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新型含偕二甲基环丙烷的 4-甲基-1,2,4-三唑硫醚化合物的合成、生物活性及三维定量构效关系(3D-QSAR)研究

虞友培[a] 段文贵*,[a] 林桂汕[a] 康国强[a] 王晓宇[a] 雷福厚[b]
([a]广西大学化学化工学院 南宁 530004)
([b]广西民族大学 广西林产化学与工程重点实验室 南宁 530008)

摘要 为了探寻有效的新型生物活性分子, 通过多步反应设计并合成了一系列新型含偕二甲基环丙烷的 4-甲基-1,2,4-三唑硫醚衍生物, 通过 UV-Vis, FTIR, NMR, ESI-MS 和元素分析等方法对所有目标化合物的结构进行了表征. 初步测定了目标化合物的抑菌和除草活性. 生物活性结果显示, 在质量浓度为 50 μg/mL 时, 有 2 个化合物对苹果轮纹病菌表现出明显的抑菌活性, 优于阳性对照百菌清. 此外, 在质量浓度为 100 μg/mL 时, 有 4 个化合物对油菜胚根生长表现出优异的抑制活性, 优于阳性对照丙炔氟草胺. 为了开发出更有效的抗苹果轮纹病菌化合物, 使用比较分子力场分析(CoMFA)方法对目标化合物的抗苹果轮纹病菌活性进行了初步的三维定量构效关系(3D-QSAR)分析, 建立了一个合理有效的 3D-QSAR 模型(r^2=0.985, q^2=0.509).

关键词 偕二甲基环丙烷; 3-蒈烯; 1,2,4-三唑硫醚; 生物活性; 三维定量构效关系(3D-QSAR)

Synthesis, Biological Activity and Three-Dimensional Quantitative Structure-Activity Relationship (3D-QSAR) Study of Novel 4-Methyl-1,2,4-triazole-thioethers Containing *gem*-Dimethylcyclopropane Ring

Yu, Youpei[a] Duan, Wengui*,[a] Lin, Guishan[a] Kang, Guoqiang[a]
Wang, Xiaoyu[a] Lei, Fuhou[b]
([a] *College of Chemistry and Chemical Engineering, Guangxi University, Nanning 530004*)
([b] *Guangxi Key Laboratory of Chemistry and Engineering of Forest Products, Guangxi University for Nationalities, Nanning 530008*)

Abstract A series of novel 4-methyl-1,2,4-triazole-thioethers containing *gem*-dimethylcyclopropane ring were designed and synthesized by multi-step reactions in search of potent novel bioactive molecules. Structures of all the target compounds were characterized by means of UV-Vis, FTIR, NMR, ESI-MS, and elemental analysis. The antifungal and herbicidal activities of the target compounds were preliminarily evaluated. As indicated in bioassay results, 2 compounds exhibited excellent antifungal activity against *Physalospora piricola*, which are much better than that of the commercial fungicide of chlorothalonil used as positive control. Also, at 100 μg/mL, 4 compounds displayed prominent herbicidal activity against the root-growth of rape (*Brassica campestris*), which are much better than that of the commercial herbicide of flumioxazin used as positive control. In the interest of developing more effective antifungal compounds against *P. piricola*, the preliminary analysis of three-dimensional quantitative structure-activity relationship (3D-QSAR) was carried out using the molecular field analysis (CoMFA) method, and a reasonable and effective 3D-QSAR model (r^2=0.985, q^2=0.509) has been established.

Keywords *gem*-dimethylcyclopropane; 3-carene; 1,2,4-triazole-thioether; biological activity; three-dimensional quantitative structure-activity relationship (3D-QSAR)

* Corresponding author. E-mail: wgduan@gxu.edu.cn
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1 Introduction

3-Carene, a naturally occurring chiral monoterpene, is mainly found in some essential oils and some turpentine oils of special pine trees.[1,2] It is one of the rare compounds in nature containing a three-membered *gem*-dimethylcyclopropane ring. As a renewable forest biomass resource, 3-carene exhibited various biological activities, such as anti-inflammatory,[3] antioxidant,[4,5] antimicrobial[4,5] and antitumor properties.[6] Various cyclopropane-containing bioactive derivatives can be synthesized through modification of the molecular structure of 3-carene.[7]

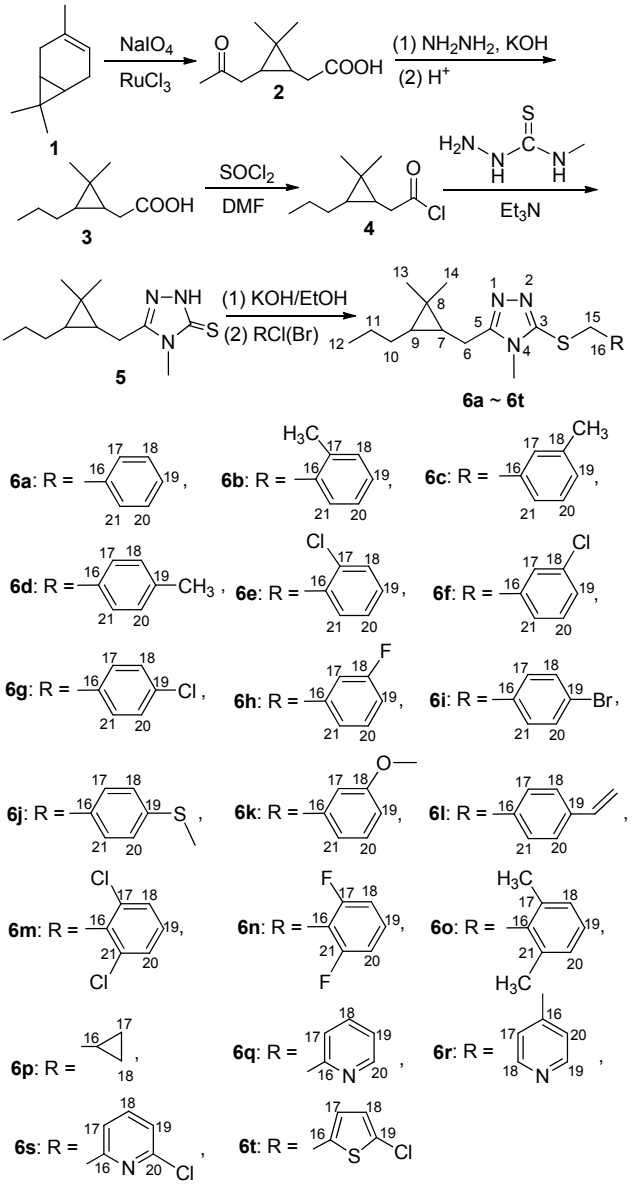
Cyclopropane derivatives, which play important roles in the fields of pesticides and medicine, have recently received considerable attention. Pyrethroids, as an important class of cyclopropane derivatives, have been used for decades because of their broad spectrum, low toxicity and highly bioactive insecticidal properties.[8] Additionally, some compounds containing cyclopropyl skeleton also displayed widespread biological activities, such as acetylcholinesterase inhibitory,[9] anticancer,[10~13] antimicrobial,[14] antifungal,[15] anti-inflammatory[16] and herbicidal.[17] On the other hand, 1,2,4-triazole derivatives are widely applied in medicine and agriculture because of their various biological activities, including antifungal,[18~20] antibacterial,[21,22] antimicrobial,[23] antiviral,[24] antitumor,[25~27] antioxidant[28] and herbicidal activities.[29~31] In continuation of our interest in the bioactive properties of natural product-based compounds,[18,32~36] a series of novel 4-methyl-1,2,4-triazole-thioethers containing *gem*-dimethylcyclopropane ring were designed and synthesized by integrating bioactive 1,2,4-triazole and thioether moieties into the skeleton of *gem*-dimethylcyclopropane converted from 3-carene (racemate). In this work, all title compounds were racemates, and their structural characterization, antifungal and herbicidal evaluation were carried out as well.

As a valuable predictive tool in the design of pharmaceuticals and agrochemicals, 3D-QSAR certainly saved time and reduced cost by facilitating the selection of the most promising candidates.[37] And a validated 3D-QSAR model was beneficial to understand the structure-activity relationships of molecules and provided the researcher an insight at the molecular level about the lead molecules for further development.[38] Therefore, in order to improve the efficiency of discovering new potential antifungal agents, the 3D-QSAR analysis of the antifungal activity against *P. piricola* of the target compounds was carried out. The effective 3D-QSAR model provided a theoretical basis for the subsequent optimization of the series of compounds and the discovery of new potential antifungal agents with high activity.

2 Results and discussion

2.1 Synthesis and characterization

As illustrated in Scheme 1, 2-(2,2-dimethyl-3-(2-oxopropyl)cyclopropyl) acetic acid (**2**) was prepared according to the reported method[39] from raw material 3-carene. And intermediate 2-(2,2-dimethyl-3-propylcyclopropyl)acetic acid (**3**) was prepared by reduction of the carbonyl group in compound **2** through Wolff-Kishner-Huang reduction method. Denitrification was critical throughout the reduction process, and the reaction temperature needed to be maintained at over 180 ℃ for 8 h. The ^{1}H NMR and ^{13}C NMR signals of compound **3** were assigned by HMBC and HSQC spectra. The intermediate 5-((2,2-dimethyl-3-propyl cyclopropyl)methyl)-4-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**5**) was prepared by *N*-acylation of 4-methyl-thiosemicarbazide with 2-(2,2-dimethyl-3-propylcyclopropyl)acetyl chloride (**4**) followed by self-cyclization reaction. Then, twenty target compounds **6a**～**6t** were synthesized by nucleophilic substitution reaction of the intermediate **5** with a series of alkyl halides.



Scheme 1 Synthesis of 4-methyl-1,2,4-triazole-thioethers **6a**～**6t** containing *gem*-dimethylcyclopropane ring

The target compounds 4-methyl-1,2,4-triazole-thioethers were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, ESI-MS, elemental analysis and UV-Vis. In the IR spectra, the strong absorption band at 1465～1488 cm^{-1} was attributed to the vibration of C═N in 1,2,4-triazole moiety. The absorption bands in the region of 680～700 cm^{-1} were due to the vibrations of C—S—C. In the ^{1}H NMR spectra, the protons of benzene ring showed signals at δ 6.76～7.41. The protons of *gem*-dimethylcyclopropane ring scaffold showed signals in the range of δ 0.59～2.73. The characteristic signals at δ 3.06～3.52 were assigned to the methyl protons of 1,2,4-triazole moiety. The protons on the saturated carbon bonded to the S atom displayed the signals at δ 3.11～4.50. The ^{13}C NMR spectra of all the target compounds showed peaks of the *gem*-dimethylcyclopropane ring scaffold carbons were in the region of δ 14.06～28.99. For the 1,2,4-triazole moiety, the signals at δ 156.26～156.99 and 148.45～150.41 were assigned to the unsaturated carbons, and at δ 28.94～30.12 to methyl. The saturated carbon bonded to the S atom displayed the signals at δ 30.01～39.81. Their molecular weights were confirmed by the ESI-MS.

2.2 Antifungal activity

The antifungal activities of all target compounds were tested by an *in vitro* method against fusarium wilt on cucumber (*Fusarium oxysporum f. sp. cucumerinum*), speckle on peanut (*Cercosporaarachidicola*), apple root spot (*Physalosporapiricola*), tomato early blight (*Alternaria solani*), wheat scab (*Gibberellazeae*), rice sheath blight (*Rhizoctoniasolani*), corn southern leaf blight (*Bipolaris maydis*), and watermelon anthracnose (*Colleterichumorbicalare*) at 50 μg/mL. The results were listed in Table 1.

It was found that, compounds **6a**～**6t** exhibited significantly different antifungal activity against the eight tested fungi at a concentration of 50 μg/mL. Compared with the intermediate **5**, the activities of most target compounds against the eight fungi were enhanced after etherification, especially for the inhibition against *P. piricola* and *R. solani*. On the whole, most of the target compounds exhibited the best antifungal activity against *P. piricola*, in which compounds **6a** (R═Ph), **6e** (R═*o*-ClC_6H_4), **6q** (R═*α*-pyridyl), **6l** (R═*p*-vinyl-C_6H_4), **6c** (R═*m*-Me-C_6H_4), **6f** (R═*m*-ClC_6H_4) and **6j** (R═*p*-MeSC_6H_4) had inhibition rates of 95.5%, 90.9%, 86.4%, 84.1%, 79.5%, 77.3% and 77.3%, respectively, showing better antifungal activity than that of the commercial fungicide of chlorothalonil with the inhibition rate of 75.0%. Also, ten target compounds showed moderate activity in the region of 70.4%～77.5% inhibition rates against *R. solani*. In addition, compound **6q** (R═*α*-pyridyl) displayed better inhibitory activity of 73.9% against *C. arachidicola* than that of the positive control with inhibition rate of 73.3%. Compounds **6a** (R═Ph) and **6e** (R═*o*-ClC_6H_4) were lead compound worthy of further study.

2.3 Herbicidal activity

The herbicidal activities of the target compounds **6a**～**6t**

Table 1 Antifungal activities of the target compounds **6a**～**6t** at 50 μg/mL[a]

Compd.	Inhibition rate/%							
	F. oxysporum f. sp. Cucumerinum	*C. arachidicola*	*P. piricola*	*A. solani*	*G. zeae*	*R. solani*	*B. myadis*	*C. orbicalare*
Chlorothalonil	100	73.3	75.0	73.9	73.1	96.1	90.4	91.3
5	24.0	43.8	55.0	42.1	30.0	51.9	33.3	42.9
6a	37.1	39.1	95.5	42.9	41.4	77.5	47.2	55.6
6b	45.7	39.1	52.3	50.0	44.8	70.4	52.8	47.2
6c	28.6	43.5	79.5	46.4	37.9	57.7	41.7	50.0
6d	37.1	30.4	75.0	42.9	51.7	70.4	52.8	50.0
6e	37.1	65.2	90.9	57.1	44.8	74.6	61.1	52.8
6f	42.9	26.1	77.3	42.9	58.6	71.8	47.2	55.6
6g	25.7	52.2	59.1	42.9	44.8	70.4	30.6	30.6
6h	31.4	30.4	75.0	42.9	44.8	70.4	55.6	38.9
6i	40.0	26.1	68.2	35.7	44.8	69.0	44.4	55.6
6j	25.7	26.1	77.3	35.7	41.4	69.0	27.8	30.6
6k	48.6	52.2	75.0	50.0	62.1	66.2	50.0	58.3
6l	25.7	21.7	84.1	39.3	37.9	70.4	52.8	50.0
6m	40.0	65.2	40.9	50.0	37.9	62.0	52.8	50.0
6n	62.9	69.6	75.0	60.7	44.8	70.4	66.7	61.1
6o	34.3	65.2	56.8	57.1	55.2	66.2	36.1	41.7
6p	37.1	21.7	52.3	42.9	58.6	69.0	36.1	52.8
6q	40.0	73.9	86.4	60.7	44.8	54.9	47.2	41.7
6r	25.7	47.8	52.3	50.0	51.7	38.0	33.3	41.7
6s	22.9	30.4	75.0	35.7	24.1	47.9	30.6	33.3
6t	42.9	21.7	68.2	35.7	37.9	70.4	27.8	44.4

[a] Chlorothalonil, a current commercial fungicide, was used as a positive control. Values are the average of three replicates.

were evaluated by the rape petri dish method and the barnyard grass beaker method against the root-growth of rape (*Brassica campestris*) and the seedling-growth of barnyard grass (*Echinochloa crusgalli*) at 10 and 100 μg/mL, respectively. The tested results were listed in Table 2.

As the bioassay results showed, at 100 μg/mL, all the target compounds except **6i** (R=*p*-BrC_6H_4) exhibited better herbicidal activity against the root-growth of rape (*B. campestris*) with 63.4%～88.0% inhibition rates than that of the commercial herbicide of flumioxazin with inhibition rate of 63.0%, in which compounds **6q** (R=*α*-pyridyl), **6p** (R=cyclopropyl), **6k** (R=*m*-$OMeC_6H_4$) and **6d** (R=*p*-MeC_6H_4) held growth inhibition rates of 88.0%, 86.7%, 83.9%, and 81.9%, respectively. Besides, compared with the intermediate **5**, the inhibitory activities of most target compounds against the root-growth of rape (*B. campestris*) were enhanced after etherification at 100 μg/mL. Compound **6q** (R=*α*-pyridyl) was a lead compound worthy of further study.

Table 2 Growth inhibition rate (%) of the target compounds **6a**～**6t** at 10 and 100 μg/mL[a]

Compd.	*B. campestris*		*E. crusgalli*	
	10 mg/L	100 mg/L	10 mg/L	100 mg/L
Flumioxazin	57.8	63.0	95.1	97.5
5	63.8	72.5	0	20
6a	39.8	79.4	0	22.9
6b	14.2	70.4	0	0
6c	18.2	74.2	0.9	4.6
6d	30.2	81.9	0	11.9
6e	15.7	78.9	6.4	19.3
6f	20.2	69.4	0	0
6g	18.2	72.1	3.4	17.4
6h	7.6	72.9	4.6	6.4
6i	0	54.1	0	0
6j	10.2	78.9	0	0
6k	22.2	83.9	0	14.4
6l	19.2	69.4	0.9	4.6
6m	7.6	63.9	0.9	2.8
6n	47.3	77.9	0	26.6
6o	0	63.9	14.4	31.5
6p	53.1	86.7	11.9	33.9
6q	43.3	88	0	0
6r	29	77.4	0	0.9
6s	13.2	76.7	0.9	8.2
6t	25.2	63.4	0	0

[a] Flumioxazin, a current commercial herbicide was used as a positive control.

2.4 CoMFA analysis

Comparative molecular field analysis (CoMFA) method has become a powerful tool for the discovery of new drug.[37] In this work, the CoMFA model with 0.509 of cross-validated coefficient (q^2), 0.985 of correlation coefficient (r^2), 89.985 of Fischer ratio (F) and 0.061 of standard error of estimate (S) was built based on the antifungal activity against *P. piricola* (Table 3). Meanwhile, the experimental and predicted ED values for the compounds **6a**～**6o** were presented in Table 4 and the scatter diagram was shown in Figure 1, where all data were concentrated near the X=Y line. These results suggested that the model was reliable and effective.

Table 3 Summary of CoMFA analysis

q^2	r^2	S	N	F	Contribution/%	
					Steric	Electrostatic
0.509	0.985	0.061	6	89.985	74.6	25.4

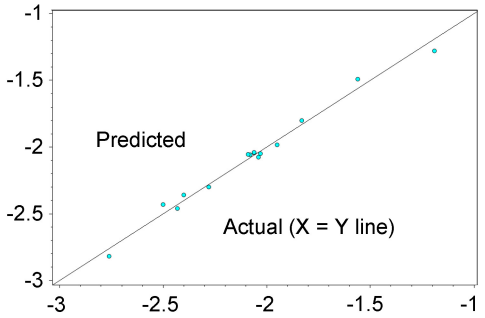


Figure 1 Predicted ED value of CoMFA model vs experimental ED value

Table 4 ED values of experimental and predicted activities[a]

Compd.	ED	ED"	Residue
6a	−1.19	−1.28	0.09
6b	−2.50	−2.43	−0.07
6c	−1.95	−1.98	0.03
6d	−2.06	−2.04	−0.02
6e	−1.56	−1.49	−0.07
6f	−2.03	−2.05	0.02
6g	−2.40	−2.36	−0.04
6h	−2.06	−2.04	−0.02
6i	−2.28	−2.30	0.02
6j	−2.04	−2.08	0.04
6k	−2.08	−2.06	−0.02
6l	−1.83	−1.80	−0.03
6m	−2.76	−2.82	0.06
6n	−2.09	−2.06	−0.03
6o	−2.43	−2.46	0.03

[a] ED=experimental value, ED"=predictive value of ED.

The steric and electrostatic contribution maps of CoMFA were shown in Figure 2. The contribution rates of the steric and electrostatic fields were 74.6% and 25.4%, respectively, indicating that the steric field of the compounds had a greater influence on the antifungal activity against *P. piricola*. In Figure 2a, there were some green regions located around the 2, 3, or 4-position of the benzene ring, indicating that the bulky groups at these positions were favorable to enhance the antifungal activity. This was in consistent with experimental result, for example, compounds **6i** (R=*p*-BrC_6H_4), **6j** (R=*p*-$MeSC_6H_4$), and **6l** (R=*p*-vinyl-C_6H_4) exhibited better antifungal activity than **6g** (R=*p*-ClC_6H_4). In Figure 2b, the electrostatic contours

were displayed in distinguishable colors: blue suggested that increase of positive charge was favorable for the increase of activity, red was the opposite. Therefore, the target compounds bearing an electron-withdrawing group at the 2 or 4-position of the benzene ring and an electron-donating group at the 3-position displayed higher activity. For instance, compounds **6l** (R=*p*-vinyl-C_6H_4) and **6e** (R = *o*-ClC_6H_4) showed higher antifungal activity against *P. piricola* than compounds **6j** (R=*p*-$MeSC_6H_4$) and **6b** (R=*o*-MeC_6H_4). In addition, compound **6c** (R=*m*-MeC_6H_4) displayed better activity than compounds **6f** (R=*m*-ClC_6H_4) and **6h** (R=*m*-FC_6H_4). Based on the results of 3D-QSAR analysis above, a new compound (Figure 3) was designed and predicted the ED by the established CoMFA model. As a result, the predicted ED was high to −1.40, showing excellent antifungal activity, however, which need to verify in experiment.

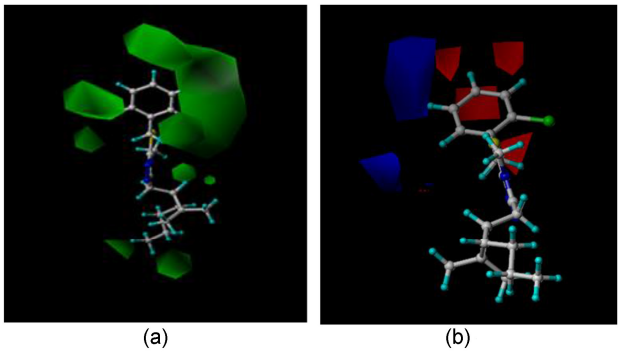


Figure 2 Contours of steric contribution (a) and electrostatic contribution (b)

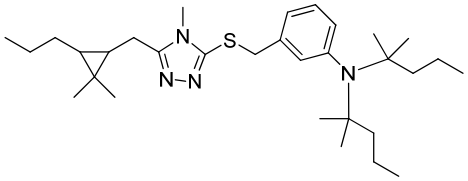


Figure3 Newly designed molecule of 3-(((5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)thio)-methyl)-*N*,*N*-bis(2-methylpentan-2-yl)aniline

2.5 Three-dimensional quantitative structure-activity relationship (3D-QSAR) analysis

In this study, the CoMFA model was built using SYBYL-X 2.1.1 software (Tripos, Inc., St. Louis, MO, USA) according to the reported method.[7] The antifungal activity against *P. piricola* was expressed in terms of activity factor (ED) by the formula ED=log{I/[(100−I)×M_W]}, where I was the percentage inhibition at 50 μg/mL and M_W was the molecular weight of the tested compounds. Complete conformational optimization of each structure was performed using a conjugate gradient procedure based on the Tripos force field. The molecular superimposition was carried out using compound **6a** as a template, in which the atoms marked with an asterisk constituted the common superimposed skeleton (Figure 4). The superposed effect of fifteen optimized compounds was shown in Figure 5. The CoMFA values were calculated by the QSAR module. Then, the partial least-squares (PLS) method was applied to establish the 3D-QSAR model, in which the CoMFA values were used as independent variables and ED values were used as dependent variables. The cross-validation with the leave-one-out method was carried out to obtain the cross-validated coefficient (q^2) and the optimal number of components. The non-cross-validation analysis under the optimal number of components was performed. The correlation between CoMFA and ED values was indicated by the squared correlation coefficient (r^2), and the prediction capability was indicated by the cross-validated coefficient (q^2).

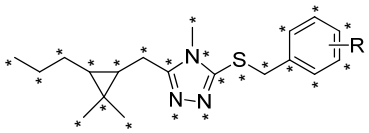


Figure 4 Asterisk skeleton of title compounds

Figure 5 Superposition modes of compounds

3 Experimental Section

3.1 General

The GC analysis was conducted on an Agilent 6890 GC (Agilent Technologies Inc., Santa Clara, CA, USA) equipped with column HP-1 (30 m, 0.530 mm, 0.88 μm). IR spectra were recorded on a Nicolet iS50 FT-IR spectrometer (Thermo Scientific Co., Ltd., Madison, WI, USA) by KBr pellet method. NMR spectra were recorded in $CDCl_3$ solvent on a Bruker Avance III HD 600 MHz spectrometer (Bruker Co., Ltd., Zurich, Switzerland) with TMS as an internal standard. MS spectra were obtained by means of the electrospray ionization (ESI) method on a TSQ Quantum Access MAX HPLC-MS instrument (Thermo Scientific Co., Ltd., Waltham, MA, USA). The UV spectra were measured on a Shimadzu UV-1800 spectrophotometer (Shimadzu Corp., Kyoto, Japan). Elemental analyses were measured using a PE 2400 II elemental analyzer (Perkin-Elmer Instruments Co., Ltd., USA). The HPLC analysis was performed on a Waters 1525 instrument (Waters Co., Ltd., USA) equipped with column SunFire C18 5 μm (4.6 mm×150 mm) and 2998 diode array detector. Melting points were determined on a MP420 automatic melting point apparatus (Hanon Instruments Co., Ltd., Jinan, China) and were not corrected. 3-Carene (GC purity 98%, racemate) was provided

by Wuzhou Pine Chemicals Co., Ltd., Wuzhou, Guangxi, China. Other reagents were purchased from commercial suppliers and used as received.

3.2 Synthesis of 2-(2,2-dimethyl-3-(2-oxopropyl)-cyclopropyl) acetic acid (2)

Compound **2** was prepared by oxidation of 3-carene under alkaline conditions.[39] 3-Carene (100 mL, 629.0 mmol) was dissolved in 500 mL of *tert*-butanol and 1000 mL of water. To this mixture were added sodium periodate (490.0 g, 2.29 mol) and ruthenium chloride hydrate (2.2 g, 4.0 mmol). The mixture was stirred vigorously for 2 h at 45 ℃, and for another 1.5 h at 55 ℃. Then, the mixture was cooled to 30 ℃ and filtered, and the residue was washed with EtOAc (500 mL). After the EtOAc layer was separated, the filtrate was extracted with EtOAc (400 mL×3). All the EtOAc phases were combined, washed with brine (400 mL), and concentrated by removal of solvent. The concentrate was alkalized to pH 10 with dilute aqueous NaOH, and the organic phase was washed with appropriate EtOAc and abandoned. The left aqueous phase was acidified with dilute hydrochloric acid to pH 3 and extracted with EtOAc (200 mL×3). The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to obtain the product as a brown liquid with yield of 68.5%. b.p. 158.0～165.0 ℃/0.67 kPa. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.45～2.38 (m, 2H, C^2-H), 2.33～2.24 (m, 2H, C^6-H), 2.19 (s, 3H, C^8-H), 1.14 (s, 3H, C^9-H or C^{10}-H), 0.97 (q, J=8.1 Hz, 2H, C^3-H and C^5-H), 0.94 (s, 3H, C^9-H or C^{10}-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 208.9 (C^7), 179.2 (C^1), 39.3, 30.1, 29.6, 28.4 (C^9 or C^{10}), 21.2, 17.3, 14.9 (C^9 or C^{10}); IR (KBr) v: 3500～2500 (COOH), 2956 (w), 2869 (w), 1712 (s, C=O) cm^{-1}; ESI-MS m/z: 185.05 $[M+H]^+$. Anal. calcd for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found C 65.12, H 8.72.

3.3 Synthesis of 2-(2,2-dimethyl-3-propylcyclopropyl)acetic acid (3)

Compound **3** was prepared by our previous work.[40] KOH (14.0 g, 245.0 mmol) was added to ethylene glycol (50 mL) under stirring and was completely dissolved. To the mixture were added compound **2** (12.9 g, 70.0 mmol) and 40 mL of hydrazine hydrate (w=80%), respectively. The reaction mixture was heated and refluxed at 160 ℃ for 3 h while a water segregator was employed to remove the excess water and hydrazine for promoting the reaction. Then, the reaction mixture was continuously heated to 180 ℃ and refluxed 8 h. When the reaction was completed, the mixture was cooled to room temperature, and acidified with 10.0% (w) aqueous HCl to pH 3.0. Afterwards, the mixture was extracted several times with cyclohexane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to obtain the product as yellow liquid with yield of 55.8%. b.p. 110.0～115.0 ℃/0.67 kPa; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.35～2.27 (m, 2H, C^2-H), 1.35 (tq, J=13.2, 6.7, 6.2 Hz, 2H, C^7-H), 1.26 (td, J=14.3, 6.4 Hz, 1H, C^6-H_a), 1.17 (td, J=14.1, 8.2 Hz, 1H, C^6-H_b), 1.07 (s, 3H, C^9-H or C^{10}-H), 0.93 (s, 3H, C^9-H or C^{10}-H), 0.91 (t, J=7.3 Hz, 3H, C^8-H), 0.85～0.81 (m, 1H, C^3-H), 0.58～0.53 (m, 1H, C^5-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 180.3 (C^1), 29.9 (C^2), 28.9 (C^9 or C^{10}), 26.5 (C^6), 26.2 (C^5), 23.1 (C^7), 21.5 (C^3), 17.1 (C^4), 14.8 (C^9 or C^{10}), 14.0 (C^8); IR (KBr) v: 3500～2500 (COOH), 2961.7, 2866.4, 1718.0 (C=O) cm^{-1}; ESI-MS m/z: 169.03 $[M-H]^-$. Anal. calcd for $C_{10}H_{18}O_2$: C 70.55, H 10.66; found C 70.52, H 10.63.

3.4 Synthesis of 5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5)

Under anhydrous atmosphere, a solution of $SOCl_2$ (5.7 g, 48.0 mmol, w=99.0%) in benzene (10 mL) was added slowly to a solution of compound **3** (6.8 g, 40.0 mmol) in benzene (15 mL) at room temperature. Subsequently, three drops of *N*,*N*-dimethylformamide (DMF) were added, and the mixture was refluxed for 5 h under stirring. Afterwards, the reaction solution was distilled at atmospheric pressure to remove the low boiling components, and evaporated *in vacuo* to give the intermediate **4** as yellow liquid with yield of 52.5% (b.p. 70.0～72.0 ℃/0.67 kPa). Under anhydrous atmosphere, in an ice-water bath, to a stirred mixture of *N*-methylhydrazinecarbothioamide (1.2 g, 11.4 mmol) in CH_2Cl_2 (30 mL) were added slowly five drops of trimethylamine and then a solution of **4** (1.9 g, 10.0 mmol) in CH_2Cl_2 (15 mL). When the addition was completed, the mixture was stirred for 1 h in an ice-water bath, and for another 1.5 h at room temperature. After quenching with HCl (5.0 mL, 2.88 mol/L), the reaction mixture was washed with 15 mL of deionized water, and dried over anhydrous Na_2SO_4. Then, CH_2Cl_2 was removed *in vacuo*, and the crude product was purified by silica gel column chromatography (ethyl acetate/petroleum ether, V∶V=1∶6) to obtain intermediate **5** as colorless solid. Yield 64.5%, HPLC purity 98.72%. m.p. 108.4～109.3 ℃; UV-Vis (EtOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 253.5 (4.30) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 11.89 (s, NH), 3.56 (s, 3H, NCH_3), 2.57 (d, J=7.1 Hz, 2H, C^6-H), 1.41～1.28 (m, 3H, C^{11}-H, C^{10}-Ha), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.09 (s, 3H, C^{13}-H or C^{14}-H), 0.97 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C_{12}-H), 0.85 (dt, J=8.4, 7.0 Hz, 1H, C^7-H), 0.65 (td, J=8.5, 6.0 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.4 (C^3), 153.2 (C^5), 30.4 (N-CH_3), 28.9 (C^6), 26.4 (C^{10}, C^{13} or C^{14}), 23.0, 22.0, 21.5, 17.5, 14.8 (C^{13} or C^{14}), 14.0; IR (KBr) v: 3116 (s, N—H), 3057 (m), 2962 (s), 2926 (s), 2854 (m), 1575 (s, N—C=S, I), 1346 (s, N—C=S, II), 1081 (m, N—C=S, III), 1507 (s, C=N), 1453 (m), 1376 (w), 1147 (w) cm^{-1}; ESI-MS m/z: 239.98 $[M+H]^+$. Anal. calcd for $C_{12}H_{21}N_3S$: C 60.21, H 8.84, N 17.55; found C 60.20, H 8.85, N 17.52.

3.5 General procedure for synthesis of 6a～6t

Compound **5** (240.0 mg, 1.0 mmol) and potassium hydroxide (120.0 mg, 2.0 mmol) were mixed in anhydrous ethanol (15 mL). Then the mixture was stirred and refluxed for 2 h. Afterwards, a solution of alkyl halide (1.5 mmol)

in 8 mL of EtOH was slowly added to the mixture and continuously refluxed for 30 min. The reaction process was monitored by thin-layer chromatography (TLC). After the solvent EtOH was removed by rotary evaporation, the residue was acidified with HCl (w=10.0%) to pH=3, and extracted with EtOAc. The separated organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography to afford the target compounds **6a**～**6t**.

3-(Benzylthio)-5-((2,2-dimethyl-3-propylcyclopropyl)-methyl)-4-methyl-4*H*-1,2,4-triazole (**6a**): Pale yellow syrup, yield 86.5%, HPLC purity 97.87%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.28～7.23 (m, 3H, ArH), 7.21 (dt, J=6.9, 1.9 Hz, 2H, ArH), 4.27 (s, 2H, C^{15}-H), 3.13 (s, 3H, NCH_3), 2.63～2.54 (m, 2H, C^6-H), 1.43～1.31 (m, 3H, C^{11}-H, C^{10}-H_a), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.80 (dt, J=8.9, 6.8 Hz, 1H, C^7-H), 0.59 (td, J=8.6, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6 (C^5), 149.3 (C^3), 137.2, 129.0 (C^{18}, C^{20}), 128.6 (C^{17}, C^{21}), 127.7, 39.3, 29.8, 29.0 (NCH_3), 26.5, 23.1, 23.0, 21.0, 17.5, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) v: 3066 (w, cyclopropyl), 3033 (w, cyclopropyl, Ar—H), 2959 (s), 2932 (s), 2861 (m), 1510 (w), 1495 (m, Ar), 1474 (s, C=N), 1453 (S), 1382 (w), 687 (w, C—S—C) cm^{-1}; ESI-MS m/z: 329.97 $[M+H]^+$. Anal. calcd for $C_{19}H_{27}N_3S$: C 69.26, H 8.26, N 12.75; found C 69.25, H 8.21, N 12.76.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-5-((2-methylbenzyl)thio)-4*H*-1,2,4-triazole (**6b**): Yellow syrup, yield 88.7%, HPLC purity 96.82%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.19～7.13 (m, 2H, C^{18}-H, C^{20}-H), 7.03 (td, J=8.5, 5.6, 2.7 Hz, 1H, C^{21}-H), 7.01～6.97 (m, 1H, C^{19}-H), 4.28 (s, 2H, C^{15}-H), 3.06 (s, 3H, NCH_3), 2.62～2.54 (m, 2H, C^6-H), 2.39 (s, 3H, C^{22}-H), 1.41～1.31 (m, 3H, C^{11}-H, C^{10}-H_a), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.3 Hz, 3H, C^{12}-H), 0.79 (dt, J=8.8, 6.8 Hz, 1H, C^7-H), 0.59 (td, J=8.6, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.61 (C^6), 149.3 (C^{15}), 136.8, 134.9, 130.6, 129.8, 128.1, 126.1, 37.5, 29.7, 29.0 (NCH_3), 26.5, 23.1, 23.0, 21.0, 19.0, 17.5, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) v: 3068 (w, cyclopropyl, Ar—H), 2956 (s), 2926 (s), 2859 (m), 1510 (m), 1498 (m, Ar), 1468 (s, C=N), 1423 (m), 1378 (m), 685 (w, C—S—C) cm^{-1}; ESI-MS m/z: 344.07 $[M+H]^+$. Anal. calcd for $C_{20}H_{29}N_3S$: C 69.93, H 8.51, N 12.23; found C 69.94, H 8.50, N 12.21.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-5-((3-methylbenzyl)thio)-4*H*-1,2,4-triazole (**6c**): Pale yellow solid, yield 90.5%, HPLC purity 97.64%. m.p. 58.2～58.9 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.14 (t, J=7.8 Hz, 1H, C^{20}-H), 7.07～7.04 (m, 2H, C^{21}-H, C^{17}-H), 7.01 (d, J=7.6 Hz, 1H, C^{19}-H), 4.25 (s, 2H, C^{15}-H), 3.17 (s, 3H, NCH_3), 2.73～2.43 (m, 2H, C^6-H), 2.30 (S, 3H, C^{22}-H), 1.41～1.30 (m, 3H, C^{11}-H and C^{10}-H_a), 1.24～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.81 (dt, J=9.0, 6.8 Hz, 1H, C^7-H), 0.60 (td, J=8.6, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5 (C^5), 149.5 (C^3), 138.3, 137.0, 129.7, 128.5, 128.4, 126.0, 39.1, 29.8, 29.0 (NCH_3), 26.5, 23.1, 23.0, 21.3, 21.0, 17.4, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) v: 2958 (s), 2925 (s), 2866 (s), 1735 (m), 1607 (w, Ar), 1592 (w), 1524 (m, Ar), 1488 (s, C=N), 1470 (m), 1375 (w), 700 (w, C—S—C) cm^{-1}; ESI-MS m/z: 344.06 $[M+H]^+$. Anal. calcd for $C_{20}H_{29}N_3S$: C 69.93, H 8.51, N 12.23; found C 69.90, H 8.52, N 12.24.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-5-((4-methylbenzyl)thio)-4*H*-1,2,4-triazole (**6d**): Yellow syrup, yield 91.0%, HPLC purity 98.23%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.11 (d, J=8.0 Hz, 2H, C^{17}-H, C^{21}-H), 7.06 (d, J=8.0 Hz, 2H, C^{18}-H, C^{20}-H), 4.25 (s, 2H, C^{15}-H), 3.15 (s, 3H, N-CH_3), 2.72～2.50 (m, 2H, C^6-H), 2.31 (s, 3H, C^{22}-H), 1.43～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.1 Hz, 3H, C^{12}-H), 0.80 (dt, J=9.0, 6.8 Hz, 1H, C^7-H), 0.59 (td, J=8.6, 5.3 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.49 (C^5), 149.48 (C^3), 137.4, 134.1, 129.3 (C^{18}, C^{20}), 128.9 (C^{17}, C^{21}), 38.9, 29.9, 29.0 (N-CH_3), 26.5, 23.1, 23.0, 21.1, 21.0, 17.4, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) v: 2961 (s), 2925 (s), 2860 (s), 1620 (w, Ar), 1522 (m, Ar), 1474 (s, C=N), 1423 (m), 1379 (m), 686 (w, C—S—C) cm^{-1}; ESI-MS m/z: 343.99 $[M+H]^+$. Anal. calcd for $C_{20}H_{29}N_3S$: C 69.93, H 8.51, N 12.23; found C 69.92, H 8.53, N 12.20.

3-((2-Chlorobenzyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6e**): Yellow syrup, yield 88.0%, HPLC purity 97.54%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37 (dt, J=7.2, 1.2 Hz, 1H, ArH), 7.20 (td, J=7.4, 1.4 Hz, 2H, ArH), 7.13～7.07 (m, 1H, ArH), 4.39 (s, 2H, C^{15}-H), 3.17 (s, 3H, N-CH_3), 2.62～2.54 (m, 2H, C^6-H), 1.41～1.30 (m, 3H, C_{11}-H and C^{10}-H_a), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 2H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.81 (dt, J=9.0, 6.8 Hz, 1H, C^7-H), 0.59 (td, J=8.6, 5.5 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.7 (C^5), 149.0 (C^3), 135.0, 134.1, 131.2, 129.7, 129.2, 126.9, 36.8, 29.8, 29.0 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.4, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) v: 3066 (w, cyclopropyl, Ar—H), 2953 (s), 2929 (s), 2866 (m), 1507 (m, Ar), 1474 (C=N), 1447 (m), 1382 (w), 684 (C—S—C) cm^{-1}; ESI-MS m/z: 363.99 $[M+H]^+$. Anal. calcd for $C_{19}H_{26}ClN_3S$: C 62.70, H 7.20, N 11.55; found C 62.71, H 7.18, N 11.54.

3-((3-Chlorobenzyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6f**): Yellow syrup, yield 88.6%, HPLC purity 98.37%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.27～7.24 (m, 1H, C^{17}-H), 7.22 (dt, J=7.8, 1.5 Hz, 1H, C^{21}-H), 7.19 (td, J=7.7, 1.5 Hz, 1H, C^{19}-H), 7.16～7.12 (m, 1H, C^{20}-H), 4.27 (s, 2H, C^{15}-H), 3.23 (s, 3H, N-CH_3), 2.57～2.64 (m, 2H, C^6-H), 1.40～1.32 (m, 3H, C^{11}-H and C^{10}-H_a), 1.24～1.17 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.83 (dt, J=8.8, 6.9 Hz, 1H, C^7-H), 0.60 (td, J=8.5, 5.3 Hz, 1H, C^9-H); ^{13}C

NMR (150 MHz, $CDCl_3$) δ: 156.7 (C^5), 149.0 (C^3), 139.3, 134.3, 129.9, 129.0, 127.8, 127.2, 38.2, 29.9, 28.93 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.5, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 3065 (w, cyclopropyl, Ar—H), 2958 (s), 2926 (s), 2861 (s), 1602 (m, Ar), 1577 (m), 1510 (m, Ar), 1475 (s, C=N), 1433 (m), 1378 (w) cm^{-1}; ESI-MS *m/z*: 364.01 $[M+H]^+$. Anal. calcd for $C_{19}H_{26}ClN_3S$: C 62.70, H 7.20, N 11.55; found C 62.69, H 7.19, N 11.52.

3-((4-Chlorobenzyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6g**): Reddish brown syrup, yield 90.5%, HPLC purity 96.79%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 224.5 (4.14) nm; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.25～7.18 (m, 4H, ArH), 4.27 (s, 2H, C^{15}-H), 3.21 (s, 3H, NCH_3), 2.65～2.56 (m, 2H, C^6-H), 1.41～1.30 (m, 3H, C^{11}-H and C^{10}-H_a), 1.24～1.15 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, *J*=7.2 Hz, 3H, C^{12}-H), 0.80 (dt, *J*=9.0, 6.8 Hz, 1H, C^7-H), 0.60 (td, *J*=8.6, 5.4 Hz, 1H, C^5-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6 (C^5), 149.0 (C^3), 135.8, 133.5, 130.4 (C^{17}, C^{21}), 128.7 (C^{18}, C^{20}), 38.0, 29.9, 28.9 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.5, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 2955 (s), 2931 (s), 2863 (m), 1598 (w, Ar), 1494 (s, Ar), 1473 (s, C=N), 1429 (w), 1381 (w), 684 (C—S—C) cm^{-1}; ESI-MS *m/z*: 363.99 $[M+H]^+$. Anal. calcd for $C_{19}H_{26}ClN_3S$: C 62.70, H 7.20, N 11.55; found C 62.66, H 7.22, N 11.53.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-5-((3-fluorobenzyl)thio)-4-methyl-4*H*-1,2,4-triazole (**6h**): Yellow syrup, yield 87.3%, HPLC purity 97.46%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 257.5 (3.36) nm; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.22 (td, *J*=7.9, 5.9 Hz, 1H, C^{20}-H), 7.02 (dt, *J*=7.7, 1.3 Hz, 1H, C^{21}-H), 6.98 (dt, *J*=9.6, 2.1 Hz, 1H, C^{19}-H), 6.94 (td, *J*=8.4, 2.7 Hz, 1H, C^{17}-H), 4.29 (s, 2H, C^{15}-H), 3.23 (s, 3H, N-CH_3), 2.65～2.56 (m, 2H, C^6-H), 1.41～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.24～1.17 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, *J*=7.2 Hz, 3H, C^{12}-H), 0.82 (dt, *J*=8.8, 6.9 Hz, 1H, C^7-H), 0.60 (td, *J*=8.7, 5.4 Hz, 1H, C^5-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.7 (d, *J*=247.0 Hz, C^{18}), 156.7 (C^5), 149.1 (C^3), 139.7 (d, *J*=7.3 Hz, C^{16}), 130.1 (d, *J*=8.3 Hz, C^{20}), 124.7 (d, *J*=2.9 Hz, C^{21}), 115.9 (d, *J*=21.8 Hz, C^{17}), 114.6 (d, *J*=21.0 Hz, C^{19}), 38.3, 29.9, 28.9 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.5, 14.8 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 2952 (s), 2872 (m), 1738 (s), 1619 (w, Ar), 1491 (m, Ar), 1470 (s, C=N), 1450 (s), 1381 (w), 681 (w, C—S—C) cm^{-1}; ESI-MS *m/z*: 348.04 $[M+H]^+$. Anal. calcd for $C_{19}H_{26}FN_3S$: C 65.67, H 7.54, N 12.09; found C 65.63, H 7.52, N 12.13.

3-((4-Bromobenzyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6i**): Yellow syrup, yield 86.5%, HPLC purity 96.95%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 224.0 (4.18) nm; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.41～7.36 (m, 2H, C^{18}-H, C^{19}-H), 7.16～7.11 (m, 2H, C^{17}-H, C^{21}-H), 4.26 (s, 2H, C^{15}-H), 3.21 (s, 3H, N-CH_3), 2.64～2.55 (m, 2H, C^6-H), 1.43～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.24～1.17 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, *J*=7.2 Hz, 3H, C^{12}-H), 0.80 (dt, *J*=9.0, 6.8 Hz, 1H, C^7-H), 0.60 (td, *J*=8.6, 5.4 Hz, 1H, C^9-H), ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6 (C^5), 149.0 (C^3), 136.3, 131.7 (C^{18}, C^{20}), 130.7 (C^{17}, C^{21}), 121.6, 38.1, 29.9, 29.0 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.5, 14.9 (C_{13}, C_{14}), 14.1; IR (KBr) ν: 2958 (s), 2931 (s), 2869 (s), 1735 (s), 1592 (w, Ar), 1512 (m, Ar), 1473 (s, C=N), 683 (w, C—S—C) cm^{-1}; ESI-MS *m/z*: 407.96 $[M+H]^+$. Anal. calcd for $C_{19}H_{26}BrN_3S$: C 55.88, H 6.42, N 10.29; found C 55.86, H 6.47, N 10.29.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-5-((4-(methylthio)benzyl)thio)-4*H*-1,2,4-triazole (**6j**): Yellow syrup, yield 91.6%, HPLC purity 97.64%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 266.5 (4.19) nm; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.14 (td, *J*=8.5, 6.5 Hz, 4H, ArH), 4.25 (s, 2H, C^{15}-H), 3.21 (s, 3H, N-CH_3), 2.64～2.55 (m, 2H, C^6-H), 2.45 (s, 3H, C^{22}-H), 1.42～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.26～1.16 (m, 1H, C^{10}-b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, *J*=7.3 Hz, 3H, C^{12}-H), 0.80 (td, *J*=8.9, 6.9 Hz, 1H, C^7-H), 0.60 (dt, *J*=8.6, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5 (C^5), 149.3 (C^3), 138.1, 133.9, 129.5 (C^{18}, C^{20}), 126.5 (C^{19}, C^{21}), 38.6, 29.9, 29.0 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.4, 15.7, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 2958 (s), 2925 (s), 2866 (m), 1601 (w, Ar), 1497 (s, Ar), 1470 (s, C=N), 1423 (w), 1378 (w), 683 (w, C—S—C) cm^{-1}; ESI-MS *m/z*: 376.05 $[M+H]^+$. Anal. calcd for $C_{20}H_{29}N_3S$: C 63.96, H 7.78, N 11.19; found C 63.93, H 7.75, N 11.18.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-5-((3-methoxybenzyl)thio)-4-methyl-4*H*-1,2,4-triazole (**6k**): Yellow syrup, yield 89.8%, HPLC purity 98.21%. UV-vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 278.5 (3.47) nm; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.17 (tt, *J*=7.9, 1.8 Hz, 1H, ArH), 6.84～6.77 (m, 2H, ArH), 6.76 (q, *J*=2.0 Hz, 1H, Ar-H), 4.25 (s, 2H, C^{15}-H), 3.75 (s, 3H, C^{22}-H), 3.21 (s, 3H, N-CH_3), 2.64～2.55 (m, 2H, C^6-H), 1.42～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, *J*=7.2 Hz, 3H, C^{12}-H), 0.80 (td, *J*=8.9, 6.9 Hz, 1H, C^7-H), 0.60 (dt, *J*=8.6, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.7 (C^5), 156.6, 149.3 (C^3), 138.6, 129.6, 121.2, 114.1, 113.6, 55.2, 39.2, 29.9, 28.9 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.4, 14.9 (C^{13}, C^{14}), 14.1 (C_{12}); IR (KBr) ν: 2958 (s), 2931 (s), 2863 (m), 1601 (m), 1583 (m, Ar), 1497 (m, Ar), 1470 (s, C=N), 1440 (w), 1375 (w), 1274 (s, C—O—C), 681 (w, C—S—C) cm^{-1}; ESI-MS *m/z*: 360.06 $[M+H]^+$. Anal. calcd for $C_{20}H_{29}N_3OS$: C 66.81, H 8.13, N 11.69; found C 66.80, H 8.12, N 11.72.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-5-((4-vinylbenzyl)thio)-4*H*-1,2,4-triazole (**6l**): Yellow syrup, yield 88.9%, HPLC purity 97.82%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 278.0 (3.41) nm; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.29 (d, *J*=8.1 Hz, 2H, C^{18}-H, C^{20}-H), 7.17 (d, *J*=8.1 Hz, 2H, C^{17}-H, C^{21}-H), 6.66 (dd, *J*=17.6, 10.9 Hz, 1H, C^{22}-H), 5.71 (d, *J*=17.6 Hz, 1H, C^{23}-H_a), 5.24 (d, *J*=10.9 Hz, 1H, C^{23}-H_b), 4.26 (s, 2H,

C^{15}-H), 3.15 (s, 3H, N-CH_3), 2.64～2.54 (m, 2H, C^6-H), 1.44～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.23～1.16 (m, 1H, C^{10}-H_b), 1.06 (s, 3H, C^{13}-H or C^{14}-H), 0.97 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.79 (dt, J=9.0, 6.8 Hz, 1H, C^7-H), 0.58 (td, J=8.6, 5.3 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6 (C^5), 149.2 (C^3), 137.0, 136.7, 136.2, 129.2 (C^{18}, C^{20}), 126.4 (C^{17}, C^{21}), 114.2, 39.0, 29.9, 29.0 (N-CH_3), 26.5, 23.1, 23.0, 21.0, 17.4, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 3089 (w), 2955 (s), 2928 (s), 2863 (s), 1631 (w, C=C), 1512 (s, Ar), 1470 (s, C=N), 1425 (m), 1375 (w), 683 (w, C—S—C) cm^{-1}; ESI-MS m/z: 356.06 $[M+H]^+$. Anal. calcd for $C_{20}H_{29}N_3OS$: C 70.94, H 8.22, N 11.82; found C 70.92, H 8.23, N 11.85.

3-((2,6-Dichlorobenzyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6m**): Pale syrup, yield 84.2%, HPLC purity 97.31%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 253.5 (4.23), 205.5 (4.39) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29 (d, J=8.0 Hz, 2H, C^{18}-H, C^{20}-H), 7.17 (dd, J=8.5, 7.6 Hz, 1H, C^{19}-H), 4.50 (s, 2H, C^{15}-H), 3.30 (s, 3H, N-CH_3), 2.70～2.60 (m, 2H, C^6-H), 1.43～1.33 (m, 3H, C^{11}-H and C^{10}-H_a), 1.25～1.18 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 1.01 (s, 3H, C^{13}-H or C^{14}-H), 0.94～0.91 (m, 3H, C^{12}-H), 0.85 (dt, J=9.0, 6.8 Hz, 1H, C^7-H), 0.61 (td, J=8.7, 5.5 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 157.0 (C^5), 148.5 (C^3), 135.8 (C^{17}, C^{21}), 133.3, 129.4 (C^{18}, C^{20}), 128.4, 35.1, 30.0, 29.0 (N-CH_3), 26.5, 23.1 (C_9, C_{11}), 21.2, 17.5, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 3077 (w, cyclopropyl, Ar—H), 2958 (s), 2925 (s), 2860 (m), 1580 (w, Ar), 1509 (w, Ar), 1473 (m, C=N), 1438 (s), 1378 (w), 683 (w, C—S—C) cm^{-1}; ESI-MS m/z: 397.96 $[M+H]^+$. Anal. calcd for $C_{19}H_{25}Cl_2N_3S$: C 57.28, H 6.33, N 10.55; found C 57.27, H 6.30, N 10.51.

3-((2,6-Difluorobenzyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6n**): Yellow syrup, yield 91.6%, HPLC purity 96.97%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.24 (tt, J=8.4, 6.5 Hz, 1H, C^{19}-H), 6.88～6.83 (m, 2H, C^{18}-H, C^{20}-H), 4.28 (s, 2H, C^{15}-H), 3.38 (s, 3H, N-CH_3), 2.70～2.61 (m, 2H, C^6-H), 1.43～1.32 (m, 3H, C^{11}-H and C^{10}-H_a), 1.26～1.18 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 1.00 (s, 3H, C^{13}-H or C^{14}-H), 0.93 (t, J=7.2 Hz, 3H, C^{12}-H), 0.86 (dt, J=8.9, 6.9 Hz, 1H, C^7-H), 0.61 (td, J=8.6, 5.5 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.2 (dd, J=250.6, 7.4 Hz, C^{17}, C^{21}), 156.90 (C^5), 148.6 (C^3), 129.7 (t, J=10.2 Hz, C^{19}), 113.2 (t, J=19.1 Hz, C^{16}), 111.4 (dd, J=20.8, 4.6 Hz, C^{18}, C^{20}), 30.0, 29.0 (N-CH_3), 26.5 (d, J=4.0 Hz, C^{10}), 26.1 (t, J=3.2 Hz, C^{15}), 23.1, 23.0, 21.1, 17.5, 14.8 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 2956 (m), 2932 (m), 2869 (w), 1629 (m), 1593 (m, Ar), 1471 (s, C=N), 1423 (w), 1376 (w), 682 (w, C—S—C) cm^{-1}; ESI-MS m/z: 366.01 $[M+H]^+$. Anal. calcd for $C_{19}H_{25}F_2N_3S$: C 62.44, H 6.89, N 11.50; found C 62.46, H 6.85, N 11.46.

3-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-5-((2,6-dimethylbenzyl)thio)-4-methyl-4*H*-1,2,4-triazole (**6o**): Pale yellow syrup, yield 90.3%, HPLC purity 97.83%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.08 (dd, J=8.1, 6.9 Hz, 1H, C^{19}-H), 7.00 (d, J=7.5 Hz, 2H, C^{18}-H, C^{20}-H), 4.39 (s, 2H, C^{15}-H), 3.15 (s, 3H, N-CH_3), 2.68～2.57 (m, 2H, C^6-H), 2.32 (s, 6H, C^{22}-H, C^{23}-H), 1.44～1.32 (m, 3H, C^{11}-H and C^{10}-H_a), 1.26～1.17 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 1.00 (s, 3H, C^{13}-H or C^{14}-H), 0.93 (t, J=7.2 Hz, 3H, C^{12}-H), 0.81 (dt, J=8.9, 6.8 Hz, 1H, C^7-H), 0.60 (td, J=8.7, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.7 (C^5), 149.8 (C^3), 137.6, 132.7 (C^{17}, C^{21}), 128.4 (C^{18}, C^{20}), 127.8, 33.6, 29.7, 29.0 (N-CH_3), 26.5, 23.1 (C^9, C^{11}), 21.0, 19.6 (C^{22}, C^{23}), 17.5, 14.9 (C^{13}, C^{14}), 14.1 (C_{12}); IR (KBr) ν: 2956 (s), 2929 (s), 2869 (m), 1590 (w, Ar), 1510 (w, Ar), 1471 (s, C=N), 1426 (w), 1379 (w), 682 (w, C—S—C) cm^{-1}; ESI-MS m/z: 358.08 $[M+H]^+$. Anal. calcd for $C_{21}H_{31}N_3S$: C 70.54, H 8.74, N 11.75; found C 70.54, H 8.76, N 11.72.

3-((Cyclopropylmethyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6p**): Yellow syrup, yield 91.5%, HPLC purity 97.39%. UV-Vis (EtOH) λ_{max} (log[ε/(L• mol^{-1}•cm^{-1})]): 243.0 (3.36), 212.0 (3.94) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.52 (s, 3H, N-CH_3), 3.11 (d, J=7.4 Hz, 2H, C^{15}-H), 2.70～2.62 (m, 2H, C^6-H), 1.42～1.32 (m, 3H, C^{11}-H and C^{10}-H_a), 1.26～1.20 (m, 1H, C^{10}-H_b), 1.19～1.13 (m, 1H), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 1.00 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.88 (dt, J=9.0, 6.8 Hz, 1H, C^7-H), 0.63～0.56 (m, 3H), 0.28～0.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.3 (C^5), 150.4 (C^3), 39.8, 30.1, 29.0 (N-CH_3), 26.5, 23.1, 21.0, 17.5, 14.9 (C^{13}, C^{14}), 14.1, 11.1, 5.8 (C^{17}, C^{18}); IR (KBr) ν: 3083 (w, cyclopropyl, Ar—H), 2955 (s), 2931 (s), 2866 (m), 1515 (w, Ar), 1470 (s, C=N), 1429 (w), 1378 (w), 681 (C—S—C) cm^{-1}; ESI-MS m/z: 294.06 $[M+H]^+$. Anal. calcd for $C_{16}H_{27}N_3S$: C 65.48, H 9.27, N 14.32; found C 65.42, H 9.32, N 14.33.

2-(((5-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)pyridine (**6q**): Reddish brown syrup, yield 82.5%, HPLC purity 98.08%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 263.5 (3.72), 210.5 (4.12) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.55 (d, J=4.9 Hz, 1H, C^{18}-H), 7.59 (td, J=7.7, 1.8 Hz, 1H, C^{20}-H), 7.36 (dt, J=7.8, 1.0 Hz, 1H, C^{21}-H), 7.18 (ddd, J=5.8, 4.9, 0.9 Hz, 1H, C^{19}-H), 4.50 (s, 2H, C^{15}-H), 3.35 (s, 3H, N-CH_3), 2.66～2.56 (m, 2H, C^6-H), 1.42～1.30 (m, 3H, C^{11}-H and C^{10}-H_a), 1.25～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.84 (dt, J=9.0, 6.9 Hz, 1H, C^7-H), 0.59 (td, J=8.6, 5.5 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.7, 156.5 (C^5), 149.6, 149.5 (C^3), 136.7, 123.7, 122.5, 39.6, 30.0 (C_6), 28.9 (N-CH_3), 26.5, 23.1, 23.0, 20.9, 17.4, 14.8 (C^{13}, C^{14}), 14.1 (C^{12}); IR (KBr) ν: 3051 (w, =CH), 2959 (s), 2932 (s), 2863 (m), 1596 (w, Ar), 1572 (w, C=C), 1474 (s, C=N), 1438 (w), 1379 (w), 681 (w, C—S—C) cm^{-1}; ESI-MS m/z: 331.04 $[M+H]^+$. Anal. calcd for $C_{18}H_{26}N_4S$: C 65.42, H 7.93, N 16.95; found C 65.41, H 7.92, N 16.94.

4-(((5-((2,2-Dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)pyridine (**6r**): Pale yellow syrup, yield 80.6%, HPLC purity 97.22%.

UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 260.0 (3.33), 205.5 (3.93) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.51 (d, J=1.7 Hz, 1H, C^{18}-H), 8.50 (d, J=1.7 Hz, 1H, C^{20}-H), 7.24 (d, J=1.7 Hz, 1H, C^{21}-H), 7.23 (d, J=1.7 Hz, 1H, C^{21}-H), 4.30 (s, 2H, C^{15}-H), 3.27 (s, 3H, N-CH_3), 2.65～2.55 (m, 2H, C^6-H), 1.40～1.31 (m, 3H, C^{11}-H and C^{10}-H_a), 1.23～1.17 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.83 (dt, J=9.0, 6.9 Hz, 1H, C^7-H), 0.60 (td, J=8.6, 5.5 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.7 (C^5), 150.0 (C^{18}, C^{20}), 148.6 (C^3), 146.3, 123.9 (C^{17}, C^{21}), 36.9, 29.9, 28.9 (N-CH_3), 26.5, 23.1, 22.9, 20.9, 17.5, 14.8 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 3033 (w, =CH), 2956 (s), 2926 (s), 2866 (m), 1605 (s, C=N), 1566 (w, C=C), 1471 (s, C=N), 1417 (s), 1379 (w), 682 (w, C—S—C) cm^{-1}; ESI-MS m/z: 331.04 [M+H]$^+$. Anal. calcd for $C_{18}H_{26}N_4S$: C 65.42, H 7.93, N 16.95; found C 65.43, H 7.90, N 16.97.

2-Chloro-6-(((5-((2,2-dimethyl-3-propylcyclopropyl)-methyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-pyridine (**6s**): Yellow solid, yield 86.5%, HPLC purity 97.25%. m.p. 66.6～67.9 ℃; UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 270.5 (3.68), 218.5 (4.27) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.34 (t, J=3.3 Hz, 1H, C^{20}-H), 7.70 (dd, J=8.0, 2.6 Hz, 1H, C^{21}-H), 7.22 (dd, J=8.1, 4.8 Hz, 1H, C^{19}-H), 4.35 (s, 2H, C^{15}-H), 3.33 (s, 3H, N-CH_3), 2.65～2.57 (m, 2H, C^6-H), 1.40～1.30 (m, 3H, C^{11}-H and C^{10}-H_a), 1.24～1.16 (m, 1H, C^{10}-H_b), 1.07 (s, 3H, C^{13}-H or C^{14}-H), 0.98 (s, 3H, C^{13}-H or C^{14}-H), 0.91 (t, J=7.2 Hz, 3H, C^{12}-H)., 0.83 (dt, J=8.9, 6.8 Hz, 1H, C^7-H), 0.60 (td, J=8.6, 5.4 Hz, 1H, C^9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.8 (C^5), 150.6, 149.9, 148.7 (C^3), 139.6, 132.3, 124.0, 34.0, 30.0, 28.9 (N-CH_3), 26.4, 23.1, 22.9, 20.9, 17.5, 14.8 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 3051 (w, =CH), 2959 (s), 2935 (s), 2866 (m), 1566 (w, C=C), 1465 (s, C=N), 1388 (w), 681 (w, C—S—C) cm^{-1}; ESI-MS m/z: 364.99 [M+H]$^+$. Anal. calcd for $C_{18}H_{25}ClN_4S$: C 59.24, H 6.91, N 15.35; found C 59.21, H 6.93, N 15.38.

3-(((5-Chlorothiophen-2-yl)methyl)thio)-5-((2,2-dimethyl-3-propylcyclopropyl)methyl)-4-methyl-4*H*-1,2,4-triazole (**6t**): Yellow syrup, yield 85.8%, HPLC purity 98.12%. UV-Vis (EtOH) λ_{max} (log[ε/(L•mol^{-1}•cm^{-1})]): 247.5 (4.02) nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.66 (d, J=1.6 Hz, 2H, C^{19}-H, C^{20}-H), 4.45 (s, 2H, C^{15}-H), 3.35 (s, 3H, N-CH_3), 2.68～2.59 (m, 2H, C^6-H), 1.41～1.32 (m, 3H, C^{11}-H and C^{10}-H_a), 1.25～1.19 (m, 1H, C^{10}-H_b), 1.08 (s, 3H, C^8-CH_3), 0.99 (s, 3H, C^8-CH_3), 0.92 (t, J=7.2 Hz, 3H, C^{12}-H), 0.85 (dt, J=8.9, 6.9 Hz, 1H, C^7-H), 0.61 (td, J=8.6, 5.5 Hz, 1H, C^9-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 156.8 (C^5), 148.9 (C$^{3)}$, 138.4, 129.9, 126.7, 125.8, 33.5, 30.0, 29.0 (NCH_3), 26.5, 23.1, 23.0, 21.0, 17.5, 14.9 (C^{13}, C^{14}), 14.1; IR (KBr) ν: 3057 (w, =CH), 2962 (s), 2929 (s), 2869 (s), 1480 (s, C=N), 1456 (s), 1379 (w), 684 (w, C—S—C) cm^{-1}; ESI-MS m/z: 369.97 [M+H]$^+$. Anal. calcd for $C_{17}H_{24}ClN_3S_2$: C 55.19, H 6.54, N 11.36; found C 55.23, H 6.52, N 11.35.

3.6 Antifungal activity test

In this work, the agar dilution method was applied to test the *in vitro* antifungal activity. The test of inhibitory rates of compounds **6a**～**6t** against the tested fungi was performed according to the literature.[41] At (24±1) ℃, the culture flat containing 50 μg/mL tested compound emulsion was cultured for 48 h. The expanded diameter of fungus tray was measured. The emulsion containing solvent and surfactant without the tested compounds was used as the blank control. There were three replicates for each tested compound. Compared with the blank assay, the relative inhibition percentage was calculated. Activity grading indicators: Grade A: ≥90%; Grade B: 70%～90%; Grade C: 50～70%; Grade D: <50%.

3.7 Herbicidal activity test

3.7.1 Inhibition of the root-growth of Rape (*B. campestris*)

The test of inhibitory rate of compounds **6a**～**6t** against the root-growth of rape (*B. campestris*) was performed by the reported method.[41] Under the support of emulsifying agent TW-80, the tested compound was modulated into the emulsion with concentration of 10 or 100 μg/mL. Then, 2 mL of emulsion was added to a 6 cm Petri dish placed with 15 seeds on a 5.6 cm filter paper. After cultivation 72 h in darkness at (28±1) ℃, the radicle lengths of seedlings were measured. The emulsion containing solvent and surfactant without the tested compounds were used as the blank control. All experiments were required to be repeated three times. The relative inhibition percentage was calculated by comparing with the control. Activity grading indicators: Grade A: ≥80%; Grade B: 60%～79%; Grade C: 40%～59%; Grade D: ≤39%.

3.7.2 Inhibition of the seedling growth of barnyard grass (*E. crusgalli*)

The test of inhibitory rate of compounds **6a**～**6t** against the seedling-growth of barnyard grass (*E. crusgalli*) was performed according to the reported method.[41] Supported by TW-80, the tested compound was modulated into 10 or 100 μg/mL emulsion. Then, 6 mL of emulsion was added to a 50 mL beaker placed with 15 germinated seeds on a filter paper. After cultivation 72 h under light irradiation (3000 Lux) at (28±1) ℃, the heights of seedlings were measured. The emulsion containing solvent and surfactant without the tested compounds were used as the blank control. All experiments were required to be repeated three times. The relative inhibition percentage was calculated by comparing with the control. Activity grading indicators: Grade A: ≥80%; Grade B: 60%～79%; Grade C: 40%～59%; Grade D: ≤39%.

4 Conclusions

Twenty novel 4-methyl-1,2,4-triazole-thioethers containing *gem*-dimethylcyclopropane ring were designed, synthesized, characterized, and evaluated for their antifungal and herbicidal activities by using the natural product

3-carene as starting material. The bioassay result revealed that, at 50 μg/mL, compounds **6a**, **6e**, **6q** and **6l** exhibited excellent antifungal activities of 84.1%～95.5% against *P. piricola*, showing much better antifungal activity than that of the commercial fungicide chlorothalonil. And compounds **6q**, **6p**, **6k** and **6d** displayed excellent herbicidal activities of 81.9%～88.0% against the root-growth of rape (*B. campestris*), showing much better herbicidal activity than that of the commercial herbicide flumioxazin at 100 μg/mL. Compounds **6a**, **6e**, and **6q** were leading compounds worthy of further investigation. In order to design more effective antifungal compounds against *P. piricola*, the 3D-QSAR analysis was carried out using the CoMFA method. A reasonable and effective 3D-QSAR model (r^2= 0.985, q^2=0.509) had been established, and a new molecule with modification on phenyl groups were designed.

Supporting Information ^{1}H NMR, ^{13}C NMR, FTIR, ESI-MS and UV-Vis for the synthesized compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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