SYNTHESIS AND FUNGICIDAL ACTIVITIES OF N-(5-((2,4-DICHLOROPHENOXY)METHYL)-1,3,4-THIADIAZOL-2-YL)-SUBSTITUTED-AMIDE

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Abstarct: Reaction of 2-amino-5-(2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazole with substituted acyl chloride yielded amide **2a-j** in good yield. The chemical structures of all compounds were established by ^{1}H NMR, FTIR, MS and elemental analysis, and some of these compounds were investigated for fungicidal activity. The bioassay results indicated that some of these compound exhibit moderate fungicidal activities.

Keywords: amide; 1,3,4-thidiazole derivatives; fungicidal activity.

Introduction

2,4-Dichlorophenoxyacetic acid (2,4-D) and their derivatives are a very important class of pesticides in the international market.[1] In the last 30 years, the founding of novel modified 2,4-D structures were interested by argo-chemists.

Additional, sulfur and nitrogen linked heterocyclic compounds received considerable attention in recent times because of their pharmacological and agricultural importance.[2-4] 1,3,4-thiadiazoles had broad-spectrum biological activity which are widely applied in medicine and agriculture as pesticides.[5-10] Amide compounds containing 1,3,4-thiadiazole

moiety also have been claimed to have beneficial medicinal and agriculturalapplications(Figure1).[11-12]

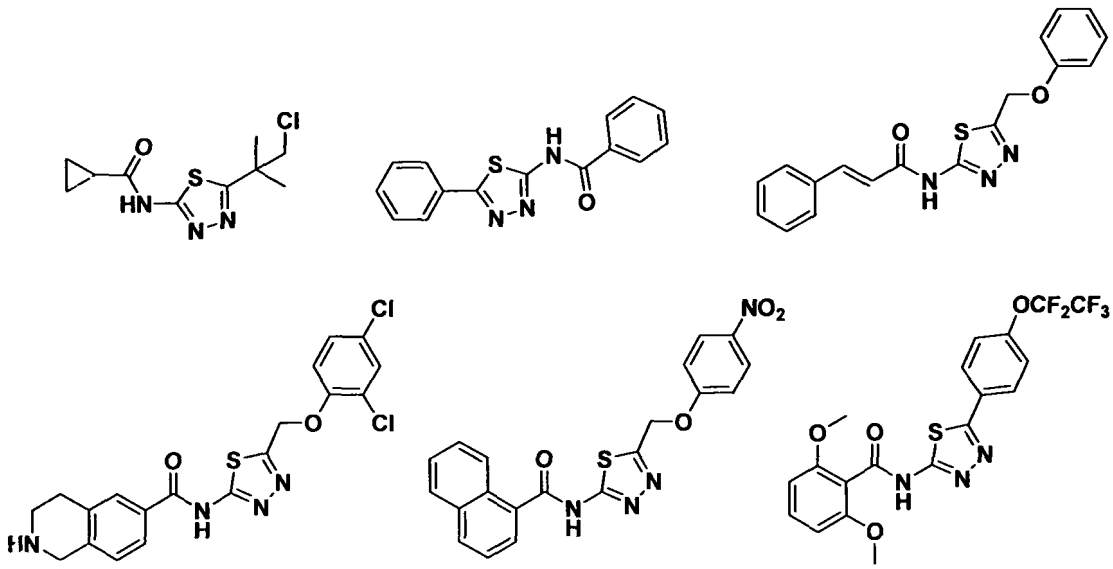
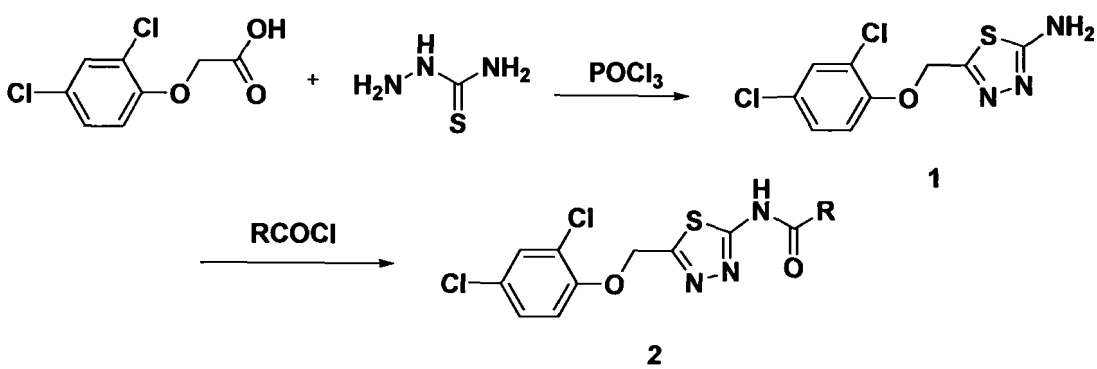


Figure 1. The pesticides containing 1,3,4-thiadizole ring

In view of this, we report herein the preparation of a series of amide compounds containing 1,3,4-thidiazoles. The preliminary fungicidal activities showed that some compounds exhibit moderate activity against *Sclerotinia sclerotiorum*(Lib.) de Bary, *Rhizoctonia solanii*, *Fusarium oxysporum*, *Corynespora cassiicola* and *Botrytis cinerea.*

Results and Discussion

The synthetic route is shown in Scheme 1.

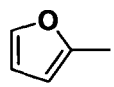


R = cyclopropan-yl, 2,4-dichloro-Ph, furan, butanyl, 2-chloro-methyl, 4-methoxy-Ph ethyl, propanyl, 2-methyl-Ph, 2-methoxy-Ph, 2-fluoro-Ph, 4-fluoro-Ph, 4-nitro-Ph

Scheme 1. The synthetic route of title compounds

Several procedures are available for the one-step synthesis of 2-amino-5-substituted-1,3,4-thiadiazoles derivative.[13-16] Yet the reaction of substitute aryl and alkyl acid with thiosemicarbazide in the presence of dehydrating agent $POCl_3$, affords a series of 2-amino-5-substituted-1,3,4-thiadiazoles.

Table 1. The physical data of title compounds

No.	R	m.p./ ℃	Yield/%
2a		185-187	82.1
2b	2,4-Cl_2-Ph	258-259	82.3
2c		238-240	85.4
2d	$CH_3CH_2CH_2CH_2$-	198-199	79.3
2e	$ClCH_2$-	211-213	88.4
2f	4-OMe-Ph	231-232	85.3
2g	CH_3CH_2-	243-244	76.5
2h	$CH_3CH_2CH_2$-	209-210	77.9
2i	2-Me-Ph	233-234	86.9
2j	2-OMe-Ph	221-222	86.5
2k	2-F-Ph	229-231	89.1
2l	4-F-Ph	232-234	88.1
2m	4-NO_2-Ph	250-251	91.3

The *in vivo* fungicidal results of five compounds against *Sclerotinia sclerotiorum*(Lib.) de Bary, *Rhizoctonia solanii*, *Fusarium oxysporum*, *Corynespora cassiicola*, and *Botrytis cinerea* were listed in Table **2**. As shown in Table **2**, Compounds **2b** and **2j** exhibit good fungicidal activity against *Cladosporium cucumerinum*. Compounds **2c and 2e** had moderate fungicidal activity against *Fusarium oxysporum*. Among them, these compounds displayed the highest fungicidal activity against *Colletotrichum orbiculare* (Berk aLMont) Arx.. All of the results in this paper will be useful

for later research.

Table 2. The Fungicidal Activity of tested Compounds

	Corynespora cassiicola	*Cladosporium cucumerinum*	*Erysiphe cichoracearum*	*Sclerotinia sclerotiorum* (Lib.) de Bary	*Colletotrichum orbiculare* (Berk aLMont) Arx.
2b	-4.00	88.00	3.31	36.69	43.82
2c	42.00	4.00	42.70	42.23	68.70
2e	38.00	19.00	35.71	31.85	66.94
2j	38.00	71.00	67.27	16.14	19.87
2m	15.00	30.00	10.00	24.23	45.11

Experimental

Melting points were determined using an X-4 melting apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Equinox 55 spectrophotometer as KBr tablets. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300MHz) using TMS as an internal standard and DMSO-d_6 as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyzer.

General Procedure for the Preparation of amide

Thiosemicarbazide (0.91g, 1 mmol), 2-(2,4-dichlorophenoxy)acetic acid (2.21g, 1 mmol) and $POCl_3$ (2 mmol) was refluxed for 2 h. After that, the excess $POCl_3$ was removed by adding water. Then added 40% NaOH, up to pH=9~10, after a night, obtained the product by filtration and recrystallized from DMF-EtOH to afford the products. The substituted acyl chloride (0.5 mmol) was dropwised into 2-amino-5-(2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazole (0.5 mmol), and added Et_3N (0.5 mmol). The mixture was refluxed about 2h. The progress of the reactions was monitored by TLC. The resulting solid was crystallized from EtOH to afford the products. The analytic data for compounds **2a–m** are as follows:

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)cyclopropanecarboxamide 2a

White crystal, ^{1}H NMR ($CDCl_3$) δ: 0.93-1.21(m, 4H, cyclopropane-H), 1.99(m, 1H, CH), 5.09(s, 2H, CH_2O), 7.10-7.68(m, 3H, ph), 12.93(s, 1H,NH),; IR/cm^{-1}: 3485 (N-H), 1656 (C=O), 1554, 1452 (Ar); ESI-MS: 343(M-1); Elemental anal. (%), calculated: C, 45.36; H, 3.22; N,12.21; found: C, 45.66; H, 3.41; N, 12.35.

2,4-dichloro-N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)benzamide 2b

White crystal, ^{1}H NMR ($CDCl_3$) δ: 5.09(s, 2H, CH_2O), 7.10-8.42(m, 6H,ph), 9.96(s, 1H, NH); IR/cm^{-1}: 3447 (N-H), 1670 (C=O), 1550, 1451 (Ar); ESI-MS: 448(M-1); Elemental anal. (%), calculated: C, 42.79; H, 2.02; N, 9.36; found: C, 42.80; H, 2.41; N, 9.45.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)furan-2-carboxamide 2c

White crystal, ^{1}H NMR ($CDCl_3$) δ: 5.03(s, 2H, CH_2O), 7.13-7.88(m, 6H, ph and furan), 8.94(s, 1H, NH); IR/cm^{-1}: 3476 (N-H), 1640 (C=O), 1551, 1457 (Ar); ESI-MS: 369(M-1); Elemental anal. (%), calculated: C, 45.42; H, 2.45; N, 11.35; found: C, 45.84; H, 2.45; N, 11.62.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)pentanamide 2d

White crystal, ^{1}H NMR ($CDCl_3$) δ: 0.92(t, 3H, CH_3), 1.00(q, 2H, CH_2), 1.73(m, 2H, CH_2), 2.03(m, 2H, CH_2), 5.01(s, 2H, CH_2O), 7.15-7.94(m, 3H, ph), 8.40(s, 2H, NH) ; IR/cm^{-1}: 3481 (N-H), 1655 (C=O), 1549, 1450 (Ar); ESI-MS: 359(M-1); Elemental anal. (%), calculated: C, 46.67; H, 4.20; N, 11.66; found: C, 46.34; H, 4.14; N, 11.74.

2-chloro-N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)acetamide 2e

White crystal, ^{1}H NMR ($CDCl_3$) δ: 3.88(s, 2H,$ClCH_2$), 5.08(s, 2H, CH_2O), 7.05-7.91(m, 3H, ph), 8.15(s, 2H, NH) ; IR/cm^{-1}: 3477 (N-H), 1670 (C=O), 1547, 1451 (Ar); ESI-MS: 351(M-1); Elemental anal. (%), calculated: C, 37.47; H, 2.29; N, 11.92; found: C, 37.05; H, 2.34; N, 11.51.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-methoxybenzamide 2f

White crystal, ^{1}H NMR ($CDCl_3$) δ: 3.86(s, 3H, OCH_3), 5.08(s, 2H, CH_2O), 7.00-7.88(m, 7H, ph), 8.17(s, 1H, NH); IR/cm^{-1}: 3482 (N-H), 1651 (C=O), 1555, 1456 (Ar); ESI-MS: 409(M-1); Elemental anal. (%), calculated: C, 49.77; H, 3.19; N, 10.24; found: C, 49.80; H, 3.41; N, 10.45.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)propionamide 2g

White crystal, ^{1}H NMR (DMSO) δ: 0.86(t, 3H, CH_3), 2.00(q, 2H, CH_2), 5.03(s, 2H, CH2O), 7.11-7.61(m, 3H, ph), 8.33(s, 1H, NH) ; IR/cm^{-1}: 3479 (N-H), 1666 (C=O), 1556, 1450 (Ar); ESI-MS: 331(M-1); Elemental anal. (%), calculated: C, 43.39; H, 3.34; N, 12.65; found: C, 43.65; H, 3.54; N, 12.78.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)butyramide 2h

White crystal, ^{1}H NMR ($CDCl_3$) δ: 0.85(m, 3H, CH_3), 1.48(m, 2H,CH_2), 2.08(t, 2H,CH_2), 5.05(s, 2H, CH_2O), 7.11-7.59(m, 3H, ph), 8.40(s, 1H, NH) ; IR/cm^{-1}: 3476 (N-H), 1657 (C=O), 1560, 1449 (Ar); ESI-MS: 345(M-1); Elemental anal. (%), calculated: C, 45.10; H, 3.78; N, 12.14; found: C, 45.45; H, 3.64; N, 12.19.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-2-methylbenzamide 2i

White crystal, ^{1}H NMR ($CDCl_3$) δ: 2.33(s, 3H, CH_3), 5.89(s, 2H, CH_2O), 7.01-7.73(m, 7H, ph), 8.25(s, 1H,NH) ; IR/cm^{-1}: 3457 (N-H), 1677 (C=O), 1551, 1451 (Ar); ESI-MS: 393(M-1); Elemental anal. (%), calculated: C, 51.79; H, 3.32; N, 10.66; found: C, 51.80; H, 3.56; N, 10.79.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide 2j

White crystal, ^{1}H NMR ($CDCl_3$) δ: 3.88(s, 3H, CH_3), 5.03(s, 2H, CH_2O), 7.13-7.66(m, 7H, ph), 8.34(s, 1H, NH) ; IR/cm^{-1}: 3478 (N-H), 1675 (C=O), 1555, 1452 (Ar) ESI-MS: 409(M-1); Elemental anal. (%), calculated: C, 49.77; H, 3.19; N, 10.24; found: C, 49.56; H, 3.41; N, 10.54.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-2-fluorobenzamide 2k

White crystal, ^{1}H NMR ($CDCl_3$) δ: 5.02(s, 2H, CH_2O), 6.91-7,90(m, 7H, ph), 8.46(s, H, NH) ; IR/cm^{-1}: 3482 (N-H), 1659 (C=O), 1551, 1453 (Ar); ESI-MS: 397(M-1); Elemental anal. (%), calculated: C, 48.26; H, 2.53; N, 10.55; found: C, 48.54; H, 2.41; N, 10.78.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-fluorobenzamide 2l

White crystal, ^{1}H NMR ($CDCl_3$) δ: 4.89(s, 2H, CH_2O), 7.10-7.71(m, 7H, ph), 8.48(s, 1H, NH) ; IR/cm^{-1}: 3488 (N-H), 1678 (C=O), 1553, 1450 (Ar); ESI-MS: 397(M-1); Elemental anal. (%), calculated: C, 48.26; H, 2.53; N, 10.55; found: C, 48.10; H, 2.88; N, 10.34.

N-(5-((2,4-dichlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-nitrobenzamide 2m

White crystal, ^{1}H NMR ($CDCl_3$) δ: 4.93(s, 2H, CH_2O), 7.05-7.58(m, 7H, ph), 8.27(s, 1H,NH) ; IR/cm^{-1}: 3478 (N-H), 1665 (C=O), 1554, 1452 (Ar); ESI-MS: 424(M-1); Elemental anal. (%), calculated: C, 45.19; H, 2.37; N, 13.18; found: C, 45.45; H, 2.45; N, 13.26.

Fungicidal Activity

Fungicidal activities of compounds of series **2** against *Sclerotinia sclerotiorum*(Lib.) de Bary, *Rhizoctonia solanii*, *Fusarium oxysporum*, *Corynespora cassiicola*, and *Botrytis cinerea* were evaluated using pot culture test according to reference[15]. The culture plates were cultivated at (24±1) . 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.

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