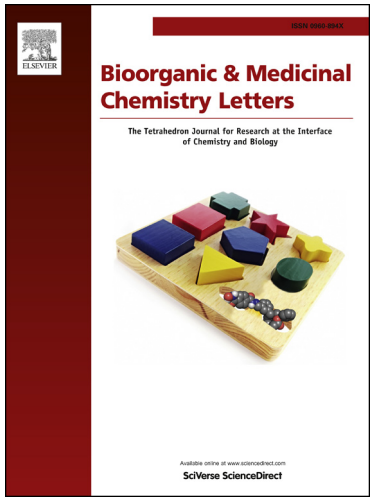

Synthesis and bioactivities of novel thioether/sulfone derivatives containing 1,2,3-thiadiazole and 1,3,4-oxadiazole/thiadiazole moiety

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Synthesis and bioactivities of novel thioether/sulfone derivatives containing 1,2,3-thiadiazole and 1,3,4-oxadiazole/thiadiazole moiety

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Abstract: A series of new thioether/sulfone compounds containing 1,2,3-thiadiazole and 1,3,4-oxadiazole/1,3,4-thiadiazole moiety were synthesized, the structures of all products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and element analysis. Preliminary antifungal activity test showed that compound **8a** exhibited moderate antifungal activity against *F. oxysporum* at 50 μg/mL. Preliminary antiviral activity results showed that compounds **7a**, **7c**, **7d**, **8a**, and **9a** displayed high antiviral activity against tobacco mosaic virus. The present work demonstrates that thioether/sulfone heterocyclic derivatives could be considered as new lead compounds for antiviral studies.

Keywords: synthesis; thioether/sulfone; heterocycle; antiviral activity;

Tobacco mosaic virus (TMV) is known to infect members of 9 plant families, and at least 125 individual species, including tobacco, tomato, pepper, cucumbers, and a

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Abbreviations used: IR, infra-red spectroscopy; ^{1}H NMR, ^{1}H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; *G. zeae*, *Gibberella zeae; F. oxysporum*, *Fusarium oxysporum; C. mandshurica*, *Cytospora mandshurica*.

number of ornamental flowers. Plants infected by TMV are more susceptible to damage by pests and pathogens, it is found that in certain fields 90-100% of the plants show mosaic or leaf necrosis by harvesting time.[1-3] There are fewer reagents that registered and commercialized to control TMV in China, moreover, there are no commercial antiviral reagent that can completely inhibit TMV once it does infect the plants, actually, the cure rate only 30%-60% by common antiviral agents (e.g., ningnanmycin, virus A, and ribavirin).[4] Because of the unsatisfactory cure rate and economic loss of tobacco, much effort has been directed toward the development of novel, potent, and structurally concise antiviral agents.

Most of the thioether/sulfone derivatives are known to be associated with a broad spectrum of bioactivity, such as insecticidal, antifungal, and herbicidal in agrichemical. [5-7] In our previous work we had demonstrated antifungal and antibacterial activities of a series of 2-substituted thioether/sulfone-5-substituted-1,3,4-thiadiazole/oxadiazole derivatives, moreover, the structure and activity relationship study confirmed that thioether/sulfone incorporated 1,3,4-oxadiazole/thiadiazole scaffold is an important pharmacophore.[8-10] The compounds bearing a 1,2,3-thiadiazole group possess versatile biological activities, including fungicide activity, insecticide activity, and herbicide activity.[11-13] As an illustration of practical application, three of them had already been commercialized in agrichemical: acibenzolar-S-methyl and tiadinil are commercialized as antiviral, thidiazuron is used as a cotton defoliate agrochemical.[14-15] Modifications substituent group on 1,2,3-thiadiazole have been performed, for example, in 2010, Fan et al. found that 4-methyl-1,2,3-thiadiazole containing 1,2,4-ttriazolo[3,4-b][1,3,4] thiadiazoles derivatives have good antiviral activity,[16] and 4-methyl-1,2,3-thiadiazole-5-carboxylates derivatives has been reported by Wang et al., which possesses good antiviral activity,[17] in 2011, Fan et al. reported that N-tert-butyl-N,N-diacylhydrazines containing 1,2,3-thiadiazoles derivatives have good antiviral activities too.[18]

Nevertheless, literature reveals that there are no reports of a molecular scaffold containing these important cores, fragment-based lead discovery has emerged as a

more rational and focused approach for molecular modification and drug design. With this view considering the biological significance of thioether/sulfone, oxadiazole, and thiadiazole and as part of our program aimed at the discovery and development of bioactive molecules, here we report the synthesis and biological activity of thioether/sulfone with 1,2,3-thiadiazoles groups (as figure **1**). The structure-activity relationship (SAR) of these compounds was also discussed.

(Figure 1)

The synthetic route designed for the sulfone analogues **9** and **10** were summarized in Scheme **1**. 4-methyl-1,2,3-thiadiazole-5-carbohydrazide **4** was synthesized from diethyl carbonate in four steps: hydrazidation, condensation, cyclization, and hydrazidation by standard synthetic methods from commercially available starting materials,[19] 5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole-2-thiol **5** and 5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole-2-thiol **6** was easily prepared by cyclization. Then, 5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole-2-thiol **5** and the analogue **6** were converted to thioether derivatives **7** and **8** by a thioetherification reaction with dimethyl(diethyl) sulfate or halide (RX).[20] Treatment of thioether **7** and **8** by $KMnO_4$ afforded the heterocyclic sulfones **9** and **10**, with good yields.

(Scheme 1)

2-(4-methyl-1,2,3-thiadiazol-5-yl)-5-(methylthio)-1,3,4-oxadiazole(7a)

White solid; mp 52-54˚C; yield 65.6%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.12 (s, 3H, CH_3), 3.45 (s, 3H, SCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.99, 157.75, 153.42, 131.58, 29.57, 14.32; Anal. Calcd for $C_6H_6N_4OS_2$: C 33.63, H 2.82, N 26.15; found: C 33.51, H 2.51, N 25.75.

2-(4-methyl-1,2,3-thiadiazol-5-yl)-5-(methylsulfonyl)-1,3,4-oxadiazole (9a)

White solid; mp 132-134˚C; yield 70.5%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.12 (s, 3H,

CH_3), 3.56 (s, 3H, SO_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.99, 157.75, 153.42, 131.58, 29.57, 14.32; IR (KBr, cm^{-1}) *v:* 2909, 1546, 1423, 676; Anal. Calcd for $C_6H_6N_4O_3S_2$: C 29.26, H 2.46, N 22.75; found: C 29.16, H 2.73, N 22.44.

Inhibition effect of heterocyclic thioether/sulfone compounds on phytopathogenic fungi was studied. Three fungi, representing typical fungi often occurring in the Chinese agro-ecosystem, *G. zeae, F. oxysporum* and *C. mandshurica*, were chosen for fungicide screening by the poison plate technique.[9] The results were compared with that of commercial agricultural fungicide Hymexazol (broad spectra fungicide), and summarized in **Table 1**.

(Table1)

As indicated in **Table 1**, at the concentration of 50 μg/mL, some compounds showed moderate antifungal activity against *F. oxysporum*, compound **8a** had an inhibition activity of 49.7% against *F. oxysporum*, compound **10a** inhibited growth of *F. oxysporum* at 45.0%, which is almost equal to commercial agricultural fungicide Hymexazol(53%). However, the results indicated that all tested compounds had inhibition activities below 21.7% against *G. zeae*; the inhibition of all the tested compounds against *C. mandshurica* was less than 32.0%, which indicated that the title compounds have low activity against to *G. zeae* and *C. mandshurica*.

To make a judgment of the antiviral potency of the heterocyclic thioether/sulfone bioactivities, the antiviral bioassay against TMV was assayed according to half-leaf juice-robbing method, the commercially available plant virucide Ningnanmycin, perhaps the most successful registered antiviral agent for plant, was used as the reference,[21] the antiviral results are listed in **Table2**.

(Table 2)

The results of activity against TMV *in vivo* indicated that (**Table 2**) most

compounds showed a certain degree of inhibition activities against TMV. At the concentration of 500 μg/mL, compounds **7a**, **7c**, **7d**, **8a**, and **9a** had curative effect against TMV at 54.1%, 48.4%, 47.1%, 48.3% and 46.8% respectively, which are almost equal to that of Ningnanmycin; compounds **8d** and **8f** had an curative rate of 37.6% and 37.3%, respectively; the other compounds showed low curative effect against TMW. 1,2,3-thiadiazole incorporating 1,3,4-oxadiazole derivatives such as compounds **7a**, **7c**, **7d**, and **9a** showed potent antiviral activities against TMV. However, slight lowering of activity was noticed with homologues of 1,2,3-thiadiazole incorporating 1,3,4-thiadiazole moiety (**Table 2**). Moreover, oxidation of heterocyclic sulfides to their corresponding sulfones reduced the values of antiviral activities slightly, such as compounds **7a**, **7c**, **7d**, and **8a** had higher activities than those corresponding sulfones compounds **9a**, **9c**, **9d**, and **10a**. Furthermore, it is worthwhile to note that the oxadiazole sulfones linked to less sterically demanding R group has the best effect, amongst the title compounds, **7a** (R = methyl), **7d** (R = ethyl) and **8a** (R = ethyl) showed potent antiviral activities against TMV being significantly higher than the rest (R = 2-fluorobenzyl, benzyl, 4-nitrobenzyl, etc.).

Additionally, some compounds were chosen for further evaluation of protection and inactivation against TMV *in vivo*. The results in **Table 2** indicate that some of the tested compounds had good inactivation activity. Among these, compounds **7a** and **7d** had inactivation rate of 90.3% and 85.5%, respectively, at 500 μg/mL, which were almost equal to that of Ningnanmycin, and the other compounds showed lower inactivation activity compere with Ningnanmycin. As for the protection activity, most of them had lower activities than the positive control, only compound **7a** stood out, had protection activity of 52.8% at 500 μg/mL, which was equal to that of the positive control, and the other compounds showed lower protection activity compare with Ningnanmycin. These results indicated that some compounds had good potential of anti-TMV bioactivity. There was observed no phytotoxicity to tobacco during the test courses of experiment.

Our studies only synthesized limited derivatives, to conclude the structure and activity relationship, it deserves further synthetic studies and mode of action determination at the molecular level. In addition, another new derivative of 1,2,3-thiadiazole had been synthesized in our group with good activity of antiviral. The results of this study indicated that our idea of combination of thioether/sulfone with 1,2,3-thiadiazole and other heterocycle is an interesting exploration.

In conclusion, we have generated a number of thioether/sulfone compounds containing 1,2,3-thiadiazole and 1,3,4-oxadiazole/1,3,4-thiadiazole moiety, Preliminary antifungal results indicated that the title compounds exhibited low to moderate antifungal activities against *F. oxysporum at* 50 μg/mL, however, the antiviral activity results showed that some of these synthesized compounds showed high antiviral activity against tobacco mosaic virus *in vivo*. Further studies in order to improve the activity profiles of the scaffolds are underway in the lab and will soon be communicated.

Acknowledgments

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Supplementary Material

The synthesis, characterization and bioactivity test methods of title compounds are available in supporting information.

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Table Legend

Table1 The antifungal activities of some title compounds at50 μg/mL

Table 2 The curative activities of some title compounds against TMV at 500 μg/mL

Figure Legend

Figure 1 Design strategy of the target compounds

Scheme Legend

Scheme 1 The synthetic route to title compounds

Table 1

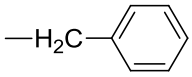
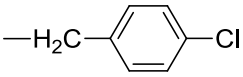
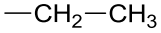
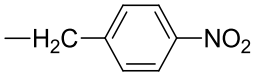
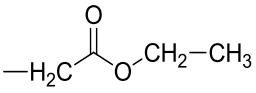
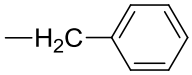
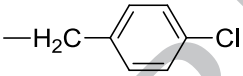
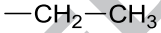
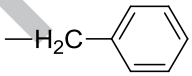
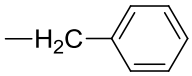
compounds	X	R	Inhibition rate (%)		
			G. zeae	*F. oxysporum*	*C. mandshurica*
7a	O		11.7±3.0	26.7±5.4	22.0±1.4
7b	O		20.7±1.0	26.7±2.4	32.0±1.4
7c	O		3.2±0.9	10.2±1.2	3.5±0.8
7d	O		-3.0±0.8	-0.8±2.3	-2.2±1.0
7e	O		-2.0±0.9	0.0±2.3	-4.5±1.5
7f	O		8.5±2.5	5.2±2.3	0.3±1.0
9a	O		-1.8±2.1	14.0±1.3	2.6±1.6
9b	O		8.5±4.6	21.0±2.4	17.1±1.2
9c	O		2.0±1.3	13.1±2.3	5.1±1.2
9d	O		4.8±0.7	8.7±2.3	9.0±1.2
8a	S		21.7±3.0	49.7±5.4	22.0±1.4
8b	S		8.5±4.6	21.0±2.4	17.1±1.2
10a	S		5.0±0.9	45.0±3.3	-4.5±1.5
10b	S		3.0±0.8	33.1±2.9	11.4±2.2
Hymexazol			60.0±1.2	53.0±2.9	66.9±2.4

Table 2

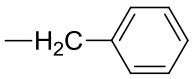
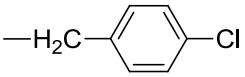
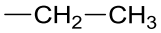
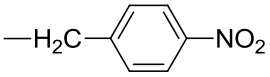
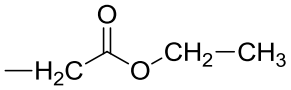
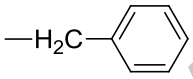
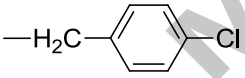
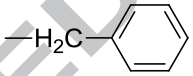
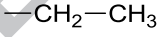
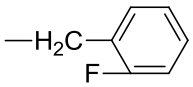
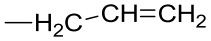
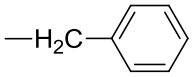
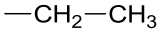
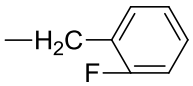
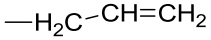
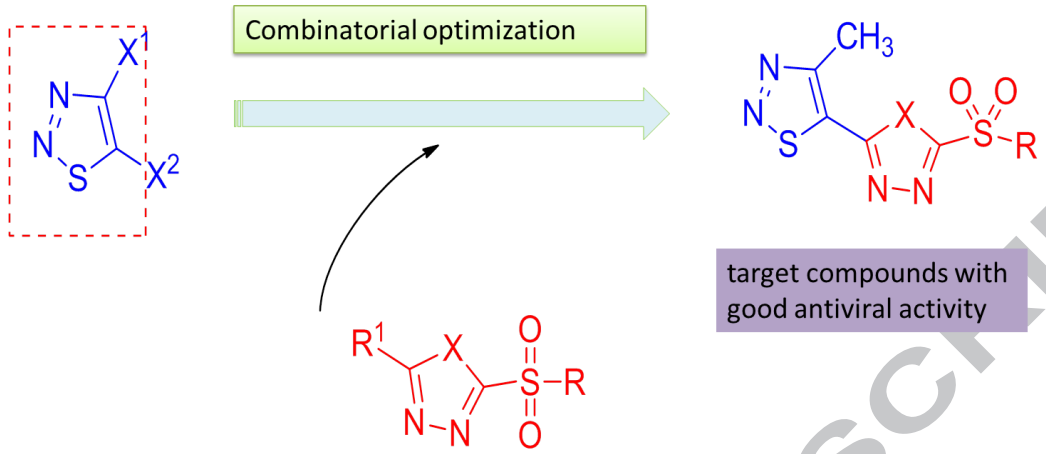
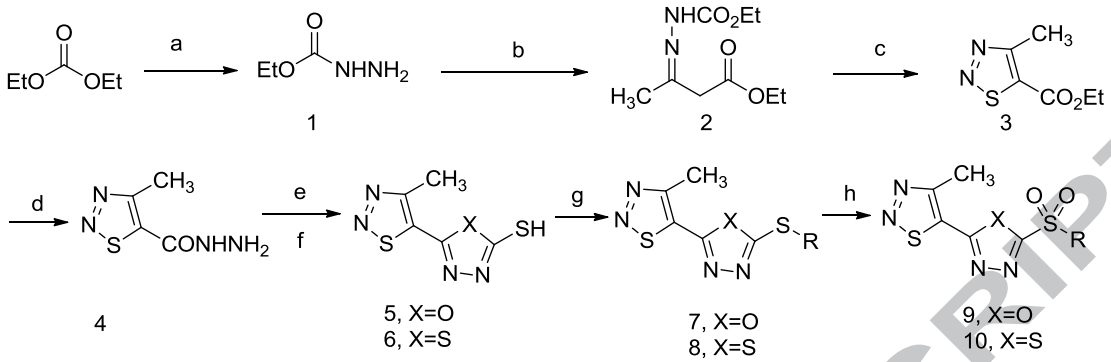
Compounds	X	R	Curative rate (%)	Inactivation rate (%)	Protection rate (%)
7a	O		54.1	90.3	52.8
7b	O		37.2	15.8	35.7
7c	O		48.4	56.4	37.5
7d	O		47.1	85.5	46.4
7e	O		35.9	-	-
7f	O		36.2	66.2	41.2
9a	O		46.8	76.8	44.8
9b	O		31.4	61.4	21.4
9c	O		33.1	43.1	13.1
8a	S		48.3	82.9	44.0
8b	S		32.6	-	-
8d	S		37.6	52.3	32.3
8e	S		21.2	41.3	25.5
8f	S		37.3	-	-
10a	S		38.4	62.5	34.7
10b	S		18.7	-	-
10d	S		21.2	51.5	31.9
10e	S		33.4	25.8	11.6
10f	S		31.3	-	-
Ningnanmycin			56.1	92.5	59.3

Figure 1



Scheme 1



Reagents and conditions: synthetic route to title compounds. (a) $NH_2NH_2 \cdot H_2O$, CH_3CH_2OH; (b) $CH_3COCH_2COOC_2H_5$, CH_2Cl_2; (c) $SOCl_2$; (d) CH_3OH, $NH_2NH_2 \cdot H_2O$; (e) for oxadiazoles KOH, CS_2, C_2H_5OH, reflux; and then 5% HCl; (f) for thiadiazole, KOH, CS_2, C_2H_5OH, room temperature; and then ice-bath for 0-5 ˚C; (g) NaOH, H_2O, RX; (h) $KMnO_4$, CH_3COOH;