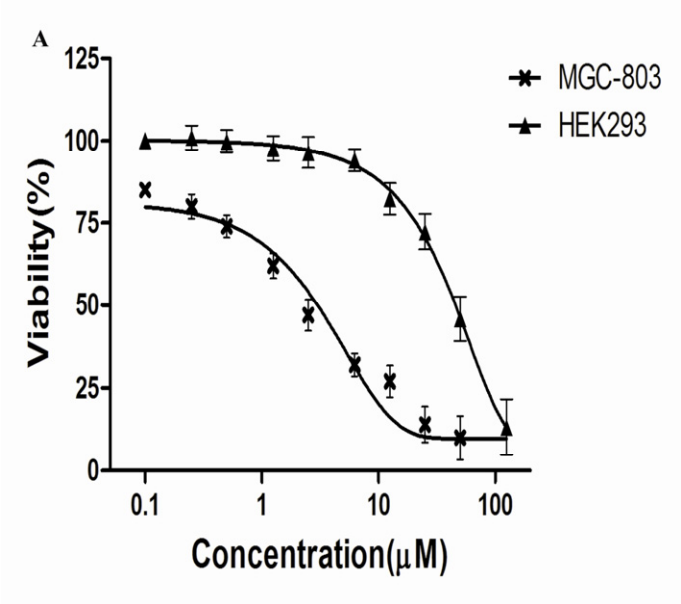
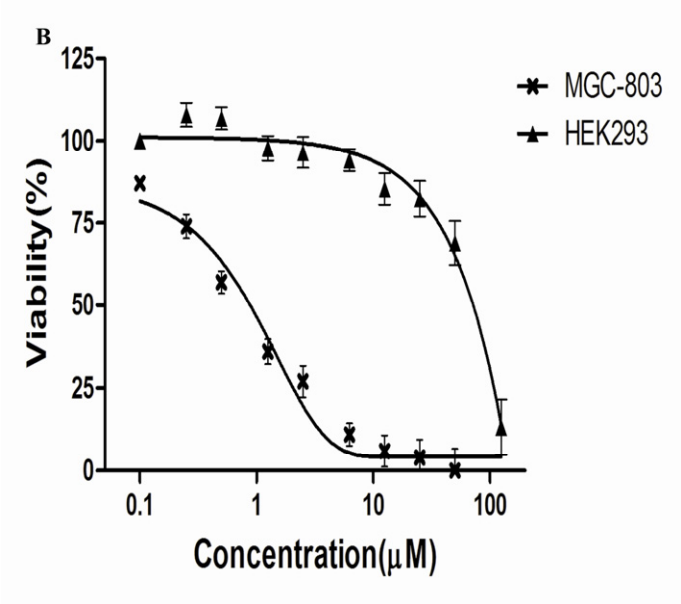


1,2,3-triazole-dithiocarbamate-urea hybrids





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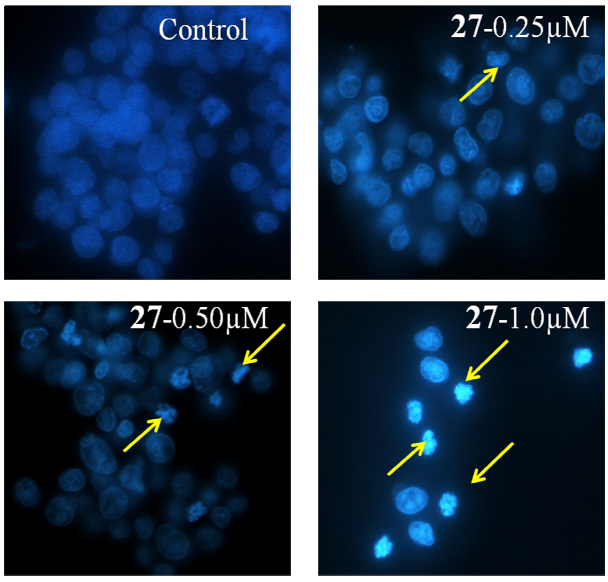

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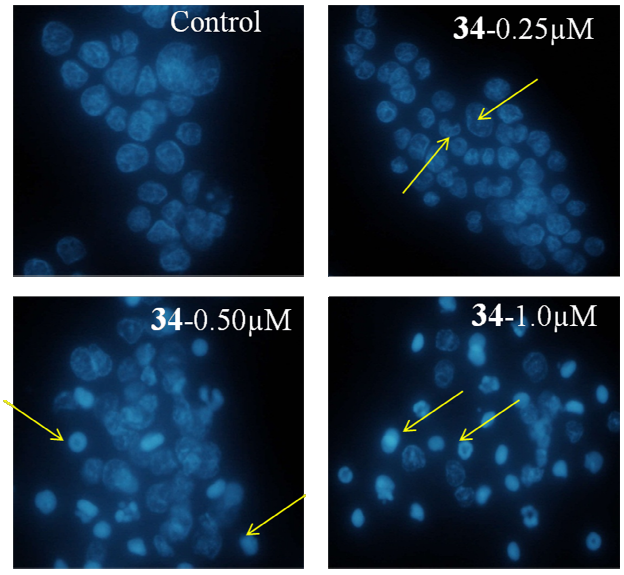

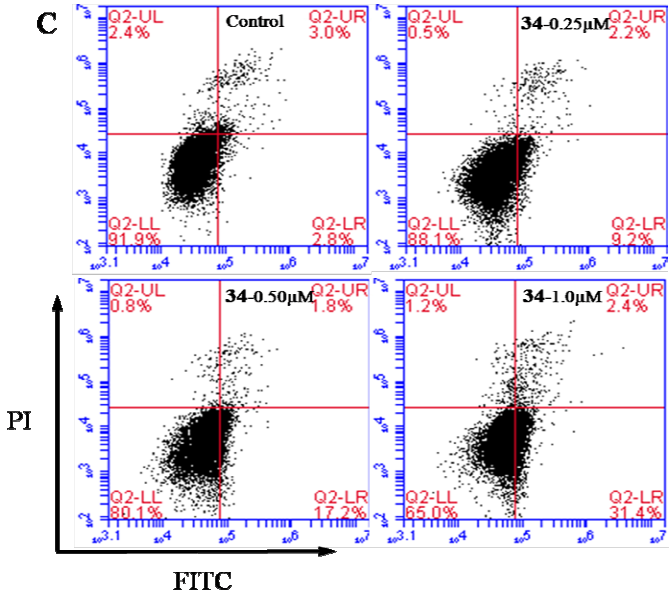

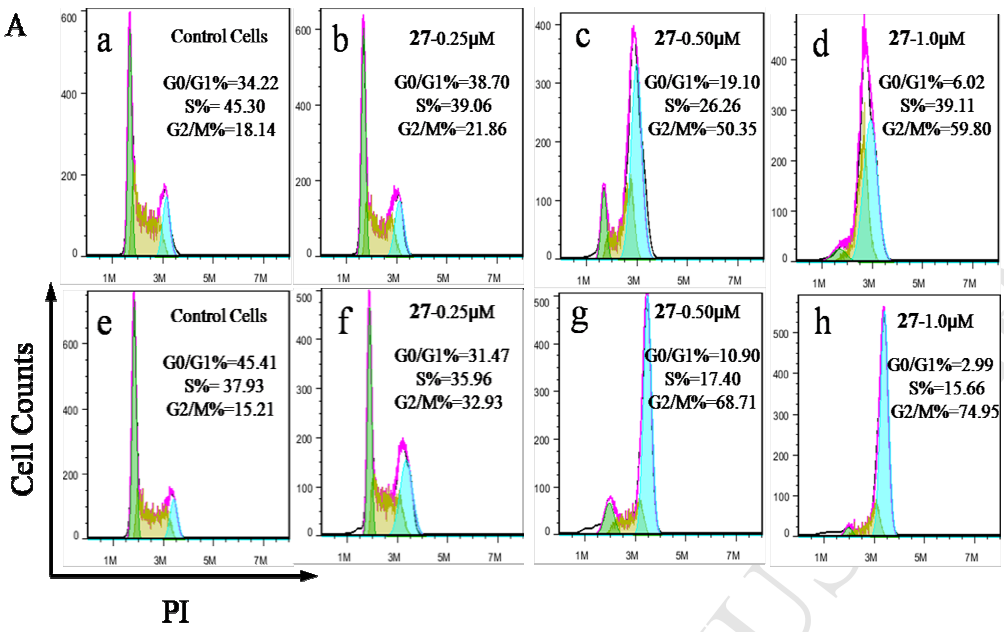

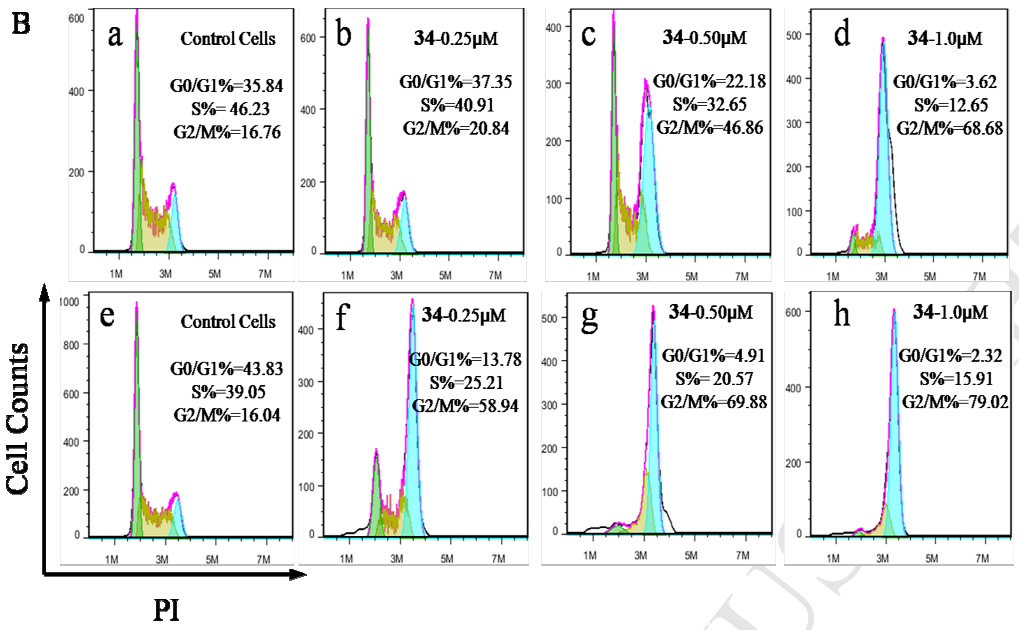

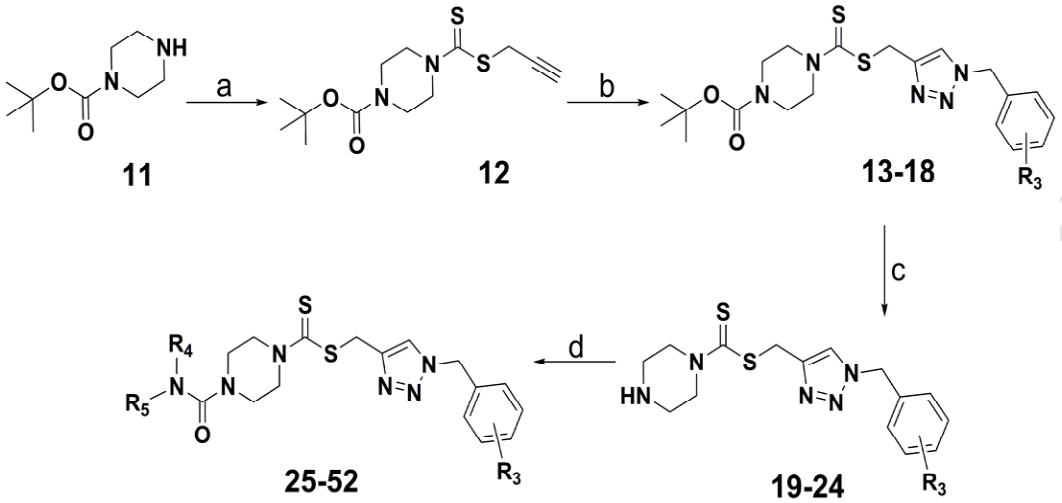

European Journal of Medicinal Chemistry

Supplementary data

Design, synthesis and antiproliferative activity studies of novel 1,2,3-triazole-dithiocarbamate-urea hybrids

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Figure S1. ^{1}H NMR ($CDCl_3$) spectrum of *tert butyl 4-((prop-2-ynylthio)carbonothioyl)piperazine-1-carboxylate* (**12**)

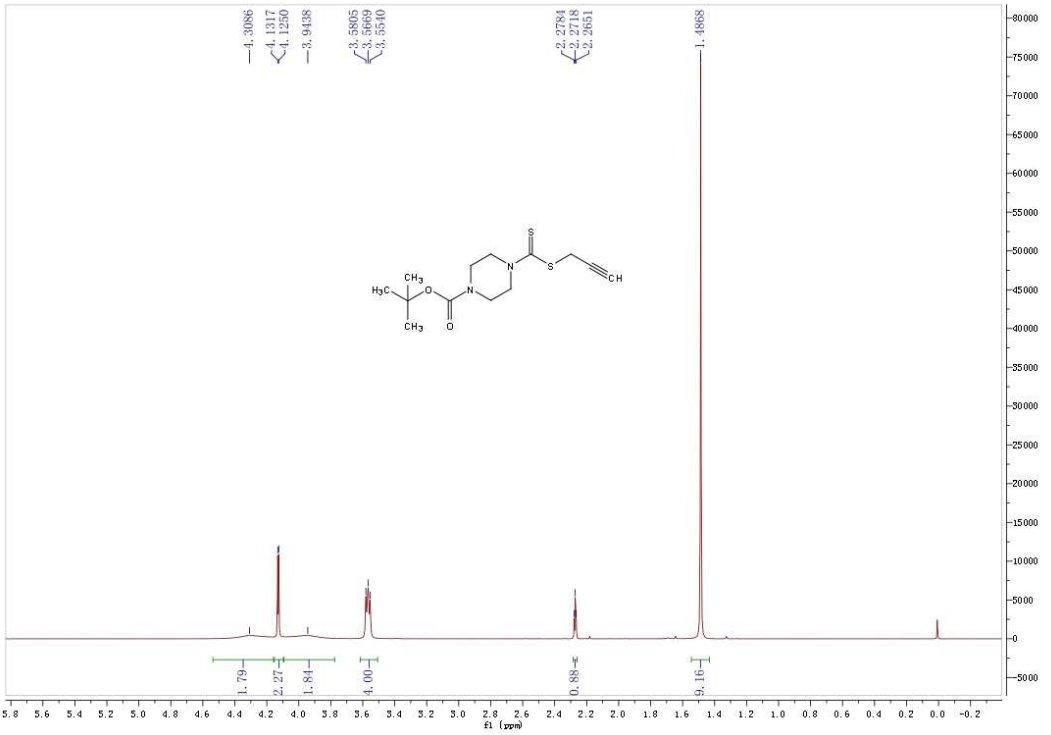

Figure S2. ^{1}H NMR ($CDCl_3$) spectrum of *tert butyl 4-(((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate* (**13**)

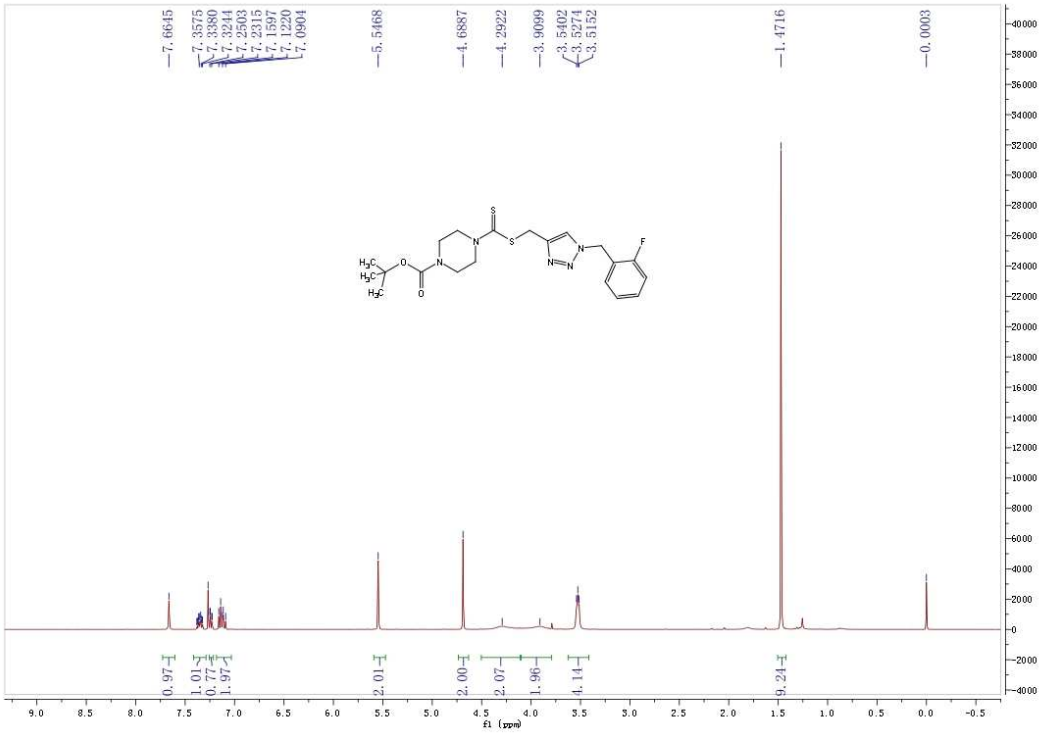

Figure S3. ^{13}C NMR (DMSO-d_6) spectrum of *tert butyl 4-(((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate* (**13**)

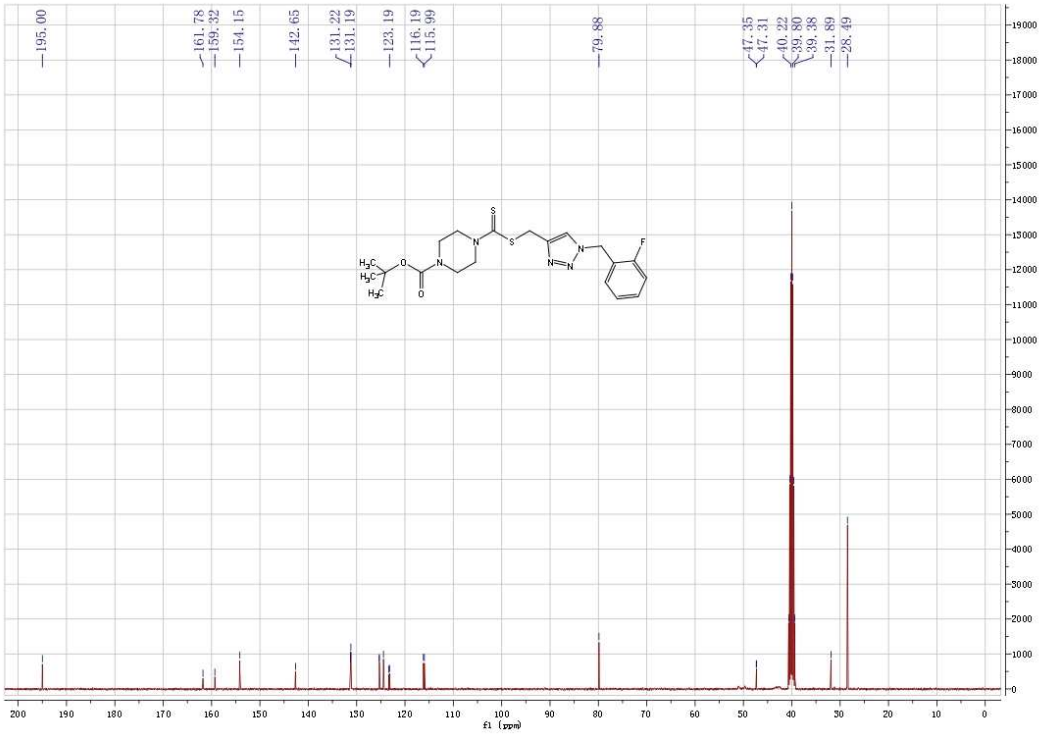

Figure S4. ^{1}H NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**14**):

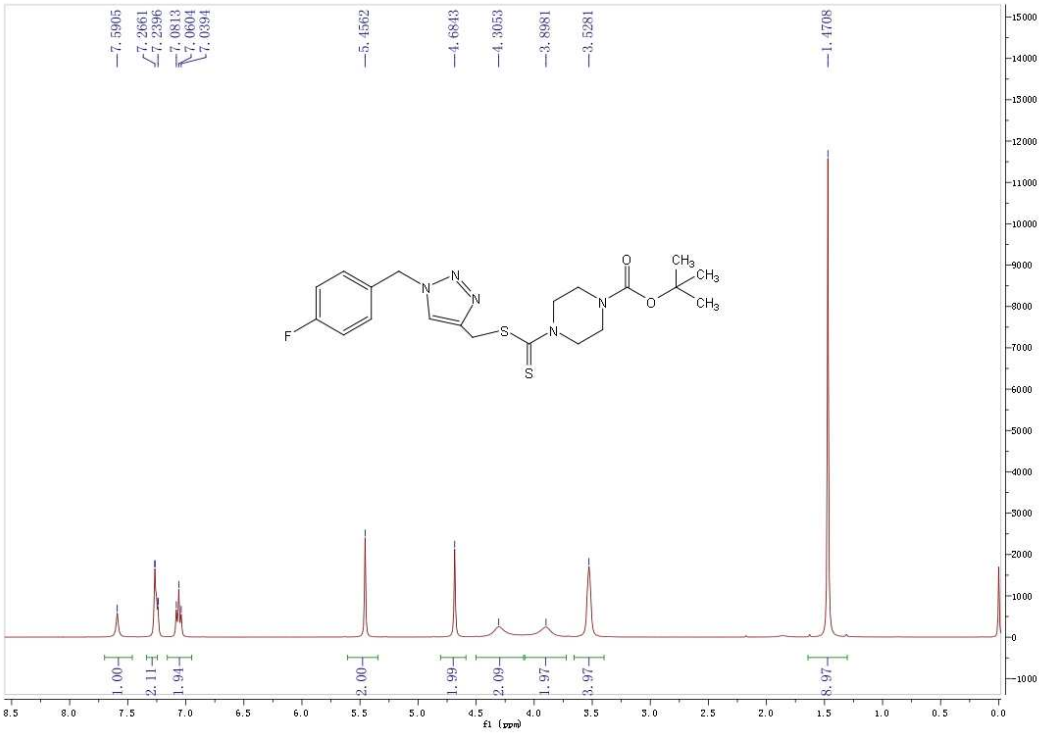

Figure S5. ^{13}C NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**14**):

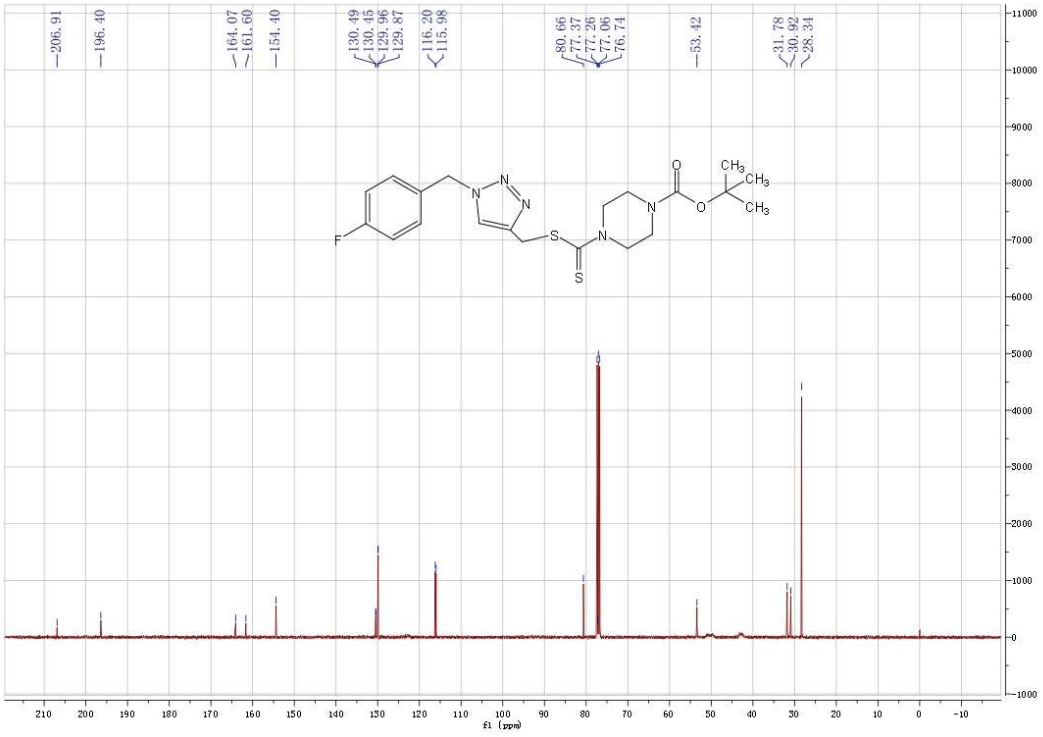

Figure S6. ^{1}H NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**15**):

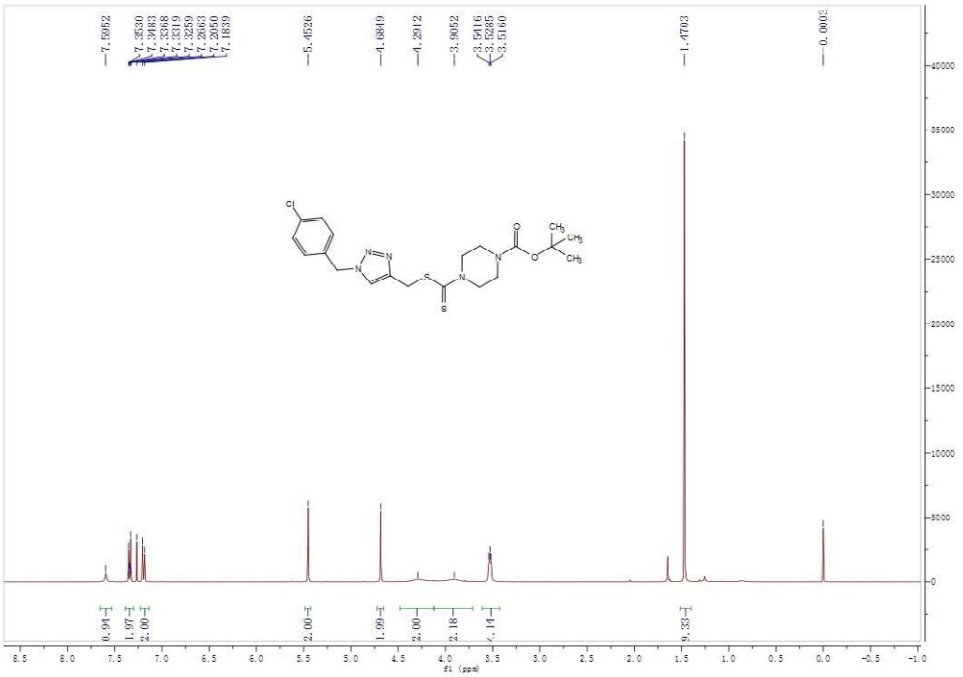

Figure S7. ^{13}C NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**15**):

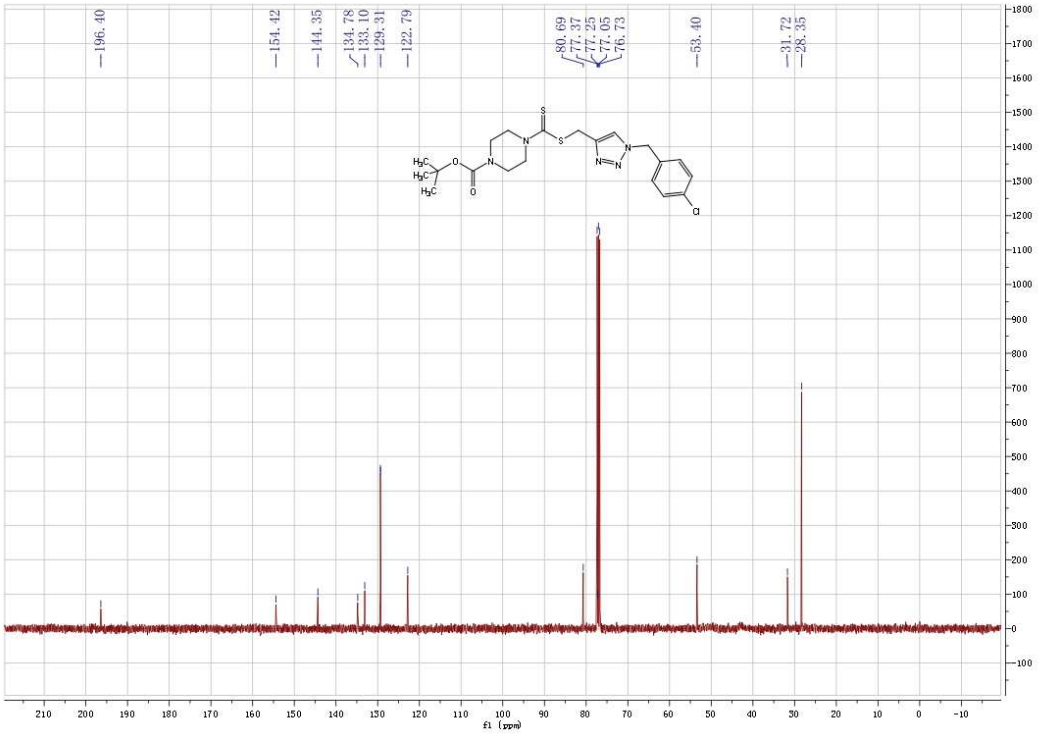

Figure S8. ^{1}H NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-arboxylate (**16**):

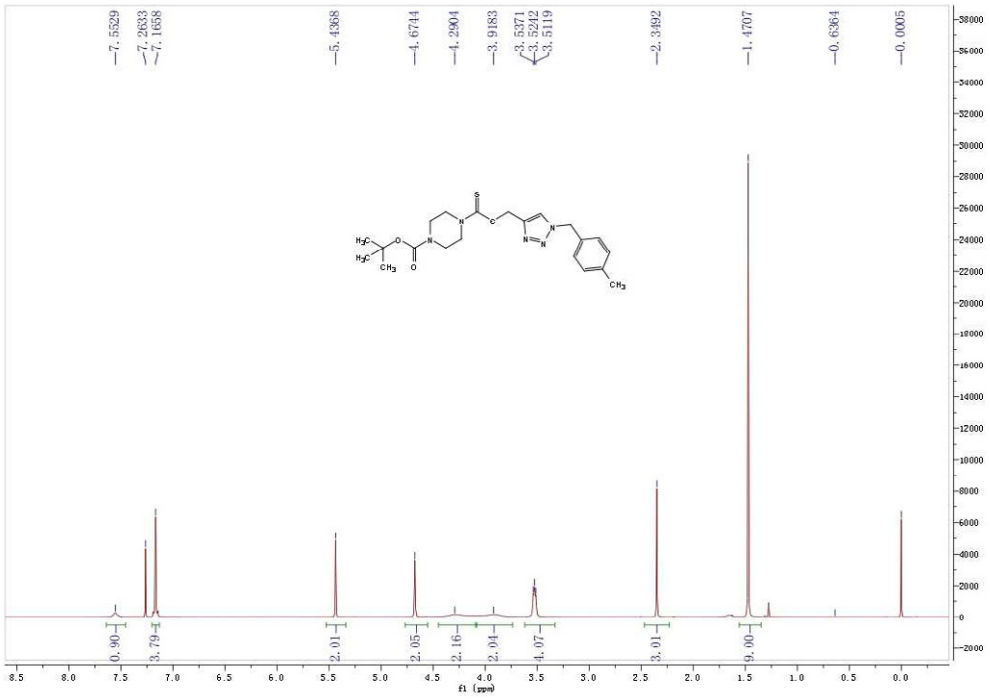

Figure S9. ^{13}C NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-arboxylate (**16**):

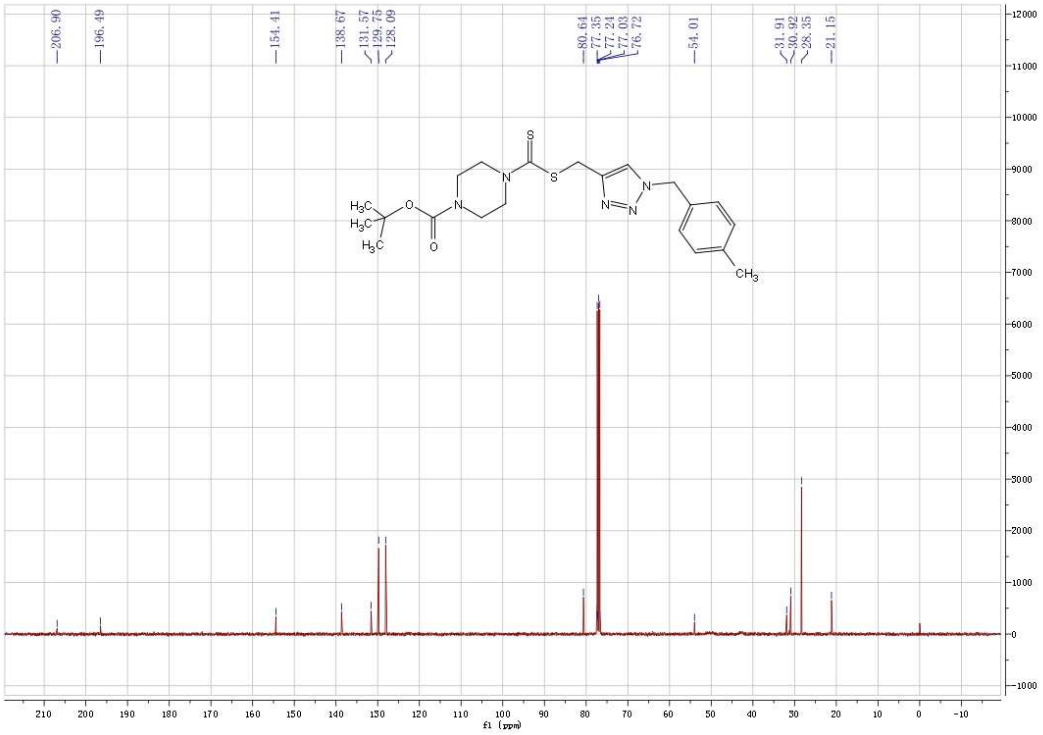

Figure S10. ^{1}H NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**17**):

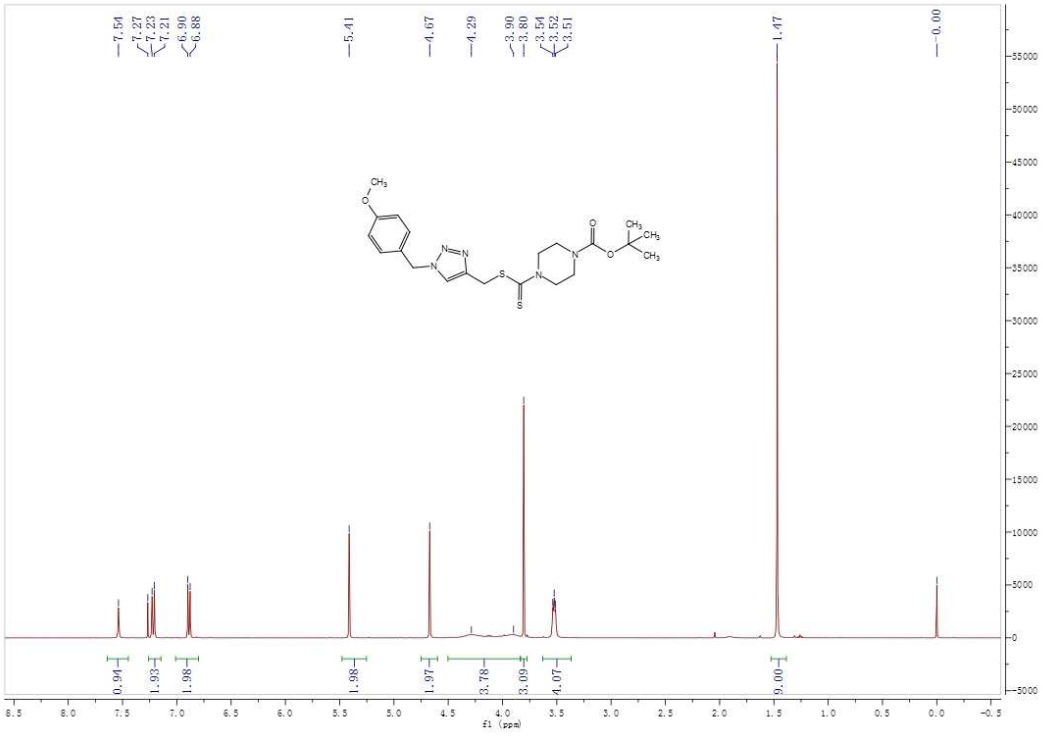

Figure S11. ^{13}C NMR ($CDCl_3$) spectrum of tert butyl 4-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate (**17**):

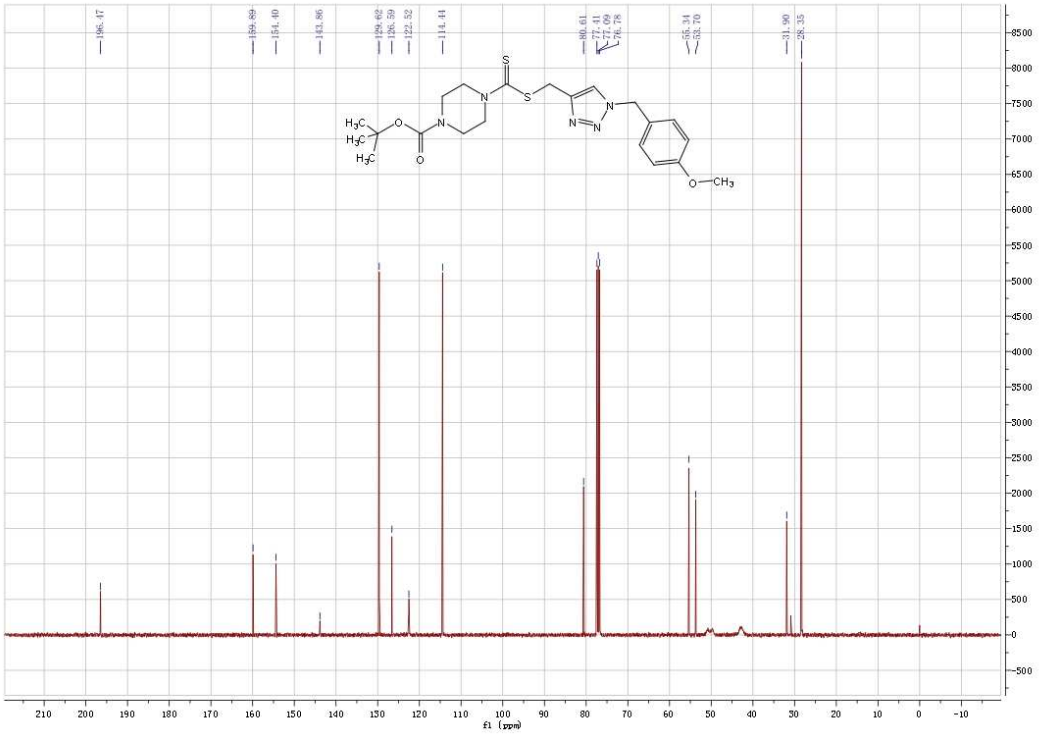

Figure S12. ^{1}H NMR ($CDCl_3$) spectrum of (1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**19**):

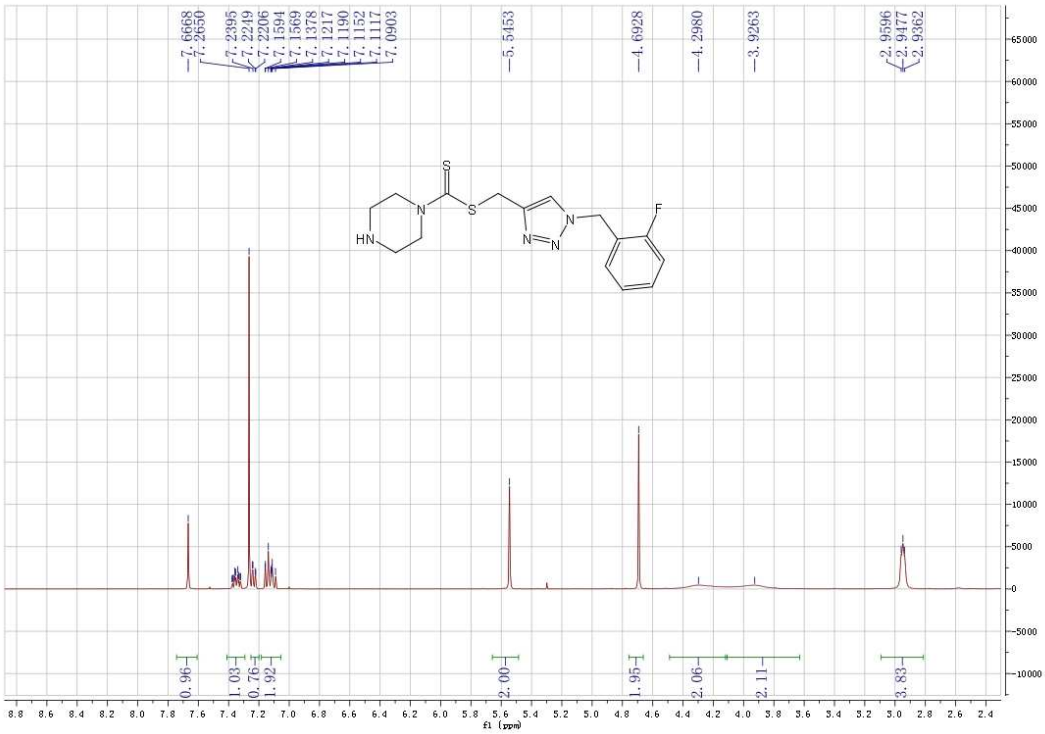

Figure S13. ^{13}C NMR ($CDCl_3$) spectrum of (1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**19**):

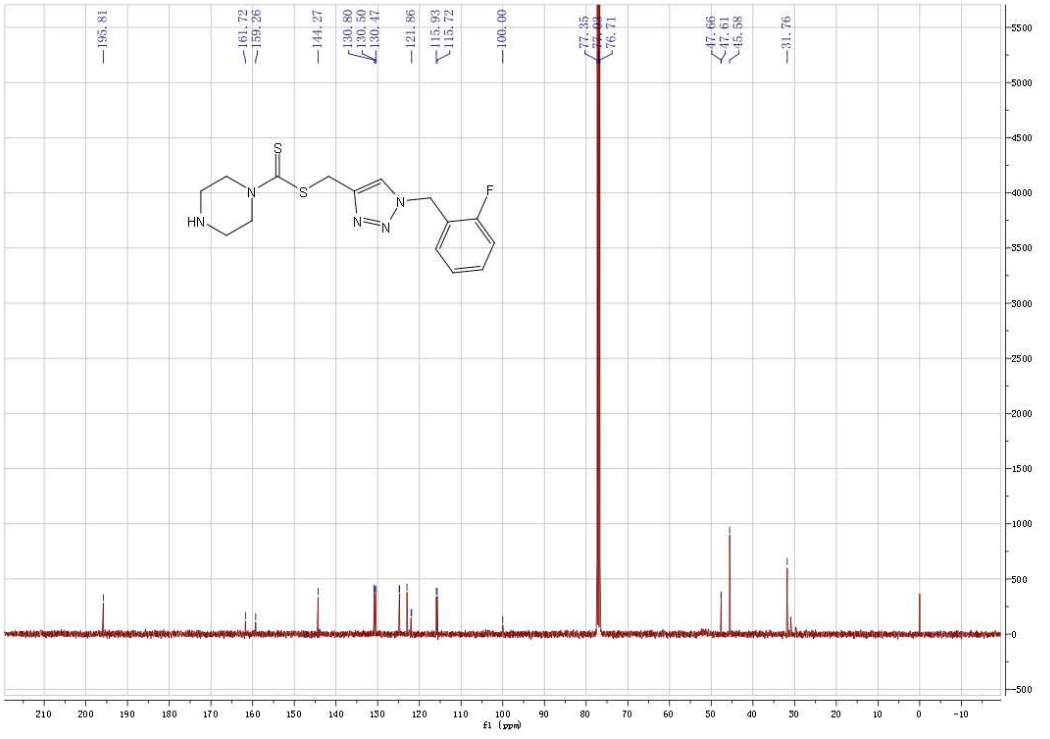

Figure S14. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate* (**20**):

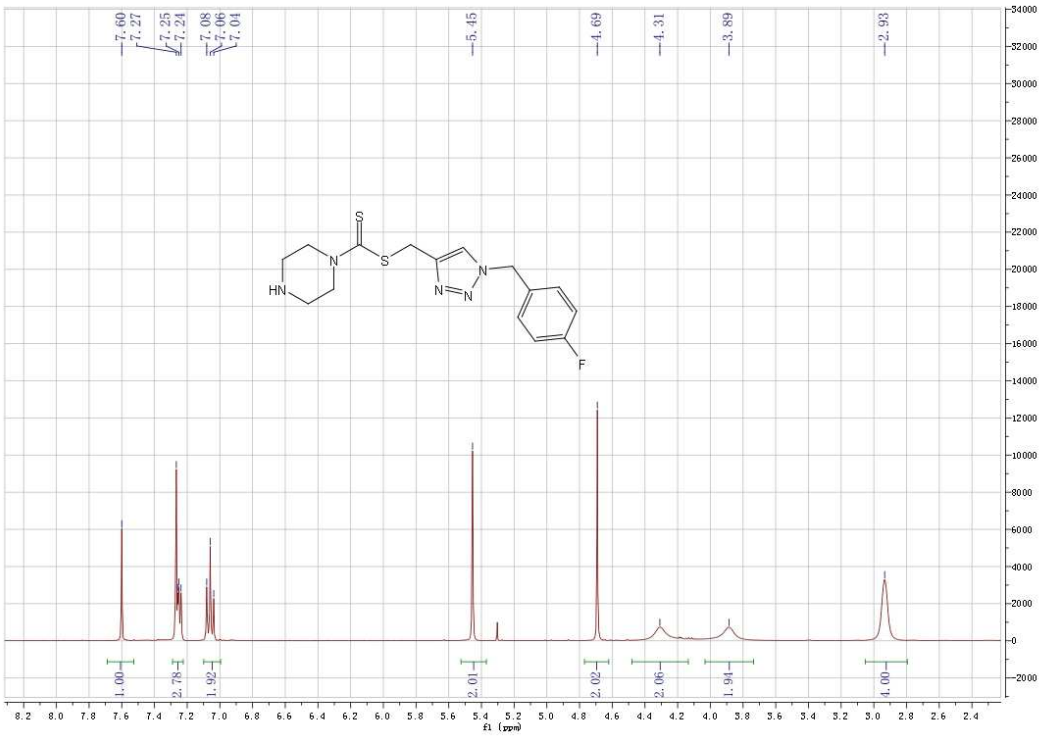

Figure S15. ^{13}C NMR ($CDCl_3$) spectrum of (1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**20**):

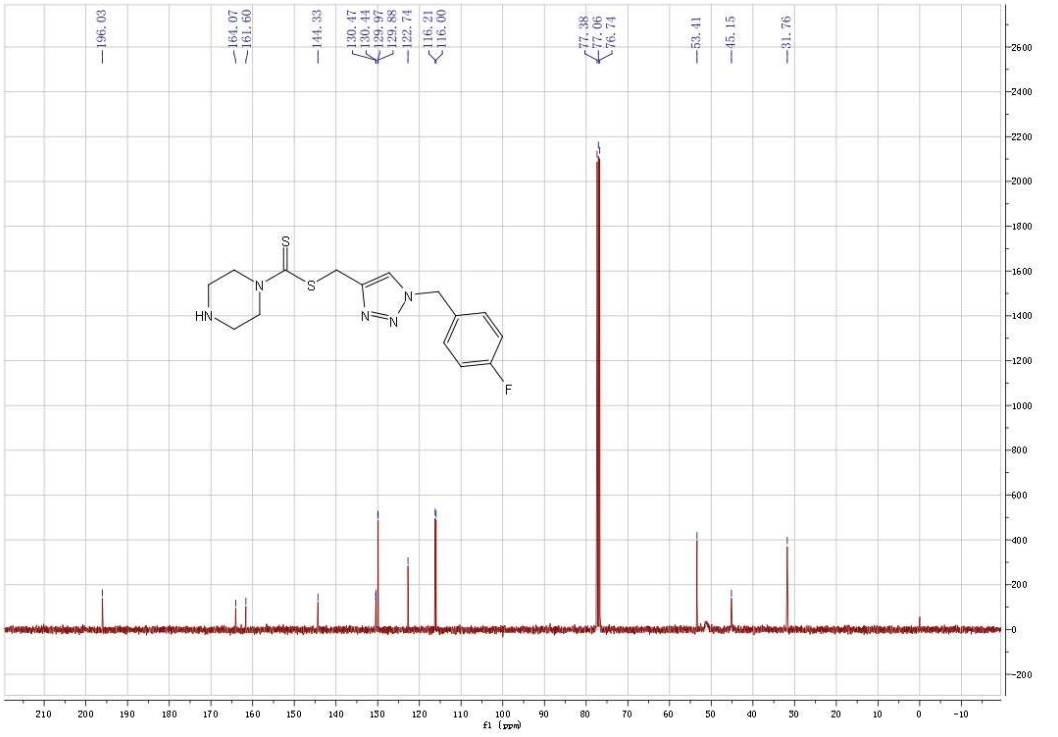

Figure S16. ^{1}H NMR ($CDCl_3$) spectrum of (1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**21**):

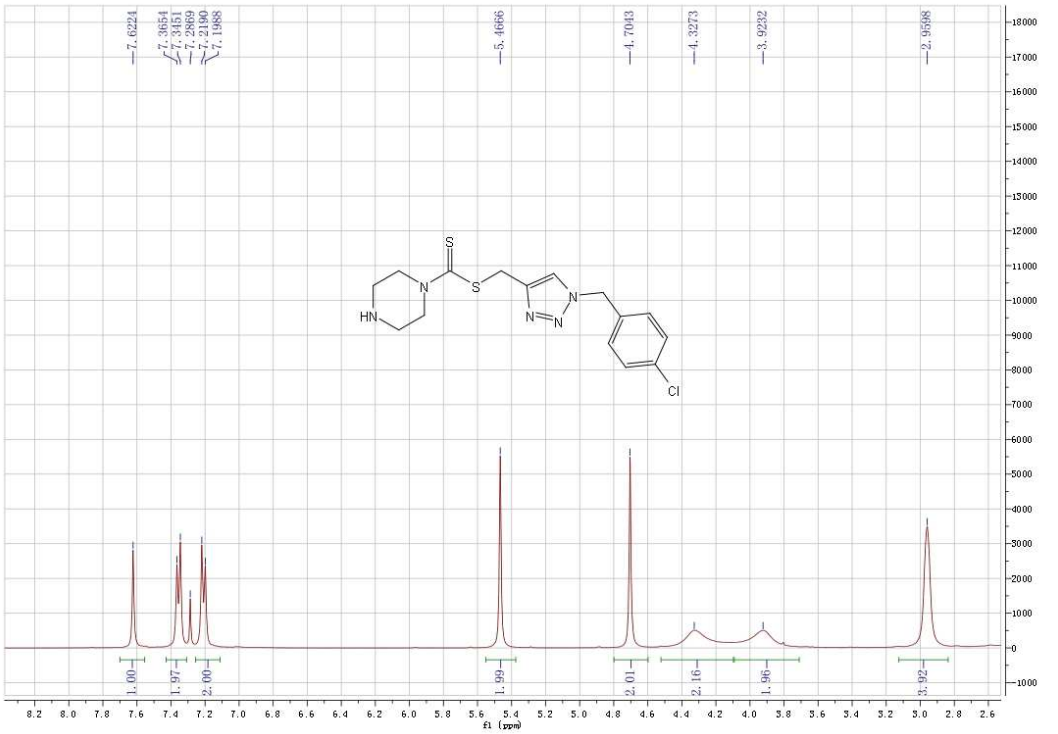

Figure S17. ^{13}C NMR ($CDCl_3$) spectrum of (1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**21**):

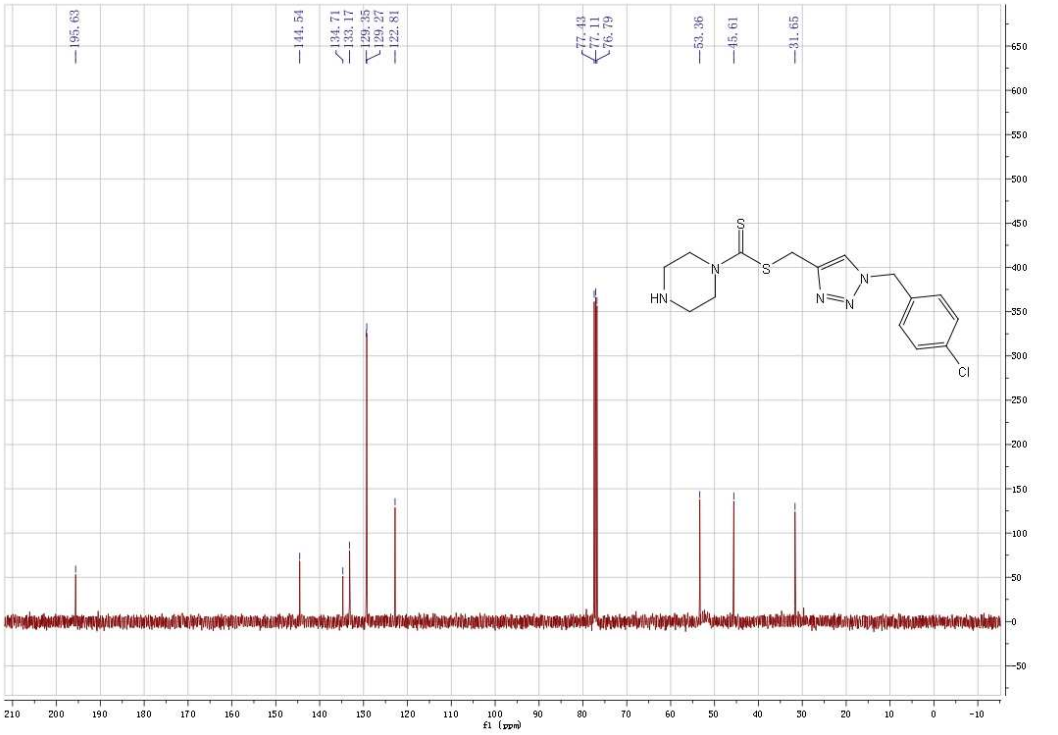

Figure S18. ^{1}H NMR ($CDCl_3$) spectrum of 1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**22**):

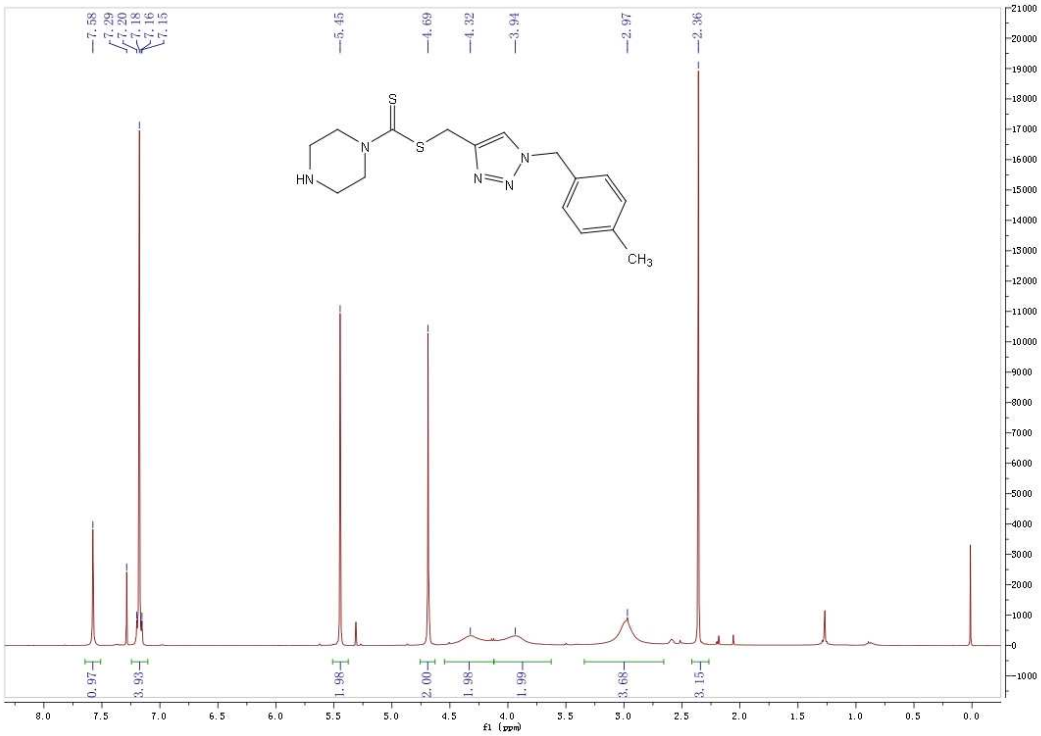

Figure S19. ^{13}C NMR ($CDCl_3$) spectrum of 1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**22**):

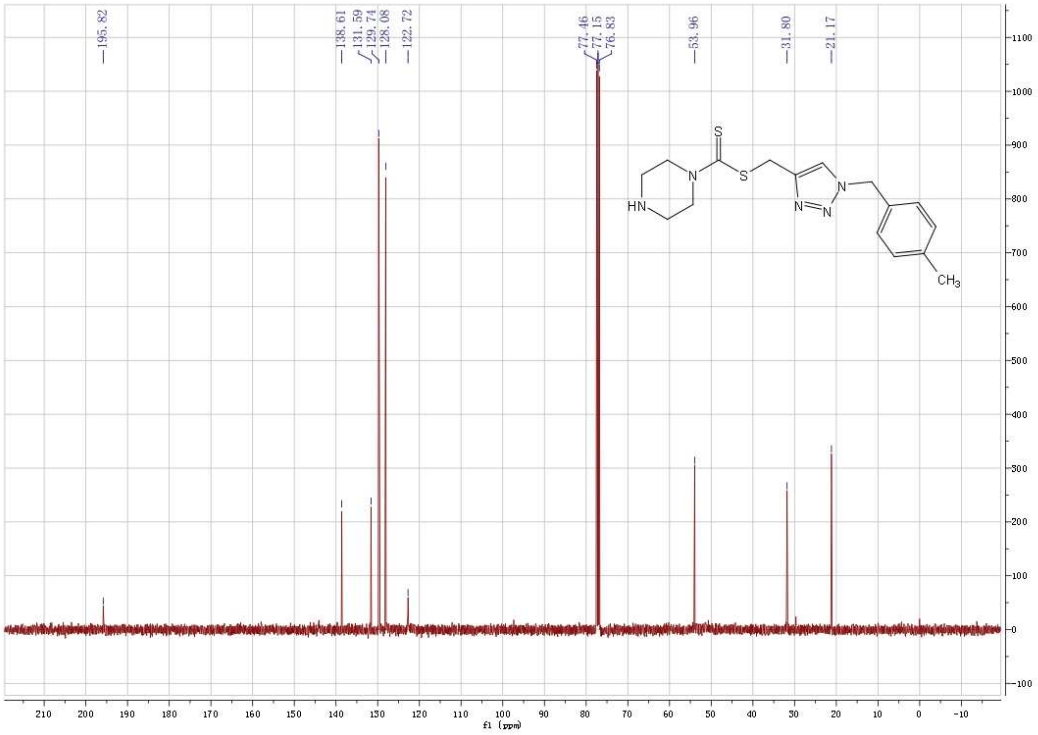

Figure S20. ^{1}H NMR ($CDCl_3$) spectrum of (1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**23**):

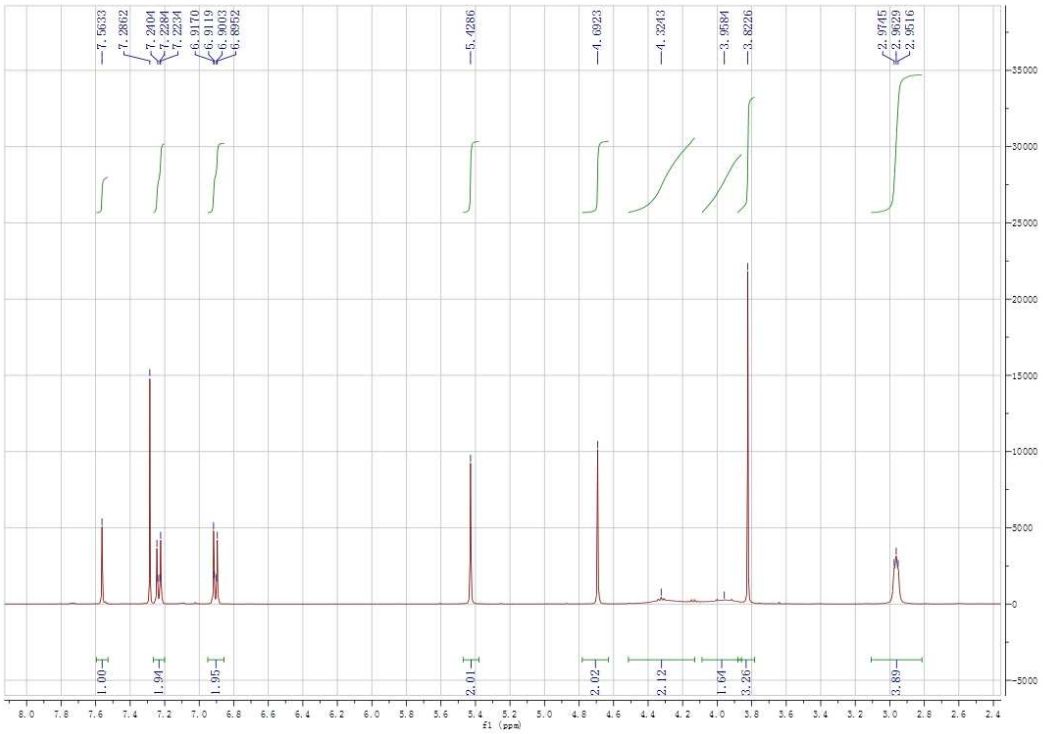

Figure S21. ^{13}C NMR ($CDCl_3$) spectrum of (1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**23**):

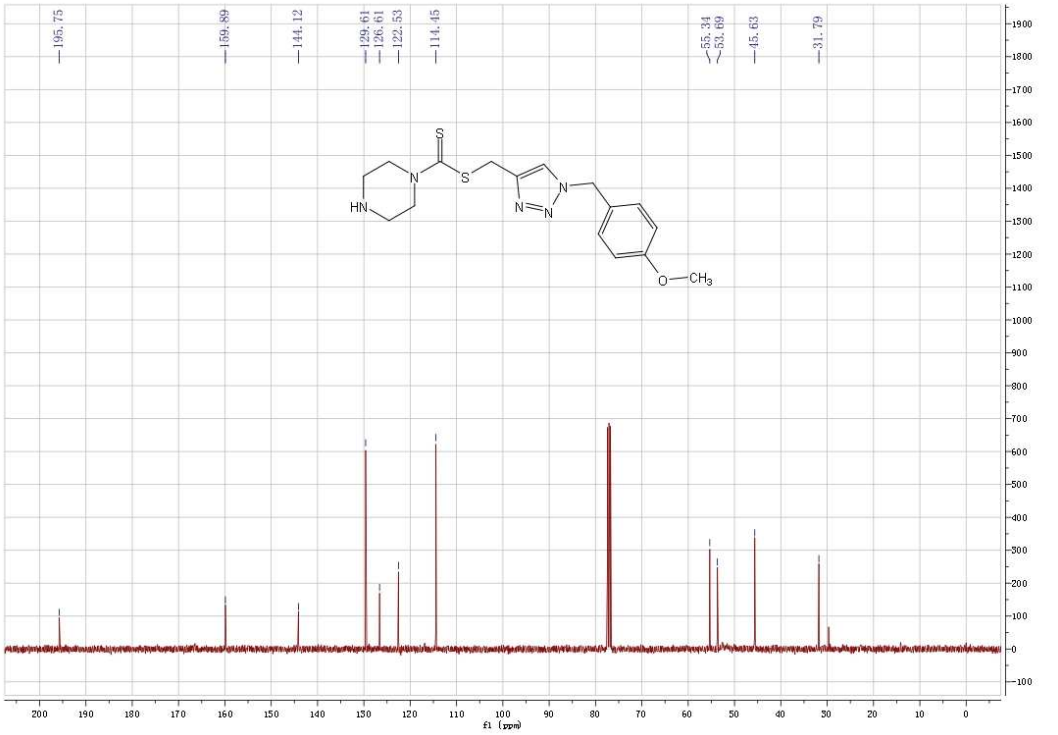

Figure S22. ^{1}H NMR ($CDCl_3$) spectrum of (1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**24**):

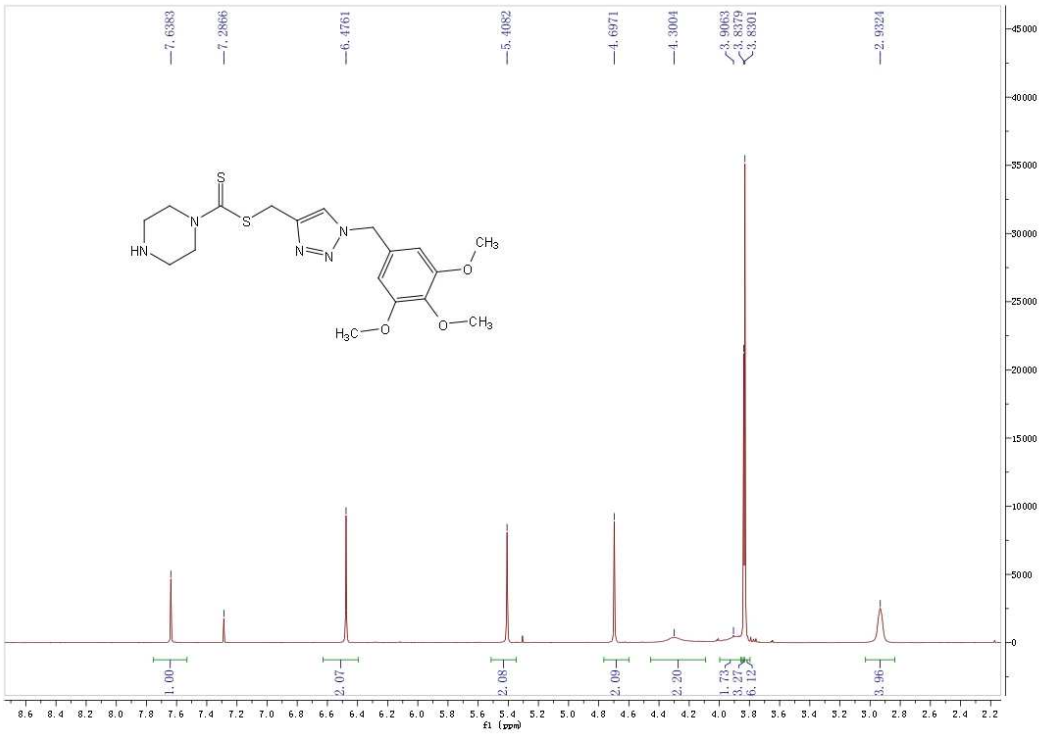

Figure S23. ^{13}C NMR ($CDCl_3$) spectrum of (1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl piperazine-1-carbodithioate (**24**):

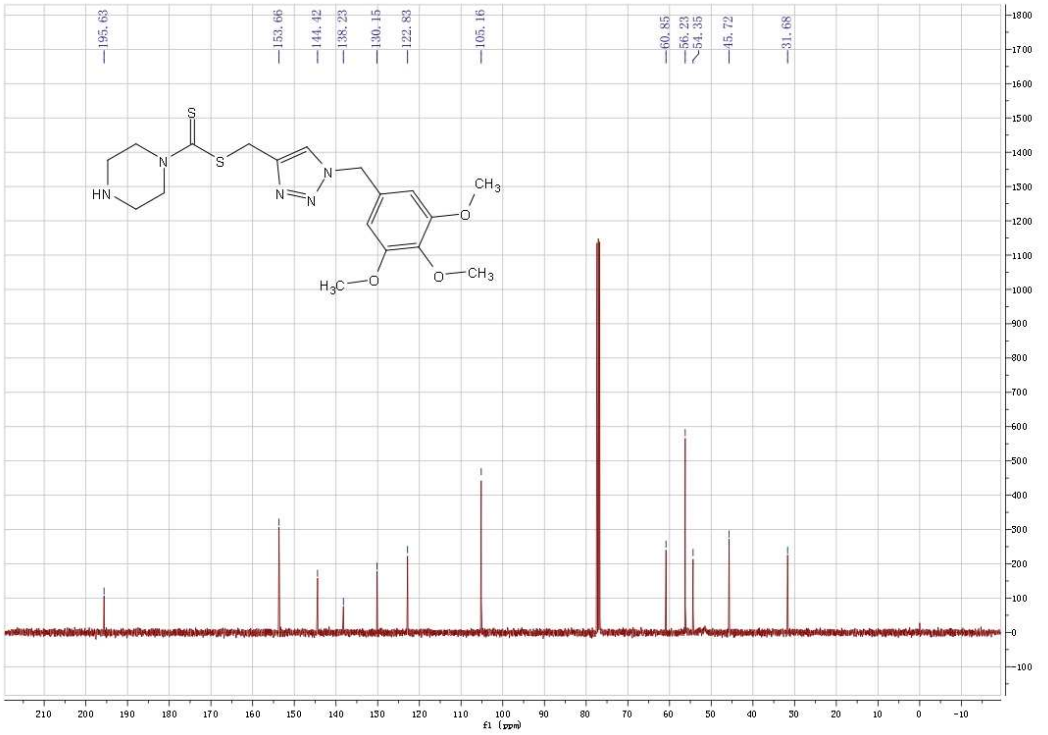

Figure S24. ^{1}H NMR (DMSO-d_6) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate* (**25**):

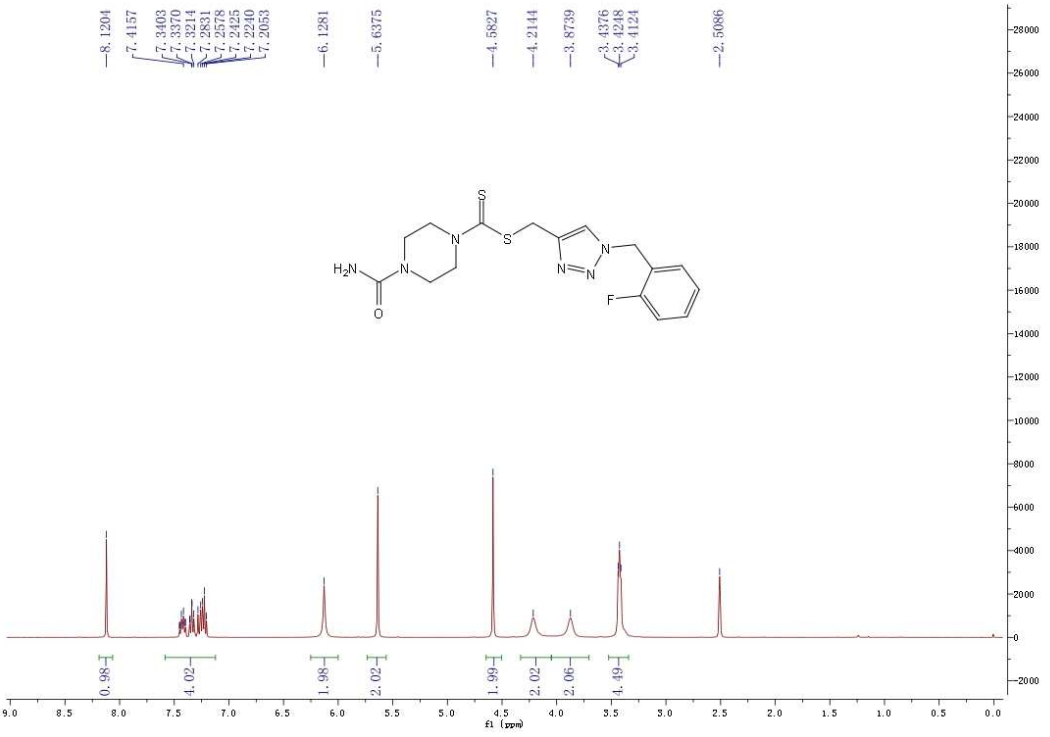

Figure S25. ^{13}C NMR (DMSO-d_6) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate* (**25**):

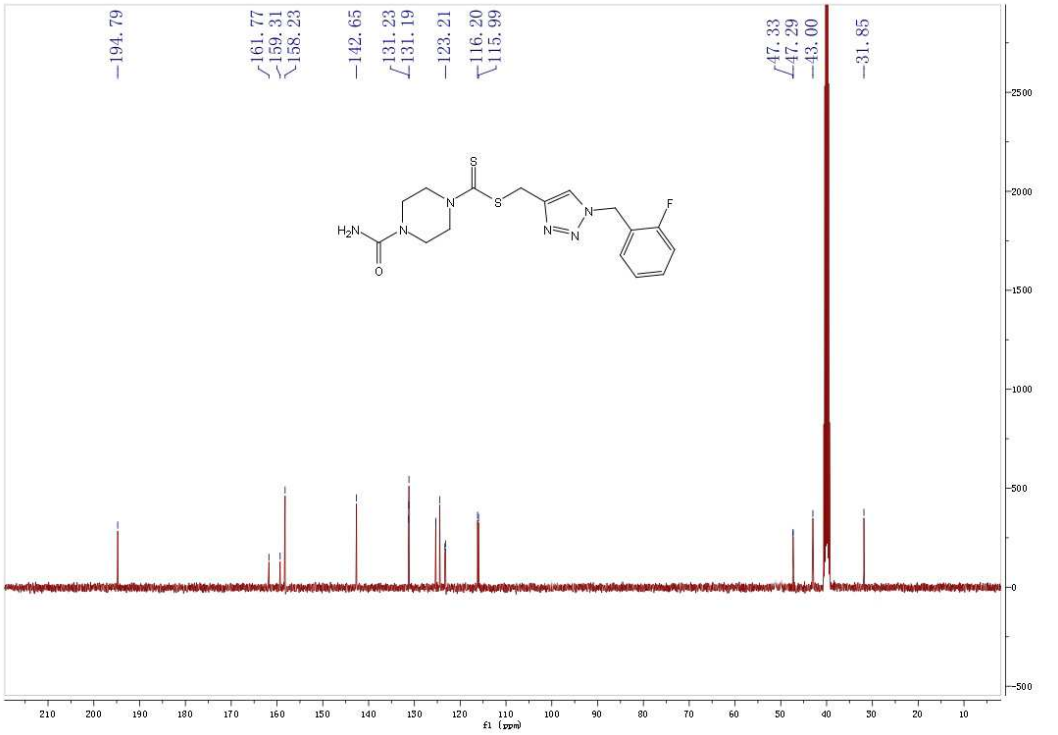

Figure S26. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate*(**26**):

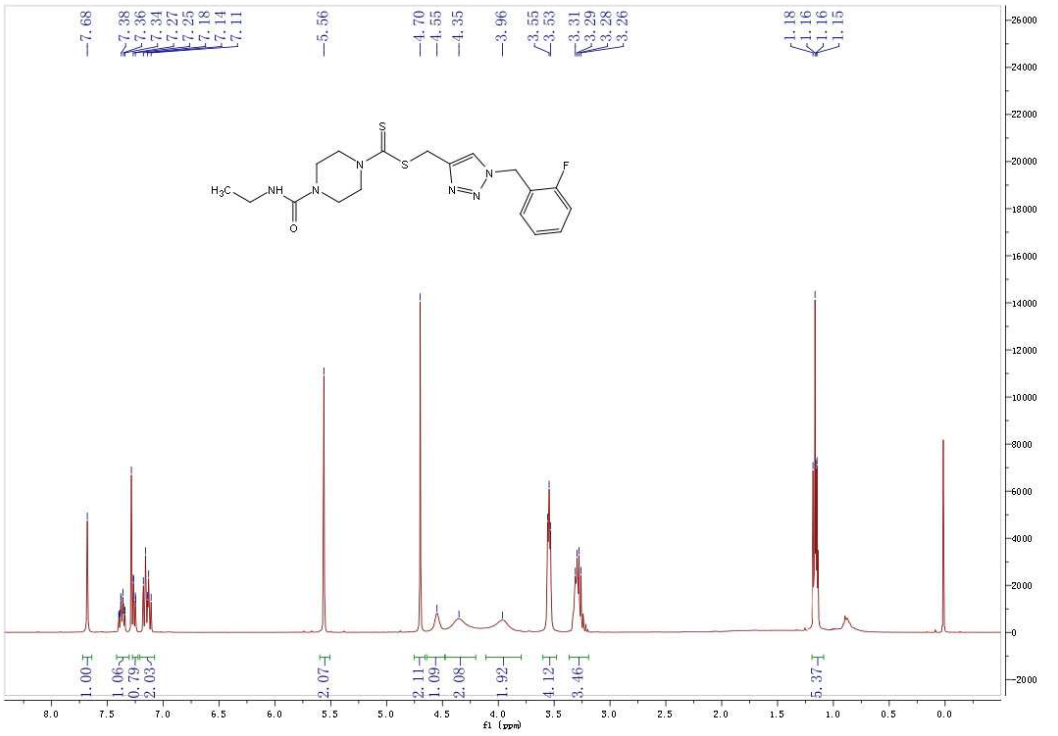

Figure S27. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate*(**26**):

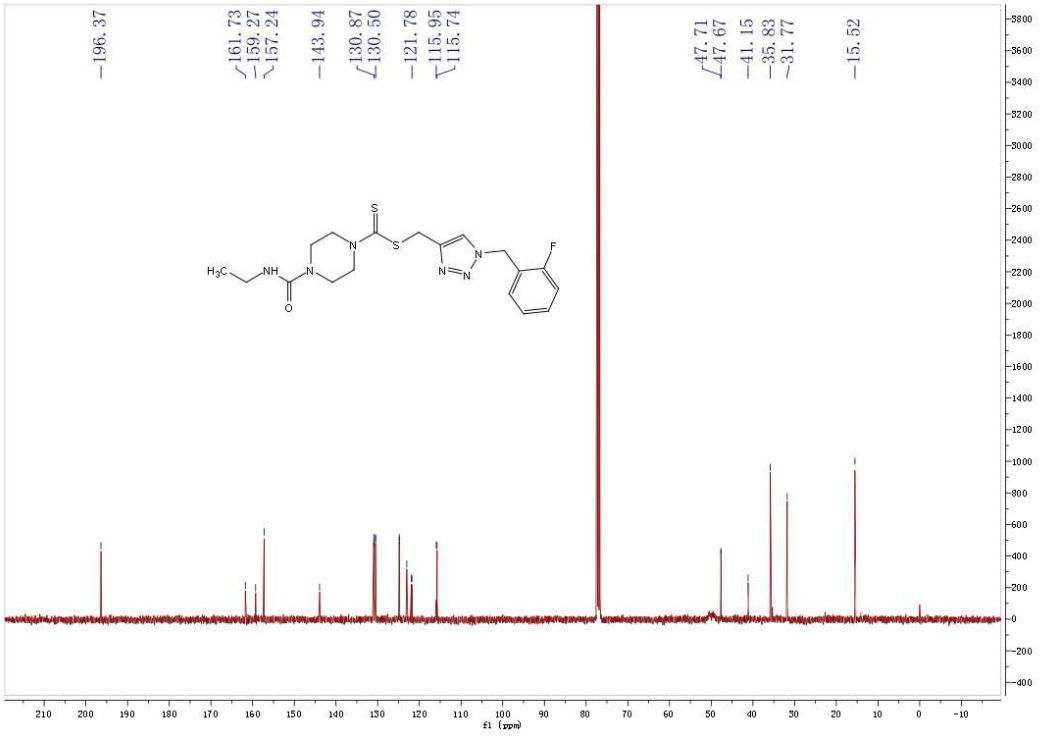

Figure S28. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**27**):

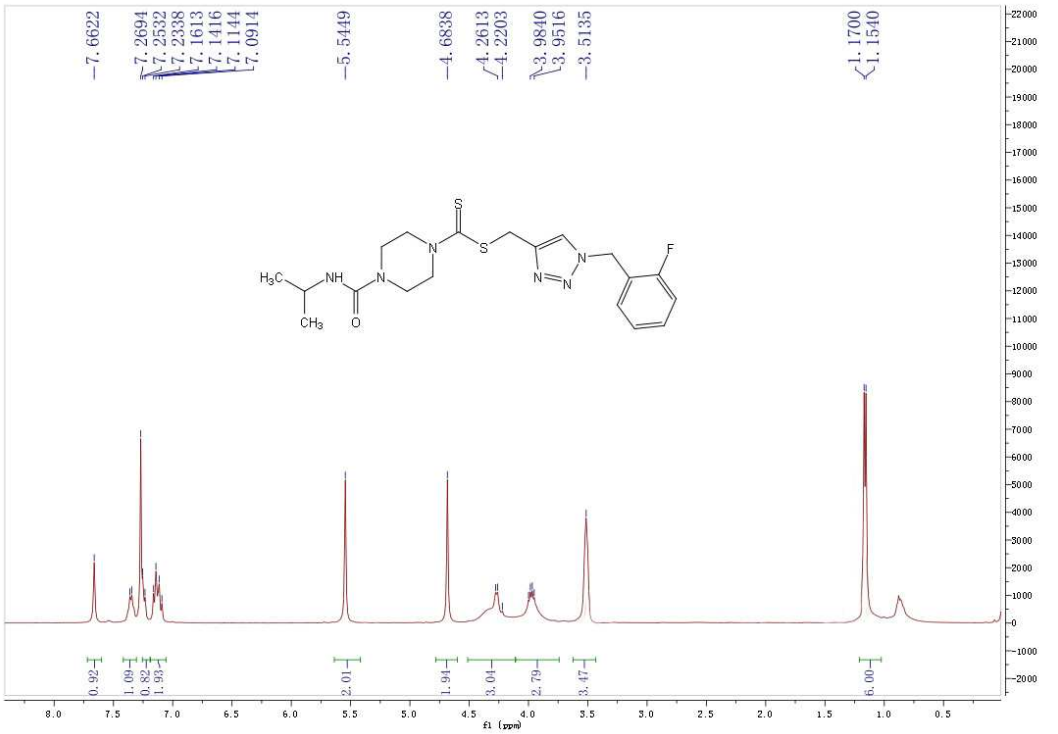

Figure S29. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**27**):

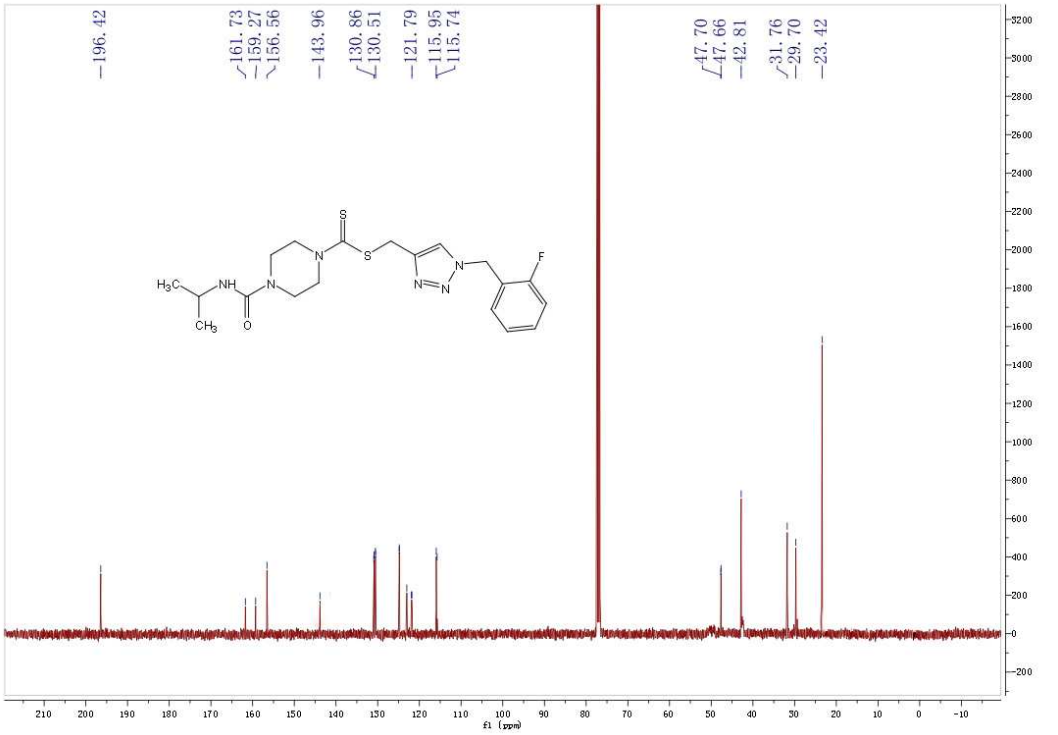

Figure S30. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(tert-butylcarbamoyl)piperazine-1-carbodithioate* (**29**):

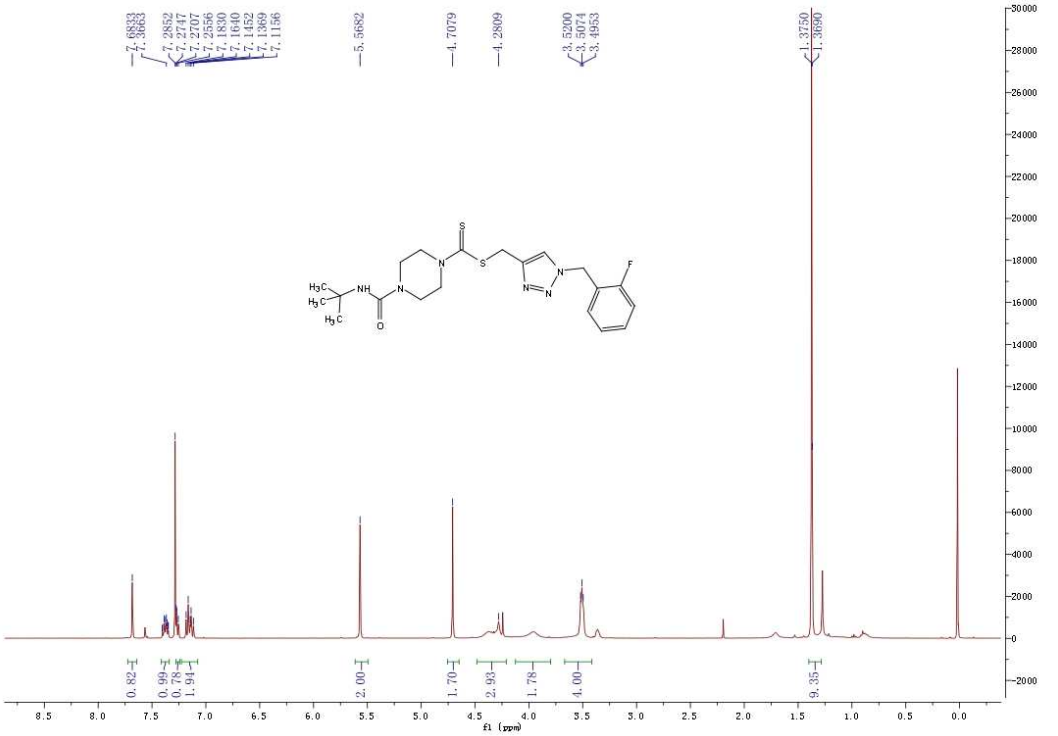

Figure S31. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(tert-butylcarbamoyl)piperazine-1-carbodithioate* (**29**):

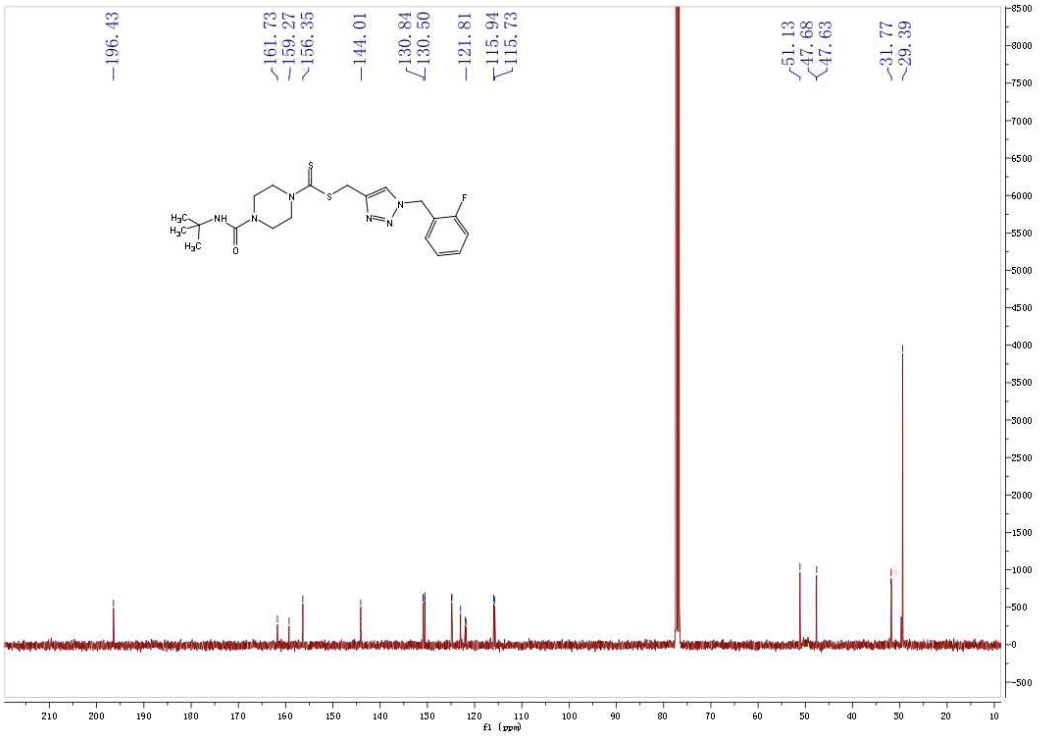

Figure S32. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(benzylcarbamoyl)piperazine-1-carbodithioate* (**31**):

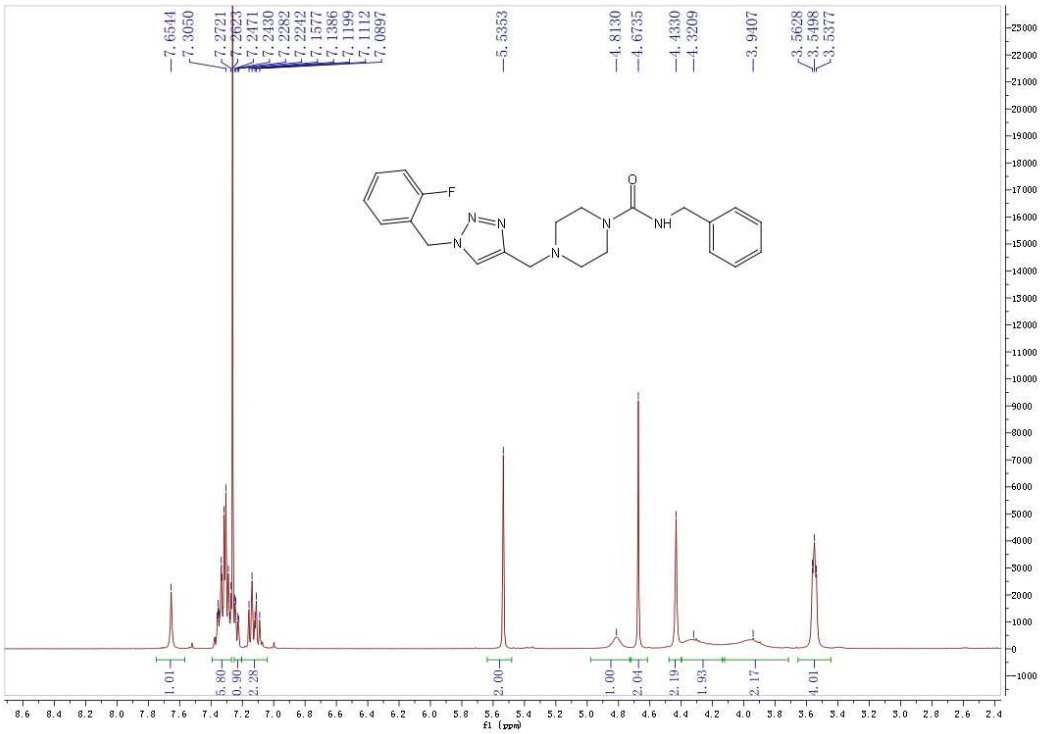

Figure S33. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(benzylcarbamoyl)piperazine-1-carbodithioate* (**31**):

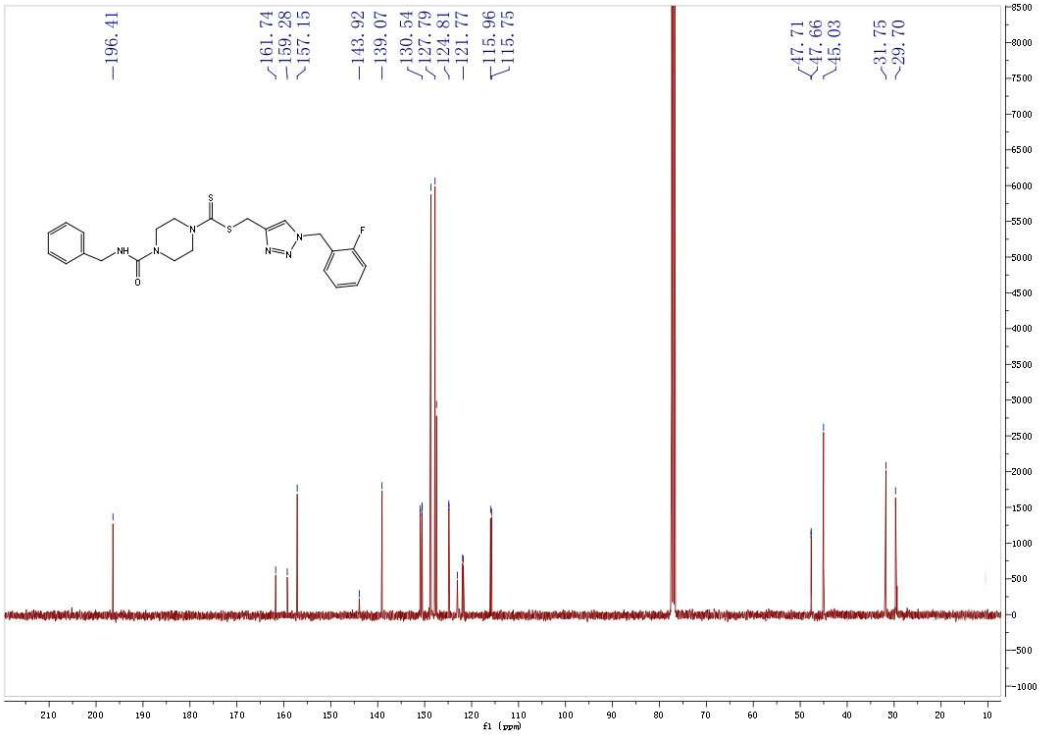

Figure S34.^{1}H NMR (Acetone-d_6) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate* (**32**):

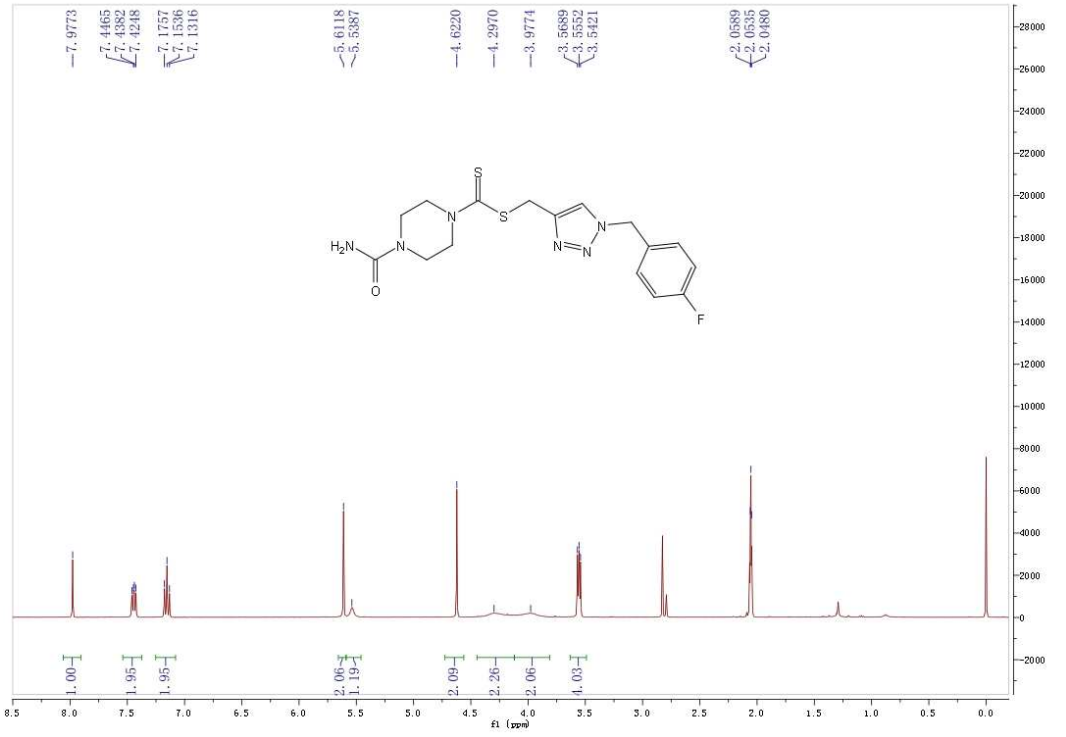

Figure S35.[13]C NMR (Acetone-d_6) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate* (**32**):

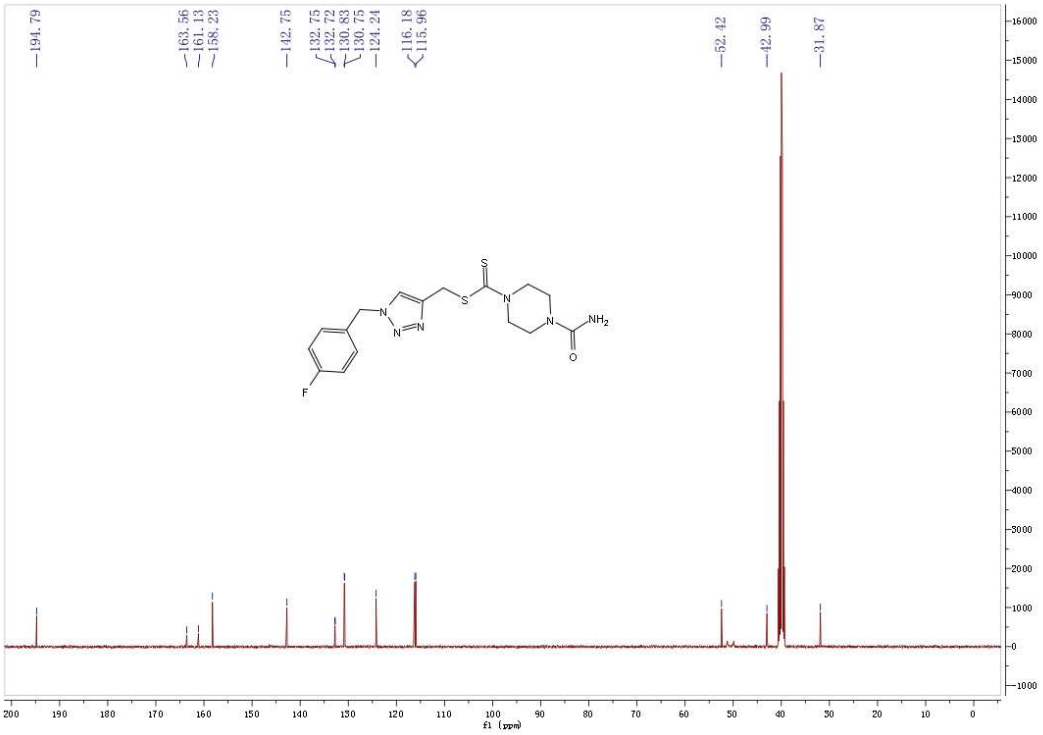

Figure S36. [1]H NMR ($CDCl_3$) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethylcarbamoyl)piperazine-1-carbodithioate*(**33**):

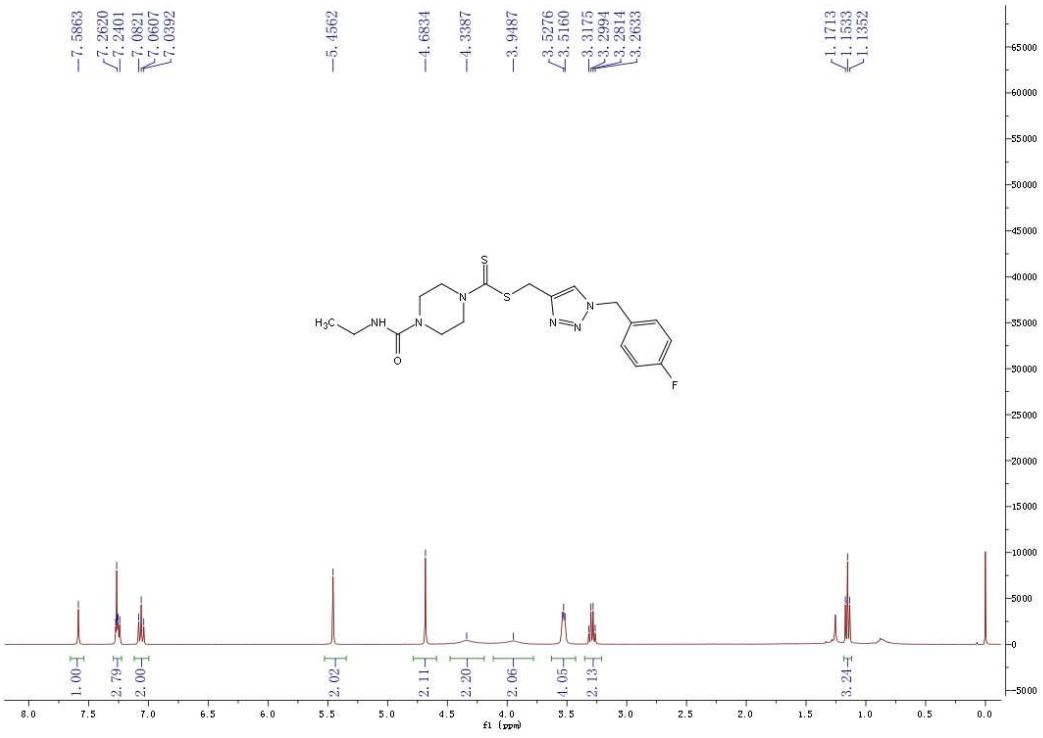

Figure S37. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(ethylcarbamoyl)piperazine-1-carbodithioate*(**33**):

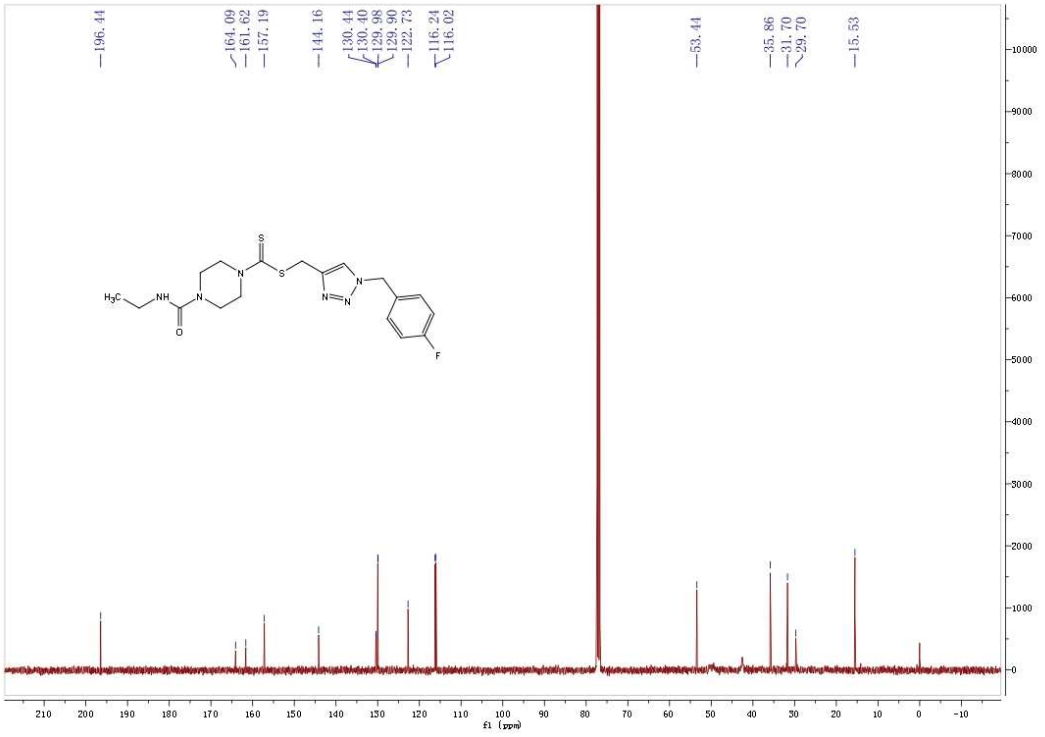

Figure S38. ^{1}H NMR (Acetone-d_6) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**34**):

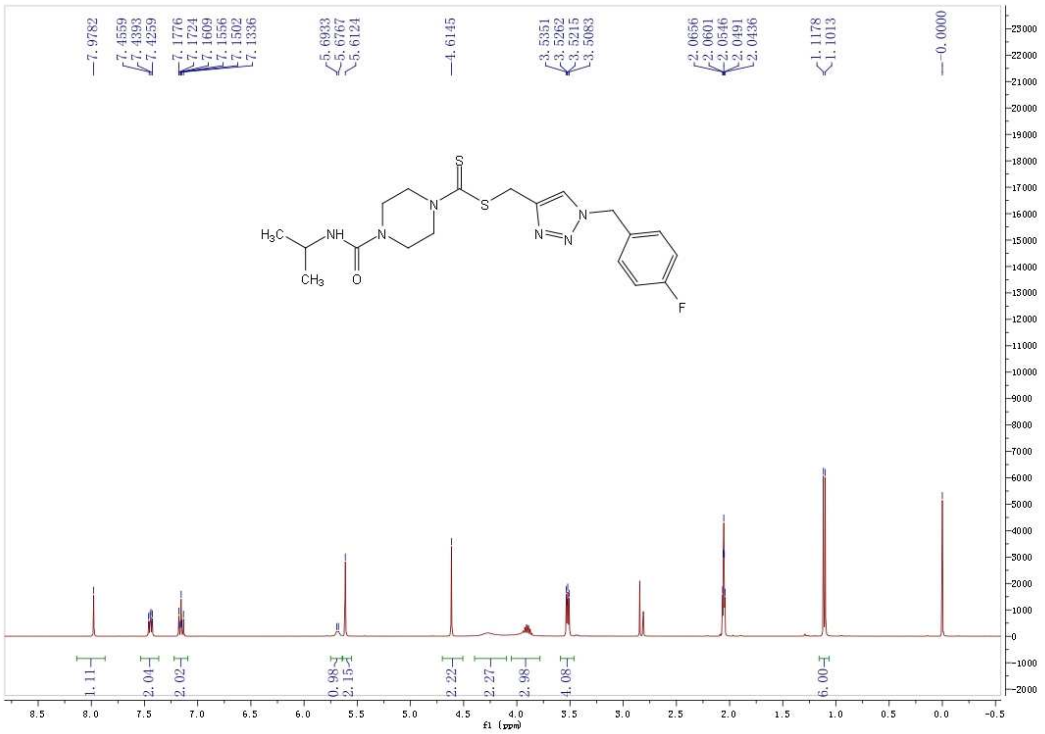

Figure S39. ^{13}C NMR (Acetone-d_6) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**34**):

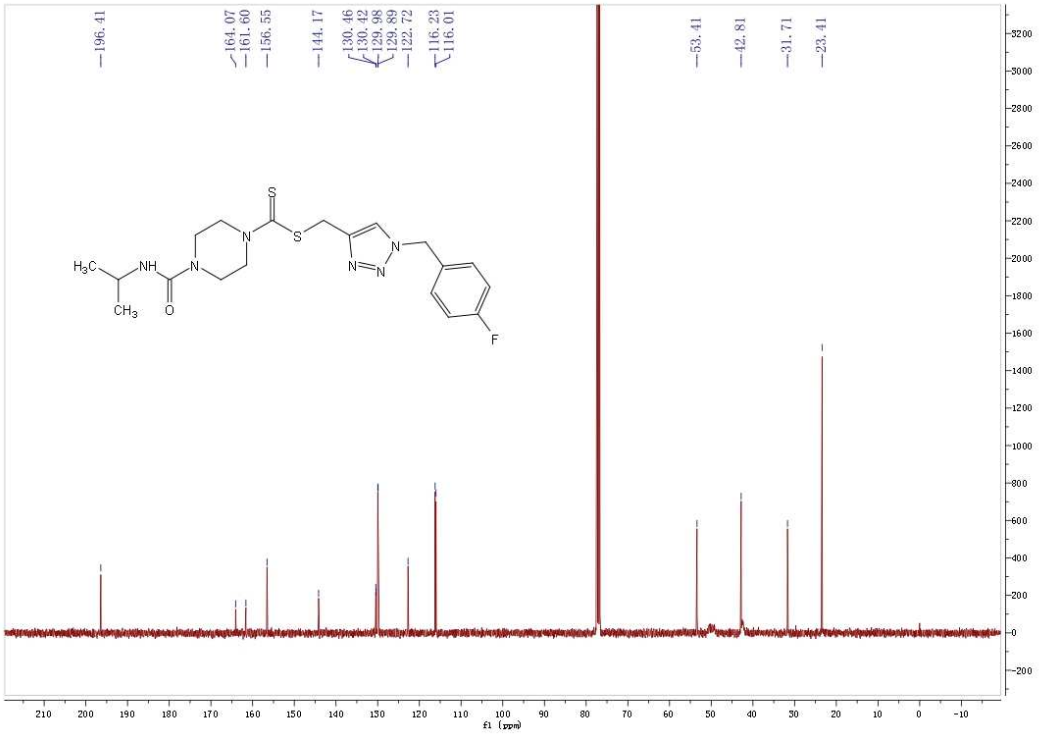

Figure S40. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate* (**35**):

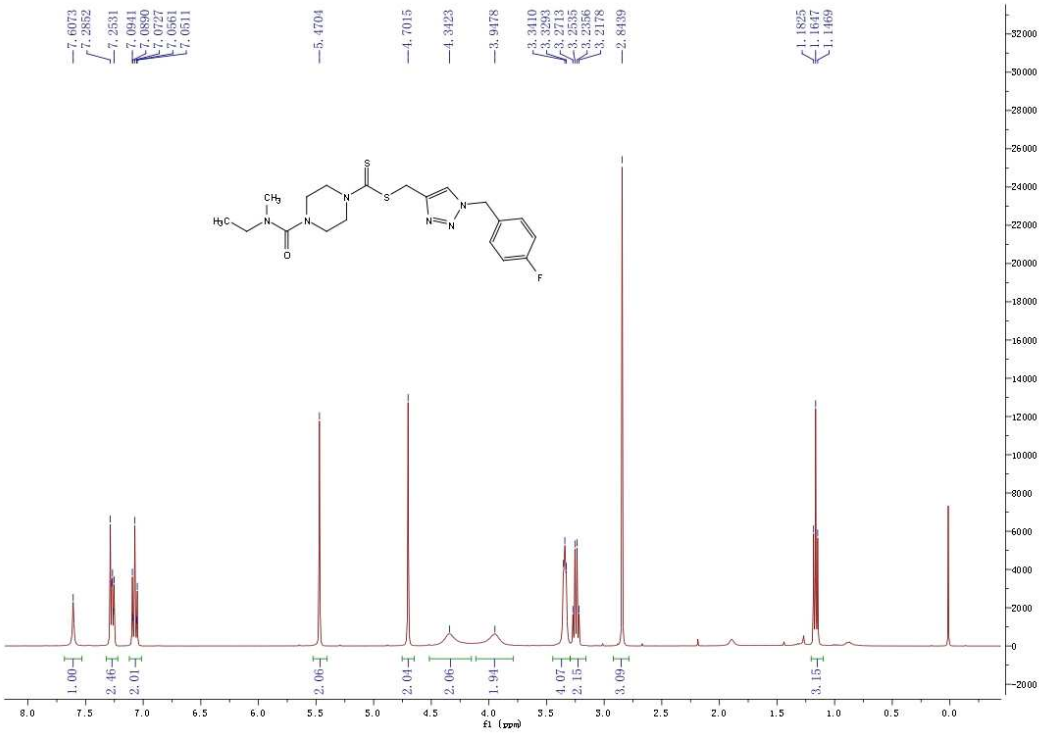

Figure S41. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate* (**35**):

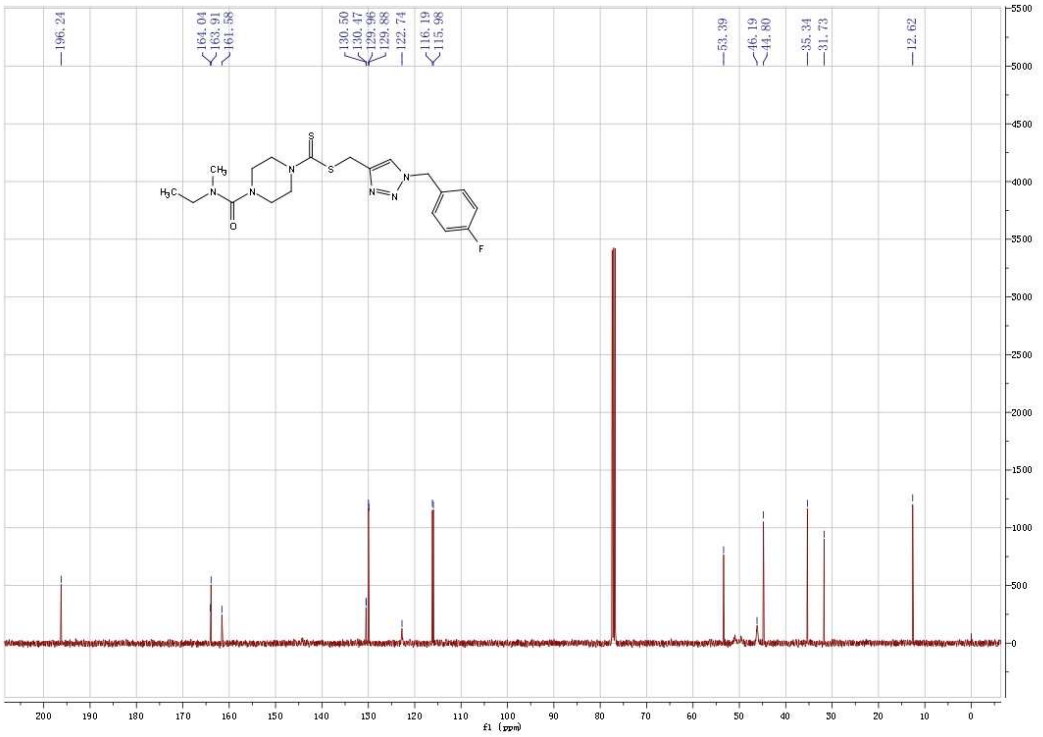

Figure S42. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate* (**38**):

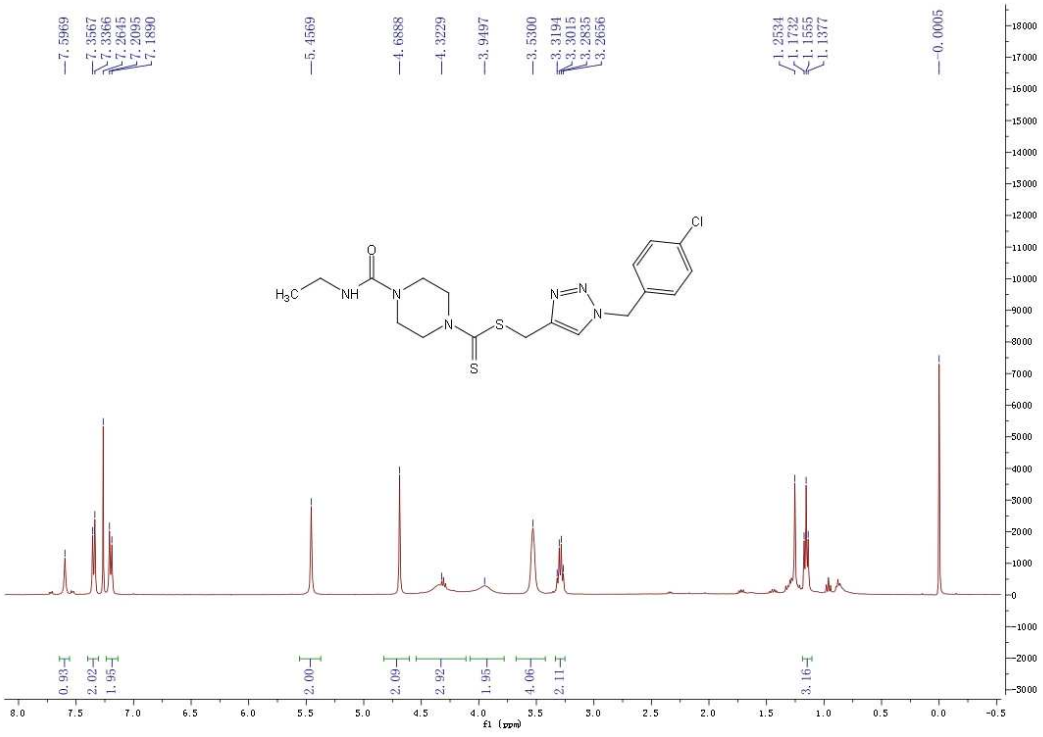

Figure S43. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate* (**38**):

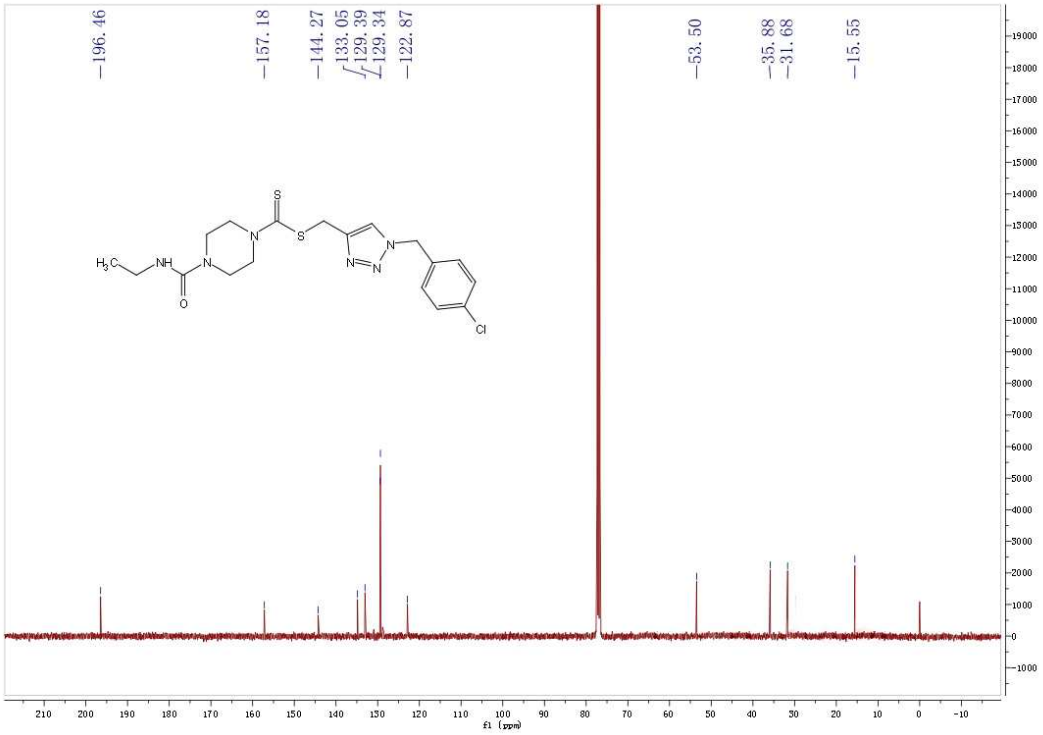

Figure S44. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**39**):

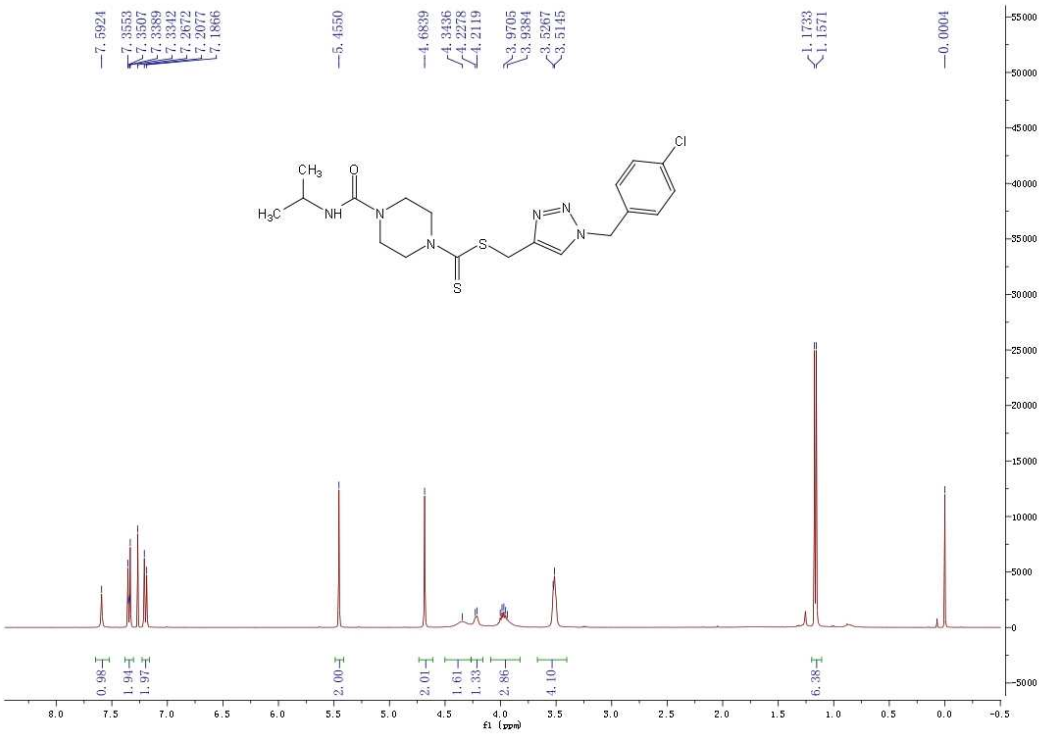

Figure S45. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**39**):

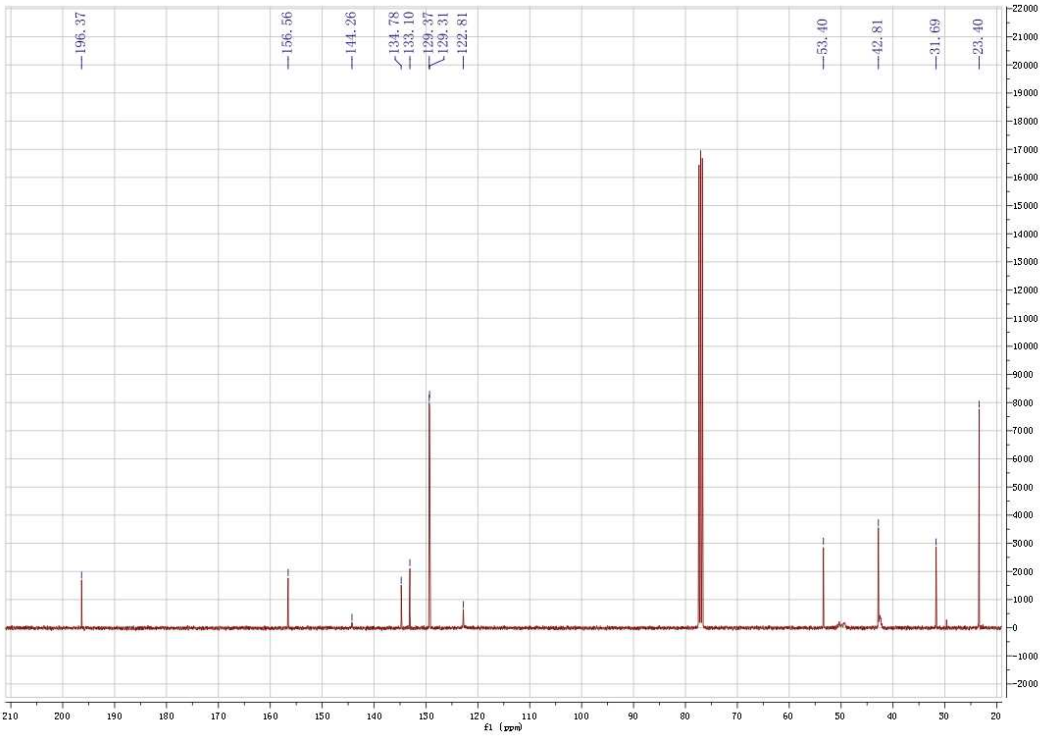

Figure S46. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate* (**40**):

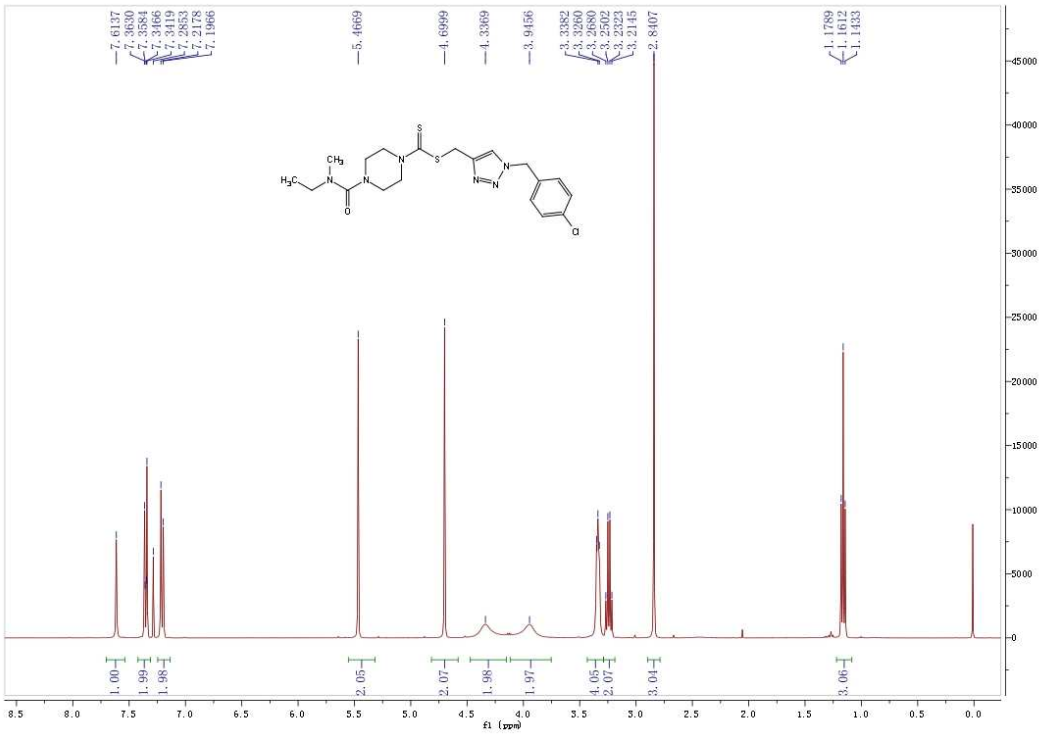

Figure S47. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate* (**40**):

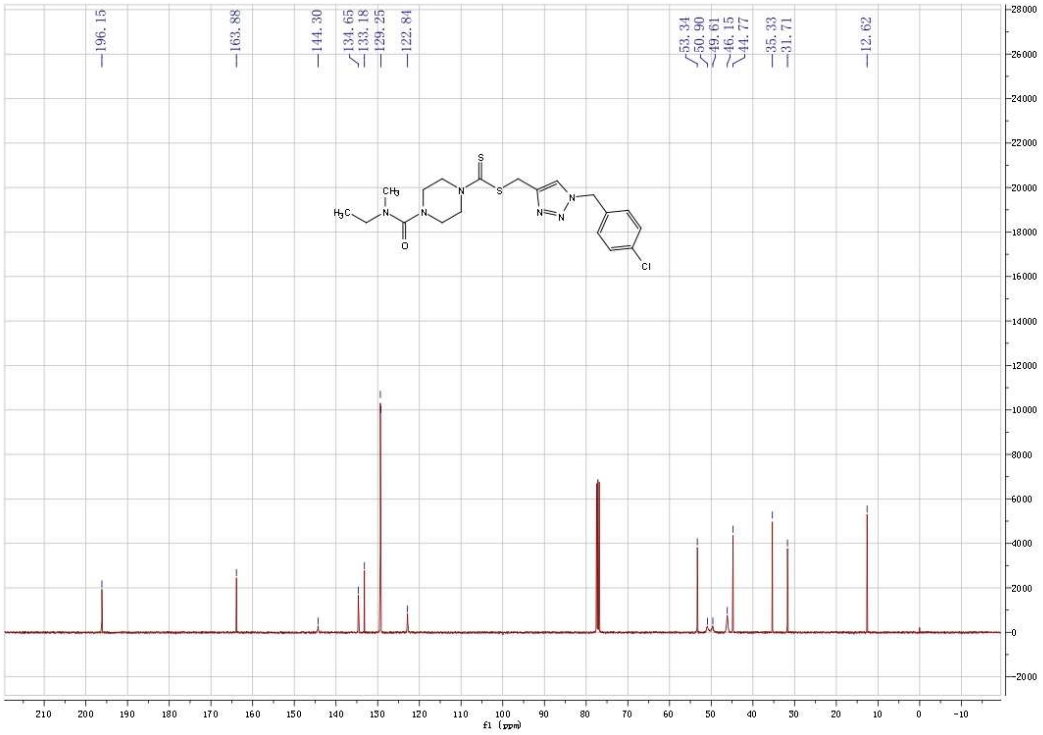

Figure S48. ^{1}H NMR (DMSO-d_6) spectrum of *(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl4-carbamoylpiperazine-1-carbodithioate* (**41**):

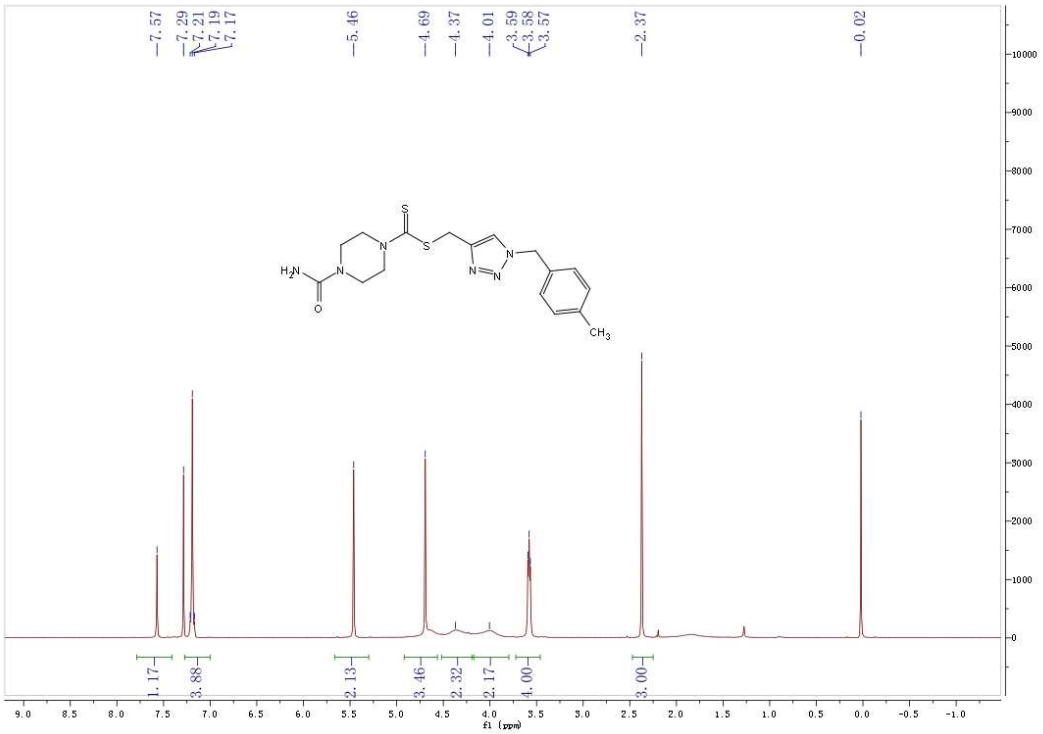

Figure S49. ^{13}C NMR (DMSO-d_6) spectrum of *(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl4-carbamoylpiperazine-1-carbodithioate* (**41**):

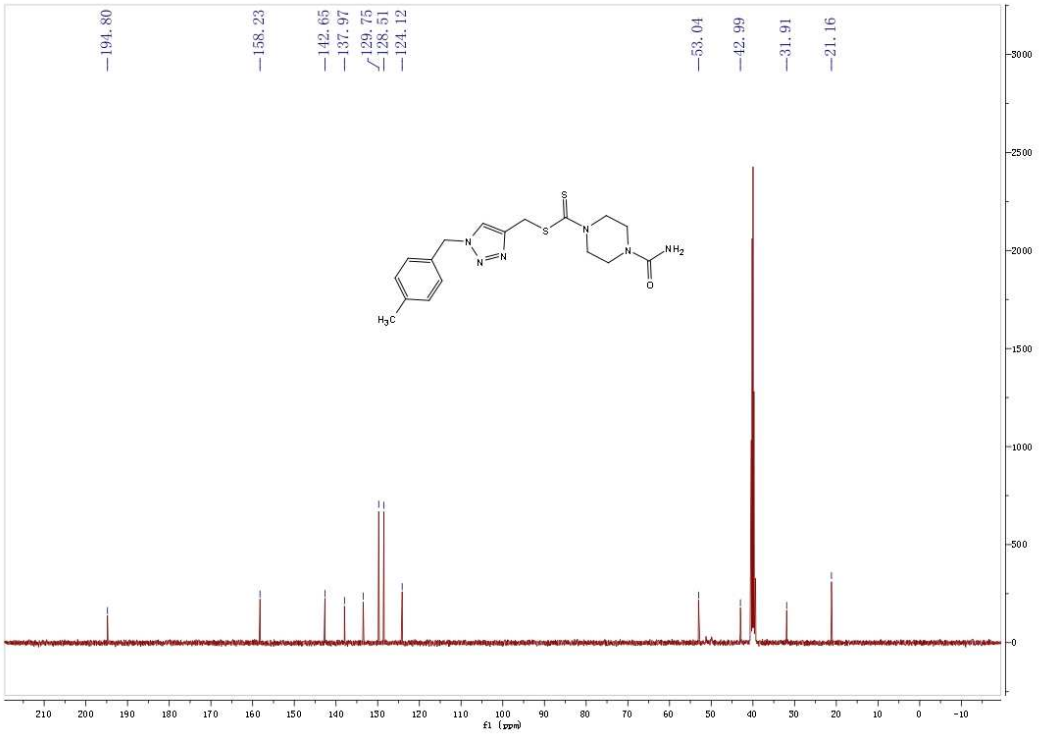

Figure S50. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**43**):

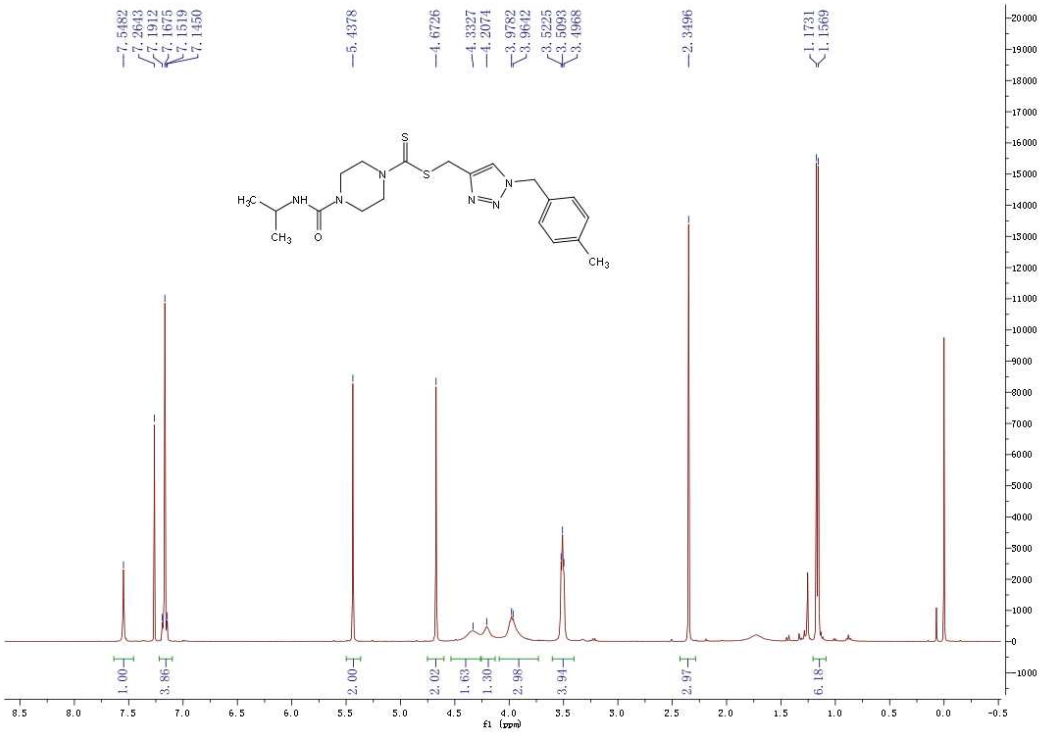

Figure S51. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1*-carbodithioate (**44**):

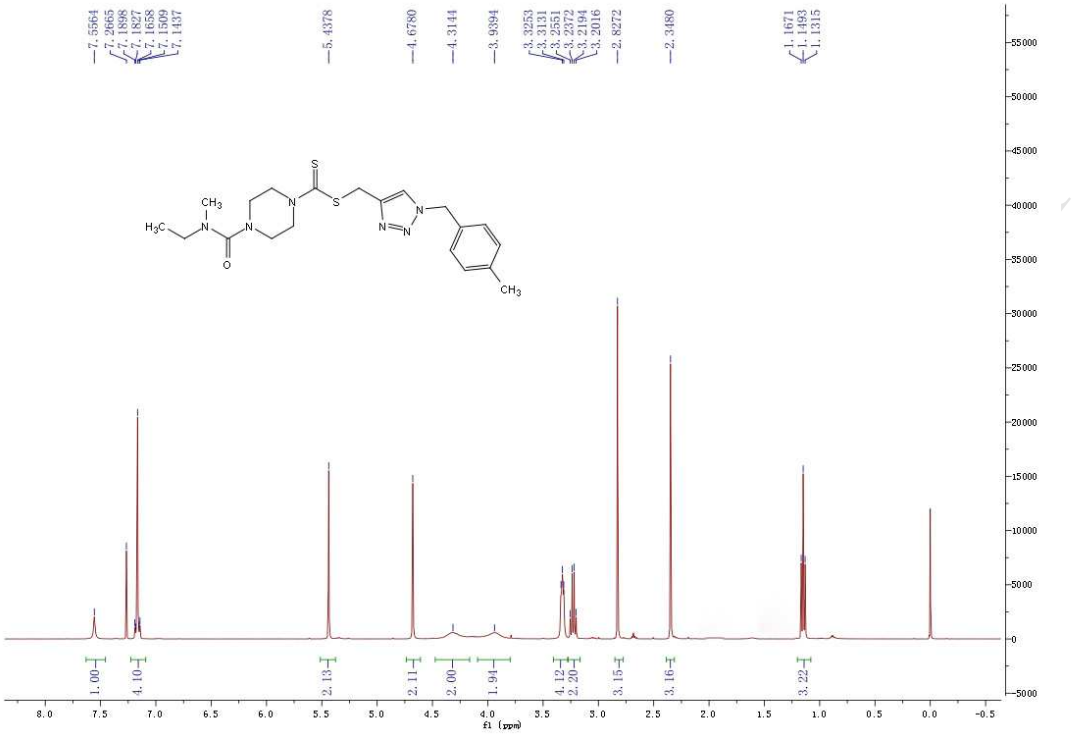

Figure S52. ^{13}C NMR ($CDCl_3$) spectrum of*(1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethyl(methyl)carbamoyl)piperazine-1*-carbodithioate (**44**):

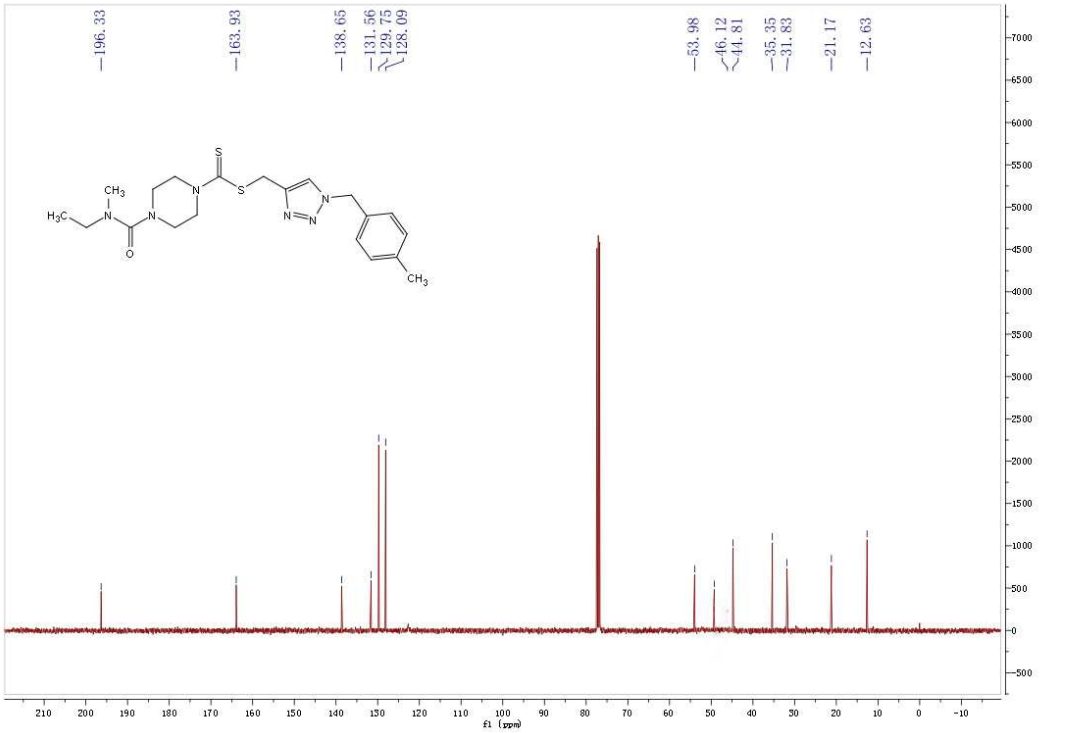

Figure S53. ^{1}H NMR (DMSO-d_6) spectrum of *(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate* (**45**):

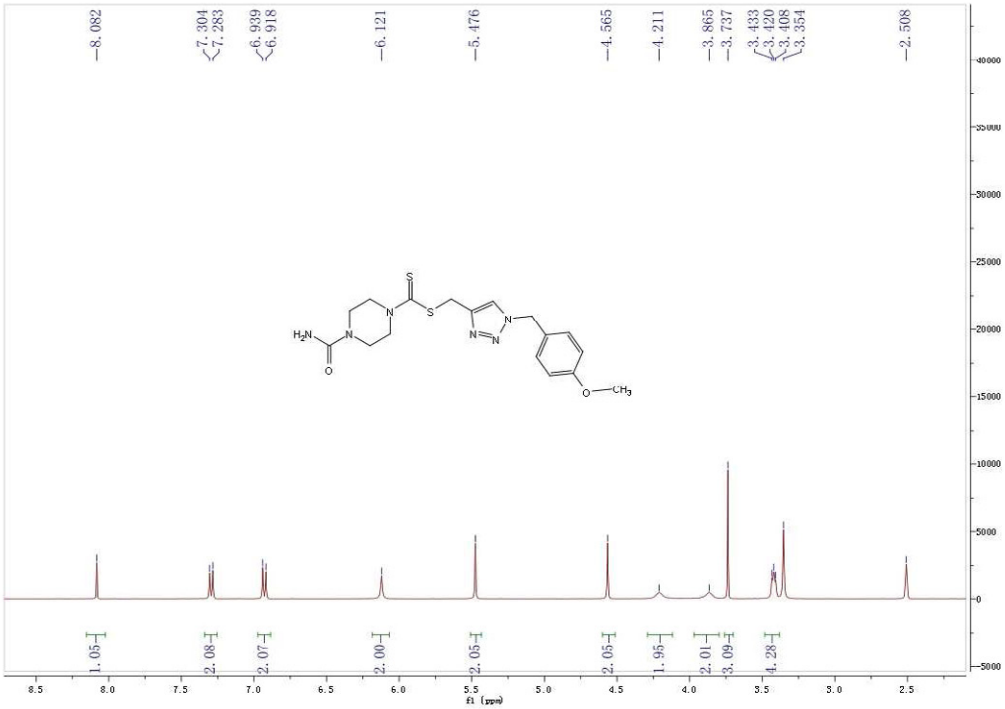

Figure S54. ^{13}C NMR (DMSO-d_6) spectrum of *(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1-carbodithioate* (**45**):

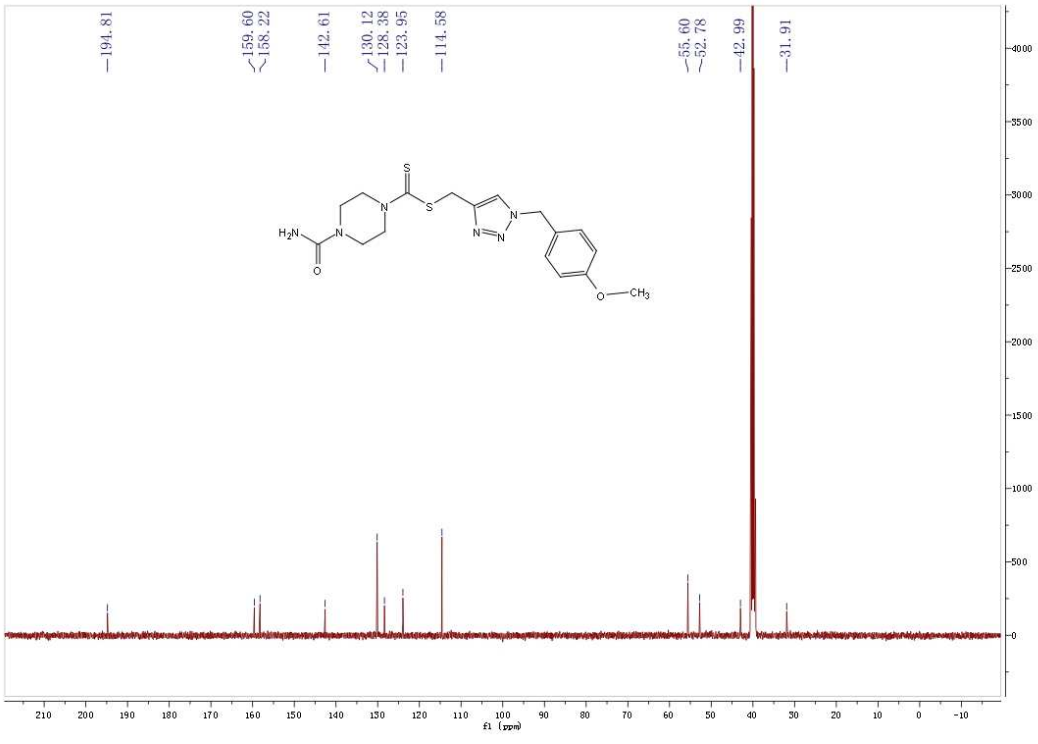

Figure S55. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate* (**46**):

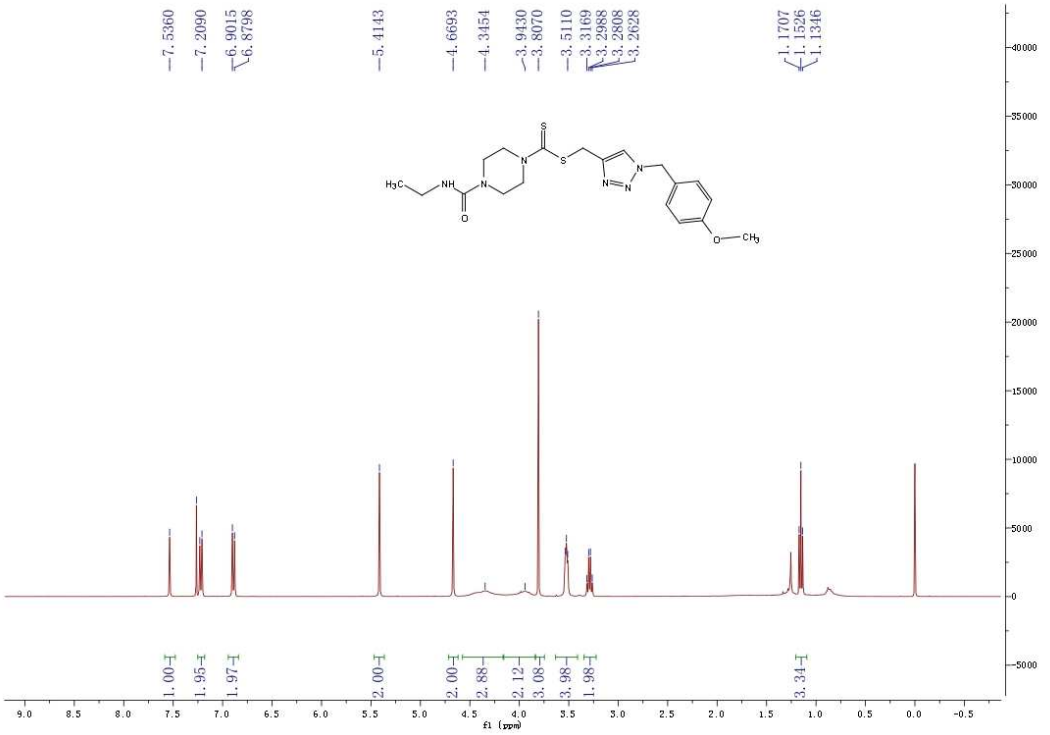

Figure S56. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate* (**46**):

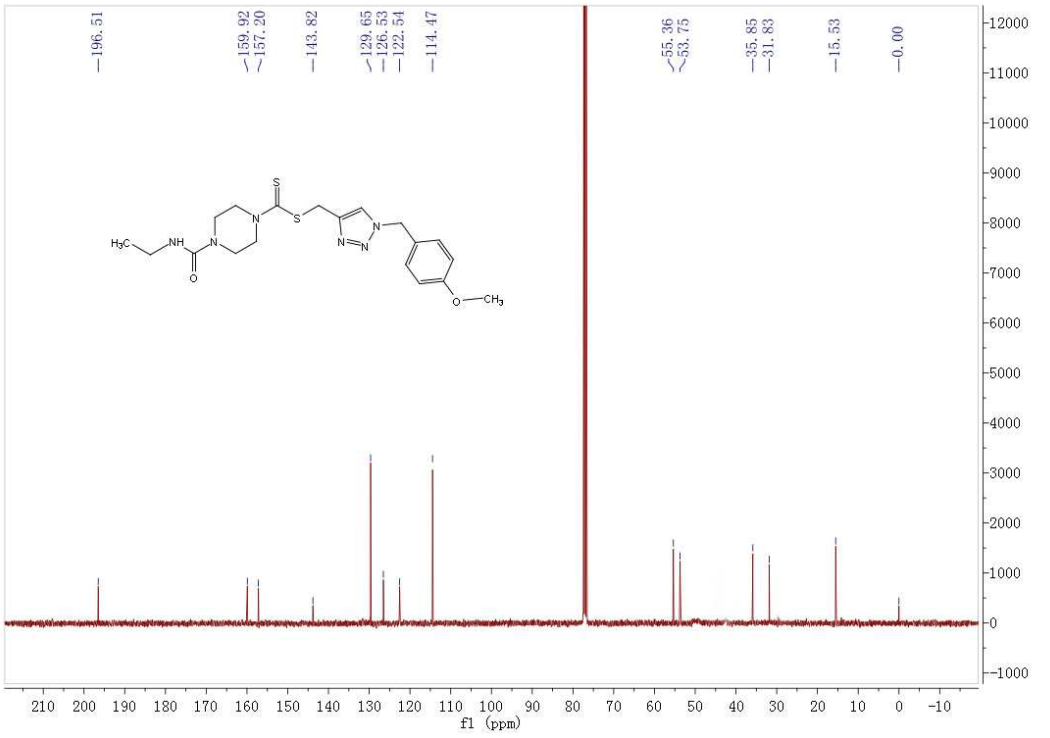

Figure S57. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**47**):

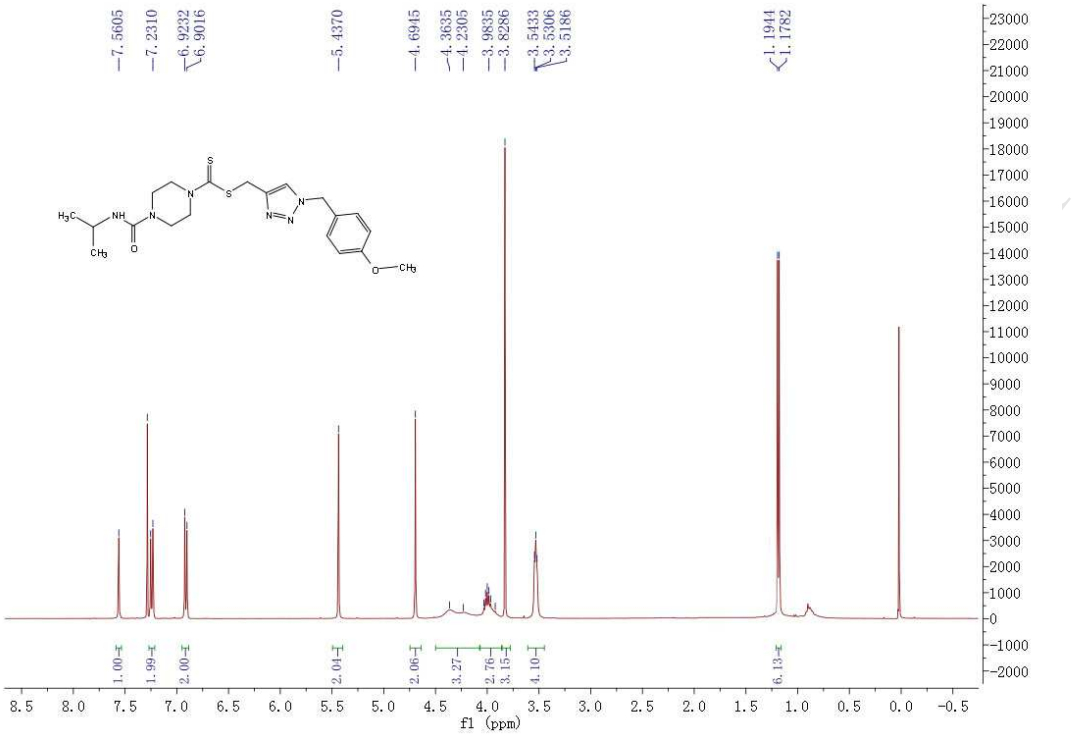

Figure S58. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**47**):

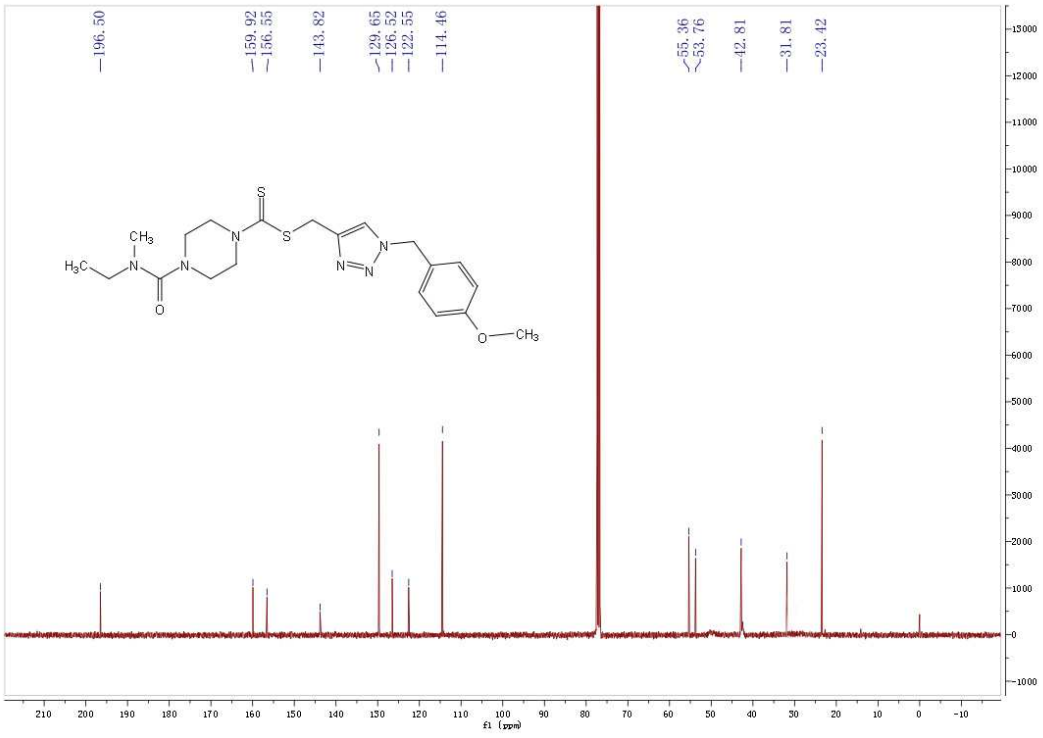

Figure S59. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1*-carbodithioate (**49**):

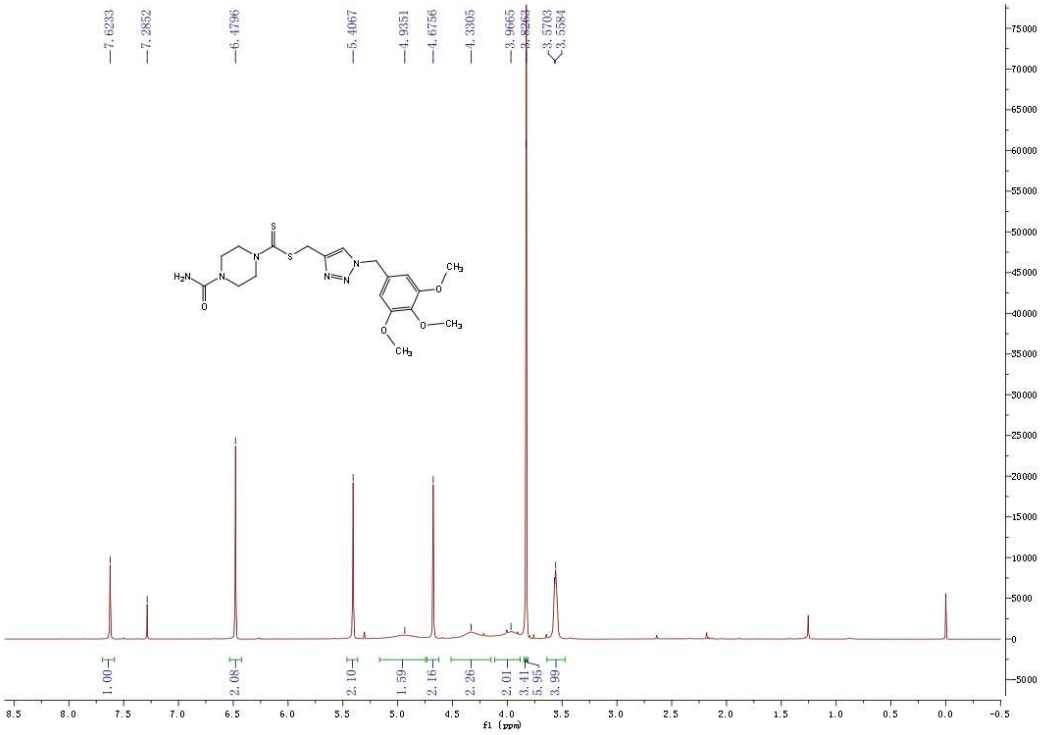

Figure S60. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 4-carbamoylpiperazine-1*-carbodithioate (**49**):

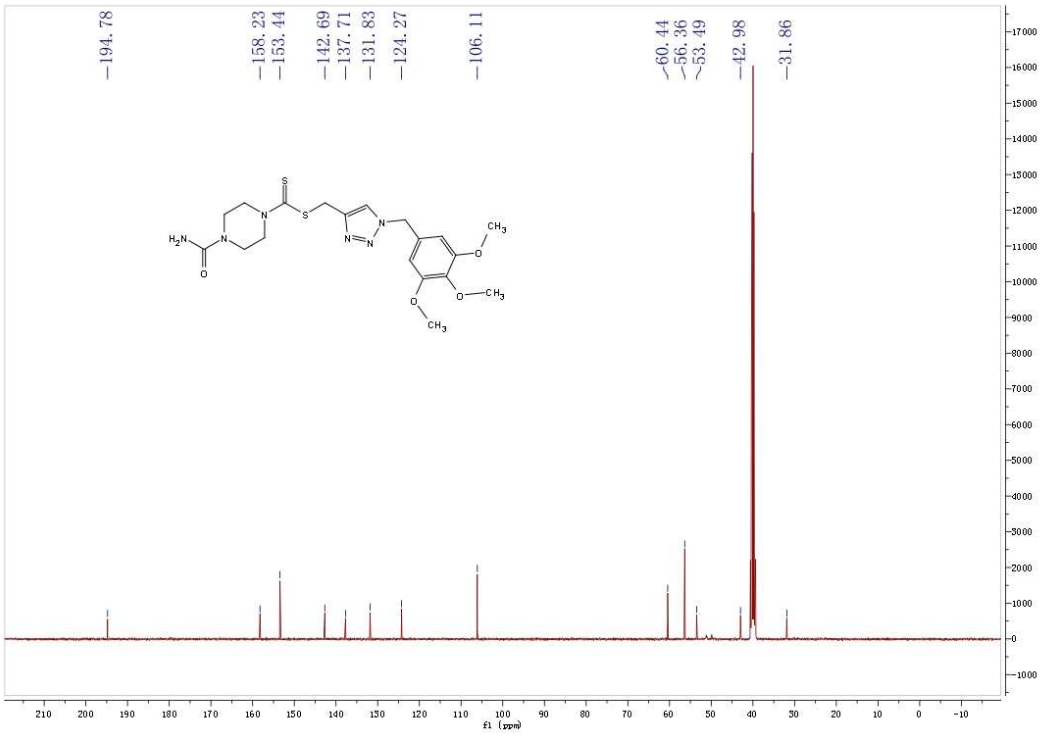

Figure S61. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate* (**50**):

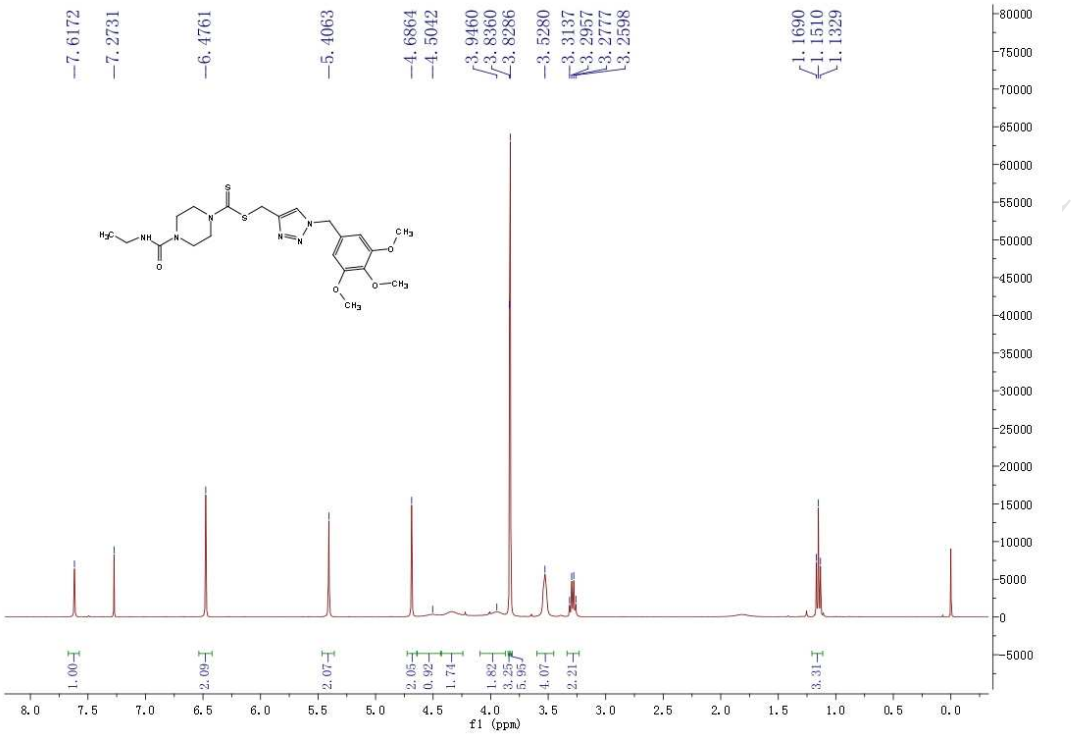

Figure S62. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl 4-(ethylcarbamoyl)piperazine-1-carbodithioate* (**50**):

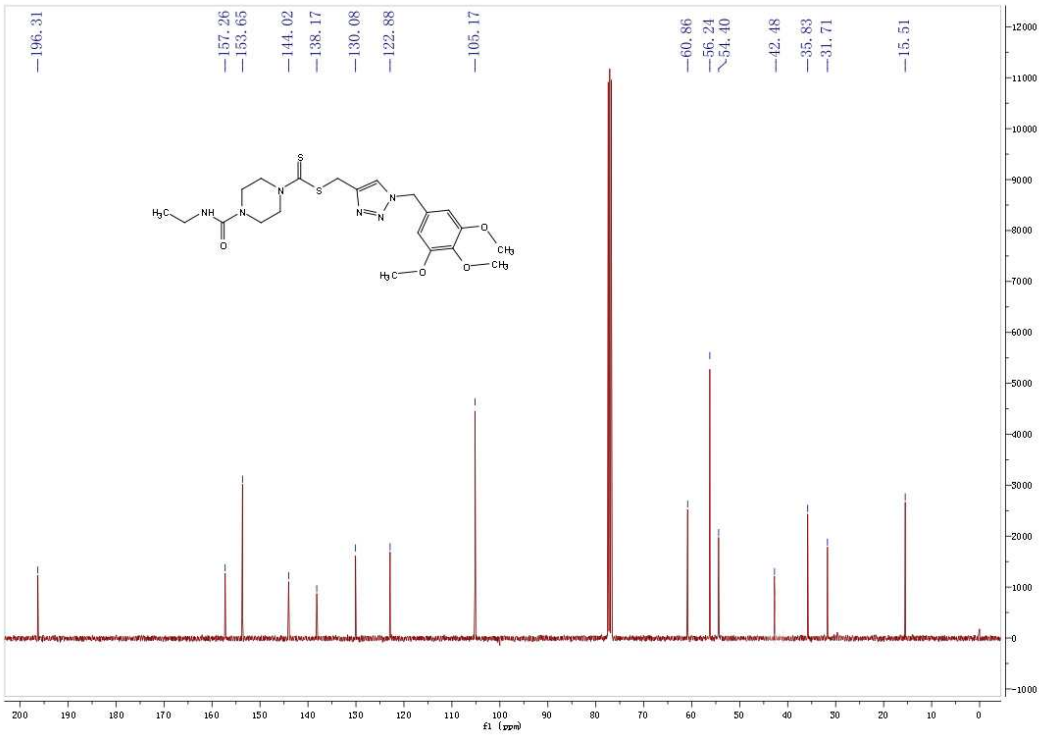

Figure S63. ^{1}H NMR ($CDCl_3$) spectrum of *(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**51**):

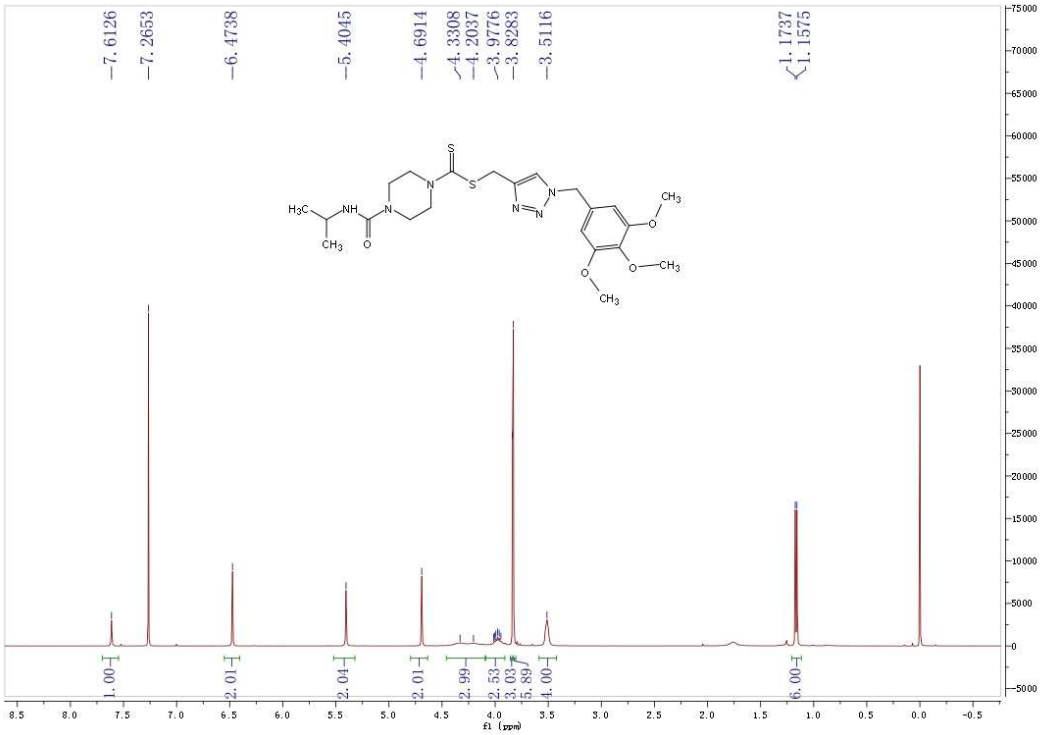

Figure S64. ^{13}C NMR ($CDCl_3$) spectrum of *(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl 4-(isopropylcarbamoyl)piperazine-1-carbodithioate* (**51**):

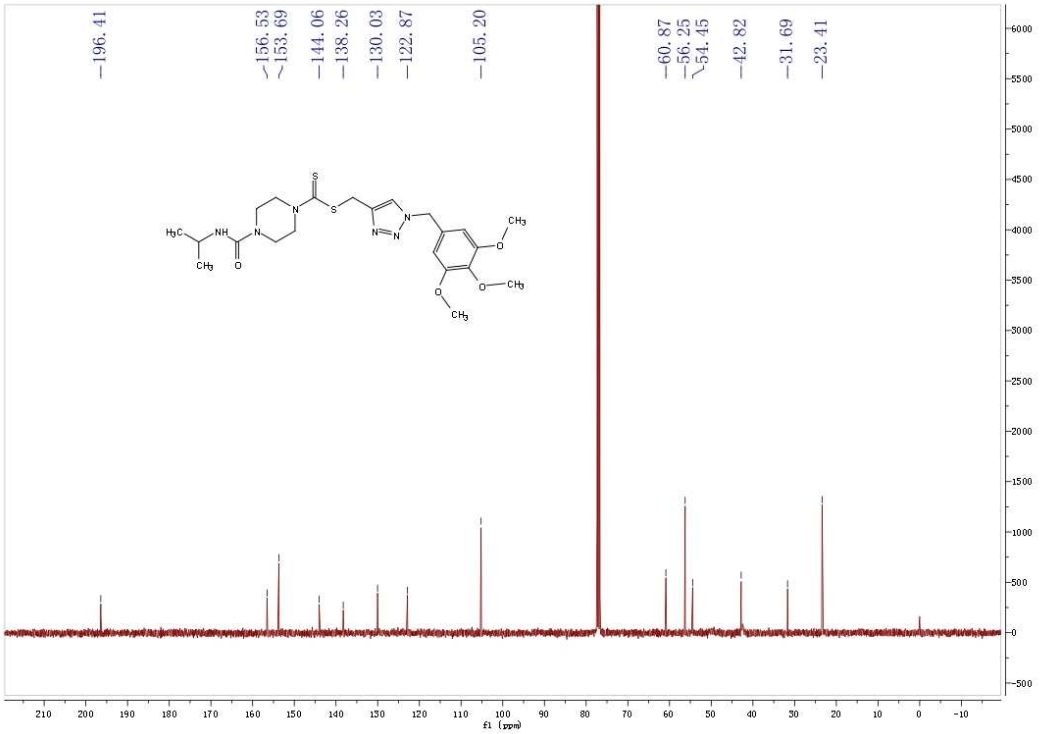

Figure S65. ^{1}H NMR ($CDCl_3$) spectrum of .(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate (**52**):

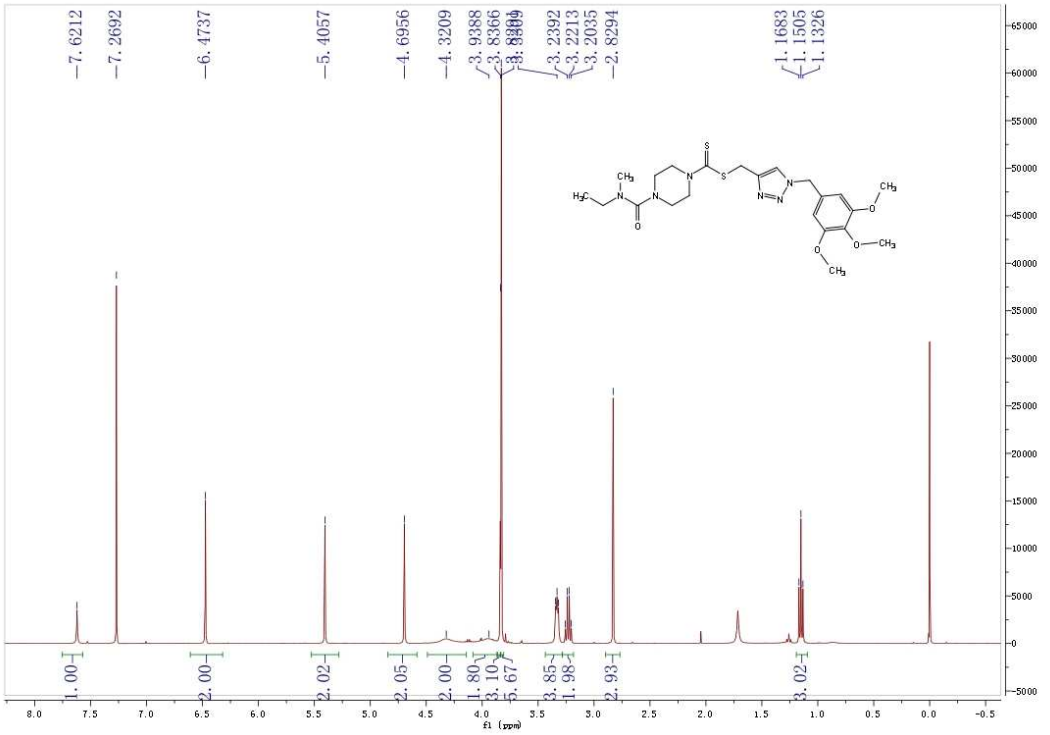

Figure S66. ^{13}C NMR ($CDCl_3$) spectrum of .(1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl 4-(ethyl(methyl)carbamoyl)piperazine-1-carbodithioate (**52**):