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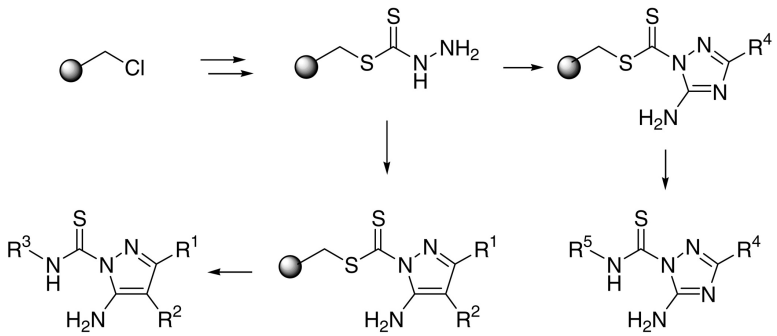

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Solid-Phase Synthesis of 5-Amino-1-(Substituted Thiocarbamoyl)pyrazole and 1,2,4-Triazole Derivatives via Dithiocarbazate Linker

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A general method is reported for the parallel solid-phase synthesis of 5-amino-1-(substituted thiocarbamoyl)-pyrazole and 1,2,4-triazole derivatives based on the cyclization of polymer-bound dithiocarbazate **3** with various electrophiles, such as 3-ethoxyacrylonitriles **8** and cyanocarboimidates **9**. The polymer-bound dithiocarbazate **3**, produced by nucleophilic reaction with carbon disulfide and Fmoc-hydrazine on the Merrifield resin, served as the key intermediate for subsequent heterocycle diversification. Further nucleophilic substitution on these polymer-bound 5-amino-1-dithiocarboxypyrazoles **4** and 1,2,4-triazoles **6** with various amines under thermal cleavage condition produced the desired 5-amino-1-(substituted thiocarbamoyl)pyrazoles **5** and 1,2,4-triazoles **7**. The progress of reactions could be monitored as polymer-bound intermediates by ATR-FTIR spectroscopy on single bead. The final compounds, obtained in good four-step overall yields and high purities upon cleavage from the resins, were characterized by LC/MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Introduction

Solid-phase synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs.[2] Pyrazole and triazole compounds can provide privileged scaffolds for generation of druglike compounds to drug discovery. The recent success of a pyrazole COX-II inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry.[3] In addition, amino-1,2,4-triazoles have been found effective for the treatment of chronic bronchial asthma[4] and have been assessed as herbicides.[5] Therefore, several reports have described solution- and solid-phase synthesis of pyrazole[6] and 1,2,4-triazole[7] libraries. As a part of our research on drug discovery program, we needed to develop a facile and rapid solid-phase parallel approach for construction of druglike small organic molecules using various heterocycles.[8] Especially, we were interested in constructing heterocycle-based thioureas, such as pyrazole, triazole, thiadiazole, and imidazole, since heterocyclic oriented thioureas have scarcely been reported in the research field of druglike library construction by solid-phase synthesis, as compared with their ureas and simple aromatic thiourea analogues.[4,6g]

Herein, we would like to report our finding about an efficient procedure for the synthesis of 5-amino-1-(substituted thiocarbamoyl)pyrazole and 1,2,4-triazole derivatives via novel dithiocarbazate linker on solid phase. The synthetic methodology described herein was validated with the synthesis of 22-member 5-amino-1-(substituted thiocarbamoyl) pyrazole **5** and 13-member 5-amino-1-(substituted thiocarbamoyl)-1,2,4-triazole **7** libraries.

Result and Discussion

We selected Merrifield resin **1** as a polymer support, since the benzyl chloride in the Merrifield resin was thought to be suitable for the introduction of a sulfur atom of carbon disulfide combined with Fmoc-hydrazine to form the dithiocarbazate linker **3**. In addition, the linker **3** served as a nucleophile for the cyclization reactions with various electrophiles, such as substituted 3-ethoxyacrylonitriles **8** and cyanocarboimidates **9** (Scheme 1). The key intermediate, the polymer-bound dithiocarbazate **3**, was prepared in a two-step procedure starting from the Merrifield resin, as shown in Scheme 1. The desired 5-amino-1-(substituted thiocarbamoyl)pyrazoles **5** and 1,2,4-triazoles **7** were finally liberated from resins **4** and **6** using various amines by thermal cleavage reaction.[9] The progress of these reactions could be monitored by ATR-FTIR spectroscopy on single beads (Figure 1).

As the first step, Fmoc-protected dithiocarbazate resin **2** was prepared from Merrifield resin **1** by reaction with carbon disulfide and Fmoc-protected hydrazine in the presence of sodium hydride in dimethylformamide (DMF) at room temperature. The formation of the Fmoc-dithiocarbazate resin **2** was confirmed by the prominent Fmoc-carbamate bands

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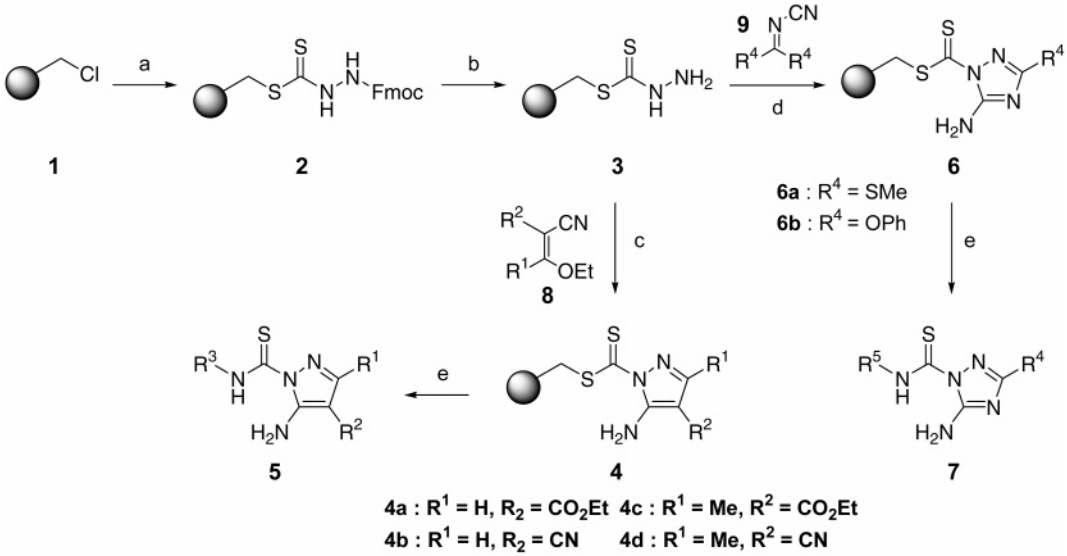
Scheme 1[a]



[a] Reagents and conditions: (a) CS_2, Fmoc-hydrazine, NaH, DMF, rt, 24 h; (b) 5% piperidine, DMF, rt, 2 h; (c) acetonitrile, 80 °C, 12 h; (d) acetonitrile, 80 °C, 12 h; (e) substituted amines, toluene, 60 °C, 6 h.

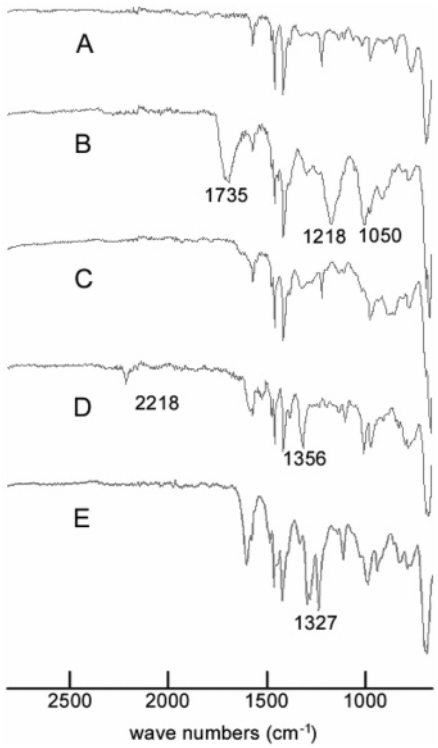


Figure 1. ATR−FTIR spectra on single bead of resin **1** (A), **2** (B), **3** (C), **4b** (D), and **6a** (E).

at 1735 and 1218 cm^{-1} and dithiocarbazate band at 1050 cm^{-1} by ATR-FTIR (Figure 1B). Deprotection of the Fmoc group of resin **2** with 5% piperidine produced the corresponding free dithiocarbazate resin **3**, which was also confirmed by the disappearance of the Fmoc-carbamate streching frequency at 1735 cm^{-1}(Figure 1C). In this step, the use of 5% piperidine was essential, because higher concentration caused the loss of the desired substrate from resin **2**.

For the heterocycle diversification on the hydrazine in the dithiocarbazate system, various 5-aminopyrazoles **4** and 5-amino-1,2,4-triazoles **6** on dithiocarbazate resin **3** were introduced by nucleophilic cyclization reactions with substituted 3-ethoxyacrylonitriles **8** and cyanocarboimidates **9** in acetonitrile (Tables 1 and 2), and the progress of the reaction was monitored by the appearance of a cyclic imine streching band of 5-amino-pyrazole resin **4b** at 1356 cm^{-1} and that of 5-amino-triazole **6a** at 1327 cm^{-1} in the ATR-FTIR spectrum, as shown in Figure 1D,E.

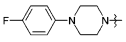
For further combination on resins **4** and **6** as well as for cleavage from the resins, we carried out thermal reaction with various primary and secondary amines in toluene at 60 °C for 6 h. As shown in Table 1, various types of amines give the desired 5-amino-1-(substituted thiocarbamoyl)-pyrazole derivatives in good four-step overall yields from Merrifield resin **1** with high purities, except sterically hindered secondary amines, such as diisopropylamine and diisbutylamine. We also could obtain the desired 5-amino-1-(substituted thiocarbamoyl)triazole derivatives **7** under the same cleavage conditions. The results are summarized in Table 2.

In conclusion, we succeeded in the development of a solid-phase synthesis of 5-amino-1-(substituted thiocarbamoyl)-pyrazoles **5** and 1,2,4-triazoles **7** via novel dithiocarbazate resin **3**. The dithiocarbazate resin **3** served as the key intermediate for heterocycle diversification with various electrophiles, such as substituted 3-ethoxyacrylonitriles **8** and cyanocarboimidates **9** to provide 5-amino-1-dithiocarboxy-pyrazoles **4** and 1,2,4-triazoles **6** resin. The final desired products, 5-amino-1-(substituted thiocarbamoyl)pyrazoles **5** and 1,2,4-triazoles **7** were liberated from resins **4** and **6** with various amines by nucleophilic substitution reaction under thermal cleavage conditions.

Experimental Section

Materials and Methods. The polystyrene Merrifield resin (1.6 mmol/g, 1% cross-linking, 100−200 mesh) was obtained from NovaBiochem. Solvents were purchased from Merck and were anhydrous and HPLC grade. Reactions, filtration, and washings were carried out on a Quest210 synthesizer

Table 1

Code	R^1	R^2	R^3	Yield[a] (%)	Purity[b] (%)
5a	H	CO_2Et	Isobutyl	33	89
5b	H	CO_2Et	Morpholino	28	100
5c	H	CO_2Et		21	91
5d	H	CO_2Et	4-F-benzyl	26	96
5e	H	CO_2Et	4-Cl-benzyl	21	67
5f	H	CO_2Et	4-NO_2-,benzyl	27	100
5g	H	CO_2Et	Furfuryl	26	93
5h	H	CO_2Et		22	96
5i	H	CN	Isobutyl	19	89
5j	H	CN	4-MeO-benzyl	21	97
5k	H	CN	4-Cl-benzyl	24	90
5l	Me	CO_2Et		18	91
5m	Me	CO_2Et	Furfuryl	27	92
5n	Me	CO_2Et		19	96
5o	Me	CO_2Et	4-MeO-benzyl	22	94
5p	Me	CO_2Et	4-Cl-benzyl	26	93
5q	Me	CO_2Et	2-Me-benzyl	20	98
5r	Me	CN	2-Cl-benzyl	23	79
5s	Me	CN	Furfuryl	17	100
5t	Me	CN	Isopropyl	22	96
5u	Me	CN	piperidino	24	97
5v	Me	CN		20	81

[a] Four-step overall yields from Merrifield resin **1** (loading capacity of the resin **1** is 1.6 mmol/g). [b] All of the final products were checked by LC/MS after short-passed silica gel column chromatography.

(Agronaut Technology) and a MiniBlock (Bohdan). Solvent evaporation was performed on a GeneVac Atlas HT-4 centrifugal evaporator. All of the intermediate resins were monitored by ATR-FTIR (SensIR Technology). The structures of the final products were confirmed by ^{1}H NMR (Bruker DPX-300 FT NMR, Varian Gemini-200FT-NMR) and ^{13}C NMR (Bruker AMX-500 FT NMR). LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer (EI) equipped with PDA (200−600 nm) detection using XTerra MS column (C_{18}, 5 μm, 4.6 × 100 mm) from Waters (U.K.). Typical gradients were 5−95% MeCN/H_2O containing 0.1% trifluoroacetic acid.

Procedure for the Preparation of the Supported Dithiocarbazate 2. To a suspension of Merrifield resin **1** (5 g, 8.0 mmol, loading 1.6 mmol/g) in DMF (50 mL) were added successively carbon disulfide (0.98 mL, 16 mmol), sodium hydride (0.64 g, 16 mmol), and Fmoc-protected hydrazine (4.07 g, 16 mmol). The suspension was shaken for 48 h at room temperature under Ar. Fmoc-dithiocarbazate resin **2** was filtered and washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}) 1735, 1218, 1050.

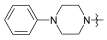
Procedure for Fmoc-Deprotection 3. Resin **2** (5.0 g, 8.0 mmol) was treated with 5% piperidine in DMF (50 mL) for 2 h and washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum.

Reprentative Synthesis for the Synthesis of the Polymer-Bound 5-Amino-1-dithiocarbamoyl Pyrazole 4a. Dithiocarbazate resin **3** (5.0 g, 8.0 mmol) reacted with ethyl (ethoxymethylene)cyanoacetate (4.1 g, 24.0 mmol) in acetonitrile at 80 °C for 12 h to afford the polymer-bound amino pyrazole **4a**. The resin was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}) 1356, 1050.

Reprentative Synthesis for the Synthesis of the Polymer-Bound 5-Amino-1-dithiocarbamoyl-1,2,4-triazole 6a. Dithiocarbazate resin **3** (5.0 g, 8.0 mmol) reacted with dimethyl *N*-cyanodithioiminocarbonate (3.5 g, 24.0 mmol) in acetonitrile at 80 °C for 12 h to afford the resin-bound amino pyrazole **6a**. The resin was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}) 1327, 1271.

Representative Procedure for the Thermal Cleavage Step 5a. To a suspension of resin **4** (200 mg, 0.32 mmol) in toluene (5 mL) was added an excess of isobutylamine (0.047 mg, 0.64 mmol) at room temperature. The mixture was heated at 60 °C for 2 h to promote thiourea formation. The resin was filtered off and washed with CH_2Cl_2 (5 mL) and

Table 2

code	R^4	R^5	Yield[a](%)	Purity[b] (%)
7a	SMe	2-Me-benzyl	26	98
7b	SMe	Furfuryl	23	100
7c	SMe	4-MeO-benzyl	27	97
7d	SMe	Isopropyl	20	98
7e	SMe	Piperidino	28	96
7f	SMe	2-Cl-benzyl	22	93
7g	SMe	2,2-diphenylethyl	19	81
7h	SMe	Isobutyl	27	98
7i	SMe		24	100
7j	OPh		18	94
7k	OPh	Morpholino	23	92
7l	OPh		25	85
7m	OPh		22	87

[a] Four-step overall yields from Merrifield resin **1** (loading capacity of the resin **1** is 1.6 mmol/g) [b] All of the final products were checked by LC/MS after short-passed silica gel column chromatography.

MeOH (5 mL). The combined filtrate was concentrated under vacuum to afford a mixture containing the desired product and excess of amine. The excess of amine was removed by short-passed silica gel chromatography to yield 5-amino-1-isobutylthiocarbamoyl-1*H*-pyrazole-4-carboxylic acid ethyl ester **5a** (29 mg, 33%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.14 (br, 1H), 8.20−7.80 (br, 2H), 7.61 (s, 1H), 4.28 (q, 2H, J = 7.1 Hz), 3.57−3.46 (m, 2H), 2.15−1.98 (m, 1H), 1.34 (t, 3H, J = 7.1 Hz), 1.01 (d, 6H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 164.0, 153.7, 140.4, 95.4, 59.8, 51.2, 27.6, 20.3, 14.5; LC/MS (ESI) *m*/*z* 271 (M + 1).

5-Amino-1-(morpholine-4-carbothioyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5b. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.64 (br, 2H), 4.28 (q, 2H, J = 7.1 Hz), 4.20−3.60 (br, 8H), 1.34 (t, 3H, J = 7.1 Hz); LC/MS (ESI) *m*/*z* 285 (M + 1).

5-Amino-1-(4-phenyl-piperazine-1-carbothioyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5c. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.04−6.85 (m, 4H), 6.65 (br, 2H), 4.29 (q, 2H, J = 7.1 Hz), 4.30−4.00 (br, 4H), 3.26 (br, 4H), 1.35 (t, 3H, J = 7.1 Hz); LC/MS (ESI) *m*/*z* 378 (M + 1).

5-Amino-1-(4-fluorobenzylthiocarbamoyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5d. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.27 (br, 1H), 8.20−7.80 (br, 2H), 7.60 (s, 1H), 7.38−7.31 (m, 2H), 7.26−7.01 (m, 2H), 4.84 (d, 2H, J = 5.3 Hz), 4.28 (q, 2H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz); LC/MS (ESI) *m*/*z* 323 (M + 1).

5-Amino-1-(4-chlorobenzylthiocarbamoyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5e. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.30 (br, 1H), 8.20−7.80 (br, 2H), 7.61 (s, 1H), 7.40−7.26 (m, 4H), 4.84 (d, 2H, J = 6.1 Hz), 4.28 (q, 2H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz); LC/MS (ESI) *m*/*z* 339 (M + 1).

5-Amino-1-(4-nitrobenzylthiocarbamoyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5f. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.48 (br, 1H), 8.22 (d, 2H, J = 8.9 Hz), 8.20−7.80 (br, 2H), 7.52 (d, 2H, J = 8.9 Hz), 5.01 (d, 2H, J = 6.1 Hz), 4.29 (q, 2H, J = 7.1 Hz), 1.35 (t, 3H, J = 7.1 Hz); LC/MS (ESI) *m*/*z* 350 (M + 1).

5-Amino-1-[(furan-2-ylmethyl)thiocarbamoyl]-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5g. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.25 (br, 1H), 8.20−7.80 (br, 2H), 7.62 (s, 1H), 7.41 (s, 1H), 6.37 (s, 2H), 4.86 (d, 2H, J = 5.3 Hz), 4.28 (q, 3H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz); LC/MS (ESI) *m*/*z* 295 (M + 1).

5-Amino-1-[(cyclopropylmethyl)thiocarbamoyl)]-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5h. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (br, 1H), 8.04 (br, 2H), 7.63 (s, 1H), 4.28 (q, 2H, J = 7.1 Hz), 3.54−3.48 (m, 2H), 1.35 (t, 3H, J = 7.1 Hz), 1.23−1.08 (m, 1H), 0.67−0.57 (m, 2H), 0.37−0.29 (m, 2H); LC/MS (ESI) *m*/*z* 269 (M + 1).

5-Amino-4-cyanopyrazole-1-carbothioic Acid 2,2-Diphenylethyl Amide 5i. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.18 (br, 1H), 7.47 (s, 1H), 7.36 (br, 2H), 3.53−3.46 (m, 2H), 2.09−1.98 (m, 1H), 1.02 (d, 6H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 154.7, 140.2, 113.1, 51.5, 27.5, 20.2; LC/MS (ESI) *m*/*z* 224 (M + 1).

5-Amino-4-cyanopyrazole-1-carbothioic Acid 4-Methoxybenzyl Amide 5j. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.29 (br, 1H), 7.46 (s, 1H), 7.37−7.26 (m, 4H), 4.83 (d, 2H, J = 5.7 Hz); LC/MS (ESI) *m*/*z* 292 (M + 1).

5-Amino-4-cyanopyrazole-1-carbothioic Acid 4-Chlorobenzyl Amide 5k. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.18 (br, 1H), 7.44 (s, 3H), 7.36 (br, 2H), 7.28 (d, 2H, J = 9.0 Hz), 6.90 (d, 2H, J = 9.0 Hz), 4.77 (d, 2H, J = 5.7 Hz), 3.81 (s, 3H); LC/MS (ESI) *m*/*z* 288 (M + 1).

5-Amino-1-[(benzo[1,3]dioxol-5-ylmethyl)thiocarbamoyl]-3-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5l. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (br, 1h), 8.50−7.80 (br, 2H), 6.86−6.77 (m, 3H), 5.97 (s, 2H), 4.76 (d, 2H, J =

5.6 Hz), 4.28 (q, 2H, $J = 7.1$ Hz), 2.29 (s, 3H), 1.35 (t, 3H, $J = 7.1$ Hz);^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 164.7, 154.9, 150.8, 148.0, 147.4, 129.7, 121.7, 108.7, 108.5, 101.2, 94.0, 59.6, 47.5, 14.5, 14.4; LC/MS (ESI) *m/z* 363 (M + 1).

5-Amino-1-[(furan-2-ylmethyl)thiocarbamoyl]-3-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5m. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (br, 1H), 7.41 (s, 1H), 6.36 (s, 2H), 4.86 (d, 2H, $J = 5.4$ Hz), 4.28 (d, 2H, $J = 7.2$ Hz), 2.30 (s, 3H), 1.35 (t, 3H, $J = 7.2$ Hz); LC/MS (ESI) *m/z* 309 (M + 1).

5-Amino-3-methyl-1-[(pyridin-4-ylmethyl)thiocarbamoyl]-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5n. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (br, 1H), 8.60 (m, 2H), 7.26 (m, 2H), 4.92 (d, 2H, $J = 6.3$ Hz), 4.30 (q, 2H, $J = 7.2$ Hz), 2.33 (s, 3H), 1.36 (t, 3H, $J = 7.2$ Hz); LC/MS (ESI) *m/z* 320 (M + 1).

5-Amino-1-(4-methoxybenzylthiocarbamoyl)-3-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5o. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (br, 1H), 7.30 (m, 2H), 6.89 (m, 2H), 4.78 (d, 2H, $J = 5.5$ Hz), 4.28 (q, 2H, $J = 7.1$ Hz), 3.81 (s, 3H), 2.28 (s, 3H), 1.35 (t, 3H, $J = 7.1$ Hz); LC/MS (ESI) *m/z* 349 (M + 1).

5-Amino-1-(4-chlorobenzylthiocarbamoyl)-3-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5p. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (br, 1H), 7.36−7.26 (m, 4H), 4.85 (d, 2H, $J = 5.8$ Hz), 4.29 (q, 2H, $J = 7.1$ Hz), 2.30 (s, 3H), 1.35 (t, 3H, $J = 7.1$ Hz); LC/MS (ESI) *m/z* 353 (M + 1).

5-Amino-3-methyl-1-(2-methylbenzylthiocarbamoyl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester 5q. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (br, 1H), 8.50−7.60 (br, 2H), 7.31−7.20 (m, 4H), 4.82 (d, 2H, $J = 5.3$ Hz), 4.29 (q, 2H, $J = 7.1$ Hz), 2.37 (s, 3H), 2.28 (s, 3H), 1.35 (t, 3H, $J = 7.1$ Hz); LC/MS (ESI) *m/z* 333 (M + 1).

5-Amino-4-cyano-3-methylpyrazole-1-carbothioic Acid 2-Chlorobenzyl Amide 5r. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 10.33 (br, 1H), 8.62 (br, 2H), 7.42−7.39 (m, 1H), 7.28−7.25 (m, 3H), 4.88 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 155.2, 150.7, 133.9, 133.2, 130.5, 129.8, 129.6, 127.1, 113.5, 45.6, 12.8; LC/MS (ESI) *m/z* 306 (M + 1).

5-Amino-4-cyano-3-methylpyrazole-1-carbothioic Acid (Furan-2-ylmethyl)amide 5s. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (br, 1H), 7.41 (s, 1H), 7.30 (br, 2H), 6.37 (s, 2H), 4.84 (d, 2H, $J = 5.4$ Hz), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 155.2, 150.7, 148.5, 142.9, 113.4, 110.6, 109.2, 40.8, 12.8; LC/MS (ESI) *m/z* 262 (M + 1).

5-Amino-4-cyano-3-methylpyrazole-1-carbothioic Acid Isopropyl Amide 5t. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (br, 1H), 7.32 (br, 2H), 4.56−4.49 (m, 1H), 2.24 (s, 3H), 1.33 (d, 6H, $J = 6.6$ Hz); LC/MS (ESI) *m/z* 224 (M + 1).

5-Amino-3-methyl-1-(piperidine-1-carbothioyl)-1*H*-pyrazole-4-carbonitrile 5u. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (br, 2H), 4.20−3.50 (m, 4H), 2.25 (s, 3H), 1.69 (br, 6H); LC/MS (ESI) *m/z* 250 (M + 1).

5-Amino-4-cyano-3-methylpyrazole-1-carbothioic Acid (Benzo[1,3]dioxol-5-ylmethyl)amide 5v. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 10.27 (br, 1H), 8.60 (br, 2H), 6.92 (s, 1H), 6.85 (d, 1H, $J = 7.8$ Hz), 6.78 (d, 1H, $J = 7.8$ Hz), 5.96 (s, 2H), 2.21 (s, 3H); LC/MS (ESI) *m/z* 316 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid 2-Methylbenzyl Amide 7a. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.72 (br, 1H), 7.32−7.18 (m, 6H), 4.82 (d, 2H, $J = 5.3$ Hz), 2.48 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 160.6, 157.1, 136.6, 133.6, 130.7, 128.7, 128.4, 126.4, 46.5, 19.2, 13.7; LC/MS (ESI) *m/z* 294 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic acid (furan-2-ylmethyl)amide 7b. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.86 (br, 1H), 7.41 (s, 1H), 7.25 (br, 2H), 6.37−6.34 (m, 2H), 4.85 (d, 2H, $J = 6.7$ Hz), 2.51 (s, 3H); LC/MS (ESI) *m/z* 270 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid 4-Methoxybenzyl Amide 7c. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.83 (br, 1H), 7.36 (br, 2H), 7.29 (d, 2H, $J = 9.0$ Hz), 6.90 (d, 2H, $J = 9.0$ Hz), 4.78 (d, 2H, $J = 6.7$ Hz), 3.81 (s, 3H), 2.48 (s, 3H); LC/MS (ESI) *m/z* 310 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid Isopropyl Amide 7d. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.45 (br, 1H), 7.36 (br, 2H), 4.56−4.45 (m, 1H), 2.53 (s, 3H), 1.32 (d, 6H, $J = 6.9$ Hz); LC/MS (ESI) *m/z* 232 (M + 1).

(5-Amino-3-methylsulfanyl-1,2,4-triazol-1-yl)(piperidin-1-yl)methanethione 7e. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.17 (br, 2H), 3.92 (br, 4H), 1.75 (s, 3H), 1.66 (br, 6H); LC/MS (ESI) *m/z* 258 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid 2-Chlorobenzyl Amide 7f. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (br, 1H), 7.47−7.41 (m, 2H), 7.39−7.25 (m, 2H), 7.16 (br, 2H), 5.96 (d, 2H, $J = 6.1$ Hz), 2.51 (s, 3H); LC/MS (ESI) *m/z* 314 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid 2,2-Diphenylethyl Amide 7g. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.62 (br, 1H), 7.39−7.22 (m, 10H), 4.45−4.40 (m, 1H), 4.37−4.24 (m, 2H), 2.32 (s, 3H); LC/MS (ESI) *m/z* 370 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid Isobutyl Amide 7h. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.75 (br, 1H), 7.34 (br, 2H), 3.53−3.46 (m, 2H), 2.53 (s, 3H), 2.12−1.98 (m, 1H), 1.01 (d, 6H, $J = 6.9$ Hz); LC/MS (ESI) *m/z* 246 (M + 1).

5-Amino-3-methylsulfanyl-1,2,4-triazole-1-carbothioic Acid Cyclopropylmethyl Amide 7i. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.72 (br, 1H), 7.20 (br, 2H), 3.53−3.46 (m, 2H), 2.55 (s, 3H), 1.59 (s, 3H), 1.19−1.11 (m, 1H), 0.67−0.57 (m, 2H), 0.37−0.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 160.4, 157.1, 49.4, 13.7, 9.5, 3.7; LC/MS (ESI) *m/z* 244 (M + 1).

5-Amino-3-phenoxy-1,2,4-triazole-1-carbothioic Acid Pyridin-4-ylmethyl Amide 7j. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 9.32 (br, 1H), 8.57−8.55 (m, 2H), 7.98 (br, 2H), 7.41−7.36 (m, 2H), 7.27−7.20 (m, 5H), 4.87 (d, 2H, $J = 6.2$ Hz); LC/MS (ESI) *m/z* 327 (M + 1).

(5-Amino-3-phenoxy-1,2,4-triazol-1-yl)(morpholin-4-yl-)methanethione 7k. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H), 7.26−7.19 (m, 3H), 6.70 (br, 2H), 4.02 (br, 2H), 3.77 (br, 4H); LC/MS (ESI) *m/z* 306 (M + 1).

5-Amino-3-phenoxy-1,2,4-triazole-1-carbothioic Acid Furan-2-ylmethyl Amide 7l. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 8.60 (br, 1H), 7.60−7.36 (m, 4H), 7.26−7.18 (m, 3H), 6.83−6.73 (m, 3H), 5.96 (s, 2H), 4.71 (d, 2H, $J = 5.7$ Hz); LC/MS (ESI) *m*/*z* 370 (M + 1).

(5-Amino-3-phenoxy-1,2,4-triazol-1-yl)(4-phenyl-piperazin-1-yl)methanethione 7m. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.21 (m, 6H), 6.92−6.88 (m, 4H), 6.41 (s, 2H), 4.10 (br, 4H), 3.31 (br, 4H); LC/MS (ESI) *m*/*z* 367 (M + 1).

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Supporting Information Available. Analytical data (^{1}H NMR and LC/MS) of the entire compounds and ^{13}C NMR spectra of representative compounds **5a**, **5l**, **5r**, **5s**, **7a**, and **7i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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