

# Synthesis, antifungal activity, and DFT calculation study of novel 1-acyl-5- amino-1,2,4-triazole-thioether derivatives containing natural gem-dimethylcyclopropane ring structure

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## Research Article

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# Abstract

A series of novel 1-acyl-5-amino-1,2,4-triazole-thioether derivatives containing natural *gem*-dimethylcyclopropane ring structure were synthesized from natural biomass resource 3-carene. Their structures were confirmed by FT-IR, NMR, ESI-MS, and elemental analysis. The possible mechanism of regioselectivity for the *N*-acylation reaction of 5-amino-1,2,4-triazole with intermediate **4** was explored by DFT theoretical calculation. All the title compounds were evaluated for antifungal activity *in vitro* against eight plant pathogens, and some target compounds showed good inhibitory activity against the tested pathogens. For example, compounds **7f** and **7g** exhibited inhibitory rates of 81.6% and 80.9% against *C. arachidicola*, and *A. solani*, respectively, better than that of the commercial fungicide thifluzamide with corresponding inhibitory rates of 75.0% and 78.6%. Besides, against *G. zea*, most of the target compounds displayed better antifungal activity than the positive control thifluzamide.

## Introduction

Natural products offer a valuable and vast chemical space in which novel bioactive compounds will be discovered. 3-Carene is a naturally occurring bicyclic monoterpene which can be mainly found in some special turpentine oils[1–2], as well as in a variety of plant essential oils. It is one of the few natural products containing a *gem*-dimethylcyclopropane ring structure. 3-Carene and its derivatives exhibited a wide range of biological activities, including antifungal,[3–5] insecticidal,[6] herbicidal,[7] antiviral,[8] anti-inflammatory,[9] and anticancer[10] activities. In addition, various bioactive cyclopropane derivatives can be obtained by its chemical modification. As reported, some compounds containing cyclopropane structure have been developed as commercial fungicides (Cyproconazole), insecticides (Permethrin), herbicides (Cyclosulfamuron), and anticancer drugs (Cabozantinib) (Fig. 1).

Heterocyclic compounds, particularly those containing nitrogen, play important roles in biologically active compounds.[11] 1,2,4-Triazoles, an important class of five-membered heterocyclic compounds containing nitrogen,[12] were demonstrated to present versatile biological activities, such as antifungal,[13–14] antiviral,[15] herbicidal,[16] insecticidal,[17] DPP-4 inhibitory,[18] and anticancer[19] activities. Besides, the thioether linkage in bioactive molecules was thought to improve drug-likeness by lowering lipophilicity and acting as a favorable H-bond acceptor.[20] The thioether linkage was frequently observed within several pesticides and drugs.[21] For example, thioether-containing fenamidone is a powerful fungicide used in potato fields to control potato late blight (*Phytophthora infestans*).[22]

In light of the aforementioned clues and our previous works on the exploration of natural product-derived bioactive compounds,[23–26] a series of novel 1-acyl-5-amino-1,2,4-triazole-thioether derivatives containing natural *gem*-dimethylcyclopropane ring structure were designed and synthesized by the fusion of *gem*-dimethylcyclopropane ring and 1,2,4-triazole-thioether moiety. Their structures were confirmed by FT-IR, NMR, ESI-MS, and elemental analysis. In addition, *in vitro* antifungal activity of the target compounds was preliminarily evaluated, and the mechanism of regioselectivity in the *N*-acylation reaction of 5-amino-1,2,4-triazole was explored by DFT theoretical calculation.

## Results And Discussion

## Synthesis and characterization

A series of 1-acyl-5-amino-1,2,4-triazole-thioether derivatives containing natural *gem*-dimethylcyclopropane ring structure **7a** – **7r** were synthesized according to Scheme 1. Intermediates **1**, **2**, **3**, and **4** were prepared by our previously reported methods[24] using renewable biomass resource 3-carene as starting material. Intermediates **6a** – **6r** were prepared by nucleophilic substitution of 3-amino-5-mercapto-1,2,4-triazole with a series of alkyl halides.[27] Finally, intermediate **3** was chloridized to obtain acyl chloride **4**, which reacted with intermediates **6a** – **6r** by *N*-acylation reaction to afford 18 target compounds **7a** – **7r**.

All the target compounds were confirmed by FT-IR, NMR, ESI-MS, and elemental analysis. In the FT-IR spectra, the strong absorption signals at the vicinity of  $3434\text{ cm}^{-1}$  and  $1718\text{ cm}^{-1}$  were attributed to the stretching vibrations of N-H and C = O, respectively. The absorption bands at  $2956 - 2862\text{ cm}^{-1}$  and  $1651 - 1535\text{ cm}^{-1}$  were respectively assigned to the vibrations of the C-H and C = N. In the  $^1\text{H}$  NMR spectra, the characteristic signals at  $\delta$  7.13 – 6.75 ppm and  $\delta$  1.12 – 0.58 ppm were assigned to the hydrogens of the amino and *gem*-dimethylcyclopropane ring, respectively. Meanwhile, the  $^1\text{H}$  NMR spectrum showed a single wide  $-\text{NH}_2$  signal peak containing two hydrogens rather than two distinct separate carboxamide  $-\text{NH}-$  proton peaks, indicating that the *N*-acylation reaction took place on the N1 ring nitrogen of 1,2,4-triazole, rather than the exocyclic  $-\text{NH}_2$  group. Besides, the structure of target compound **7o** was further confirmed by NOESY. The result was shown in Fig. 2, the  $-\text{NH}_2$  of 1,2,4-triazole exhibited a strong correlation with the hydrogen atoms of C7, implying that the *N*-acylation reaction occurred on the N1 ring nitrogen of the 1,2,4-triazole. Actually, some similar situations have been observed in the reported literatures.[27–28] In the  $^{13}\text{C}$  NMR spectra, the characteristic signals for the carbonylic and *gem*-dimethylcyclopropane skeletal carbons of target compounds were found at about  $\delta$  174 ppm and  $\delta$  31 – 14 ppm, respectively. Besides, the peaks at about  $\delta$  161 – 157 ppm were assigned to the 1,2,4-triazole moiety scaffold carbons. Their molecular weights and elemental ratios (C, H, N) were confirmed by ESI-MS and elemental analyzer, respectively. Interestingly, it was found that the intermediate **6** could exist in three tautomers (i. e. N1-H, N2-H, and N4-H forms),[29] but only one new peak was monitored in the process of *N*-acylation reaction by HPLC.

## Antifungal activity

All the title compounds were tested for antifungal activity *in vitro* against eight plant pathogens, including *A. solani*, *C. arachidicola*, *G. zeae*, *C. orbiculare*, *F. oxysporum* f. sp. *cucumerinum*, *R. solani*, *B. maydis*, and *P. piricola*, using the agar dilution method, with the commercial fungicide thifluzamide as positive control. The results are listed in Table 1.

Table 1  
Antifungal activity of target compounds **7a** – **7r** at 50  $\mu\text{g/mL}$

Compd.	Relative inhibitory rate / %							
	<i>A. solani</i>	<i>C. arachidicola</i>	<i>G. zeae</i>	<i>C. orbiculare</i>	<i>F. oxysporum</i> <i>f. sp. cucumerinum</i>	<i>R. solani</i>	<i>B. maydis</i>	<i>P. piricola</i>
<b>7a</b>	53.9	55.9	57.1	57.1	49.3	33.3	56.0	0
<b>7b</b>	66.1	66.8	46.8	35.5	27.9	27.4	34.0	32.0
<b>7c</b>	58.8	61.4	49.7	43.3	31.4	21.6	32.0	17.3
<b>7d</b>	61.2	61.4	42.4	59.0	67.1	21.6	56.0	46.6
<b>7e</b>	71.0	66.8	71.8	37.5	31.4	21.6	28.0	27.1
<b>7f</b>	66.1	81.6	46.8	53.1	47.5	19.3	48.0	27.1
<b>7g</b>	80.9	66.8	64.4	43.3	27.9	24.0	26.0	0
<b>7h</b>	41.7	55.9	52.6	59.0	36.8	15.8	44.0	24.6
<b>7i</b>	63.7	66.8	49.7	37.5	40.4	21.6	32.0	39.3
<b>7j</b>	53.9	66.8	54.1	39.4	54.6	21.6	42.0	0
<b>7k</b>	66.1	64.1	52.6	55.1	51.1	39.1	58.0	32.0
<b>7l</b>	63.7	66.8	64.4	49.2	38.6	27.4	44.0	36.8
<b>7m</b>	66.1	66.8	64.4	51.2	42.1	24.0	42.0	41.7
<b>7n</b>	58.8	61.4	57.1	51.2	45.7	21.6	48.0	0
<b>7o</b>	45.3	22.5	31.2	19.5	13.8	31.7	14.8	13.8
<b>7p</b>	21.8	16.3	31.2	19.5	21.5	42.6	14.8	13.8
<b>7q</b>	51.2	22.5	31.2	29.0	13.8	42.6	24.3	36.9
<b>7r</b>	45.3	22.5	31.2	19.5	21.5	47.0	19.5	36.9
Thiﬂuzamide*	78.6	75.0	22.2	37.5	47.4	97.6	27.8	73.2
*The commercial fungicide as positive control.								

Most of the target compounds showed certain antifungal activity against the tested plant pathogens at a concentration of 50  $\mu\text{g/mL}$ . The compounds **7f** and **7g** showed inhibitory rates of 81.6% and 80.9% against *C. arachidicola*, and *A. solani*, respectively, better than that of the commercial fungicide thiﬂuzamide with corresponding inhibitory rates of 75.0% and 78.6%. Meanwhile, compound **7e** had inhibitory rates against *A. solani*, *C. arachidicola*, and *G. zeae* of 71.0%, 66.8%, and 71.8%, respectively, similar to that of thiﬂuzamide. On the whole, most target compounds displayed better antifungal activity than the positive control thiﬂuzamide against *G. zeae*.

## DFT calculation

The 5-amino-1,2,4-triazole exists in three tautomers, that is, there may be four possible products in the reaction, but only one product was observed during *N*-acylation the reaction. To further explore the mechanism of regioselectivity in the *N*-acylation reaction of 5-amino-1,2,4-triazole with intermediate **4**, the DFT theoretical calculation was carried out. The essence of *N*-acylation reaction is the reaction process of nucleophilic addition and then elimination, in which the charge density of nucleophiles is an important factor affecting the nucleophilic addition reaction. Based on this, the surface electrostatic potential (ESP) of intermediate **6f** (R = *p*-Cl Ph) was analyzed by Gaussian 16 and Multiwfn 3.8 software.[30–31]

As illustrated in Fig. 4, the minimum points existed at the exocyclic –NH<sub>2</sub> group and the N-N bond of the 1,2,4-triazole ring respectively, and the negative charge at the N-N bond in the 1,2,4-triazole ring was much greater than that of the exocyclic –NH<sub>2</sub> group, which would be conducive to the occurrence of the nucleophilic addition reaction. Besides, a maximum point existed at the exocyclic –NH<sub>2</sub> group, and the nucleophilic addition reaction was hindered by the positive charge. It was worth noting that a strong positive charge was shown in the N4 position of the 1,2,4-triazole ring, which was detrimental to the nucleophilic addition reaction. In the nucleophilic addition process, there may be four active intermediates. Then these four active intermediates and its corresponding products were optimized [DFT/B3LYP/6-31G (d, p)] and their energies were calculated [DFT/B3LYP/6-311++G (d, p)] by Gaussian 16 program package.

According to Fig. 5, in reaction process **1** (i. e. *N*-acylation reaction at N1 position), the intermediate and its corresponding product had the lowest energies, indicating that the obtained intermediate and product were relatively stable, namely, the *N*-acylation reaction was easier to occur at the N1 position. In reaction process **3** (i. e. *N*-acylation reaction at N4 position), the intermediate and its corresponding product had the highest energies, indicating that the obtained intermediate and product were unstable. Therefore, the *N*-acylation reaction was hard to occur at the N4 position. Based on the above clues, the mechanism of regioselectivity in the *N*-acylation reaction of 5-amino-1,2,4-triazole was preliminarily explained, which also provided a theoretical basis for conforming the structure of the target compounds.

## Experimental

### Materials and instruments

The NMR spectra were determined on a Bruker Avance III HD spectrometer at 600 MHz (Switzerland Bruker Co., Ltd., Zurich, Switzerland). The GC analysis was obtained on an Agilent 6890 GC (Agilent Technologies Inc., Santa Clara, CA, USA). The HPLC analysis was conducted on Waters 1525 HPLC instrument (Waters Co., Ltd., Milford, MA, USA) equipped with Waters 2998 PDA detector and column C18 5  $\mu$ m (4.6 mm  $\times$  150 mm). The FT-IR spectra were conducted by using a Nicolet iS50 FT-IR spectrometer (Thermo Scientific Co., Ltd., Madison, WI, USA). Mass spectra were performed on a TSQ Quantum Access MAX HPLC-MS instrument (Thermo Scientific Co., Ltd., Waltham, MA, USA). Elemental analyses were recorded by PE 2400 II elemental analyzer (PerkinElmer Instruments Co., Ltd., USA). 3-Carene (GC purity 98%) was provided by Wuzhou Pine Chemicals Co., Ltd. (Wuzhou, Guangxi, China). Other reagents were purchased from commercial suppliers and used as received.

### General procedure for the synthesis of intermediates **6a** – **6r**

3-Amino-5-mercapto-1,2,4-triazole (0.4 g, 3.4 mmol) was dispersed in CH<sub>3</sub>CN (20 mL), and Et<sub>3</sub>N was added. The mixture was refluxed for 1 h. Subsequently, the corresponding substituted alkyl halide (3.4 mmol) in CH<sub>3</sub>CN (20

mL) was added dropwise to the reaction system. The mixture was stirred and refluxed for 4 – 5 h. The mixture solution was concentrated under reduced pressure and extracted with EA after the reaction was completed. The separated organic layer was washed with distilled water and dried with anhydrous  $\text{MgSO}_4$ . Finally, the crude product was purified further in DCM by recrystallization to obtain intermediates **6a – 6r**.<sup>[27]</sup>

## General procedure for the synthesis of the title compounds **7a – 7r**

The intermediates **1**, **2**, **3**, and **4** were prepared by the method reported in our previous work.<sup>[24]</sup> Then, a solution of intermediate **4** (0.2g, 1.1 mmol) dissolved in dry DCM (10 mL) was slowly added to a mixed solution of the intermediate **5** (1.0 mmol) and  $\text{Et}_3\text{N}$  in dry DCM (20 mL) under an anhydrous atmosphere and with ice bath cooling. After the reaction was completed, some saturated aqueous  $\text{NaHCO}_3$  was added to quench the unreacted intermediate **4**. Subsequently, the DCM layer was separated, washed three times with distilled water, dried over anhydrous  $\text{MgSO}_4$ , and concentrated under reduced pressure. Finally, the crude product was purified on column chromatography (PE : EA = 5 : 1, V/V) to afford the target compounds (**7a – 7r**).

### 1-(5-Amino-3-((cyclopropylmethyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (**7a**)

Pale yellow liquid, yield: 84.0%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3436 (N-H), 2956, 2928, 2863 (C-H), 1719 (C = O), 1644 (C = N, Ar), 1485, 1378 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.03 (s, 2H, N-H), 3.02 (d,  $J$  = 7.2 Hz, 2H,  $\text{C}_{16}\text{-H}$ ), 2.91 (qd,  $J$  = 18.1, 7.3 Hz, 2H,  $\text{C}_7\text{-H}$ ), 1.40–1.33 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.31–1.26 (m, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.23–1.14 (m, 2H,  $\text{C}_{11}\text{-H}_b$  and  $\text{C}_{17}\text{-H}$ ), 1.10 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.91 (t,  $J$  = 7.3 Hz, 4H,  $\text{C}_{13}\text{-H}$  and  $\text{C}_8\text{-H}$ ), 0.65–0.58 (m, 3H,  $\text{C}_{18}\text{-H}$  and  $\text{C}_{10}\text{-H}$ ), 0.32 (q,  $J$  = 4.8 Hz, 2H,  $\text{C}_{19}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.33, 161.40, 157.19, 36.97, 31.12, 28.95, 26.70, 26.28, 23.10, 20.91, 17.15, 15.05, 14.06, 10.90, 5.85; ESI-MS  $m/z$ : 385.20  $[\text{M} + \text{H}]^+$  Anal. calcd. for  $\text{C}_{16}\text{H}_{26}\text{N}_4\text{OS}$ : C 59.59, H 8.13, N 17.37; found, C 59.62, H 8.10, N 17.34.

### 1-(5-Amino-3-((2-methylbenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (**7b**)

Pale yellow liquid, yield: 85.5%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3435 (N-H), 2955, 2928, 2862 (C-H), 1719 (C = O), 1643 (C = N, Ar), 1490 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J$  = 7.4 Hz, 1H,  $\text{C}_{19}\text{-H}$ ), 7.20–7.15 (m, 2H,  $\text{C}_{21}\text{-H}$  and  $\text{C}_{22}\text{-H}$ ), 7.15–7.09 (m, 1H,  $\text{C}_{20}\text{-H}$ ), 6.93 (s, 2H, N-H), 4.30 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.96 (dd,  $J$  = 18.2, 7.0 Hz, 1H,  $\text{C}_7\text{-H}_a$ ), 2.89 (dd,  $J$  = 18.2, 7.5 Hz, 1H,  $\text{C}_7\text{-H}_b$ ), 2.42 (s, 3H,  $\text{C}_{23}\text{-H}$ ), 1.43–1.34 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.31–1.25 (m, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.24–1.17 (m, 1H,  $\text{C}_{11}\text{-H}_b$ ), 1.11 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.94–0.89 (m, 4H,  $\text{C}_{13}\text{-H}$  and  $\text{C}_8\text{-H}$ ), 0.64–0.59 (m, 1H,  $\text{C}_{10}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.25, 160.99, 157.19, 136.93, 134.60, 130.50, 130.03, 127.82, 126.00, 33.50, 31.19, 28.94, 26.71, 26.26, 23.11, 20.81, 19.28, 17.16, 15.04, 14.07; ESI-MS  $m/z$ : 373.20  $[\text{M} + \text{H}]^+$  Anal. calcd. for  $\text{C}_{20}\text{H}_{28}\text{N}_4\text{OS}$ : C 64.48, H 7.58, N 15.04; found, C 64.49, H 7.61, N 15.05.

### 1-(5-Amino-3-((3-methylbenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (**7c**)

Pale yellow liquid, yield: 89.1%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3434 (N-H), 2955, 2926, 2862 (C-H), 1718 (C = O), 1643 (C = N, Ar), 1485 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23–7.16 (m, 3H,  $\text{C}_{18}\text{-H}$ ,  $\text{C}_{21}\text{-H}$  and  $\text{C}_{22}\text{-H}$ ), 7.06 (d,  $J$  = 6.8 Hz, 1H,  $\text{C}_{20}\text{-H}$ ), 6.91 (s, 2H, N-H), 4.25 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.94 (dd,  $J$  = 18.2, 7.0 Hz, 1H,  $\text{C}_7\text{-H}_a$ ), 2.88 (dd,  $J$  = 18.2, 7.6 Hz, 1H,  $\text{C}_7\text{-H}_b$ ),

H<sub>b</sub>), 2.33 (s, 3H, C<sub>23</sub>-H), 1.40–1.34 (m, 2H, C<sub>12</sub>-H), 1.31–1.26 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.23–1.18 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.10 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.95 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.92 (t, *J* = 7.3 Hz, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.64–0.59 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.25, 160.90, 157.18, 138.15, 137.00, 129.69, 128.32, 128.21, 126.09, 35.35, 31.16, 28.94, 26.70, 26.26, 23.11, 21.37, 20.81, 17.15, 15.05, 14.07; ESI-MS *m/z*: 373.21 [M + H]<sup>+</sup> Anal. calcd. for C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>OS: C 64.48, H 7.58, N 15.04; found, C 64.47, H 7.60, N 15.02.

#### **1-(5-Amino-3-((4-methylbenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7d)**

Pale yellow liquid, yield: 85.4%; FT-IR (KBr, ν/cm<sup>-1</sup>): 3435 (N-H), 2955, 2926, 2862 (C-H), 1719 (C = O), 1643 (C = N, Ar), 1514, 1485 (Ar); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.29 (d, *J* = 8.0 Hz, 2H, C<sub>18</sub>-H and C<sub>22</sub>-H), 7.10 (d, *J* = 7.9 Hz, 2H, C<sub>19</sub>-H and C<sub>21</sub>-H), 6.82 (s, 2H, N-H), 4.25 (s, 2H, C<sub>16</sub>-H), 2.94 (dd, *J* = 18.2, 7.0 Hz, 1H, C<sub>7</sub>-H<sub>a</sub>), 2.87 (dd, *J* = 18.2, 7.5 Hz, 1H, C<sub>7</sub>-H<sub>b</sub>), 2.32 (s, 3H, C<sub>23</sub>-H), 1.41–1.35 (m, 2H, C<sub>12</sub>-H), 1.31–1.26 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.24–1.18 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.10 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.95 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.94–0.89 (m, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.64–0.59 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.26, 160.94, 157.10, 137.11, 134.08, 129.14, 128.93, 35.15, 31.17, 28.94, 26.70, 26.26, 23.11, 21.12, 20.78, 17.15, 15.03, 14.07; ESI-MS *m/z*: 373.21 [M + H]<sup>+</sup> Anal. calcd. for C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>S: C 64.48, H 7.58, N 15.04; found, C 64.47, H 7.60, N 15.02.

#### **1-(5-Amino-3-((2-chlorobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7e)**

Pale yellow liquid, yield: 89.4%; FT-IR (KBr, ν/cm<sup>-1</sup>): 3434 (N-H), 2954, 2926, 2861 (C-H), 1719 (C = O), 1643 (C = N, Ar), 1473, 1443 (Ar); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.53 (dd, *J* = 7.1, 2.2 Hz, 1H, C<sub>19</sub>-H), 7.36 (dd, *J* = 7.5, 1.7 Hz, 1H, C<sub>22</sub>-H), 7.22–7.14 (m, 2H, C<sub>20</sub>-H and C<sub>21</sub>-H), 7.00 (s, 2H, N-H), 4.39 (s, 2H, C<sub>16</sub>-H), 2.95 (dd, *J* = 18.2, 7.0 Hz, 1H, C<sub>7</sub>-H<sub>b</sub>), 2.88 (dd, *J* = 18.2, 7.6 Hz, 1H, C<sub>7</sub>-H<sub>a</sub>), 1.42–1.33 (m, 2H, C<sub>12</sub>-H), 1.32–1.25 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.24–1.17 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.10 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.95 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.92 (t, *J* = 7.4 Hz, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.64–0.59 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.20, 160.60, 157.26, 135.06, 134.33, 130.97, 129.61, 128.84, 126.67, 33.00, 31.19, 28.94, 26.70, 26.26, 23.11, 20.77, 17.15, 15.03, 14.07; ESI-MS *m/z*: 393.14 [M + H]<sup>+</sup> Anal. calcd. for C<sub>19</sub>H<sub>25</sub>ClN<sub>4</sub>OS: C 58.08, H 6.41, N 14.26; found, C 58.10, H 6.39, N 14.28.

#### **1-(5-Amino-3-((4-chlorobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7f)**

Pale yellow liquid, yield: 88.4%; FT-IR (KBr, ν/cm<sup>-1</sup>): 3435 (N-H), 2956, 2928, 2862 (C-H), 1719 (C = O), 1643 (C = N, Ar), 1490, 1378 (Ar); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.4 Hz, 2H, C<sub>18</sub>-H and C<sub>22</sub>-H), 7.25 (d, *J* = 8.4 Hz, 2H, C<sub>19</sub>-H and C<sub>21</sub>-H), 6.87 (s, 2H, N-H), 4.23 (s, 2H, C<sub>16</sub>-H), 2.92 (dd, *J* = 18.2, 7.0 Hz, 1H, C<sub>7</sub>-H<sub>a</sub>), 2.84 (dd, *J* = 18.2, 7.6 Hz, 1H, C<sub>7</sub>-H<sub>b</sub>), 1.40–1.34 (m, 2H, C<sub>12</sub>-H), 1.29–1.25 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.24–1.17 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.10 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.94 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.93–0.89 (m, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.64–0.59 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.21, 160.44, 157.14, 135.93, 133.19, 130.33, 128.56, 34.64, 31.17, 28.93, 26.70, 26.24, 23.10, 20.75, 17.16, 15.02, 14.07; ESI-MS *m/z*: 393.14 [M + H]<sup>+</sup> Anal. calcd. for C<sub>19</sub>H<sub>25</sub>ClN<sub>4</sub>OS: C 58.08, H 6.41, N 14.26; found, C 58.05, H 6.41, N 14.29.

#### **1-(5-Amino-3-((2,6-dichlorobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7g)**

Pale yellow liquid, yield: 90.4%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3435, 3292 (N-H), 2955, 2928, 2862 (C-H), 1719 (C=O), 1644 (C=N, Ar), 1561, 1485 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (d,  $J$  = 8.1 Hz, 2H,  $\text{C}_{19}\text{-H}$  and  $\text{C}_{21}\text{-H}$ ), 7.16 (t,  $J$  = 8.1 Hz, 1H,  $\text{C}_{20}\text{-H}$ ), 6.97 (s, 2H, N-H), 4.66 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.94 (qd,  $J$  = 18.3, 7.3 Hz, 2H,  $\text{C}_7\text{-H}$ ), 1.39–1.34 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.32–1.27 (m, 1H, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.23–1.17 (m, 1H, 1H,  $\text{C}_{11}\text{-H}_b$ ), 1.11 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.92 (t,  $J$  = 7.3 Hz, 3H,  $\text{C}_{13}\text{-H}$ ), 0.93 – 0.90 (m, 1H,  $\text{C}_8\text{-H}$ ), 0.62 (m, 1H,  $\text{C}_{10}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.48, 160.64, 157.35, 136.17, 132.94, 129.34, 128.48, 31.65, 31.27, 29.03, 26.79, 26.36, 23.19, 20.93, 17.23, 15.15, 14.15; ESI-MS  $m/z$ : 428.12  $[\text{M} + \text{H}]^+$  Anal. calcd. for  $\text{C}_{19}\text{H}_{24}\text{Cl}_2\text{N}_4\text{OS}$ : C 53.40, H 5.66, N 13.11; found, C 53.43, H 5.67, N 13.10.

#### 1-(5-Amino-3-(benzylthio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7h)

Pale yellow liquid, yield: 88.1%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3435 (N-H), 2955, 2927, 2862 (C-H), 1718 (C=O), 1643 (C=N, Ar), 1495, 1454 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J$  = 7.2 Hz, 2H,  $\text{C}_{18}\text{-H}$  and  $\text{C}_{22}\text{-H}$ ), 7.29 (t,  $J$  = 7.8 Hz, 2H,  $\text{C}_{19}\text{-H}$  and  $\text{C}_{21}\text{-H}$ ), 7.27–7.22 (t,  $J$  = 7.3 Hz, 1H,  $\text{C}_{20}\text{-H}$ ), 6.84 (s, 2H, N-H), 4.28 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.94 (dd,  $J$  = 18.2, 7.0 Hz, 1H,  $\text{C}_7\text{-H}_a$ ), 2.87 (dd,  $J$  = 18.2, 7.6 Hz, 1H,  $\text{C}_7\text{-H}_b$ ), 1.40–1.34 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.31–1.26 (m, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.23–1.18 (m, 1H,  $\text{C}_{11}\text{-H}_b$ ), 1.10 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.92 (t,  $J$  = 7.3 Hz, 3H,  $\text{C}_{13}\text{-H}$ ), 0.93 – 0.90 (m, 1H,  $\text{C}_8\text{-H}$ ) 0.64–0.59 (m, 1H,  $\text{C}_{10}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.29, 160.86, 157.16, 137.25, 129.05, 128.48, 127.43, 35.42, 31.21, 28.97, 26.73, 26.29, 23.14, 20.81, 17.19, 15.07, 14.11; ESI-MS  $m/z$ : 359.19  $[\text{M} + \text{H}]^+$  Anal. calcd. for  $\text{C}_{19}\text{H}_{26}\text{N}_4\text{OS}$ : C 63.66, H 7.31, N 15.63; found, C 63.65, H 7.29, N 15.60.

#### 1-(5-Amino-3-((2-fluorobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7i)

Pale yellow liquid, yield: 84.6%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3435 (N-H), 2955, 2928, 2862 (C-H), 1719 (C=O), 1644 (C=N, Ar), 1491, 1455 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (td,  $J$  = 7.6, 1.5 Hz, 1H,  $\text{C}_{20}\text{-H}$ ), 7.25–7.20 (m, 1H,  $\text{C}_{19}\text{-H}$ ), 7.08–7.01 (m, 2H,  $\text{C}_{21}\text{-H}$  and  $\text{C}_{22}\text{-H}$ ), 6.89 (s, 2H, N-H), 4.31 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.94 (dd,  $J$  = 18.3, 7.0 Hz, 1H,  $\text{C}_7\text{-H}_a$ ), 2.87 (dd,  $J$  = 18.3, 7.6 Hz, 1H,  $\text{C}_7\text{-H}_b$ ), 1.41–1.34 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.32–1.26 (m, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.24–1.18 (m, 1H,  $\text{C}_{11}\text{-H}_b$ ), 1.10 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.94–0.90 (m, 4H,  $\text{C}_{13}\text{-H}$  and  $\text{C}_8\text{-H}$ ), 0.64–0.59 (m, 1H,  $\text{C}_{10}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.28, 160.98 (d,  $J$  = 247.68), 160.57, 157.21, 131.08 (d,  $J$  = 3.32), 129.26, 124.63 (d,  $J$  = 14.37), 123.97 (d,  $J$  = 4.42), 115.40 (d,  $J$  = 22.12), 31.15, 28.95, 28.40 (d,  $J$  = 3.49), 26.70, 26.28, 23.13, 20.75, 17.16, 15.03, 14.08; ESI-MS  $m/z$ : 377.19  $[\text{M} + \text{H}]^+$  Anal. calcd. for  $\text{C}_{19}\text{H}_{25}\text{FN}_4\text{OS}$ : C 60.61, H 6.69, N 14.88; found, C 60.60, H 6.71, N 14.88.

#### 1-(5-Amino-3-((3-fluorobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7j)

Pale yellow liquid, yield: 87.3%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3435 (N-H), 2956, 2928, 2863 (C-H), 1719 (C=O), 1643 (C=N, Ar), 1589, 1488 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28–7.22 (m, 1H,  $\text{C}_{21}\text{-H}$ ), 7.17 (d,  $J$  = 7.7 Hz, 1H,  $\text{C}_{22}\text{-H}$ ), 7.16–7.12 (m, 1H,  $\text{C}_{20}\text{-H}$ ), 7.02 (s, 2H, N-H), 6.93 (td,  $J$  = 8.3, 2.2 Hz, 1H,  $\text{C}_{18}\text{-H}$ ), 4.24 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.93 (dd,  $J$  = 18.2, 7.0 Hz, 1H,  $\text{C}_7\text{-H}_a$ ), 2.86 (dd,  $J$  = 18.2, 7.6 Hz, 1H,  $\text{C}_7\text{-H}_b$ ), 1.41–1.34 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.31–1.26 (m, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.23–1.16 (m, 1H,  $\text{C}_{11}\text{-H}_b$ ), 1.10 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.93–0.90 (m, 4H,  $\text{C}_{13}\text{-H}$  and  $\text{C}_8\text{-H}$ ), 0.64–0.59 (m, 1H,  $\text{C}_{10}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.23, 162.69 (d,  $J$  = 245.25 Hz), 160.37, 157.29, 139.99 (d,  $J$  = 6.63 Hz), 129.88 (d,  $J$  = 7.74 Hz), 124.61 (d,  $J$  = 3.32 Hz), 116.01 (d,  $J$  = 22.12 Hz), 114.34 (d,  $J$  =



21.01 Hz), 34.77 (d,  $J = 1.7$  Hz), 31.20, 28.94, 26.67, 26.27, 23.12, 20.76, 17.16, 15.01, 14.06; ESI-MS  $m/z$ : 377.17  $[M + H]^+$  Anal. calcd. for  $C_{19}H_{25}FN_4OS$ : C 60.61, H 6.69, N 14.88; found, C 60.61, H 6.70, N 14.85.

**1-(5-Amino-3-((4-fluorobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7k)**

Pale yellow liquid, yield: 86.3%; FT-IR (KBr,  $\nu/cm^{-1}$ ): 3436 (N-H), 2956, 2929, 2863 (C-H), 1720 (C = O), 1643 (C = N, Ar), 1509, 1378 (Ar);  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.40–7.34 (m, 2H,  $C_{18}$ -H and  $C_{22}$ -H), 7.00–6.93 (m, 2H,  $C_{19}$ -H and  $C_{21}$ -H), 6.80 (s, 2H, N-H), 4.25 (s, 2H,  $C_{16}$ -H), 2.93 (dd,  $J = 18.2, 7.0$  Hz, 1H,  $C_7$ -H<sub>a</sub>), 2.86 (dd,  $J = 18.2, 7.6$  Hz, 1H,  $C_7$ -H<sub>b</sub>), 1.41–1.34 (m, 2H,  $C_{12}$ -H), 1.30–1.26 (m, 1H,  $C_{11}$ -H<sub>a</sub>), 1.24–1.17 (m, 1H,  $C_{11}$ -H<sub>b</sub>), 1.10 (s, 3H,  $C_{14}$ -H or  $C_{15}$ -H), 0.94 (s, 3H,  $C_{14}$ -H or  $C_{15}$ -H), 0.94–0.89 (m, 4H,  $C_{13}$ -H and  $C_8$ -H), 0.65–0.59 (m, 1H,  $C_{10}$ -H);  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  174.24, 162.09 (d,  $J = 245.85$  Hz), 160.64, 157.12, 133.09 (d,  $J = 3.32$  Hz), 130.63 (d,  $J = 7.74$  Hz), 115.32 (d,  $J = 22.11$  Hz), 34.63, 31.18, 28.94, 26.71, 26.26, 23.11, 20.77, 17.17, 15.03, 14.07; ESI-MS  $m/z$ : 377.18  $[M + H]^+$  Anal. calcd. for  $C_{19}H_{25}FN_4OS$ : C 60.61, H 6.69, N 14.88; found, C 60.59, H 6.72, N 14.85.

**1-(5-Amino-3-((3-methoxybenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7l)**

Pale yellow liquid, yield: 87.3%; FT-IR (KBr,  $\nu/cm^{-1}$ ): 3436 (N-H), 2955, 2862 (C-H), 1719 (C = O), 1640 (C = N, Ar), 1600, 1585 (Ar);  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.21 (t,  $J = 7.9$  Hz, 1H,  $C_{21}$ -H), 6.98 (d,  $J = 7.6$  Hz, 1H,  $C_{22}$ -H), 6.97–6.95 (m, 1H,  $C_{18}$ -H), 6.93 (s, 2H, N-H), 6.79 (dd,  $J = 8.2, 2.2$  Hz, 1H,  $C_{20}$ -H), 4.25 (s, 2H,  $C_{16}$ -H), 3.78 (s, 3H,  $C_{23}$ -H), 2.94 (dd,  $J = 18.2, 7.0$  Hz, 1H,  $C_7$ -H<sub>a</sub>), 2.87 (dd,  $J = 18.2, 7.5$  Hz, 1H,  $C_7$ -H<sub>b</sub>), 1.41–1.34 (m, 2H,  $C_{12}$ -H), 1.31–1.25 (m, 1H,  $C_{11}$ -H<sub>a</sub>), 1.24–1.17 (m, 1H,  $C_{11}$ -H<sub>b</sub>), 1.10 (s, 3H,  $C_{14}$ -H or  $C_{15}$ -H), 0.95 (s, 3H,  $C_{14}$ -H or  $C_{15}$ -H), 0.93–0.90 (m, 4H,  $C_{13}$ -H and  $C_8$ -H), 0.64–0.58 (m, 1H,  $C_{10}$ -H);  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  174.26, 160.74, 159.65, 157.19, 138.67, 129.43, 121.35, 114.68, 112.85, 55.16, 35.38, 31.18, 28.94, 26.67, 26.26, 23.11, 20.79, 17.14, 15.02, 14.06; ESI-MS  $m/z$ : 389.19  $[M + H]^+$  Anal. calcd. for  $C_{20}H_{28}N_4O_2S$ : C 61.83, H 7.26, N 14.42; found, C 61.81, H 7.23, N 14.41.

**1-(5-Amino-3-((4-methoxybenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7m)**

Pale yellow liquid, yield: 89.5%; FT-IR (KBr,  $\nu/cm^{-1}$ ): 3441 (N-H), 2955, 2930, 2858 (C-H), 1719 (C = O), 1635 (C = N, Ar), 1512 (Ar);  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.31 (d,  $J = 8.6$  Hz, 2H,  $C_{18}$ -H and  $C_{22}$ -H), 7.13 (s, 2H, N-H), 6.82 (d,  $J = 8.7$  Hz, 2H,  $C_{19}$ -H and  $C_{21}$ -H), 4.23 (s, 2H,  $C_{16}$ -H), 3.77 (s, 3H,  $C_{23}$ -H), 2.94 (dd,  $J = 18.2, 7.0$  Hz, 1H,  $C_7$ -H<sub>a</sub>), 2.89 (dd,  $J = 18.2, 7.5$  Hz, 1H,  $C_7$ -H<sub>b</sub>), 1.39–1.35 (m, 2H,  $C_{12}$ -H), 1.29–1.26 (m, 1H,  $C_{11}$ -H<sub>a</sub>), 1.23–1.17 (m, 1H,  $C_{11}$ -H<sub>b</sub>), 1.10 (s, 3H,  $C_{14}$ -H or  $C_{15}$ -H), 0.95 (s, 3H,  $C_{14}$ -H or  $C_{15}$ -H), 0.92–0.90 (m, 4H,  $C_{13}$ -H and  $C_8$ -H), 0.63–0.59 (m, 1H,  $C_{10}$ -H);  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  174.20, 160.61, 157.25, 130.18, 129.02, 127.61, 113.85, 55.21, 34.91, 31.17, 28.93, 26.69, 26.25, 23.10, 20.77, 17.14, 15.03, 14.06; ESI-MS  $m/z$ : 389.19  $[M + H]^+$  Anal. calcd. for  $C_{20}H_{28}N_4O_2S$ : C 61.83, H 7.26, N 14.42; found, C 61.80, H 7.26, N 14.45.

**1-(5-Amino-3-((2-bromobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7n)**

Pale yellow liquid, yield: 89.7%; FT-IR (KBr,  $\nu/cm^{-1}$ ): 3434, 3292 (N-H), 2955, 2928, 2862 (C-H), 1719 (C = O), 1643 (C = N, Ar), 1485, 1439 (Ar);  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.61–7.53 (m, 2H,  $C_{19}$ -H and  $C_{22}$ -H), 7.25 (td,  $J = 7.5, 1.0$  Hz, 1H,  $C_{21}$ -H), 7.14 (td,  $J = 7.7, 1.6$  Hz, 1H,  $C_{20}$ -H), 6.84 (s, 2H, N-H), 4.43 (s, 2H,  $C_{16}$ -H), 2.97 (dd,  $J = 18.2$ ,

7.0 Hz, 1H, C<sub>7</sub>-H<sub>a</sub>), 2.90 (dd, *J* = 18.2, 7.6 Hz, 1H, C<sub>7</sub>-H<sub>b</sub>), 1.43–1.36 (m, 2H, C<sub>12</sub>-H), 1.34–1.28 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.26–1.19 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.12 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.97 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.94 (t, *J* = 7.3 Hz, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.66–0.61 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.23, 160.65, 157.14, 136.75, 132.94, 131.02, 129.05, 127.32, 124.76, 35.69, 31.21, 28.94, 26.71, 26.26, 23.11, 20.77, 17.16, 15.04, 14.08; ESI-MS *m/z*: 438.11 [M + H]<sup>+</sup> Anal. calcd. for C<sub>19</sub>H<sub>25</sub>BrN<sub>4</sub>OS: C 52.17, H 5.76, N 12.81; found, C 52.15, H 5.79, N 12.80.

#### **1-(5-Amino-3-((2-nitrobenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7o)**

Pale yellow solid, m.p. 119.8–121.3°C, yield: 91.1%; FT-IR (KBr, ν/cm<sup>-1</sup>): 3409 (N-H), 2955, 2922, 2861 (C-H), 1729 (C = O), 1651 (C = N, Ar), 1525, 1497 (Ar); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.01 (dd, *J* = 8.2, 1.1 Hz, 1H, C<sub>19</sub>-H), 7.70 (dd, *J* = 7.7, 1.0 Hz, 1H, C<sub>22</sub>-H), 7.53 (td, *J* = 7.6, 1.2 Hz, 1H, C<sub>21</sub>-H), 7.44–7.37 (m, 1H, C<sub>20</sub>-H), 6.75 (s, 2H, N-H), 4.62 (s, 2H, C<sub>16</sub>-H), 2.91 (dd, *J* = 18.3, 7.0 Hz, 1H, C<sub>7</sub>-H<sub>a</sub>), 2.84 (dd, *J* = 18.3, 7.6 Hz, 1H, C<sub>7</sub>-H<sub>b</sub>), 1.42–1.34 (m, 2H, C<sub>12</sub>-H), 1.33–1.26 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.24–1.17 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.10 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.95 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.94–0.88 (m, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.65–0.59 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.17, 160.50, 157.12, 148.49, 133.85, 133.10, 132.40, 128.45, 125.13, 32.33, 31.15, 28.94, 26.69, 26.26, 23.11, 20.73, 17.16, 15.02, 14.07; ESI-MS *m/z*: 404.16 [M + H]<sup>+</sup> Anal. calcd. for C<sub>19</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>S: C 56.56, H 6.25, N 17.36; found, C 56.55, H 6.25, N 17.35.

#### **1-(5-Amino-3-((2-(trifluoromethyl)benzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7p)**

Pale yellow liquid, yield: 87.7%; FT-IR (KBr, ν/cm<sup>-1</sup>): 3438 (N-H), 2956, 2925, 2858 (C-H), 1720 (C = O), 1640 (C = N, Ar), 1496, 1466 (Ar); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.73 (d, *J* = 7.8 Hz, 1H, C<sub>19</sub>-H), 7.64 (d, *J* = 7.8 Hz, 1H, C<sub>22</sub>-H), 7.48 (t, *J* = 7.6 Hz, 1H, C<sub>20</sub>-H), 7.36 (t, *J* = 7.6 Hz, 1H, C<sub>20</sub>-H), 6.85 (s, 2H, N-H), 4.50 (s, 2H, C<sub>16</sub>-H), 2.87 (qd, *J* = 18.2, 7.3 Hz, 2H, C<sub>7</sub>-H), 1.39–1.32 (m, 2H, C<sub>12</sub>-H), 1.28–1.23 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.21–1.14 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.09 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.92 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.91–0.88 (m, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.62–0.58 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.32, 160.59, 157.23, 135.97, 132.04, 131.16, 128.60 (q, *J* = 29.85 Hz), 127.49, 126.07 (q, *J* = 5.53 Hz), 124.31 (q, *J* = 274.22 Hz), 31.71 (d, *J* = 1.96 Hz), 31.11, 28.92, 26.63, 26.26, 23.09, 20.78, 17.15, 14.96, 14.02; ESI-MS *m/z*: 427.17 [M + H]<sup>+</sup> Anal. calcd. for C<sub>20</sub>H<sub>25</sub>F<sub>3</sub>N<sub>4</sub>OS: C 56.32, H 5.91, N 13.14; found, C 56.35, H 5.90, N 13.17.

#### **1-(5-Amino-3-((4-vinylbenzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7q)**

Pale yellow liquid, yield: 85.7%; FT-IR (KBr, ν/cm<sup>-1</sup>): 3435 (N-H), 2955, 2928, 2862 (C-H), 1719 (C = O), 1643 (C = N, Ar), 1485, 1378 (Ar); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.36 (d, *J* = 8.3 Hz, 2H, C<sub>19</sub>-H and C<sub>21</sub>-H), 7.33 (d, *J* = 8.3 Hz, 2H, C<sub>18</sub>-H and C<sub>22</sub>-H), 6.84 (s, 2H, N-H), 6.68 (dd, *J* = 17.6, 10.9 Hz, 1H, C<sub>23</sub>-H), 5.72 (d, *J* = 17.6 Hz, 1H, C<sub>24</sub>-H<sub>a</sub>), 5.23 (d, *J* = 10.9 Hz, 1H, C<sub>24</sub>-H<sub>b</sub>), 4.26 (s, 2H, C<sub>16</sub>-H), 2.93 (dd, *J* = 18.2, 7.0 Hz, 1H, C<sub>7</sub>-H<sub>b</sub>), 2.86 (dd, *J* = 18.2, 7.6 Hz, 1H, C<sub>7</sub>-H<sub>a</sub>), 1.41–1.33 (m, 2H, C<sub>12</sub>-H), 1.31–1.26 (m, 1H, C<sub>11</sub>-H<sub>a</sub>), 1.23–1.17 (m, 1H, C<sub>11</sub>-H<sub>b</sub>), 1.10 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.95 (s, 3H, C<sub>14</sub>-H or C<sub>15</sub>-H), 0.94–0.89 (m, 4H, C<sub>13</sub>-H and C<sub>8</sub>-H), 0.64–0.58 (m, 1H, C<sub>10</sub>-H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.24, 160.74, 157.11, 136.80, 136.77, 136.35, 129.21, 126.26, 113.93, 35.16, 31.17, 28.93, 26.69, 26.25, 23.11, 20.77, 17.15, 15.03, 14.07; ESI-MS *m/z*: 385.20 [M + H]<sup>+</sup> Anal. calcd. for C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>OS: C 65.59, H 7.34, N 14.57; found, C 65.60, H 7.34, N 14.55.

## 1-(5-Amino-3-((4-(methylthio)benzyl)thio)-1 H -1,2,4-triazol-1-yl)-2-(2,2-dimethyl-3-propylcyclopropyl)ethan-1-one (7r)

Pale yellow liquid, yield: 92.1%; FT-IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3435 (N-H), 2955, 2924, 2861 (C-H), 1718 (C=O), 1641 (C=N, Ar), 1492, 1378 (Ar);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (d,  $J$  = 8.3 Hz, 2H,  $\text{C}_{19}\text{-H}$  and  $\text{C}_{21}\text{-H}$ ), 7.18 (d,  $J$  = 8.3 Hz, 2H,  $\text{C}_{18}\text{-H}$  and  $\text{C}_{22}\text{-H}$ ), 6.85 (s, 2H, N-H), 4.23 (s, 2H,  $\text{C}_{16}\text{-H}$ ), 2.93 (dd,  $J$  = 18.2, 7.0 Hz, 1H,  $\text{C}_7\text{-H}_a$ ), 2.86 (dd,  $J$  = 18.2, 7.6 Hz, 1H,  $\text{C}_7\text{-H}_b$ ), 2.46 (s, 3H,  $\text{C}_{23}\text{-H}$ ), 1.41–1.34 (m, 2H,  $\text{C}_{12}\text{-H}$ ), 1.31–1.25 (m, 1H,  $\text{C}_{11}\text{-H}_a$ ), 1.24–1.18 (m, 1H,  $\text{C}_{11}\text{-H}_b$ ), 1.10 (s, 3H, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.95 (s, 3H, 3H,  $\text{C}_{14}\text{-H}$  or  $\text{C}_{15}\text{-H}$ ), 0.94–0.90 (m, 4H,  $\text{C}_{13}\text{-H}$  and  $\text{C}_8\text{-H}$ ), 0.64–0.59 (m, 1H,  $\text{C}_{10}\text{-H}$ );  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.23, 160.70, 157.11, 137.62, 134.05, 129.49, 126.58, 34.98, 31.18, 28.93, 26.70, 26.25, 23.11, 20.76, 17.15, 15.83, 15.04, 14.08. ESI-MS  $m/z$ : 405.18  $[\text{M} + \text{H}]^+$  Anal. calcd. for  $\text{C}_{20}\text{H}_{28}\text{N}_4\text{OS}_2$ : C 59.37, H 6.98, N 13.85; found, C 59.35, H 7.01, N 13.83.

## Antifungal activity assay

The *in vitro* antifungal activities of all the target compounds against eight plant pathogens were tested using the agar dilution method, and the plant pathogens used in the test were obtained from the Biological Assay Center, Nankai University, China. The commercial fungicide thifluzamide was used as positive control. The PSA culture plate containing the corresponding target compound solution at a concentration of 50  $\mu\text{g}/\text{mL}$  was incubated at  $24 \pm 1^\circ\text{C}$  for 48 hours, and then, the relative inhibition rate was calculated by comparing the mycelium diameter of the fungus treated with the target compound solution with that of the blank control, with 3 duplicates per experiment.

## DFT calculation

The conformers were initially optimized at DFT/B3LYP/6-31G (d, p) level in DCM using the IEFPCM polarizable conductor calculation model, and single point energy of target compounds and intermediates were calculated at DFT/B3LYP/6-311++G (d, p) level. All theoretical calculations were carried out on the high-performance computing platform of Guangxi University, and the results were viewed on GaussView 6.0, Multiwfn 3.8, and CYLview 20 (Legault, C. Y., Université de Sherbrooke, 2020 (<http://www.cylview.org>)) software.

## Conclusion

In summary, 18 novel 1-acyl-5-amino-1,2,4-triazole-thioether derivatives containing natural *gem*-dimethylcyclopropane ring structure were synthesized from natural biomass resource 3-carene and characterized by FT-IR, NMR, ESI-MS, and elemental analysis. Besides, the possible mechanism of regioselectivity for the *N*-acylation reaction of 5-amino-1,2,4-triazole with intermediate **4** was explored by DFT theoretical calculation. The preliminary antifungal activity test showed that the target compounds displayed certain antifungal activity against the tested eight plant pathogens. For example, the compounds **7f** and **7g** showed inhibitory rates of 81.6% and 80.9% against *C. arachidicola*, and *A. solani*, respectively, better than that of the commercial fungicide thifluzamide with corresponding inhibitory rates of 75.0% and 78.6%. Meanwhile, compound **7e** had inhibitory rates against *A. solani*, *C. arachidicola*, and *G. zeae* of 71.0%, 66.8%, and 71.8%, respectively, similar to that of thifluzamide. On the whole, most target compounds displayed better antifungal activity than the positive control thifluzamide against *G. zeae*. Overall, compounds **7f** and **7g** deserved further study as lead compounds.

## Declarations

**Supplementary Information** The online version contains supplementary material available at [https:// doi.org/](https://doi.org/).

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**Ethical Approval** Not applicable.

**Competing interests** The authors declare no competing financial interests.

**Authors' contributions** Yucheng Cui carried out the experimental work, participated in the discussion of biological activities, and wrote the paper; Guishan Lin and Wengui Duan constructed the target compound structure, designed the experimental scheme, directed and supervised the whole experimentation, and theoretical calculation, discussed the biological activities, and revised the paper; Xiaocui Wu, Kaiyue Wu, and Baoyu Li participated in the synthesis of target compounds and the discussion of biological activities. All authors have read and agreed to the published version of the manuscript.

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**Availability of data and materials** All the data can be accessed in Supplementary Information.

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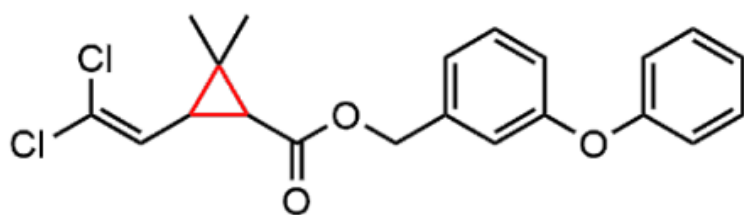
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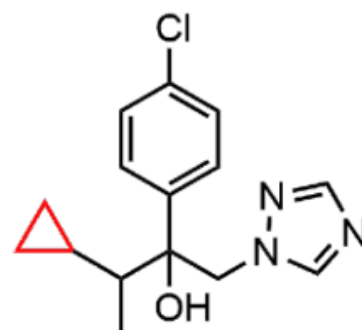
## Scheme

Scheme 1 is available in the Supplementary Files section.

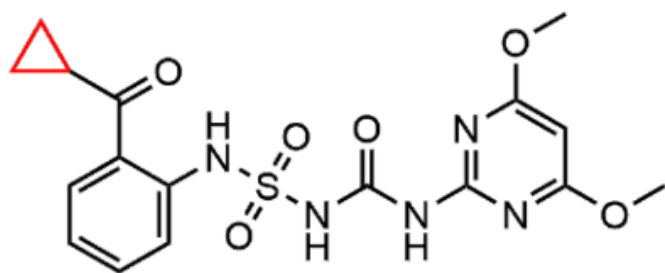
## Figures



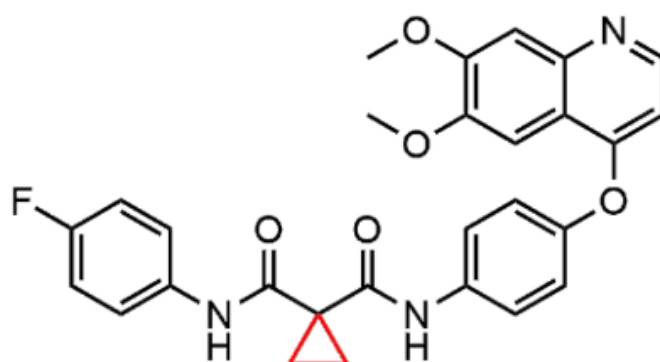
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**Cyproconazole**



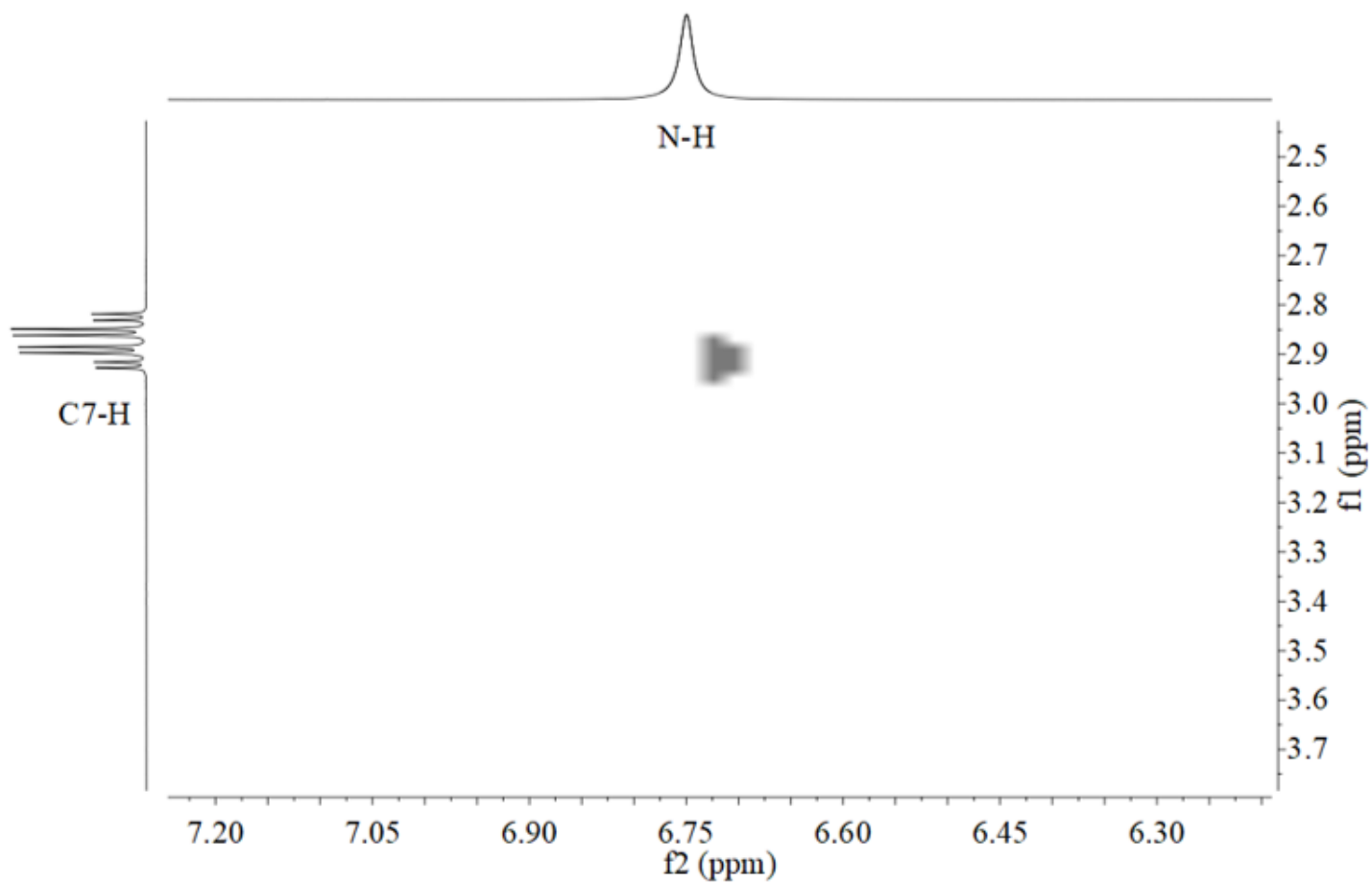
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**Cabozantinib**

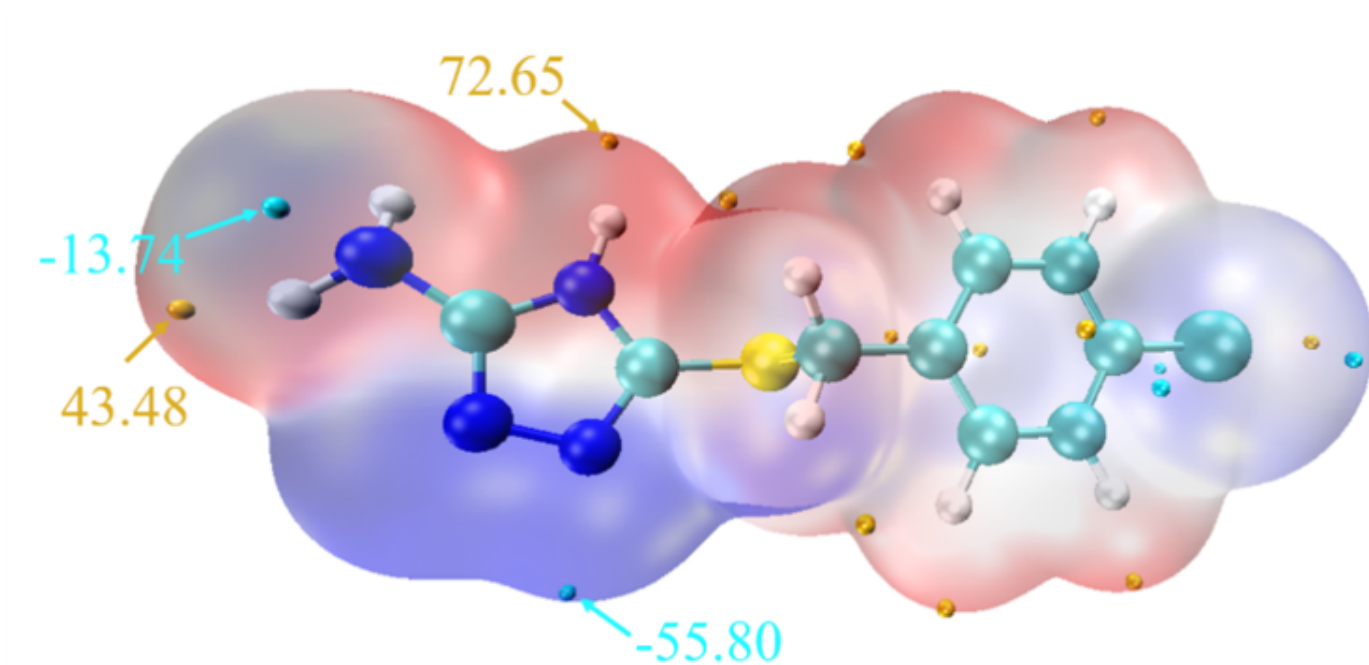
**Figure 1**

Structures of commercial drugs and pesticides with cyclopropane group



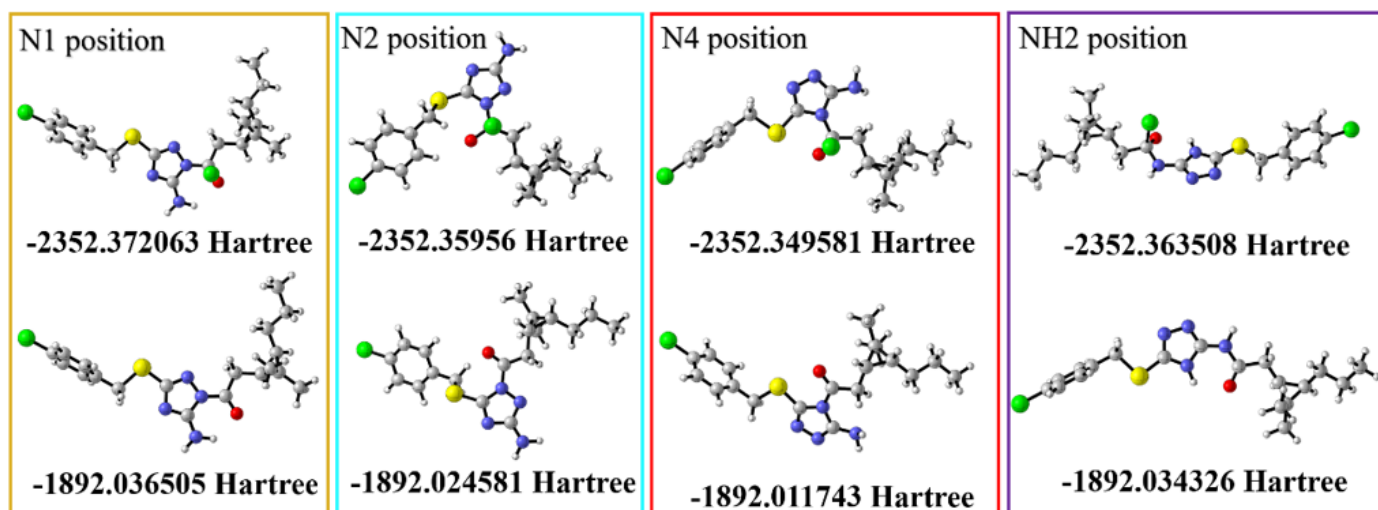
**Figure 2**

Expanded NOESY spectrum of the target compound **7o**



**Figure 3**

**4** The surface electrostatic potential of intermediate **6f**



**Figure 4**

**5** Energy for the intermediates and their corresponding products in *N*-acylation reaction

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryInformation.docx](#)
- [Scheme1.png](#)