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Study on the bioactivity changes of hydroxylated sulfonylureas derivatives: A possible metabolism

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Abstract

Some new sulfonylureas and their hydroxylation products had been synthesized from 2-amino-4-methylpyrimidine. Their bioactivities against *E. coli* AHAS II in *vitro* were tested and the results indicated that the hydroxylation decreased the inhibition activities of sulfonylureas significantly. Subsequently herbicidal tests against stem-growth of barnyard grass and root-growth of rape confirmed the above conclusion. The preliminary molecular docking studies were also carried out to investigate the binding modes of non-hydroxylated and hydroxylated sulfonylureas with AHAS.

Keywords: Sulfonylureas; Metabolism; Hydroxylation; *E. coli* AHASII; Molecular docking

Sulfonylureas are a widely used group of herbicides for controlling a range of weeds and some grasses in a variety of crops and vegetables [1]. Several studies have indicated that sulfonylureas block acetohydroxyacid synthase (AHAS) [EC 2.2.1.6; formerly EC 4.1.3.18] [2,3] to kill plants, AHAS is the vital enzyme for biosynthesis of branch-chain amino acids, so it is the most important target for the design of environmental-benign herbicides [4]. Study on the metabolism of sulfonylureas may provide crucial information for environmental protection and new herbicides design and discovery. The main metabolic pathways of sulfonylureas herbicides include hydroxylation, glycosylation and *O*-alkylation *etc*. [5–7] and it has been reported that hydroxylation of the methyl on triazine ring is the metabolic pathway of some sulfonylureas [5,6]. Our present work is to investigate whether hydroxylation could result in bioactivity changes for pyrimidine-containing sulfonylureas.

We synthesized some new sulfonylureas **4a–c** and **7a–c**, and conducted their bioassay tests in *vitro* and in *vivo*. The synthetic route of these compounds is shown in the Scheme 1. The structures of the compounds were confirmed by elemental analysis and spectral analysis [8].

The intermediate **2** was prepared by bromination of 2-amino-4-methylpyrimidine **1** using 0.5 eq. bromine at room temperature for 1 h. Substituted benzenesulfonyl isocyanates were reacted with **2** over night to give the compounds **4a–c** according to the literature method [9].

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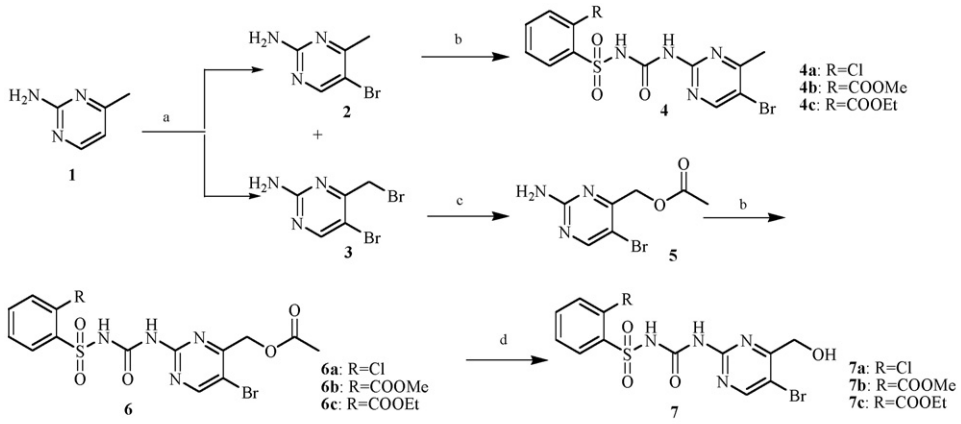

Reagents and conditions: (a)Br_2, CH_3COOH, r.t., 1h, the yields of **2** and **3** were 56% and 15% respectively; (b)$RC_6H_4SO_2NCO$, CH_3CN, r.t., over night, 23-90%; (c)CH_3COONa, DMSO, ultrasonic wave, 3 h, 32%; (d) 30% $NH_3{\cdot}H_2O$, CH_3CH_2OH, r.t., over night, 45-80%.

Scheme 1.

2-Amino-4-methylpyrimidine **1** was brominated by 1.5 eq. bromine at room temperature for 1 h to afford the intermediate **3**. The compound **5** was prepared by nucleophilic attack on **3** by sodium acetate in DMSO under ultrasonic wave for three hours. The compounds **6a–c** were obtained by reaction of the intermediate **5** with substituted benzenesulfonyl isocyanates. The compounds **7a–c** were prepared by hydrolysis of compounds **6a–c** with 30% ammonia overnight.

Reagents and conditions: (a) Br_2, CH_3COOH, r.t., 1 h, the yields of **2** and **3** were 56% and 15%, respectively; (b) $RC_6H_4SO_2NCO$, CH_3CN, r.t., over night, 23–90%; (c) CH_3COONa, DMSO, ultrasonic wave, 3 h, 32%; (d) 30% $NH_3{\cdot}H_2O$, CH_3CH_2OH, r.t., over night, 45–80%.

The K_i^{app} values of sulfonylureas against *E. coli* AHASII in *vitro* were measured according to the Westerfeld and Singh's methods [10,11]. The data shown in the Table 1 indicated that the hydroxylation of the methyl on pyrimidine ring resulted in 10–100-fold decrease in inhibition. This result suggested that hydroxylation may be the metabolic pathway of sulfonylureas. The further bioactivity test against root-growth of rape and stem-growth of barnyard grass confirmed the above conclusion (Table 2).

Table 1
The influence on K_i^{app} values of sulfonylureas by hydroxylation in *vitro*

Compound	K_i^{app} (mol/L)	Compound	K_i^{app} (mol/L)	Compound	K_i^{app} (mol/L)
4a	$2.92 \pm 0.73 \times 10^{-7}$	**4b**	$5.70 \pm 1.72 \times 10^{-9}$	**4c**	$4.83 \pm 0.39 \times 10^{-9}$
7a	$2.54 \pm 2.23 \times 10^{-6}$	**7b**	$4.75 \pm 0.93 \times 10^{-7}$	**7c**	$3.46 \pm 0.11 \times 10^{-8}$
7a/4a	11.5	**7b/4b**	120.0	**7c/4c**	14.0

Table 2
The influence on inhibition against stem-growth of barnyard grass

Compound	Inhibition against stem-growth of barnyard grass		Inhibition against root-growth of rape		
	100 μg/mL (%)	10 μg/mL (%)	1 μg/mL (%)	0.1 μg/mL (%)	0.01 μg/mL (%)
4a	11.0	0	56.1	22.9	0
7a	0	0	3.3	1.8	0
4b	68.9	41.8	70.3	69.0	8.9
7b	11.4	0	10.7	2.6	0
4c	53.0	21.4	74.1	71.3	27.8
7c	3.6	0	29.3	19.7	0