Organic & Biomolecular Chemistry

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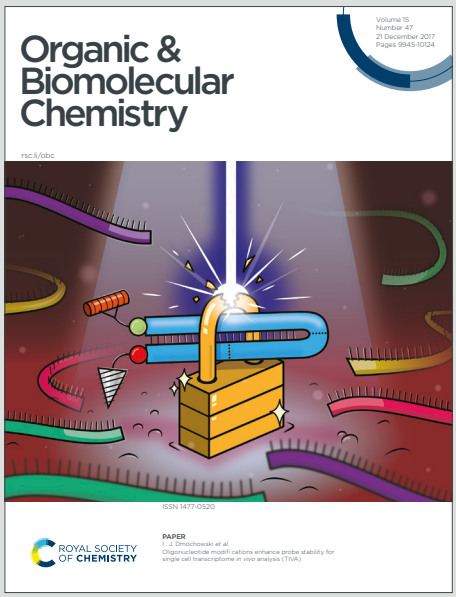

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DOI: 10.1039/C9OB02514F

Journal Name

ARTICLE

Selective C-H Dithiocarbamation of Drug Skeletons and their Antifungal Activity

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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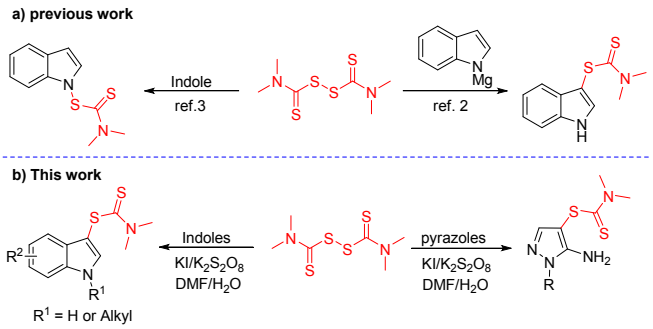
This paper discloses a transition metal-free selective C-H dithiocarbamation of drug skeletons using disulfiram (DSF) in the presence of KI/$K_2S_2O_8$ in DMF/H_2O. Drug skeletons, including 5-aminopyrazoles, indoles, pyrroloquinoline, and Julolidine, underwent C-H dithiocarbamation smoothly to afford a variety of drug-like molecules in moderate to good yields. It was found that the *in situ* formed 5-aminopyrazole iodide is the key intermediate for the dithiocarbamation. Bioassay results show that some of these *N*-heterocyclic dithiocarbamate derivatives exhibit good antifungal activity against *Colletotrichum gloeosprioides* and *Fusarium oxysporum*, *F. proliferatum*, *Fusarium solani*, *Geotrichum candidum*, *Penicillium digitatum*, *Penicillium italicum*, *Phyricularia grisea*.

Introduction

Dithiocarbamate (DTC) compounds have consistently been a major focus of the pharmaceutical and pesticide industry due to their unique molecular structures and numerous biological properties; they possess anti-tumor, antibacterial, antioxidation and insecticidal activities.[1] Thus, the introduction of dithiocarbamate motifs into drug scaffolds is of great interest in drug design and development. The C-H dithiocarbamation of biologically useful *N*-heterocycles is a straightforward and atom economic strategy for the development of new drug molecules.[2-5] In recent years, a number of methodologies have been developed in order to achieve this goal. In 2005, Knochel and coauthors reported a dithiocarbamation of metallized indoles with disulfiram (scheme 1a).[2] However, the metallized indoles are not commercially available and cannot be readily prepared. Furthermore, the C-H dithiocarbamation of indoles still remains challenging in terms of reaction selectivity because the *N*-site of the indole tends to couple with DSF in the presence of base (Scheme 1a).[3] In 2016, we developed a mild and efficient method for the direct dithiocarbamation of imidazoheterocycles in the presence of I_2 and FeF_3.[4] Unfortunately, this protocol is not particularly suitable for the dithiocarbamation of pyrazoles and indoles, giving the corresponding products in very low yields (see Table 2, products **3** and **13**). Although Halimehjani and coauthors have reported a C-H dithiocarbamation of indoles via an iodine-mediated three-component reaction of secondary amines, carbon disulfide and indoles,[5] this method is not compatible with primary amines which are frequently found in many biological molecules.[6] Due to the importance of 5-aminopyrazoles[7] and indoles in medicine and pesticides,[8] the development of a selective C-H dithiocarbamation strategy for the modification of these compounds is highly desirable. Disulfiram is an ideal dithiocarbamoyl source as it is inexpensive and possesses low toxicity.[9] However, problems associated with reaction selectivity remain unaddressed for the C-H dithiocarbamation of 5-aminopyrazoles because disulfiram can react with amines to form sulfocarbamides.[10] Herein, we report an environmentally benign selective C-H dithiocarbamation of 5-aminopyrazoles and indoles in the presence of KI/$K_2S_2O_8$ in DMF/H_2O (Scheme 1b).



Scheme 1. Dithiocarbamation of indoles and pyrazoles.

Results and discussion

Our study began with the reaction of 1-methyl-1*H*-pyrazol-5-amine **1a** with thiram **2a** in the presence of KI (10 mol%) and

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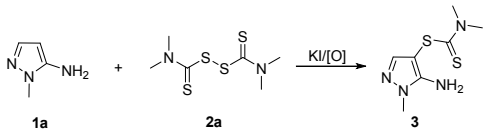
Electronic Supplementary Information (ESI) available:See DOI: 10.1039/x0xx00000x

$K_2S_2O_8$ (2 equiv.) at 80 °C. Solvents such as hexane, DCE, DMSO, CH_3CN, and DMF, were examined (Table 1, entries 1-5). No reaction occurred in hexane or DMSO (Table 1, entries 1 and 3). The reaction was carried out in DCE, affording product **3** in 11% yield (Table 1, entry 2). Both CH_3CN and DMF were effective, and the yield of the desired product increased to 35% and 36%, respectively, using these solvents (Table 1, entries 4 and 5). To improve the solubility of $K_2S_2O_8$, the reaction was conducted in a mixed solvent system of DMF/H_2O (5:1), giving the product **3** in 48% yield (Table 1, entry 6).

Table 1. Screening of Optimal Conditions[a]



1a 2a 3

Entry	Cat. (mol%)	Oxidant	Solvent (ml)	Temp (°C)	Yield (%)
1	KI (10)	$K_2S_2O_8$	hexane	80	trace
2	KI (10)	$K_2S_2O_8$	DCE	80	11
3	KI (10)	$K_2S_2O_8$	DMSO	80	trace
4	KI (10)	$K_2S_2O_8$	CH_3CN	80	35
5	KI (10)	$K_2S_2O_8$	DMF	80	36
6	KI (10)	$K_2S_2O_8$	DMF/H_2O	80	48
7	KI (10)	$K_2S_2O_8$	DMF/H_2O	60	62
8	KI (10)	$K_2S_2O_8$	DMF/H_2O	40	58
9	KI (10)	$K_2S_2O_8$	DMF/H_2O	rt	32
10[b]	KI (10)	$K_2S_2O_8$	DMF/H_2O	60	20
11[c]	KI (10)	$K_2S_2O_8$	DMF/H_2O	60	49
12[d]	KI (10)	$K_2S_2O_8$	DMF/H_2O	60	63
13	KI (1)	$K_2S_2O_8$	DMF/H_2O	60	47
14	KI (5)	$K_2S_2O_8$	DMF/H_2O	60	48
15	KI (20)	$K_2S_2O_8$	DMF/H_2O	60	78
16	KI (50)	$K_2S_2O_8$	DMF/H_2O	60	53
17	KI (100)	$K_2S_2O_8$	DMF/H_2O	60	56
18	KI (20)	Oxone	DMF/H_2O	60	16
19	KI (20)	DTBP	DMF/H_2O	60	11
20	KI (20)	TBHP	DMF/H_2O	60	36
21	KI (20)	DCP	DMF/H_2O	60	trace
22	KI (20)	H_2O_2	DMF/H_2O	60	40
23	KI (20)	—	DMF/H_2O	60	trace
24	—	$K_2S_2O_8$	DMF/H_2O	60	trace
25	I_2 (20)	$K_2S_2O_8$	DMF/H_2O	60	72
26	I_2 (100)	—	DMF/H_2O	60	59

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv), oxidant (2 equiv), solvent (1 mL) DMF/H_2O= 5:1, reaction for 12 hours. [b] DMF/H_2O= 1:1. [c] DMF/H_2O= 5:1. [d] DMF/H_2O= 9:1.

Higher yields of product were obtained at lower temperatures, e.g. 62% at 60 °C and 58% at 40 °C (Table 1, entries 7 and 8). The effective reaction conditions give product **3** in 32% yield even at room temperature (Table 1, entry 9). Next, the volume ratio of DMF/H_2O was examined (Table 1, entries 10-12). Results show that a ratio of 5:1 DMF/H_2O was the best for this reaction. The effect of the amount of KI (from 1 mol% to 100 mol%) was also studied (Table 1, entries 13-17). Conducting the reaction in the presence of 20 mol% KI gave product **3** in 78% yield (Table 1, entry 15). Oxidants, including Oxone, DTBP (di-*tert*-butyl peroxide), TBHP (*tert*-Butyl hydroperoxide), DCP (dicumyl peroxide), and H_2O_2 were examined (Table 1, entries 18-22). Except for DCP, all these oxidants were effective for this reaction, but were not as effective as $K_2S_2O_8$. Both KI and $K_2S_2O_8$ are essential for this transformation; the reaction does not proceed in the absence of these reagents (Table 1, entries 23 and 24). The replacement of KI with I_2 afforded product **3** in 72% yield (Table 1, entry 25). An alternative iodination reaction occurred when one equivalent of I_2 was used in the absence of $K_2S_2O_8$, and the yield of the desired product decreased to 59% (Table 1, entry 26).

With the optimized reaction conditions in hand, the reaction scope was studied (Table 1, entry 15). We firstly focused on the dithiocarbamation of 5-aminopyrazoles, as such compounds are privileged scaffolds in pesticides.[7] Both 1-methyl and 1-phenyl substituted 5-aminopyrazoles underwent reaction to provide their corresponding products in moderate to good yields (products **3-12**). Substituents, such as methyl, *t*-butyl, and phenyl groups at the C3 position of the pyrazoles are compatible with the reaction conditions. The bulky *t*-butyl group had no effect on the reaction, giving product **7** in 60% yield. Other disulfiram derivatives were also examined and both *N,N*-diethyl and *N,N*-diisopropyl groups are well tolerated. The steric hindrance of the *N,N*-diisopropyl group led to a decrease in yield of the corresponding product **12** (34% yield).

Next, the introduction of dithiocarbamate into indole compounds was explored (products **13-29**). Although the C-H dithiocarbamation of indoles using disulfirams remains challenging, the C-H dithiocarbamation proceeded well under the standard conditions. For example, C-H dithiocarbamation selectively occurred at the C3 site of the indoles without a protecting group on the nitrogen atom; no reaction was observed at the *N*-atom as reported in the previous work (products **13-19**).[3] 2-Methylindole underwent reaction to afford product **14** in 90% yield. 2-Phenylindole also gave product **15** in 74% yield. *N*-alkyl substituted indoles are also amenable to the reaction conditions, affording their corresponding products in moderate to good yields (products **20-24**). However, a substrate bearing a bromo group on the benzene ring gave its corresponding product in low yield (24%, product **21**). Both *N,N*-diethyl and *N,N*-diisopropy difulfiram were also reacted with various indoles to afford their corresponding products **25-28** in moderate yields. It is noteworthy that the medicinal compound, pyrroloquinoline, is also tolerated under the reaction conditions, affording product **29** in 89% yield. C-H dithiocarbamation also occurs with Julolidine (potential fluorescent dyes for biological use[11]), albeit giving the corresponding product in 34% yield (product **30**). The electron-rich *m*-trimethoxybenzene was also amenable to this transformation,

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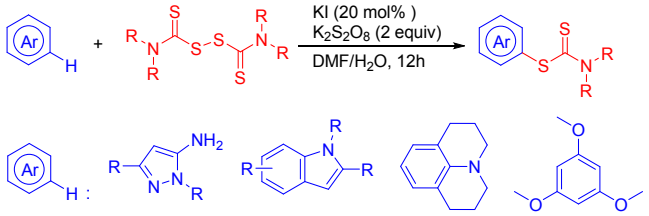
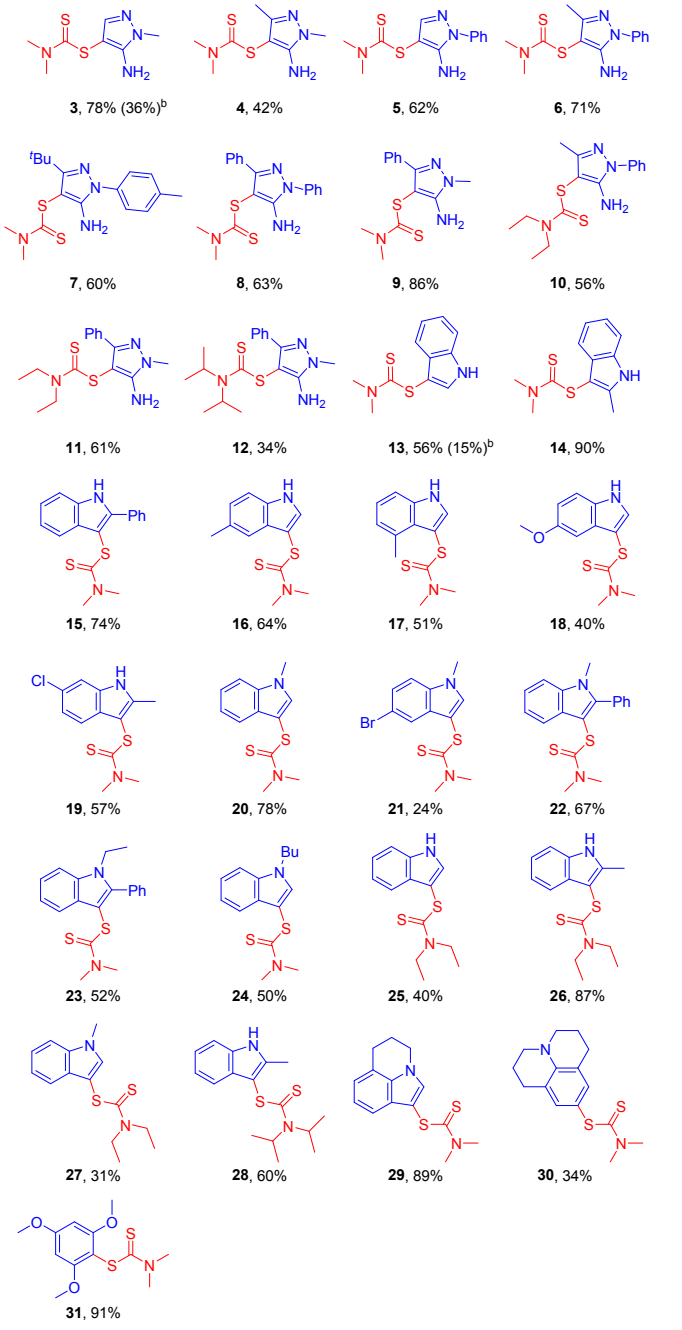
Table 2. Reaction scope[a]

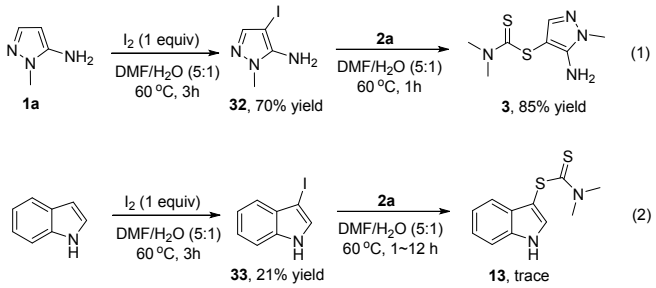




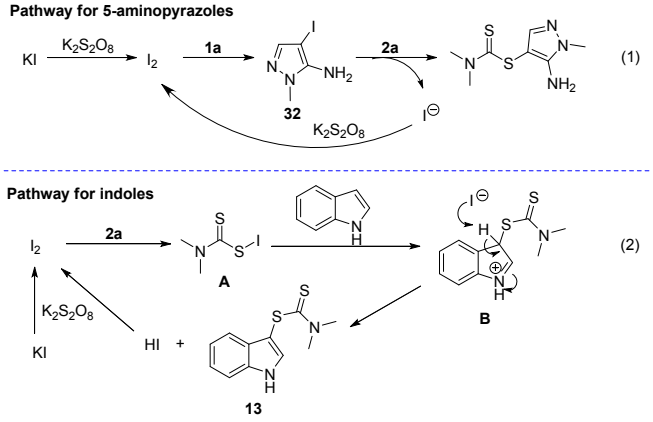
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv), KI (20 mol%), $K_2S_2O_8$ (0.4 mmol, 2 equiv), DMF/H_2O (2 mL, 5:1), at 60°C for 12 h. [b] using the standard reaction conditions of ref.4a.

affording product **31** in 91% yield. It is worth noting that this C-H dithiocarbamation protocol is much more effective than the previously reported method using an I_2/FeF_3 system.[4a] For example, product **3** and **13** were obtained in only 36% and 15% yields, respectively, using these conditions.

In order to elucidate possible reaction pathways, control experiments were conducted (Scheme 2). We found that in the absence of $K_2S_2O_8$, 5-aminopyrazole could react with I_2 to afford compound **32** in 70% yield in DMF/H_2O at 60 °C over three hours. The reaction between compound **32** and **2a** gave product **3** in 85% yield in the absence of any additives (Scheme 2, Eq 1). The iodination of indole still occurred to afford 3-iodo-1*H*-indole **33** in 21% yield in DMF/H_2O at 60 °C for three hours. However, the reaction of 3-iodo-1*H*-indole **33** with **2a** only afford a trace amount of product **13**, even the reaction time was prolonged to twelve hours. These results indicate that the dithiocarbamation of 5-aminopyrazoles is different from indoles.



Scheme 2 Control Experiments.



Scheme 3 Possible Reaction Pathways.

Based on the current results and previous reports,[4,5] Possible reaction pathways for the dithiocarbamation of 5-aminopyrazoles and indoles have been proposed, respectively (Scheme 3). For the reaction pathway of 5-aminopyrazole (Scheme 3, Eq 1), firstly, a catalytic amount of I_2 is formed via the oxidization of KI with $K_2S_2O_8$. Next, the iodination of pyrazole **1a** occurs to afford intermediate **32**, which undergoes nucleophilic substitution with **2a** to produce the desired product **3**. The adjacent amino group may be involved in this nucleophilic substitution. For the reaction

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pathway of indoles (Scheme 3, Eq 2), the *in situ* formed I_2 may react with **2a** to form intermediate **A**, which undergoes a Friedel-Crafts type reaction with indole to produce intermediate **B**. The dehydrogenation of the intermediate **B** allows to provide product **13**. The formed HI is oxidized by $K_2S_2O_8$ to produce I_2 for the next reaction cycle.

The antifungal activity of these compounds against eight phytopathogenic fungi was evaluated using the disc diffusion method as a reference.[12] Eight compounds displayed obvious inhibitory effects towards at least one indicator fungus at a concentration of 50 μg/disc (Table 3). After further determination of the antifungal activity of the eight compounds, the results showed that four compounds (compounds **10**, **12**, **29** and **31**) exhibited strong antifungal activity against at least one indicator fungus. The MIC values of compounds **10**, **12** and **29** toward *F. proliferatum* were equal to that of the positive controls cycloheximide and amphotericin B (12.5μg/mL). Furthermore, the MIC value of compound **31** toward *P. grisea* is equal to that of the positive control amphotericin B. In addition, compound **27** exhibited strong antifungal activity against *C. gloeosprioides*, *F. proliferatum* and *F. solani*. The MIC values of compound **27** toward the three indicator fungi are equal or close to that of the positive controls of cycloheximide and amphotericin B.

Conclusion

In summary, we have developed a transition metal-free $KI/K_2S_2O_8$-promoted selective C-H dithiocarbamation of *N*-heterocycles with DSF using mild conditions. It is noteworthy that the reaction selectivity of 5-aminopyrazoles and indoles can be controlled under the environmentally benign conditions. *N*-heterocycles, including 5-aminopyrazoles, indoles, pyrroloquinoline, and Julolidine, are biologically useful medicinal or pesticidal scaffolds. Significantly, some of these *N*-heterocyclic-dithiocarbamate derivatives exhibit good antifungal activity against *Colletotrichum gloeosprioides*, *Fusarium oxysporum*, *F. proliferatum*, *Fusarium solani*, *Geotrichum candidum*, *Penicillium digitatum*, *Penicillium italicum*, and *Phyricularia grisea*. The modification of these compounds and their application in agriculture are underway in our laboratory.

Table 3. The antifungal activity of eight compounds against eight phytopathogenic fungi.

Compounds	The minimum inhibitory concentrations (MIC)/ μ g/mL							
	CG	FO	FP	FS	GC	PD	PI	PG
5	/	/	/	/	25	/	/	25
10	>25	>25	12.5	>25	>25	>25	>25	>25
12	>25	>25	12.5	>25	>25	>25	>25	>25
25	>25	>25	>25	>25	>25	>25	>25	/
26	>25	>25	>25	>25	25	>25	>25	/
27	12.5	>25	25	25	>25	>25	>25	/
29	>25	>25	12.5	>25	>25	25	>25	/
31	/	/	/	/	25	/	/	6.25
Cy	6.25	6.25	12.5	25	12.5	12.5	25	3.13
AB	6.25	6.25	12.5	25	12.5	6.25	12.5	6.25

CG = *Colletotrichum gloeosprioides*. FO = *Fusarium oxysporum*. FP = *F. proliferatum*. FS = *Fusarium solani*. GC = *Geotrichum candidum*. PD = *Penicillium digitatum*. PI = *Penicillium italicum*. PG = *Phyricularia grisea*. Cy = *Cycloheximide*. AB = *Amphotericin B*. / = no test

Experimental

General remarks

^1H and ^{13}C NMR spectra were measured on a Bruker Avance-Ⅲ 600 instrument (600MHz for ^1H, 151 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts for ^1H and ^{13}C NMR were referred to internal Me_4Si (0 ppm) as the standard. The following abbreviations (or combinations thereof) were used to explain chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants (*J*) in hertz (Hz). IR spectra were measured on a Nicolet IS10. Mass spectra were measured on an Agilent GC-MS-5975C Plus spectrometer (EI). LCMS (ESI) analysis was measured on an AB Sciex API3200. HRMS (ESI) analysis was measured on a Thermo Scientific LTQ Orbitrap XL.

General procedure for the C-H dithiocarbamation with disulfiram: A 10-mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **1a** (0.20 mmol), dithiocarbamate **2a** (0.20 mmol), KI (20 mol%) and $K_2S_2O_8$ (0.4 mmol), DMF:H_2O (5:1, 2 mL) was then added sequentially. The tube was then capped and stirred at 60 °C for 12 h, the crude mixture was diluted with DCM, and washed with sat. aq NaCl solution. The organic phase was dried ($MgSO_4$), filtered through a Celite pad, and washed with EtOAc. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (Petroleum-EtOAc) to afford product **3** as a white solid.

Experimental procedure for the synthesis of compound 32: A 10-mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **1a** (0.20 mmol) and I_2 (0.20 mmol, 1 equiv.). DMF:H_2O (5:1, 2 mL) was then added. The tube was then capped and stirred at 60 °C for 3 h. the crude mixture was diluted with DCM and washed with sat. aq NaCl solution. The organic phase was dried ($MgSO_4$), filtered through a Celite pad, and washed with EtOAc. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (Petroleum-EtOAc) to afford compound **32** in 70% yield.

The experimental procedure for the synthesis of compound **33** is the same as the one of compound **32**.

Determination of antifungal activity

These compounds were selected to determine the antifungal activity against eight phytopathogenic fungi, including *Colletotrichum gloeosprioides*, *Fusarium oxysporum*, *Fusarium proliferatum*, *Fusarium solani*, *Geotrichum candidum*, *Penicillium digitatum*, *Penicillium italicum* and *Phyricularia grisea* using the disc diffusion method.[12] Briefly, the phytopathogenic fungi were cultured on a PDA (potatoes 200g, glucose 20g, agar 20g and water 1000mL) plate at 28 °C for 7 days. Next, the aqueous suspensions (about 10^6 spores/mL) of fungal spores for inoculation were prepared with sterilized water containing 0.02% (v/v) of Tween 80. All the tested compounds were dissolved in dimethyl sulfoxide (DMSO) (10 mg/mL). A 100 μL of spore suspensions were added on a PDA plate and evenly spread on to it. Paper discs loaded with 50 μg samples were placed on the inoculated plates. Cycloheximide (5 μg/disc) and amphotericin B (5 μg/disc) were used as positive controls. The paper disc loaded with 2.5 μL of DMSO was used as the negative control. The antifungal activity was determined after culturing for 3-5 days at 28 °C.

The minimum inhibitory concentrations (MICs) of these compounds displaying obvious antifungal activity (50 μg/disc) were further determined by a traditional method in 96-well microplates (Bao et al., 2018). An aliquot of 200 μL of the fungal suspension was distributed in each well containing 2-fold serial dilution of the positive controls and tested compounds. The final concentrations of positive controls and tested compounds were 25, 12.5, 6.25, 3.13, 1.56 and 0.78 μg/mL. The microplates were incubated at 28 °C for 3 days, and then the optical density of each well was measured at 600 nm spectrophtometrically. MIC values were defined as the lowest concentration of each compound or positive control that produced an obvious decrease in fungal growth (inhibition ≥ 50%).

Analytical data for products

5-amino-1-methyl-1H-pyrazol-4-yl dimethylcarbamodithioate (3): yield (34 mg, 78%); White solid, mp 161.8 – 162.9 °C; v_{max}/cm^{-1} 3386 (NH_2), 2956, 2921, 2850, 1630, 1377, 1049 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.28 (s, 1H, *Ar*), 3.92 (s, 2H, *NH_2*), 3.70 (s, 3H, *Me*), 3.53 (s, 3H, *Me*), 3.48 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 197.4, 148.9, 143.3, 90.1, 46.1, 41.7, 35.2; LRMS (EI, 70 eV) m/z (%): 216 (16), 128 (7), 88 (100); HRMS (ESI) m/z calcd for $C_7H_{13}N_4S_2^+$ $(M + H)^+$ 217.05761, found 217.05754.

5-amino-1,3-dimethyl-1H-pyrazol-4-yl dimethylcarbamodithioate (4): yield (19 mg, 42%); Yellow solid, mp 150.1 – 151.2 °C; v_{max}/cm^{-1} 3314 (NH_2), 2922, 2851, 1625, 1377, 1049 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 3.89 (s, 2H, *NH_2*), 3.62 (s, 3H, *Me*), 3.52 (s, 3H, *Me*), 3.48 (s, 3H, *Me*), 2.08 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 197.4, 151.3, 149.2, 89.0, 46.0, 41.5, 34.7, 12.2; LRMS (EI, 70 eV) m/z (%): 230 (17), 88 (100), 57 (10); HRMS (ESI) m/z calcd for $C_8H_{15}N_4S_2^+$ $(M + H)^+$ 231.07326, found 231.07329.

5-amino-1-phenyl-1H-pyrazol-4-yl dimethylcarbamodithioate (5): yield (35 mg, 62%); White solid, mp 148.1 – 151.1 °C; v_{max}/cm^{-1} 3356 (NH_2), 2921, 2851, 1616, 1600, 1511, 1455 (Ph), 1377, 1050 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.59 (d, *J* = 7.8 Hz, 2H, *Ar*), 7.49 (t, *J* = 7.9 Hz, 2H, *Ar*), 7.46 (s, 1H, *Ar*), 7.37 (t, *J* = 7.5 Hz, 1H, *Ar*), 4.24 (s, 2H, *NH_2*), 3.55 (s, 3H, *Me*), 3.50 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 196.8, 149.0, 145.0, 138.4, 129.5, 127.7, 123.8, 90.2, 46.1, 41.7; LRMS (EI, 70 eV) m/z (%): 278 (11), 88 (100), 77 (12); HRMS (ESI) m/z calcd for $C_{12}H_{15}N_4S_2^+$ $(M + H)^+$ 279.07326, found 279.07355.

5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl dimethylcarbamodithioate (6): yield (42 mg, 71%); White solid, mp 178.8 – 180.2 °C; v_{max}/cm^{-1} 3386 (NH_2), 2958, 2922, 2851, 1500, 1456 (Ph), 1377, 1048(CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.56 (d, *J* = 7.6 Hz, 2H, *Ar*), 7.45 (t, *J* = 7.9 Hz, 2H, *Ar*), 7.32 (t, *J* = 7.4 Hz, 1H, *Ar*), 4.17 (s, 2H, *NH2*), 3.54 (s, 3H, *Me*), 3.51 (s, 3H, *Me*), 2.17 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 196.8, 153.0, 149.1, 129.4, 127.3, 123.6, 89.5, 46.0, 41.57, 12.3; LRMS (EI, 70 eV) m/z (%): 292 (13), 119 (12), 88 (100), 77 (13); HRMS (ESI) m/z calcd for $C_{13}H_{17}N_4S_2^+$ $(M + H)^+$ 293.08891, found 293.08859.

5-amino-3-tert-butyl-1-p-tolyl-1H-pyrazol-4-yl dimethylcarbamodithioate (7): yield (42 mg, 60%); White solid, mp 152.0 – 153.6 °C; v_{max}/cm^{-1} 3362 (NH_2), 2881, 1612, 1499 (Ph), 1370, 1083 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.46 (d, *J* = 8.3 Hz, 2H, *Ar*), 7.26 (d, *J* = 8.0 Hz, 2H, *Ar*), 4.05 (s, 2H, *NH_2*), 3.56 (s, 3H, *Me*), 3.53 (s, 3H, *Me*), 2.38 (s, 3H, *Me*), 1.36 (s, 9H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 196.7, 161.6, 150.2, 137.3, 130.0, 123.9, 87.1, 46.1, 41.6, 33.4, 29.4, 21.1; LRMS (EI, 70 eV) m/z (%): 348 (12), 88 (100), 77 (13); HRMS (ESI) m/z calcd for $C_{17}H_{25}N_4S_2^+$ $(M + H)^+$ 349.15151, found 349.15192.

5-amino-1,3-diphenyl-1H-pyrazol-4-yl dimethylcarbamodithioate (8): yield (45 mg, 63%); White solid, mp 78.8 – 79.7 °C; v_{max}/cm^{-1} 3356 (NH_2), 2882, 1611 (Ph), 1503, 1437, 1377, 1083 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.82 – 7.79 (m, 2H, *Ar*), 7.68 (d, *J* = 7.6 Hz, 2H, *Ar*), 7.51 (t, *J* = 7.9 Hz, 2H, *Ar*), 7.41 – 7.37 (m, 3H, *Ar*), 7.35 – 7.32 (m, 1H, *Ar*), 4.26 (s, 2H, *NH_2*), 3.56 (s, 3H, *Me*), 3.49 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 196.5, 150.1, 138.4, 132.6, 129.5, 128.1, 128.1, 128.1, 127.8, 124.0, 46.1, 41.7; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_4S_2^+$ $(M + H)^+$ 355.10456, found 355.10495.

5-amino-1-methyl-3-phenyl-1H-pyrazol-4-yl dimethylcarbamodithioate (9): yield (50 mg, 86%); White solid, mp 177.6 – 178.3 °C; v_{max}/cm^{-1} 3356 (NH_2), 2882, 1619 (Ph), 1506, 1439, 1379, 1084 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.72 – 7.69 (m, 2H, *Ar*), 7.35 (t, *J* = 7.4 Hz, 2H, *Ar*), 7.32 – 7.29 (m, 1H, *Ar*), 3.95 (s, 2H, *NH_2*), 3.75 (s, 3H, *Me*), 3.55 (s, 3H, *Me*), 3.47 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 197.1, 152.5, 150.0, 132.8, 128.1, 127.9, 127.9, 88.3, 46.11, 41.64, 35.15; LRMS (EI, 70 eV) m/z (%): 292 (16), 88 (100); HRMS (ESI) m/z calcd for $C_{13}H_{17}N_4S_2^+$ $(M + H)^+$ 293.08891, found 293.08920.

5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl diethylcarbamodithioate (10): yield (36 mg, 56%); Yellow oil; v_{max}/cm^{-1} 3416 (NH_2), 2976, 2930, 2873, 1598 (Ph), 1490, 1454, 1270, 1067 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.58 – 7.56 (m, 2H, *Ar*), 7.45 (t, *J* = 7.9 Hz, 2H, *Ar*), 7.32 (t, *J* = 7.4 Hz, 1H, *Ar*), 4.18 (s, 2H, NH_2), 4.01 (q, *J* = 7.0 Hz, 2H, CH_2), 3.88 (q, *J* = 7.1 Hz, 2H, CH_2), 2.18 (s, 3H, *Me*), 1.40 (t, *J* = 7.1 Hz, 3H, *Me*), 1.27 (t, *J* = 7.1 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 195.2, 153.0, 149.3, 138.5, 129.4, 127.3, 123.6, 50.3, 46.8, 12.8, 12.3, 11.5; LRMS (EI, 70 eV) m/z (%): 320 (9), 116 (100), 88 (50), 77 (17), 60 (19); HRMS (ESI) m/z calcd for $C_{15}H_{21}N_4S_2^+$ (M + H)$^+$ 321.12021, found 321.12054.

5-amino-1-methyl-3-phenyl-1H-pyrazol-4-yl diethylcarbamodithioate (11): yield (39 mg, 61%); Yellow solid, mp 112.3 – 115.4 °C; v_{max}/cm^{-1} 3418 (NH_2), 2977, 2934, 2877, 1618, 1504, 1452 (Ph), 1380, 1073 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.69 (d, *J* = 7.1 Hz, 2H, *Ar*), 7.34 (t, *J* = 7.3 Hz, 2H, *Ar*), 7.32 – 7.28 (m, 1H, *Ar*), 4.03 (q, *J* = 7.1 Hz, 2H, CH_2), 3.97 (s, 2H, NH_2), 3.85 (q, *J* = 7.1 Hz, 2H, CH_2), 3.77 (s, 3H, *Me*), 1.36 (t, *J* = 7.1 Hz, 3H, *Me*), 1.29 (t, *J* = 7.1 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 195.6, 152.5, 150.3, 132.9, 128.1, 127.9, 127.9, 88.5, 50.4, 46.9, 35.2, 13.0, 11.7; LRMS (EI, 70 eV) m/z (%): 320 (8), 173 (10), 116 (100), 88 (47), 60 (18); HRMS (ESI) m/z calcd for $C_{15}H_{21}N_4S_2^+$ (M + H)$^+$ 321.12021, found 321.12070.

5-amino-1-methyl-3-phenyl-1H-pyrazol-4-yl diisopropylcarbamodithioate (12): yield (24 mg, 34%); Yellow solid, mp 68.0 – 70.7 °C; v_{max}/cm^{-1} 3406 (NH_2), 2969, 2927, 2854, 1620 (Ph), 1506, 1441, 1378 (Me), 1140 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.75 – 7.58 (m, 2H, *Ar*), 7.35 – 7.31 (m, 2H, *Ar*), 7.31 – 7.27 (m, 1H, *Ar*), 6.60 – 5.29 (m, 1H, *CH*), 5.29 – 4.77 (m, 1H, *CH*), 4.01 (s, 2H, NH_2), 3.76 (s, 3H, *Me*), 1.43 (s, 12H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 152.4, 150.6, 133.0, 128.0, 127.8, 88.9, 35.1, 19.7; HRMS (ESI) m/z calcd for $C_{17}H_{25}N_4S_2^+$ (M + H)$^+$ 349.15151, found 349.15190. (There is no ^{13}C NMR signal peak of the carbonyl and the CH, which may result from the steric hindrance of the amide. Please also see the NMR spectra of tetraisopropylthiuram disulfide at the end of the supporting information.)

1H-indol-3-yl dimethylcarbamodithioate (13): yield (27 mg, 56%); Pink solid, mp 173.2 – 175.4 °C; v_{max}/cm^{-1} 3388 (NH), 2957, 2920, 2850, 1503 (Ph), 1454, 1376, 1049 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.74 (s, 1H, *NH*), 7.68 – 7.57 (m, 1H, *Ar*), 7.35 – 7.32 (m, 1H, *Ar*), 7.29 (d, *J* = 2.6 Hz, 1H, *Ar*), 7.23 – 7.17 (m, 2H, *Ar*), 3.60 (s, 6H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.8, 136.2, 132.6, 129.1, 122.8, 120.9, 119.2, 112.0, 102.6, 46.1, 41.9; LRMS (EI, 70 eV) m/z (%): 236 (27), 148 (11), 88 (100); HRMS (ESI) m/z calcd for $C_{11}H_{13}N_2S_2^+$ (M + H)$^+$ 237.05147, found 237.05155.

2-methyl-1H-indol-3-yl dimethylcarbamodithioate (14): yield (45 mg, 90%); White solid, mp 164.4 – 165.0 °C; v_{max}/cm^{-1} 3416 (NH), 2978, 2921, 2850, 1598 (Ph), 1496 (Ph), 1452, 1378, 1052 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.45 (s, 1H, *NH*), 7.54 – 7.45 (m, 1H, *Ar*), 7.29 – 7.26 (m, 1H, *Ar*), 7.16 – 7.12 (m, 2H, *Ar*), 3.59 (d, *J* = 11.3 Hz, 6H, *Me*), 2.39 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.2, 143.2, 135.2, 130.2, 121.9, 120.7, 118.4, 111.0, 46.0, 41.7, 12.4; LRMS (EI, 70 eV) m/z (%): 250 (27), 162 (11), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2S_2^+$ (M + H)$^+$ 251.06712, found 251.06725.

2-phenyl-1H-indol-3-yl dimethylcarbamodithioate (15): yield (46 mg, 74%); Yellow solid, mp 87.7 – 89.8 °C; v_{max}/cm^{-1} 3386 (NH), 2924, 2853, 1601 (Ph), 1499 (Ph), 1455, 1376, 1146 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.80 (s, 1H, *NH*), 7.60 – 7.65 (m, 2H, *Ar*), 7.58 (d, *J* = 7.4 Hz, 1H, *Ar*), 7.40 – 7.34 (m, 3H, *Ar*), 7.27 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.19 – 7.13 (m, 2H, *Ar*), 3.60 (s, 3H, *Me*), 3.55 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.4, 143.4, 135.7, 131.2, 130.8, 128.6, 128.5, 128.3, 123.1, 121.1, 119.2, 111.5, 99.6, 45.9, 41.8; LRMS (EI, 70 eV) m/z (%): 312 (22), 223 (17), 88 (100); HRMS (ESI) m/z calcd for $C_{17}H_{17}N_2S_2^+$ (M + H)$^+$ 313.08277, found 313.08295.

5-methyl-1H-indol-3-yl dimethylcarbamodithioate (16): yield (32 mg, 64%); Gray solid, mp 183.7 – 184.9 °C; v_{max}/cm^{-1} 3386 (NH), 2978, 2921, 2853, 1505 (Ph), 1375, 1090 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.70 (s, 1H, *NH*), 7.37 (s, 1H, *Ar*), 7.22 – 7.19 (m, 2H, *Ar*), 7.03 (d, *J* = 8.3 Hz, 1H, *Ar*), 3.60 (d, *J* = 6.3 Hz, 6H, *Me*), 2.46 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 199.0, 134.5, 132.7, 130.3, 129.4, 124.5, 118.8, 111.6, 102.1, 46.1, 41.8, 21.5; LRMS (EI, 70 eV) m/z (%): 250 (28), 162 (11), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2S_2^+$ (M + H)$^+$ 251.06712, found 251.06721.

4-methyl-1H-indol-3-yl dimethylcarbamodithioate (17): yield (26 mg, 51%); Purple solid, mp 185.3 – 186.4 °C; v_{max}/cm^{-1} 3386 (NH), 2923, 2853, 1506 (Ph), 1376, 1056 (CS-S-); δH (600 MHz; DMSO; Me_4Si) 11.67 (s, 1H, *NH*), 7.57 (d, *J* = 2.8 Hz, 1H, *Ar*), 7.20 (d, *J* = 7.3 Hz, 1H, *Ar*), 6.99 – 6.94 (m, 2H, *Ar*), 3.54 (s, 3H, *Me*), 3.45 (s, 3H, *Me*), 2.50 (s, 3H, *Me*); ^{13}C NMR (151 MHz; DMSO; Me_4Si) 197.0, 135.9, 133.6, 129.0, 122.2, 121.3, 120.1, 116.1, 100.93, 45.5, 41.5, 16.6; LRMS (EI, 70 eV) m/z (%): 250 (28), 162 (11), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2S_2^+$ (M + H)$^+$ 251.06712, found 251.06723.

5-methoxy-1H-indol-3-yl dimethylcarbamodithioate (18): yield (21 mg, 40%); Gray solid, mp 198.7 – 200.7 °C; v_{max}/cm^{-1} 3384 (NH), 2922, 2852, 1501 (Ph), 1484, 1375, 1084 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.57 (s, 1H, *NH*), 7.31 (s, 1H, *Ar*), 7.26 (t, *J* = 4.4Hz, 1H, *Ar*), 7.00 (d, *J* = 2.4 Hz, 1H, *Ar*), 6.87 (dd, *J* = 8.7, 2.3 Hz, 1H, *Ar*), 3.85 (s, 3H, *Me*), 3.60 (s, 6H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.8, 155.2, 133.1, 131.1, 130.0, 113.4, 112.7, 100.7, 55.8, 46.1, 41.8; LRMS (EI, 70 eV) m/z (%): 266 (27), 178 (10), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2OS_2^+$ (M + H)$^+$ 267.06203, found 267.06247.

6-chloro-2-methyl-1H-indol-3-yl dimethylcarbamodithioate (19): yield (33 mg, 57%); White solid, mp 211.0 – 211.7 °C; v_{max}/cm^{-1} 3386 (NH), 2923, 2852, 1499 (Ph), 1372, 1083(CS-S-), 786 (Cl); δH (600 MHz; DMSO; Me_4Si) 11.83 (s, 1H, *NH*), 7.37 (d, *J* = 8.5 Hz, 1H, *Ar*), 7.24 (d, *J* = 1.7 Hz, 1H, *Ar*), 7.08 (dd, *J* = 8.5, 2.0 Hz, 1H, *Ar*), 3.55 (s, 3H, *Me*), 3.46 (s, 3H, *Me*), 2.34 (s, 3H, *Me*); ^{13}C NMR (151 MHz; DMSO; Me_4Si) 196.0, 145.9, 134.1, 131.8, 124.7, 121.1, 117.0, 112.9, 98.1, 45.8, 41.7, 12.2; LRMS (EI, 70 eV) m/z (%): 284 (16), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{14}ClN_2S_2^+$ (M + H)$^+$ 285.02814, found 285.02847.

1-methyl-1H-indol-3-yl dimethylcarbamodithioate (20): yield (39 mg, 78%); Pink solid, mp 151.8 – 153.7 °C; v_{max}/cm^{-1} 2921, 2882, 1511 (Ph), 1452, 1373, 1126 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.59 (d, *J* = 7.9 Hz, 1H, *Ar*), 7.38 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.31 – 7.27 (m, 2H, *Ar*), 7.23 – 7.19 (m, 1H, *Ar*), 3.85 (s, 3H, *Me*), 3.58 (s, 6H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.8, 137.3, 136.6, 129.9, 122.4, 120.6, 119.4, 109.9, 100.8, 46.0, 41.7, 33.3; LRMS (EI,

70 eV) m/z (%): 250 (30), 162 (14), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2S_2^+$ (M + H)$^+$ 251.06712, found 251.06722.

5-bromo-1-methyl-1H-indol-3-yl dimethylcarbamodithioate (21): yield (16 mg, 24%); White solid, mp 150.0 – 151.0 °C; v_{max}/cm^{-1} 2975, 2921, 2850, 1509 (Ph), 1372, 1084 (CS-S-), 613 (Br); δH (600 MHz; $CDCl_3$; Me_4Si) 7.69 (d, *J* = 1.9 Hz, 1H, *Ar*), 7.34 (dd, *J* = 8.6, 1.9 Hz, 1H, *Ar*), 7.25 (s, 1H, *Ar*), 7.22 (d, *J* = 8.7 Hz, 1H, *Ar*), 3.81 (s, 3H, *Me*), 3.56 (s, 6H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.2, 137.8, 136.0, 131.7, 125.4, 122.1, 114.4, 111.5, 100.7, 46.1, 41.8, 33.5; LRMS (EI, 70 eV) m/z (%): 328 (12), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{14Br}N_2S_2^+$ (M + H)$^+$ 328,97763, found 328,97775.

1-methyl-2-phenyl-1H-indol-3-yl dimethylcarbamodithioate (22): yield (44 mg, 67%); White solid, mp 154.5 – 156.3 °C; v_{max}/cm^{-1} 2954, 2922, 2851, 1633, 1496 (Ph), 1451, 1378, 1153 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.62 (d, *J* = 7.9 Hz, 1H, *Ar*), 7.58 – 7.54 (m, 2H, *Ar*), 7.52 – 7.46 (m, 3H, *Ar*), 7.44 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.32 (t, *J* = 7.4 Hz, 1H, *Ar*), 7.25 (t, *J* = 7.4 Hz, 1H, *Ar*), 3.73 (s, 3H, *Me*), 3.56 (s, 3H, *Me*), 3.48 (s, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.7, 146.8, 137.3, 130.6, 130.4, 129.8, 128.7, 128.1, 122.6, 121.0, 119.4, 110.0, 100.1, 45.8, 41.6, 31.6; LRMS (EI, 70 eV) m/z (%): 326 (31), 238 (15), 223 (23), 88 (100); HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2S_2^+$ (M + H)$^+$ 327.09842, found 327.09885.

1-ethyl-2-phenyl-1H-indol-3-yl dimethylcarbamodithioate (23): yield (35 mg, 52%); Yellow solid, mp 155.1 – 156.1 °C; v_{max}/cm^{-1} 2974, 2921, 2851, 1633, 1495 (Ph), 1458, 1377, 1148 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.59 (d, *J* = 7.9 Hz, 1H, *Ar*), 7.55 – 7.50 (m, 2H, *Ar*), 7.47 – 7.41 (m, 4H, *Ar*), 7.29 – 7.26 (m, 1H, *Ar*), 7.22 – 7.19 (m, 1H, *Ar*), 4.13 (q, *J* = 7.2 Hz, 2H, CH_2), 3.50 (s, 3H, *Me*), 3.42 (s, 3H, *Me*), 1.31 (t, *J* = 7.2 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.7, 146.6, 136.1, 130.8, 130.4, 130.1, 128.7, 128.1, 122.4, 120.9, 119.5, 110.3, 100.4, 45.8, 41.6, 39.5, 15.4; LRMS (EI, 70 eV) m/z (%): 340 (34), 252 (17), 223 (29), 88 (100); HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2S_2^+$ (M + H)$^+$ 341.11407, found 341.11447.

1-butyl-1H-indol-3-yl dimethylcarbamodithioate (24): yield (29 mg, 50%); Brown oil; v_{max}/cm^{-1} 2957, 2929, 2872, 1509 (Ph), 1459, 1373, 1154 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.58 (d, *J* = 7.9 Hz, 1H, *Ar*), 7.39 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.31 (s, 1H, *Ar*), 7.27 – 7.24 (m, 1H, *Ar*), 7.18 (t, *J* = 7.5 Hz, 1H, *Ar*), 4.17 (t, *J* = 7.1 Hz, 2H, CH_2), 3.56 (s, 6H, *Me*), 1.90 – 1.80 (m, 2H, CH_2), 1.40 – 1.30 (m, 2H, CH_2), 0.94 (t, *J* = 7.4 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 198.9, 136.5, 135.8, 130.1, 122.2, 120.5, 119.4, 110.1, 100.7, 46.6, 46.0, 41.7, 32.0, 20.0, 13.6; LRMS (EI, 70 eV) m/z (%): 292 (25), 88 (100); HRMS (ESI) m/z calcd for $C_{15}H_{21}N_2S_2^+$ (M + H)$^+$ 293.11407, found 293.11441.

1H-indol-3-yl diethylcarbamodithioate (25): yield (21 mg, 40%); White solid, mp 128.6 – 129.5 °C; v_{max}/cm^{-1} 3374 (NH),2957, 2929, 2872, 1509 (Ph), 1459, 1373, 1154 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.82 (s, 1H, *NH*), 7.65 – 7.53 (m, 1H, *Ar*), 7.30 – 7.27 (m, 1H, *Ar*), 7.25 (d, *J* = 2.7 Hz, 1H, *Ar*), 7.22 – 7.15 (m, 2H, *Ar*), 4.08 (q, *J* = 7.1 Hz, 2H, CH_2), 3.98 (q, *J* = 7.1 Hz, 2H, CH_2), 1.49 (t, *J* = 7.1 Hz, 3H, *Me*), 1.33 (t, *J* = 7.1 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 197.3, 136.3, 132.9, 129.2, 122.7, 120.9, 119.2, 112.1, 102.2, 50.4, 47.2, 12.9, 11.7; LRMS (EI, 70 eV) m/z (%):264 (21), 148 (23), 121 (11), 88 (67), 77 (12), 60 (27); HRMS (ESI) m/z calcd for $C_{13}H_{17}N_2S_2^+$ (M + H)$^+$ 265.08277, found 265.08337.

2-methyl-1H-indol-3-yl diethylcarbamodithioate (26): yield (48 mg, 87%); Yellow solid, mp 130.6 – 131.0 °C; v_{max}/cm^{-1} 3386 (NH), 2981, 2922, 2851, 1489 (Ph), 1455, 1380, 1142 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 8.55 (s, 1H, *NH*), 7.49 (d, *J* = 6.5 Hz, 1H, *Ar*), 7.22 (d, *J* = 6.8 Hz, 1H, *Ar*), 7.16 – 7.12 (m, 2H, *Ar*), 4.07 (q, *J* = 7.3 Hz, 2H, CH_2), 3.99 (q, *J* = 7.3 Hz, 2H, CH_2), 2.32 (s, 3H, *Me*), 1.49 (t, *J* = 5.9 Hz, 3H, *Me*), 1.32 (t, *J* = 5.9 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 196.8, 143.4, 135.3, 130.4, 121.8, 120.7, 118.4, 111.2, 99.4, 50.3, 47.1, 13.0, 12.4, 11.8; LRMS (EI, 70 eV) m/z (%):278 (28), 162 (16), 116 (100), 88 (61), 60 (21); HRMS (ESI) m/z calcd for $C_{14}H_{19}N_2S_2^+$ (M + H)$^+$ 279.09842, found 279.09897.

1-methyl-1H-indol-3-yl diethylcarbamodithioate (27): yield (17 mg, 31%); White solid, mp 105.1 – 106.3 °C; v_{max}/cm^{-1} 3382 (NH), 2975, 2922, 2872, 2850, 1511 (Ph), 1459, 1374, 1143 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.60 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.38 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.32 – 7.27 (m, 2H, *Ar*), 7.24 – 7.20 (m, 1H, *Ar*), 4.06 (q, *J* = 7.0 Hz, 2H, CH_2), 3.96 (q, *J* = 7.2 Hz, 2H, CH_2), 3.84 (s, 3H, *Me*), 1.47 (t, *J* = 7.1 Hz, 3H, *Me*), 1.31 (t, *J* = 7.1 Hz, 3H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 197.1, 137.2, 136.6, 130.1, 122.3, 120.6, 119.4, 109.8, 100.7, 50.1, 46.9, 33.2, 12.8, 11.6; LRMS (EI, 70 eV) m/z (%):278 (29), 162 (23), 116 (100), 88 (65), 77 (10), 60 (25); HRMS (ESI) m/z calcd for $C_{14}H_{19}N_2S_2^+$ (M + H)$^+$ 279.09842, found 279.09824.

2-methyl-1H-indol-3-yl diisopropylcarbamodithioate (28): yield (37 mg, 60%); White solid, mp 206.7 – 207.3 °C; v_{max}/cm^{-1} 3363 (NH), 2975, 2922, 2851, 1454 (Ph), 1370, 1193 (CS-S-); δH (600 MHz; DMSO; Me_4Si) 11.57 (s, 1H, *NH*), 7.34 (d, J = 7.9 Hz, *Ar*), 7.26 (d, *J* = 7.7 Hz, 1H, *Ar*), 7.09 – 7.05 (m, 1H, *Ar*), 7.01 (t, J = 7.4 Hz, 1H, *Ar*), 6.22 – 4.92 (m, 1H, *CH*), 4.81 – 3.72 (m, 1H, *CH*), 2.34 (s, 3H, *Me*), 1.46 (s, 12H, *Me*); ^{13}C NMR (151 MHz; DMSO; Me_4Si) 144.6 , 135.9 , 130.9 , 121.3 , 120.1 , 118.1 , 111.6 , 12.5; LRMS (EI, 70 eV) m/z (%):306 (5), 162 (32), 144 (64), 130 (17), 118 (16), 102 (100), 60 (22); HRMS (ESI) m/z calcd for $C_{16}H_{23}N_2S_2^+$ (M + H)$^+$ 307.12972, found 307.12985. (There is no ^{13}C NMR signal peak of the carbonyl and the CH, which may result from the steric hindrance of the amide. Please also see the NMR spectra of tetraisopropylthiuram disulfide at the end of the supporting information.)

5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl dimethylcarbamodithioate (29): yield (49 mg, 89%); White solid, mp 225.8 – 226.2 °C; v_{max}/cm^{-1} 3078, 2959, 2926, 2880, 1504 (Ph), 1461, 1376, 1152 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 7.38 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.28 (s, 1H, *Ar*), 7.12 – 7.09 (m, 1H, *Ar*), 6.97 (d, *J* = 7.1 Hz, 1H, *Ar*), 4.24 – 4.21 (m, 2H, CH_2), 3.58 (s, 6H, *Me*), 3.02 (t, *J* = 6.1 Hz, 2H, CH_2), 2.30 – 2.25 (m, 2H, CH_2); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 199.2, 134.8, 133.9, 127.8, 122.3, 121.1, 119.5, 116.9, 100.7, 46.0, 44.6, 41.8, 24.5, 22.8; LRMS (EI, 70 eV) m/z (%):276 (33), 188 (19), 160 (11), 88 (100); HRMS (ESI) m/z calcd for $C_{14}H_{17}N_2S_2^+$ (M + H)$^+$ 277.08277, found 277.08258.

1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-9-yl dimethylcarbamodithioate (30): yield (20 mg, 34%); Brown solid, mp 129.6 – 131.0 °C; v_{max}/cm^{-1} 2786, 1589 (Ph), 1498, 1431, 1370, 1084 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si) 6.84 (s, 2H, *Ar*), 3.56 (s, 3H, *Me*), 3.46 (s, 3H, *Me*), 3.20 (t, 4H, CH_2), 2.75 (t, *J* = 6.4 Hz, 4H, CH_2), 1.99 – 1.93 (m, 4H, CH_2); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 200.6, 144.0, 135.3, 121.6, 114.8, 49.8, 45.7, 41.7, 27.5, 21.5; LRMS (EI, 70 eV) m/z (%): 188 (100), 160 (27), 134 (13), 106 (20),

78 (23); HRMS (ESI) m/z calcd for $C_{15}H_{21}N_2S_2^+$ $(M + H)^+$ 293.11407, found 293.11465.

2,4,6-trimethoxyphenyl dimethylcarbamodithioate (31): yield (52 mg, 91%); White solid, mp 163.3 – 164.8 °C; ν_{max}/cm^{-1} 2973, 1595 (Ph), 1497, 1429, 1344, 1123 (CS-S-); δH (600 MHz; $CDCl_3$; Me_4Si)6.21 (s, 2H, *Ar*), 3.85 (s, 3H, *Me*), 3.82 (s, 6H, *Me*), 3.53 (s, 6H, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 197.5, 163.7, 162.5, 100.0, 91.3, 56.4, 55.3, 45.8, 41.8; LRMS (EI, 70 eV) m/z (%): 287 (21), 256 (12), 88 (100); HRMS (ESI) m/z calcd for $C_{12}H_{18}NO_3S_2^+$ $(M + H)^+$ 288.07226, found 288.07214.

4-iodo-1-methyl-1*H*-pyrazol-5-amine (32): yield (45 mg, 73%); Yellow solid, mp 112.0 – 112.7 °C; ν_{max}/cm^{-1} 3313 (NH_2), 3183, 2938, 1665, 1557, 1510, 1426, 1401, 1317, 1267, 1182, 949, 846, 759, 493 (C-I); δH (600 MHz; $CDCl_3$; Me_4Si) 7.22 (s, 1H, *Ar*), 3.73 – 3.60 (m, 5H, NH_2, *Me*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 145.3 , 141.5 , 42.0 , 35.4; HRMS (ESI) m/z calcd for $C_4H_7IN_3^+$ $(M + H)^+$ 223.96792, found 223.96807.

3-iodo-1*H*-indole (33): yield (10 mg, 21%); δH (600 MHz; $CDCl_3$; Me_4Si) 8.23 (s, 1H, *NH*), 7.52 – 7.42 (m, 1H, *Ar*), 7.33 (d, J = 8.0 Hz, 1H, *Ar*), 7.26 – 7.19 (m, 3H, *Ar*); ^{13}C NMR (151 MHz; $CDCl_3$; Me_4Si) 135.6 , 129.8 , 123.2 , 121.0 , 120.8 , 57.5. LRMS (EI, 70 eV) m/z (%): 243 (100), 116 (51), 89 (32), 63 (13).

Conflicts of interest

"There are no conflicts to declare".

Acknowledgments

We thank the Guangdong Basic and Applied Basic Research Foundation (No. 2019B151502052) for its financial support.

Notes and references

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