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SYNTHESIS AND FUNGICIDAL ACTIVITIES OF 5-ARYL-1,3,4-OXADIAZOLYL 2-THIOETHER DERIVATIVES CONTAINING STROBILURIN MOTIF

Hongtao Wang, Wenliang Zhang, and Xiaohua Du*

Catalytic Hydrogenation Research Center, Zhejiang Key Laboratory of Green Pesticides and Cleaner Production Technology, Zhejiang University of Technology, Hangzhou 310014, China, Correspondence: duxiaohua@zjut.edu.cn; Tel.: +86-571-88320430

Abstract – A novel class of 2,5-disubstituted 1,3,4-oxadiazole derivatives was synthesized through active substructure splicing by using kresoxim-methyl as the lead compound. The structure of the title compound was confirmed via structural characterization, and the preliminary assessment of the fungicidal activities revealed that compounds **6b**, **6k**, **6m**, **6n**, and **6o** are active against *Pyricularia oryza*e Cav. to a comparable degree to kresoxim-methyl (50 mg/L). Further, control experiments revealed that **6o** exhibited in vitro fungicidal activity against *P. oryzae* Cav., having a median effective concentration (EC_{50}) of 10.03 mg/L, slightly higher than that of kresoxim-methyl (14.21 mg/L). Therefore, **6o** is a promising lead compound that warrants further investigation.

Since the discovery of the fungicidal activity of the natural substance strobilurin A,[1] strobilurin analogs have been of research interest. Notably, these compounds are promising fungicides,[2-4] insecticide[5,6] and herbicides.[7,8] As fungicides, numerous commercial strobilurin fungicides have been developed, and these have become popular commercial fungicides because of their low toxicity to mammals, high efficiency, and broad acitvity,[9] and examples include azoxystrobin, kresoxim-methyl, pyraclostrobin, metominostrobin, picoxystrobin, and trifloxystrobin (Figure 1). However, the frequent and widespread use of commercial strobilurin fungicides in Japan and China has resulted in the development of resistance.[10–14] Consequently, new fungicides containing the strobilurin motif are required.

1,3,4-Oxadiazole compounds have been known for about 90 years,[15] and the investigation of their biological activities has intensified in the last thirty years. Notably, these compounds exhibit a wide range of pharmacological activities, having anticancer[16,17] antibacterial,[18–20] fungicidal,[21,22]

herbicidal,[23,24] and insecticidal[25–27] effects. In particular, the presence of an -N=C-O moiety in 1,3,4-oxadiazole compounds enhances the biological activity because this moiety can form hydrogen bonds with electron-rich target sites.[28] Furthermore, the presence of a thioether linker can reduce lipophilicity and act as an additional hydrogen bond acceptor, which is considered to be beneficial for improving the bioactivity of these molecules.[29]

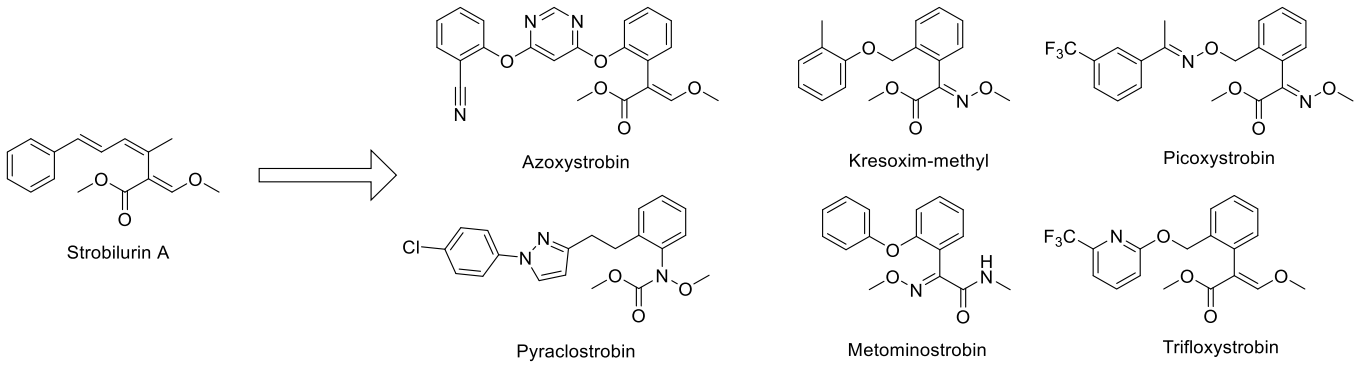
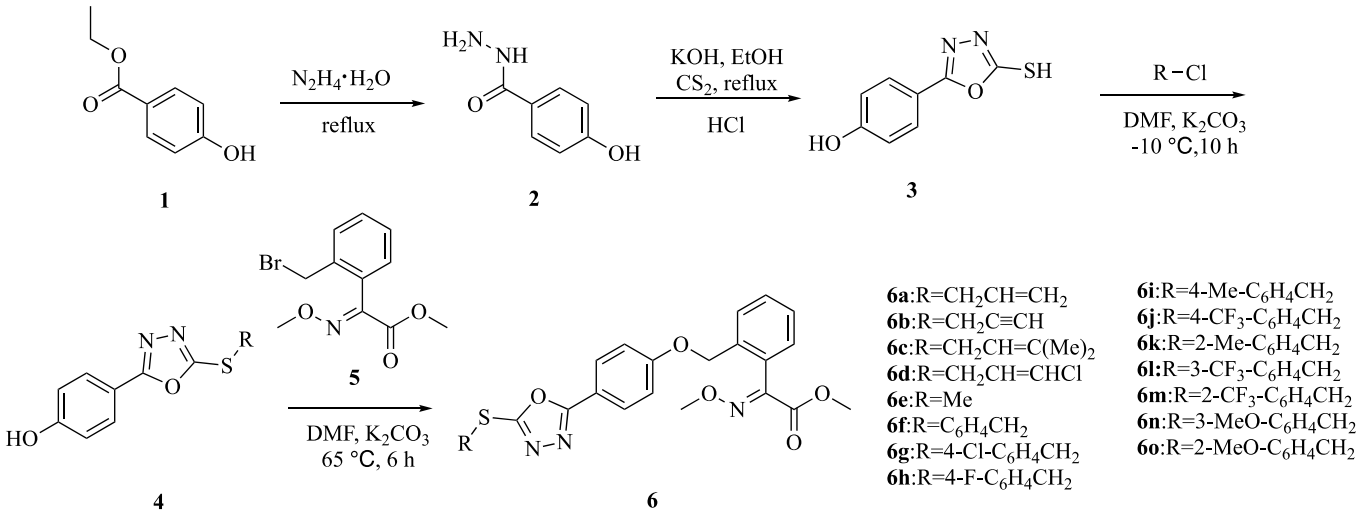


Figure 1. Structures of strobilurin A and related compounds

In this study, we designed a class of novel compounds containing the 1,3,4-oxadiazole group, the strobilurin motif and a thioether linker via active substructure splicing. The fungicidal activities of these 2-aryl-1,3,4-oxadiazolyl 5-thioether derivatives were studied by preliminary screening, and their half-maximal effective concentrations were determined. Additionally, the structures of the target compounds were confirmed by ^{1}H NMR and ^{13}C NMR, as well as high-resolution mass spectroscopy (HRMS) measurements.

CHEMISTRY

The synthetic route to the title compounds is outlined in Scheme 1. Intermediate **2** was synthesized by refluxing starting material **1** with hydrazine hydrate, whereas intermediate **3** was obtained by refluxing the hydrazides with carbon disulfide in an ethanolic potassium hydroxide solution. Intermediates **4A–4o** are synthesized from intermediate **3** and substituted chloroalkenes or chloroalkynes via substitution reactions. Next, the nucleophilic substitution reaction of intermediates **4a–4o** and intermediate **5** using *N,N*-dimethylformamide as a solvent, and potassium carbonate as an acid-binding agent was carried out. The structures of **6a–6o** were determined by NMR and HRMS characterization.



Scheme 1. Synthesis of the title compounds

FUNGICIDAL ACTIVITY

Table 1. Chemical structures, appearance, and in vitro fungicidal activities (inhibition rate, *I*/%) of the compounds (50 mg/L)

Compd.	*R*	Appearance	Fungicidal activity(I/%)				
			A. s.	*P. o.*	*S. s.*	*T. c.*	*H. m.*
6a	$CH_2CH=CH_2$	Yellow solid	37.5	55.6	26.7	42.3	50.0
6b	$CH_2C\equiv CH$	White solid	50.0	**77.8**	60.0	40.8	50.0
6c	$CH_2CH=C(Me)_2$	White solid	37.5	66.7	73.3	38.0	40.0
6d	$CH_2CH=CHCl$	White solid	43.8	61.1	46.7	76.1	45.0
6e	Me	Yellow solid	56.3	44.4	80.0	40.8	45.0
6f	$C_6H_4CH_2$	White solid	37.5	55.6	66.7	32.4	35.0
6g	4-Cl-$C_6H_4CH_2$	Yellow solid	37.5	61.1	53.3	35.2	20.0
6h	4-F-$C_6H_4CH_2$	Yellow solid	31.3	22.2	73.3	35.2	20.0
6i	4-Me-$C_6H_4CH_2$	White solid	37.5	66.7	66.7	35.2	30.0
6j	4-CF_3-$C_6H_4CH_2$	White solid	37.5	66.7	73.3	28.2	40.0
6k	2-Me-$C_6H_4CH_2$	White solid	43.8	**77.8**	66.7	38.0	55.0
6l	3-CF_3-$C_6H_4CH_2$	Brown solid	25.0	33.3	60.0	0.0	20.0
6m	2-CF_3-$C_6H_4CH_2$	White solid	37.5	**77.8**	66.7	42.3	40.0
6n	3-MeO-$C_6H_4CH_2$	White solid	37.5	**72.2**	73.3	70.4	50.0
6o	2- MeO-$C_6H_4CH_2$	White solid	43.8	**77.8**	53.3	49.3	55.0
Kresoxim-methyl			100.0	77.8	90.7	65.3	75.0

[a]*A. s., Alternaria solani.*; *P. o., Pyricularia oryae Cav.*; *S. s., Sclerotinia sclerotiorum*; *T. c., Thanatephorus cucumers.*; *H. m., Helminthosporiu mmaydis*

As show in Table 1, most compounds showed high activities against *Pyricularia oryzae* but low activities against *Alternaria solani*. Further, the compounds had weak inhibitory activity against *A. solani* and *Helminthosporiu mmaydis*, and some compounds showed weak to moderate inhibitory activity against

Sclerotinia sclerotiorum and *Thanatephorus cucumers*. Notably, nearly half of the compounds showed generally good inhibitory activity against *P. oryzae*. Among them, the fungicidal activities of compounds **6b**, **6k**, **6m**, **6n**, and **6o** against *P. oryzae* are comparable to that of kresoxim-methyl. The charge distribution in the structure may affect the interaction between the compound and the receptor, suggesting that the candidate compound have higher interactions with key receptors in *P. oryzae*.

Based on the fungicidal activity of **6b**, **6k**, **6m**, **6n**, and **6o** against *P. oryzae*, further fungicidal activity tests were carried out using other fungi. As shown in Table 2, the tests using **6b**, **6k**, **6m**, **6n**, and **6o** against six other fungi (see Table 2) at 50 mg/L revealed some activity, suggesting the promise of these compounds as leads for further research.

Table 2. In vitro fungicidal activities (%) of **6b**, **6k**, **6m**, **6n**, **and 6o** at 50 mg/L

Compd.	*P. c.*	*P. p.*	*B. c.*	*C .c.*	*P. a.*	*A..r.*
6b	44.0	26.5	33.3	40.0	31.6	41.7
6k	44.0	46.9	41.7	33.3	42.1	41.7
6m	52.0	24.5	33.3	26.7	36.8	25.0
6n	44.0	22.4	33.3	33.3	36.8	41.7
6o	44.0	22.4	25.0	33.3	42.1	37.5
Kresoxim-methyl	60.0	36.7	22.7	53.3	62.5	66.7

[a] *P. c., Phytophthora capsici; P. p., Physalos porapiricola; B. c., Botrytis cinerea; C. c., Corynespora cassiicola; P. a., Pythium aphanidermatum; A. r., Alternariamali rob*

In addition, as shown in Table 3, **6o** had an inhibition rate of nearly 50% against *P. oryzae* at 6.25 mg/L, which is better than the activity of kresoxim- methyl at the same concentration.

Table 3. Fungicidal activities of candidate compounds against *P. oryzae* Cav.

Compd.	Dosage/(mg/L)				EC_{50}/mg/L	Regression equation
	50	25	12.5	6.25		
6b	77.8	54.5	40.9	27.3	17.98	*y*=1.6344x+2.9492
6k	77.8	54.5	45.5	18.2	18.50	*y*=1.7353x+2.8008
6m	77.8	51.5	36.4	27.3	18.07	*y*=1.3251x+3.3345
6n	72.2	54.5	45.5	27.3	18.84	*y*=1.5170x+3.0658
6o	77.8	63.6	54.5	**45.5**	10.03	*y*=1.0640x+3.9348
Kresoxim-methyl	77.8	63.6	50.0	27.3	14.21	*y*=3.3542x+1.4278

Further, using structure–activity relationship (SAR) analysis, it was found that, when the R group was a substituted phenyl and R was changed to *ortho*-substituted, *meta*-substituted, and *para*-substituted phenyl groups, the fungicidal activities of the candidate compounds, such as that against *P. oryzae*, were reduced, and the following order was obtained **6j** (4-CF_3-Bn) < **6l** (3-CF_3-Bn) < **6m** (2-CF_3-Bn). Notably, when a

hydrogen atom of the terminal alkenyl R group was substituted, the fungicidal activity of the candidates was enhanced; for example, **6c** ($CH_2CH=C(Me)_2$) and **6d** ($CH_2CH=CHCl$) showed higher fungicidal activities than **6a** ($CH_2CH=CH_2$). More studies on the SAR of 2-aryl-1,3,4-oxadiazolyl 5-thioether derivatives concerning their fungicidal activities are in progress.

A series of new 2-aryl-1,3,4-oxadiazolyl 5-thioether derivatives containing strobilurin moieties were designed and synthesized as potential fungicides. The fungicidal activity assays revealed that compounds **6b**, **6k**, **6m**, **6n**, and **6o** possessed good activity against *P. oryzae*, and the activities were comparable to that of kresoxim-methyl. The analysis of the activity and structural characteristics revealed that the activity against *P. oryzae* could be improved by introducing a benzene ring with an *ortho* substituent, and **6o** [(EC_{50}) = 10.03 mg/L] displayed the highest activity. These findings, thus, provide a new direction for further structural optimization of 2-aryl-1,3,4-oxadiazolyl 5-thioether derivatives containing strobilurin motifs as fungicides.

EXPERIMENTAL

General: The spectroscopic measurements of the intermediates used deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent, whereas those of the target compounds used chloroform-*d* ($CDCl_3$) as the solvent. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400-MHz spectrometer (Bruker Co., Switzerland). HRMS data were recorded on 6545 Q-TOF LC-MS mass spectrometer (Agilent Co., USA). The melting points were determined on B-540 melting point apparatus (Büchi Co., Switzerland) and were uncorrected. All reagents were commercially available and used without further purification. The fungi were provided by Nankai University Pesticide National Engineering Research Center and showed some drug resistance.

The intermediates (**2** and **3**) were synthesized as reported in the literature[30,31] without modification of the reaction conditions. Intermediate **5** was synthesized by multi-step synthesis following a patented method.[32]

Synthesis of 4a–4o: To a stirred solution of intermediate **2** (1.03 mmol) in anhydrous dimethyl-formamide (DMF, 5 mL), K_2CO_3 (1.24 mmol) was added, and the mixture was stirred at -10 °C for 0.5 h. Subsequently, a substituted chloroalkene or chloroalkyne (1.13 mmol) was added dropwise. The mixture was then stirred at -10 °C for 10 h, and the reaction was monitored by thin-layer chromatography (TLC). After the reaction had completed, pure water was added to the reaction solution. Then, 6 N aqueous HCl was added dropwise until the solution became acidic (pH = 5.0). The mixture was extracted three times with EtOAc (30 mL × 3), and the EtOAc phase was successively washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Then, the concentrate was treated by silica gel column

chromatography to yield compounds **4a**–**4o**. The eluent was petroleum ether/EtOAc (3:1, v/v). Melting points and ^{1}H NMR and ^{13}C NMR data for intermediates **4a**–**4o** are provided in the Supporting Information.

General procedure for target compounds (6a-6o)

K_2CO_3 (1.5 mmol) was added to intermediates **4a**–**4o** (1 mmol) in anhydrous DMF (5 mL) with constant stirring, and, then, the mixture was stirred at room temperature for 0.5 h. Subsequently, DMF solution containing intermediate **5** (2 mmol) was added dropwise, and the temperature was increased to 65 °C. The mixture was then stirred for 3 h, and 6 N aqueous HCl was added dropwise until the solution became acidic (pH = 5.0). The mixture was extracted three times with EtOAc (3 × 30 mL). Then, the EtOAc phase was successively washed with saturated brine, dried over MgSO4, and concentrated in vacuo. The concentrate was treated by silica gel column chromatography to yield compounds **6a**–**6o**. The eluent was petroleum ether/EtOAc (3:1, v/v).

Fungicidal assay: The target compound (3 mg) was dissolved in DMSO (0.1 mL) to yield a 30000 ppm mother solution. Then, the mother solution (50 μL) was removed with a pipette and dissolved in water containing Tween (2.95 mL) to yield a 500 ppm solution. Then, the drug solution (1 mL) was removed with a pipette and placed in a sterilized Petri dish with liquid potato dextrose agar (PDA, 9 mL). The mixture was well shaken and allowed to cool. After setting, a round fungus cake was punched out and placed in the center of the Petri dish with an inoculation needle. Then, the Petri dish was placed in an incubator at 27 °C for cultivation, and the colony diameter was measured after 48–72 h. After 3 days, the colony diameter was measured, and the growth inhibition rate (%) was calculated.The results are listed in Table 1.

In Equation (1), D is the diameter of growth of the colony, D_1 represents diameter of the colony, and D_2 represents the diameter of the fungicidal cake.

$$D = D_1 - D_2 \quad (1)$$

In Equation (2), I is mycelial growth inhibition rate, D_0 is the diameter of growth of the blank control colony, and D_t is the diameter of growth of the colony treated with the drug.

$$I\,(\%) = (D_0 - D_t)/D_0 \times 100\% \quad (2)$$

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-(allylthio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)-phenyl)acetate (6a): Yield: 40.3%. mp 97.6-98.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.9 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.24 (dd, J = 7.3, 1.3 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 6.03 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 5.43 – 5.36 (m, 1H), 5.23 (d, J = 10.0 Hz, 1H), 5.04 (s, 2H), 4.04 (s, 3H), 3.92 (d, J = 7.0 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.70, 163.20, 162.94, 161.01, 149.30, 134.46, 131.76, 129.64, 129.40, 128.67, 128.39, 128.03, 127.75, 119.67, 116.50, 115.23, 68.52, 63.83, 52.99, 35.26. HRMS calcd for $C_{22}H_{21}N_3O_5S$ $[M+Na]^+$ 462.1094, found 462.1095.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-(prop-2-yn-1-ylthio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6b): Yield: 25.0%. mp 113.5-114.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H), 7.59 – 7.53 (m, 1H), 7.46 (dtd, *J* = 16.4, 7.4, 1.5 Hz, 2H), 7.24 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.06 – 6.93 (m, 2H), 6.29 (t, *J* = 6.3 Hz, 1H), 5.20 (d, *J* = 6.3 Hz, 2H), 5.04 (s, 2H), 4.05 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.00, 163.26, 161.91, 161.17, 149.34, 134.47, 129.72, 129.43, 128.72, 128.55, 128.11, 127.80, 116.39, 115.29, 80.78, 80.59, 77.24, 68.57, 63.92, 53.08. HRMS calcd for $C_{22}H_{19}N_3O_5S$ $[M+Na]^+$ 460.0938, found 460.0940.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((3-methylbut-2-en-1-yl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6c): Yield: 58.8%. mp 89.4-90.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9 Hz, 2H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.46 (dtd, *J* = 16.3, 7.3, 1.3 Hz, 2H), 7.27 – 7.18 (m, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.44 (ddq, *J* = 9.4, 6.5, 1.4 Hz, 1H), 5.04 (s, 2H), 4.05 (s, 3H), 3.95 (d, *J* = 7.9 Hz, 2H), 3.87 (s, 3H), 1.77 (d, *J* = 3.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.60, 163.71, 163.26, 160.99, 149.35, 139.29, 134.52, 129.71, 129.43, 128.71, 128.42, 128.10, 127.82, 117.40, 116.64, 115.24, 68.55, 63.92, 53.08, 30.98, 25.75, 17.93. HRMS calcd for $C_{24}H_{25}N_3O_5S$ $[M+Na]^+$ 490.1407, found 490.1414.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((3-chloroallyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6d): Yield: 56.8%. mp 104.3-105.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 2H), 7.58 – 7.51 (m, 1H), 7.45 (dtd, *J* = 16.2, 7.4, 1.6 Hz, 2H), 7.26 – 7.18 (m, 1H), 7.05 – 6.94 (m, 2H), 6.46 – 6.25 (m, 1H), 6.24 – 6.05 (m, 1H), 5.04 (s, 2H), 4.08 (dd, *J* = 7.3, 1.0 Hz, 1H), 4.05 (s, 3H), 3.92 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.02, 165.92, 163.26, 162.79, 162.42, 161.12, 161.11, 149.34, 134.48, 129.72, 129.44, 128.73, 128.49, 128.47, 128.12, 127.82, 127.08, 125.91, 123.30, 122.82, 116.43, 116.39, 115.30, 115.28, 68.57, 63.92, 53.08, 32.39, 28.56. HRMS calcd for $C_{22}H_{20}ClN_3O_5S$ $[M+Na]^+$ 490.0704, found 490.0706.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-(methylthio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6e):Yield: 63.1%. mp 142.1-142.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.87 (m, 2H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.45 (dtd, *J* = 16.3, 7.4, 1.4 Hz, 2H), 7.24 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.05 – 6.90 (m, 2H), 5.04 (s, 2H), 4.04 (s, 3H), 3.86 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.66, 164.35, 163.23, 160.99, 149.32, 134.50, 129.66, 129.41, 128.68, 128.38, 128.05, 127.76, 116.55, 115.23, 68.53, 63.86, 53.01, 14.63. HRMS calcd for $C_{20}H_{19}N_3O_5S$ $[M+Na]^+$ 436.0938, found 436.0934.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6f): Yield: 72.8%. mp 128.5-129.3 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.51 – 7.40 (m, 4H), 7.40 – 7.29 (m, 3H), 7.24 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.04 (s, 2H), 4.53 (s, 2H), 4.05 (s, 3H), 3.87 (s, 3H). ^{13}C NMR

(101 MHz, $CDCl_3$) δ 165.71, 163.26, 163.21, 161.05, 149.35, 135.67, 134.50, 129.72, 129.43, 129.17, 128.82, 128.72, 128.45, 128.10, 127.82, 116.50, 115.26, 68.56, 63.92, 53.08, 36.88. HRMS calcd for $C_{26}H_{23}N_3O_5S$ $[M+Na]^+$ 512.1251, found 512.1265.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((4-chlorobenzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6g): Yield: 51.4%. mp 133.0-134.5 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.39 (m, 4H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.24 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.04 – 6.93 (m, 2H), 5.04 (s, 2H), 4.47 (s, 2H), 4.04 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.84, 163.26, 162.82, 161.11, 149.35, 134.49, 134.41, 133.99, 130.53, 129.70, 129.44, 128.95, 128.72, 128.44, 128.10, 127.80, 116.42, 115.29, 68.57, 63.90, 53.05, 36.07. HRMS calcd for $C_{26}H_{22}ClN_3O_5S$ $[M+Na]^+$ 546.0861, found 546.0857.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((4-fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6h): Yield: 12.3%. mp 140.7-143.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.40 (m, 4H), 7.24 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.09 – 6.92 (m, 4H), 5.04 (s, 2H), 4.49 (s, 2H), 4.04 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.79, 163.69, 163.26, 162.95, 161.24, 161.09, 149.35, 134.49, 131.63, 131.60, 130.95, 130.87, 129.70, 129.44, 128.72, 128.44, 128.10, 127.80, 116.45, 115.83, 115.61, 115.28, 68.56, 63.90, 53.05, 36.07. HRMS calcd for $C_{26}H_{22}FN_3O_5S$ $[M+Na]^+$ 530.1156, found 530.1154.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((4-methylbenzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6i): Yield: 32.4%. mp 131.8-132.3 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.84 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 (dtd, *J* = 16.4, 7.4, 1.6 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.24 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.08 – 6.90 (m, 2H), 5.04 (s, 2H), 4.50 (s, 2H), 4.05 (s, 3H), 3.87 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.66, 163.31, 163.26, 161.03, 149.35, 137.94, 134.52, 132.57, 129.71, 129.50, 129.43, 129.08, 128.72, 128.44, 128.10, 127.81, 116.57, 115.25, 68.56, 63.91, 53.07, 36.72, 21.18. HRMS calcd for $C_{27}H_{25}N_3O_5S$ $[M+Na]^+$ 526.1407, found 526.1407.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((4-(trifluoromethyl)benzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6j): Yield: 71.5%. mp 108.2-109.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9 Hz, 2H), 7.61 (s, 4H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.26 – 7.19 (m, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.04 (s, 2H), 4.54 (s, 2H), 4.04 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.95, 163.26, 162.56, 161.15, 149.34, 140.07, 134.47, 130.41, 130.08, 129.70, 129.53, 129.45, 128.72, 128.45, 128.11, 127.80, 125.75, 125.71, 125.31, 122.60, 116.34, 115.29, 68.57, 63.89, 53.05, 36.05. HRMS calcd for $C_{27}H_{22}F_3N_3O_5S$ $[M+Na]^+$ 580.1124, found 580.1129.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((2-methylbenzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6k): Yield: 57.9%. mp 92.3-93.5 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ

7.93 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.45 (dt, *J* = 15.7, 7.2 Hz, 3H), 7.28 – 7.15 (m, 4H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 2H), 4.56 (s, 2H), 4.05 (s, 3H), 3.87 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.69, 163.33, 163.26, 161.06, 149.36, 137.13, 134.52, 133.14, 130.76, 130.30, 129.70, 129.45, 128.72, 128.54, 128.45, 128.09, 127.81, 126.41, 116.55, 115.27, 68.57, 63.90, 53.06, 35.22, 19.23. HRMS calcd for $C_{27}H_{25}N_3O_5S$ $[M+Na]^+$ 526.1407, found 526.1409.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((3-(trifluoromethyl)benzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6l): Yield: 42.1%. mp 124.3-125.2 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.76 – 7.68 (m, 2H), 7.56 (dd, *J* = 12.8, 7.6 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.24 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.04 (s, 2H), 4.55 (s, 2H), 4.04 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.93, 163.26, 162.57, 161.14, 149.35, 137.01, 134.48, 132.60, 131.32, 131.00, 129.70, 129.45, 129.30, 128.72, 128.46, 128.10, 127.81, 125.88, 125.84, 125.21, 124.94, 124.90, 122.50, 116.36, 115.29, 68.57, 63.89, 53.04, 36.15. HRMS calcd for $C_{27}H_{22}F_3N_3O_5S$ $[M+Na]^+$ 580.1124, found 580.1129.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((2-(trifluoromethyl)benzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6m): Yield: 63.3%. mp 127.8-128.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.50 – 7.40 (m, 3H), 7.24 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.04 (s, 2H), 4.72 (s, 2H), 4.04 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.95, 163.25, 163.14, 161.12, 149.35, 134.61, 134.60, 134.49, 132.41, 132.04, 129.70, 129.44, 128.81, 128.72, 128.46, 128.41, 128.31, 128.10, 127.80, 126.42, 126.36, 125.60, 122.87, 116.42, 115.29, 68.57, 63.90, 53.05, 33.26. HRMS calcd for $C_{27}H_{22}F_3N_3O_5S$ $[M+Na]^+$ 580.1124, found 580.1125.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((3-methoxybenzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6n): Yield: 58.4%. mp 110.1-110.5 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.45 (dt, *J* = 15.1, 7.3 Hz, 2H), 7.34 – 7.21 (m, 2H), 7.02 (dd, *J* = 20.9, 8.2 Hz, 4H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.04 (s, 2H), 4.50 (s, 2H), 4.05 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.72, 163.26, 163.20, 161.05, 159.84, 149.35, 137.11, 134.51, 129.85, 129.70, 129.44, 128.72, 128.45, 128.09, 127.80, 121.40, 116.52, 115.27, 114.57, 113.78, 68.56, 63.90, 55.28, 53.05, 36.91. HRMS calcd for $C_{27}H_{25}N_3O_6S$ $[M+Na]^+$ 542.1356, found 542.1353.

Methyl (*E*)-2-(methoxyimino)-2-(2-((4-(5-((2-methoxybenzyl)thio)-1,3,4-oxadiazol-2-yl)phenoxy)methyl)phenyl)acetate (6o): Yield: 72.6%. mp 104.7-105.9 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.31 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.95 – 6.87 (m, 2H), 5.04 (s, 2H), 4.54 (s, 2H), 4.04 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.61, 164.03, 163.26, 160.97, 157.50, 149.36, 134.54, 130.84, 129.70, 129.61, 129.44, 128.71, 128.39, 128.08, 127.81, 124.32, 120.57,

116.68, 115.24, 110.60, 68.55, 63.90, 55.51, 53.05, 32.06. HRMS calcd for $C_{27}H_{25}N_3O_6S$ $[M+Na]^+$ 542.1356, found 542.1349.

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