Synthesis and Evaluation of 1,3,4-Thiadiazole Derivatives Containing Cyclopentylpropionamide as Potential Antibacterial Agent

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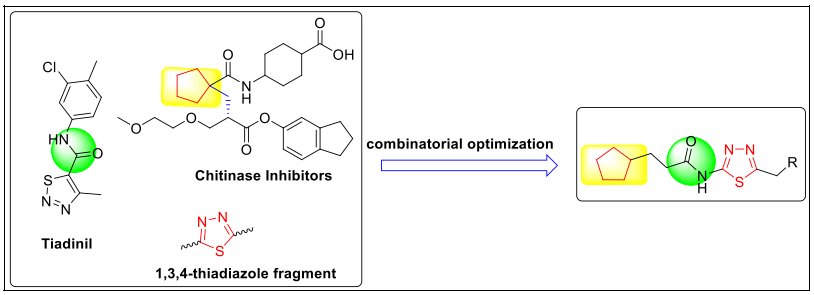


This study aimed to identify new strategies for the control of these plant bacterial diseases by combining a pharmacophoric group of different bioactive compounds. A series of 3-cyclopentylpropionamide containing 1,3,4-thiadiazole derivatives was synthesized and characterized *via* ^{1}H-NMR, ^{13}C-NMR, and HRMS. Bioassay results indicated that compounds **7a**, **7d**, **7j**, **7m**, **7n**, and **7s** had excellent antibacterial activity compared with the positive control. Among them, compound **7a** exhibited remarkable inhibitory effect against *Xoo* with an EC_{50} of 21.41 μg/mL, which surpassed that of thiodiazole copper (67.71 μg/mL) and bismerthiazol (69.05 μg/mL). Greenhouse condition tests further revealed that **7a** had approximately equal curative activity and better protection activity (41.58%) against bacterial leaf blight of rice than that of thiodiazole copper and bismerthiazol (46.86 and 42.25%, respectively). Structure–activity relationship analysis exhibited that sulfone fragment favored inhibition. Overall, this study suggested that derivatives containing 1,3,4-thiadiazole 3-cyclopentylpropanamide can be used as new lead compounds for bactericide studies.

INTRODUCTION

Bacterial diseases are very common, and more than 500 kinds of plant bacterial diseases have been recorded. Among the bacterial diseases, tomato bacterial wilt, citrus canker, and rice bacterial leaf blight were caused by the pathogens of *Rs*, *Xac*, and *Xoo*, respectively, which has attracted considerable attention worldwide. Because of its high mortality rate with a global distribution and an unusual wide host range, *Rs* is one of the most devastating plant pathogens worldwide [1,2]. *Xac* is a common plant disease throughout the areas of tropical and subtropical world [3] that affects most of the commercial varieties of citrus, such as citrus canker, decreases the quality and quantity of citrus fruits, and results in huge economic losses [4]. *Xoo* is a pathogenic Gram-negative bacterium in rice cultivation that can invade rice xylem tissues through wounds or stomata [5,6], which causes systemic infection and results in rice bacterial leaf blight. Rice bacterial leaf blight disease has a serious impact on each stage of rice growth and seriously limits the yields of rice with huge economic impact worldwide. Rice bacterial leaf blight causes a yield loss of up to 80% [7–9].

Currently, chemical pesticides have frequently been used to prevent bacterial diseases, such as bismerthiazol and thiodiazole copper. However, chemical pesticides enhance the resistance of host plants and cannot effectively treat infected plants under field conditions because of their low efficiency and high phytotoxicity [10,11]. Thus, searching for novel alternative antibacterial agents can still be a challenge in the field of bactericide [12]. Heterocyclic compounds have attracted the interest of pharmaceutical chemists because of their special chemical structures and diverse biological characteristics [13,14]. 1,3,4-Thiadiazole derivatives possess widely biological activities [15], such as antiviral [16,17], antibacterial [18,19], insecticide [20], antifungal [21,22], anticancer [23], and anti-inflammatory [24]. Cyclopentane is well known because of its dimensional structure known as the half-chair conformation of lower-energy state. However, cyclopentane has emerged in several active compounds, especially those connected with a flexible bond (2 carbon or 3 carbon) and as an important pharmacophore. Cyclopentamine is a sympathomimetic alkylamine and is classified as a vasoconstrictor [25]. Peramivir could protect healthy cells from novel viruses, as a neuraminidase inhibitor [26,27]. Candoxatril is a new

effective therapeutic used in the treatment of people with mild heart failure. The beneficial effects may begin to improve the well-being of patients during everyday activities [28]. Alfaprostol is developed as a stable and selective analogue of prostaglandin F2α and is widely used as a potent luteolytic agent in cows, mares, and several new applications [29,30] (Fig. 1). Furthermore, drugs containing flexible side chains, such as $–CH_2CH_2–$, are conducive in improving the biological activity in most cases.

In our previous work [31], we demonstrated that 1,3,4-thiadiazole derivatives have remarkable antibacterial activity against plant pathogens; however, no study has been reported on cyclopentane (flexible side chains) that focuses on the pharmacophoric group of 1,3,4-thiadiazole. Biologically active fragments were incorporated by versatile amides because of the biological importance of 1,3,4-thiadiazole and cyclopentane with flexible side chains to discover and develop bioactive molecules. Here, we report a series of novel 3-cyclopentylpropionamide containing 1,3,4-thiadiazole sulfide or sulfone derivatives, their synthesis, and antibacterial activity (Scheme 1).

RESULTS AND DISCUSSION

Chemistry. The multistep synthesis of 3-cyclopentyl propionamides bearing 1,3,4-thiadiazole sulfide or sulfone scaffold was successfully accomplished. In the present work, a solution of thiosemicarbazide and carbon disulfide and disulfide mixture refluxed for 4 h and acidified with concentrated HCl to obtain synthetic chemistry involves the ring closure of thiosemicarbazide into 5-amino-1,3,4-thiadiazole thiol **2** [32], converting to 1,3,4-thiadiazole sulfide intermediate **3(a–w)** by a substitution reaction with a halogenated hydrocarbon in an aqueous solution of potassium hydroxide at room temperature [6,8,12]. Intermediate **5** is obtained by heating to reflux with thionyl chloride using 3-cyclopentylpropionic acid using pyridine as a catalyst [33]. Further, intermediate **3(a–w)** and **5** were stirred under dichloromethane for 4 h to obtain compound **6(a–w)**. Finally, it was oxidized with H_2O_2 under acidic conditions of glacial acetic acid to obtain a series of 3-cyclopentylpropionamide derivatives **7(a–u)** containing 1,3,4-thiadiazole sulfide/sulfone. All compounds displayed ^{1}H-NMR and ^{13}C-NMR and HRMS consistent with the assigned structures. For the ^{1}H-NMR spectra of compound **6**, the single peak at 12.80–13.36 and 2.73–4.51 ppm reveals the presence of –CONH and $–SCH_2–$, respectively. For the ^{1}H-NMR spectra of compound **7**, the singlet at 12.55–13.26 and 3.40–5.10 ppm reveals the presence of –CONH and $–SO_2CH_2–$ groups, respectively. Moreover, in HRMS spectra, the considerable abundance of $[M + H]^+$ ions indicated that the structure of the title compounds is stable.

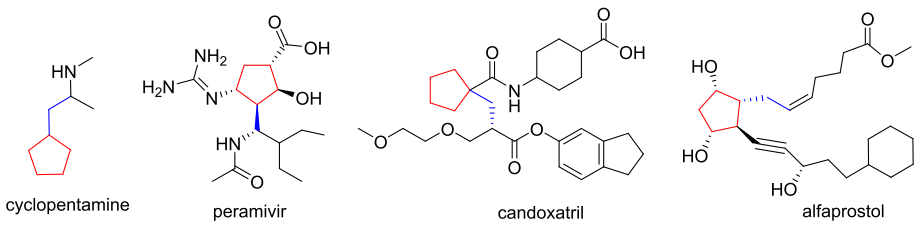
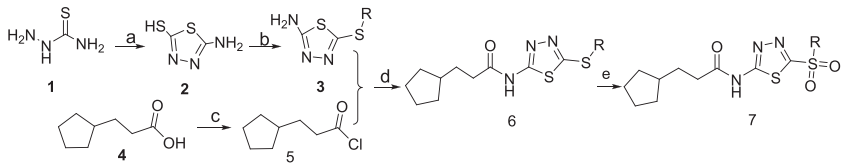


Figure 1. Structure of several drugs containing cyclopentyl fragment. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthetic route to the title compounds. Reagent and conditions: (a) Na2CO3, CS2, reflux, 4 h; (b) R–X, KOH, H2O, 25°C, stir, 8 h; (c) SOCl2, CH2Cl2; (d) CH2Cl2, 25°C, stir; and (e) H2O2, (NH4)6MoO24.4H2O, acetic acid, stir.



a: R=CH_3 **b**: R=CH_2CH_3 **c**: R=$CH_2CH=CH_2$
d: R=$CH_2CH_2CH_3$ **e**: R=$CH(CH_3)_2$ **f**: R=$CH_2CH_2CH_2CH_3$
g: R=$CH_2CH_2CH_2CH_2CH_3$ **h**: R=$CH(CH_3)CH_2CH_3$ **i**: R=$CH_2CH(CH_3)CH_2CH_3$
j: R=$CH_2COOCH_2CH_3$ **k**: R=Benzyl **l**: R=3-CN-Benzyl
m: R=4-CN-Benzyl **n**: R=2-CH_3-Benzyl **o**: R=3-CH_3-Benzyl
p: R=4-CH_3-Benzyl **q**: R=2-F-Benzyl **r**: R=3-F-Benzyl
s: R=4-F-Benzyl **t**: R=4-CF_3-Benzyl **u**: R=3-OCH_3-Benzyl
v: R=CH_2CH_2Br **w**: R=4-Cl-Benzyl

Bioactivities. ***In vitro antibacterial activity.*** The *in vitro* antibacterial evaluation of title compounds against *Rs*, *Xoo*, and *Xac* were tested by the method of turbidimetric assay. The results are compared with that of commercial antibacterial agent thiodiazole copper (20% suspending agent) and bismerthiazol (20% wettable powder), and the results are listed in Tables 1–3.

Table 1 indicates that most of the title compounds exerted satisfactory efficacy against *Rs*, *Xoo*, and *Xac*, compared with the positive control. For the antibacterial activity against *Rs*, compounds **6f**, **6n**, **6t**, and **6n** exhibited excellent activity. Their control efficacies at 100 μg/mL were 74.52, 73.90, 69.62, and 80.51%, respectively, and 54.72, 51.13, 49.55, and 61.20%, respectively, at 50 μg/mL, which outperforms that of thiodiazole copper (48.44% at 100 μg/mL and 26.12% at 50 μg/mL) and bismerthiazol (52.90 and 37.88%). For *Xac*, compounds **6c**, **6d**, **6p**, **6s**, and **6t** exhibited excellent activities, and their control efficacies were 81.12–90.43 and 51.30–66.10% at 100 and 50 μg/mL, which were preferable to thiodiazole copper (56.30% at 100 μg/mL and 37.49% at 50 μg/mL) and bismerthiazol (69.60 and 44.38%). For *Xoo*, **6t** exhibited the most activity with inhibition of 79.9% at 100 μg/mL and 58.55% at 50 μg/mL, which were better than thiodiazole copper (62.04% at 100 μg/mL and 39.77% at 50 μg/mL) and bismerthiazol (56.43 and 44.06%).

As indicated in Table 2, several evaluated compounds had excellent efficacy against *Rs*, *Xoo*, and *Xac* compared with that of the positive control. For antibacterial activity against *Rs*, compounds **7a**, **7h**, **7l**, **7m**, and **7o** exhibited excellent activity, and their control efficacies were 79.27–92.34% at 100 μg/mL, and compounds **7h**, **7l**, **7m**, and **7o** showed 75.68, 66.06, 73.82, and 72.72% at 50 μg/mL, respectively, which were better than thiodiazole copper (48.44% at 100 μg/mL and 26.12% at 50 μg/mL) and bismerthiazol (52.90 and 37.88%). For *Xac*, compounds **7a**, **7c**, and **7f** exhibited the most activity with inhibition of 93.56, 97.47, and 82.23% at 100 μg/mL, which was superior to thiodiazole copper (56.30% at 100 μg/mL) and bismerthiazol (69.60% at 100 μg/mL). For antibacterial activity against *Xoo*, most compounds indicated significant activities, compared with the positive control. At 100 μg/mL, compounds **7a**, **7j**, **7m**, and **7s** exhibited excellent activity, and their control efficacies were 94.03, 83.47, 84.15, and 80.74%, respectively. At 50 μg/mL, compound **7a** exhibited the most activity with inhibition of 82.97%, which was superior to thiodiazole copper (62.04% at 100 μg/mL and 39.77% at 50 μg/mL) and bismerthiazol (56.43 and 44.06%).

Table 1

Antibacterial activities of compound **6** (%).

	Ralstonia solanacearum		*Xac*		*Xoo*	
Compound	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL
6a	23.25 ± 1.40	56.42 ± 1.25	61.18 ± 0.59	70.49 ± 2.69	33.29 ± 1.20	49.33 ± 0.49
6b	33.49 ± 2.40	52.98 ± 0.82	43.59 ± 0.51	57.80 ± 1.42	31.43 ± 1.31	52.36 ± 1.44
6c	28.69 ± 2.29	40.10 ± 2.31	66.1 ± 1.15	90.43 ± 0.95	37.63 ± 1.08	61.87 ± 0.82
6d	23.31 ± 0.54	26.76 ± 1.45	64.64 ± 0.94	79.92 ± 1.99	22.60 ± 1.54	46.53 ± 0.57
6e	40.55 ± 1.12	58.60 ± 1.20	39.04 ± 4.04	46.73 ± 1.86	36.42 ± 1.74	48.62 ± 0.87
6f	54.72 ± 0.90	74.52 ± 1.46	31.97 ± 0.45	53.56 ± 3.69	25.40 ± 0.93	44.58 ± 1.32
6g	20.78 ± 0.61	—	38.13 ± 7.62	47.39 ± 4.54	23.11 ± 2.27	40.48 ± 0.83
6h	42.62 ± 1.91	62.13 ± 1.37	31.44 ± 1.01	59.01 ± 1.32	30.71 ± 0.49	51.20 ± 1.10
6i	18.11 ± 4.52	48.21 ± 1.08	38.57 ± 7.01	43.89 ± 12.59	28.61 ± 4.30	43.74 ± 2.15
6j	—	47.82 ± 1.91	45.00 ± 0.91	55.46 ± 0.17	24.63 ± 3.13	48.26 ± 1.07
6k	45.63 ± 2.10	67.88 ± 0.42	64.06 ± 1.08	67.07 ± 0.56	19.36 ± 2.11	36.43 ± 1.78
6l	42.46 ± 0.49	65.99 ± 2.12	41.97 ± 1.22	63.11 ± 0.66	38.94 ± 0.78	57.18 ± 0.40
6m	20.10 ± 0.42	55.29 ± 7.03	48.15 ± 4.94	58.07 ± 0.58	27.32 ± 1.41	47.83 ± 0.82
6n	51.13 ± 0.33	73.90 ± 1.04	44.56 ± 2.26	50.98 ± 0.67	34.72 ± 0.45	58.73 ± 0.66
6o	41.79 ± 1.21	62.17 ± 0.82	42.08 ± 0.37	62.55 ± 1.55	31.89 ± 2.56	62.17 ± 1.88
6p	24.13 ± 1.06	41.75 ± 13.36	57.59 ± 0.78	81.92 ± 0.21	27.66 ± 2.25	46.07 ± 0.77
6q	47.15 ± 1.56	63.31 ± 0.63	47.75 ± 1.16	69.07 ± 0.78	44.82 ± 0.62	59.78 ± 0.87
6r	49.28 ± 1.25	65.34 ± 0.64	25.28 ± 0.46	52.27 ± 1.16	36.18 ± 2.03	62.75 ± 0.79
6s	—	20.19 ± 1.94	51.30 ± 1.33	83.12 ± 1.94	42.58 ± 0.60	69.44 ± 1.63
6t	49.55 ± 0.62	69.62 ± 0.20	42.37 ± 0.88	71.35 ± 1.07	58.55 ± 1.02	79.90 ± 0.80
6u	61.20 ± 1.05	80.51 ± 0.56	24.04 ± 1.26	52.94 ± 2.94	33.80 ± 2.07	48.60 ± 1.58
6v	23.69 ± 1.28	35.39 ± 2.72	43.85 ± 5.22	63.61 ± 2.92	16.07 ± 1.12	39.43 ± 2.25
6w	40.95 ± 1.22	63.25 ± 2.26	—	31.32 ± 1.22	20.32 ± 1.18	47.66 ± 2.72
Thiodiazole copper	26.12 ± 3.52	48.44 ± 4.52	37.49 ± 3.63	56.30 ± 2.09	39.77 ± 2.77	62.04 ± 0.67
Bismerthiazol	41.46 ± 0.81	66.89 ± 0.64	44.38 ± 1.14	69.6 ± 0.79	44.06 ± 1.79	56.43 ± 1.37

Table 2

Antibacterial activities of target compound **7** (inhibition rate, %).

	Ralstonia solanacearum		*Xac*		*Xoo*	
Compound	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL
7a	39.81 ± 3.26	79.52 ± 5.28	42.31 ± 1.46	93.56 ± 5.03	82.97 ± 8.49	94.03 ± 0.57
7b	52.52 ± 0.57	73.52 ± 0.40	38.58 ± 0.59	66.42 ± 1.46	48.36 ± 1.88	68.35 ± 1.39
7c	—	—	51.82 ± 12.36	97.47 ± 1.99	24.58 ± 4.12	69.34 ± 7.28
7d	38.11 ± 12.36	78.28 ± 8.82	—	—	51.85 ± 6.55	77.85 ± 0.35
7e	34.53 ± 1.00	48.39 ± 1.28	20.09 ± 0.67	33.41 ± 1.38	37.15 ± 1.08	52.78 ± 0.93
7f	67.63 ± 4.95	72.72 ± 5.73	33.78 ± 1.23	82.23 ± 4.24	15.72 ± 9.34	38.98 ± 9.76
7g	32.95 ± 1.86	49.35 ± 0.65	34.79 ± 4.03	52.01 ± 0.27	31.66 ± 2.11	49.94 ± 0.64
7h	75.68 ± 2.81	80.16 ± 0.81	16.27 ± 7.34	—	—	—
7i	—	74.39 ± 3.68	55.96 ± 5.83	64.36 ± 0.73	12.75 ± 6.67	45.93 ± 2.28
7j	41.13 ± 9.02	—	47.39 ± 6.45	51.78 ± 3.61	60.86 ± 7.20	83.47 ± 4.68
7k	53.24 ± 3.52	77.74 ± 7.92	—	55.21 ± 8.92	26.13 ± 0.78	—
7l	66.06 ± 2.17	82.19 ± 1.08	—	44.47 ± 7.82	20.45 ± 2.84	64.26 ± 0.89
7m	73.82 ± 7.88	79.27 ± 2.60	42.81 ± 2.50	67.34 ± 1.84	59.23 ± 6.33	84.15 ± 0.76
7n	46.62 ± 13.16	60.26 ± 0.93	27.53 ± 1.29	53.69 ± 2.15	—	78.24 ± 2.57
7o	72.72 ± 5.73	92.34 ± 1.62	45.67 ± 2.88	53.25 ± 8.13	37.84 ± 5.43	54.62 ± 4.89
7p	34.90 ± 7.79	75.71 ± 12.27	25.9 ± 7.73	43.54 ± 2.03	33.69 ± 2.67	—
7q	51.53 ± 10.93	70.62 ± 8.32	48.95 ± 7.49	59.01 ± 0.59	34.90 ± 12.76	—
7r	35.86 ± 10.87	64.60 ± 6.67	30.25 ± 6.62	43.44 ± 6.15	57.47 ± 5.78	76.04 ± 4.85
7s	43.34 ± 5.87	58.80 ± 9.74	49.45 ± 0.5	57.15 ± 0.25	53.51 ± 7.85	80.74 ± 9.34
7t	60.54 ± 6.40	76.46 ± 4.88	41.19 ± 0.75	47.00 ± 2.08	72.65 ± 3.43	75.81 ± 3.59
7u	48.47 ± 5.01	—	38.78 ± 13.85	53.73 ± 1.27	67.18 ± 5.19	—
Thiodiazole copper	26.12 ± 3.25	48.44 ± 4.52	34.12 ± 4.29	56.30 ± 2.09	39.77 ± 2.77	62.04 ± 0.67
Bismerthiazol	41.46 ± 0.81	66.89 ± 0.64	44.38 ± 1.14	69.6 ± 0.79	44.06 ± 1.79	56.43 ± 1.37

Table 3

EC_{50} values of several target compounds against *Xoo*.

Compound	R_1	Toxic regression	r^2	EC_{50} (μg/mL)
7a	CH_3	$y = 2.2958x + 1.952$	0.9857	21.41 ± 0.85
7d	$CH_2CH_2CH_3$	$y = 1.779x + 2.159$	0.9893	39.53 ± 1.43
7j	$CH_2CO_2C_2H_5$	$y = 1.6039x + 2.707$	0.9747	26.89 ± 0.91
7m	4-CN-Benzyl	$y = 2.4209x + 1.17$	0.9976	38.19 ± 0.63
7r	3-F-Benzyl	$y = 1.6484x + 2.2875$	0.9224	44.21 ± 1.68
7s	4-F-Benzyl	$y = 1.773x + 2.1948$	0.9809	38.21 ± 2.42
Thiodiazole copper	—	$y = 1.7806x + 1.7405$	0.9985	67.71 ± 0.79
Bismerthiazol	—	$y = 1.8829x + 1.537$	0.9422	69.05 ± 1.21

Several compounds displayed excellent antibacterial activities, and their EC_{50} values against *Xoo* were tested, calculated, and listed in Table 3. Compounds **7a**, **7d**, **7j**, **7m**, and **7s** showed excellent activity against *Xoo*, the EC_{50} values were 21.41, 39.53, 26.89, 38.19, and 38.21 μg/mL, respectively, which were better than thiodiazole copper (67.71 μg/mL) and bismerthiazol (69.05 μg/mL).

In vivo antibacterial activity. The results of antibacterial activities *in vivo* are listed in Table 4 and Figure 2.

At 14 days after spraying, the positive control and test compound were morbidity in total and showed different disease indexes and different control activities. At 200 μg/mL, compound **7a** showed curative activity of 46.61% against rice bacterial leaf blight *in vivo*, which surpassed bismerthiazol (30.21%) and thiodiazole copper (40.86%). Compound **7a** displayed remarkable protective activity of 41.58% against rice bacterial leaf blight, which has approximately equal activity compared with bismerthiazol (42.25%) and thiodiazole copper (46.86%). The leaves treated by compound **7a** grew uniformly and vigorously with small leaf blight.

As previously mentioned, the differences of target compounds were due to their different moieties of thioester (compound **6** series) and sulfone (compound **7** series) and with different substituents of R group next to sulfur. On the basis of the biological test results, the structure–activity relationship can be evaluated based on the parallel activity comparison between compound **6** and **7** series against antibacterial activity at the same

Table 4

Activity of **7a** against rice bacterial leaf blight *in vivo* at 200 μg/mL.

Treatment	Morbidity (%)	Curative activity		Protection activity	
		Disease index (%)	Efficiency (%)[a]	Disease index (%)	Efficiency (%)[a]
7a	100	37.86	$46.61 \pm 1.77_{b}$	41.43	$41.58 \pm 0.94_{c,d}$
Thiodiazole copper	100	41.94	$40.86 \pm 1.22_{c,d}$	37.68	$46.86 \pm 0.70_{d}$
Bismerthiazol	100	49.55	$30.12 \pm 2.15_{b,c}$	40.95	$42.25 \pm 1.68_{b,c,d}$
Control Check (CK)	100	70.91	/	70.91	/

Different lowercase letters indicate the values of curative activity, and there was a significant difference between the different treatment groups, $p < 0.05$.
[a]Statistical analysis was performed using the analysis of variance method under the condition of equal variances assumed ($p > 0.05$) and equal variances not assumed ($p < 0.05$).

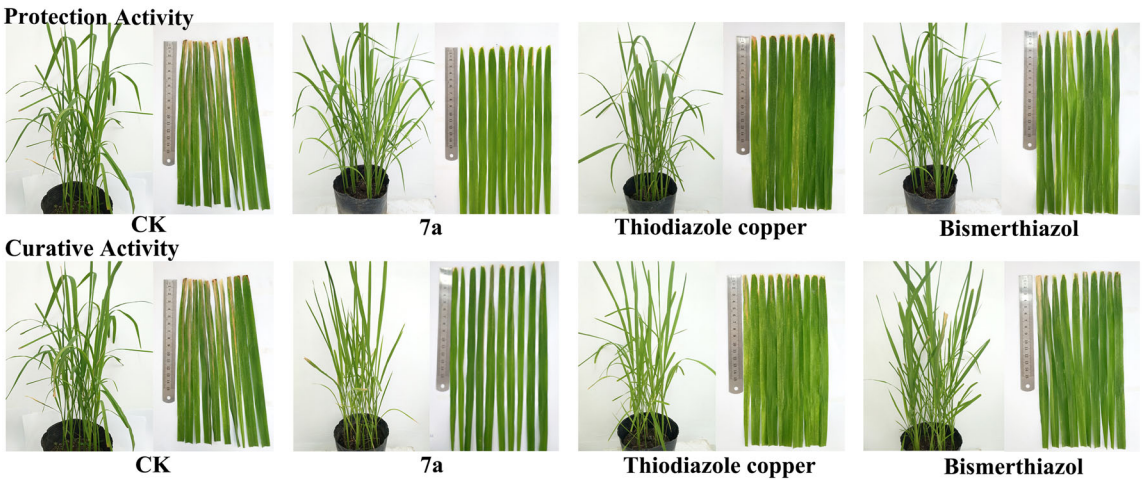


Figure 2. Curative and protection activities of **7a** against rice bacterial leaf blight under greenhouse conditions at 200 μg/mL. [Color figure can be viewed at wileyonlinelibrary.com]

concentration (100 and 50 μg/mL), EC_{50} values, and *in vivo* antibacterial activity test of several used compounds. Most of the compounds exerted remarkable antibacterial activity. However, in total, thioester derivative (compound **6** series) showed lower activities than that of sulfone derivative (compound **7** series). For *Rs*, the antibacterial inhibition values were **6a** < **7a**, **6b** < **7b**, **6d** < **7d**, **6h** < **7h**, **6k** < **7k**, **6l** < **7l**, and **6m** < **7m**. For *Xoo*, the antibacterial inhibition values were **6a** < **7a**, **6b** < **7b**, **6c** < **7c**, **6d** < **7d**, **6k** < 7**k**, **6l** < **7l**, and **6m** < **7m**. The R group mainly includes alkane and aromatic groups. In general, no obvious differences were observed between the different substituents. However, some subtle differences were observed, in which the length of the alkane carbon chain has an effect on the activity, and the short carbon chain favors activity. For *Xoo*, the antibacterial inhibition values were **7a** > **7b**, **7c**, **7d**, and **7e**. When the R group is aromatic, there are small differences in activities of the title compounds for electron-donating or electron-withdrawing groups.

CONCLUSIONS

In summary, two series of derivatives containing 1,3,4-thiadiazole were designed and synthesized by merging the structural features of thioester/sulfone and cyclopentylpropanamide. Bioassay results showed that several compounds, such as **7a**, **7d**, **7j**, **7m**, **7n**, and **7s** show excellent antibacterial activity compared with that of the positive control. Preliminary structure–activity relationship analysis exhibited that an aromatic amino acid fragment, such as phenylalanine or tryptophan, is essential for the inhibition. Among them, compound **7a** exhibited remarkable inhibitory effect against *Xoo*, in which its EC_{50} value is 21.41 μg/mL, which was higher than that of thiodiazole copper (67.71 μg/mL) and bismerthiazol (69.05 μg/mL). Furthermore, greenhouse condition tests revealed that **7a** has better protection activity (41.58%) against bacterial leaf blight of rice than that of thiodiazole copper and bismerthiazol (46.86 and 42.25%, respectively). These results suggested that **7a** can be extensively developed as potential antibacterial agents.

EXPERIMENTAL

Instruments. The melting points (uncorrected) were measured with micromelting point apparatus (Beijing Tech. Instrument, Beijing, China), by tetramethylsilane as the internal standard. ^{1}H-NMR and ^{13}C-NMR were measured with a Bruker ASCEND 400 NMR spectrometer (Bruker Corp., Billerica, MA) and a JEOL-ECX 500 NMR spectrometer (JEOL, Japan) in $CDCl_3$ or DMSO-d_6. Q Exactive apparatus (The United States, Thermo Scientific) was used conducting HRMS. All reagents are analytical reagent or CP.

Preparation for 5-amino-1,3,4-thiadiazole-2-thiol (2). A solution of thiosemicarbazide (0.1 mol) in absolute ethanol (50 mL), anhydrous sodium carbonate (0.045 mol), and carbon disulfide (0.1 mol) was added slowly, refluxed, and stirred for 4 h. The solvent was removed under reduced pressure, and the solid was dissolved with 50 mL water and acidified with concentrated hydrochloric acid to afford corresponding solid product 11.3 g, yield 85%, mp 233–235°C [31].

Preparation for 3-cyclopentylpropanoyl chloride (5). A solution of thionyl chloride (0.3 mol) was added to 3-cyclopentylpropanoic acid (0.1 mol), pyridine (1 mmol) was added dropwise as catalyst. The mixture was stirred and heated for reflux for 5 h, then slowly added to ice water to remove excess oxaloyl chloride and pyridine, colorless liquid product was afford by extracting and then vacuum freeze drying at −50°C for 1 h, yield 83.85% [32].

Preparation for 3-cyclopentyl-*N*-(5-(methylthio)-1,3,4-thiadiazol-2-yl)propanamide (6a–6w). The intermediate 3 (2.1 mmol) was dissolved with 40 mL methylene chloride and slowly added 3-cyclopentyl propionyl chloride (2 mmol). The mixture was stirred at room temperature for 4 h. The mixture was poured into 20 mL water and extracted with dichloromethane. Then, anhydrous Na_2SO_4 was used to dry the organic layer and decompress the solvent. Finally, anhydrous ethanol was used for recrystallization to obtain the corresponding solid products.

3-Cyclopentane-N-(5-(methylthio)-1,3,4-thiadiazol-2-yl) propanamide (6a). White solid, yield 74.5%, mp 146–146.8°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.24 (s, 1H, NH), 2.78–2.74 (m, 5H, $COCH_2$, SCH_3), 1.91–1.77 (m, 5H, cyclopentane–H), 1.64–1.58 (m, 2H, cyclopentane–H), 1.56–1.49 (m, 2H, cyclopentane–H), 1.21–1.12 (m, 2H, CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.27, 161.17, 160.47, 39.83, 35.49, 32.42, 31.43, 25.17, 16.04. ESI-MS *m*/*z*: 272.0 $[M + H]^+$.

3-Cyclopentane-N-(5-(ethylthio)-1,3,4-thiadiazol-2-yl)propanamide (6b). White solid, yield 52%, mp 135–136.2°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.58 (s, 1H, NH), 3.25–3.19 (m, 2H, SCH_2), 2.50–2.46 (m, 2H, $COCH_2$), 1.78–1.67 (m, 3H, cyclopentane–H), 1.63–1.55 (m, 4H, cyclopentane–H), 1.52–1.42 (m, 2H, cyclopentane–H), 1.34 (t, J = 7.3 Hz, 3H, CH_3), 1.10–1.06 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 172.14, 159.01, 158.81, 34.58, 32.40, 31.25, 28.48, 25.13, 15.22. ESI-MS *m*/*z*: 286.1 $[M + H]^+$.

N-(5-(Allylthio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6c). White solid, yield 70.3%, mp 153.9–154.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.22 (s, 1H, NH), 6.03–5.92 (m, 1H, CH), 5.30 (d, J = 16.9 Hz, 1H, CH=CH_2), 5.18 (d, J = 10.0 Hz, 1H, CH=CH_2), 3.86 (d, J = 7.0 Hz, 2H, SCH_2), 2.78–2.74 (m, 2H, $COCH_2$), 1.84–1.77 (m, 5H, cyclopentane–H), 1.66–1.58 (m, 2H, cyclopentane–H), 1.56–1.49 (m, 2H, cyclopentane–H), 1.21–1.12 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.27, 161.00, 159.16, 132.27, 119.29, 39.79, 36.87, 35.49, 32.45, 31.40, 25.15. ESI-MS *m*/*z*: 298.10385 $[M + H]^+$.

3-Cyclopentyl-N-(5-(propylthio)-1,3,4-thiadiazol-2-yl)propanamide (6d). White solid, yield 67.2%, mp 114.3–115.7°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.22 (s, 1H, NH), 3.24–3.20 (m, 2H, SCH_2), 2.78–2.74 (m, 2H, $COCH_2$), 1.88–1.81 (m, 5H, cyclopentane–H), 1.79–1.77 (m, 2H, cyclopentane–H), 1.66–1.60 (m, 2H, cyclopentane–H), 1.56–1.51 (m, 2H, cyclopentane–H), 1.21–1.14 (m, 2H, cyclopentane–CH_2), 1.06 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.25, 160.61, 160.33, 39.79, 36.03, 35.47, 32.45, 31.43, 25.16, 22.79, 13.27. ESI-MS *m*/*z*: 300.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-(isopropylthio)-1,3,4-thiadiazol-2-yl) propanamide (6e). White solid, yield 44.7%, mp 144.7–145.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.27 (s, 1H, NH), 3.89–3.79 (1H, SCH), 2.79–2.75 (m, 2H, $COCH_2$), 1.88–1.79 (m, 5H, cyclopentane–H), 1.66–1.60 (m, 2H, cyclopentane–H), 1.54–1.50 (m, 2H, cyclopentane–H), 1.46–1.45 (d, J = 6.8 Hz, 6H, $2CH_3$), 1.18–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.30, 161.15, 159.11, 40.13, 39.78, 35.50, 32.43, 31.41, 25.15, 23.33. ESI-MS *m*/*z*: 300.1 $[M + H]^+$.

N-(5-(Butylthio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6f). White solid, yield 65.8%, mp 129.6–130.4°C. ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 13.23 (s, 1H, NH), 3.26–3.23 (m, 2H, SCH_2), 2.78–2.74 (m, 2H, $COCH_2$), 1.92–1.78 (m, 5H, cyclopentane–H), 1.76–1.72 (m, 2H, cyclopentane–H), 1.66–1.59 (m, 2H, cyclopentane–H), 1.55–1.43 (m, 4H, $2CH_2$), 1.20–1.12 (m, 2H, cyclopentane–CH_2), 0.95 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.26, 160.60, 160.39, 39.78, 35.46, 33.82, 32.46, 31.44, 31.36, 25.16, 21.83, 13.57. ESI-MS *m*/*z*: 314.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-(pentylthio)-1,3,4-thiadiazol-2-yl)propanamide (6g). White solid, yield 55%, mp 158.6–159.4°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 13.27 (s, 1H, NH), 3.24–

3.21 (m, 2H, SCH_2), 2.77–2.71 (m, 2H, $COCH_2$), 1.88–1.76 (m, 7H, cyclopentane–H), 1.62–1.57 (m, 2H, cyclopentane–H), 1.52–1.50 (m, 2H, CH_2), 1.44–1.38 (m, 2H, CH_2), 1.36–1.30 (m, 2H, CH_2), 1.18–1.11 (m, 2H, cyclopentane–CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.36, 160.65, 160.48, 39.85, 35.55, 34.15, 32.54, 31.53, 30.93, 29.09, 25.25, 22.30, 14.05. ESI-MS *m*/*z*: 328.1 $[M + H]^+$.

N-(5-(sec-Butylthio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6h). White solid, yield 56%, mp 86.2–87.4°C. ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 13.36 (s, 1H, NH), 3.71–3.62 (m, 1H, SCH), 2.79–2.76 (m, 2H, $COCH_2$), 1.88–1.79 (m, 5H, cyclopentane–H), 1.77–1.73 (m, 2H, CH_2CH_3), 1.66–1.60 (m, 2H, cyclopentane–H), 1.56–1.51 (m, 2H, cyclopentane–H), 1.44 (d, J = 6.8 Hz, 3H, CH_3), 1.20–1.12 (m, 2H, cyclopentane–CH_2), 1.05 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.34, 161.13, 159.19, 46.69, 39.79, 35.49, 32.45, 31.42, 29.71, 25.15, 20.92, 11.40. ESI-MS *m*/*z*: 314.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((2-methylbutyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6i). White solid, yield 77%, mp 100.3–101.6°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.35 (s, 1H, NH), 3.31–3.26 (m, 1H, SCH), 3.14–3.09 (m, 1H, S–CH), 2.79–2.75 (m, 2H, $COCH_2$), 1.88–1.77 (m, 7H, cyclopentane–H, CH_2), 1.64–1.60 (m, 2H, cyclopentane–H), 1.55–1.51 (m, 2H, cyclopentane–H), 1.35–1.24 (m, 1H, CH), 1.20–1.12 (m, 2H, cyclopentane–CH_2), 1.04 (d, J = 6.7 Hz, 3H, CH_3), 0.93 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.30, 160.78, 160.53, 40.81, 39.78, 35.45, 34.80, 32.48, 31.45, 28.60, 25.17, 18.73, 11.28. ESI-MS *m*/*z*: 328.1 $[M + H]^+$.

Ethyl 2-((5-(3-cyclopentylpropionylamino)-1,3,4-thiadiazol-2-yl)thio)acetate (6j). White solid, yield 63%, mp 121.2–121.7°C. ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 13.21 (s, 1H, NH), 4.25–4.20 (m, 2H, CH_2), 4.05 (s, 2H, SCH_2), 2.76–2.72 (m, 2H, $COCH_2$), 1.88–1.77 (m, 5H, cyclopentane–H), 1.67–1.61 (m, 2H, cyclopentane–H), 1.58–1.52 (m, 2H, cyclopentane–H), 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.17–1.12 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.26, 167.90, 161.19, 158.21, 62.13, 39.72, 35.43, 32.45, 31.42, 25.16, 14.14. ESI-MS *m*/*z*: 378.0 $[M + H]^+$.

N-(5-(Benzylthio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6k). White solid, yield 63%, mp 166–167°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 13.27 (s, 1H, NH), 7.40–7.37 (m, 2H, Ar–H), 7.34–7.26 (m, 3H, Ar–H), 4.47 (s, 2H, SCH_2), 2.79–2.75 (m, 2H, $COCH_2$), 1.88–1.75 (m, 5H, cyclopentane–H), 1.63–1.55 (m, 2H, cyclopentane–H), 1.53–1.45 (m, 2H, cyclopentane–H), 1.20–1.11 (dd, J = 19.1, 7.1 Hz, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.35, 160.99, 159.54, 136.05, 129.10, 128.86, 128.03, 39.88, 38.29, 35.59, 32.55, 31.51, 25.23. ESI-MS *m*/*z*: 348.1 $[M + H]^+$.

N-(5-((3-Cyanobenzyl)thio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6l). White solid, yield 68.7%, mp 162.8–163.5°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.18 (s, 1H, NH), 7.70 (s, 1H, Ar–H), 7.65 (d, J = 7.8 Hz, 1H, Ar–H), 7.59 (d, J = 7.8 Hz, 1H, Ar–H), 7.45 (t, J = 7.8 Hz, 1H, Ar–H), 4.49 (s, 2H, SCH_2), 2.78–2.74 (m, 2H, $COCH_2$), 1.86–1.77 (m, 5H, cyclopentane–H), 1.62–1.55 (m, 2H, CH_2), 1.50–1.46 (m, 2H, cyclopentane–H), 1.19–1.11 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.17, 161.13, 158.34, 138.14, 133.38, 132.41, 131.55, 129.61, 118.40, 112.89, 39.77, 36.93, 35.44, 32.45, 31.35, 25.14. ESI-MS *m*/*z*: 373.1 $[M + H]^+$.

N-(5-((4-Cyanobenzyl)thio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6m). White solid, yield 61%, mp 167.5–168.8°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 13.21 (s, 1H, NH), 7.59 (d, J = 8.0 Hz, 2H, Ar–H), 7.49 (d, J = 8.1 Hz, 2H, Ar–H), 4.48 (s, 2H, SCH_2), 2.74–2.71 (m, 2H, $COCH_2$), 1.80–1.74 (m, 5H, cyclopentane–H), 1.59–1.53 (m, 2H, cyclopentane–H), 1.47–1.44 (m, 2H, cyclopentane–H), 1.15–1.08 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.23, 161.19, 158.43, 141.97, 132.59, 129.78, 118.57, 111.80, 39.84, 37.42, 35.50, 32.53, 31.42, 25.22. ESI-MS *m*/*z*: 373.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((2-methylbenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6n). White solid, yield 88.6%, mp 128.3–129.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.21 (s, 1H, NH), 7.27 (d, J = 8.0 Hz, 2H, Ar–H), 7.13 (d, J = 7.9 Hz, 2H, Ar–H), 4.44 (s, 2H, SCH_2), 2.78–2.75 (m, 2H, $COCH_2$), 2.33 (s, 3H, CH_3), 1.90–1.77 (m, 5H, cyclopentane–H), 1.66–1.59 (m, 2H, cyclopentane–H), 1.55–1.47 (m, 2H, cyclopentane–H), 1.25–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.24, 160.89, 159.66, 137.06, 133.47, 130.77, 130.10, 128.38, 126.34, 39.81, 36.66, 35.58, 32.47, 31.44, 25.16, 19.20. ESI-MS *m*/*z*: 362.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((3-methylbenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6o). White solid, yield 71.6%, mp 165.6–166.3°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 13.30 (s, 1H, NH), 7.23–7.17 (m, 3H, Ar–H), 7.11 (s, 1H, Ar–H), 4.44 (s, 2H, SCH_2), 2.79–2.76 (m, 2H, $COCH_2$), 2.34 (s, 3H, CH_3), 1.86–1.77 (m, 5H, cyclopentane–H), 1.60–1.57 (m, 2H, cyclopentane–H), 1.50–1.46 (m, 2H. cyclopentane–H), 1.18–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.33, 160.89, 159.71, 138.59, 135.77, 129.78, 128.76, 126.14, 39.86, 38.28, 35.58, 32.53, 31.51, 25.21, 21.47. ESI-MS *m*/*z*: 362.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((4-methylbenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6p). White solid, yield 73.8%, mp 178.7–179.6°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.21 (s, 1H, NH), 7.27 (d, J = 8.0 Hz, 2H, Ar–H), 7.13 (d, J = 7.9 Hz, 2H, Ar–H), 4.44 (s, 2H, SCH_2), 2.80–2.74

(m, 2H, $COCH_2$), 2.33 (s, 3H, CH_3), 1.88–1.77 (m, 5H, cyclopentane–H), 1.66–1.59 (m, 2H, cyclopentane–H), 1.53–1.47 (m, 2H, cyclopentane–H), 1.18–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR(101 MHz, $CDCl_3$) δ: 172.23, 160.84, 159.66, 137.73, 132.85, 129.46, 128.92, 39.81, 38.09, 35.51, 32.46, 31.43, 25.16, 21.18. ESI-MS *m/z*: 362.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((2-fluorobenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6q). White solid, yield 59%, mp 145.8–146.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.29 (s, 1H, NH), 7.42–7.38 (m, 1H, Ar–H), 7.28–7.25 (m, 1H, Ar–H), 7.10–7.04 (m, 2H, Ar–H), 4.51 (s, 2H, SCH_2), 2.79–2.76 (m, 2H, $COCH_2$), 1.90–1.79 (m, 5H, cyclopentane–H), 1.61–1.55 (m, 2H, cyclopentane–H), 1.50–1.47 (m, 2H, cyclopentane–H), 1.20–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.29, 162.17, 161.15, 159.70, 159.02, 130.00, 130.96, 129.88, 129.80, 124.32, 124.28, 123.55, 123.40, 115.79, 115.58, 39.77, 35.48, 32.46, 31.42, 25.14. ESI-MS *m/z*: 366.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((3-fluorobenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6r). White solid, yield 66%, mp 145.4–146.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.16 (s, 1H, NH), 7.31–7.27 (m, 1H, Ar–H), 7.16–7.10 (d, *J* = 7.7 Hz, 2H, Ar–H), 7.00–6.95 (m, 1H, Ar–H), 4.45 (s, 2H, SCH_2), 2.78–2.74 (m, 2H, $COCH_2$), 1.90–1.75 (m, 5H, cyclopentane–H), 1.64–1.57 (m, 2H, cyclopentane–H), 1.51–1.47 (m, 2H, cyclopentane–H), 1.17–1.11 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.20, 164.05, 161.60, 161.01, 158.95, 138.70, 138.63, 130.29, 130.21, 124.63, 124.60, 116.07, 115.85, 115.03, 114.82, 39.77, 37.51, 35.47, 32.44, 31.38, 25.13. ESI-MS *m/z*: 366.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((4-fluorobenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6s). White solid, yield 55.1%, mp 164.3–165.1°C. ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 13.07 (s, 1H, NH), 7.37–7.34 (m, 2H, Ar–H), 7.01 (t, *J* = 8.6 Hz, 2H, Ar–H), 4.44 (s, 2H, SCH_2), 2.77–2.73 (m, 2H, $COCH_2$), 1.87–1.77 (m, 5H, cyclopentane–H), 1.62–1.59 (m, 2H, cyclopentane–H), 1.53–1.47 (m, 2H, cyclopentane–H), 1.20–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.21, 160.80, 159.67, 138.53, 135.74, 129.71, 128.74, 126.07, 39.80, 38.28, 35.52, 32.46, 31.44, 25.15, 21.38. ESI-MS *m/z*: 366.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((4-(trifluoromethyl)benzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6t). White solid, yield 49.2%, mp 211.8–212.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.80 (s, 1H, NH), 7.58 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.51 (d, *J* = 8.2 Hz, 2H, Ar–H), 4.51 (s, 2H, SCH_2), 2.75–2.71 (m, 2H, $COCH_2$), 1.88–1.76 (m, 5H, cyclopentane–H), 1.61–1.59 (m, 2H, cyclopentane–H), 1.55–1.47 (m, 2H, cyclopentane–H), 1.17–1.10 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.00, 160.83, 158.80, 140.36, 130.29, 129.30, 125.72, 125.68, 122.60, 39.75, 37.36, 35.47, 32.44, 31.35, 25.12. ESI-MS *m/z*: 416.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((3-methoxybenzyl)thio)-1,3,4-thiadiazol-2-yl)propanamide (6u). White solid, yield 49.2%, mp 114.3–115.7°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.24 (s, 1H, NH), 7.26–7.22 (m, 1H, Ar–H), 6.97–6.94 (m, 2H, Ar–H), 6.84–6.81 (m, 1H, Ar–H), 4.45 (s, 2H, SCH_2), 3.79 (s, 3H, OCH_3), 2.79–2.75 (m, 2H, $COCH_2$), 1.92–1.77 (m, 5H, cyclopentane–H), 1.63–1.55 (m, 2H, cyclopentane–H), 1.53–1.47 (m, 2H, cyclopentane–H), 1.20–1.12 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.25, 160.90, 159.85, 159.48, 137.40, 129.79, 121.32, 114.66, 113.37, 55.26, 39.79, 38.24, 35.51, 32.46, 31.42, 25.16. ESI-MS *m/z*: 378.1 $[M + H]^+$.

N-(5-((2-Bromoethyl)sulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6v). White solid, yield 52.7%, mp 246.9–247.5°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.20 (s, 1H, NH), 3.74–3.69 (m, CH_2Br), 3.67–3.63 (m, 2H, SCH_2), 2.79–2.75 (m, 2H, $COCH_2$), 1.90–1.79 (m, 5H, cyclopentane–H), 1.65–1.59 (m, 2H, cyclopentane–H), 1.57–1.52 (m, 2H, cyclopentane–H), 1.20–1.14 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.26, 161.12, 158.28, 39.68, 35.47, 34.91, 32.52, 31.41, 29.23, 25.18. ESI-MS *m/z*: 364.0 $[M + H]^+$.

N-(5-((4-Chlorobenzyl)thio)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (6w). White solid, yield 74.1%, mp 188.4–189.2°C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 12.95 (s, 1H, NH), 7.30 (d, *J* = 6.8 Hz, 4H, Ar–H), 4.43 (s, 2H, SCH_2), 2.74 (s, 2H, $COCH_2$), 1.80 (m, 5H, cyclopentane–H), 1.54 (m, 4H, cyclopentane–H), 1.15 (m, 2H, cyclopentane–CH_2). ^{13}CNMR (101 MHz, $CDCl_3$) δ: 172.09, 160.86, 159.03, 134.69, 133.81, 130.32, 128.93, 39.78, 37.44, 35.48, 32.45, 31.37, 25.14. ESI-MS *m/z*: 382.0 $[M + H]^+$.

Preparation for 3-cyclopentyl-*N*-(5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7a–7u). After compound **6** (1 mmol) dissolved in glacial acetic acid (20 mL), a solution of 30% hydrogen peroxide (3 mmol) and ammonium molybdate (0.005 mmol) were added in batches, after stirring for 1 h at room temperature and adding to water (50 mL). The product was filtered and recrystallized from ethanol give the title compound **7**.

3-Cyclopentyl-N-(5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl) propanamide (7a). White solid, yield 71.8%, mp 187.1–187.4°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.73 (s, 1H, NH), 3.40 (s, 3H, SO_2CH_3), 2.79–2.75 (m, 2H, $COCH_2$), 1.89–1.80 (m, 5H, cyclopentane–H), 1.65–1.62 (m, 2H, cyclopentane–H), 1.56–1.52 (m, 2H, cyclopentane–H), 1.21–1.12 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.27, 163.93, 163.40, 43.28, 39.70, 35.66, 32.40, 31.27, 25.15. ESI-MS *m/z*: 304.0 $[M + H]^+$.

3-Cyclopentyl-N-(5-(ethylsulfonyl)-1,3,4-thiadiazol-2-yl) propanamide (7b). White solid, yield 68%, mp 189.7–190.6°C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 13.22 (s, 1H, NH), 3.62–3.58 (m, 2H, $SOCH_2$), 2.54–2.51 (m, 2H, $COCH_2$), 1.73–1.67 (m, 3H, cyclopentane–H), 1.62–1.58 (m, 2H, cyclopentane–H), 1.55–1.53 (m, 2H, cyclopentane–H), 1.46–1.43 (m, 2H, cyclopentane–H), 1.21 (t, J = 7.3 Hz, 3H, CH_3), 1.07–1.03 (t, J = 9.2 Hz, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 173.15, 163.02, 161.20, 50.20, 34.74, 32.46, 31.12, 25.21, 7.52. ESI-MS m/z: 318.0 $[M + H]^+$.

N-(5-(Allylsulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (7c). White solid, yield 68%, mp 189.7–190.6°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.96 (s, 1H, NH), 5.94–5.83 (m, 1H, CH), 5.47 (d, J = 10.8 Hz, 1H, CH), 5.36 (d, J = 17.0 Hz, 1H, CH), 4.19 (d, J = 7.4 Hz, 2H, SO_2CH_2), 2.81–2.77 (m, 2H, $COCH_2$), 1.90–1.81 (m, 5H, cyclopentane–H), 1.66–1.62 (m, 2H, cyclopentane–H), 1.56–1.53 (m, 2H, cyclopentane–H), 1.21–1.13 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.38, 164.29, 161.77, 126.61, 123.04, 60.05, 39.70, 35.68, 32.42, 31.30, 25.16. ESI-MS m/z: 330.0 $[M + H]^+$.

3-Cyclopentyl-N-(5-(propylsulfonyl)-1,3,4-thiadiazol-2-yl) propanamide (7d). White solid, yield 54.6%, mp 185.4–186.2°C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 13.22 (s, 1H, NH), 3.60–3.57 (m, 2H, $SOCH_2$), 2.54–2.51 (m, 2H, $COCH_2$), 1.73–1.65 (m, 5H, cyclopentane–H), 1.62–1.58 (m, 2H, CH_2), 1.55–1.51 (m, 2H, cyclopentane–H), 1.48–1.43 (m, 2H, cyclopentane–H), 1.06–1.04 (m, 2H, cyclopentane–CH_2), 0.93 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 173.15, 163.01, 161.67, 56.85, 34.74, 32.46, 31.13, 25.21, 16.55, 12.93. ESI-MS m/z: 332.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-(isopropylsulfonyl)-1,3,4-thiadiazol-2-yl) propanamide (7e). White solid, yield 72.4%, mp 226.1–228.5°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.05 (s, 1H, NH), 3.67–3.57 (m, 1H, SO_2CH), 2.81–2.77 (m, 2H, $COCH_2$), 1.88–1.80 (m, 5H, cyclopentane–H), 1.65–1.61 (m, 2H, cyclopentane–H), 1.56–1.52 (m, 2H, cyclopentane–H), 1.48 (d, J = 6.9 Hz, 6H, CH_3), 1.20–1.11 (m, J = 15.1, 7.6 Hz, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.42, 164.36, 161.25, 56.49, 39.70, 35.69, 32.40, 31.30, 25.14, 15.43. ESI-MS m/z: 344.1 $[M + H]^+$.

N-(5-(Butylsulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (7f). White solid, yield 63.2%, mp 183.3–184.3°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.25 (s, 1H, NH), 3.66–3.62 (m, 2H, SO_2CH_2), 2.58–2.54 (m, 2H, $COCH_2$), 1.79–1.71 (m, 3H, cyclopentane–H), 1.66–1.62 (m, 4H, cyclopentane–H, CH_2), 1.59–1.55 (m, 2H, cyclopentane–H), 1.50–1.45 (dd, J = 16.9, 5.3 Hz, 2H, cyclopentane–H), 1.39–1.35 (m, 2H, CH_2), 1.11–1.06 (m, 2H, cyclopentane–CH_2), 0.86 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.09, 162.93, 161.61, 55.03, 34.67, 32.39, 31.06, 25.14, 24.53, 21.13, 13.85. ESI-MS m/z: 346.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-(pentylsulfonyl)-1,3,4-thiadiazol-2-yl) propanamide (7g). White solid, yield 75%, mp 216.3–217.1°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.25 (s, 1H, NH), 3.65–3.65–3.61 (m, 2H, SO_2CH_2), 2.58–2.54 (m, 2H, $COCH_2$), 1.74–1.62 (m, 7H, cyclopentane–H, CH_2), 1.59–1.53 (m, 2H, cyclopentane–H), 1.52–1.44 (m, 2H, cyclopentane–H), 1.36–1.26 (m, 4H, $2CH_2$), 1.11–1.06 (m, 2H, cyclopentane–CH_2), 0.83 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.08, 162.92, 161.62, 55.18, 34.67, 32.39, 31.06, 29.89, 25.13, 22.20, 21.97, 14.08. ESI-MS m/z: 360.1 $[M + H]^+$.

N-(5-(sec-Butylsulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (7h). White solid, yield 75%, mp 210.1–210.4°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.94 (s, 1H, NH), 3.40–3.40–3.36 (m, 1H, SO_2CH), 2.78–2.75 (m, 2H, $COCH_2$), 2.17–2.13 (m, 2H, CH_2), 1.83–1.79 (m, 5H, cyclopentane–H), 1.64–1.61 (m, 2H, cyclopentane–H), 1.54–1.51 (m, 2H, cyclopentane–H), 1.44 (d, J = 6.9 Hz, 3H, CH_3), 1.16–1.12 (m, 2H, cyclopentane–CH_2), 1.05 (t, J = 1.05 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.46, 164.35, 161.68, 62.36, 39.78, 35.76, 32.48, 31.35, 25.22, 22.47, 12.56, 11.19. ESI-MS m/z: 346.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((2-methylbutyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7i). White solid, yield 64.6%, mp 163.1–165.2°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.00 (s, 1H, NH), 3.53–3.48 (m, 1H, SO_2CH), 3.34–3.29 (m, 1H, SO_2CH), 2.80–2.77 (m, 2H, $COCH_2$), 1.89–1.80 (m, 5H, cyclopentane–H), 1.66–1.62 (m, 2H, cyclopentane–H), 1.57–1.50 (m, 4H, cyclopentane–H, CH_2), 1.43–1.34 (m, 1H, CH), 1.21–1.16 (m, 2H, cyclopentane–CH_2), 1.14 (d, J = 6.7 Hz, 3H, CH_3), 0.92 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.36, 164.06, 163.52, 61.41, 39.76, 35.68, 32.42, 31.27, 29.98, 29.35, 25.15, 19.33, 10.76. ESI-MS m/z: 360.1 $[M + H]^+$.

Ethyl 2-((5-(3-cyclopentylpropanamido)-1,3,4-thiadiazol-2-yl)sulfonyl)acetate (7j). White solid, yield 89%, mp 176.8–178.4°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.99 (s, 1H, NH), 4.48 (s, 2H, SO_2CH_2), 4.23–4.19 (m, J = 7.1 Hz, 2H, CH_2CH_3), 2.78–2.75 (m, 2H, $COCH_2$), 1.87–1.79 (m, 5H, cyclopentane–H), 1.63–1.60 (m, 2H, cyclopentane–H), 1.53–1.51 (m, 2H, cyclopentane–H), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.18–1.11 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.50, 164.66, 162.00, 161.64, 63.15, 59.64, 39.75, 35.73, 32.47, 31.36, 25.22, 14.02. ESI-MS m/z: 376.0 $[M + H]^+$.

N-(5-(Benzylsulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (7k). White solid, yield 67.3%, mp 201.4–202.6°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.97 (s, 1H, NH), 7.36–7.32 (m, 3H, Ar–H), 7.26 (d, J = 6.0 Hz, 2H, Ar–H), 4.69 (s, 2H, SO_2CH_2), 2.78–2.75 (m, 2H, $COCH_2$), 1.89–1.79 (m, 5H, cyclopentane–H),

1.66–1.60 (m, 2H, cyclopentane–H), 1.57–1.53 (m, 2H, cyclopentane–H), 1.19–1.14 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.38, 164.53, 161.89, 131.16, 129.66, 129.22, 126.05, 62.07, 39.81, 35.78, 32.52, 31.37, 25.26. ESI-MS *m/z*: 380.1 $[M + H]^+$.

N-(5-((3-Cyanobenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (7l). White solid, yield 65%, mp 168.7–169.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.29 (s, 1H, NH), 7.88 (d, *J* = 7.1 Hz, 1H, Ar–H), 7.73 (s, 1H, Ar–H), 7.62–7.59 (m, 2H, Ar–H), 5.17 (s, 2H, SO_2CH_2), 2.57–2.54 (m, 2H, $COCH_2$), 1.72 (s, 3H, cyclopentane–H), 1.63–1.62 (m, 7.8 Hz, 4H, cyclopentane–H), 1.49–1.48 (d, *J* = 6.6 Hz, 2H, cyclopentane–H), 1.08 (s, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.15, 163.31, 160.49, 136.63, 135.21, 133.12, 130.39, 129.59, 118.69, 111.95, 60.25, 34.69, 32.38, 31.01, 25.13. ESI-MS *m/z*: 405.1 $[M + H]^+$.

N-(5-((4-Cyanobenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)-3-cyclopentylpropanamide (7m). White solid, yield 64.8%, mp 218.4–219°C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 13.23 (s, 1H, NH), 7.82 (d, *J* = 6.9 Hz, 2H, Ar–H), 7.46 (d, *J* = 7.0 Hz, 2H, Ar–H), 5.19 (s, 2H, SO_2CH_2), 2.52 (t, *J* = 7.5 Hz, 2H, $COCH_2$), 1.68–1.61 (m, 3H, cyclopentane–H), 1.60–1.56 (m, 2H, cyclopentane–H), 1.55–1.51 (m, 2H, cyclopentane–H), 1.45–1.43 (m, 2H, cyclopentane–H), 1.04–1.02 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 173.19, 163.33, 160.65, 133.46, 132.95, 132.77, 118.95, 112.21, 60.80, 34.75, 32.45, 31.06, 25.20. ESI-MS *m/z*: 405.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((2-methylbenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7n). White solid, yield 57.4%, mp 196.5–197.1°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.23 (s, 1H, NH), 7.25–7.17 (m, 2H, Ar–H), 7.08–7.04 (m, 2H, Ar–H), 4.98 (s, 2H, SO_2CH_2), 2.58–2.57–2.53 (m, 2H, $COCH_2$), 2.25 (s, 3H, CH_3), 1.77–1.70 (m, 3H, cyclopentane–H), 1.65–1.60 (m, 2H, cyclopentane–H), 1.58–1.56 (m, 2H, cyclopentane–H), 1.50–1.45 (m, 2H, cyclopentane–H), 1.10–1.06 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.07, 163.15, 161.05, 138.17, 132.31, 129.98, 128.93, 128.85, 127.42, 61.34, 34.67, 32.39, 31.02, 25.13, 21.28. ESI-MS *m/z*: 394.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((3-methylbenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7o). White solid, yield 50%, mp 179.4–180.1°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.79 (s, 1H, NH), 7.21–7.18 (m, 2H, Ar–H), 7.14 (s, 1H, Ar–H), 7.01 (d, *J* = 6.9 Hz, 1H, Ar–H), 4.66 (s, 2H, SO_2CH_2), 2.78–2.75 (m, 2H, $COCH_2$), 2.33 (s, 3H, CH_3), 1.88–1.81 (t, *J* = 9.5 Hz, 5H, cyclopentane–H), 1.66–1.61 (m, 2H, cyclopentane–H), 1.56–1.54 (m, 2H, cyclopentane–H), 1.22–1.15 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.27, 164.36, 162.00, 138.99, 131.85, 130.37, 128.92, 128.08, 125.70, 62.00, 39.73, 35.69, 32.44, 31.28, 25.18, 21.34. ESI-MS *m/z*: 394.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((4-methylbenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7p). White solid, yield 59.8%, mp 210–211.2°C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 13.18 (s, 1H, NH), 7.10 (d, *J* = 15.7 Hz, 4H, Ar–H), 4.94 (s, 2H, SO_2CH_2), 2.52–2.49 (m, 2H, $COCH_2$), 2.25 (s, 3H, CH_3), 1.72–1.68 (m, 3H, cyclopentane–H), 1.57–1.53 (m, 4H, cyclopentane–H), 1.46–1.43 (m, 2H, cyclopentane–H), 1.04–1.02 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 173.13, 163.18, 161.10, 138.87, 131.68, 129.69, 124.55, 61.09, 34.74, 32.45, 31.07, 25.20, 21.31. ESI-MS *m/z*: 394.1 $[M + H]^+$.

3-Cyclopentyl-N-(5-((2-fluorobenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7q). White solid, yield 50%, mp 205.6–206.1°C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 13.23 (s, 1H, NH), 7.44–7.39 (m, 1H, Ar–H), 7.33 (t, *J* = 7.6 Hz, 1H, Ar–H), 7.20–7.16 (m, 2H, Ar–H), 5.02 (s, 2H, SO_2CH_2), 2.54–2.51 (m, 2H, $COCH_2$), 1.72–1.66 (m, 3H, cyclopentane–H), 1.60–1.56 (m, 2H, cyclopentane–H), 1.55–1.50 (m, 2H, cyclopentane–H), 1.45–1.43 (m, 2H, cyclopentane–H), 1.07–1.01 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.21, 170.30, 163.34, 162.49, 160.02, 132.70, 132.67, 131.24, 131.16, 124.63, 124.59, 115.81, 115.66, 115.60, 115.51, 56.30, 39.74, 35.68, 32.39, 31.32, 25.16. ESI-MS *m/z*: 398.0 $[M + H]^+$.

3-Cyclopentyl-N-(5-((3-fluorobenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7r). White solid, yield 67%, mp 195.4–196.2°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.25 (s, 1H, NH), 7.43–7.38 (m, 1H, Ar–H), 7.22 (t, *J* = 8.6 Hz, 1H, Ar–H), 7.13 (t, *J* = 7.7 Hz, 2H, Ar–H), 5.10 (s, 2H, SO_2CH_2), 2.57–2.53 (m, 2H, $COCH_2$), 1.77–1.72 (m, 3H, cyclopentane–H), 1.65–1.57 (m, 4H, cyclopentane–H), 1.51–1.46 (m, 2H, cyclopentane–H), 1.09–1.05 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.15, 163.44, 163.29, 161.01, 160.68, 131.07, 130.98, 130.30, 130.22, 127.97, 127.94, 118.56, 118.34, 116.42, 116.22, 60.61, 34.70, 32.38, 31.00, 25.13. ESI-MS *m/z*: 398.0 $[M + H]^+$.

3-Cyclopentyl-N-(5-((4-fluorobenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7s). White solid, yield 60.8%, mp 210.6–211.1°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.23 (s, 1H, NH), 7.34–7.31 (m, 2H, Ar–H), 7.23–7.18 (t, *J* = 8.9 Hz, 2H, Ar–H), 5.06 (s, 2H, SO_2CH_2), 2.57–2.53 (m, 2H, $COCH_2$), 1.77–1.69 (m, 3H, cyclopentane–H), 1.65–1.56 (m, 4H, cyclopentane–H), 1.52–1.46 (m, 2H, cyclopentane–H), 1.10–1.05 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.09, 164.13, 163.20, 161.69, 160.78, 133.96, 133.88, 124.03, 116.15, 115.93, 60.33, 34.68, 32.39, 30.99, 25.13. ESI-MS *m/z*: 398.0 $[M + H]^+$.

3-Cyclopentyl-N-(5-((4-(trifluoromethyl)benzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7t). White solid, yield 83.3%, mp 229.5–230.1°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.26 (s, 1H, NH), 7.76 (d, *J* = 8.1 Hz, 2H,

Ar–H), 7.53 (d, J = 8.0 Hz, 2H, Ar–H), 5.22 (s, 2H, SO_2CH_2), 2.57–2.53 (m, 2H, $COCH_2$), 1.77–1.72 (m, 4H, cyclopentane–H), 1.61–1.59 (m, 3H, cyclopentane–H), 1.58–1.56 (m, 2H, cyclopentane–H), 1.50–1.45 (m, 2H, cyclopentane–H), 1.10–1.07 (m, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.10, 163.26, 160.69, 132.63, 132.55, 131.86, 129.91, 125.92,125.88, 123.15, 60.61, 34.67, 32.38, 31.00, 25.12. ESI-MS m/z: 448.0 $[M + H]^+$.

3-Cyclopentyl-N-(5-((3-methoxybenzyl)sulfonyl)-1,3,4-thiadiazol-2-yl)propanamide (7u). White solid, yield 85.3%, mp 164.2–164.6°C. ^{1}H-NMR (400 MH, $CDCl_3$) δ: 12.55 (s, 1H, NH), 7.22 (d, J = 7.8 Hz, 1H, Ar–H), 6.91–6.79 (m, 3H, Ar–H), 4.67 (s, 2H, SO_2CH_2), 3.78 (s, 3H, OCH_3), 2.76–2.73 (m, 2H, $COCH_2$), 1.83–1.82 (m, 5H, cyclopentane–H), 1.54 (s, 2H, cyclopentane–H), 1.54 (s, 2H, cyclopentane–H), 1.17 (s, 2H, cyclopentane–CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 172.18, 164.24, 161.88, 159.92, 130.08, 127.25, 123.28, 116.61, 115.17, 61.97, 55.35, 39.69, 35.66, 32.44, 31.24, 25.17. ESI-MS m/z: 410.1 $[M + H]^+$.

***In vitro* antibacterial activity test.** According to the turbidimeter test, the target compounds were evaluated *in vitro* antibacterial activity against *Rs*, *Xac*, and *Xoo* [34]. Dimethyl sulfoxide in sterile distilled water served as the blank control, and commercial antibacterial agents, thiodiazole copper and bismerthiazol, were assayed together as the positive control under the same conditions. Nutrient broth (NB) medium (1 L of distilled water, 10 g of glucose, 3 g of beef extract, 5 g of peptone, and 1 g of yeast powder, pH 7.0–7.2) was sterilized. Then, NB (4 mL) and a test compound or commercial bactericide solution (1 mL) were added to a 15 mL tube, and final active ingredient concentrations of 100 and 50 μg/mL were obtained with the addition of bacterial solution. The tubes were incubated for 24–48 h in a constant temperature shaker (180 r.p.m., 28 ± 1°C). The optical density (OD) value (OD_{595}) of the bacterial solution treated with each concentration of the drug was measured when the optical density (OD_{595}) of the blank control group was 0.6 to 0.8 on a microplate reader (Model 680, Bio-Rad, Hercules, CA). Using the following formula to calculate the inhibition rate I (%), A represents the calibration of absorbance values (OD_{595}) of the untreated NB medium, and B represents the calibration of absorbance values (OD_{595}) of the treated NB medium.

$$\text{Inhibition rate } I\ (\%) = (A - B)/A \cdot 100.$$

EC_{50} values were tested on three separate growth inhibition assays and calculated in IBM SPSS STATISTICS.

In vivo antibacterial activity test. We used Schaad's standard leaf clipping method to evaluate the curative and protection activities against *Xoo in vivo* with three replications [35].

Curative activity of compound 7a against Xoo in vivo. Compound 7a and commercial controls (thiodiazole copper and bismerthiazol) were formulated in drug-containing solutions at 200 μg/mL concentration containing 0.1% Tween. After planting "Fengyou xiangzhan" rice seed for approximately one and a half month, sterile scissors were used to cut the leaf tip by 1 to 2 cm, and the wound was soaked in the bacterial solution for 10 s. At the same time, the clear water control and bacterial liquid control without medicament were set. On the next day, a drug solution with 200 μg/mL concentration was sprayed on the surface of the rice leaf until a droplet dripped. A total of 20 rice seedlings were treated for each treatment, which was repeated three times, and the incidence was evaluated 14 days after application. The length of lesions in rice leaves was recorded, and the disease index and control effect were calculated.

Protective activity of compound 7a against Xoo in vivo. The protection activity against potted plants of *Xoo* was assessed under greenhouse conditions. Compound **7a** and commercial controls (thiodiazole copper and bismerthiazol) were formulated in drug-containing solutions at 200 μg/mL concentration containing 0.1% Tween. After planting "Fengyouxiangzhan" rice seeds for approximately one and a half month, the drug-containing solution was sprayed on the surface of rice leaves until droplets dripped. On the next day, sterile scissors were used to cut the leaf tip by 1 to 2 cm, and the wound was soaked in the bacterial solution for 10 s. At the same time, the clear water control and bacterial liquid control without the drug were set. Inoculated rice plants were grown in a greenhouse (28°C and 61% relative humidity). A total of 20 rice seedlings were treated for each treatment, which was repeated three times, and the incidence was evaluated 14 days after application. The length of lesions in rice leaves was recorded, and the disease index and control effect were calculated.

The control effect of the curative and protective activities was calculated according to the following formula, where A represents the disease index of the negative control group and B represents the disease index of the treatment group.

$$\text{Control effect } (\%) = (A - B)/A \cdot 100.$$

The disease marker was graded as follows: level 0, no disease; level 1, the lesions occupy ≤15% of the leaf area; level 2, the lesions accounted for 16–30% of leaf area; level 3, the lesions accounted for 31–50% of leaf area; level 4, the lesions accounted for 51–75% of leaf area; and level 5, the lesions accounted for more than 76% of leaf area.

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AUTHOR CONTRIBUTION

All authors have given approval to the final version of the manuscript.

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