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Synthesis and biological evaluation of nonsymmetrical aromatic disulfides as novel inhibitors of acetohydroxyacid synthase

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ABSTRACT

46 Novel nonsymmetrical aromatic disulfides containing [1,3,4]thiadiazole or [1,3,4]oxadiazole groups were synthesized and their biological activities were evaluated as inhibitors of acetohydroxyacid synthase (AHAS, EC 2.2.1.6). Besides their strong in vitro inhibition against plant AHAS, compounds **3e** and **3f** also display 80–100% post-emergence herbicidal activities in greenhouse bioassay at 1500 g/ha dosage. The assay of exogenous branched-chain amino acids supplementation on rape root growth of **3e** suggests that the herbicidal activity has relationship with AHAS inhibition.

The biosynthesis of branched-chain amino acids (BCAA) catalyzed by acetohydroxyacid synthase (AHAS, EC 2.2.1.6) exists only in plants and micro-organisms,[1] which has made AHAS an attractive biological target for the design of 'green herbicide' since the mid-1980s.[2,3] With the overuse of the current AHAS inhibiting herbicides such as sulfonylureas and imidazolinones, resistant weed strains have become a major problem in many areas.[4–6] There is an urgent need to develop novel herbicidal AHAS inhibitors to defeat the weed resistance. The crystal structures of AHAS, which were determined by Guddat and co-workers,[7–10] have helped scientists to understand the mechanism of AHAS catalysis and inhibition,[11–13] to interpret herbicide resistance from specific enzyme residue mutations,[14] and to design structurally novel AHAS inhibitors based on the herbicide binding site.[15–19]

Inspired from the structural information of AHAS inhibitors identified from our early research and from the study by Yoon and co-workers,[20–22] we have recently reported a series of novel nonsymmetrical aryl disulfides containing [1,2,4]triazole groups and their biological activities.[18] Besides their potent inhibition against wild type *Arabidopsis thaliana* AHAS (*At*AHAS), those disulfides also display weak resistance factors to mutant type W574L. In order to further explore this family of novel AHAS inhibitors, we have designed and synthesized some other novel nonsymmetrical aryl disulfides in this research, replacing the [1,2,4]triazole groups with [1,3,4]thiadiazole or [1,3,4]oxadiazole groups. The preliminary bioassay indicated that, the newly synthesized disulfides with different heterocycles not only show strong *At*AHAS inhibition, but also exhibit improved herbicidal activity in the greenhouse pot assay. Supplement of exogenous BCAAs to the rape root growth experiment media weakened the herbicidal activity, indicating that the herbicidal activity has relationship with AHAS inhibition.

The nonsymmetrical disulfide compounds are of interest since they are useful tools in the research of dynamic combinatorial chemistry.[23] The nonsymmetrical disulfides have also been reported to display a variety of biological activities. For examples, Turos et al. reported that some nonsymmetrical aryl–alkyl disulfides are inhibitors of methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*,[24] while Khosla and co-workers published some nonsymmetrical disulfides that can selectively inhibit extracellular thioredoxin.[25] Our current research shows that some of the nonsymmetrical aromatic disulfides can also be studied as potential herbicides.

The synthesis procedures for disulfides **3**–**5** are shown in Scheme 1. The chemical synthesis and characterizations of the compounds are detailed in the Supplementary data. The nonsymmetrical disulfides were synthesized via a simple reaction in which the substituted 2-mercapto-[1,3,4]thiadiazole or substituted 2-mercapto-[1,3,4]oxadiazole (**1**) serves as a nucleophilic reagent to attack the sulfur atom in the arenesulfenyl chloride (**2**).[26] As discussed previously, we did not add any water into the reaction mixture and the yields were all very satisfactory.[18]

The chemical structures, the in vitro wild type *At*AHAS inhibition and in vivo rape root growth inhibition values of all the newly

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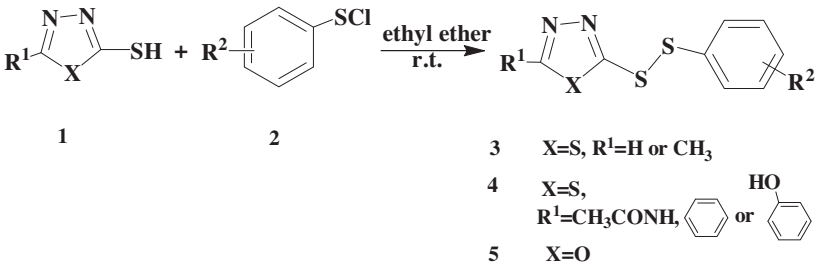
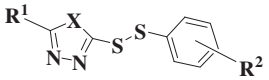
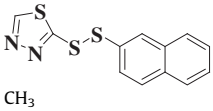
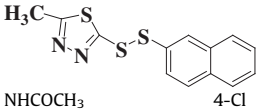
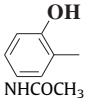


Scheme 1. Synthetic route of the nonsymmetrical disulfide compounds.

Table 1
Chemical structures of the nonsymmetrical disulfides and their biological activities



No.	R^1	R^2	X	*At*AHAS inhibition (%)		Rape root growth inhibition (%)	
				100 mg/L	10 mg/L	3 mg/L	100 mg/L
3a	H	2-$COOCH_3$	S	95	86	45	75.4
3b	H	2,4-di-NO_2	S	70	0	0	60.4
3c	H	2-NO_2	S	76	0	0	79.0
3d	H	2-$COOC_2H_5$	S	55	0	0	38.2
3e	H	H	S	97	92	76	92.6
3f	H	4-CH_3	S	98	92	77	87.8
3g	H	4-Cl	S	92	80	29	77.2
3h	H	4-Br	S	84	71	38	59.8
3i	H	2-CH_3	S	94	81	54	63.3
3j				59	2	0	0
3k	CH_3	H	S	90	76	39	55.2
3l	CH_3	4-Cl	S	55	43	0	24.9
3m	CH_3	2-$COOCH_3$	S	60	46	0	0
3n	CH_3	2-NO_2	S	56	0	0	0
3o	CH_3	2-F	S	68	9	0	57.3
3p	CH_3	4-Br	S	50	0	0	10.0
3q				37	0	0	0
4a	$NHCOCH_3$	4-Cl	S	87	73	62	14.0
4b		4-CH_3	S	80	77	27	0
4c		2-NO_2	S	76	67	18	11.7
4d		2,4-di-NO_2	S	65	53	38	5.9
4e		2-$COOC_2H_5$	S	70	63	39	0
4f		4-CH_3	S	70	20	0	3.0
4g		H	S	62	0	0	66.5
4h		2-$COOCH_3$	S	59	0	0	0
4i		2-$COOC_2H_5$	S	70	20	0	9.9
4j	$NHCOCH_3$	4-CH_3	S	71	44	0	30.1
4k	$NHCOCH_3$	2-NO_2	S	48	33	0	0
4l	$NHCOCH_3$	4-OCH_3	S	90	68	28	0
5a		2-$COOC_2H_5$	O	81	49	0	0