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# 含天然蒎烯结构的 4-酰基-3-氨基-1,2,4-三唑-硫醚衍生物的合成、抑菌活性、三维定量构效关系及分子对接研究

王 秀[a] 段文贵*,[a] 林桂汕*,[a] 李宝谕[a] 张文静[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** 为了探寻以天然可再生资源为基础的生物活性分子, 设计并合成了 24 个新型含天然蒎烯结构的 4-酰基-3-氨基-1,2,4-三唑-硫醚衍生物, 通过 IR, $^1$H NMR, $^{13}$C NMR, ESI-MS 和元素分析对所有目标化合物的结构进行了表征. 初步的离体抑菌活性测试结果表明, 在质量浓度为 50 μg/mL 时, 目标化合物对测试的 8 种植物病原菌表现出一定的抑菌活性, 其中有 4 个化合物对苹果轮纹病菌有优良的抑菌活性, 远优于阳性对照百菌清; 2 个化合物对花生褐斑病菌有良好的抑制活性, 远优于阳性对照百菌清. 使用比较分子力场分析法(CoMFA)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, 建立了一个合理的 3D-QSAR 模型($r^2$=0.961, $q^2$=0.613). 此外, 分子对接结果表明, 目标化合物诺卜醇基 4-(4'-氟苯甲酰基)-3-氨基-1,2,4-三唑-硫醚(**5k**)在琥珀酸脱氢酶(SDH)活性口袋的结合模式与商品杀菌剂萎锈灵相似.

**关键词** *β*-蒎烯; 诺卜醇; 1,2,4-三唑-硫醚; 3D-QSAR; 分子对接; 抑菌活性

# Synthesis, Antifungal Activity, Three-Dimensional Quantitative Structure-Activity Relationship and Molecular Docking Study of 4-Acyl-3-amino-1,2,4-triazole-thioether Derivatives Containing Natural Pinene Structure

Wang, Xiu[a] Duan, Wengui*,[a] Lin, Guishan*,[a] Li, Baoyu[a]
Zhang, Wenjing[a] Lei, Fuhou[b]
([a] *School 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** Twenty-four 4-acyl-3-amino-1,2,4-triazole-thioether derivatives containing natural pinene structure were designed and synthesized in search of novel natural product-based bioactive molecules. Their structures were characterized by IR, $^1$H NMR, $^{13}$C NMR, ESI-MS, and elemental analysis. The *in vitro* antifungal activity test of the target compounds showed that, at the concentration of 50 μg/mL, the target compounds displayed certain antifungal activity against the eight tested plant pathogens, in which 4 compounds exhibited good to excellent antifungal activity against *Physalospora piricola*, much better than that of the positive control chlorothalonil. Also, 2 compounds exhibited good inhibitory activity against *Cercospora arachidicola*, much better than that of the positive control chlorothalonil. The preliminary analysis of three-dimensional quantitative structure-activity relationship (3D-QSAR) was carried out using the molecular field analysis (CoMFA) method for the inhibitory activity of the target compounds against *P. piricola*, and a reasonable 3D-QSAR model ($r^2$=0.961, $q^2$=0.613) has been established. Furthermore, the molecular docking results showed that the binding mode of the target compound nopol-derived 4-(4'-fluorobenzoyl)-3-amino-1,2,4-triazole-thioether (**5k**) in the active cavity of succinate dehydrogenase (SDH) was similar to that of the commercial fungicide carboxin.

* Corresponding authors. E-mail: wgduan@gxu.edu.cn; gxlinguas@sina.com
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**Keywords** *β*-pinene; nopol; 1,2,4-triazole-thioether; 3D-QSAR; molecular docking; antifungal activity

## 1 Introduction

Plant diseases derived from phytopathogens have always been one of the main reasons for crop yield reduction, and the use of fungicides is the primary control measures for crop diseases in agriculture and has contributed greatly to increase crop yields and quality benefits.[1] However, long-term use of available traditional fungicides has caused environmental pollution, pesticide residual toxicity, the resistance of plant fungal diseases and plant health.[2] Therefore, it is of great significance to develop novel and promising antifungal agents for plant protection.

Succinate dehydrogenase (SDH), also known as succinate-ubiquinone reductase, has been definitely recognized as one of the most significant targets in the development of new fungicides to fight against destructive plant pathogens. It is also a key enzyme complex in the citric acid cycle that catalyzes the electron transfers from succinate to ubiquinone in the mitochondrial matrix.[3] Since the first succinate dehydrogenase inhibitors (SDHI) fungicide carboxin was launched in 1966,[4] twenty-three SDHIs have been successfully employed in the world market and more are still being developed according to the statistics from the Fungicide Resistance Action Committee (FRAC). Recently, a series of commercial SDHI fungicides (examples in Figure 1) have been successfully developed by structural modification of the amide group, including penthiopyrad, pydiflumetofen, isoflucypram and so on,[5] and our target compounds in this work contain similar amide groups.

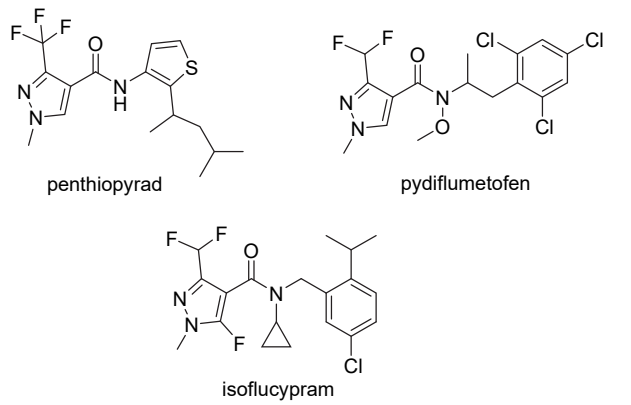



**Figure 1** Commercial SDHI fungicides developed by structural modification of the amide group

Turpentine oil is a natural and preponderant biomass resource which can be obtained by the steam distillation of the oleoresin exudate from living pine trees.[6] Its two major components are *α*-pinene and *β*-pinene, which have received much attention in recent years due to their various biological activities.[7] The content of *β*-pinene in turpentine oil of *Pinus elliottii* can be as high as about 25%～35%.[8] Nopol, in which molecular scaffold of the natural *α*-pinene is maintained, can be prepared by Prins reaction of *β*-pinene with paraformaldehyde under catalysis of Lewis acid.[9,10] Nopol and its derivatives exhibited a broad spectrum of biological activities, such as antifungal,[11] antiplasmodial,[12] antitumor,[13] repellent,[14] antifeedant,[15] as well as for treatment of irritable bowel syndrome.[16] In recent years, our research group reported several classes of nopol derivatives and found that some of the target compounds exhibited excellent to good antifungal activity.[17,18] Therefore, nopol is worthy of further research for agrochemical or pharmaceutical uses based on its bioactive property and chemical reactivity.

Besides, 1,2,4-triazoles are an important class of heterocyclic compounds, which has aroused considerable interests due to their remarkable biological properties including antibacterial,[19] antifungal,[20] antitumor,[21] antiviral,[22] and other biological activities.[23-26] Notably, introduction of 1,2,4-triazole group as a potent pharmacophore into our target compounds might promote discovery of new fungicides differentiating from the current structures of SDHIs. On the other hand, the amide functional group is an important moiety in medicinal and pesticide chemistry. It and its derivatives possess a wide spectrum of biological activities, such as anticancer,[27,28] antifungal,[29] antibacterial,[30] insecticidal,[31,32] anti-inflammatory,[33] and antiviral[34] activities *etc.*

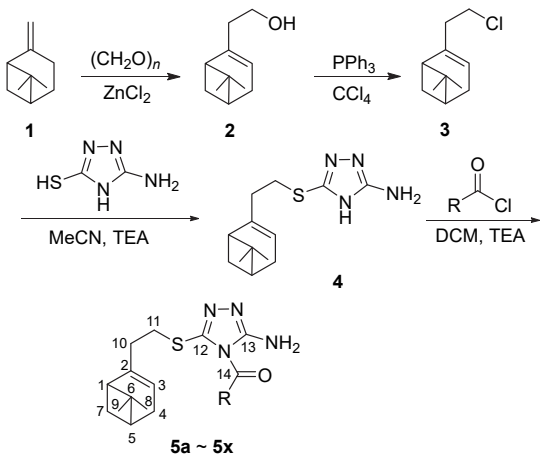
In continuation of our focus on developing natural product-based bioactive compounds,[17,35-40] twenty-four 4-acyl-3-amino-1,2,4-triazole-thioether derivatives containing natural pinene structure were designed and synthesized by the strategy of molecular docking-based virtual screening based on the crystal structure of SDH. Structural confirmatiom and antifungal evaluation of all the target compounds were complished as well. In addition, a three-dimensional quantitative structure-activity relationship (3D-QSAR) model for the antifungal activity of the target compounds against *P. piricola* was established by the comparative molecular field analysis (CoMFA) method.

## 2 Results and discussion

### 2.1 Synthesis and characterization

The synthetic route of 4-acyl-3-amino-1,2,4-triazole-thioether derivatives containing natural pinene structure **5a**～**5x** is shown in Scheme 1. Firstly, (−)-nopol **2** was prepared by Prins reaction of *β*-pinene **1** with paraformaldehyde under catalysis of Lewis acid $ZnCl_2$.[41] Then, (−)-nopyl chloride **3** was prepared by Appel reaction of (−)-nopol **2** with triphenylphosphine in a good yield,[42] followed by nucleophilic substitution reaction of (−)-nopyl chloride **3** with 3-amino-5-mercapto-1,2,4-triazole to afford the key intermediate **4**. Finally, twenty-four 4-acyl-3-amino-1,2,4-triazole-thioether derivatives **5a**～**5x** containing natural pinene structure were synthesized by *N*-acylation reaction of compound **4** with a series of substituted acyl chlorides.[43]




**5a**: R = $C_6H_5$, **5b**: R = *o*-$CH_3C_6H_4$, **5c**: R = *m*-$CH_3C_6H_4$, **5d**: R = *p*-$CH_3$-$C_6H_4$, **5e**: R = *o*-$CH_3OC_6H_4$, **5f**: R= *m*-$CH_3OC_6H_4$, **5g**: R = *p*-$CH_3CH_2$-$OC_6H_4$, **5h**: R = *p*-$CH_3CH_2C_6H_4$, **5i**: R = *o*-$FC_6H_4$, **5j**: R = *m*-$FC_6H_4$, **5k**: R = *p*-$FC_6H_4$, **5l**: R = *o*-$ClC_6H_4$, **5m**: R = *m*-$ClC_6H_4$, **5n**: *o*-$BrC_6H_4$, **5o**: R = *m*-$BrC_6H_4$, **5p**: R = *p*-$BrC_6H_4$, **5q**: R = *p*-$CNC_6H_4$, **5r**: R = *o*-$O_2NC_6H_4$, **5s**: R = *p*-$O_2NC_6H_4$, **5t**: R = *p*-$CF_3C_6H_4$, **5u**: R = *o*,*m*-$Cl_2C_6H_3$, **5v**: R = *o*,*p*,*o*-$(CH_3)_3C_6H_2$, **5w**: R = cyclohexyl; **5x**: R = *α*-thienyl

**Scheme 1** Synthetic route of 4-acyl-3-amino-1,2,4-triazolethioether derivatives **5a**～**5x** containing natural pinene structure

According to the literatures,[44~46] compound **4** can exist in three tautomers, namely, 1*H*-, 2*H*-, and 4*H*-forms. The *N*-acylation reaction process was monitored by high performance liquid chromatography (HPLC), and only one new peak was observed. When the $^1$H NMR spectrum of compound **4** was compared with those of the target compounds, it was found that the signals of the amino group were preserved, implying that the *N*-acylation reaction did not occur on the primary amino group. The result was further confirmed by nuclear overhauser effect spectroscopy (NOESY) of the target compound **5v** (*o*,*p*,*o*- $(CH_3)_3C_6H_2$). As shown in Figure 2, the hydrogen atom bonded to C-3 showed a strong correlation with the hydrogen atoms on the benzene ring and the methyl groups bonded to the benzene ring, indicating that the *N*-acylation reaction occurred on the nitrogen atom of the 4*H*-site.

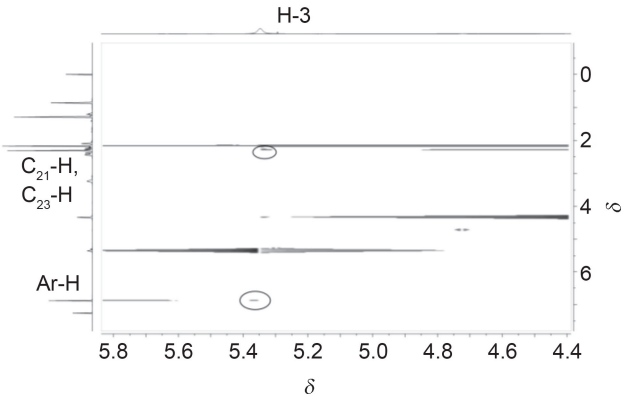



**Figure 2** Expanded NOESY spectrum of the target compound **5v**

The structures of all the target compounds (**5a**～**5x**) were confirmed by FT-IR, $^1$H NMR, $^{13}$C NMR, ESI-MS, and elemental analysis. In IR spectra, the obvious absorption bands at about 3400～3200 cm$^{-1}$ were assigned to the stretching vibrations of N—H bonds. The signals ranging from 1711 to 1675 cm$^{-1}$ were attributed to the stretching vibrations of C=O in the target compounds. And the weak absorption bands at about 1640 and 650 cm$^{-1}$ were due to the vibrations of C=N and C—S—C, respectively. In the $^1$H NMR, the appearance of a singlet with 2H integral areas at about $\delta$ 6.90 was assigned to the $NH_2$ group of 1,2,4-triazole. The characteristic signals of the olefinic protons at nopol scaffold showed about $\delta$ 5.30, and the other protons bonded to the saturated carbons of the nopol moiety displayed signals in the range of $\delta$ 0.78～3.30. The $^{13}$C NMR spectra of all the target compounds **5a**～**5x** showed peaks for the olefinic carbons of the nopol moiety at about $\delta$ 146.10 and 118.20, and the other saturated carbons displayed signals in the region of $\delta$ 15.1～45.68. For the 1,2,4-triazole moiety, the signal at about $\delta$ 162.5 was assigned to the carbon bonded to $NH_2$. The carbons of C=O showed characteristic peaks at $\delta$ 162.44～167.90. Their molecular weights and the C, H, and N element ratios were confirmed by ESI-MS and elemental analysis, respectively.

## 2.2 *In vitro* antifungal activity

The *in vitro* antifungal activities of the target compounds **5a**～**5x** and the commercial antifungal agent chlorothalonil selected as a positive control were evaluated against eight plant pathogens by the agar dilution method, including *Fusarium oxysporum* f. sp. *cucumerinum*, *Cercospora arachidicola*, *Physalospora piricola*, *Alternaria solani*, *Gibberella zeae*, *Rhizoeotnia solani*, *Bipolaris maydis* and *Colleterichum orbicalare* at the concentration of 50 μg/mL. The preliminary bioassay results were listed in Table 1.

As seen from Table 1, at the concentration of 50 μg/mL, the target compounds exhibited the best antifungal activity against *P. piricola*, in which compounds **5k** (R=*p*-$FC_6H_4$) and **5u** (R=*o*,*m*-$Cl_2C_6H_3$) had inhibition rates of 93.9% and 93.5%, respectively, much better than that of the positive control chlorothalonil. Compounds **5e** (R = *o*-$CH_3OC_6H_4$) held inhibition rate of 84.1% against *A. solani* and **5p** (R=*p*-$BrC_6H_4$) held inhibition rate of 84.5% against *G. zeae*, much better than that of the positive control chlorothalonil, and they also held inhibition rates of 90.5% and 89.6%, respectively, against *R. solani*. Apparently, compound **5p** (R=*p*-$BrC_6H_4$) showed good broad-spectrum antifungal activity and deserved further study. It was also found that the R groups displayed a noticeable influence on antifungal activity against *P. piricola*, so a 3D- QSAR study was then carried out.

## 2.3 3D-QSAR analysis

According to the above bioassay results, the target compounds showed the best antifungal activity against *P. piricola*. Herein, to further study the relationship between the structures of the target compounds with aromatic R substituents and their inhibitory activities against *P. piricola*, 3D-QSAR model was established by comparative molecular field analysis (CoMFA) method. The inhibition

**Table 1** *In vitro* antifungal activity of the target compounds **5a**～**5x** 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* |
| **5a** | 24.5 | 48.6 | 45.0 | 41.4 | 58.7 | 63.5 | 43.8 | 40.0 |
| **5b** | 42.2 | 82.9 | 83.0 | 66.2 | 66.6 | 21.2 | 49.8 | 39.6 |
| **5c** | 29.1 | 34.3 | 45.0 | 48.6 | 52.3 | 57.0 | 34.3 | 35.0 |
| **5d** | 33.6 | 27.1 | 38.8 | 34.3 | 29.7 | 30.9 | 34.3 | 30.0 |
| **5e** | 66.3 | 74.3 | 85.2 | 84.1 | 73.4 | 90.5 | 77.4 | 72.9 |
| **5f** | 24.5 | 27.1 | 38.8 | 41.4 | 26.5 | 41.7 | 24.8 | 30.0 |
| **5g** | 33.6 | 41.4 | 54.4 | 41.4 | 42.6 | 35.2 | 34.3 | 35.0 |
| **5h** | 24.5 | 41.4 | 51.3 | 34.3 | 45.8 | 59.1 | 43.8 | 35.0 |
| **5i** | 24.5 | 24.3 | 28.8 | 27.1 | 61.9 | 30.9 | 29.5 | 30.0 |
| **5j** | 24.5 | 48.6 | 41.9 | 34.3 | 39.4 | 59.1 | 43.8 | 40.0 |
| **5k** | 51.5 | 80.0 | 93.9 | 79.0 | 47.6 | 24.9 | 34.9 | 33.7 |
| **5l** | 29.1 | 41.4 | 41.9 | 41.4 | 36.1 | 30.9 | 29.5 | 30.0 |
| **5m** | 38.2 | 41.4 | 70.0 | 41.4 | 71.6 | 57.0 | 34.3 | 40.0 |
| **5n** | 24.5 | 34.3 | 38.8 | 41.4 | 36.1 | 41.7 | 34.3 | 30.0 |
| **5o** | 24.5 | 41.4 | 54.4 | 48.6 | 58.7 | 50.4 | 43.8 | 35.0 |
| **5p** | 88.2 | 77.1 | 70.0 | 77.1 | 84.5 | 89.6 | 67.6 | 80.0 |
| **5q** | 33.6 | 41.4 | 51.3 | 48.6 | 55.5 | 57.0 | 39.0 | 30.0 |
| **5r** | 24.5 | 41.4 | 45.0 | 41.4 | 45.8 | 70.0 | 29.5 | 40.0 |
| **5s** | 38.2 | 34.3 | 32.5 | 41.4 | 52.3 | 46.1 | 43.8 | 30.0 |
| **5t** | 45.9 | 68.6 | 61.3 | 61.0 | 37.2 | 27.3 | 41.3 | 39.6 |
| **5u** | 42.2 | 74.3 | 93.5 | 71.3 | 66.6 | 26.1 | 34.9 | 39.6 |
| **5u** | 33.6 | 34.3 | 35.6 | 41.4 | 26.5 | 28.7 | 39.0 | 30.0 |
| **5w** | 16.2 | 30.4 | 47.6 | 40.0 | 34.0 | 12.3 | 18.9 | 33.3 |
| **5x** | 24.5 | 27.1 | 38.8 | 41.4 | 52.3 | 37.4 | 24.8 | 30.0 |
| Chlorothalonil | 100 | 73.3 | 75.0 | 73.9 | 73.1 | 96.1 | 90.4 | 91.3 |

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

rates of the compounds **5a**～**5v** were converted into the available active factor (AF) values, which were listed in Table 2. Briefly, the model is firstly validated by the partial least squares (PLS) regression analysis method. The 3D-QSAR model with reliable predictive ability must satisfy the following conditions: a correlation coefficient squared $r^2$ (close to 1), a cross-validated squared $q^2$ (>0.5), a standard deviation $S$ (close to 0), a Fisher validation value $F$ (>100), and an optimal number of component (ONC). Their values for the built 3D-QSAR model were shown in Table 3. The $r^2$ was 0.961, $q^2$ was 0.613, $S$ was 0.016, $F$ was 124.113, and ONC was 5, suggesting that the model was reliable. The correlation between the experimental AF and predicted activities AF' was shown in Figure 3, where all data were concentrated near the X=Y line, also indicating that the 3D-QSAR model was reliable and had a good predictive ability.

The results of the CoMFA model contributions of steric and electrostatic fields were 78.2% and 21.8%, respectively, indicating that the steric field of the compounds had a greater influence on the antifungal activity against *P. piricola*. In the steric field (Figure 4A), the green contours represent that the introduction of bulky groups will enhance the antifungal activity, while the yellow contour defines the opposite. For example, compound **5e** (R=*o*-$CH_3OC_6H_4$) with a bigger substituent group in 2-position

**Table 2** Experimental and predicted AF values[a]

| Compd. | R | MW | AF | AF" | Residue |
|---|---|---|---|---|---|
| **5a** | $C_6H_5$ | 368.17 | −2.65 | −2.68 | 0.03 |
| **5b** | *o*-$CH_3C_6H_4$ | 382.18 | −1.89 | −1.94 | 0.05 |
| **5c** | *m*-$CH_3C_6H_4$ | 382.18 | −2.67 | −2.79 | 0.12 |
| **5d** | *p*-$CH_3C_6H_4$ | 382.18 | −2.78 | −2.66 | −0.12 |
| **5e** | *o*-$CH_3OC_6H_4$ | 398.18 | −1.84 | −1.84 | 0.00 |
| **5f** | *m*-$CH_3OC_6H_4$ | 398.18 | −2.8 | −2.82 | 0.02 |
| **5g** | *p*-$CH_3CH_2OC_6H_4$ | 412.19 | −2.54 | −2.63 | 0.09 |
| **5h** | *p*-$CH_3CH_2C_6H_4$ | 396.20 | −2.58 | −2.63 | 0.05 |
| **5i** | *o*-$FC_6H_4$ | 386.16 | −2.98 | −3.14 | 0.16 |
| **5j** | *m*-$FC_6H_4$ | 386.16 | −2.73 | −2.71 | −0.02 |
| **5k** | *p*-$FC_6H_4$ | 386.16 | −1.40 | −1.44 | 0.04 |
| **5m** | *m*-$ClC_6H_4$ | 402.13 | −2.24 | −2.40 | 0.16 |
| **5o** | *m*-$BrC_6H_4$ | 446.08 | −2.57 | −2.45 | −0.12 |
| **5p** | *p*-$BrC_6H_4$ | 446.08 | −2.28 | −2.14 | −0.14 |
| **5q** | *p*-$NCC_6H_4$ | 393.16 | −2.57 | −2.61 | 0.04 |
| **5r** | *o*-$O_2NC_6H_4$ | 413.15 | −2.70 | −2.75 | 0.05 |
| **5t** | *p*-$CF_3C_6H_4$ | 436.15 | −2.44 | −2.45 | 0.01 |
| **5l*** | *o*-$ClC_6H_4$ | 402.13 | −2.75 | −2.49 | −0.26 |
| **5n*** | *o*-$BrC_6H_4$ | 446.08 | −2.85 | −2.51 | −0.34 |
| **5s*** | *p*-$O_2NC_6H_4$ | 413.15 | −2.93 | −2.68 | −0.25 |
| **5u*** | *o*,*m*-$Cl_2C_6H_3$ | 436.09 | −1.48 | −1.73 | 0.25 |
| **5v*** | *o*,*o*,*p*-$(CH_3)_3C_6H_2$ | 410.21 | −2.87 | −3.08 | 0.21 |

[a] AF=experimental value; AF'=predicted value; * test-set compounds.

**Table 3** PLS analysis parameters for the built 3D-QSAR model

| Statistical parameters | CoMFA |
|---|---|
| $r^2$ [a] | 0.961 |
| $q^2$ [b] | 0.613 |
| $S$ [c] | 0.016 |
| $F$-value[d] | 124.113 |
| ONC[e] | 5 |
| **Field contribution/%** | **CoMFA** |
| Steric | 78.2 |
| Electrostatic | 21.8 |

[a] Non-cross-validated correlation coefficient. [b] Cross-validated correlation coefficient after the leave-one-out procedure. [c] Standard error of estimate. [d] F-test value. [e] Optiml number of components.

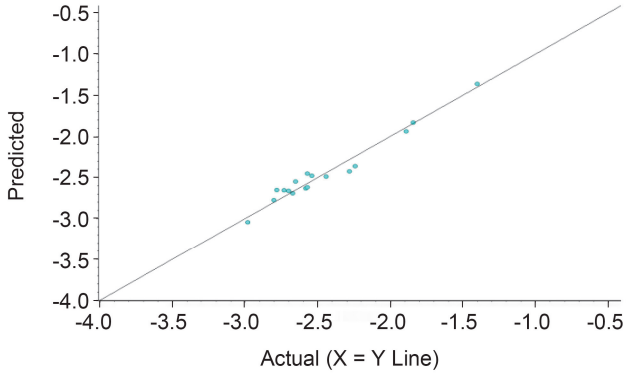



**Figure 3** Correlation between predicted AF vs experimental AF for CoMFA model

showed higher inhibitory activities than that of compounds **5i** (R=*o*-$FC_6H_4$) and **5l** (R=*o*-$ClC_6H_4$). In the electrostatic field (Figure 4B), the electrostatic contours were displayed in two distinguishable colors: the blue enclosed volume represented that the R group with an electron-donating surface embedding in this area will favor the increase in activity but red defines the opposite. The introduction of the electron-donating group at the 2-position of benzene ring played a crucial role in the antifungal activity. For instance, compound **5b** (R=*o*-$CH_3C_6H_4$) with an electron-donating group at 2-position displayed better antifungal activity against *P. piricola* than that of compounds **5n** (R = *o*-$BrC_6H_4$) and **5r** (R = *o*-$O_2NC_6H_4$) with an electron-drawing group at 2-position. Moreover, the antifungal activity of **5b** (R=*o*-$CH_3C_6H_4$) and **5e** (R=*o*-$CH_3OC_6H_4$) was better than that of the unsubstituted compound **5a** (R=$C_6H_5$). The 3D-QSAR study of these title compounds can provide useful information for the further structural modification of this kind of novel nopol derivatives.

### 2.4 Molecular docking study

Molecular docking was performed to investigate the interaction between compound **5k** and SDH. For comparison, carboxin, the earliest launched SDHI, was also docked into the theoretically binding site of SDH. The binding modes of compound **5k** and carboxin with SDH, respectively, were illustrated in Figure 5. It was found that compound **5k** fit in the cavity composed of subunit B, C and D,

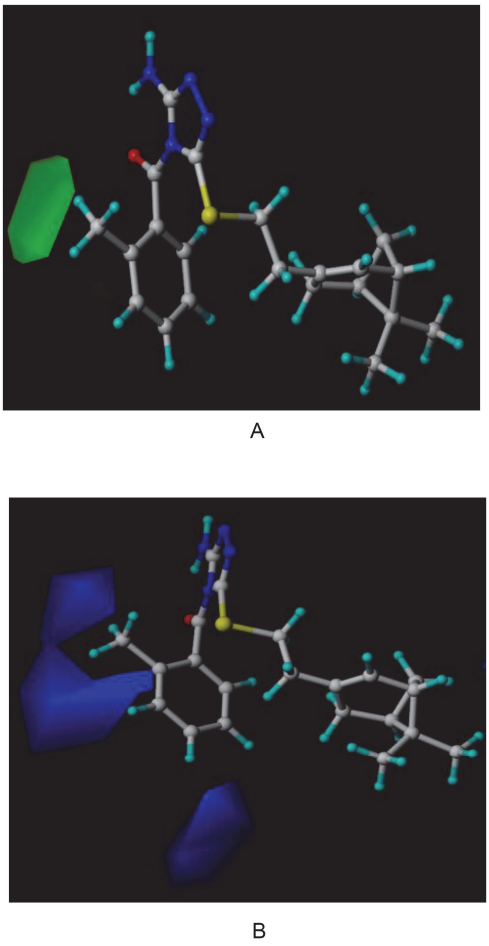



**Figure 4** Contour maps of the CoMFA steric (A) and electrostatic (B)

and stretched into the binding pocket consisting of the residues B/TRP206, C/HIS64, C/PHE65, C/TRP74, C/ARG81, D/ASP127, D/TYR128, *etc*. Meanwhile, a π-π stacking interaction (distance=2. 73 Å) was observed between the phenyl group of compound **5k** and the residue C/PHE65. In addition, two H-bonds were formed by the nitrogen atom of 1,2,4-triazole and the residue C/TYR128 in the SDH-binding site (*d*=2.09, 2.76 Å), which were essential to stabilize the binding between SDHIs and SDH. Based on these results, the binding domain and the binding mode of compound **5k** were both similar to that of carboxin.

## 3 Conclusions

Using natural renewable biomass resource *β*-pinene as starting material, twenty-four novel 4-acyl-3-amino-1,2,4-triazole-thioether derivatives containing natural pinene structures **5a**～**5x** were designed, synthesized, and characterized by means of IR, NMR, ESI-MS, and elemental analysis. The preliminary bioassays results indicated that, at the concentration of 50 μg/mL, compounds **5k** (R=*p*-F-$C_6H_4$), **5u** (R=*o*,*m*-$Cl_2C_6H_3$), **5e** (R=*o*-$CH_3OC_6H_4$), and **5b** (R=*o*-$CH_3C_6H_4$) had inhibition rates of 93.9%, 93.5%, 85.2%, and 83.0%, respectively, much better than that of the positive control chlorothalonil. Compounds **5b** (R=*o*-$CH_3$-

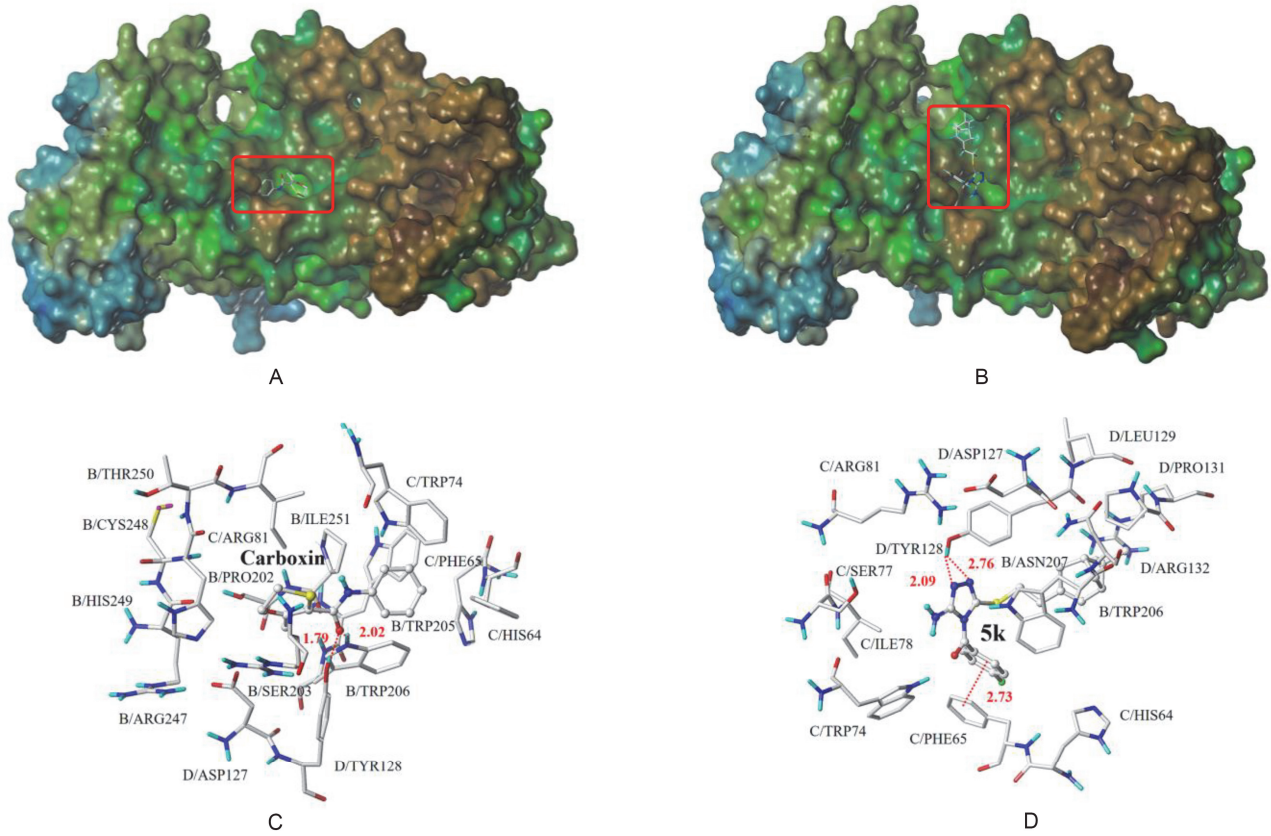



**Figure 5** (**A**) Binding cavity of carboxin with SDH; (**B**) Binding cavity of compound **5k** with SDH; (**C**) 3D interactions map of carboxin with SDH; (**D**) 3D interactions map of compound **5k** with SDH

$C_6H_4$) and **5k** (R=*p*-F$C_6H_4$) had inhibition rates of 82.9% and 80.0%, respectively, against *C. arachidicola*, much better than that of the positive control chlorothalonil. Compound **5p** (R=*p*-Br$C_6H_4$) showed good broad-spectrum antifungal activity and deserves further study. In addition, a reasonable 3D-QSAR model ($r^2$=0.961, $q^2$=0.613) for the antifungal activity of the target compounds against *P. piricola* has been established by CoMFA method. Molecular docking study revealed that the target compound **5k** could bind to the key residues of the binding cavity in SDH by hydrogen bonding interactions, π-π interaction and hydrophobic interactions.

## 4 Experimental section

### 4.1 General

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker spectrometer (Avance III HD 500/600 and 125/150 MHz, respectively) and deuterated chloroform ($CDCl_3$) as solvent. IR spectra were recorded on a Nicolet iS50 FT-IR spectrometer (Thermo Scientific Co., Ltd., Madison, WI, USA) by KBr pellet method. 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). Elemental analyses were measured using a PE 2400 II elemental analyzer (Perkin-Elmer Instruments Co., Ltd., USA). GC analysis was performed on an Agilent 6890 GC (Agilent Technologies Inc., Santa Clara, CA, USA) equipped with an HP-1 (30 m, 0.530 mm, 0.88 μm) column. Melting points were tested using an uncorrected MP420 automatic melting point apparatus (Hanon Instruments Co., Ltd., Jinan, China). *β*-Pinene (GC purity 98%) was provided by Jiangxi Xuesong Natural Medicinal Oil Co., Ltd. (Ji'an, Jiangxi, China). All other materials and reagents were purchased from commercial suppliers and used as received.

### 4.2 Synthesis of (−)-nopol (**2**)

A mixture of *β*-pinene **1** (300 mL, 1.90 mol) and paraformaldehyde (85.7 g, 0.95 mol) was magnetically stirred under solvent-free condition. When the mixture was heated to 75 ℃, a catalytic quantity of anhydrous $ZnCl_2$ was added to the reaction system. Afterwards, the reaction mixture was stirred at 75 ℃ for 1 h, and then continuously stirred at 110 ℃ for 10 h. When the reaction was completed, the reaction mixture was cooled to room temperature. Then, the organic layer was separated, washed three times with deionized water, and dried over anhydrous $Na_2SO_4$. The crude product was further purified by vacuum distillation to obtain (−)-nopol (**2**) as colorless transparent liquid in yield of 70% at 60～70 ℃/1333 Pa (GC purity 94.5%). $[\alpha]_D^{25}$ −76.0 (*c* 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) *δ*: 5.36～5.35 (m, 1H, C$^3$-H), 3.62～3.58 (m, 2H, C$^{11}$-H), 2.40 (dt, *J*=8.6, 5.6 Hz, 1H, C$^1$-H), 2.32～2.21 (m, 4H, C$^7$-H, C$^{10}$-H), 2.14～2.10 (m, 1H, C$^5$-H), 2.05 (td,

$J$=5.6, 1.4 Hz, 1H, $C^4$-H), 1.51 (s, 1H, $C^{12}$-H), 1.29 (s, 3H, $C^9$-H), 1.16 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.86 (s, 3H, $C^8$-H); $^{13}$C NMR (150MHz, $CDCl_3$) $\delta$: 144.72, 119.38, 59.98, 45.61, 40.72, 40.22, 37.90, 31.76, 31.39, 26.25, 21.19; IR (KBr) $v$: 3370 (s, OH), 3025 (w, C=C—H), 2991, 2914, 2831 (s, C—H), 1468 (m, $CH_2$), 1381, 1368 (m, $CMe_2$), 1046 (s, C—O) $cm^{-1}$. These spectral data were in agreement with that of the literatures.[47-48]

### 4.3 Synthesis of (−)-nopyl chloride (**3**)

Under magnetic stirring, a solution of triphenylphosphine (25.3 g, 0.09 mol) and (−)-nopol (**2**) (14.6 g, 15 mL, 0.09 mol) dissolved in carbon tetrachloride (52 mL) was refluxed for 3 h. After cooling to room temperature, a white precipitate was removed by filtration. The filtrate was evaporated to give a yellowish oil, which was subsequently washed with petroleum ether and further purified by vacuum distillation to obtain (−)-nopyl chloride (**3**) as a pale yellow liquid in the yield of 80% at 80～90 ℃/1333 Pa (GC purity 94.0%). $[\alpha]_D^{25}$ −71.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 5.38～5.33 (m, 1H, $C^3$-H), 3.59～3.44 (m, 2H, $C^{11}$-H), 2.47～2.37 (m, 3H, $C^1$-H, $C^{10}$-H), 2.32～2.20 (m, 2H, $C^7$-H), 2.11～2.10 (m, 1H, $C^5$-H), 2.05 (td, $J$=4.8, 2.4 Hz, 1H, $C^4$-H), 1.30 (s, 3H, $C^9$-H), 1.19 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.86 (s, 3H, $C^8$-H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 144.41, 119.27, 45.57, 42.64, 40.71, 40.16, 38.06, 31.64, 31.32, 26.27, 21.21; IR (KBr) $v$: 3029 (w, C=C—H), 2987, 2916, 2981, 2831 (s, C—H), 1470 (m, $CH_2$), 1383, 1368 (m, $CMe_2$),741 (w, C—Cl) $cm^{-1}$. These spectral data were in agreement with that of the literature.[42]

### 4.4 Synthesis of (−)-nopol-derived 3-amino-1,2,4-triazole-thioether (**4**)

Triethylamine (2.6 g, 26 mmol) was added dropwise to a solution of the intermediate **3** (4.6 g, 25 mmol) and 3-amino-5-mercapto-4*H*-1,2,4-triazole (2.9 g, 25 mmol) in acetonitrile (25 mL). The mixture was refluxed for 5 h until the reaction was completed. The reaction mixture was concentrated under reduced pressure, and the crude product was dissolved in ethyl acetate (100 mL). The solution was washed with saturated sodium bicarbonate (20 mL×3) and brine (20 mL×3). The organic layer was dried over anhydrous sodium sulfate, and purified by silica gel column chromatography (petroleum ether/ethyl acetate, $V$∶$V$=2∶1) to afford (−)-nopol-derived 3-amino-1,2,4-triazolethioether (**4**) in yield of 82%. $[\alpha]_D^{25}$ −79.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 12.41 (s, NH), 5.30～5.28 (m, 1H, $C^3$-H), 4.94 (s, 2H, $NH_2$), 3.16～3.03 (m, 2H, $C^{11}$-H), 2.36 (dt, $J$=14.8, 6.0 Hz, 3H, $C^1$-H, $C^{10}$-H), 2.28～2.18 (m, 2H, $C^7$-H), 2.10～2.07 (m, 1H, $C^5$-H), 2.03 (td, $J$=5.6, 1.4 Hz, 1H, $C^4$-H), 1.27 (s, 3H, $C^9$-H), 1.15 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.83 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 158.27, 155.95, 145.83, 118.19, 45.55, 40.73, 38.02, 37.07, 31.66, 31.28, 30.88, 26.26, 21.22; ESI-MS $m/z$: 265.28 $[M+H]^+$. Anal. calcd for C 59.06, H 7.63, N 21.19; found C 59.05, H 7.62, N 21.17.

### 4.5 General procedure for the synthesis of 4-acyl-3-amino-1,2,4-triazole-thioether derivatives containing natural pinene structure **5a**～**5x**

Under an anhydrous atmosphere and with ice-bath cooling, a solution of acyl chloride (2 mmol) dissolved in dry dichloromethane (DCM) (5 mL) was added slowly to the mixed solution of the intermediate **4** (264.1 mg, 1 mmol) and triethylamine (101.2 mg, 1 mmol) in dry DCM (15 mL). The reaction process was monitored by TLC. After reaction was completed, a certain amount of saturated aqueous $NaHCO_3$ was added to destroy the unreacted acyl chloride. Then, the organic layer was separated, washed with deionized water three times, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was further recrystallized from the mixed solution of petroleum ether and ethyl acetate to afford 4-acyl-3-amino-1,2,4-triazole-thioether derivatives **5a**～**5x** containing natural pinene structure.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-*4H*-1,2,4-triazol-4-yl)(phenyl)methanone (**5a**): White granular, 74% yield. m.p. 119.9～120.0 ℃; $[\alpha]_D^{25}$ −45.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 8.27～8.21 (m, 2H, Ar-H), 7.65～7.60 (m, 1H, Ar-H), 7.50 (t, $J$=7.8 Hz, 2H, Ar-H), 6.94 (s, 2H, -$NH_2$), 5.33～5.29 (m, 1H, $C^3$-H), 3.14～3.03 (m, $C^{11}$-H), 2.45～2.40 (m, 2H, $C^{10}$-H), 2.37 (dt, $J$=8.5, 5.6 Hz, 1H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.10 (dd, $J$=4.9, 2.3 Hz, 1H, $C^4$-H), 2.05 (td, $J$=5.7, 1.2 Hz, 1H, $C^5$-H), 1.27 (s, 3H, $C^9$-H), 1.19 (d, $J$=8.5 Hz, 1H, $C^4$-H), 0.85 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 167.48, 162.09, 158.70, 146.19, 133.18, 131.66, 131.28, 128.00, 118.11 , 45.51, 40.75, 38.02, 36.96, 31.69, 31.29, 29.16, 26.29, 21.29; IR (KBr) $v$: 3422, 3285, 3189 (m, N—H), 3100 (w, =C—H), 1675 (s, C=O), 1641 (m, C=N), 683 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 369.18 $[M+H]^+$. Anal. calcd for C 65.19, H 6.57, N 15.20; found C 65.18, H 6.56, N 15.18.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(*o*-methylphenyl)methanone (**5b**): White granular, 85% yield. m.p. 104.2～104.4 ℃; $[\alpha]_D^{25}$ −20.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.57 (d, $J$=7.7 Hz, 1H, Ar-H), 7.46～7.40 (m, 1H, Ar-H), 7.29 (t, $J$=4.7 Hz, 2H, Ar-H), 6.79 (s, 2H, -$NH_2$), 5.23～5.20 (m, 1H, $C^3$-H), 3.06～2.84 (m, 2H, $C^{11}$-H), 2.42 (s, 3H, $CH_3$), 2.36～2.30 (m, 3H, $C^{10}$-H, $C^1$-H), 2.27～2.16 (m, 2H, $C^7$-H), 2.10～2.05 (m, 1H, $C^4$-H), 1.91 (t, $J$=5.0 Hz, 1H, $C^5$-H), 1.25 (s, 3H, $C^9$-H), 1.13 (d, $J$=8.5 Hz, 1H, $C^4$-H), 0.80 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 169.56, 162.18, 157.91, 146.16, 136.95, 132.55, 131.16, 130.64, 128.96, 125.11, 118.05, 45.35, 40.71, 37.96, 36.91, 31.66, 31.25, 29.11, 26.28, 21.27, 20.02; IR (KBr) $v$: 3425, 3281, 3195 (m, N—H), 3114 (w, =C—H), 1689 (s, C=O), 1645 (m, C=N), 668 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 383.20 $[M+H]^+$. Anal. calcd for C 65.94, H 6.85, N 14.65; found C 65.93, H 6.84, N 14.63.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(*m*-methylphen-

yl)-methanone (**5c**): White granular, 78% yield. m.p. 114.2～114.3 ℃; $[\alpha]_D^{25}$ −27.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.05 (d, *J*=7.7 Hz, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 7.43 (d, *J*=7.6 Hz, 1H, Ar-H), 7.38 (t, *J*=7.7 Hz, 1H, Ar-H), 6.89 (s, 2H, $NH_2$), 5.32～5.29 (m, 1H, $C^3$-H), 3.15～3.02 (m, 2H, $C^{11}$-H), 2.45 (s, 3H, $CH_3$), 2.45～2.38 (m, 3H, $C^{10}$-H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.10 (dd, *J*=4.5, 2.7 Hz, 1H, $C^4$-H), 2.04 (td, *J*=5.7, 1.2 Hz, 1H, $C^5$-H), 1.27 (s, 3H, $C^9$-H), 1.18 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.85 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 167.76, 161.97, 158.65, 146.18, 137.83, 133.96, 131.59, 128.46, 127.84, 118.08, 45.54, 40.75, 38.02, 36.91, 31.69, 31.28, 29.16, 26.27, 21.41, 21.27; IR (KBr) *v*: 3420, 3281, 3191 (m, N—H), 3110 (w, =C—H), 1679 (s, C=O), 1643 (m, C=N), 677 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 383.20 $[M+H]^+$. Anal. calcd for C 65.94, H 6.85, N 14.65; found C 65.93, H 6.83, N 14.64.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(*p*-methylphenyl)methanone (**5d**): White granular, 82% yield. m.p. 100.7～101.1 ℃; $[\alpha]_D^{25}$ −35.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.17 (d, *J*=8.3 Hz, 2H, Ar-H), 7.30 (d, *J*=8.1 Hz, 2H, Ar-H), 6.95 (s, 2H, -$NH_2$), 5.33～5.30 (m, 1H, $C^3$-H), 3.15～3.01 (m, 2H, $C^{11}$-H), 2.46 (s, 3H, $CH_3$), 2.45～2.35 (m, 3H, $C^{10}$-H, $C^1$-H), 2.32～2.20 (m, 2H, $C^7$-H), 2.11 (ddd, *J*=5.6, 3.0, 1.9 Hz, 1H, $C^4$-H), 2.06 (td, *J*=5.7, 1.3 Hz, 1H, $C^5$-H), 1.28 (s, 3H, $C^9$-H), 1.19 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.86 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 167.37, 161.80, 158.74, 146.22, 144.13, 131.48, 128.81, 128.75, 118.09, 45.51, 40.76, 38.01, 36.97, 31.70, 31.29, 29.16, 26.27, 21.75, 21.28; IR (KBr) *v*: 3420, 3283, 3189 (m, N—H), 3104 (w, =C—H), 1679 (s, C=O), 1643 (m, C=N), 631 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 383.21 $[M+H]^+$. Anal. calcd for C 65.94, H 6.85, N 14.65; found C 65.92, H 6.84, N 14.64.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2-methoxyphenyl)methanoe (**5e**): White granular, 83% yield. m.p. 108.9～109.1 ℃; $[\alpha]_D^{25}$ −23.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 7.53～7.47 (m, 2H, Ar-H), 7.03 (ddd, *J*=18.8, 12.8, 4.7 Hz, 2H, Ar-H), 6.76 (s, 2H, -$NH_2$), 5.22～5.19 (m, 1H, $C^3$-H), 3.85 (s, 3H, -$OCH_3$), 3.01～2.84 (m, 2H, $C^{11}$-H), 2.34～2.31 (m, 3H, $C^{10}$-H, $C^1$-H), 2.27～2.16 (m, 2H, $C^7$-H), 2.10～2.05 (m, 1H, $C^4$-H), 1.90 (td, *J*=5.7, 1.4 Hz, 1H, $C^5$-H), 1.24 (s, 3H, $C^9$-H), 1.13 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.80 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 167.90, 161.62, 157.65, 157.29, 146.25, 132.73, 129.60, 122.78, 120.05, 118.01, 111.41, 55.81, 45.36, 40.71, 37.95, 36.86, 31.71, 31.24, 29.11, 26.28, 21.29; IR (KBr) *v*: 3425, 3283, 3145 (m, N—H), 3083 (w, =C—H), 1677 (s, C=O), 1641 (m, C=N), 666 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 399.29 $[M+H]^+$. Anal. calcd for C 63.29, H 6.58, N 14.06; found C 63.28, H 6.57, N 14.04.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(3-methoxyphenyl)methanoe (**5f**): White granular, 85% yield, m.p. 94.3～94.6 ℃; $[\alpha]_D^{25}$ −37.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 7.85 (d, *J*=7.8 Hz, 1H, Ar-H), 7.77～7.74 (m, 1H, Ar-H), 7.40 (t, *J*=8.0 Hz, 1H, Ar-H), 7.17 (dd, *J*=8.3, 2.6 Hz, 1H, Ar-H), 7.06 (s, 2H, -$NH_2$), 5.33～5.29 (m, 1H, $C^3$-H), 3.88 (s, 3H, -$OCH_3$), 3.10～3.06 (m, 2H, $C^{11}$-H), 2.44～2.34 (m, 3H, $C^{10}$-H, $C^1$-H), 2.31～2.19 (m, 2H, $C^7$-H), 2.10 (dd, *J*=5.0, 2.2 Hz, 1H, $C^4$-H), 2.03 (td, *J*=5.7, 1.2 Hz, 1H, $C^5$-H), 1.27 (s, 3H, $C^9$-H), 1.18 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.84 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 167.27, 162.02, 159.09, 158.80, 146.11, 132.77, 129.02, 123.81, 119.64, 118.15, 115.85, 55.46, 45.52, 40.74, 38.01, 36.87, 31.68, 31.29, 29.15, 26.27, 21.25; IR (KBr) *v*: 3429, 3285, 3195 (m, N—H), 3116 (w, =C—H), 1675 (s, C=O), 1643 (m, C=N), 677 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 399.20 $[M+H]^+$. Anal. calcd for C 63.29, H 6.58, N 14.06; found C 63.27, H 6.57, N 14.05.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(4-(methoxymethyl)phenyl)methanone (**5g**): White granular, 72% yield. m.p. 111.9～112.2 ℃; $[\alpha]_D^{25}$ −26.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.35～8.29 (m, 2H, Ar-H), 6.98～6.91 (m, 2H, Ar-H), 6.81 (s, 2H, $NH_2$), 5.34～5.31 (m, 1H, $C^3$-H), 4.13 (q, *J*=7.0 Hz, 2H, -$CH_2$-), 3.14～3.04 (m, 2H, $C^{11}$-H), 2.45～2.41 (m, 2H, $C^{10}$-H), 2.38 (dt, *J*=8.5, 5.6 Hz, 1H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.13～2.09 (m, 1H, $C^4$-H), 2.08～2.05 (m, 1H, $C^5$-H), 1.47～1.44 (m, 3H, -$OCH_3$), 1.27 (s, 3H, $C^9$-H), 1.19 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.86 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 166.51, 163.12, 161.65, 158.77, 146.23, 134.03, 123.42, 118.07, 113.82, 63.80, 45.80, 45.54, 40.76, 38.02, 36.97, 31.70, 31.30, 29.17, 26.28, 21.30; IR (KBr) *v*: 3437, 3289, 3193 (m, N—H), 3110 (w, =C—H), 1681 (s, C=O), 1643 (m, C=N), 652 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 413.32 $[M+H]^+$. Anal. calcd for C 64.05, H 6.84, N 13.58; found C 64.04, H 6.83, N 13.56.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(4-ethylphenyl)-methanone (**5h**): White granular, 78% yield. m.p. 109.9～110.2 ℃; $[\alpha]_D^{25}$ −25.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.23～8.17 (m, 2H, Ar-H), 7.32 (d, *J*=8.4 Hz, 2H, Ar-H), 6.93 (s, 2H, $NH_2$), 5.34～5.31 (m, 1H, $C^3$-H), 3.17～3.01 (m, 2H, $C^{11}$-H), 2.76 (q, *J*=7.6 Hz, 2H, -$CH_2$-), 2.44 (td, *J*=7.9, 1.3 Hz, 2H, $C^{10}$-H), 2.38 (dt, *J*=8.5, 5.6 Hz, 1H, $C^1$-H), 2.32～2.21 (m, 2H, $C^7$-H), 2.14～2.09 (m, 1H, $C^4$-H), 2.07 (td, *J*=5.6, 1.3 Hz, 1H, $C^5$-H), 1.31 (d, *J*=7.6 Hz, 3H, $CH_3$), 1.28 (s, 3H, $C^9$-H), 1.20 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.86 (s, 3H, $C^8$-H);$^{13}C$ NMR(125 MHz, $CDCl_3$) *δ*: 167.36, 161.84, 158.74, 150.27, 146.23, 131.62, 128.99, 127.58, 118.10, 45.53, 40.76, 38.02, 36.99, 31.71, 31.30, 29.18, 29.03, 26.29, 21.31, 15.10; IR (KBr) *v*: 3431, 3283, 3189 (m, N—H), 3100 (w, =C—H), 1679 (s, C=O), 1641 (m, C=N), 666 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 397.32 $[M+H]^+$. Anal. calcd for C 66.63, H 7.12, N 14.13; found C 66.62, H 7.11, N 14.11.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2-fluorophenyl)methanone (**5i**): White granular, 84% yield. m.p. 139.3～139.5 ℃; $[\alpha]_D^{25}$ −35.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz,

$CDCl_3$) $\delta$: 7.73～7.67 (m, 1H, Ar-H), 7.57 (ddd, $J$=8.3, 5.2, 1.7 Hz, 1H, Ar-H), 7.30～7.24 (m, 1H, Ar-H), 7.18 (t, $J$=9.1 Hz, 1H, Ar-H), 6.88 (s, 2H, $NH_2$), 5.25～5.22 (m, 1H, $C^3$-H), 3.01-2.89 (m, 2H, $C^{11}$-H), 2.34 (ddd, $J$=11.2, 8.4, 3.4 Hz, 3H, $C^{10}$-H, $C^1$-H), 2.28～2.17 (m, 2H, $C^7$-H), 2.11～2.06 (m, 1H, $C^4$-H), 1.94 (td, $J$=5.7, 1.2 Hz, 1H, $C^5$-H), 1.25 (s, 3H, $C^9$-H), 1.15 (d, $J$=8.5 Hz, 1H, $C^4$-H), 0.81 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 165.11, 162.46, 161.02, 158.99, 157.76, 146.20, 133.75, 133.68, 130.66, 130.65, 123.75, 123.72, 121.56, 121.45, 118.01, 116.27, 116.10, 45.40, 40.72, 37.97, 36.82, 31.67, 31.25, 29.11, 26.28, 21.27; IR (KBr) $v$: 3408, 3293, 3225 (m, N—H), 3033 (w, =C—H), 1700 (s, C=O), 1650 (m, C=N), 662 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 387.32 $[M+H]^+$. Anal. calcd for C 62.15, H 6.00, N 14.50; found C 62.14, H 5.99, N 14.49.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(3-fluorophenyl)methanone (**5j**): White granular, 76% yield. m.p. 133.0～133.2 ℃; $[\alpha]_D^{25}$ −40.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 8.03 (ddd, $J$=10.7, 9.7, 4.8 Hz, 2H, Ar-H), 7.48 (td, $J$=8.1, 5.6 Hz, 1H, Ar-H), 7.33 (td, $J$=8.2, 2.3 Hz, 1H, Ar-H), 7.02 (s, 2H, $NH_2$), 5.34～5.30 (m, 1H, $C^3$-H), 3.15～3.03 (m, 2H, $C^{11}$-H), 2.42～2.37 (m, 3H, $C^{10}$-H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.13～2.08 (m, 1H, $C^4$-H), 2.04 (td, $J$=5.7, 1.2 Hz, 1H, $C^5$-H),1.27 (s, 3H, $C^9$-H), 1.18 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.85 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 165.97, 165.95, 162.95, 162.57, 160.98, 158.75, 146.07, 133.53, 133.47, 129.69, 129.63, 127.12, 127.09, 120.37, 120.20, 118.50, 118.31, 118.21, 45.52, 40.75, 38.02, 36.89, 31.67, 31.27, 29.16, 26.25, 21.26; IR (KBr) $v$: 3427, 3285, 3193 (m, N—H), 3108 (w, =C—H), 1683 (s, C=O), 1643 (m, C=N), 668 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 387.18 $[M+H]^+$. Anal. calcd for C 62.15, H 6.00, N 14.50; found C 62.13, H 5.99, N 14.48.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(4-fluorophenyl)methanone (**5k**): White granular, 77% yield. m.p. 136.5～136.7 ℃; $[\alpha]_D^{25}$ −42.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 8.37～8.32 (m, 2H, Ar-H), 7.20～7.15 (m, 2H, Ar-H), 6.93 (s, 2H, $NH_2$), 5.34～5.30 (m, 1H, $C^3$-H), 3.14～3.03 (m, 2H, $C^{11}$-H), 2.42 (td, $J$=7.8, 1.2 Hz, 2H, $C^{10}$-H), 2.38 (dt, $J$=8.6, 5.6 Hz, 1H, $C^1$-H), 2.32～2.21 (m, 2H, $C^7$-H), 2.12～2.10 (m, 1H, $C^4$-H), 2.05 (td, $J$=5.6, 1.4 Hz, 1H, $C^5$-H), 1.28 (s, 3H, $C^9$-H), 1.19 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.86 (s, 3H, $C^8$-H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 166.56, 166.13, 164.86, 162.33, 158.76, 146.15, 134.21, 127.76, 118.16, 115.35, 115.21, 45.54, 40.75, 38.02, 36.93, 31.69, 31.29, 29.16, 26.27, 21.28; IR (KBr) $v$: 3431, 3287, 3191 (m, N—H), 3110 (w, =C—H), 1679 (s, C=O), 1647 (m, C=N), 627 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 387.30 $[M+H]^+$. Anal. calcd for C 62.15, H 6.00, N 14.50; found C 62.14, H 5.98, N 14.49.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2-chlorophenyl)methanone (**5l**): White granular, 77% yield. m.p. 152.9～153.1 ℃; $[\alpha]_D^{25}$ −42.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.55 (d, $J$=7.8 Hz, 1H, Ar-H), 7.47 (d, $J$=3.8 Hz, 2H, Ar-H), 7.42～7.36 (m, 1H, Ar-H), 6.87 (s, 2H, $NH_2$), 5.20 (d, $J$=1.1 Hz, 1H, $C^3$-H), 2.98～2.83 (m, 2H, $C^{11}$-H), 2.34～2.31 (m, 3H, $C^{10}$-H, $C^1$-H), 2.26～2.15(m, 2H, $C^7$-H), 2.07 (s, 1H, $C^4$-H), 1.88 (t, $J$=5.6 Hz, 1H, $C^5$-H), 1.24 (s, 3H, $C^9$-H), 1.13 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.79 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 166.69, 162.70, 157.65, 146.22, 133.03, 131.89, 131.77, 129.85, 129.39, 126.37, 118.01, 45.33, 40.70, 37.96, 36.81, 31.67, 31.24, 29.12, 26.29, 21.28; IR (KBr) $v$: 3441, 3297, 3201 (m, N—H), 3105 (w, =C—H), 1701 (s, C=O), 1651 (m, C=N), 659 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 403.14 $[M+H]^+$. Anal. calcd for C 59.62, H 5.75, N 13.90; found C 59.61, H 5.74, N 13.88.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(3-chlorophenyl)methanone (**5m**): White granular, 76% yield. m.p. 103.3～103.5 ℃; $[\alpha]_D^{25}$ −37.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 8.25 (t, $J$=1.8 Hz, 1H, Ar-H), 8.17～8.12 (m, 1H, Ar-H), 7.60 (ddd, $J$=8.0, 2.0, 0.9 Hz, 1H, Ar-H), 7.44 (t, $J$=8.0 Hz, 1H, Ar-H), 7.02 (s, 2H, $NH_2$), 5.33～5.30 (m, 1H, $C^3$-H), 3.15～3.03 (m, 2H, $C^{11}$-H), 2.41 (dd, $J$=14.6, 6.8 Hz, 2H, $C^{10}$-H), 2.39～2.35 (m, 1H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.13～2.08 (m, 1H, $C^4$-H), 2.04 (td, $J$=5.6, 1.2 Hz, 1H, $C^5$-H), 1.27 (s, 3H, $C^9$-H), 1.18 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.85 (s, 3H, $C^8$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 165.99, 162.55, 158.69, 146.04, 134.18, 133.25, 133.16, 131.27, 129.38, 129,29, 118.20, 45.54, 40.75, 38.03, 36.82, 31.70, 31.28, 29.16, 26.28, 21.27; IR (KBr) $v$: 3427, 3287, 3193 (m, N—H), 3108 (w, =C—H), 1679 (s, C=O), 1639 (m, C=N), 660 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 403.29 $[M+H]^+$. Anal. calcd for C 59.62, H 5.75, N 13.90; found C 59.60, H 5.74, N 13.89.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2-bromophenyl)methanone (**5n**): White granular, 78% yield. m.p. 133.9～134.2 ℃; $[\alpha]_D^{25}$ −54.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.65 (dd, $J$=7.8, 0.8 Hz, 1H, Ar-H), 7.51 (dd, $J$=7.6, 1.8 Hz, 1H, Ar-H), 7.43 (td, $J$=7.6, 1.2 Hz, 1H, Ar-H), 7.39 (td, $J$=7.8, 1.6 Hz, 1H, Ar-H), 6.91 (s, 2H, $NH_2$), 5.21～5.18 (m, 1H, $C^3$-H), 2.97～2.83 (m, 2H, $C^{11}$-H), 2.32 (ddd, $J$=11.2, 7.6, 4.8 Hz, 3H, $C^{10}$-H, $C^1$-H), 2.26～2.15 (m, 2H, $C^7$-H), 2.07 (dd, $J$=7.2, 3.0 Hz, 1H, $C^4$-H), 1.87 (td, $J$=5.6, 1.2 Hz, 1H, $C^5$-H), 1.24 (s, 3H, $C^9$-H), 1.13 (d, $J$=8.6 Hz, 1H, $C^4$-H), 0.78 (s, 3H, $C^8$-H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 167.29, 162.66, 157.69, 146.23, 135.19, 132.93, 131.90, 129.33, 126.92, 119.98, 118.01, 45.31, 40.70, 37.96, 36.82, 31.68, 31.24, 29.12, 26.30, 21.29; IR (KBr) $v$: 3439, 3293, 3200 (m, N—H), 3110 (w, =C—H), 1702 (s, C=O), 1652 (m, C=N), 647 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 447.25 $[M+H]^+$. Anal. calcd for C 53.69, H 5.18, N 12.52; found C 53.68, H 5.17, N 12.50.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(3-bromophen-

yl)methanone (**5o**): White granular, 80% yield. m.p. 134.9～135.1 ℃; $[\alpha]_D^{25}$ −42.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) *δ*: 8.40 (s, 1H, Ar-H), 8.19 (dd, *J*=7.8, 0.8 Hz, 1H, Ar-H), 7.78～7.71 (m, 1H, Ar-H), 7.38 (t, *J*=7.8 Hz, 1H, Ar-H), 6.93 (s, 2H, $NH_2$), 5.31 (d, *J*=1.2 Hz, 1H, $C^3$-H), 3.19～3.01 (m, 2H, $C^{11}$-H), 2.42 (t, *J*=7.6 Hz, 2H, $C^{10}$-H), 2.37 (dt, *J*=8.6, 5.6 Hz, 1H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.13～2.08 (m, 1H, $C^4$-H), 2.08～2.02 (m, 1H, $C^5$-H), 1.27 (s, 3H, $C^9$-H), 1.19 (d, *J*=8.6 Hz, 1H, $C^4$-H), 0.85 (s, 3H, $C^8$-H); $^{13}C$ NMR (150 MHz, $CDCl_3$) *δ*: 165.88, 162.68, 158.64, 146.05, 136.06, 134.14, 133.47, 129.82, 129.53, 122.06, 118.20, 45.55, 40.75, 38.04, 36.80, 31.72, 31.29, 29.16, 26.30, 21.29; IR (KBr) *ν*: 3433, 3289, 3193 (m, N—H), 3104 (w, =C—H), 1683 (s, C=O), 1650 (m, C=N), 664 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 447.09 $[M+H]^+$. Anal. calcd for C 53.69, H 5.18, N 12.52; found C 53.67, H 5.17, N 12.51.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(4-bromophenyl)methanone (**5p**): White granular, 81% yield. m.p. 132.1～132.2 ℃; $[\alpha]_D^{25}$ −51.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.18～8.10 (m, 2H, Ar-H), 7.68～7.61 (m, 2H, Ar-H), 6.84 (s, 2H, $NH_2$), 5.33～5.29 (m, 1H, $C^3$-H), 3.17～2.97 (m, 2H, $C^{11}$-H), 2.40 (tdd, *J*=11.2, 8.2, 3.4 Hz, 3H, $C^{10}$-H, $C^1$-H), 2.32～2.21 (m, 2H, $C^7$-H), 2.11 (dd, *J*=4.5, 2.6 Hz, 1H, $C^4$-H), 2.08～2.01 (m, 1H, $C^5$-H), 1.28 (s, 3H, $C^9$-H), 1.19 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.85 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 166.47, 162.50, 158.60, 146.12, 132.82, 131.38, 130.43, 128.48, 118.19, 45.53, 40.75, 38.01, 36.92, 31.69, 31.29, 29.16, 26.28, 21.28; IR (KBr) *ν*: 3416, 3277, 3179 (m, N—H), 3093 (w, =C—H), 1683 (s, C=O), 1643 (m, C=N), 662 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 447.11 $[M+H]^+$. Anal. calcd for C 53.69, H 5.18, N 12.52; found C 53.68, H 5.17, N 12.50.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazole-4-carbonyl)benzonitrile (**5q**): White granular, 82% yield. m.p. 145.1～145.4 ℃; $[\alpha]_D^{25}$ −47.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.31 (d, *J*=8.3 Hz, 2H, Ar-H), 7.80 (d, *J*=8.3 Hz, 2H, Ar-H), 7.08 (s, 2H, $NH_2$), 5.29 (s, 1H, $C^3$-H), 3.15～2.96 (m, 2H, $C^{11}$-H), 2.38 (dt, *J*=11.6, 6.6 Hz, 3H, $C^{10}$-H, $C^1$-H), 2.32～2.20 (m, 2H, $C^7$-H), 2.12 (s, 1H, $C^4$-H), 2.00 (t, *J*=5.4 Hz, 1H, $C^5$-H), 1.28 (s, 3H, $C^9$-H), 1.17 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.84 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 165.69, 163.08, 158.62, 145.99, 135.55, 131.71, 131.57, 118.25, 117.79, 116.38, 45.54, 40.71, 38.01, 36.81, 31.68, 31.28, 29.13, 26.28, 21.27; IR (KBr) *ν*: 3435, 3293, 3189 (m, N—H), 3104 (w, =C—H), 2227 (m, CN), 1685 (s, C=O), 1652 (m, C=N), 691(w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 394.31 $[M+H]^+$. Anal. calcd for C 64.10, H 5.89, N 17.80; found C 64.09, H 5.88, N 17.78.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2-nitrophenyl)methanone (**5r**): White granular, 73% yield. m.p. 132.7～132.9 ℃; $[\alpha]_D^{25}$ −25.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) *δ*: 8.20 (dd, *J*=8.2, 0.9 Hz, 1H, Ar-H), 7.82 (td, *J*=7.5, 1.1 Hz, 1H, Ar-H), 7.75～7.71 (m, 1H, Ar-H), 7.68 (dd, *J*=7.6, 1.4 Hz, 1H, Ar-H), 6.90 (s, 2H, $NH_2$), 5.17 (dd, *J*=2.8, 1.4 Hz, 1H, $C^3$-H), 2.89～2.76 (m, 2H, $C^{11}$-H), 2.33 (dt, *J*=8.6, 5.6 Hz, 1H, $C^1$-H), 2.28～2.14 (m, 4H, $C^{10}$-H, $C^7$-H), 2.10～2.06 (m, 1H, $C^4$-H), 1.87 (td, *J*=5.6, 1.4 Hz, 1H, $C^5$-H), 1.26 (s, 3H, $C^9$-H), 1.13 (d, *J*=8.6 Hz, 1H, $C^4$-H), 0.79 (s, 3H, $C^8$-H); $^{13}C$ NMR (150 MHz, $CDCl_3$) *δ*: 165.82, 163.32, 157.29, 146.91, 146.06, 134.01, 131.56, 129.52, 129.43, 123.88, 117.99, 45.33, 40.70, 37.98, 36.57, 31.65, 31.23, 28.92, 26.29, 21.26; IR (KBr) *ν*: 3429, 3295, 3204 (m, N—H), 3118 (w, =C—H), 1710 (s, C=O), 1650 (m, C=N), 706 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 414.31 $[M+H]^+$. Anal. calcd for C 58.09, H 5.61, N 16.94; found C 58.08, H 5.60, N 16.92.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(4-nitrophenyl)methanone (**5s**): White granular, 79% yield. m.p. 135.5～135.6 ℃; $[\alpha]_D^{25}$ −20.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.41～8.32 (m, 4H, Ar-H), 7.07 (s, 2H, $NH_2$), 5.31～5.28 (m, 1H, $C^3$-H), 3.13～3.00 (m, 2H, $C^{11}$-H), 2.43～2.35 (m, 3H, $C^{10}$-H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.11 (dd, *J*=4.5, 2.8 Hz, 1H, $C^4$-H), 2.03～1.99 (m, 1H, $C^5$-H), 1.26 (s, 3H, $C^9$-H), 1.17 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.84 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 165.47, 163.22, 158.59, 150.12, 145.97, 137.12, 132.21, 123.05, 118.30, 45.55, 40.71, 38.00, 36.81, 31.66, 31.26, 29.14, 26.23, 21.26; IR (KBr) *ν*: 3431, 3289, 3195 (m, N—H), 3114 (w, =C—H), 1685 (s, C=O), 1647 (m, C=N), 710 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 414.33 $[M+H]^+$. Anal. calcd for C 58.09, H 5.61, N 16.94; found C 58.07, H 5.60, N 16.93.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (**5t**): White granular, 86% yield. m.p. 120.1～120.3 ℃; $[\alpha]_D^{25}$ −46.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 8.33 (d, *J*=8.2 Hz, 2H, Ar-H), 7.77 (d, *J*=8.4 Hz, 2H, Ar-H), 6.94 (s, 2H, $NH_2$), 5.32～5.28 (m, 1H, $C^3$-H), 3.12～3.00 (m, 2H, $C^{11}$-H), 2.45～2.39 (m, 2H, $C^{10}$-H), 2.39～2.35 (m, 1H, $C^1$-H), 2.31～2.20 (m, 2H, $C^7$-H), 2.13～2.09 (m, 1H, $C^4$-H), 2.03 (td, *J*=5.7, 1.2 Hz, 1H, $C^5$-H), 1.27 (s, 3H, $C^9$-H), 1.18 (d, *J*=8.5 Hz, 1H, $C^4$-H), 0.84 (s, 3H, $C^8$-H); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 166.22, 162.91, 158.58, 146.07, 134.94, 131.52, 124.99, 124.96, 118.23, 45.53, 40.72, 38.00, 36.89, 31.64, 31.24, 29.15, 26.21, 21.26; IR (KBr) *ν*: 3425, 3287, 3193 (m, N—H), 3097 (w, =C—H), 1687 (s, C=O), 1647 (m, C=N), 668 (w, C—S—C) $cm^{-1}$; ESI-MS *m/z*: 437.32 $[M+H]^+$. Anal. calcd for C 57.79, H 5.31, N 12.84; found C 57.78, H 5.30, N 12.82.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2,3-dichlorophenyl)methanone (**5u**): White granular, 84% yield. m.p. 161.2～161.4 ℃; $[\alpha]_D^{25}$ −35.0 (*c* 0.1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) *δ*: 7.52～7.50 (m, 2H, Ar-H), 7.38 (dd, *J*=8.4, 1.8 Hz, 1H, Ar-H), 6.84 (s, 2H, $NH_2$), 5.21 (dd, *J*=2.8, 1.4 Hz, 1H, $C^3$-H), 2.99～2.82 (m, 2H, $C^{11}$-H), 2.37～

2.31 (m, 3H, $C^{10}$-H, $C^{1}$-H), 2.28～2.17 (m, 2H, $C^{7}$-H), 2.11～2.07 (m, 1H, $C^{4}$-H), 1.88 (td, $J$=5.6, 1.4 Hz, 1H, $C^{5}$-H), 1.26 (s, 3H, $C^{9}$-H), 1.14 (d, $J$=8.6 Hz, 1H, $C^{4}$-H), 0.80 (s, 3H, $C^{8}$-H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 165.70, 163.04, 157.60, 146.17, 137.59, 132.92, 131.40, 130.45, 129.90, 126.86, 118.12, 45.40, 40.72, 37.94, 36.81, 31.62, 31.26, 29.10, 26.25, 21.26; IR (KBr) $v$: 3447, 3293, 3202 (m, N—H), 3102 (w, =C—H), 1693 (s, C=O), 1647 (m, C=N), 670 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 437.23 $[M+H]^+$. Anal. calcd for C 54.92, H 5.07, N 12.81; found C 54.91, H 5.05, N 12.80.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(2,4,6-trimethylphenyl)methanone (**5v**): White granular, 81% yield. m.p. 219.1～219.3 ℃; $[\alpha]_D^{25}$ −41.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 6.88 (s, 2H, Ar-H), 5.35 (s, 1H, $C^{3}$-H), 4.33 (s, 2H, $NH_2$), 3.24 (d, $J$=7.6 Hz, 2H, $C^{11}$-H), 2.43 (d, $J$=14.8 Hz, 2H, $C^{10}$-H), 2.39 (dt, $J$=8.6, 5.6 Hz, 1H, $C^{1}$-H), 2.31 (s, 3H, $CH_3$), 2.29～2.20 (m, 2H, $C^{7}$-H), 2.17 (s, 6H, $CH_3$), 2.10 (d, $J$=3.6 Hz, 2H, $C^{4}$-H, $C^{5}$-H), 1.29 (s, 3H, $C^{9}$-H), 1.20 (d, $J$=8.6 Hz, 1H, $C^{4}$-H), 0.86 (s, 3H, $C^{8}$-H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 162.97, 160.12, 145.79, 139.85, 134.51, 131.47, 128.25, 118.33, 45.61, 40.77, 38.09, 35.68, 31.70, 31.30, 30.41, 26.32. 21.33, 21.26, 19.26; IR (KBr) $v$: 3475, 3450, 3304, 3220 (m, N—H), 1689 (s, C=O), 1637 (m, C=N), 627 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 411.36 $[M+H]^+$. Anal. calcd for C 67.28, H 7.37, N 13.65; found C 67.27, H 7.35, N 13.64.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(cyclohexyl)methanone (**5w**): White granular, 78% yield. m.p. 169.1～169.3 ℃; $[\alpha]_D^{25}$ −37.0 ($c$ 0.1, $CHCl_3$);$^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 6.75 (s, 2H, $NH_2$), 5.35～5.30 (m, 1H, $C^{3}$-H), 3.35 (tt, $J$=11.6, 3.4 Hz, 1H, $C^{15}$-H), 3.15～2.99 (m, 2H, $C^{11}$-H), 2.46～2.36 (m, 3H, $C^{10}$-H, $C^{1}$-H), 2.31～2.19 (m, 2H, $C^{7}$-H), 2.10 (dd, $J$=10.6, 4.8 Hz, 2H, $C^{4}$-H, $C^{5}$-H), 2.01 (dd, $J$=12.8, 1.6 Hz, 2H, $C^{16}$-H), 1.88～1.82 (m, 2H, $C^{20}$-H), 1.78～1.72 (m, 1H, $C^{18}$-H), 1.55～1.47 (m, 2H, $C^{17}$-H), 1.43～1.34 (m, 2H, $C^{19}$-H), 1.30 (s, 3H, $C^{9}$-H), 1.28 (d, $J$=5.5 Hz, 1H, $C^{18}$-H), 1.20 (d, $J$=8.6 Hz, 1H, $C^{4}$-H), 0.87 (s, 3H, $C^{8}$-H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 176.87, 161.30, 157.32, 146.26, 118.05, 45.58, 42.79, 40.77, 38.06, 37.03, 31.69, 31.29, 29.17, 28.47, 26.32, 25.73, 25.37, 21.30; IR (KBr) $v$: 3435, 3287, 3188 (m, N—H), 3102 (w, =C—H), 1711 (s, C=O), 1649 (m, C=N), 669 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 375.36 $[M+H]^+$. Anal. calcd for C 64.14, H 8.07, N 14.96; found C 64.12, H 8.06, N 14.95.

(−)-(3-Amino-5-((2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)thio)-4*H*-1,2,4-triazol-4-yl)(thiophen-2-yl)-methanone (**5x**): White granular, 77% yield. m.p. 172.7～172.8 ℃; $[\alpha]_D^{25}$ −41.0 ($c$ 0.1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 8.41 (dd, $J$=3.9, 1.2 Hz, 1H, Ar-H), 7.79 (dd, $J$=5.0, 1.2 Hz, 1H, Ar-H), 7.24～7.18 (m, 1H, Ar-H), 6.90 (s, 2H, $NH_2$), 5.39～5.36 (m, 1H, $C^{3}$-H), 3.30～3.13 (m, 2H, $C^{11}$-H), 2.51 (dd, $J$=13.9, 4.0 Hz, 2H, $C^{10}$-H), 2.41 (dt, $J$=8.5, 5.6 Hz, 1H, $C^{1}$-H), 2.34～2.23 (m, 2H, $C^{7}$-H), 2.14 (t, $J$=5.2 Hz, 2H, $C^{4}$-H, $C^{5}$-H), 1.31 (s, 3H, $C^{9}$-H), 1.23 (d, $J$=8.5 Hz, 1H, $C^{4}$-H), 0.91 (s, 3H, $C^{8}$-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 162.44, 159.87, 158.24, 146.22, 138.16, 137.30, 132.62, 127.48, 118.05, 45.68, 40.79, 38.05, 36.59, 31.72, 31.34, 29.20, 26.33, 21.35; IR (KBr) $v$: 3414, 3281, 3189 (m, N—H), 3104 (w, =C—H), 1675 (s, C=O), 1639 (m, C=N), 662 (w, C—S—C) $cm^{-1}$; ESI-MS $m/z$: 375.14 $[M+H]^+$. Anal. calcd for C 57.73, H 5.92, N 14.96; found C 57.72, H 5.91, N 14.95.

### 4.6 *In vitro* antifungal activity test

The antifungal activities of all synthesized compounds **5a**～**5x** were evaluated for their *in vitro* antifungal activities against eight plant fungi through the agar dilution method at the concentrations of 50 μg/mL according to the literature.[49] The strains were incubated in petri dishes with Potato-Sugar-Agar (PSA) culture medium to culture new mycelia for the antifungal assay. Each tested compound was dissolved in acetone before mixing with diluted with Sorporl-144 (200 mg/L) as an emulsifier to prepare the solution with a concentration of 500 mg/L. The stock solution (1 mL) was added to the Potato-Sugar-Agar (PSA, 9 mL) culture medium. Then, mycelion dishes of 5 mm diameter were cut along the external edge of the mycelium, transferred to the center of flat containing the tested compound and put it in equilateral triangular style in triplicate. After culturing 48 h at (24±1) ℃ in the incubator, the expanded colony diameters of strains were measured and compared with that treated with aseptic distilled water, and then calculated the relative inhibition percentage. The corresponding aseptic distilled water without the test samples was served as a blank control and the commercial protective fungicide chlorothalonil was employed as the positive control. The inhibitory rate of the tested compound was calculated by the formula:

Inhibitory rate(%)=[(the average extended mycelium diameter of the blank assay−the average extended mycelium diameter after treatment with emulsion)/the average extended mycelium diameter of the blank assay]×100%.

### 4.7 3D-QSAR study

The 3D-QSAR model was performed using the Sybyl-X 2.1.1 software to investigate the relationship between the antifungal activity and the structure of the compounds according to our previous report.[50] The stable three-dimensional conformations of the compounds **5a**～**5v** were optimized by a conjugate gradient procedure based on the Tripos force field, with the termination convergence energy of 0.005 kcal/(mol•Å), a maximum iteration coefficient of 1000, and Gasteiger-Hückel charge as the parameters. The other parameters were set as the default values unless otherwise specified. The compound **5k** with the best activity against *P. piricola* was selected as the template compound, of which the atoms marked with an asterisk (Figure 6) were used as the common superimposed skeleton. Seventeen compounds using as the training set were aligned to form a superimposed model (Figure 7). Their inhibitor

rates against *P. piricola* were converted to the active factor (AF) values by the formula:

$$AF = \log\{I/[(100-I)\times M_w]\}$$

where $I$ was the inhibition rate at 50 μg/mL and $M_w$ was the molecular weight.

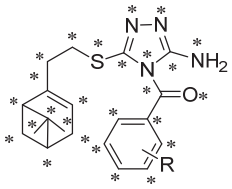


**Figure 6** Asterisk skeleton of title compounds

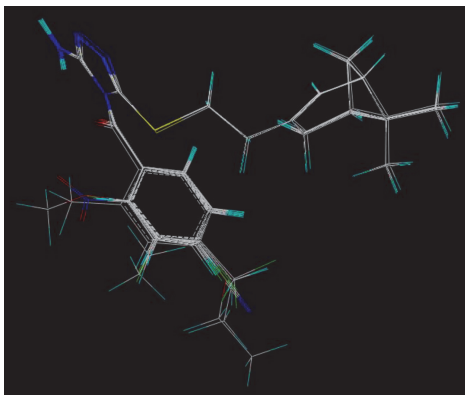


**Figure 7** Superposed mode of the compounds

### 4.8 Homologous modeling and molecular docking

Using the protein template of avian SDH (PDB code 2WQY) with carboxin as the inhibitor binding to the active site, the homology of amino acid sequence was aligned. The NCBI protein database (http://www.ncbi.nlm.nih.gov/) was used to search the SDH amino acid sequences (CEL53558.1, CCO28606.1, and CEL58000.1 refer to subunit B, C and D, respectively) of *R. solani*. SWISS-MODEL was used to build homology models of *R. solani* SDH based on the crystal structure of 2WQY.[51,52] The ligand carboxin (C/CBE144) was extracted, and all bound water molecules and other ligands were eliminated from this crystal complex. The homologous modeling in detail was included in the Supporting Information. Ramachandran plot showed that 95.23% of the residue was located in the favored regions of resulting model and the overall sequences identity was 54.25%. Subsequently, the representative compound **5k** with the best antifungal activity against *P. piricola* was selected to perform molecular docking on Sybyl X 2.1.1 program, and the homologous model of *R. solani* SDH was employed as the receptor.

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

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