Synthesis of some new N-pyridylpyrazoles and determination of their fungicidal activity

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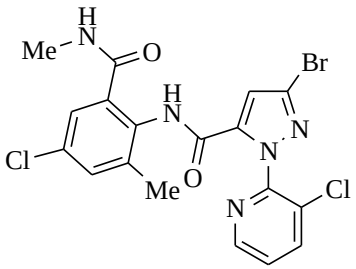
Abstract
Two series of novel *N*-pyridylpyrazole derivatives were designed and synthesized, and their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, high-resolution mass spectroscopy, elemental analysis and single crystal X-ray diffraction analysis. The fungicidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent fungicidal activities, which were comparable to the commercial fungicides.

Keywords: N-Pyridylpyrazole derivatives, heterocyclic, synthesis, fungicidal activity

Introduction

Since the public introduction of phthalic acid diamides and anthranilic diamides by Nihon Nohyaku,[1] Bayer CropScience[2] and DuPont[3,4] respectively, diamides had been the focus of synthetic activity within the agrochemical industry.[5] Especially anthranilic diamides and their chemical synthesis have recently attracted considerable attention in the field of novel agricultural insecticides,[6,7] owing to their prominent insecticidal activity, unique modes of action and good environmental profiles. Work in this area has led to the discovery of Rynaxypyr™, a highly potent and selective activator of insect ryanodine receptors with exceptional activity on a broad range of Lepidoptera, as the first new insecticide from this class.[8,9] Furthermore, anthranilic diamides also displayed good herbicidal and fungicidal activities.[10,11]



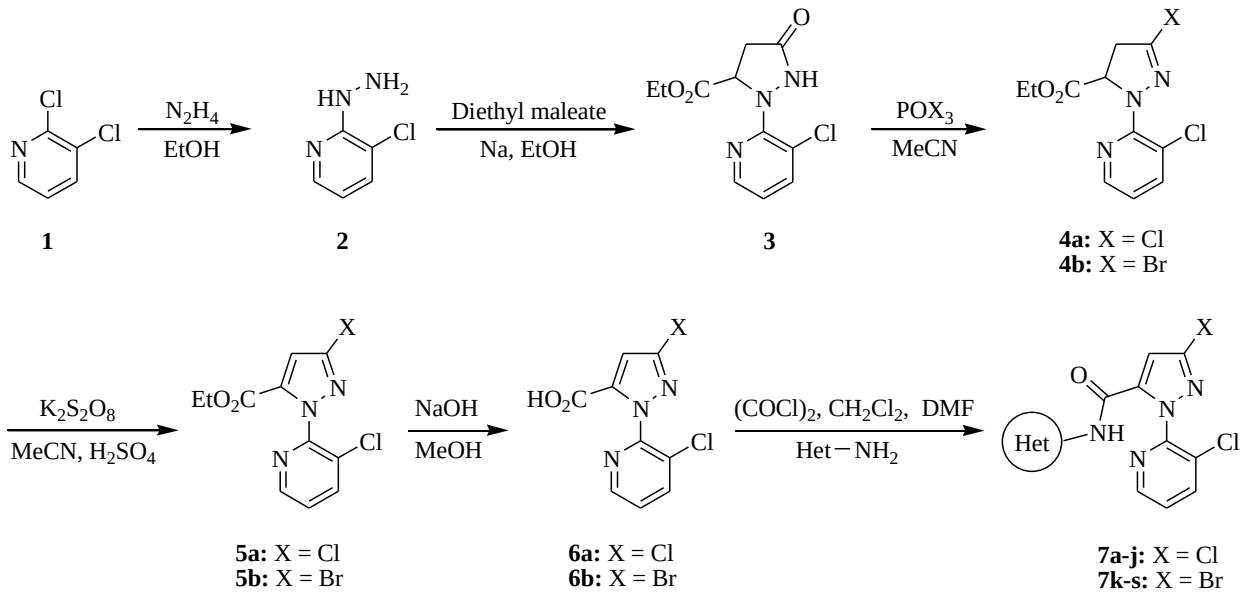
Rynaxypyr™

Heterocyclic compounds represent an important class of biologically active molecules. Specifically, those containing the pyrazole nucleus have been shown to possess high biological activities as herbicides, fungicides, and analgesics.[12,13] Encouraged by these reports, an idea was developed that the introduction of an heterocyclic substituent into Rynaxypyr molecule by replacing the benzene ring section with a heterocyclic ring could improve biological properties and broaden activity spectrum. Therefore, in a search for new molecules with improved profiles, two series of novel *N*-pyridylpyrazole derivatives were designed and synthesized (Scheme 1).

Results and Discussion

Synthesis

In the present work, two series of novel N-pyridylpyrazole derivatives were prepared, and their fungicidal activities were tested. The preliminary biological tests showed that some compounds exhibited good activity to *Pseudoperonospora cubensis, Pseudomonas syringae* pv *lachrymans, Corynespora cassiicola, Fusarium oxysporum, Sphaerotheca fuligenea, Xanthomonas axonopodis* and *Rhizoctonia solanii*. The title compounds **7** were synthesized by a simple and convenient six-step procedure starting from 2,3-dichloropyridine. The (3-chloropyridin-2-yl)-hydrazine **2** was prepared from hydrazine hydrate and 2,3-dichloropyridine that were refluxed for 36 h. The compound **2** was reacted with diethyl maleate in ethanol to yield ethyl 2-(3-chloropyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylate **3**, and subsequent treatment using phosphorus oxyhalides as halogenating reagents provided the intermediates **4**. The compounds **4** were treated with $K_2S_2O_8$ in acetonitrile to yield intermediates **5**, and subsequent hydrolysis using sodium hydroxide gave key intermediates **6**. The carbonyl chloride was prepared from the acids **6** and $SOCl_2$, and without isolation further reacted with appropriate heterocyclic amine at room temperature to yield the title compounds **7** (Scheme 1).



1 **2** **3**

4a: X = Cl
4b: X = Br

5a: X = Cl
5b: X = Br

6a: X = Cl
6b: X = Br

7a-j: X = Cl
7k-s: X = Br

Scheme 1. General synthetic route of the title compounds **7a-s.**

Table 1. List of the title compounds.

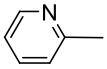
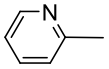
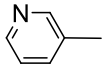
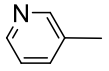
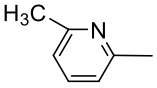
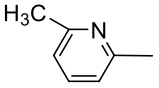
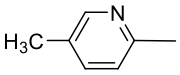
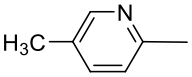
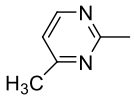
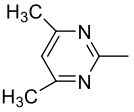
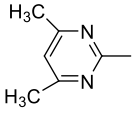
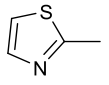
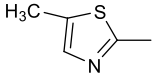
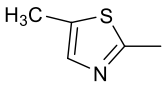
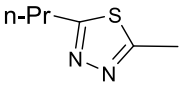
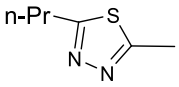
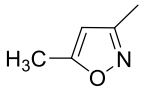
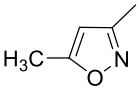
Compd.	X	Het.	Compd.	X	Het.
7a	Cl		**7k**	Br	
7b	Cl		**7l**	Br	
7c	Cl		**7m**	Br	
7d	Cl		**7n**	Br	
7e	Cl		**7o**	Br	
7f	Cl		**7p**	Br	
7g	Cl		**7q**	Br	

Table 1. (continued)

Compd.	X	Het.	Compd.	X	Het.
7h	Cl		**7r**	Br	
7i	Cl		**7s**	Br	
7j	Cl				

Fungicidal activity

The newly synthesized compounds **7a-s** were tested for their fungicidal activity against *Pseudoperonospora cubensis*, *Pseudomonas syringae* pv *lachrymans*, *Corynespora cassiicola*, *Fusarium oxysporum*, *Sphaerotheca fuligenea*, *Xanthomonas axonopodis* and *Rhizoctonia solanii*. The results of fungicidal activity are listed in Table 2. Compounds **7m** and **7o** displayed good fungicidal activity against *Pseudoperonospora cubensis*. Some of the target compounds exhibited promising promotion effects against *Sphaerotheca fuligenea*. For instance, the fungicidal activity of compounds **7c**, **7p** and **7s** against *Sphaerotheca fuligenea* at 500 μg mL^{-1} were 68.2, 73.8 and 82.5%, respectively. And some title compounds exhibited moderate fungicidal activity against *Xanthomonas axonopodis* and *Corynespora cassiicola* in the concentration of 500 μg mL^{-1}. For example, the results indicated that the activity of compounds **7k** and **7m** against *Xanthomonas axonopodis* at 500 μg mL^{-1} were 78.7 and 74.5%. In particular, some compounds exhibited good fungicidal activity against *Pseudomonas syringae* pv *lachrymans* and *Fusarium oxysporum*. The fungicidal activity of compounds **7f** and **7h** against *Pseudomonas syringae* pv *lachrymans* were 68.2 and 66.0%, which were comparable to that of the commercialized zhongshengmycin. The results indicated that the activity of compounds **7f** and **7r** against *Fusarium oxysporum* at 500 μg mL^{-1} were 81.2 and 77.4%, which were equal or superior to that of commercial thiophanate methyl and chlorothalonil. All compounds did not exhibit obvious fungicidal activity against *Rhizoctonia solanii*.

As regards the relationships between the structure of the nitrogen heterocyclic compounds and the detected fungicidal activity, it seemed that there was no significant difference. Probably in these cases the nature of the heterocyclic ring was not that important for fungicidal activity. Nevertheless, the nature of the halogen on the pyrazole did affect the activity: From the data presented in Table 2, we found that the bromo-substituted derivatives showed higher fungicidal activity than the corresponding chloro-substituted derivatives. Further studies on structural optimization and structure-activity relationships of these novel *N*-pyridylpyrazole derivatives are in progress.

Conclusions

In summary, two series of novel *N*-pyridylpyrazole derivatives were designed and synthesized, and their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, high-resolution mass spectroscopy, elemental analysis and in one case (compound **7m**) single crystal X-ray diffraction analysis. The fungicidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent fungicidal activities, which were comparable to the commercial fungicides. The modification of the heterocyclic ring of the parent compounds offers a promising prospect and highly active analogues are expected to be found by further work.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in ppm. Elemental analyses were determined on a Yanaco CHN Corder MT-3 elemental analyzer. HRMS data was obtained on a FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China). Infrared spectra were obtained on a Bruker Vector 27 FT-IR spectrometer (Bruker, Ettlingen, Germany). All solvents and liquid reagents were dried by standard methods and distilled before use. The key intermediate **6** was synthesized according to reference 14.

Synthetic procedure for (3-chloropyridin-2-yl)-hydrazine 2. To a suspension of 2,3-dichloropyridine 1 (100 g, 0.676 mol) in anhydrous ethanol (420 mL) was added 50% hydrazine hydrate (280 mL, 2.88 mol). The resulting mixture was refluxed for 36 h, and then cooled to room temperature. The product precipitated out of solution, the white crystals were collected by filtration, washed thoroughly with cold ethanol and dried to give white crystals (74.4 g, 77%), mp 163-164 ^{o}C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, 1H, J = 3.9 Hz, pyridyl-H), 7.47 (d, 1H, J = 8.1 Hz, pyridyl-H), 6.64 (dd, 1H, J_1 = 3.9 Hz, J_2 = 8.1 Hz, pyridyl-H), 6.21 (s, 1H, NH), 3.97 (br s, 2H, NH_2).

Ethyl 2-(3-chloropyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylate 3. To absolute ethanol (200 mL) in a 500 mL three-necked round-bottomed flask was added 6.9 g (0.3 mol) of sodium cut in pieces of suitable size. When all the sodium has reacted, the mixture was heated to reflux and (3-chloropyridin-2-yl)-hydrazine (**2**) (39.82 g, 0.28 mol) was added. The mixture was refluxed for 10 min, then diethyl maleate (51.65 g, 0.30 mol) was added dropwise. The resulting orange-red solution was held at reflux for 30 min. After being cooled to 65 ^{o}C, the reaction mixture was treated with glacial acetic acid (30 g, 0.51 mol). The mixture was diluted with water

(30 mL). After removal of most solvent, the residue was treated with water (300 mL). The slurry formed was dissolved in aqueous ethanol (70%, 200 mL) and was stirred thoroughly. The solid was collected by filtration, washed with aqueous ethanol (50%, 3×50 mL) to give the title compound **3** (36.6 g, 49%), mp 132-134 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.18 (s, 1H, NH), 8.25 (d, J = 4.8 Hz, 1H, pyridyl-H), 7.91 (d, J = 7.4 Hz, 1H, pyridyl-H), 7.18 (dd, J_1 = 4.8 Hz, J_2 =7.4 Hz, 1H, pyridyl-H), 4.81 (d, J = 9.8 Hz, 1H, CH), 4.17 (q, J = 7.0 Hz, 2H, OCH_2), 2.89 (dd, J_1 = 9.8 Hz, J_2 = 16.8 Hz, 1H, CH_2-H), 2.34 (d, J = 16.8 Hz, 1H, CH_2-H), 1.20 (t, J = 7.0 Hz, 3H, CH_3).

Ethyl 5-bromo-2-(3-chloropyridin-2-yl)-3,4-dihydro-2*H*-pyrazole-3-carboxylate 4b. To a solution of ethyl 2-(3-chloropyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylate (**3**) (27 g, 0.1 mol) in acetonitrile (300 mL) was added phosphorus oxybromide (34.4 g, 0.12 mmol). The reaction mixture was refluxed for 5 h, then 250 mL of solvent was removed by distillation. The concentrated reaction mixture was slowly poured into saturated aq. Na_2CO_3 (250 mL) and was stirred vigorously for 30 min. The resulting mixture was extracted with CH_2Cl_2 (2×250 mL), the organic extract was separated, dried, filtered, concentrated and purified by silica gel chromatography to afford the title compound **4b** (31.0 g, 93%), mp 59-60 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.10 (d, J = 4.4 Hz, 1H, pyridyl-H), 7.83 (d, J = 7.7 Hz, 1H, pyridyl-H), 6.98 (dd, J_1 = 4.4 Hz, J_2 = 7.7 Hz, 1H, pyridyl-H), 5.17 (dd, J_1 = 8.7 Hz, J_2 = 11.8 Hz, 1H, CH), 4.08 (q, 2H, J = 7.0 Hz, OCH_2), 3.27 (dd, J = 8.7, 17.6 Hz, 1H, CH_2-H), 3.57 (dd, J = 11.8, 17.6 Hz, 1H, CH_2-H), 1.12 (t, J = 7.0 Hz, 3H, CH_3).

Ethyl 5-chloro-2-(3-chloropyridin-2-yl)-3,4-dihydro-2*H*-pyrazole-3-carboxylate 4a was also prepared with similar results using phosphorus oxychloride as the chlorination reagent: yellow oily liquid, 95%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, J_1 =1.5 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.65 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H, pyridyl-H), 6.87-6.85 (m, 1H, pyridyl-H), 5.31-5.29 (m, 1H, CH), 4.18 (q, 2H, J = 7.1 Hz, OCH_2), 3.38-3.36 (m, 1H, CH_2-H), 3.18-3.16 (m, 1H, CH_2-H), 1.20 (t, J = 7.1 Hz, 3H, CH_3).

Ethyl 5-bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylate 5b. To a solution of ethyl 5-bromo-2-(3-chloropyridin-2-yl)-3,4-dihydro-2*H*-pyrazole-3-carboxylate (**4b**) (17 g, 51 mmol) in acetonitrile (250 mL) was added sulfuric acid (98%, 10 g, 102 mmol). After being stirred for several minutes, the reaction mixture was treated with $K_2S_2O_8$ (21 g, 76.5 mmol) and was refluxed for 4.5 h. After being cooled to 60 °C, the mixture was filtered to remove a fine powder, the filter cake was washed with acetonitrile (30 mL). The filtrate was concentrated to 100 mL, then was added slowly to water (250 mL) under stirring. The solid was collected by filtration, washed with acetonitrile (3×30 mL), water (30 mL), and then dried to give the title compound **5b** (15.6 g, 93%), mp 117-118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.52 (d, J = 4.8 Hz, 1H, pyridyl-H), 7.92 (d, J = 8.1 Hz, 1H, pyridyl-H), 7.45 (dd, 1H, J_1 = 4.8 Hz, J_2 = 8.1 Hz, pyridyl-H), 6.95 (s, 1H, pyrazolyl-H), 4.24 (q, 2H, J = 7.2 Hz, CH_2), 1.21 (t, 3H, J = 7.2 Hz, CH_3).

Ethyl 5-chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylate 5a was also prepared using a similar method. The yield was 87%, mp 109-110 °C. ^{1}H NMR ($CDCl_3$，300MHz): 8.51 (d, J = 3.9 Hz, 1H, pyridyl-H), 7.92 (d, 1H, J = 7.5 Hz, pyridyl-H), 7.45 (dd, 1H, J_1 = 7.5 Hz, J_2 =

3.9 Hz, pyridyl-H), 6.95 (s, 1H, pyrazolyl-H), 4.23 (q, 2H, *J* = 7.2 Hz, CH_2), 1.22 (t, 3H, *J* = 7.2Hz, CH_3).

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid 6b. To a mixture of the ethyl 5-bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylate (**5b**) (15.6 g, 47.2 mmol) in methanol (120 mL) was added aqueous NaOH solution (60 mL, 1 mol L^{-1}). The solution was stirred at room temperature for 6 h, then was concentrated *in vacuo* to about 50 mL. The concentrated mixture was diluted with H_2O (150 mL), and washed with ethyl acetate (150 mL). The aqueous solution was acidified using concentrated HCl to pH = 2. The solid was collected by filtration, washed with ether (30 mL), and then dried to give the title compound **6b** (12.75 g, 89%), mp 197-200 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.52 (dd, J_1 = 1.5 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.94 (dd, J_1 = 1.5 Hz, J_2 = 8.1 Hz, 1H, pyridyl-H), 7.48 (dd, 1H, *J* = 4.8, 8.1 Hz, pyridyl-H), 7.10 (s, 1H, pyrazolyl-H).

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (**6a**) can be prepared using the same method. The yield was 74%, mp 200-201 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): 8.54 (d, *J* = 4.8 Hz, 1H, pyridyl-H), 8.23 (d, *J* = 8.0 Hz, 1H, pyridyl-H), 7.66 (dd, 1H, J_1 = 4.8 Hz, J_2 = 8.0 Hz, pyridyl-H), 7.23 (s, 1H, pyrazolyl-H).

Synthetic procedure for the title compounds 7a-s

To a suspension of *N*-pyridylpyrazole acid **6** (1 mmol) in dichloromethane (20 mL) was added oxalyl chloride (3 mmol) and DMF (2 drops). The solution was stirred at ambient temperature for 6 h. Then the mixture was concentrated in vacuo to give the crude acid chloride. The crude acid chloride in dichloromethane (10 mL) was added slowly to a stirred solution of appropriate heterocyclic amine (1.2 mmol) in dichloromethane (20 mL) in an ice bath. After 5 min, triethylamine (1.2 mmol) was added dropwise. The solution was stirred at ambient temperature for 12 h. Then the solution was diluted with dichloromethane (20 mL), and washed with 1 N aq. HCl solution (15 mL), saturated aq. $NaHCO_3$ (15 mL), and brine (15 mL). The organic extract was separated, dried, filtered, and concentrated and purified by silica gel chromatography to afford the desired title compound **7**.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid pyridin-2-ylamide 7a. White solid, yield 68%, mp 197-199 ºC; IR (KBr, cm^{-1}) *v* 3340 (NH), 1685 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.25 (s, 1H, CONH), 8.51 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.39-8.37 (m, 1H, pyridyl-H), 8.22 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.86-7.84 (m, 1H, pyridyl-H), 7.77-7.74 (m, 1H, pyridyl-H), 7.65 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.56 (s, 1H, pyrazolyl-H), 7.18-7.15 (m, 1H, pyridyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 156.0, 150.7, 148.7, 147.9, 147.0, 141.5, 139.3, 139.0, 138.6, 128.9, 125.9, 120.6, 114.9, 107.3. Anal. Calcd. (%) for $C_{14}H_9Cl_2N_5O$: C, 50.32; H, 2.71; N, 20.96. Found: C, 50.19; H, 3.00; N, 20.69. FTICR-MS for $C_{14}H_9{}^{35}Cl^{35}ClN_5O$ $[M+Na]^+$: calcd. 356.0076, found 356.0080.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid pyridin-3-ylamide 7b. White solid, yield 63%, mp 211-212 ºC; IR (KBr, cm^{-1}) *v* 3350 (NH), 1684 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 10.81 (s, 1H, CONH), 8.74 (d, 1H, *J* = 2.4 Hz, pyridyl-H), 8.51 (dd, J_1

= 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.32-8.30 (m, 1H, pyridyl-H), 8.23 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.01-7.98 (m, 1H, pyridyl-H), 7.66-7.63 (m, 1H, pyridyl-H), 7.35 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.42 (s, 1H, pyrazolyl-H). ^{13}C NMR (DMSO-d_6, 400 MHz), δ 156.0, 148.2, 147.2, 145.3, 141.8, 139.6, 139.6, 139.1, 134.5, 127.7, 127.4, 126.8, 123.7, 107.8. Anal. Calcd. (%) for $C_{14}H_9Cl_2N_5O$: C, 50.32; H, 2.71; N, 20.96. Found: C, 50.36; H, 2.91; N, 20.88. FTICR-MS for $C_{14}H_9{}^{35}Cl^{35}ClN_5O$ $[M+H]^+$: calcd. 334.0257, found 334.0258.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (6-methylpyridin-2-yl)-amide 7c. White solid, yield 63%, mp 183-184 ºC; IR (KBr, cm^{-1}) ν 3390 (NH), 2932 (CH), 1686 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.18 (s, 1H, CONH), 8.52 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.22 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 7.69-7.61 (m, 3H, pyridyl-H), 7.59 (s, 1H, pyrazolyl-H), 7.02 (d, 1H, J = 7.2 Hz, pyridyl-H), 2.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 157.2, 155.7, 149.7, 148.8, 147.0, 141.6, 139.3, 139.0, 138.8, 129.0, 125.9, 120.1, 111.4, 107.0, 24.0. Anal. Calcd. (%) for $C_{15}H_{11}Cl_2N_5O$: C, 51.74; H, 3.18; N, 20.11. Found: C, 51.54; H, 3.10; N, 20.19. FTICR-MS for $C_{15}H_{11}{}^{35}Cl^{35}ClN_5O$ $[M+Na]^+$: calcd. 370.0233, found 370.0232.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (5-methylpyridin-2-yl)-amide 7d. White solid, yield 66%, mp 140-142 ºC; IR (KBr, cm^{-1}) ν 3384 (NH), 2926 (CH), 1685 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.18 (s, 1H, CONH), 8.51 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.24-8.22 (m, 2H, pyridyl-H), 7.78-7.75 (m, 1H, pyridyl-H), 7.67-7.63 (m, 2H, pyridyl-H), 7.56 (s, 1H, pyrazolyl-H), 2.24 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 155.9, 148.8, 148.5, 147.7, 147.0, 141.5, 139.3, 139.3, 139.1, 130.2, 129.0, 125.9, 114.4, 107.3, 17.9. Anal. Calcd. (%) for $C_{15}H_{11}Cl_2N_5O$: C, 51.74; H, 3.18; N, 20.11. Found: C, 51.65; H, 3.22; N, 20.33. FTICR-MS for $C_{15}H_{11}{}^{35}Cl^{35}ClN_5O$ $[M+Na]^+$: calcd. 370.0233, found 370.0233.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (4-methylpyrimidin-2-yl)-amide 7e. White solid, yield 54%, mp 183-184 ºC; IR (KBr, cm^{-1}) ν 3305 (NH), 2953 (CH), 1694 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.32 (s, 1H, CONH), 8.52-8.50 (m, 2H, pyridyl-H, pyrimidinyl-H), 8.21 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.66-7.63 (m, 1H, pyridyl-H), 7.48 (s, 1H, pyrazolyl-H), 6.43-6.42 (m, 1H, pyrimidinyl-H), 2.40 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 169.1, 158.0, 156.7, 154.8, 146.9, 141.5, 139.3, 138.7, 129.1, 125.8, 117.1, 111.3, 107.4, 24.1. Anal. Calcd. (%) for $C_{14}H_{10}Cl_2N_6O$: C, 48.16; H, 2.89; N, 24.07. Found: C, 48.23; H, 3.04; N, 24.29. FTICR-MS for $C_{14}H_{10}{}^{35}Cl^{35}ClN_6O$ $[M+Na]^+$: calcd. 371.0185, found 371.0183.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (4,6-dimethyl pyrimidin-2-yl)-amide 7f. White solid, yield 60%, mp 216-218 ºC; IR (KBr, cm^{-1}) ν 3271 (NH), 2944 (CH), 1690 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.22 (s, 1H, CONH), 8.51 (d, J = 4.4 Hz, 1H, pyridyl-H), 8.22 (d, J = 8.4 Hz, 1H, pyridyl-H), 7.65 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.48 (s, 1H, pyrazolyl -H), 7.01 (s, 1H, pyrimidinyl-H), 2.34 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 168.5, 156.6, 154.8, 148.7, 146.9, 141.4, 139.3, 139.0, 129.0, 125.8, 116.6, 110.8, 107.5, 24.0, 23.8. Anal. Calcd. (%) for $C_{15}H_{12}Cl_2N_6O$: C, 49.60; H, 3.33; N, 23.14. Found: C, 49.79; H, 3.20; N, 23.39. FTICR-MS for $C_{15}H_{12}{}^{35}Cl^{35}ClN_6O$ $[M+Na]^+$: calcd. 385.0342,

found 385.0341.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid thiazol-2-ylamide 7g. White solid, yield 80%, mp 233-234 ºC; IR (KBr, cm^{-1}) *v* 3466 (NH), 1673 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 13.03 (br s, 1H, CONH), 8.40 (dd, J_1 = 4.4 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 8.25 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 7.68 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.55 (s, *J* = 3.6 Hz, 1H, thiazolyl-H), 7.51 (s, 1H, pyrazolyl-H), 7.27 (d, *J* = 3.6 Hz, 1H, thiazolyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz), *δ* 159.0, 155.6, 148.3, 147.0, 141.7, 139.6, 137.8, 137.0, 128.8, 126.0, 114.5, 108.5. Anal. Calcd. (%) for $C_{12}H_7Cl_2N_5OS$: C, 42.37; H, 2.07; N, 20.59. Found: C, 42.29; H, 2.12; N, 20.66. FTICR-MS for $C_{12}H_7{}^{35}Cl{}^{35}ClN_5OS$ $[M+Na]^+$: calcd. 361.9641, found 361.9645.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (5-methylthiazol-2-yl) amide 7h. White solid, yield 69%, mp 236-237 ºC; IR (KBr, cm^{-1}) *v* 3476 (NH), 2952 (CH), 1682 (CO). ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* 12.36 (br s, 1H, CONH), 8.53 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.94 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.46 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1H, pyridyl-H), 6.96 (s, 1H, thiazolyl-H), 6.89 (s, 1H, pyrazolyl-H), 2.38 (d, *J* = 0.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), *δ* 157.6, 155.6, 148.4, 147.0, 141.6, 139.5, 138.0, 133.7, 128.8, 128.5, 126.0, 108.4, 11.6. Anal. Calcd. (%) for $C_{13}H_9Cl_2N_5OS$: C, 44.08; H, 2.56; N, 19.77. Found: C, 44.15; H, 2.69; N, 19.69. FTICR-MS for $C_{13}H_9{}^{35}Cl{}^{35}ClN_5OS$ $[M+Na]^+$: calcd. 375.9797, found 395.9796.

5-Chloro-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (5-propyl-[1,3,4] thiadiazol-2-yl)-amide 7i. White solid, yield 68%, mp 228-230 ºC; IR (KBr, cm^{-1}) *v* 3426 (NH), 2931 (CH), 1677 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 13.62 (br s, 1H, CONH), 8.53 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 8.25 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 7.68 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.54 (s, 1H, pyrazolyl-H), 2.92 (t, *J* = 7.2 Hz, 2H, CH_2), 1.69-1.65 (m, 2H, CH_2CH_3) 0.90 (t, *J* = 7.2 Hz, 3H, $CH_2C\mathit{H}_3$). ^{13}C NMR ($CDCl_3$, 400 MHz), *δ* 165.4, 160.3, 155.8, 149.0, 147.0, 142.1, 139.2, 136.5, 129.1, 125.9, 110.1, 31.7, 22.7, 13.6. Anal. Calcd. (%) for $C_{14}H_{12}Cl_2N_6OS$: C, 43.87; H, 3.16; N, 21.93. Found: C, 43.79; H, 3.20; N, 21.99. FTICR-MS for $C_{14}H_{12}{}^{35}Cl{}^{35}ClN_6OS$ $[M+Na]^+$: calcd. 405.0063, found 405.0064.

3-Chloro-1-(3-chloropyridin-2-yl)-*N*-(5-methylisoxazol-3-yl)-1*H*-pyrazole-5-carboxamide7j. White solid, yield 62%, mp 250-252 ºC; IR (KBr, cm^{-1}) *v* 3436 (NH), 2962 (CH), 1697 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 11.77 (br s, 1H, CONH), 8.52 (d, *J* = 4.8 Hz, 1H, pyridyl-H), 8.23 (d, *J* = 8.0 Hz, 1H, pyridyl-H), 7.65 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.49 (s, 1H, pyrazolyl-H), 6.53 (s, 1H, isoxazolyl-H), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*$_6$, 400 MHz), *δ* 170.1, 157.4, 155.1, 148.3, 147.3, 139.5, 138.1, 127.8, 126.9, 126.8, 111.6, 96.6, 12.0. Anal. Calcd. (%) for $C_{13}H_9Cl_2N_5O_2$: C, 46.17; H, 2.68; N, 20.71. Found: C, 46.02; H, 2.55; N, 20.60. FTICR-MS for $C_{13}H_9{}^{35}Cl{}^{35}ClN_5O_2$ $[M+Na]^+$: calcd. 360.0026, found 360.0031.

5-Bromo-2-(3-chloropyridin-2-yl)-2H-pyrazole-3-carboxylic acid pyridin-2-ylamide 7k. White solid, yield 53%, mp 205-206 ºC; IR (KBr, cm^{-1}) *v* 3253 (NH), 1685 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 11.24 (s, 1H, CONH), 8.52 (dd, J_1 = 4.4 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 8.39-8.38 (m, 1H, pyridyl-H), 8.22 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H),

7.88-7.86 (m, 1H, pyridyl-H), 7.77-7.73 (m, 1H, pyridyl-H), 7.65 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.63 (s, 1H, pyrazolyl-H), 7.18-7.15 (m, 1H, pyridyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 156.0, 150.9, 148.7, 147.9, 147.0, 139.4, 139.2, 138.7, 128.9, 128.0, 125.9, 120.6, 114.9, 110.8. Anal. Calcd. (%) for $C_{14}H_9BrClN_5O$: C, 44.41; H, 2.40; N, 18.50. Found: C, 44.29; H, 2.24; N, 18.59. FTICR-MS for $C_{14}H_9{}^{79}Br^{35}ClN_5O$ $[M+Na]^+$: calcd. 399.9571, found 399.9573.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid pyridin-3-ylamide 7l. White solid, yield 61%, mp 207-208 ºC; IR (KBr, cm^{-1}) ν 3295 (NH), 1683 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 10.75 (s, 1H, CONH), 8.74 (d, J = 2.4 Hz, 1H, pyridyl-H), 8.52 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.31 (dd, J_1 = 4.4 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 8.23 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.00-7.98 (m, 1H, pyridyl-H), 7.67-7.63 (m, 1H, pyridyl-H), 7.35 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1H, pyridyl-H), 7.45 (s, 1H, pyrazolyl-H). ^{13}C NMR (DMSO-d_6, 400 MHz), δ 155.7, 148.2, 147.2, 145.3, 141.6, 139.5, 139.1, 134.5, 127.7, 127.3, 126.8, 126.8, 123.7, 111.1. Anal. Calcd. (%) for $C_{14}H_9BrClN_5O$: C, 44.41; H, 2.40; N, 18.50. Found: C, 44.33; H, 2.45; N, 18.43. FTICR-MS for $C_{14}H_9{}^{79}Br^{35}ClN_5O$ $[M+Na]^+$: calcd. 399.9571, found 399.9569.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (6-methylpyridin-2-yl)-amide 7m. White solid, yield 68%, mp 182-183 ºC; IR (KBr, cm^{-1}) ν 3188 (NH), 2956 (CH), 1685 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.17 (s, 1H, CONH), 8.52 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.21 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.69-7.60 (m, 4H, pyridyl-H, pyrazolyl-H), 7.02 (d, J = 1.6 Hz, 1H, pyridyl-H), 2.49 (d, J = 0.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 157.2, 155.5, 149.7, 148.8, 147.0, 139.3, 139.2, 138.8, 129.0, 128.1, 125.9, 120.1, 111.3, 110.3, 24.0. Anal. Calcd. (%) for $C_{15}H_{11}BrClN_5O$: C, 45.88; H, 2.82; N, 17.84. Found: C, 45.79; H, 3.03; N, 17.68. FTICR-MS for $C_{15}H_{11}{}^{79}Br^{35}ClN_5O$ $[M+Na]^+$: calcd. 413.9728, found 413.9731.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (5-methylpyridin-2-yl)-amide 7n. White solid, yield 48%, mp 139-141 ºC; IR (KBr, cm^{-1}) ν 3234 (NH), 2957 (CH), 1683 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.14 (s, 1H, CONH), 8.51 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.23-8.21 (m, 2H, pyridyl-H), 7.77-7.75 (m, 1H, pyridyl-H), 7.66-7.56 (m, 3H, pyridyl-H, pyrazolyl-H), 2.24 (d, J = 0.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 155.7, 148.8, 148.5, 147.8, 147.0, 139.3, 139.4, 139.2, 130.2, 129.0, 128.0, 125.9, 114.3, 110.6, 17.9. Anal. Calcd. (%) for $C_{15}H_{11}BrClN_5O$: C, 45.88; H, 2.82; N, 17.84. Found: C, 45.97; H, 2.83; N, 17.60. FTICR-MS for $C_{15}H_{11}{}^{79}Br^{35}ClN_5O$ $[M+Na]^+$: calcd. 413.9728, found 413.9727.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (4,6-dimethyl-pyrimidin-2-yl)-amide 7o. White solid, yield 71%, mp 227-228 ºC; IR (KBr, cm^{-1}) ν 3260 (NH), 2961 (CH), 1690 (CO). ^{1}H NMR (DMSO-d_6, 400 MHz), δ 11.19 (s, 1H, CONH), 8.51 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.21 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 7.64 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1H, pyridyl-H), 7.53 (s, 1H, pyrazolyl-H), 7.00 (s, 1H, pyrimidinyl-H), 2.34 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 168.5, 156.6, 154.6, 148.7, 146.9, 139.3, 139.2, 129.0, 127.9, 125.8, 116.6, 110.8, 24.0. Anal. Calcd. (%) for $C_{15}H_{12}BrClN_6O$: C, 44.19; H, 2.97; N, 20.62. Found: C, 44.29; H, 3.08; N, 20.55. FTICR-MS for $C_{15}H_{12}{}^{79}Br^{35}ClN_6O$ $[M+Na]^+$:

calcd. 428.9837, found 428.9830.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid thiazol-2-ylamide 7p. White solid, yield 82%, mp 250-252 ºC; IR (KBr, cm^{-1}) *v* 3146 (NH), 1672 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 13.07 (br s, 1H, CONH), 8.54 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.25 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.68 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.56-7.54 (m, 2H, thiazolyl-H, pyrazolyl-H), 7.26 (d, 1H, *J* = 3.6 Hz thiazolyl-H). ^{13}C NMR (DMSO-*d*$_6$, 400 MHz), *δ* 148.3, 147.3, 139.6, 127.8, 127.1, 126.9, 114.3, 111.7. Anal. Calcd. (%) for $C_{12}H_7BrClN_5OS$: C, 37.47; H, 1.83; N, 18.21. Found: C, 37.45; H, 2.03; N, 18.39. FTICR-MS for $C_{12}H_7{}^{79}Br^{35}ClN_5OS$ $[M+Na]^+$: calcd. 405.9135, found 405.9137.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (5-methyl-thiazol-2-yl)-amide 7q. White solid, yield 65%, mp 228-229 ºC; IR (KBr, cm^{-1}) *v* 3172 (NH), 2954 (CH), 1681 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 12.89 (br s, 1H, CONH), 8.53 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.23 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, pyridyl-H), 7.67 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.49 (s, 1H, pyrazolyl-H), 7.21 (d, 1H, thiazolyl-H), 2.29 (d, *J* = 0.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), *δ* 157.6, 155.5, 148.4, 147.0, 139.5, 138.1, 133.8, 128.8, 128.5, 128.1, 126.0, 111.8, 11.6. Anal. Calcd. (%) for $C_{13}H_9BrClN_5OS$: C, 39.17; H, 2.28; N, 17.57. Found: C, 39.29; H, 2.11; N, 17.38. FTICR-MS for $C_{13}H_9{}^{79}Br^{35}ClN_5OS$ $[M+Na]^+$: calcd. 419.9292, found 419.9294.

5-Bromo-2-(3-chloropyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (5-propyl-[1,3,4] thiadiazol-2-yl)-amide 7r. White solid, yield 70%, mp 241-242 ºC; IR (KBr, cm^{-1}) *v* 3296 (NH), 2962 (CH), 1675 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 13.53 (br s, 1H, CONH), 8.54 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 8.25 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, pyridyl-H), 7.68 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.59 (s, 1H, pyrazolyl-H), 2.07 (t, *J* = 7.2 Hz, 2H, CH_2), 1.67-1.63 (m, 2H, CH_2CH_3) 0.89 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 400 MHz), *δ* 165.4, 160.4, 155.6, 149.0, 147.0, 139.2, 136.6, 129.1, 128.7, 125.9, 113.5, 31.7, 22.8, 13.7. Anal. Calcd. (%) for $C_{14}H_{12}BrClN_6OS$: C, 39.31; H, 2.83; N, 19.65. Found: C, 39.22; H, 2.67; N, 19.69. FTICR-MS for $C_{14}H_{12}{}^{79}Br^{35}ClN_6OS$ $[M+Na]^+$: calcd. 448.9557, found 448.9561.

3-Bromo-1-(3-chloropyridin-2-yl)-*N*-(5-methylisoxazol-3-yl)-1*H*-pyrazole-5-carboxamide 7s. White solid, yield 61%, mp 257-258 ºC; IR (KBr, cm^{-1}) *v* 3438 (NH), 2968 (CH), 1696 (CO). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), *δ* 11.75 (br s, 1H, CONH), 8.55 (d, *J* = 4.8 Hz, 1H, pyridyl-H), 8.23 (d, *J* = 8.0 Hz, 1H, pyridyl-H), 7.66 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, pyridyl-H), 7.54 (s, 1H, pyrazolyl-H), 6.52 (s, 1H, isoxazolyl-H), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*$_6$, 400 MHz), *δ* 170.1, 157.4, 155.2, 148.3, 147.3, 139.7, 138.0, 127.8, 126.8, 126.6, 111.1, 96.6, 12.0. Anal. Calcd. (%) for $C_{13}H_9BrClN_5O_2$: C, 40.81; H, 2.37; N, 18.30. Found: C, 40.79; H, 2.50; N, 18.17. FTICR-MS for $C_{13}H_9{}^{79}Br^{35}ClN_5O_2$ $[M+Na]^+$: calcd. 403.9520, found 403.9528.

Crystal structure analysis

Compound **7m** was recrystallized from ethyl acetate/petroleum ether to give colorless crystals suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a = 18.418(4) Å, b = 13.254(3) Å, c = 14.175(3) Å, α = 90°, β = 116.44(3)°, γ = 90°, μ = 2.837 mm^{-1},

V = 3098.2(11) Å^3, Z = 4, D_x = 1.684 Mg m^{-3}, F (000) = 1568, T = 113(2) K, 2.87° ≤ θ ≤25.01°, and the final R factor, R_1 = 0.0306, ωR_2 = 0.0786. The crystal is monoclinic.

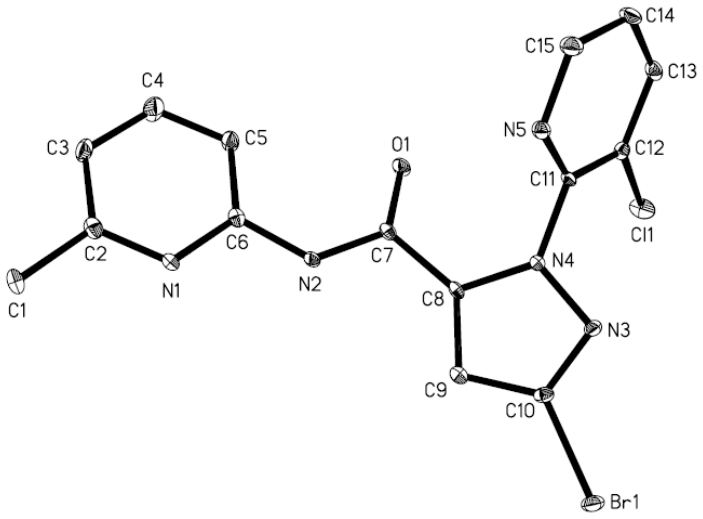


Figure 1. Molecular structure of the compound **7m**.

The molecular structure of **7m** contains the following three-plane subunit: the substituted pyridine ring C2-C6-N1 (*p1*), the pyridine ring C11-C15-N5 (*p2*), and the pyrazole ring (*p3*). The dihedral angle between the plane of the pyridine ring *p1* and the plane of the pyrazole ring *p3* is about 60.1°. The crystal packing structure of this compound is shown in Figure 2**.**

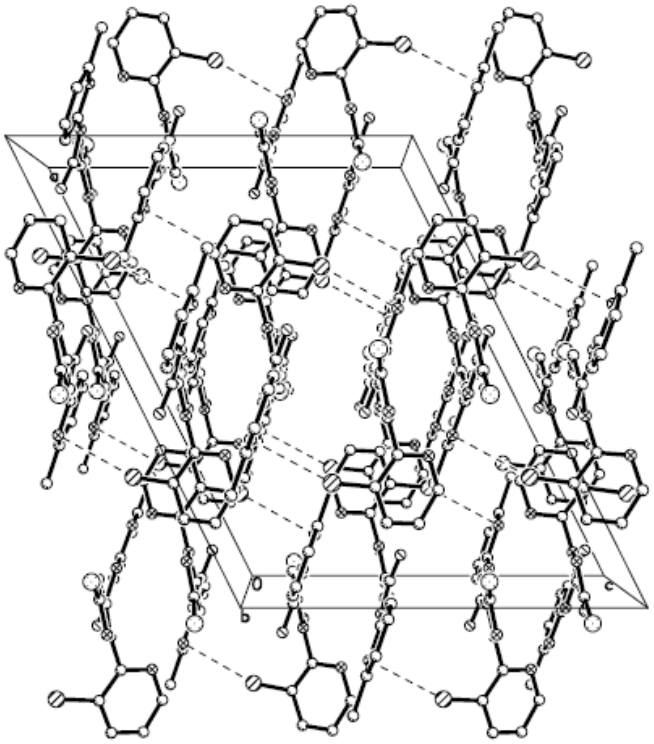


Figure 2. Packing diagram of the compound **7m**.

Biological assays

Fungicidal activities of compounds **7a-s** against *Pseudoperonospora cubensis, Pseudomonas syringae* pv *lachrymans, Corynespora cassiicola, Fusarium oxysporum, Sphaerotheca fuligenea, Xanthomonas axonopodis* and *Rhizoctonia solanii* were evaluated (Table 2) using pot culture test according to reference.[15] The culture plates were cultivated at (24±1) ºC. Fungicidal activities of commercial fungicides dimehachlon, jinggangmycin, thiophanate methyl, chlorothalonil, pyrimethanil as a control against above mentioned seven fungi were evaluated at the same conditions. The relative inhibition rate of the circle mycelium compared to blank assay was calculated via the following equation:

$$\text{Relative inhibition rate (\%)} = \frac{d_{ex} - d'_{ex}}{d_{ex}} \times 100\%$$

where d_{ex} is the extended diameter of the circle mycelium during the blank assay; and d'_{ex} is the extended diameter of the circle mycelium during testing.

Table 2. The antifungal activities of title compounds *in vivo* at 500 μg mL^{-1}

Compd.	*Pseudoperonospora cubensis*	*Pseudomonas syringae* pv *lachrymans*	*Corynespora cassiicola*	*Fusarium oxysporum*	*Sphaerotheca fuligenea*	*Xanthomonas axonopodis*	*Rhizoctonia solanii*
7a	62.74	50.74	34.60	68.65	43.98	57.79	23.37
7b	62.47	44.32	52.61	76.18	43.85	58.17	16.04
7c	26.11	50.62	33.93	61.13	68.16	67.58	14.55
7d	83.97	56.16	14.41	61.13	52.60	22.53	11.42
7e	62.70	38.93	47.38	54.86	40.34	69.95	9.08
7f	42.92	68.20	20.25	81.19	37.64	12.32	18.92
7g	44.11	58.08	45.92	57.37	47.23	41.33	15.79
7h	44.05	66.02	20.75	72.41	50.85	8.47	10.84
7i	25.05	61.00	47.38	73.67	49.09	68.70	6.73
7j	44.78	25.73	36.60	59.87	45.03	72.26	4.15
7k	50.74	49.15	32.16	69.91	49.28	78.65	21.33
7l	66.66	36.71	38.18	69.91	46.59	54.58	19.05
7m	87.41	38.27	19.48	47.34	37.43	74.45	21.98
7n	38.42	49.18	23.92	67.40	49.07	43.19	16.74
7o	85.57	57.35	31.84	41.07	41.12	66.40	13.46
7p	55.66	49.81	29.55	76.18	73.81	18.28	19.05
7q	25.40	44.35	27.59	57.37	23.80	72.58	9.66
7r	34.90	54.84	25.82	77.43	50.97	31.77	10.14
7s	63.76	28.82	57.29	61.13	82.54	54.92	16.12

Table 2. (continued)

Compd.	*Pseudoperonospora cubensis*	*Pseudomonas syringae* pv *lachrymans*	*Corynespora cassiicola*	*Fusarium oxysporum*	*Sphaerotheca fuligenea*	*Xanthomonas axonopodis*	*Rhizoctonia solanii*
dimethomorph	99.17		62.59				
thiophanate methyl				78.68			
chlorothalonil	95.78		63.96	63.64			
validamycin							93.84
zhongshengmycin		75.19			65.08	87.86	

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