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DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL SULFONYLUREA OXAZOLIDINES

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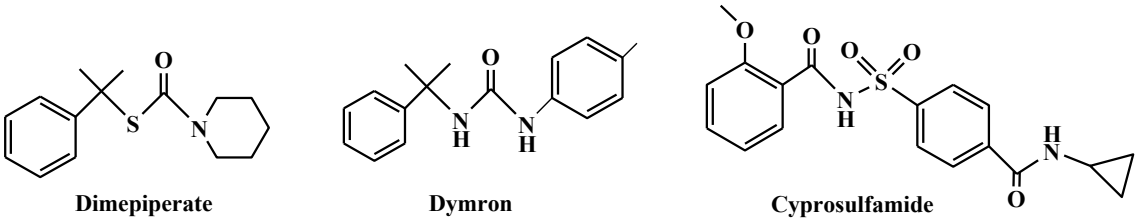
Abstract – A series of *N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide **4** was synthesized by cycloaddition and acylation reaction with alkamine, ketones, and *p*-methylbenzenesulfonyl isocyanate as the starting materials. The structures of all the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The configuration of **4d** was determined by X-ray crystallography. The preliminary biological test showed that all compounds could protect maize against injury caused by chlorsulfuron to certain extent. The sulfonylurea oxazolidines were possible acted as antagonists of sulfonylureas herbicides at target enzyme pocket site by docking analysis.

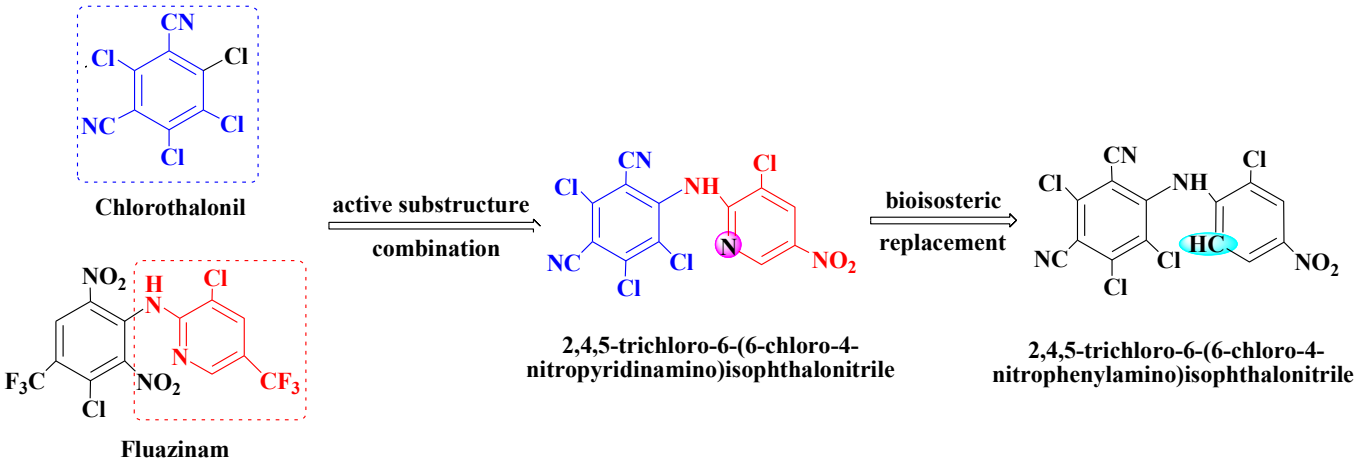
Sulfonylureas (SUs) compounds have a wide range of practical applications such as insecticides,[1] antimicrobial agents,[2] anticancer agents,[3] as well as herbicides.[4] SUs are the very popular herbicides used for controlling a range of weeds and some grasses in a variety of crops and vegetables because of their good herbicidal activity, low mammalian toxicity, high selectivity, and benign environmental activity. However their phytotoxicities and the residues to succeeding crops have caused some concerns. Some sulfonylurea herbicides (such as Chlorsulfuron, Metsulfuron, Chlorimuron-ethyl) are long residual herbicides, and persistent in soil which is poisonous to susceptive crops.[5] More and more novel safeners for SUs herbicides have been commercialized, such as Dimepiperate, Dymron, and Cyprosulfamide (**Scheme 1**).[6]

Structure-activity relationship theory (SAR) are very important in the search for bioactive materials because it provides useful molecular structure information that are necessary for the target bioactivity.[7] Base on the SAR, active substructure combination, and bioisosteric replacement, the novel aniline derivatives of Chlorothalonil was designed and synthesized by substitution of Cl atom on Chlorothalonil with aryl amine moiety of Fluazinam, another commercially available agent (**Scheme 2**).[8] Recently many

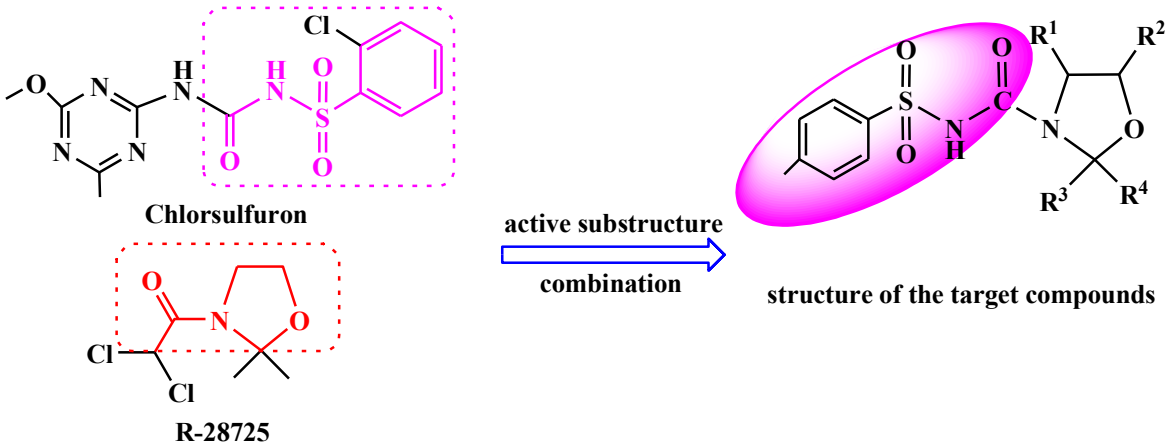
such successful cases have been reported.[9] In the same way, the safeners could be used as herbicide antidotes if the herbicides and their respective safeners are similar at the molecular level. Based on the above and continuous our previous work on *N*-containing heterocycles herbicide safeners,[10] herein we designed a series of novel *N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide utilizing active substructure combination and similarity theory (**Scheme 3**).



Scheme 1. Safeners for sulfonylurea herbicides

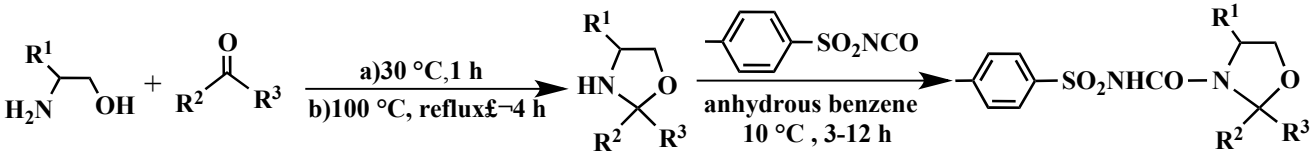


Scheme 2. Design of novel aniline derivatives of Chlorothalonil



Scheme 3. Design of the target compound

Several approaches had been developed to sulfonylurea derivatives with isocyanate[11] or carbamic ester[12] as the starting materials. Riehen reported the *N*-(2-methoxyethoxyphenylsulfony)-*N*`-(*p*-methoxy-6-methylpyrimidin-2-yl)urea being synthesized by acylation and aminolysis reaction with sulfonamide, dimethylformamide and 2-amino-4-methoxy-6-methylpyrimidine as the starting materials at low temperature with about 60% yield.[13] Hagana reported the synthesis of Nicosulfuron by amidation reaction with aminopyrimidine, phosgene (which is highly toxic and the procedure is difficult to control) and phenyl carbamate as the starting materials at room temperature with the yield of 80%.[14] Most of these reported methods required harsh reaction conditions, expensive materials, or phosgene. In view of the facts mentioned above, substituted *N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide **4** were synthesized with alkamine, ketone and *p*-methylbenzenesulfonyl isocyanate as the starting materials *via* cyclization and acylation reactions (**Scheme 4**).



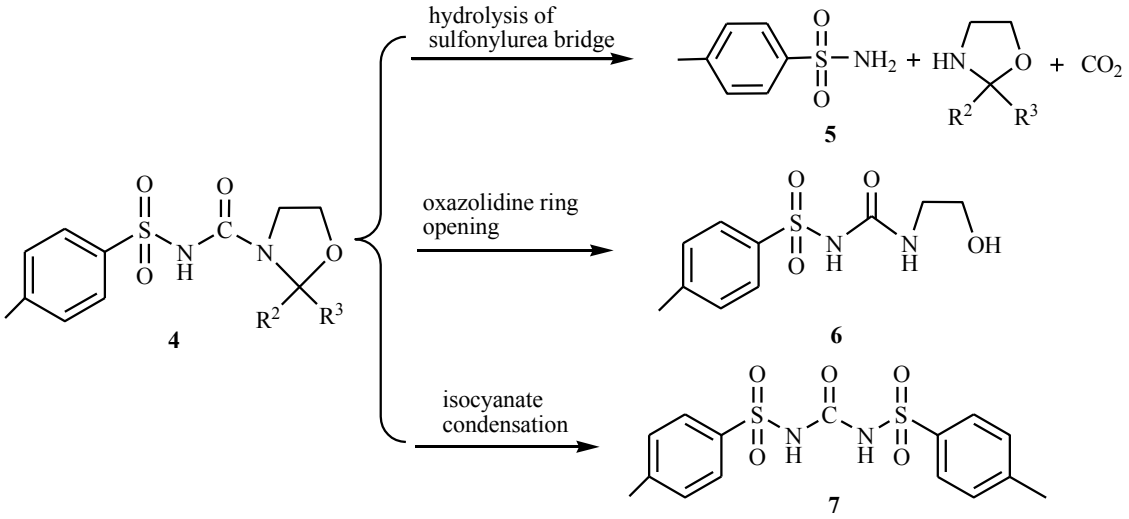
1 **2** **3a-k** **4a-k**

a) R^1=H, R^2=R^3=Me; b) R^1=H, R^2=Me, R^3=Et; c) R^1=H, R^2=Me, R^3=*n*-propyl;
d) R^1=H, R^2=Me, R^3=phenethyl; e) R^1=H, R^2~R^3=$(CH_2)_4$; f) R^1=H, R^2~R^3=$(CH_2)_5$;
g) R^1=Et, R^2=R^3=Me; h) R^1=Et, R^2=Me, R^3=Et; i) R^1=Et, R^2=Me, R^3=phenethyl;
J) R^1=Et, R^2~R^3=$(CH_2)_4$; k) R^1=Et, R^2~R^3=$(CH_2)_5$.

Scheme 4. Route for synthesis of the target compound **4**

Oxazolidine derivatives were synthesized according to the literature.[11] Acylation reaction proceeded smoothly in anhydrous benzene with compound **3** and *p*-methylbenzenesulfonyl isocyanate to give the target compound **4**. The yields of compounds **4f**, **4k** were more than 90%. However, the yield of **4i** was the lowest. The yields were significantly influenced by steric hindrance of alkyls connecting to at C-4 position of oxazolidine. The yields were lower as the structure of R^1 being ethyl. It was hard for *p*-methylbenzenesulfonyl isocyanate to react with *N* atom. It was failed in getting the target molecule when there were two methyl at C-4 position of oxazolidine. The effects of R^2 and R^3 were negligible because they were not at the same plane with oxazolidine. But they were related with the oxazolidine stability.[10] When R^2 and R^3 forming a spiro compound, the oxazolidine was very stabile. Six-membered ring yields (**4f** and **4k**) were significantly better than the five-membered ring (**4e** and **4j**). Chiral compounds would be obtained when R^2 and R^3 being different alkyl moieties.

It was worth note that the solvent must be water-free otherwise compound **5** would be obtained. In addition, compound **6** was obtained when the crude product was washed with water. Different solvents were employed to synthesize the target compound, but the isocyanate condensation carried out when alcohol was used as solvent (**Scheme 5**).



Scheme 5. The schematic diagram of the cleavage products

The structures of all the target compounds **4** were supported by MS, IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. The IR spectra of compounds 4**a-k** showed bands at 3268-3350 cm^{-1} due to N-H; 1665-1699 cm^{-1} due to C=O, 1134-1167 and 1354-1370 cm^{-1} due to S=O, which confirmed the formation of urea bridge. The ^{1}H NMR spectra of compounds **4a-k** exhibited a single signal in the range δ 10.41-10.79 for the proton of N-H; multiplet in the range δ 3.99-3.50 for the proton of oxazolidine. The elemental analysis of **4a-k** agreed with the molecular formula of all these compounds.

Finally, the single crystal of **4d** was obtained by dissolving it in CH_2Cl_2 and light petroleum, followed by slow evaporation at room temperature. The diffraction data of 4**d** was collected with a Bruker AXS Ⅱ CCD area detector using a graphite monochromated Mo *K*α radiation (λ=0.71073 Å) at 293(2) K. The structure was solved by direct methods using SHELXS-97,[15] and refined by full matrix least squares on F^2, SHELXL-97.[16]

The molecular structure of compound **4d** is shown in **Figure 1**. In the structure the oxazolidine, phenethyl and *p*-methylphenylsulfonylamine groups are not in a coplane. The dihedral angle of oxazolidine and phenethyl is 63.3°, and the dihedral angle of phenethyl group and *p*-methylphenylsulfonylamine group is 42.0°.

As depicted in the crystal packing of compound **4d**, two molecules are connected by one intermolecular hydrogen bond (C5-H5…O3) in **Figure 2**. Intermolecular and adjacent molecules are assembled through strong C-H…***π*** stacking interaction in **Figure 3.** No significant π-π interactions were found in the crystal structure.

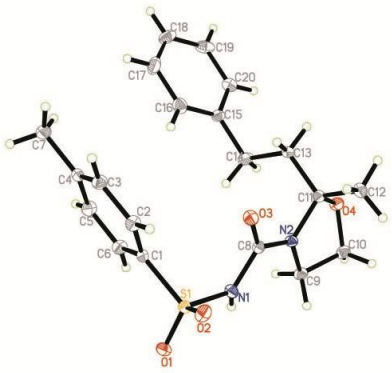


Figure 1. Molecular structure of product **4d**

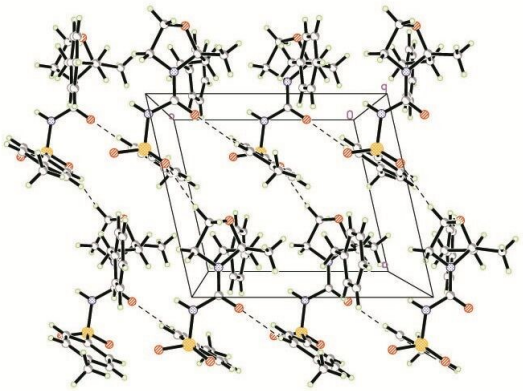


Figure 2. Packing diagram of finacompound **4d** in a unit cell

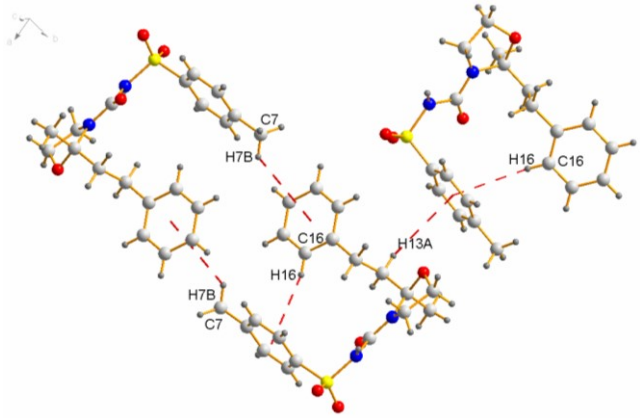


Figure 3. C-H… π interactions of the compound **4d**

The bioactivity determination of all the novel compounds **4a-k** was carried out on maize from the injury of Chlorsulfuron. The results were summarized in **Table 1**. The recovery rates of the growth index could be attained almost 50% with 10 mg/kg of the **4a-k** when the concentration of Chlorsulfuron in the soil was 2 μg/kg. Among the compounds tested, **4j** and **4k** showed the best activity against the injury of Chlorsulfuron, similar as the commercial safener R-28725. Further bioassay was carrying out to probe the structure-activity relationship.

For the structural similarity of safener and herbicide, the competition of the target enzyme was probed. The acetolactate synthetase (ALS) crystal structure data was taken from the PDB data bank (PDB ID: 1N0H). Docking calculations were performed by using Docking Suite. Molecular structure of **4k** was constructed and optimized using SKETCH and MINIMIZE option, and Gasteiger−Hückel charges were calculated for them. Geometry optimization was carried out using Triops force field supplied within SYBYL, with convergence criterion set at 0.005 kcal/(Å mol), and iterations criterion set at 1000.

Docking calculations were performed on the two molecules using Docking Suite option. The protein was prepared with BIOPOLYMER option. Docked structure was scored by the built-in scoring function and clustered by 0.8 Å of root-mean-square deviation (RMSD) criterions. The best binding modes were determined by docking scores and also the comparison to available complex crystal structure of ALS. Standard Amber FF99 force field parameters were assigned to protein, and general AMBER force field (gaff) was assigned to ligand. The safener **4k** was binding by hydrogen bonds with two active site residues (Ser163 and Ala117). The cofactor FAD 701 and AYD 700 were surrounding the active site pocket (**Figure 4).** The urea linkage moiety was binding by two active site residues at the entrance of the pocket. The oxazolidine moiety was deeply buried in the active site pocket (**Figure 5)**. Based on the SAR, active substructure combination, docking analysis and the bioactivity data, the sulfonylurea oxazolidine safeners were possible acted as antagonists of SUs herbicides at target enzyme pocket site.

Table 1. Effect of detoxification of compounds **4a-k** to growth index of maize[a,b,c]

Compound	Recovery of root length (%)	Recovery of plant height (%)	Recovery of root weight (%)	Recovery of plant weight (%)
R-28725	52.57	73.39	108.43	105.13
4a	36.21	33.19	6.51	38.46
4b	58.88	65.58	81.54	52.56
4c	60.75	38.83	36.6	18.59
4d	64.72	45.05	45.83	74.36
4e	42.29	53.73	23.36	89.10
4f	53.27	70.21	49.44	122.44
4g	37.62	26.98	55.46	27.56
4h	35.05	74.12	56.26	103.21
4i	57.01	90.02	95.59	130.77
4j	89.95	65.58	61.48	89.74
4k	84.81	92.34	101.60	142.31

[a]data are means of three replicates

[b]$\text{Recovery Rate}(\%) = \dfrac{\text{Treat with compounds - Treat with Chlorsulfuron}}{\text{Contrast - Treat with Chlorsulfuron}}$

[c]water treated was used as contrast

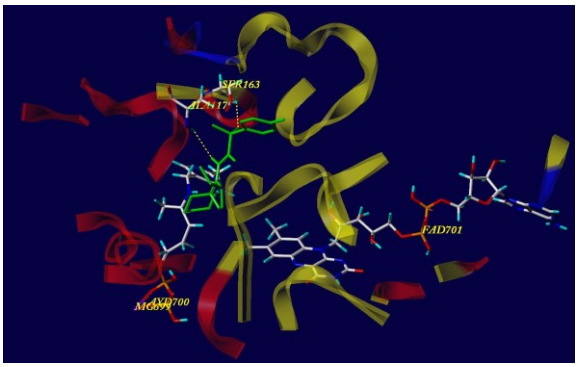


Figure 4. Safener **4k** in the ALS active site

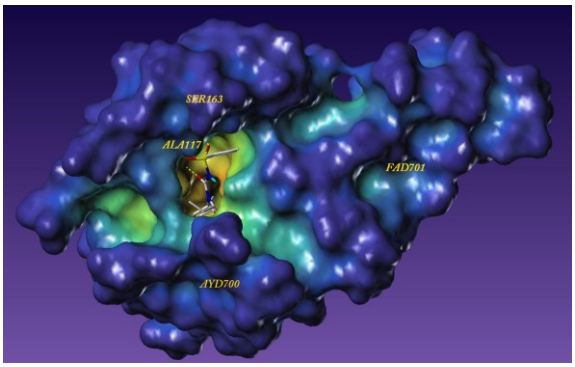


Figure 5. Active pocket of ALS occupied by Safener **4k**

In conclusion, we have developed an efficient, fast and convenient method for the preparation of *N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide derivatives. The advantages of this method were readily available starting materials, mild reaction conditions, and good yields. The preliminary bioactivity results showed that compound **4j and 4k** attained the best herbicide safener activity to Chlorsulfuron. The sulfonylurea oxazolidine were possible acted as antagonists of sulfonylureas herbicides at target enzyme pocket site by docking analysis.

EXPERIMENTAL

The IR spectra were taken on a KJ-IN-27G infrared spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANVE 300 MHz or 400 MHz, respectively, with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. The elemental analysis was performed on FLASH EA1112 elemental analyzer. The mass spectrum was recorded on a Waters Xevo TQ spectrometer. X-Ray diffraction data were collected on a Brukcr AXS Ⅱ CCD area-detector diffractometer, Mo K_{α}. The melting points were determined on a Beijing Taike melting point apparatus(X-4) and are uncorrected. All the reagents were of analytical reagents grade.

General procedure for the preparation of *N*-[(*p*-Methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide(4a-k)

Solution of *p*-methylbenzenesulfonyl isocyanate (1.98g, 0.01 mol, in 10 mL anhydrous benzene) was added dropwise to a stirred mixture of oxazolidine **3** (0.01 mol) and anhydrous benzene (50 mL) at 10-12 °C for 3 h. After the reaction completed, the product was recovered by filtration, extraction and drying, the crude product **4** was received. The pure product was obtained by soaking and filtration with a mixture of benzene and a little of CH_2Cl_2.

2,2-Dimethyl-*N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide (4a). Yield 84%. White solid, mp 95-96 °C. IR (KBr, cm^{-1}): *v* 3268 (N-H), 1696 (C=O), 1166, 1364 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 7.34-7.77 (m, 4H, Ph-H), 3.88 (t, 2H, *J*=6.1Hz, N-CH_2), 3.51 (t, 2H, *J*=6.3Hz, O-CH_2), 2.37

(s, 3H, Ph-CH_3), 1.34 (s, 6H, C-$(CH_3)_2$); ^{13}C NMR (DMSO-d_6, 75MHz): δ 151.93, 144.06, 137.96, 129.92, 127.72, 60.15, 42.27, 21.53; ESI-MS: 299 [M+H$^+$]. *Anal.* Calcd for $C_{13}H_{18}N_2O_4S$: C 52.33, H 6.08, N 9.39, S 10.75. Found: C 52.48, H 6.02, N 9.31, S 10.65.

2-Ethyl-2-methyl-*N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide (4b). Yield 72%. White solid, mp 98-99 °C. IR (KBr, cm^{-1}): *v* 3274 (N-H), 1699 (C=O), 1165, 1363 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.60 (s, 1H, N-H), 7.35-7.76 (m, 4H, Ph-H), 3.79-3.98 (m, 2H, N-CH_2), 3.45-3.64 (m, 2H, O-CH_2), 2.37 (s, 3H, Ph-CH_3), 0.59-1.86 (m, 8H, C-CH_2 and C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 149.49, 143.27, 138.98, 129.59, 127.74, 96.05, 63.37, 46.49, 29.89, 23.27, 21.52, 7.82; ESI-MS: 313 [M+H$^+$]. *Anal.* Calcd for $C_{14}H_{20}N_2O_4S$: C 53.83, H 6.45, N 8.97, S 10.26. Found: C 53.75, H 6.52, N 8.88, S 10.32.

2-Methyl-*N*-[(*p*-methylphenyl)sulfonyl]-2-propyl-1,3-oxazolidine-3-carboxamide (4c). Yield 52%. White solid, mp 90-91 °C. IR (KBr, cm^{-1}): *v* 3342 (N-H), 1700, 1673 (C=O), 1157, 1364 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.65 (s, 1H, N-H), 7.36-7.76 (m, 4H, Ph-H), 3.80-3.96 (m, 2H, N-CH_2), 3.41-3.61 (m, 2H, O-CH_2), 2.37 (s, 3H, Ph-CH_3), 0.69-1.82 (m, 10H, C-CH_2 and C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 149.00, 143.61, 138.42, 129.65, 127.85, 95.91, 63.39, 46.26, 23.38, 21.52, 16.51, 14.33; ESI-MS: 327 [M+H$^+$]. *Anal.* Calcd for $C_{15}H_{22}N_2O_4S$: C 55.19, H 6.79, N 8.58, S 9.82. Found: C 55.26, H 6.66, N 8.48, S 9.96.

2-Methyl-*N*-[(*p*-methylphenyl)sulfonyl]-2-(2-phenylethyl)-1,3-oxazolidine-3-carboxamide (4d). Yield 85%. White solid, mp 115-116 °C. IR (KBr, cm^{-1}): *v* 3344 (N-H), 1698 (C=O), 1161, 1361 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.74 (s, 1H, N-H), 6.81-7.82 (m, 9H, Ph-H), 3.86-4.05 (m, 2H, N-CH_2), 3.51-3.66 (m, 2H, O-CH_2), 1.78-2.43 (m, 4H, $(CH_2)_2$), 1.34 (s, 3H, C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 148.99, 143.73, 142.10, 138.27, 129.70, 128.81, 128.66, 128.59, 128.01, 126.09, 95.66, 63.55, 46.31, 29.61, 23.47, 21.56; ESI-MS: 389 [M+H$^+$]. *Anal.* Calcd for $C_{20}H_{24}N_2O_4S$: C 61.83, H 6.23, N 7.21, S 8.25. Found: C 61.78, H 6.26, N 7.39, S 8.14.

Crystal data for compound 4d: $C_{20}H_{24}N_2O_4S$, monoclinic, space group $P2_1/c$, a=9.3912(19) Å, b=19.483(4) Å, c=10.837(2) Å, V=1933.7(7) Å^3, β= 102.78(3), Z=4, D_c=1.334 cm^{-3}, μ=0.196 mm^{-1}, F(000)= 824. Independent reflections were obtained in the range of 3.05° < θ < 27.48, 4369. The final least-square cycle gave R_1= 0.0385, ωR_2 = 0.0960 for 3412 reflections with $I > 2\sigma$(I). The maximum and minimum differences of peak and hole are 0.509 and -0.289 e/Å^3, respectively.

***N*-[(*p*-Methylphenyl)sulfonyl]-1-oxa-4-aza-spiro[4.4]nonane-4-carboxamide (4e).** Yield 68%. White solid, mp 102-103 °C. IR (KBr, cm^{-1}): *v* 3276 (N-H), 1695 (C=O), 1165, 1364 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.72 (s, 1H, N-H), 7.37-7.76 (m, 4H, Ph-H), 3.84-3.86 (m, 2H, N-CH_2), 2.94-3.48 (t, 2H, O-CH_2), 2.38 (s, 3H, Ph-CH_3), 1.48-2.32 (m, 8H, C_4H_8); ^{13}C NMR (DMSO-d_6, 75MHz): δ 163.81, 157.62, 140.34, 129.64, 128.69, 127.77, 127.35, 103.43, 63.39, 60.86, 45.92, 34.75, 24.24,

21.53, 21.38; ESI-MS: 325 [M+H$^+$]. *Anal.* Calcd for $C_{15}H_{20}N_2O_4S$: C 55.54, H 6.21, N 8.64, S 9.88. Found: C 55.44, H 6.30, N 8.68, S 9.75.

***N*-[(*p*-Methylphenyl)sulfonyl]-1-oxa-4-aza-spiro[4.5]decane-4-carboxamide (4f).** Yield 92%. White solid, mp 105-106 °C. IR (KBr, cm^{-1}): *v* 3275 (N-H), 1693 (C=O), 1165, 1361 (S=O); ^{1}H NMR (DMSO-d_6, 400MHz): δ 7.34-7.75 (m, 4H, Ph-H), 3.85 (t, 2H, *J*=3.0Hz, N-CH_2), 3.50 (t, 2H, *J*=6.0Hz, O-CH_2), 2.36 (s, 3H, Ph-CH_3), 1.35-2.13 (m, 10H, C_5H_{10}); ^{13}C NMR (DMSO-d_6, 100MHz): δ 151.94, 151.87, 149.98, 144.07, 143.25, 139.05, 137.93, 137.88, 129.60, 127.86, 95.04, 62.98, 45.93, 32.27, 23.29, 21.52; ESI-MS: 339 [M+H$^+$]. *Anal.* Calcd for $C_{16}H_{22}N_2O_4S$: C 56.78, H 6.55, N 8.28, S 9.47. Found: C 56.72, H 6.64, N 8.35, S 9.41.

4-Ethyl-2,2-dimethyl-*N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide (4g). Yield 80%. White solid, mp 120-121 °C. IR (KBr, cm^{-1}): *v* 3283(N-H), 1686 (C=O), 1167, 1363 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.70 (s, 1H, N-H), 7.36-7.75 (m, 4H, Ph-H), 4.01 (s, 1H, N-CH), 3.74-3.84 (m, 2H, O-CH), 2.37 (s, 3H, Ph-CH_3), 0.86-1.60 (m, 11H, C-CH_2 and C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 148.77, 143.59, 138.62, 129.71, 127.83, 94.45, 66.45, 57.26, 27.20, 25.86, 23.68, 21.53, 10.42; ESI-MS: 327 [M+H$^+$]. *Anal.* Calcd for $C_{15}H_{22}N_2O_4S$: C 55.19, H 6.79, N 8.58, S 9.82. Found: C 55.32, H 6.71, N 8.49, S 9.84.

2,4-Diethyl-2-methyl-*N*-[(*p*-methylphenyl)sulfonyl]-1,3-oxazolidine-3-carboxamide (4h). Yield 53%. White solid, mp 121-122 °C. IR (KBr, cm^{-1}): *v* 3301 (N-H), 1695 (C=O), 1153, 1367 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.68 (s, 1H, N-H), 7.36-7.78 (m, 4H, Ph-H), 3.96 (m, 1H, N-CH), 3.76-3.86 (m, 2H, O-CH_2), 2.37 (s, 3H, Ph-CH_3), 0.88-1.88 (m, 13H, C-CH_2 and C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 148.61, 143.58, 138.57, 139.70, 127.80, 96.89, 66.24, 57.09, 31.00, 26.07, 21.74, 21.53, 10.66, 8.55; ESI-MS: 341 [M+H$^+$]. *Anal.* Calcd for $C_{16}H_{24}N_2O_4S$: C 56.45, H 7.11, N 8.23, S 9.42. Found: C 56.54, H 7.22, N 8.15, S 9.35.

4-Ethyl-2-methyl-*N*-[(*p*-methylphenyl)sulfonyl]-2-(2-phenylethyl)-1,3-oxazolidine-3-carboxamide (4i). Yield 23%. White solid, mp 117-118 °C. IR (KBr, cm^{-1}): *v* 3281 (N-H), 1686 (C=O), 1156, 1354 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.79 (s, 1H, N-H), 6.81-7.78 (m, 9H, Ph-H), 3.72-4.00 (m, 3H, O-CH and N-CH_2), 2.34 (s, 3H, Ph-CH_3), 1.40-2.23 (m ,4H, C(CH_2)$_2$-Ph), 0.89-1.25 (m, 5H, CH_2CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 148.99, 143.60, 142.33, 138.58, 129.68, 128.63, 127.91, 126.12, 96.33, 68.04, 66.33, 57.17, 30.32, 26.19, 21.52, 10.71; ESI-MS: 417 [M+H$^+$]. *Anal.* Calcd for $C_{22}H_{28}N_2O_4S$: C 63.44, H 6.78, N 6.73, S 7.70. Found: C 63.52, H 6.65, N 6.77, S 7.62.

3-Ethyl-*N*-[(*p*-methylphenyl)sulfonyl]-1-oxa-4-aza-spiro[4.4]nonane-4-carboxamide (4j). Yield 45%. White solid, mp 108-109 °C. IR (KBr, cm^{-1}): *v* 3259 (N-H), 1688 (C=O), 1160, 1370 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.78 (s, 1H, N-H), 7.36-7.77 (m, 4H, Ph-H), 4.03 (s, 1H, N-CH), 3.74 (m, 2H, O-CH_2), 2.37 (s, 3H, Ph-CH_3), 0.85-2.23 (m, 13H, 5×CH_2 and C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ

149.21, 142.33, 138.85, 129.63, 127.68, 103.78, 66.78, 56.79, 36.22, 34.09, 25.53, 24.41, 24.11, 21.52, 10.16; ESI-MS: 353 [M+H$^+$]. *Anal.* Calcd for $C_{17}H_{24}N_2O_4S$: C 57.93, H 6.86, N 7.95, S 9.10. Found: C 57.85, H 6.96, N 7.91, S 9.13.

3-Ethyl-*N*-[(*p*-methylphenyl)sulfonyl]-1-oxa-4-aza-spiro[4.5]decane-4-carboxamide (4k). Yield 90%. White solid, mp 164-165 °C. IR (KBr, cm^{-1}): *v* 3284 (N-H), 1687 (C=O), 1165, 1366 (S=O); ^{1}H NMR (DMSO-d_6, 300MHz): δ 10.41 (s, 1H, N-H), 7.35-7.75 (m, 4H, Ph-H), 3.99 (s, 1H, N-CH), 3.49-3.76 (s, 2H, O-CH_2), 2.37 (s, 3H, Ph-CH_3), 0.85-1.90 (m, 15H, 6×CH_2 and C-CH_3); ^{13}C NMR (DMSO-d_6, 75MHz): δ 149.21, 143.37, 138.93, 129.65, 127.80, 95.64, 66.20, 57.28, 35.20, 30.17, 26.07, 24.73, 23.45, 21.52, 10.50; ESI-MS: 367 [M+H$^+$]. *Anal.* Calcd for $C_{18}H_{26}N_2O_4S$: C 58.99, H 7.15, N 7.64, S 8.75. Found: C 59.06, H 7.21, N 7.52, S 8.71.

1-(2'-Hydroxyethyl)-3-*p*-methylphenyl)sulfonylurea (6). White solid, mp 136-137 °C. IR (KBr, cm^{-1}): *v* 3338 (N-H), 1673 (C=O), 1157, 1335 (S=O). ^{1}H NMR (DMSO-d_6, 400MHz): δ 10.42 (s,1H, SO_2N-H), 7.36-7.74 (m, *J*=8.4Hz, 8H, Ph-H), 6.43 (t, *J*=5.2Hz, 1H, O-H), 4.68 (s, 1H, N-H),3.29 (s, 2H, OH), 2.98 (t, *J*=5.6Hz, 2H, N-CH_2), 2.36 (s, 3H, Ph-CH_3); ^{13}C NMR (DMSO-d_6, 100MHz): δ 151.89, 144.03, 137.94, 129.89, 129.89, 127.68, 127.68, 60.12, 42.24, 21.49. *Anal.* Calcd for $C_{10}H_{14}N_2O_4S$: C 46.50, H 5.46, N 10.85, S 12.41. Found: C 46.44, H 5.52, N 10.78, S 12.55.

1,3-Bis(*p*-methylphenyl)sulfonylurea (7). White solid, mp 69-70 °C. IR (KBr, cm^{-1}): *v* 3299-3181 (N-H), 1701, 1748 (C=O), 1348 (S=O). ^{1}H NMR ($CDCl_3$, 400MHz): δ 8.86 (s, 2H, N-H), 7.25-7.79 (m, 8H, Ph-H), 2.38 (s, 6H, 2×Ph-CH_3); ^{13}C NMR (DMSO-d_6, 100MHz): δ 172.06, 147.02, 147.02, 145.58, 145.58, 135.24, 135.24, 129.93, 129.93, 129.93, 129.93, 127.95, 127.95, 127.95,127.95, 60.81, 21.68, 21.68, 14.14. *Anal.* Calcd for $C_{15}H_{16}N_2O_5S_2$: C 48.90, H 4.38, N 7.60, S 17.41. Found: C 48.88, H 4.42, N 7.68, S 17.56.

Biological activity: Maize (Dongnong 253) seeds were moistened with warm water about 30 min. The untreated or safener-treated maize were soaked by title compounds (10 mg/kg) for 12 h, and then germinated for 24 h at 26.5 °C. The seeds were planted 1.5 cm deep in plastic trays, in which soil was treated with 2 μg/kg Chlorsulfuron. Trays were incubated at 28 °C for 7 days. The effects of the title compound on the detoxification of Chlorsulfuron in soil were determined by testing the growth level.

SUPPLEMENTARY MATERIAL

Crystallographic data for the structural analysis of **4d** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1044046). These data can be obtained free of charge from The Cambridge Crystallographic Data *via* www.ccdc.cam.ac.uk/data_request/cif.

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