Synthesis and Herbicidal Activities of Sulfonylureas Bearing 1,3,4-Thiadiazole Moiety

Xiang-Hai Song,[a] Ning Ma,[a]* Jian-Guo Wang,[b] Yong-Hong Li,[b] Su-Hua Wang,[b] and Zheng-Ming Li[b]*

[a]Department of Chemistry, School of Science, Tianjin University, Tianjin 300072
[b]State Key Laboratory of Elemento Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071
*E-mail: mntju@tju.edu.cn or nkzml@vip.163.com

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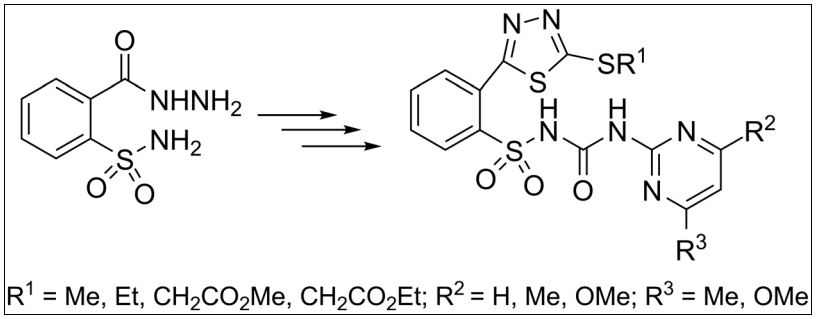

In this article, we report the synthesis and herbicidal activities of sulfonylureas bearing the 1,3,4-thiadiazole moiety. The target compounds **9a–l** were synthesized using 2-hydrazinocarbonyl benzenesulfonamide (**4**) and phenyl pyrimidinecarbamates as starting materials. The key intermediate, 2-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)benzenesulfonamide (**5**), was prepared from **4** and CS_2 *via* a conventional method or an improved method. The improved method, in which sulfonamido group acts as a directing group for the cyclization reaction, is more concise and efficient. The structures of the target compounds were determined by IR, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. Their herbicidal activities were screened by Petri dish tests and pot tests. As the results, sulfonylureas **9h** and **9j** inhibited *Brassica napus*, *Amaranthus retroflexus,* and *Echinochloa crusgalli* at the 15 g/ha level, which is at the same level as azimsulfuron. Moreover, the safety tests showed that **9j** was safe to wheat at dosage of 60 g/ha and might develop further into a herbicide in wheat field.

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INTRODUCTION

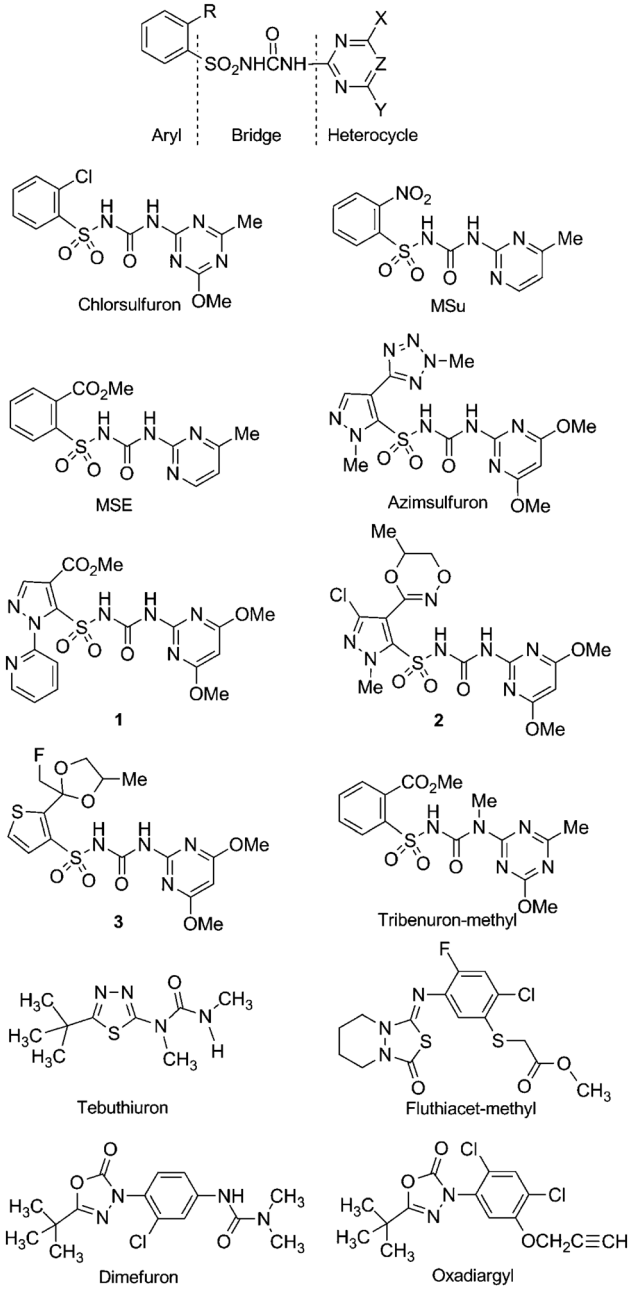
Sulfonylureas (SUs) are a popular herbicide because of their low dosage, low mammalian toxicity, high selectivity, and benign environmental activity. Approximately, 30 different SU herbicides have been marketed since the commercialization of chlorsulfuron in 1981 [1]. According to structure–activity relationship proposed by Levitt, the herbicidal SUs are composed of three distinct parts (Scheme 1), and the heterocycle should contain a 4,6-disubstituted pyrimidine or similarly substituted 1,3,5-triazine [2]. To our delight, we found monosubstituted pyrimidine SUs also presented the same level of herbicidal activity as the 4,6-disubstituted pyrimidine SUs. Two of the monosubstituted SUs, monosulfuron (MSu) and monosulforon-ester (MSE), were developed as commercial herbicides by Li and coworkers [3]. To investigate the monosubstituted patterns, a variety of monosubstituted pyrimidine SUs were synthesized and screened for herbicidal activities [4]. Based on the results of the biological screen, structure–activity relationships were proposed [5]. The crystal structures of MSu and MSE in complex with acetohydroxyacid synthase (AHAS) were reported, which helps to understand the mode of interaction for this class of AHAS inhibitors [6].

Currently, azimsulfuron is the only commercialized SU herbicide that bears a heterocycle on the aryl group at the ortho position to the bridge (Scheme 1). Recently, herbicidal SUs **1**–**3** have been reported to share structural similarity to azimsulfuron [1c]. 1,3,4-Thiadiazole compounds have already been used as herbicides. For examples, tebuthiuron is a broad-spectrum herbicide for control of various classes of weeds, and fluthiacet-methyl is served as a postemergence herbicide for control of broad-leaved weeds (Scheme 1) [7a]. Other herbicidal 1,3,4-thiadiazole compounds were also reported recently [7b]. Besides, some 1,3,4-oxadiazole compounds have found their uses as herbicides in which dimefuron and oxadiargyl are typical examples [7a]. In this article, we aim to introduce a 1,3,4-thiadiazole or 1,3,4-oxazodiazole ring to the ortho position on the aryl ring of SUs and investigate if the herbicidal activities of this new type of compounds will be changed.

RESULTS AND DISCUSSION

Initially, condition (method A, Scheme 2) developed by Baron and Wilson was used to prepare 2-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)benzenesulfonamide (**5**) from

Scheme 1



4 and CS_2 [8]. However, in an attempt to prepare 2-(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**7**) as described in the literature [8], we discovered an alternate method (method B, Scheme 2). Comparing with our initial condition (method A), method B provided a higher yield of the final product which was pure enough for next step. Purification of **5** was somewhat difficult, although it was not required for purification in most cases. It was surprising that the product of method B was **5** instead of **7.** According to the literature [8], treating substituted benzoyl hydrazines with CS_2 and KOH in 95% ethanol under reflux condition affords 5-aryl-1,3,4-oxadiazole-2-thiones in 20–64% yield, whereas treating potassium benzoyldithiocarbazates (obtained from reaction of benzoyl hydrazines with CS_2 and KOH in 95% ethanol at 0–5°C) with sulfuric acid at 0–5°C furnishes 5-aryl-1,3,4-thiadiazole-2-thiones in 17–35% yield. Therefore, the sulfonamido group acts as a directing group to induce the unexpected product **5**. This directing effect can be attributed to the intramolecular H-bond between the carbonyl O atom and the sulfonamide N-H in orthosulfonamido benzeneamide, which were disclosed by both Woodward group and our group [9]. It seems that the H-bond activates the carbonyl group toward nucleophilic attack by the dithiocarboxy anion and facilitates the formation of 1,3,4-thiadiazole (Scheme 3).

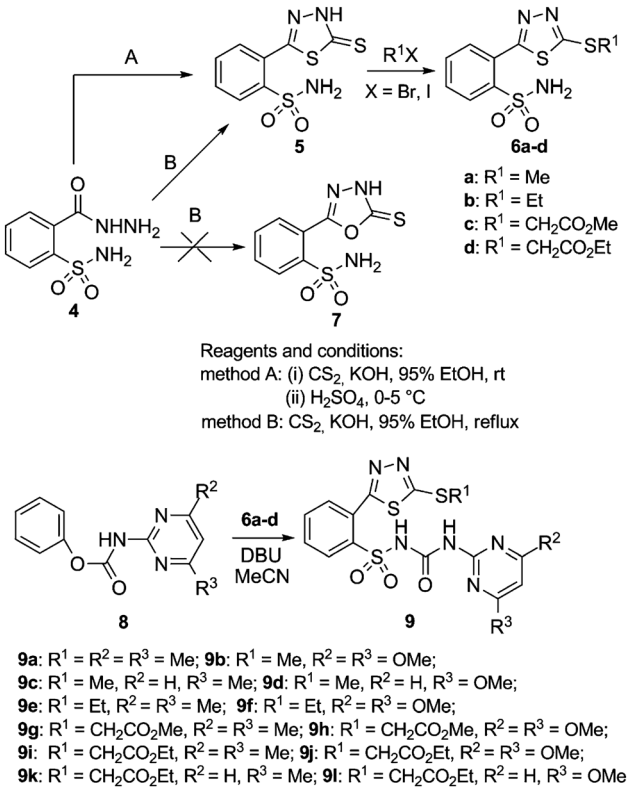
SUs **9a**, **9b**, **9e**, **9f**, **9h,** and **9j** showed good activity in the Petri dish herbicidal tests (Table 1). Tribenuron-methyl, not azimsulfuron, was used as reference standard because the former is a total herbicide with fairly high activity (commonly used at dosage of 4–7.5 g/ha), whereas the latter is a selective compound for control of specified weeds and grasses. The monosubstituted pyrimidine SUs **9c**, **9d**, **9k,** and **9l** showed lower activity than the disubstituted SUs **9a**, **9b**, **9i,** and **9j**, respectively. Because of their high herbicidal activity in the Petri dish screens, SUs **9b**, **9f**, **9h,** and **9j** were screened further by pot tests (Table 2). SUs **9h** and **9j** showed satisfactory inhibition to *Brassica napus*, *amaranthus retroflexus,* and *Echinochloa crusgalli* at the dosage of 15 g/ha. This activity fell into the same level as that of azimsulfuron, which is normally used at dosage of 20–25 g/ha. Notably, both **9h** and **9j** showed better inhibition to *E. crusgalli* than tribenuron-methyl. Further safety test uncovered that **9j** is safe to wheat even at dosage of 60 g/ha (Table 3).

In conclusion, a 1,3,4-thiadiazole ring was introduced to the ortho position on the aryl ring of SUs, and a series of new SUs possessing 1,3,4-thiadiazole ring were synthesized using 2-hydrazinocarbonyl benzenesulfonamide and phenyl pyrimidinecarbamates as starting materials. An improved method, in which an ortho sulfonamide group acts as a directing group, was proposed to prepare the key intermediate, 2-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl) benzenesulfonamide. The herbicidal tests show that the introduction of a 1,3,4-thiadizole group at the ortho position of the bridge does not affect the activity of SU herbicide remarkably. This modification may provide a new SU herbicide with good inhibition to various weeds and grasses in wheat field.

EXPERIMENTAL

Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR (400 MHz and 100 MHz, respectively) spectra were recorded on a Bruker

Scheme 2



AVANCE III 400 spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm using TMS as internal standard. MS (ESI) data were obtained on the Thermo Fisher LCQ Advantage MAX apparatus. HRMS data were obtained on microOTOF-Q II instrument. All reagents are commercially available without further purification unless otherwise noted. 2-Hydrazinocarbonyl benzenesulfonamide (**4**) was prepared as we described by Ma and coworkers [9b]. Phenyl pyrimidinecarbamates (**8**) were prepared as described in the literatures [10].

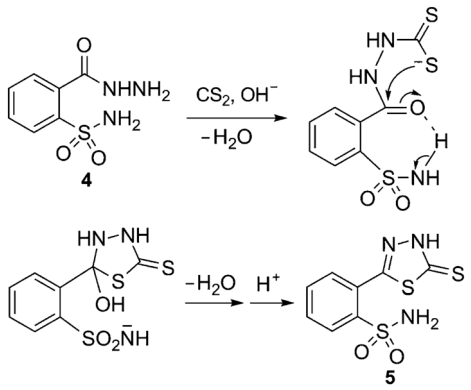
2-(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)benzenesulfonamide (5). Method A: 12.5 g (0.06 mol) **4** was added to a solution of 4.79 g KOH (82%) in 150 mL 95% ethanol; the mixture was cooled (0–5°C) with an ice bath and 7.2 mL carbon disulfide was added dropwise. After carbon disulfide was added, the bath was withdrawn, and the mixture was stirred for 2 h. Then, the precipitate was filtered, washed with 95% ethanol, and potassium 3-(2-sulfamoylbenzoyl) dithiocarbazate was precipitated as a white (sometimes slightly yellow) solid. The solid was added to 90 mL H_2SO_4 in batches at 0–5°C. After stirred for 30 min at 0–5°C, the solution was poured into 400 g crushed ice. The precipitate was filtered, washed with cold water, and dried under ambient conditions. A total of 6.2 g yellow solid was obtained (38% yield, mp 194–197°C, dec.). This crude product **5** was used directly into the next step without further purification.

Method B: 12.5 g (0.06 mol) **4** was added to a solution of 6.18 g KOH (82%) in 300 mL 95% ethanol, then 7.2 mL carbon disulfide was dropped in. The mixture was heated slowly to boiling and refluxed for 5 h. The solvent was distilled *in vacuo* until the volume of the residue solution was about 40 mL, and two hundred milliliters of water was added. After the mixture was stirred for 5 min, the undissolved solid was filtered off, and the filtrate was acidified to pH = 2–3 with 20% HCl. The precipitate was filtered, washed with water and dried. A total of 10.2 g of yellow solid was obtained (63% yield, mp 197–198°C, dec.). ^{1}H-NMR (DMSO-d_6, ppm): 7.65 (s, 2H, SO_2NH_2), 7.70–7.82 (m, 3H, Ar-H), 8.05–8.07 (d, 1H, Ar-H), 14.81 (N-H). HRMS (ESI): Found: *m/z* 295.9594 ([M+Na]$^+$); Calcd for $C_8H_7N_3NaO_2S_3$: 295.9598. This crude product **5** was directly carried on without further purification.

2-(5-Methylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamide (6a). A total of 2.56 g (ca. 0.01 mol) crude **5**, 0.82 g KOH (82%) was added to 100 mL methanol, then 1.42 g (0.01 mol) methyl iodide. The mixture was stirred for 4 h at room temperature. The precipitate was filtered, washed with a 50% aqueous ethanol solution, and dried under ambient conditions. A total of 2.30 g of slightly yellow crystals was obtained (83% yield, mp 159–161°C, dec.). IR (KBr, cm^{-1}): 3286, 3180 (N-H), 1342, 1170 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 2.86 (s, 3H, SCH_3), 6.13 (s, 2H, SO_2NH_2), 7.59–7.68 (m, 3H, Ar-H), 8.26–8.28 (m, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$, ppm): 16.35, 126.58, 127.85, 131.14, 132.25, 132.84, 142.32, 164.83, 168.88; MS (ESI), *m/z*: 311 ([M+Na]$^+$, 100%), 288 ([M+H]$^+$, 55%).

2-(5-Ethylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamide (6b). Similarly, **6b** was prepared with **5** and ethyl iodide in ethanol as slightly yellow crystals with a yield of 79%, mp 117–118°C; IR (KBr, cm^{-1}): 3295, 3181 (N-H), 1345, 1164 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.53 (t, 3H, J = 7.5Hz, $SCH_2C\mathbf{H}_3$), 3.42 (q, 2H, J = 7.5Hz, $SC\mathbf{H}_2CH_3$), 6.12 (br, s, 2H, SO_2NH_2), 7.58–7.68 (m, 3H, Ar-H), 8.26–8.28 (m, 1H,

Scheme 3



Ar-H); ^{13}C-NMR ($CDCl_3$, ppm): 14.53, 28.76, 127.09, 129.24, 131.11, 132.62, 132.80, 141.59, 166.40, 168.26; MS (ESI), *m/z*: 325 ([M+Na]$^+$, 100%), 303 ([M+H]$^+$, 73%).

Methyl (5-(2-sulfamoylphenyl)-1,3,4-thiadiazol-2-ylthio)acetate (6c). A total of 2.56 g (ca. 0.01 mol) crude **5** and 0.82 g KOH (82%) was added to 100 mL methanol, then 1.53 g (0.01 mol) methyl bromoacetate. The mixture was stirred for 6 h at room temperature. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. A viscous liquid was obtained. After 30 mL water was added, a solid precipitated and was filtered, recrystallized with an aqueous ethanol solution to provide slightly yellow crystals. The yield was 75%, mp 77–79°C; IR (KBr, cm^{-1}): 3318, 3234 (N-H), 1732 (C═O), 1338, 1168 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 3.83 (s, 3H, CH_3), 4.23 (s, 2H, SCH_2), 7.58–7.72 (m, 3H, Ar-H), 8.26–8.29(m, 1H Ar-H) ; ^{13}C-NMR ($CDCl_3$, ppm): 35.17, 53.14, 126.72, 129.16, 131.19, 132.55, 132.70, 141.52, 165.89, 167.11, 168.16; MS, ESI), *m/z*: 347 ([M+H]$^+$, 100%), 369 ([M+Na]$^+$, 86%).

Ethyl (5-(2-sulfonamidophenyl)-1,3,4-thiadiazol-2-ylthio) acetate (6d). 6d was prepared similarly with **5** and ethyl bromoacetate in ethanol as slightly yellow crystals. The yield was 70%, mp 87–89°C; IR (KBr, cm^{-1}): 3305, 3214 (N-H), 1741 (C═O), 1343, 1168 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.33 (t, 3H, J = 7.2Hz, $CO_2CH_2C\mathbf{H}_3$), 4.22 (s, 2H, SCH_2), 4.29 (q, 2H, J = 7.2Hz, $CO_2C\mathbf{H}_2CH_3$), 6.12 (br, s, 2H, SO_2NH_2), 7.58–7.71 (m, 3H, Ar-H), 8.26–8.29 (m, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$, ppm): 14.09, 35.45, 62.40, 126.71, 129.15, 131.18, 132.58, 132.72, 141.47, 166.00, 167.06, 167.68; MS (ESI), *m/z*: 382 ([M+Na]$^+$, 100%), 361 ([M+H]$^+$, 79%).

1-(2-(5-Methylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamido)-3-(4,6-dimethylpyrimidin-2-yl)urea (9a). A total of 0.15 g DBU (1,8-diazabicyclo[5.4.0]undec-11-ene) was dropped into a stirred suspension of 0.27 g (1 mmol) 2-(5-methylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamide (**6a**) and 0.24 g (1 mmol) phenyl (4,6-dimethylprimidin-2-yl)carbamate in 10 mL acetonitrile. The mixture was stirred at room temperature for 2 h, and then diluted with 15 mL of water. After the solid was filtered off, the filtrate was acidified to pH = 5–6 with 20% hydrochloride acid. The precipitate was filtered and washed with water (10 mL × 2). After dried under ambient conditions and recrystallized with dichloromethane-acetone (1:1 v/v), **9a** was obtained as a white solid, yield 52%, mp 176–177°C (dec.); IR (KBr, cm^{-1}): 1698 (C═O), 1347, 1171 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 2.52 (s, 6H, CH_3), 2.79 (s, 3H, SCH_3), 6.78 (s, 1H, Pyrim-H), 7.50 (s, 1H, CONH-Pyrim), 7.54–7.57 (m, 1H, Ar-H), 7.71–7.74 (m, 2H, Ar-H), 8.51–8.54 (m, 1H, Ar-H), 13.04 (br, s, 1H, SO_2NH); ^{13}C-NMR (DMSO-d_6, ppm): 16.67, 23.67, 115.22, 127.95, 131.47, 131.81, 133.46, 134.25, 138.37, 149.50, 156.73, 163.53, 168.17, 169.23; MS (ESI), *m/z*: 437 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{16}H_{16}N_6O_3S_3$: C, 44.02; H 3.69; N, 19.25. Found: C, 43.86; H, 4.03; N, 19.12.

The following compounds **9b-l** were synthesized similarly.

1-(2-(5-Methylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamido)-3-(4,6-dimethoxypyrimidin-2-yl)urea (9b). White solid, yield 54%, m.p. 177–178°C (dec.); IR (KBr, cm^{-1}): 1707 (C═O), 1358, 1168 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 2.78 (s, 3H, SCH_3), 3.91 (s, 6H, OCH_3), 5.81 (s, 1H, Pyrim-H), 7.26 (s, 1H, CONH-Pyrim), 7.53–7.56 (m, 1H, Ar-H), 7.73–7.77 (m, 2H, Ar-H), 8.51–8.54 (m, 1H, Ar-H), 12.47 (br, s, 1H, SO_2NH); ^{13}C-NMR ($CDCl_3$, ppm): 16.20, 54.86, 85.47, 128.43, 130.81, 132.65, 133.14, 133.57, 138.13, 148.82, 155.40, 163.96, 168.79, 171.61; MS, *m/z* (ESI) 491 ([M+Na]$^+$, 100%), 469 ([M+H]$^+$, 76%). Anal. Calcd. for $C_{16}H_{16}N_6O_5S_3$: C, 41.02; H 3.44; N, 17.94. Found: C, 41.10; H, 3.79; N, 17.70.

1-(2-(5-Methylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamido)-3-(4-methylpyrimidin-2-yl) urea (9c). Yellow solid, yield 50%, m. p. 172–174°C (dec.); IR (KBr, cm^{-1}): 1712 (C═O), 1359, 1169 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 2.63 (s, 3H, CH_3), 2.79 (s, 3H, SCH_3), 6.91 (d, 1H, J = 5.1Hz, Pyrim-H_5), 7.54–7.57 (m, 1H, Ar-H), 7.72–7.75 (m, 2H, Ar-H), 8.50–8.56 (m, 2H, Ar-H, Pyrim-H_6), 8.95 (br, s, 1H, CONH-Pyrim), 12.85 (br, s, 1H, SO_2CONH); ^{13}C-NMR (DMSO-d_6, ppm): 16.14, 23.41, 115.35, 127.42, 130.94, 131.07, 132.92, 133.70, 137.88, 148.92, 156.31, 157.27, 162.95, 168.40, 168.79; MS (ESI), *m/z*: 445 ([M+Na]$^+$, 100%), 423 ([M+H]$^+$, 32%). Anal. Calcd. for $C_{15}H_{14}N_6O_3S_3$: C, 42.64; H 3.34; N, 19.89. Found: C, 42.54; H, 3.42; N, 19.78.

(1-(2-(5-Methylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamido)-3-(4-methoxypyrimidin-2-yl) urea (9d). White solid, yield 61%, m.p. 173–175°C (dec.); IR (KBr, cm^{-1}): 1720 (C═O), 1356, 1164 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 2.78 (s, 3H, SCH_3), 3.97 (s, 3H, OCH_3), 6.47 (d, 1H, J = 6.0Hz, Pyrim-H_5), 7.54–7.57 (m, 1H, Ar-H), 7.72–7.76 (m, 2H, Ar-H), 8.35 (d, 1H, J = 6.0Hz, Pyrim-H_6), 8.50–8.52 (m, 2H, Ar-H), 12.71 (br, s, 1H, SO_2CONH); ^{13}C-NMR ($CDCl_3$, ppm): 16.25, 54.51, 103.22, 128.29, 130.69, 132.41, 132.58, 133.35, 138.22, 148.92, 156.24, 156.71, 163.78, 168.72, 170.30; MS (ESI), *m/z*: 461 ([M+Na]$^+$, 100%), 439([M+H]$^+$, 51%). Anal. Calcd. for

Table 1

Rape-root growth method tests of the compounds **9a–l**.

Dosage (μg/mL)	**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	**9i**	**9j**	**9k**	**9l**	Tribenuron-methyl
1	37.4	45.2	20.5	0	27.8	0	8.1	38.6	0	42.4	0	0	61.0
10	54.3	57.8	40.5	21.7	50.7	58.8	19.0	42.8	30.5	45.2	0	0	
100	64.2	67.4	42.8	36.7	62.1	72.6	42.4	47.8	36.2	48.1	5.2	0	

Table 2

Pot herbicidal tests of the compounds **9b**, **9f**, **9h**, and **9j**.

	Dosage (g/ha)	*Brassica napus*		*Amaranthus retroflexus*		*Digitaria adscendens*		*Echinochloa crusgalli*			
		S	F	S	F	S	F	S		F	
9b	3.75	16.0	27.5	1.6	30.2	0	0	0	3.5[a]	22.6	32.0[a]
	7.5	24.5	63.2	1.6	32.5	4.0	0	0	6.1[a]	32.2	32.8[a]
	15	29.8	68.8	51.8	39.2	7.4	0	11.4	17.7[a]	38.7	31.7[a]
	30	68.1	71.7	23.3	39.9	9.6	21.1	61.8	58.8[a]	67.4	32.3[a]
9f	3.75	0	60.3	0	26.4	0	8.9	4.7	5.8[a]	3.6	30.7[a]
	7.5	23.4	76.2	9.9	42.9	0	15.5	5.5	6.2[a]	25.2	27.6[a]
	15	24.5	93.8	19.9	47.4	0	21.6	8.3	16.9[a]	56.2	38.1[a]
	30	74.5	94.9	34.9	100.0	4.0		39.4	50.3[a]	72.2	36.3[a]
9h	3.75	42.6	55.2	33.3	39.5	8.5	14.0	35.0	41.6[a]	26.8	23.9[a]
	7.5	46.8	77.3	66.6	50.9	20.6	15.0	75.6	61.3[a]	53.8	32.3[a]
	15	57.4	87.5	93.3	82.8	39.3	40.5	80.4	63.7[a]	68.5	32.1[a]
	30	90.4	96.0	98.3	87.7	66.9	61.3	84.6	66.4[a]	71.5	28.0[a]
9j	3.75	55.3	68.3	11.0	34.6	0	0	16.9	29.7[a]	23.9	26.7[a]
	7.5	64.9	64.9	60.0	38.7	0	16.0	54.3	56.3[a]	37.8	30.4[a]
	15	89.4	79.0	100.0	39.2	41.5	51.1	77.6	63.4[a]	66.1	29.3[a]
	30	91.5	100.0	100.0	86.5	40.4	65.4	83.8	65.7[a]	72.8	29.1[a]
A	3.75	88.4		69.4		24.0		35.1			
	7.5	90.2		80.6		35.6		39.6			
	15	92.2		83.3		40.4		46.2			
	30	95.2		88.9		48.1		48.1			

A, tribenuron-methyl; S, soil treatment; F, foliage spray.
[a]Inhibition percentage calculated by the height of grass upon the soil surface; all the other data were calculated by the fresh weight of grass upon the soil surface.

$C_{15}H_{14}N_6O_4S_3$: C, 41.09; H 3.22; N, 19.17. Found: C, 40.90; H, 3.57; N, 19.01.

1-(2-(5-Ethylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamido)-3-(4,6-dimethylpyrimidin-2-yl) urea (9e). White solid, yield 57%, m.p. 152–154°C; IR (KBr, cm^{-1}): 1699 (C═O), 1358, 1168 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.49 (t, 3H, *J* = 7.5Hz, $SCH_2C\mathbf{H}_3$), 2.53 (s, 6H, CH_3), 3.33 (q, 2H, *J* = 7.5Hz, $SC\mathbf{H}_2CH_3$), 6.78 (s, 1H, Pyrim-H), 7.55–7.76 (m, 4H, Ar-H, CONH-Pyrim), 8.50–8.54 (m, 1H, Ar-H), 13.03 (br, s, 1H, SO_2CONH); ^{13}C-NMR (DMSO-d_6, ppm): 14.30, 23.13, 28.14, 114.71, 127.39, 130.95, 131.26, 132.94, 133.72, 137.90, 148.94, 156.20, 163.20, 167.32, 167.62; MS (ESI), *m/z*: 451 ($[M+H]^+$, 100%), 473($[M+Na]^+$, 62%). Anal. Calcd. for $C_{17}H_{18}N_6O_3S_3$: C, 45.32; H 4.03; N, 18.65. Found: C, 45.05; H, 4.16; N, 18.55.

1-(2-(5-Ethylthio-1,3,4-thiadiazol-2-yl)benzenesulfonamido)-3-(4,6-dimethoxypyrimidin-2-yl)urea (9f). White solid, yield 51%, m.p. 160–162°C; IR (KBr, cm^{-1}): 1706 (C═O), 1359, 1167 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.49 (t, 3H, *J* = 7.5Hz, $SCH_2C\mathbf{H}_3$), 3.34 (q, 2H, *J* = 7.5Hz, $SC\mathbf{H}_2CH_3$), 3.91 (s, 6H, OCH_3), 5.80 (s, 1H, Pyrim-H), 7.23 (s, 1H, CONH-Pyrim), 7.54–7.56 (m, 1H, Ar-H), 7.72–7.77 (m, 2H, Ar-H), 8.51–8.54 (m, 1H, Ar-H), 12.49 (br, s, 1H, SO_2NH); ^{13}C-NMR ($CDCl_3$, ppm): 14.62, 28.52, 54.86, 85.46, 128.45, 130.77, 132.70, 133.17, 133.57, 138.07, 148.84, 155.39, 163.99, 168.11, 171.61; MS (ESI), *m/z*: 505 ($[M+Na]^+$, 100%), 483 ($[M+H]^+$, 95%). Anal. Calcd. for $C_{17}H_{18}N_6O_5S_3$: C, 42.31; H 3.76; N, 17.42. Found: C, 42.35; H, 3.92; N, 17.54.

1-(2-(5-Methoxycarbonylmethylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamido)-3-(4,6-dimethylpyrimidin-2-yl)urea (9g). Yellow solid, yield 65%, m.p. 172–173°C; IR (KBr, cm^{-1}): 1745, 1695 (C═O), 1353, 1166 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 2.52 (s, 6H, CH_3), 3.79 (s, 3H, CO_2CH_3), 4.15 (s, 2H, SCH_2), 6.78 (s, 1H, Pyrim-H), 7.54–7.57 (m, 1H, Ar-H), 7.65 (s, 1H, CONH-Pyrim), 7.72–7.75 (m, 2H, Ar-H), 8.51–8.54 (m, 1H, Ar-H), 13.07 (br, s, 1H, SO_2NH); ^{13}C-NMR (DMSO-d_6, ppm): 23.13, 34.79, 52.57, 114.69, 127.25, 130.97, 131.34, 132.95, 133.71, 137.83, 149.00, 156.18, 164.02, 165.97, 167.63, 168.14; MS (ESI), *m/z*: 517 ($[M+Na]^+$, 100%), 495 ($[M+H]^+$, 89%). Anal. Calcd. for $C_{18}H_{18}N_6O_5S_3$: C, 43.72; H 3.67; N, 16.99. Found: C, 43.33; H, 4.04; N, 17.12.

1-(2-(5-Methoxycarbonylmethylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamido)-3-(4,6-dimethoxypyrimidin-2-yl)urea (9h). Yellow solid, yield 61%, m.p. 154–155°C; IR (KBr, cm^{-1}): 1742, 1704 (C═O), 1363, 1168 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 3.81 (s, 3H, CO_2CH_3), 3.90 (s, 6H, OCH_3), 4.16 (s, 2H, SCH_2), 5.82 (s, 1H, Pyrim-H), 7.23 (s, 1H, CONH-Pyrim), 7.53–7.56

Table 3

Safety tests of **9h**, **9j** against wheat.

	Dosage (g/hm)	Soil treatment		Foliage spray	
		H	*W*	*H*	*W*
9h	30	12.5	–4.0	6.4	–7.7
	60	20.3	–6.6	6.5	1.6
	120	33.5	13.3	16.5	25.7
9j	30	–0.4	–15.2	5.1	9.3
	60	9.1	1.3	14.9	15.4
	120	27.9	6.9	15.0	20.7

H, inhibition percentage calculated by the height of plant upon the ground; W, inhibition percentage calculated by the fresh weight of plant upon the ground.

(m, 1H, Ar-H), 7.73–7.78 (m, 2H, Ar-H), 8.52–8.55 (m, 1H, Ar-H), 12.52 (br, s, 1H, SO_2NH); ^{13}C-NMR (DMSO-d_6, ppm): 34.68, 52.57, 54.46, 83.77, 127.24, 131.10, 131.65, 133.02, 133.94, 137.46, 148.51, 155.79, 163.96, 166.29, 168.19, 171.03; MS (ESI), *m/z*: 549 ([M+Na]$^+$, 100%), 527 ([M+H]$^+$, 59%). Anal. Calcd. for $C_{18}H_{18}N_6O_7S_3$: C, 41.06; H 3.45; N, 15.96. Found: C, 41.08; H, 3.67; N, 16.05.

1-(2-(5-Ethoxycarbonylmethylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamido)-3-(4,6-dimethylpyrimidin-2-yl)urea (9i). Yellow solid, yield 57%, m.p. 179–180°C (dec.); IR (KBr, cm^{-1}): 1724 (C═O), 1363, 1165 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.30 (t, 3H, *J* = 7.2Hz, $CO_2CH_2C\mathbf{H}_3$), 2.52 (s, 6H, CH_3), 4.13 (s, 2H, SCH_2), 4.25 (q, 2H, *J* = 7.2Hz, $CO_2C\mathbf{H}_2CH_3$), 6.78 (s, 1H, Pyrim-H), 7.54–7.57 (m, 1H, Ar-H), 7.71–7.76 (m, 3H, Ar-H, CONH-Pyrim), 8.50–8.53 (m, 1H, Ar-H), 13.07 (br, s, 1H, SO_2NH); ^{13}C-NMR ($CDCl_3$, ppm): 14.21, 23.86, 35.58, 62.37, 115.33, 128.16, 130.87, 132.63, 132.81, 133.42, 138.32, 149.25, 156.20, 165.02, 165.60, 167.66, 168.55; MS (ESI), *m/z*: 531 ([M+Na]$^+$, 100%), 509 ([M+H]$^+$, 96%). Anal. Calcd. for $C_{19}H_{20}N_6O_5S_3$: C, 44.87; H 3.96; N, 16.52. Found: C, 44.63; H, 4.30; N, 16.68.

1-(2-(5-Ethoxycarbonylmethylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamido)-3-(4,6-dimethoxypyrimidin-2-yl)urea (9j). Yellow solid, yield 54%, m.p. 147–148°C; IR (KBr, cm^{-1}): 1741, 1711 (C═O), 1357, 1166 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.31 (t, 3H, *J* = 7.2Hz, $CO_2CH_2C\mathbf{H}_3$), 3.91 (s, 6H, OCH_3), 4.14 (s, 2H, SCH_2), 4.26 (q, 2H, *J* = 7.2Hz, $CO_2C\mathbf{H}_2CH_3$), 5.82 (s, 1H, Pyrim-H), 7.22 (s, 1H, CONH-Pyrim), 7.53–7.56 (m, 1H, Ar-H), 7.73–7.76 (m, 2H, Ar-H), 8.52–8.55 (m, 1H, Ar-H), 12.50 (br, s, 1H, SO_2NH); ^{13}C-NMR ($CDCl_3$, ppm): 13.88, 34.92, 54.48, 61.48, 83.78, 127.28, 131.11, 131.72, 133.02, 133.98, 137.41, 148.53, 155.80, 163.93, 166.36, 167.65, 171.02; MS (ESI), *m/z*: 541 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{19}H_{20}N_6O_7S_3$: C, 42.22; H 3.73; N, 15.55. Found: C, 41.92; H, 4.05; N, 15.78.

1-(2-(5-Ethoxycarbonylmethylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamido)-3-(4-methylpyrimidin-2-yl)urea (9k). Yellow solid, yield 64%, m.p. 87–89°C (dec.); IR (KBr, cm^{-1}): 1730, 1710 (C═O), 1359, 1167 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.30 (t, 3H, *J* = 7.2Hz, $CO_2CH_2C\mathbf{H}_3$), 2.62 (s, 3H, CH_3), 4.14 (s, 2H, SCH_2), 4.25 (q, 2H, *J* = 7.2Hz, $CO_2C\mathbf{H}_2CH_3$), 6.92 (d, 1H, *J* = 5.1Hz, Pyrim-H_5), 7.55–7.58 (m, 1H, Ar-H), 7.71–7.77 (m, 2H, Ar-H), 8.50–8.53 (m, 1H, Ar-H), 8.57 (s, 1H, *J* = 5.1Hz, Pyrim-H_6), 8.80 (br, s, 1H, CONH-Pyrim), 12.89 (br, s, 1H, SO_2NH); ^{13}C-NMR ($CDCl_3$, ppm): 14.09, 24.11, 35.46, 62.27, 115.51, 128.05, 130.78, 132.47, 132.57, 133.33, 138.27, 149.27, 156.37, 157.79, 164.86, 165.61, 167.56, 169.11; MS (ESI), *m/z*: 517 ([M+Na]$^+$, 100%), 495 ([M+H]$^+$, 53%). Anal. Calcd. for $C_{18}H_{18}N_6O_5S_3$: C, 43.72; H 3.67; N, 16.99. Found: C, 43.41; H, 3.83; N, 17.16.

1-(2-(5-Ethoxycarbonylmethylthio-1,3,4-thiadiazol-2-yl) benzenesulfonamido)-3-(4-methoxypyrimidin-2-yl)urea (9l). Yellow solid, yield 67%, m.p. 99–101°C (dec.); IR (KBr, cm^{-1}): 1716 (C═O), 1358, 1163 (S═O); ^{1}H-NMR ($CDCl_3$, ppm): 1.31 (t, 3H, *J* = 7.2Hz, $CO_2CH_2C\mathbf{H}_3$), 3.97 (s, 3H, OCH_3), 4.14 (s, 2H, SCH_2), 4.26 (q, 2H, *J* = 7.2Hz, $CO_2C\mathbf{H}_2CH_3$), 6.51 (d, 1H, *J* = 6.0Hz, Pyrim-H_5), 7.55–7.58 (m, 1H, Ar-H), 7.72–7.77 (m, 2H, Ar-H), 8.34 (s, 1H, *J* = 6.0Hz, Pyrim-H_6), 8.49–8.52 (m, 1H, Ar-H). ^{13}C-NMR ($CDCl_3$, ppm): 14.34, 35.54, 54.86, 62.56, 103.39, 128.21, 131.07, 132.66, 132.84, 133.65, 138.34, 149.39, 156.50, 164.99, 166.06, 167.88, 170.42; MS (ESI), *m/z*: 511 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{18}H_{18}N_6O_6S_3$: C, 42.35; H 3.55; N, 16.46. Found: C, 42.32; H, 3.81; N, 16.24.

The herbicidal activities of the compounds **9a–l** were screened by rape-root growth method in Petri dishes [11]. In brief, rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6-cm Petri dish, to which 2 mL of inhibitor solution had been added in advance. Usually, 10 seeds were used on each plate. Duplicate was tested for each trial. The plate was placed in a dark room and allowed to germinate for 72 h at 28 (±1)°C. The lengths of 10 rape roots were measured and the means were calculated. The percentage inhibition was calculated relative to controls using distilled water instead of the inhibitor solution and listed in Table 1. Some compounds of high activities were selected to pot tests (Table 2). In brief, in plastic pots was added definite weight of soil and water, then various weed seeds were sown on the surface. Another batch of soil with water (foliage spray test) or spray of inhibitor (soil treatment test) was added. The test pots were kept in a green house under stable temperature and humidity, and they were covered with transparent material before germination. Fixed volume of water was sprayed in everyday to keep the continuous growth of the weeds. Foliage treatment was carried out in the 1- to 2-leaf stage after emergence. The inhibition rate (Table 2) was calculated 20 days after the treatment by height and/or fresh weight of grass upon the soil surface in comparison with the control sample (only using water). Similar to pot tests mentioned above, safety tests were carried out by using wheat as the test crop instead of weeds and the results were listed in Table 3.

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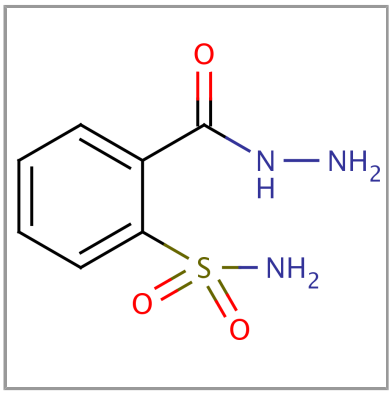
4



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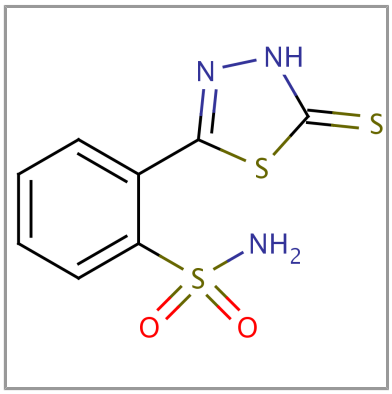

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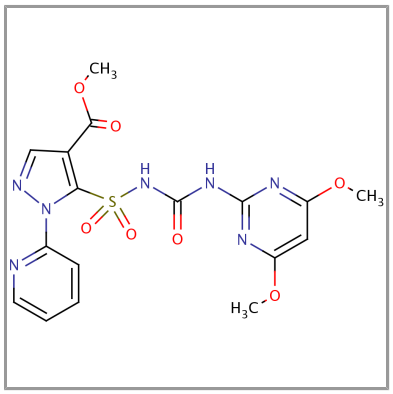

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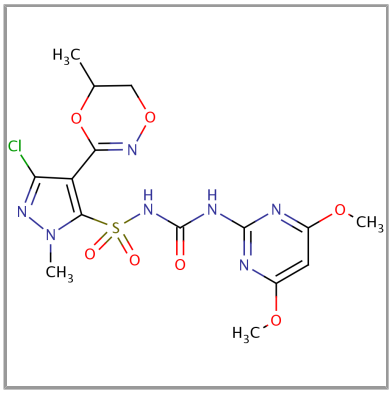

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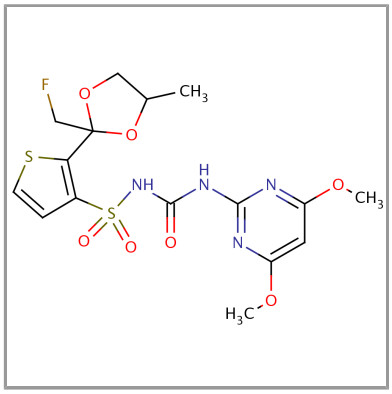

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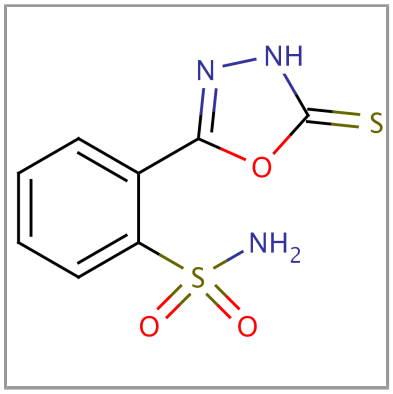

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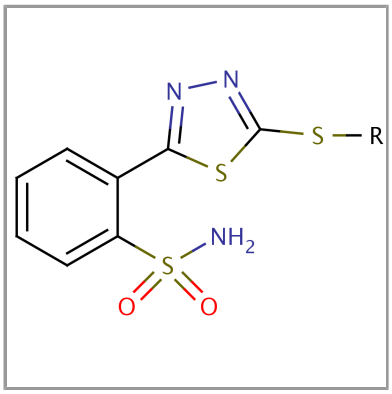

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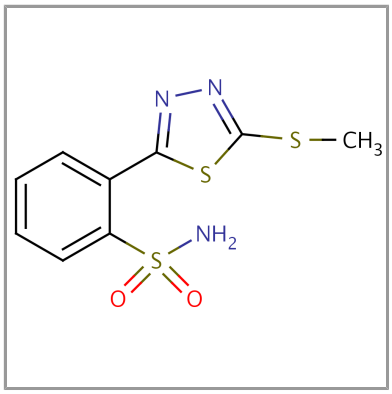

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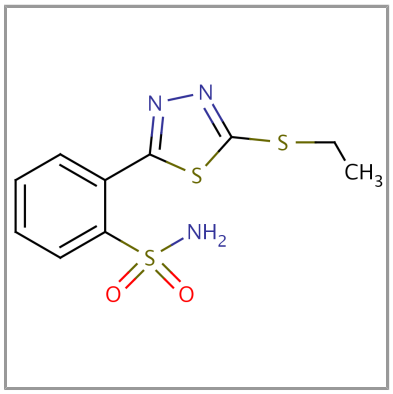

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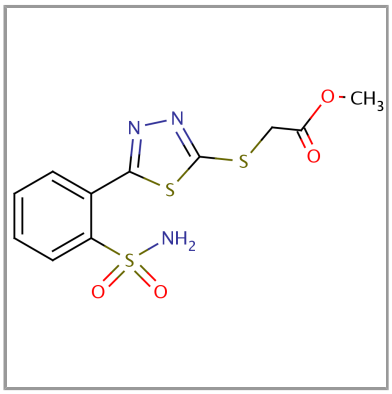

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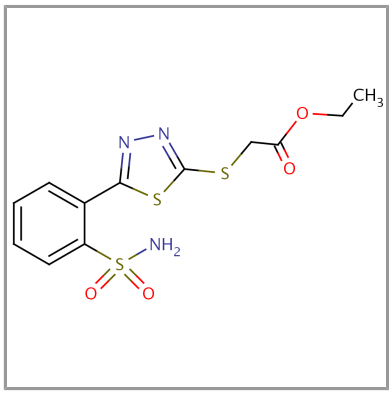

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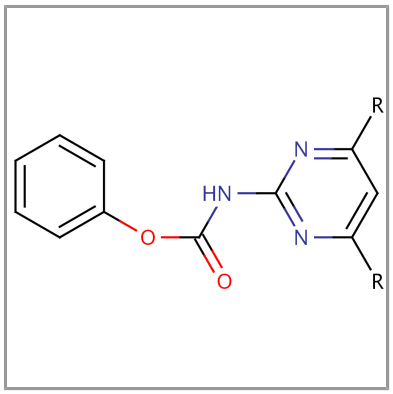

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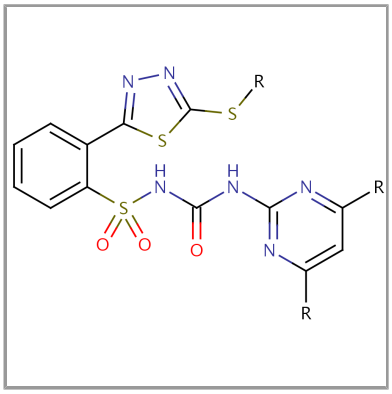

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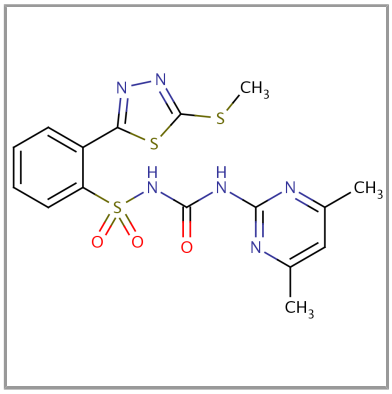

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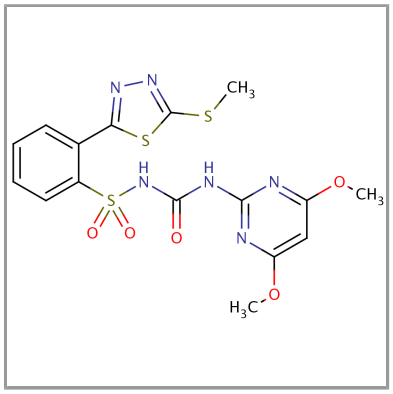

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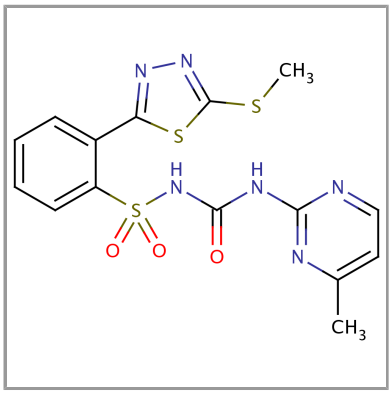

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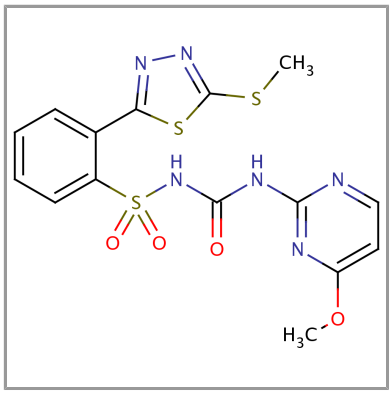

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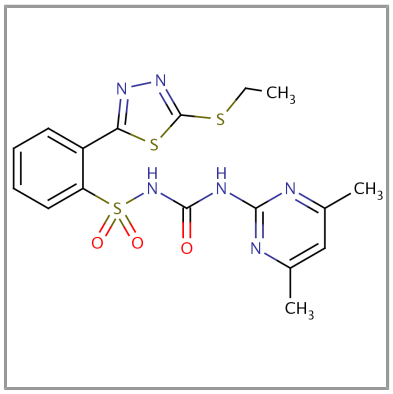

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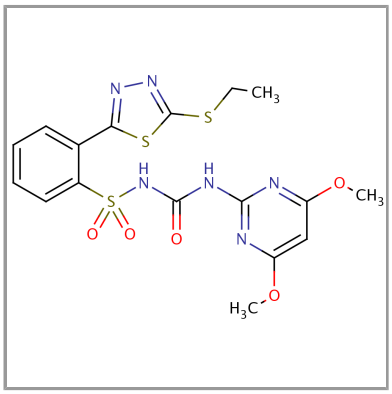

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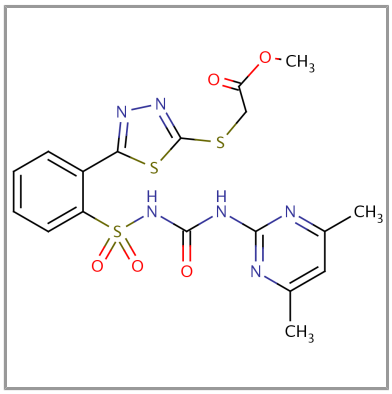

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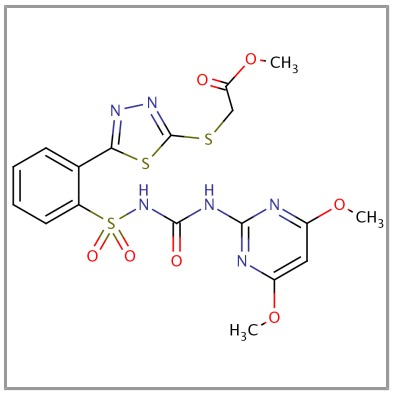
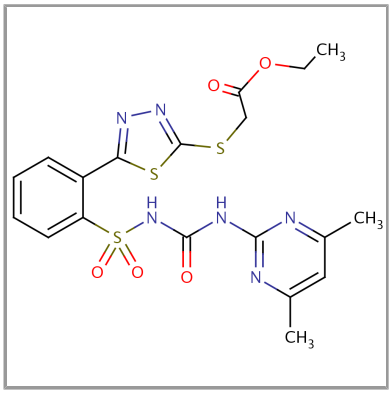


Compound Details Structure Search

9i



Compound Details Structure Search

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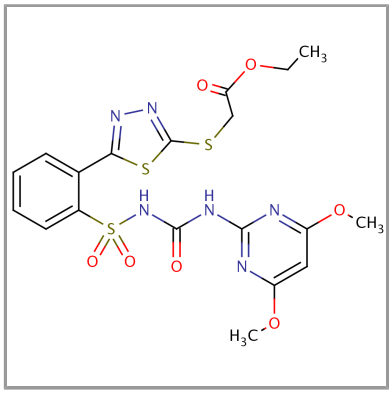

Compound Details Structure Search

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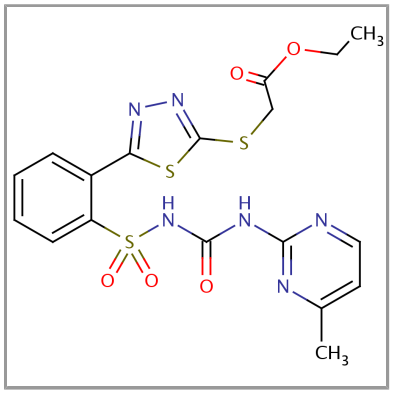

Compound Details Structure Search

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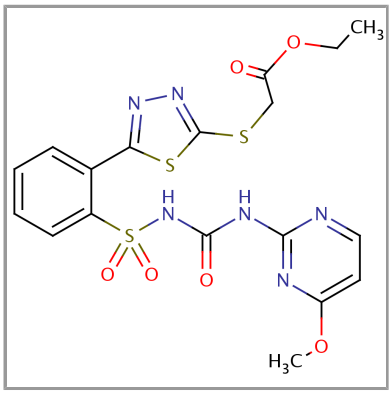

Compound Details Structure Search