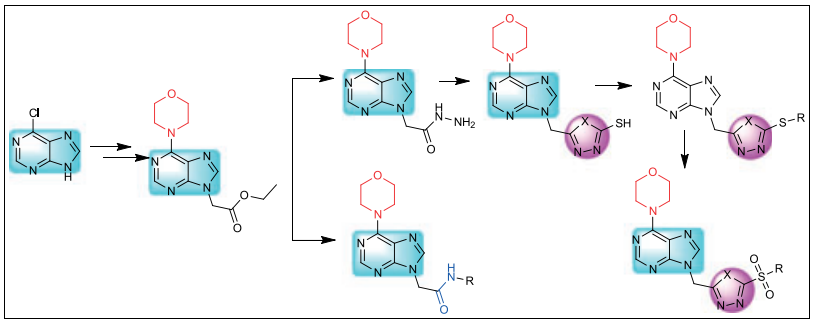
Synthesis and Antibacterial Activity of Novel Substituted Purine Derivatives

Wen-Neng Wu,[a,b] Man-Ni Gao,[a] Hong Tu,[a] and Gui-Ping Ouyang[a]*

[a]State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for Research and Development of Fine Chemicals, Guizhou University, Guiyang 550025, People's Republic of China
[b]Food and Pharmaceutical Engineering Institute, Guiyang College, Guiyang 550003, People's Republic of China
*E-mail: oygp710@163.com

Received June 23, 2015
DOI 10.1002/jhet.2527
Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel *N*-substituted-2-(6-morpholino-9*H*-purin-9-yl)acetamide and 4-(9-((5-substituted-1,3,4-oxadiazole/thiadiazole-2-yl)methyl)-9*H*-purin-6-yl)-morpholine derivatives were synthesized and evaluated their antibacterial activities against rice bacterial leaf blight and tobacco bacterial wilt caused by *Xanthomonas oryzae pv*. *oryzae* (*Xoo*) and *Ralstonia solanacearum* (*R*. *solanacearum*) via the turbidimeter test *in vitro*. Antibacterial bioassay indicated that most compounds demonstrated good inhibitory effect against *Xoo* and *R*. *solanacearum*. Especially, compound **6a** demonstrated the best inhibitory effect against *Xoo* with half-maximal effective concentration (EC_{50}) value of 8.39 μg/mL, which was even better than those of commercial agents Bismerthiazol and Thiodiazole copper. The synthesized purine derivatives containing amide and 1,3,4-oxadiazole/thiadiazole moieties exhibited excellent *antibacterial activities against Xanthomonas oryzae pv*. *oryzae* and *R*. *solanacearum in vitro*.

INTRODUCTION

Purines are the most ubiquitous components containing nitrogen heterocycle in nature [1]. They are constituted for DNA and RNA and consequently of fundamental importance in life processes [2–4]. The biological importance of naturally occurring purines has led to an interest in studies of the biological activities of synthetically modified purines [5]. A wide range of purine derivatives, such as purine, purines nucleosides, and their analogs, have been developed, and have exhibited potential activity as enzyme inhibitors [6], cytotoxic [7], antiviral [8], antihyperglycemic [9], immunostimulator [10], anticonvulsant [11], antimalarial [12], anticancer [13], anti-inflammatory [14], anti-lipid peroxidation [15], antifungal [16], and antibacterial [17] activities.

1,3,4-Oxadiazole/thiadiazole, a privileged structure, represents a key motif in heterocyclic chemistry and has shown excellent performances in antibacterial [18], antiviral [19,20],antifungal [21], anti-inflammatory [22], anti-anxiety [23], and antitubercular [24] activities. Meanwhile, sulfone derivatives are also known to exhibit a wide spectrum biological activities because the sulfone group is an important core found in many biologically active compounds with a wide range of biological activity including antibacterial [25], antifungal [26], insecticidal [27], antiviral [28], herbicidal [29], anticancer [30], anti-HIV-1 [31], antihepatitis [32], antitumor [33], and anti-inflammatory [34] properties. In recent years, our research group designed and synthesized a series of 2-substituted 1,3,4-oxadiazole/thiadiazole derivatives and 2-substituted 1,3,4-oxadiazole/thiadiazole sulfone derivatives which showed excellent antibacterial activities [35,36].

The union of active group is a versatile technology for searching for new broad-spectrum and high-performance bactericide. Herein, we attempt to design and synthesize a series of purine derivatives via union of active group based on taking into account the above findings, and evaluated their antibacterial activities. It is believed that these purine derivatives have a very promising prospect in bactericide.

RESULTS AND DISCUSSION

Chemistry. The detailed synthetic route for the preparation of *N*-substituted-2-(6-morpholino-9*H*-purin-9-yl) acetamide and 4-(9-((5-substituted-1,3,4-oxadiazole/thiadiazole-

2-yl)methyl)-9*H*-purin-6-yl)-morpholine derivatives is summarized in **Scheme** 1. Ethyl 2-(6-morpholino-9*H*-purin-9-yl)acetate (**2**) was prepared by 6-chloro-9*H*-purine (**1**) on reaction with ethyl 2-chloroacetate in the presence of potassium carbonate in the DMF. The key intermediate ethyl 2-(6-morpholino-9*H*-purin-9-yl)acetate (**3**) was synthesized from ethyl 2-(6-morpholino-9*H*-purin-9-yl)-acetate (**2**) reacting with morpholine in the presence of ethanol. Compounds **4a–4i** were prepared by the ethyl 2-(6-morpholino-9*H*-purin-9-yl)acetate (**3**) and arylalkylamine in ethanol under reflux conditions. Compounds **5–8** were synthesized from ethyl 2-(6-morpholino-9*H*-purin-9-yl)-acetate (**3**) through sequential reactions including hydrazidation, cyclization, thioetherification, and oxidation [19,20,25]. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis.

The structures of compounds **4a–4h** and **5–8** were confirmed by spectral method. The IR spectrum of **4a–4h** and **5–8** displayed absorption bands between 1680.4 and 1473.4 cm^{-1} corresponding to C=C and C=N. The ^{1}H NMR spectrum of **7b** in DMSO-d_6 displayed a triplet at δ 1.35 ppm and a quartet at δ 3.31 ppm that corresponds to —S—CH_2CH_3 functionality, a triplet at δ 3.73 ppm and a multiplet at δ 4.21 ppm that corresponds to morpholine functionality, and a singlet at δ 5.74 ppm integrating for two protons was assigned to —CH_2— protons of Imidazole–CH_2. A singlet that appeared at δ 8.27 ppm was observed because of the protons of Imidazole. It was noteworthy that the pyrimidine proton appeared down-filed (δ 8.32 ppm) in DMSO-d_6 solvent. The structure of **7b** was also confirmed by its mass spectral data. In its mass spectrum, the molecular ion peak was noticed m/z at 348.1 ([M+H]$^+$), 370.1 ([M+Na]$^+$) corresponding to its molecular weight.

Antibacterial activity of the synthesized compounds. A series of *N*-substituted-2-(6-morpholino-9*H*-purin-9-yl)-acetamide and 4-(9-((5-substituted-1,3,4-oxadiazole/thiadiazole-2-yl)methyl)-9*H*-purin-6-yl)-morpholine were tested *in vitro* antibacterial activities against *Xanthomonas oryzae pv. oryzae* (*Xoo*) and *Ralstonia solanacearum* (*R. solanacearum*) by the turbidimeter test [25,37,38], and the commercial agricultural antibacterial agents Bismerthiazol and Thiodiazole copper were used as the references. As shown in Table 1, compounds **6a**, **7a**, **7b**,

Table 1

Antibacterial activity of the synthesized compounds against *Xanthomonas oryzae pv. oryzae and Ralstonia solanacearum in vitro*.

	Inhibition rate (%)[a]			
	Xanthomonas oryzae pv. oryzae		*Ralstonia solanacearum*	
Compds.	200 (mg/L)	100 (mg/L)	200 (mg/L)	100 (mg/L)
3	25 ± 1.01	12 ± 0.61	32 ± 1.33	19 ± 1.57
4a	30 ± 0.94	16 ± 2.13	37 ± 0.73	21 ± 1.85
4b	32 ± 1.48	18 ± 1.50	40 ± 0.63	26 ± 3.01
4c	35 ± 2.41	21 ± 2.15	42 ± 0.78	26 ± 1.37
4d	38 ± 1.22	25 ± 3.03	46 ± 0.96	29 ± 1.81
4e	61 ± 2.40	35 ± 1.33	58 ± 2.06	36 ± 0.85
4f	45 ± 0.72	27 ± 1.69	50 ± 0.62	32 ± 2.56
4g	40 ± 1.94	26 ± 3.32	48 ± 2.71	30 ± 2.05
4h	67 ± 1.45	39 ± 2.26	61 ± 0.68	39 ± 2.71
5	52 ± 3.46	31 ± 0.94	51 ± 1.76	33 ± 3.09
6a	100 ± 1.24	100 ± 1.08	79 ± 0.67	52 ± 1.60
6′a	100 ± 0.49	87 ± 1.73	63 ± 1.18	33 ± 1.24
7a	100 ± 0.51	100 ± 1.72	76 ± 2.11	50 ± 1.50
7b	100 ± 1.06	100 ± 1.17	70 ± 0.97	46 ± 1.28
7′a	100 ± 1.55	100 ± 0.84	54 ± 1.36	30 ± 2.15
7′b	100 ± 0.98	78 ± 1.21	47 ± 2.31	26 ± 1.40
8a	85 ± 1.25	51 ± 2.13	63 ± 3.41	43 ± 1.82
8b	77 ± 1.20	45 ± 1.93	51 ± 1.37	25 ± 1.80
8′a	73 ± 3.43	42 ± 3.33	54 ± 1.63	43 ± 1.45
8′b	66 ± 2.51	37 ± 1.39	42 ± 1.16	26 ± 1.07
Bismerthiazol	72 ± 0.65	54 ± 1.23	50 ± 2.11	30 ± 5.41
Thiodiazole copper	64 ± 2.76	43 ± 3.15	/	/

[a]The experiments were repeated three times.

Scheme 1. Synthetic route to compounds **2–8**.

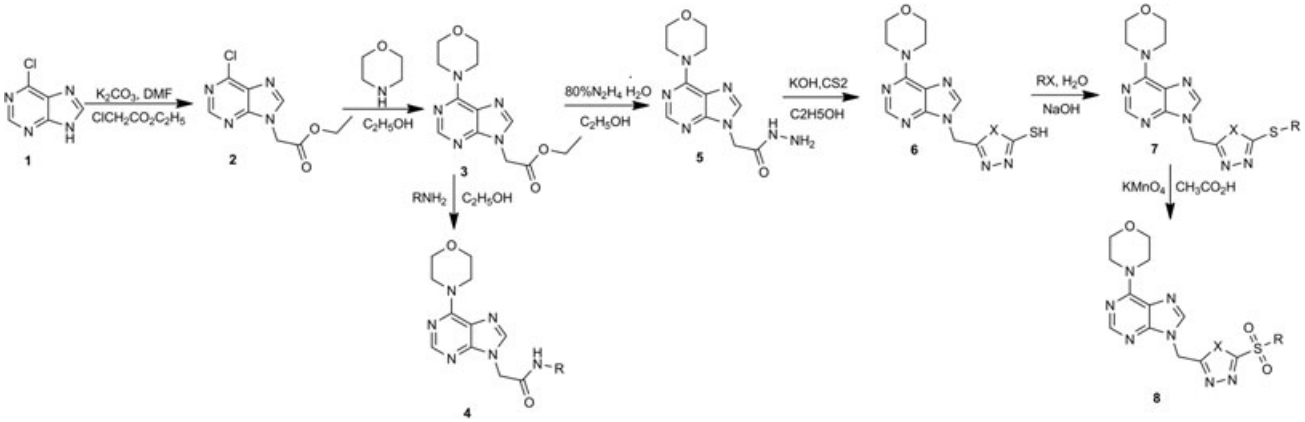


Table 2

Antibacterial activity of the test compounds against *Xanthomonas oryzae pv. oryzae*.

Compds.	EC_{50} (μg/mL)	Toxic regression equation	*R*
6a	8.39 ± 1.56	y = 1.558x + 4.410	0.98
6′a	32.28 ± 1.87	y = 2.351x + 1.177	0.98
7a	10.29 ± 2.34	y = 1.674x + 3.756	0.96
7b	15.38 ± 0.68	y = 1.409x + 4.538	0.97
7′a	19.61 ± 1.98	y = 1.327x + 3.285	0.99
7′b	37.66 ± 2.91	y = 1.723x + 2.281	0.97
8a	67.80 ± 2.76	y = 1.336x + 3.285	0.99
8b	73.52 ± 2.48	y = 1.845x + 1.372	0.99
8′a	79.84 ± 2.13	y = 1.950x + 1.298	0.99
Bismerthiazol	91.54 ± 2.14	y = 1.499x + 2.051	0.98
Thiodiazole copper	124.68 ± 3.32	y = 1.540x + 1.790	0.98

and **7′a** possessed excellent antibacterial activity against *Xoo*, with an inhibition rate of 100% at 200 and 100 μg/mL, respectively, which was even better than those of Bismerthiazol (72% and 54%, respectively) and Thiodiazole copper (64% and 43%, respectively). Meanwhile, Table 1 showed that compounds **6a**, **6′a**, **7a**, **7b**, **8a**, and **8′a** showed excellent antibacterial activity against *R. solanacearum* at 200 μg/mL, with inhibition rates of 79%, 63%, 76%, 70%, 63%, and 54%, respectively, which were better compared with standard drug Bismerthiazol (50%).

As illustrated in the previous bioassays, the half-maximal effective concentration (EC_{50}) values of some of the synthesized compounds as well as for Bismerthiazol and Thiodiazole copper were presented in Table 2. Table 2 showed that all of the test compounds showed moderate to excellent activity against *Xoo*, with EC_{50} values of 8.39–79.84 μg/mL. Excitingly, compounds **6a**, **7a**, **7b**, and **7′a** showed prominent activity against *Xoo in vitro*, with EC_{50} values of 8.39, 10.29, 15.38, and 19.61 μg/mL, respectively, which were even better than that of the commercial bactericide Bismerthiazol (92.61 μg/mL).

CONCLUSIONS

A series of purine derivatives containing amide and 1,3,4-oxadiazole/thiadiazole moieties were synthesized and evaluated their antibacterial activities against *Xoo* and *R. solanacearum* by the turbidimeter test *in vitro*. The bioassays result demonstrated that some of the synthesized compounds exhibited excellent antibacterial activity against *Xoo*. Among these compounds, compound **6a** against *Xoo*, with EC_{50} value of 8.39 μg/mL, which was better than those of Bismerthiazol and Thiediazole copper. This work demonstrated that the compound **6a** can be used to develop potential bactericides for plants.

EXPERIMENTAL

General procedure. Unless otherwise noted, all common reagents and solvents were used as obtained from commercial supplies without further purifications. The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. ^{1}H and ^{13}C NMR (solvent DMSO-d_6) spectra were recorded on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Infrared spectra were recorded in KBr on a Bruker VECTOR 22 spectrometer. Mass spectral studies were conducted on an Agilent 5973 organic mass spectrometer. TLC was performed on silica gel GF254. All anhydrous solvents were dried and purified according to standard techniques before use.

General procedure for synthesis of ethyl 2-(6-chloro-9*H*-purin-9-yl)acetate (2). Ethyl 2-chloroacetate (1.47 g, 12 mmol) was added dropwise to a solution of 6-chloro-9*H*-purine (**1**) (1.54 g, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) in DMF (10 mL), then the reaction mixture was stirred at room temperature. After stirring for 5 h, the mixture was evaporated under the reduced pressure, and subsequently diluted with water. The mixture was filtered and the obtained solids were recrystallized from ethanol to give ethyl 2-(6-chloro-9*H*-purin-9-yl)acetate (**2**).

Ethyl 2-(6-chloro-9H-purin-9-yl)acetate (2). White solid; yield 76.2%; m.p. 206–207°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.65 (s, 1H, Pyrimidine–H), 8.19 (s, 1H, Imidazole–H), 5.11 (s, 2H), 4.22–4.25 (m, 2H), 1.25 (t, 3H, J = 6.85 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 168.60, 153.78, 152.64, 151.40, 141.14, 119.20, 61.90, 45.62, 14.53; MS (ESI) m/z: 240.1 ([M + H]$^+$), 362.1([M + Na]$^+$).

General procedure for synthesis of ethyl 2-(6-morpholino-9*H*-purin-9-yl)-acetate (3). To an ice-bath cool solution of ethyl 2-(6-chloro-9*H*-purin-9-yl)acetate (**2**) (2.40 g, 10 mmol) in ethanol (20 mL) was added dropwise morpholine (1.05 g, 12 mmol). After heating and stirring for 6 h, the reaction mixture was cooled, poured into ice-water, and the precipitated solid was filtered, washed with water and recrystallized from ethanol and DMF to give ethyl 2-(6-morpholino-9*H*-purin-9-yl)-acetate (3).

Ethyl 2-(6-morpholino-9H-purin-9-yl)acetate (3). White solid; yield 70.1%; m.p. 223–225°C; IR (KBr, cm^{-1}): v 3519.2, 3373.6, 2993.5, 2851.4, 1654.0, 1628.9, 1673.9, 1486.2, 1240.2, 1115.9, 1041.6, 817.8, 650.1; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.25 (s, 1H, Pyrimidine–H), 8.19 (s, 1H, Imidazole–H), 5.09 (s, 2H), 4.20–4.25 (m, 5H), 3.73 (t, 5H, J = 5.15 Hz), 1.23 (t, 3H, J = 6.85 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 168.40, 153.73, 152.53, 151.37, 141.11, 119.13, 66.71, 61.92, 45.52, 14.54; MS (ESI) m/z: 292.1 ([M + H]$^+$), 314.1([M + Na]$^+$).

General procedure for synthesis of *N*-substituted-2-(6-morpholino-9*H*-purin-9-yl)acetamide 4a–4h. To a solution of ethyl 2-(6-morpholino-9*H*-purin-9-yl)-acetate (0.59 g, 2 mmol) in ethanol (20 mL) was added dropwise arylalkylamine (10 mmol). After heating and stirring for 10 h, the mixture was evaporated under the reduced pressure, subsequently diluted with water, and was filtered and the solid obtained and recrystallized from ethanol to give compounds **4a–4h**.

***N*-methyl-2-(6-morpholino-9H-purin-9-yl)acetamide (4a).** White solid; yield 71.3%; m.p. 221–222°C; IR (KBr, cm^{-1}): *v* 3292.6, 2993.5, 1658.8, 1586.5, 1481.3, 1327.0, 1263.4, 1114.9, 996.2, 794.7, 648.1; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.23 (s, 1H, Pyrimidine–H), 8.19 (s, 1H, CONH), 8.13 (s, 1H, Imidazole–H), 4.84 (s, 2H), 4.19–4.23 (m, 3H), 3.73 (t, 5H, J = 5.15 Hz), 2.62 (d, 3H, J = 4.6 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 167.18, 153.69, 152.30, 151.42, 141.64, 119.21, 66.75, 45.53, 26.17; MS (ESI) m/z: 277.1 ($[M+H]^+$), 299.1($[M+Na]^+$); *Anal*. Calcd. for $C_{12}H_{16}N_6O_2$: C 52.16, H 5.84, N 30.42; found C 52.19, H 5.82, N 30.40.

***N*-ethyl-2-(6-morpholino-9H-purin-9-yl)acetamide (4b).** White solid; yield 78.2%; m.p. 215–216°C; IR (KBr, cm^{-1}): *v* 3289.7, 2993.5, 2943.1, 1676.2, 1654.0, 1591.3, 1570.1, 1480.4, 1250.8, 1112.9, 1004.9, 791.8, 647.1; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.28 (s, 1H, CONH), 8.23 (s, 1H, Pyrimidine–H), 8.13 (s, 1H, Imidazole–H), 4.83 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 5H, J = 5.15 Hz), 3.24 (q, 2H, J = 7.4 Hz), 1.05 (t, 2H, J = 6.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 166.38, 153.69, 152.28, 151.43, 141.69, 119.21, 66.75, 45.51, 34.21, 15.12; MS (ESI) m/z: 291.2 ($[M+H]^+$), 313.1($[M+Na]^+$); *Anal*. Calcd. for $C_{13}H_{18}N_6O_2$: C 53.78, H 6.25, N 28.95; found C 53.75, H 6.23, N 28.94.

***N*-isopropyl-2-(6-morpholino-9H-purin-9-yl)acetamide (4c).** White solid; yield 80.2%; m.p. 139–140°C; IR (KBr, cm^{-1}): *v* 3275.2, 2995.2, 2971.3, 2850.4, 1653.0, 1590.3, 1558.5, 1457.2, 1222.9, 1121.6, 1007.8, 793.4, 647.1; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.25 (s, 1H, CONH), 8.23 (s, 1H, Pyrimidine–H), 8.19 (s, 1H, Imidazole–H), 5.09 (s, 2H), 4.20–4.25 (m, 4H), 3.72 (t, 5H, J = 4.55 Hz), 1.05 (t, 6H, J = 7.45 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 168.40, 153.74, 152.53, 151.37, 141.12, 119.13, 66.70, 61.92, 44.52, 22.85, 34.21, 14.54; MS (ESI) m/z: 305.2 ($[M+H]^+$), 327.1($[M+Na]^+$); *Anal*. Calcd. for $C_{14}H_{20}N_6O_2$: C 55.25, H 6.62, N 27.61; found C 55.28, H 6.61, N 27.63.

***2*-(6-Morpholino-9H-purin-9-yl)-*N*-propylacetamide (4d).** Yellow solid; yield 80.2%; m.p. 207–208°C; IR (KBr, cm^{-1}): *v* 3285.8, 2997.5, 2963.1, 2963.1, 1659.8, 1585.5, 1572.0, 1557.5, 1453.4, 1248.9, 1124.5, 1010.7, 796.6, 648.1; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.27 (s, 1H, CONH), 8.23 (s, 1H, Pyrimidine–H), 8.13 (s, 1H, Imidazole–H), 4.84 (s, 2H), 4.18–4.22 (m, 3H), 3.73 (t, 5H, J = 5.15 Hz), 3.05 (q, 2H, J = 6.85 Hz), 1.45–1.47 (m, 2H), 0.85 (t, 3H, J = 7.45 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 166.58, 153.69, 152.28, 151.43, 141.69, 119.21, 66.75, 45.52, 41.08, 22.78, 11.90; MS (ESI) m/z: 305.2 ($[M+H]^+$), 327.1($[M+Na]^+$); *Anal*. Calcd. for $C_{14}H_{20}N_6O_2$: C 55.25, H 6.62, N 27.61; found C 55.24, H 6.63, N 27.59.

***N*-(2-aminoethyl)-2-(6-morpholino-9H-purin-9-yl)acetamide (4e).** Yellow solid; yield 68.5%; m.p. 184–185°C; IR (KBr, cm^{-1}): *v* 3326.3, 2997.4, 2961.1, 1675.2, 1588.4, 1569.1, 1476.5, 1285.6, 1248.9, 1112.0, 1004.9, 868.9, 642.3; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.27 (s, 1H, CONH), 8.23 (s, 1H, Pyrimidine–H), 8.13 (s, 1H, Imidazole–H), 4.85 (s, 2H), 4.19–4.22 (m, 3H), 3.73 (t, 5H, J = 5.15 Hz), 3.34 (s, 2H, NH_2), 3.08 (t, 2H, J = 6.3 Hz), 3.41 (t, 2H, J = 5.7 Hz), 2.59 (t, 2H, J = 6.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 166.77, 153.71, 152.28, 151.44, 141.70, 119.21, 66.75, 45.59, 43.13, 41.74; MS (ESI) m/z: 306.2 ($[M+H]^+$), 328.1($[M+Na]^+$); *Anal*. Calcd. for $C_{13}H_{19}N_7O_2$: C 51.14, H 6.27, N 32.11; found C 51.11, H 6.30, N 32.13.

***2*-(6-Morpholino-9H-purin-9-yl)-1-(pyrrolidin-1-yl)ethanone (4f).** white solid; yield 75.6%; m.p. 232–234°C; IR (KBr, cm^{-1}): *v* 2997.4, 2961.1, 2912.3, 1672.3, 1585.5, 1573.0, 1450.3, 1334.8, 1301.0, 1248.9, 1105.2, 1021.3, 788.9, 687.6, 644.2; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.24 (s, 1H, Pyrimidine–H), 8.09 (s, 1H, Imidazole–H), 5.06 (s, 2H), 4.19–4.22 (m, 3H), 3.73 (t, 5H, J = 5.15 Hz), 3.59 (t, 2H, J = 6.9 Hz), 3.34 (t, 2H, J = 5.75 Hz), 1.63–1.66 (m, 4H), 1.45–1.47 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 164.84, 153.71, 152.24, 151.58, 141.66, 119.11, 66.74, 46.35, 45.68, 45.19, 26.18, 24.24; MS (ESI) m/z: 317.2 ($[M+H]^+$), 339.1($[M+Na]^+$); *Anal*. Calcd. for $C_{15}H_{20}N_6O_2$: C 56.95, H 6.37, N 26.56; found C 56.95, H 6.37, N 26.56.

***2*-(6-Morpholino-9H-purin-9-yl)-1-(piperidin-1-yl)ethanone (4g).** White solid; yield 80.2%; m.p. 193–195°C; IR (KBr, cm^{-1}): *v* 2996.9, 2953.4, 2853.8, 1648.2, 1585.5, 1569.1, 1559.5, 1473.6, 1447.6, 1326.1, 1253.7, 1122.6, 1016.5, 814.0, 789.8, 651.0; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.23 (s, 1H, Pyrimidine–H), 8.09 (s, 1H, Imidazole–H), 5.13 (s, 2H), 4.19–4.23 (m, 3H), 3.73 (t, 5H, J = 5.15 Hz), 3.51 (t, 2H, J = 4.3 Hz), 3.41 (t, 2H, J = 5.7 Hz), 1.61–1.65 (m, 4H), 1.45–1.47 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 164.87, 153.71, 152.21, 151.64, 141.85, 119.14, 66.75, 45.63, 44.61, 40.54, 26.41, 25.67, 24.39; MS (ESI) m/z: 331.2 ($[M+H]^+$), 353.1($[M+Na]^+$); *Anal*. Calcd. for $C_{16}H_{22}N_6O_2$: C 58.17, H 6.71, N 25.44; found C 58.15, H 6.74, N 25.42.

***1*-Morpholino-2-(6-morpholino-9H-purin-9-yl)ethanone (4h).** White solid; yield 80.2%; m.p. 208–209°C; IR (KBr, cm^{-1}): *v* 3526.9, 3373.6, 2978.9, 2903.4, 2855.7, 1652.1, 1589.4, 1575.9, 1569.1, 1486.2, 1426.4, 1240.2, 1115.8, 1041.6, 995.3, 816.8, 650.0, 575.7; ^{1}H NMR

(DMSO-d_6, 500 MHz) δ: 8.24 (s, 1H, Pyrimidine–H), 8.09 (s, 1H, Imidazole–H), 5.18 (s, 2H), 4.19–4.21 (m, 3H), 3.73 (t, 5H, J = 4.6 Hz), 3.57–3.62 (m, 6H), 3.44 (t, 2H, J = 4.55 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 165.59, 153.71, 152.25, 151.64, 141.75, 119.13, 66.74, 66.50, 66.45, 45.16, 45.54, 40.37; MS (ESI) m/z: 333.2 ([M + H]$^+$), 355.1([M + Na]$^+$); *Anal*. Calcd. for $C_{15}H_{20}N_6O_3$: C 54.21, H 6.07, N 25.29; found C 54.19, H 6.06, N 25.32.

General procedure for synthesis of 2-(6-morpholino-9*H*-purin-9-yl)aceto hydrazide (5). To an ice-bath cool solution of ethyl 2-(6-chloro-9*H*-purin-9-yl)acetate (5.86 g, 20 mmol) in ethanol (40 mL), was added dropwise 80% hydrazine hydrate (5 mL) in ethanol (8 mL). After the addition, the reaction mixture was stirred 2 h at room temperature. The reaction mixture was cooled and collected on filter.

2-(6-Morpholino-9H-purin-9-yl)acetohydrazide (5). White solid; yield 90.6%; m.p. 234–235°C; IR (KBr, cm^{-1}): v 3312.8, 2995.7, 2863.4, 1653.0, 1594.2, 1570.1, 1550.8, 1477.3, 1262.4, 1111.0, 1010.7, 641.3; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.41 (s, 1H, CONH), 8.19 (s, 1H, Pyrimidine–H), 8.11 (s, 1H, Imidazole–H), 5.13 (s, 2H), 4.27 (s, 2H), 4.17–4.20 (m, 3H), 3.69 (t, 5H, J = 4.6 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 166.30, 153.69, 152.30, 151.37, 141.59, 119.23, 66.75, 44.33; MS (ESI) m/z: 278.1 ([M + H]$^+$), 300.1 ([M + Na]$^+$); *Anal*. Calcd. for $C_{11}H_{15}N_7O_2$: C 47.65, H 5.45, N 35.36; found C 47.67, H 5.44, N 35.38.

General procedure for synthesis of 5-((6-morpholino-9*H*-purin-9-yl)methyl)-1,3,4-oxadiazole-2-thiol (6). 2-(6-Morpholino-9*H*-purin-9-yl)acetohydrazide (**5**) (20 mmol), potassium hydroxide (20 mmol), and 100 mL of ethanol were added into a round-bottom flask and stirred for 10 min, followed by addition of carbon disulfide (24 mmol) to the mixture. The resulting mixture was refluxed for 4 h and monitored by TLC until completion. The mixture was evaporated under the reduced pressure and subsequently diluted with water. The mixture was neutralized with concentrated hydrochloric acid and the precipitated solid was filtered, washed with water, and recrystallized from ethanol and DMF to give the compound **6**.

5-((6-Morpholino-9H-purin-9-yl)methyl)-1,3,4-oxadiazole-2-thiol (6). White solid; yield 83.5%; m.p. 153–155°C; IR (KBr, cm^{-1}): v 3372.6, 2994.2, 2962.4, 2859.8, 1592.3, 1570.1, 1506.4, 1476.5, 1256.6, 1004.9, 942.2, 633.6; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.31 (s, 1H, Pyrimidine–H), 8.28 (s, 1H, Imidazole–H), 5.62 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 5H, J = 5.15 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 178.44, 159.63, 153.75, 152.79, 151.12, 140.65, 119.18, 66.68, 38.27; MS (ESI) m/z: 320.1 ([M + H]$^+$), 342.1([M + Na]$^+$); *Anal*. Calcd. for $C_{12}H_{13}N_7O_2S$: C 45.13, H 4.10, N 30.70; found C 45.10, H 4.11, N 30.70.

General procedure for synthesis of 5-((6-morpholino-9*H*-purin-9-yl)methyl)-1,3,4-thiadiazole-2-thiol (6′). 2-(6-Morpholino-9*H*-purin-9-yl)acetohydrazide (**5**) (20 mmol), potassium hydroxide (20 mmol), and 400 mL ethanol were added in round-bottom flask equipped for 20 min. Then carbon disulfide (24 mmol) was added dropwise to the above precooled reaction mixture, which resulted in formation of a white precipitate. The white precipitate was filtered and repeatedly washed with cold ethanol (3 × 30 mL) and dried in an oven. The dried salt was added in very small portion to cooled concentrated sulfuric acid (30 mL, 0°C) taken in a round-bottomed flask and stirred till the solution became homogenous. The mixture was poured into crushed ice (1000 g). The mixture was neutralized with sodium bicarbonate, and the precipitated solid was filtered, washed with water, and recrystallized from ethanol and DMF to give the compound **6′**.

5-((6-Morpholino-9H-purin-9-yl)methyl)-1,3,4-thiadiazole-2-thiol (6′). White solid; yield 88.3%; m.p. 244–246°C; IR (KBr, cm^{-1}): v 3480.7, 2989.5, 2940.1, 2847.2, 1594.6, 1573.0, 1475.6, 1326.0, 1249.9, 1065.7, 994.3, 789.8, 645.2; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.28 (s, 1H, Pyrimidine–H), 8.27 (s, 1H, Imidazole–H), 5.61 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 5H, J = 5.15 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 159.53, 153.74, 152.70, 151.00, 140.58, 119.29, 66.68, 42.17; MS (ESI) m/z: 336.1 ([M + H]$^+$); *Anal*. Calcd. for $C_{12}H_{13}N_7OS_2$: C 42.97, H 3.91, N 29.23; found C 42.96, H 3.90, N 29.25.

General procedure for synthesis of 4-(9-((5-substituted-1,3,4-oxadiazole/thiadiazole-2-yl)-methyl)-9*H*-purin-6-yl)morpholine. To a solution of 5-((6-morpholino-9*H*-purin-9-yl)methyl)-1,3,4-oxadiazole/thiadiazole-2-thiol (4 mmol) and sodium hydroxide (4.2 mmol) in water (25 mL). The mixture was stirred at room temperature for 20 min, and then dimethyl sulfate (4.2 mmol) and diethyl sulfate (4.2 mmol) were added to the reaction mixture and stirred at room temperature for 2 h. The mixture was filtered, and the solid was obtained and recrystallized from DMF and ethanol to give compounds **7** and **7′**.

4-(9-((5-(Methylthio)-1,3,4-oxadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (7a). White solid; yield 89.6%; m.p. 137–138°C; IR (KBr, cm^{-1}): v 3230.7, 2992.2, 2855.8, 1582.6 1575.9, 1558.5, 1476.5, 1255.7, 1163.1, 1112.0, 1003.0, 789.8, 645.2; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.32 (s, 1H, Pyrimidine–H), 8.26 (s, 1H, Imidazole–H), 5.73 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 5H, J = 5.15 Hz), 2.67 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 165.90, 163.59, 153.74, 152.75, 151.11, 140.64, 119.20, 66.69, 38.09, 14.83; MS (ESI) m/z: 334.2 ([M + H]$^+$), 366.1([M + Na]$^+$); *Anal*. Calcd. for $C_{13}H_{15}N_7O_2S$: C 46.84, H 4.54, N 29.41; found C 46.85, H 4.56, N 29.40.

4-(9-((5-(Ethylthio)-1,3,4-oxadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (7b). Yellow solid; yield 88.5%; m.p. 131–132°C; IR (KBr, cm^{-1}): *v* 3237.3, 2995.7, 2871.4, 1589.3 1574.5, 1558.5, 1476.1, 1250.7, 1112.7, 786.9, 647.5; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.32 (s, 1H, Pyrimidine–H), 8.27 (s, 1H, Imidazole–H), 5.74 (s, 2H), 4.19–4.22 (m, 3H), 3.73 (t, 5H, $J = 5.15$ Hz), 3.31 (q, 2H, $J = 7.4$ Hz), 1.35 (t, 2H, $J = 7.15$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 164.96, 163.62, 153.75, 152.73, 151.13, 141.66, 119.23, 66.70, 38.11, 27.18, 15.27; MS (ESI) m/z: 348.1 ($[M+H]^+$), 370.1($[M+Na]^+$); *Anal*. Calcd. for $C_{14}H_{17}N_7O_2S$: C 45.13, H 4.10, N 30.70; found C 45.10, H 4.11, N 30.70.

4-(9-((5-(Methylthio)-1,3,4-thiadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (7′a). White solid; yield 85.2%; m.p. 203–204°C; IR (KBr, cm^{-1}): *v* 3430.5, 2997.3, 2963.1, 2853.1, 1593.2, 1570.1, 1472.7, 1329.9, 1249.9, 1111.0, 1004.9, 791.8, 638.4; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.36 (s, 1H, Pyrimidine–H), 8.29 (s, 1H, Imidazole–H), 5.86 (s, 2H), 4.18–4.21 (m, 3H), 3.72 (t, 5H, $J = 5.15$ Hz), 2.71 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 169.48, 165.19, 153.75, 152.69, 150.91, 140.54, 119.38, 66.69, 41.84, 16.99; MS (ESI) m/z: 350.1 ($[M+H]^+$), 372.1($[M+Na]^+$); *Anal*. Calcd. for $C_{13}H_{15}N_7OS_2$: C 44.68, H 4.33, N 28.06; found C 44.71, H 4.35, N 28.04.

4-(9-((5-(Ethylthio)-1,3,4-thiadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (7′b). Yellow solid; yield 87.3%; m.p. 155–156°C; IR (KBr, cm^{-1}): *v* 3430.6, 2999.6, 2963.7, 2857.1, 1591.3, 1575.9, 1479.4, 1470.7, 1327.0, 1248.9, 1111.0, 1001.1, 790.8, 639.4; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.36 (s, 1H, Pyrimidine–H), 8.29 (s, 1H, Imidazole–H), 5.87 (s, 2H), 4.19–4.23 (m, 3H), 3.73 (t, 5H, $J = 5.15$ Hz), 3.24 (q, 2H, $J = 7.4$ Hz), 1.35 (t, 2H, $J = 7.45$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 167.81, 165.42, 153.74, 152.68, 150.93, 140.56, 119.38, 66.69, 41.83, 28.76, 14.93; MS (ESI) m/z: 364.1 ($[M+H]^+$), 386.1($[M+Na]^+$); *Anal*. Calcd. for $C_{14}H_{17}N_7OS_2$: C 46.26, H 4.71, N 26.98; found C 46.24, H 4.73, N 27.01.

General procedure for synthesis of 4-(9-((5-(substituted-sulfonyl)-1,3,4-oxadiazole/thiadiazole-2-yl)methyl)-9*H*-purin-6-yl)morpholine. A solution of 4-(9-((5-substituted-1,3,4-oxadiazole/thiadiazole-2-yl)-methyl)-9*H*-purin-6-yl)morpholine (3 mmol) in glacial acetic acid was treated dropwise at 10°C with potassium permanganate as a 5% aqueous solution over 30 min. The reactions were reacted for 20–35 min at room temperature. Then, the redundant potassium permanganate of the mixture was deoxidized by 10% sodium bisulfite solution and distilled water, dried under vacuum, and recrystallized from ethanol to give pure products **8** and **8′**.

4-(9-((5-(Methylsulfonyl)-1,3,4-oxadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (8a). Yellow needle; yield 60.5%; m.p. 132–134°C; IR (KBr cm^{-1}): *v* 3430.5, 2994.2, 2971.1, 2851.6, 1589.4, 1569.1, 1558.5, 1479.4, 1457.2, 1349.2, 1262.4, 1112.9, 1003.9, 743.5, 645.2; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.32 (s, 1H, Pyrimidine–H), 8.26 (s, 1H, Imidazole–H), 5.73 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 5H, $J = 5.15$ Hz), 3.53 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 165.90, 163.59, 153.74, 152.75, 151.11, 140.64, 119.20, 66.69, 38.09, 31.23; MS (ESI) m/z: 366.1 ($[M+H]^+$), 388.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{13}H_{15}N_7O_4S$: C 42.73, H 4.14, N 26.84; found C 42.70, H 4.11, N 26.83.

4-(9-((5-(Ethylsulfonyl)-1,3,4-oxadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (8b). Yellow solid; yield 62.4%; m.p. 127–129°C; IR (KBr, cm^{-1}): *v* 3435.5, 2994.8, 2951.1, 2856.6, 1594.2, 1565.3, 1559.5, 1473.4, 1456.3, 1330.9, 1292.3, 1259.5, 1146.7, 1004.9, 776.3, 730.0, 637.5, 484.1; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.32 (s, 1H, Pyrimidine–H), 8.27 (s, 1H, Imidazole–H), 5.74 (s, 2H), 4.19–4.22 (s, 3H), 3.73 (t, 5H, $J = 5.15$ Hz), 3.60–3.63 (m, 2H), 1.35 (t, 2H, $J = 7.15$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 164.96, 163.62, 153.75, 152.73, 151.13, 141.66, 119.23, 66.70, 38.11, 30.68, 7.58; MS (ESI) m/z: 380.1 ($[M+H]^+$), 402.1($[M+Na]^+$); *Anal*. Calcd. for $C_{15}H_{17}N_7O_4S$: C 44.32, H 4.52, N 25.84; found C 44.35, H 4.51, N 25.84.

4-(9-((5-(Methylsulfonyl)-1,3,4-thiadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (8′a). Yellow solid; yield 64.3%; m.p. 150–151°C; IR (KBr, cm^{-1}): *v* 3445.5, 2995.6, 2961.4, 2851.0, 1590.3, 1565.1, 1558.5, 1476.6, 1329.9, 1254.7, 1157.3, 1006.8, 763.8, 643.2, 531.4; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.36 (s, 1H, Pyrimidine–H), 8.29 (s, 1H, Imidazole–H), 5.86 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 5H, $J = 5.15$ Hz), 3.53 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 169.48, 165.19, 153.75, 152.69, 150.91, 140.54, 119.38, 66.69, 49.68, 41.84; MS (ESI) m/z: 382.1 ($[M+H]^+$), 404.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{13}H_{15}N_7O_3S_2$: C 40.93, H 3.96, N 25.70; found C 40,91, H 3.97, N 25.72.

4-(9-((5-(Ethylsulfonyl)-1,3,4-thiadiazole-2-yl)methyl)-9H-purin-6-yl)morpholine (8′b). Yellow solid; yield 67.2%; m.p. 136–137°C; IR (KBr, cm^{-1}): *v* 3444.8, 2995.3, 2951.9, 2854.3, 1593.2, 1568.1, 1564.3, 1558.5, 1474.6, 1331.9, 1292.3, 1259.5, 1146.7, 1005.9, 776.3, 637.5, 533.34, 483.1; ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.38 (s, 1H, Pyrimidine–H), 8.29 (s, 1H, Imidazole–H), 6.05 (s, 2H), 4.19–4.22 (m, 3H), 3.72 (t, 7H, $J = 6.85$ Hz), 1.32 (t, 3H, $J = 7.45$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 171.29, 169.58, 153.76, 152.71, 150.95, 140.62, 119.35, 66.69, 50.04, 42.09, 7.34; MS (ESI) m/z: 396.1 ($[M+H]^+$); *Anal*. Calcd. for $C_{14}H_{17}N_7O_3S_2$: C 42.52, H 4.33, N 24.79; found C 42.53, H 4.33, N 24.81.

Antibacterial activity. The antibacterial activities of some title compounds against *Xoo* and *R. solanacearum* were evaluated by the turbidimeter test. Dimethylsulfoxide in sterile distilled water served as a blank control; Bismerthiazol and Thiodiazole copper served as positive controls. Approximately 40 μL of solvent M210 (8.0 g of casein enzymatic hydrolysate,

5.0 g of sucrose, 4.0 g of yeast powder, 3.0 g of K_2HPO_4, 0.3 g of $MgSO_4 \cdot 7H_2O$, and 1000 mL of distilled water; pH = 7.0) containing *Xoo* and *R. solanacearum* was added to 5 mL of solvent M210 containing the test compounds and positive controls. The inoculated test tubes were incubated at 28 ± 1°C and continuously shaken at 180 rpm for 24 h. The growth of the cultures was monitored on a microplate reader by measuring the optical density at 595 nm (OD_{595}) given by $\text{turbidity}_{\text{corrected values}} = OD_{\text{bacterial wilt}} - OD_{\text{no bacterial wilt}}$, and then the inhibition rate I was calculated by $I\ (\%) = (C_{tur} - T_{tur})/C_{tur} \times 100$. C_{tur} is the corrected turbidity values of bacterial growth on untreated M210 (blank control), and T_{tur} is the corrected turbidity values of bacterial growth on treated M210. Some of the title compounds were tested against at five double declining concentrations method were expressed by EC_{50}. The average EC_{50} was computed from at least three separate analyses for growth inhibition using the basic EC_{50} program version SPSS 17.0.

Acknowledgments. We gratefully acknowledge the Project Enterprises and Business (H110039) for providing the financial support.

REFERENCES AND NOTES

[1] Rosenmeyer, H. Chem Biodivers 2004, 1, 361.
[2] Strouse, J. J.; Gešelnik, M.; Jeffery, B. Arterburn Acta Chim Slov 2005, 52, 187.
[3] Dolezal, K.; Popa, I.; Krystof, V.; Spichal, L.; Fojtikova, M.; Holub, J.; Lenobel, R.; Schmulling, T.; Strnad, M. Bioorg Med Chem 2006, 14, 875.
[4] Legraverend, M.; Grierson, D. S. Bioorg Med Chem 2006, 14, 3987.
[5] Laufer, S. F.; Domeyer, D. M.; Scior, T. R. F.; Albrecht, W.; Hauser, D. R. J. J Med Chem 2005, 48, 710.
[6] Hocek, M.; Naus, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. J. J Med Chem 2005, 48, 5869.
[7] De Clercq, E. Antiviral Res 2005, 67, 56.
[8] Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C. I.; Yoon, S. S. Eur J Med Chem 2014, 84, 574.
[9] Jin, G.; Wu, C. C. N.; Tawatao, R. I.; Chan, M.; Carson, D. A.; Cottam, H. B. Bioorg Med Chem Lett 2006, 16, 4559.
[10] Wang, S. B.; Jin, P.; Li, F. N.; Quan, Z. S. Eur J Med Chem 2004, 39, 433.
[11] Mallari, J. P.; Guiguemde, W. A.; Guy, R. K. Bioorg Med Chem Lett 2009, 19, 3546.
[12] Conejo-García, A.; García-Rubiño, M. E.; Marchal, J. A.; Neúñz, M. C.; Ramírez, A.; Cimino, S.; García, M. A.; Aránega, A.; Gallo, M. A.; Campos, J. M. Eur J Med Chem 2011, 46, 3795.
[13] Liu, H. X.; Li, L. B.; Qurat-ul-ain, S.; Jiang, T. J Heterocyclic Chem 2015, 52, 473.
[14] Bordon-Pallier, F.; Jullian, N.; Ferrari, P.; Girard, A. M.; Bocquel, M. T.; Biton J.; Bouquin, N.; Haesslein, J. L. Biochim Biophys Acta 2004, 1697, 211.
[15] Thalassitis, A. N.; Hadjipavloulitina, D. J.; Litinas, K. J Heterocyclic Chem 2015, 52, 366.
[16] Tuncbilek, M.; Ates-Alagöz, Z.; Altanlar, N.; Karayel, A.; Özbey, S. Bioorg Med Chem 2009, 17, 1693.
[17] Gadhave, A. G.; Gaikar, R. B.; Kuchekar, S. R.; Karacle, B. K. J Heterocyclic Chem 2014, 51, 1849.
[18] Galge, R.; Raju, A.; Degani, M. S.; Torat, B. N. J Heterocyclic Chem 2015, 52, 352.
[19] Wu, W. N.; Chen, Q.; Tai, A. Q.; Jiang, G. Q.; Ouyang, G. P. Bioorg Med Chem Lett 2015, 25, 2243.
[20] Wu, W. N.; Tai, A. Q.; Chen, Q.; Ouyang, G. P. J Heterocyclic Chem 2015, DOI: 10.1002/jhet.2435
[21] Shelke, S. H.; Mhaske, P. C.; Kasm, S. K.; Bobade, V. D. J Heterocyclic Chem 2014, 51, 1893.
[22] Liu, Z. M.; Yang, G. F.; Qing, X. H. J Chem Technol Biotechnol 2001, 76, 1154.
[23] Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altinok, G. Farmaco 2002, 57, 101.
[24] Harfenist, M.; Heuser, D. J.; Joyner, C. T.; Batchelor, J. F.; White, H. L. J Med Chem 1996, 39, 1857.
[25] Li, P.; Yin, J.; Xu, W. M.; Wu, J.; He, M.; Hu, D. Y.; Yang, S.; Song, B. A. Chem Biol Drug Des 2013, 82, 546.
[26] Xu, W. M.; He, J.; He, M.; Han, F. F.; Chen, X. H.; Pan, Z. X.; Wang, J.; Tong, M. G. Molecules 2011, 16, 9129.
[27] Scarf, M. E.; Siegfried, B. D.; Meinke, L. J.; Chandler, L. D. Pest Manag Sci 2000, 56, 757.
[28] Frantz, V.; Thomas J.; Brown, K. C.; Beverly, A.; Heinz, L. A.; Shipley, K. S. S.; Joseph, T.; Lori M. V.; Wayne, A. S. J Med Chem 1997, 40, 1511.
[29] Li, Y. X.; Wang, Y. M.; Liu, B.; Wang, S. H.; Li, Z. M. Heteroatom Chem 2005, 16, 255.
[30] Vedula, M. S.; Pulipaka, A. B.; Venna, C.; Chintakunta, V. K.; Jinnapally, S.; Kattuboina, V. A.; Vallakati, R. K.; Basetti, V.; Akella, V.; Rajgopai, S.; Reka, A. K.; Teepireddy, S. K.; Mamnoor, P. K.; Rajagopalan, R.; Bulusu, G.; Khandelwal, A.; Upreti, V. V.; Mamidi, S. R. Eur J Med Chem 2003, 38, 811.
[31] Silvestri, R.; Artico, M.; Regina, G. L. Farmaco 2004, 59, 201.
[32] Gong, P.; Chai, H. F.; Zhao, Y. F.; Zhao, C. S. Bioorg Med Chem 2006, 14, 2552.
[33] Tai, X. S.; Yin, X. H.; Tan, M. Y. Chin J Struc Chem 2003, 22, 411.
[34] Guimaraes, C. R. W.; Boger, D. L.; Jorgensen, W. L. J Am Chem Soc 2005, 127, 17377.
[35] Li, P.; Shi, L.; Yang, X.; Yang, L.; Chen, X. W.; Wu, F.; Shi, Q. C.; Xu, W. M.; He, M.; Hu, D. Y.; Song, B. A. Bioorg Med Chem Lett 2014, 24, 1677.
[36] Li, P.; Shi, L.; Gao, M. N.; Yang, X.; Xue, W.; Jin, L. H.; Hu, D. Y.; Song, B. A. Bioorg Med Chem Lett 2015, 25, 481.
[37] Paw, D.; Thomas, R.; Laura, K.; Karina, N.; Thomas, A. M. Int J Food Microbiol 1994, 23, 391.
[38] Xu, W. M.; Han, F. F.; He, M.; Hu, D. Y.; He, J.; Yang, S.; Song, B. A. J Agric Food Chem 2012, 60, 1036.