Article

Solvent Free Synthesis and Safener Activity of Sulfonylurea Benzothiazolines

Ying Fu [1], Jing-Yi Wang [1], Dong Zhang [1], Yu-Feng Chen [1], Shuang Gao [1], Li-Xia Zhao [1], and Fei Ye [1,*]

Department of Applied Chemistry, College of Science, Northeast Agricultural University, Harbin, 150030, China; fuying@neau.edu.cn (Y.F.); wang-jingyi@foxmail.com(J.-Y.W.); zhangdong-qlc@163.com (D.Z.); cyf1989919@163.com (Y.-F.C.); gaoshuang@neau.edu.cn (S.G.); zhaolixia@neau.edu.cn (L.-X.Z.)

*Correspondence: yefei@neau.edu.cn (F. Ye); Tel.: +86-451-55191507 (F. Ye)

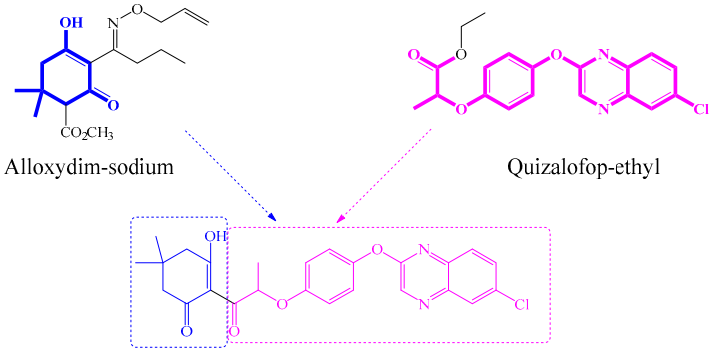
Abstract: A series of novel sulfonylurea benzothiazoline were designed by splicing active groups and bioisosterism. A solvent-free synthetic route was developed for the sulfonylurea benzothiazoline derivatives via the cyclization and carbamylation. All the compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, HRMS. The biological activity tests indicated the compounds could protect maize against the injury caused by chlorsulfuron to some extent. The molecular docking result showed that the new compound competed with chlorosulfuron to bind with the herbicide target enzyme active site to attain detoxification.

Keywords: active subunit combination; sulfonylurea benzothiazoline; solvent-free synthesis; safener activity

1 Introduction

Sulfur and nitrogen-containing heterocyclic compounds play key role in the pharmaceutical and chemical industry [1,2]. Especially sulfur-containing heterocyclic compounds are widely used in agricultural field. Several new benzothiazole compounds had been synthesized as potential antimicrobial and antiparasitic agents [3]. 1,2-Benzisothiazolin-3-one, used as fungicide, was good sterilization, anti-corrosion performance [4]. Thiazole compounds are also reported as herbicide safener[5].

Some bioactive compounds have been discovered by combining active subunits of known active molecules. For example, the new triketone derivative with better herbicidal activity had been designed by splicing active groups alloxydim-sodium into quizalofop-ethyl (Scheme 1) [6]. Many successful cases have been reported in recent years [7].



Scheme 1. The exploitation of the new herbicide

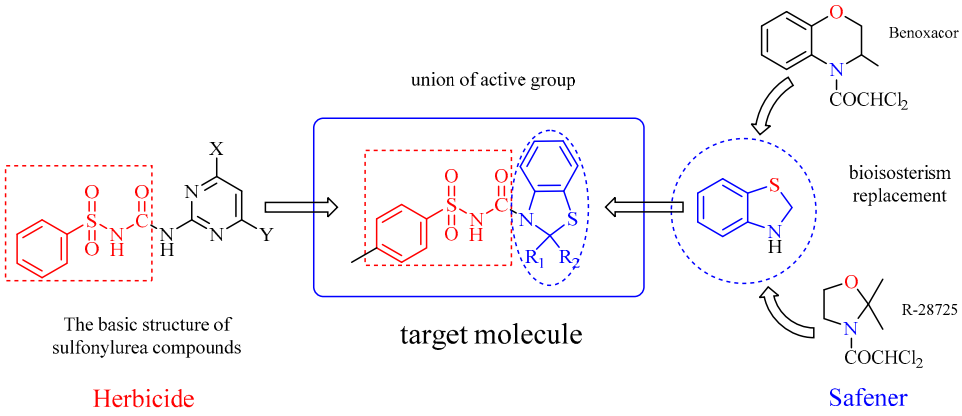
Herbicide and its safener may share common molecular characteristics according to the structure-activity relationships (SAR) and mechanism of safeners [8]. A systematic review of the chemical characteristics and SAR of herbicide safeners indicated that there is a close similar structural

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 September 2017 doi:10.20944/preprints201709.0056.v1

Peer-reviewed version available at Molecules 2017, 22, 1601; doi:10.3390/molecules22101601

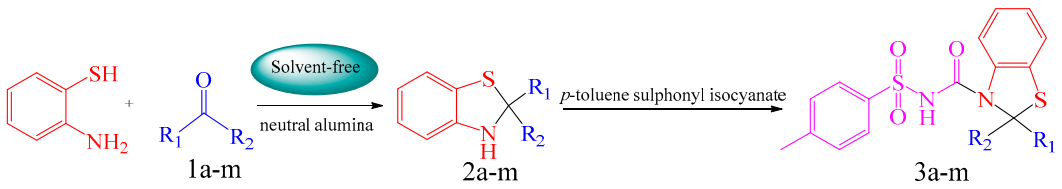
features between the herbicides and safeners [9]. For example, the sulfamide compounds may be an antidote to protect plants from the injury caused by sulfonylurea herbicides.

According to the facts mentioned above and continuous of our previous research, a series of sulfonylurea substituted benzothiazoline compounds **3a-3m** were designed based on active subunit combination, bioisosteric replacement and SAR, the sulfur and nitrogen-containing heterocyclic was retained and modified on the sulfonylurea functional groups (Scheme 2) [10-12].



Scheme 2. The design of the target compounds

A number of synthetic routes for benzothiazoline have been reported. The most common method is the condensation of *o*-aminothiophenol with carbonyl compounds in the presence of *p*-toluenesulfonic acid with $Ga(OTf)_3$ as catalyst [13,14]. Other methods included the reaction of 2,2'-dinitrodiphenyl disulfide with ketones in the presence of $TiCl_4$/Sm and SmI_2/HMPA [15,16].Nevertheless, all these reported methods suffered some drawbacks, such as the use of expensive or toxic catalyst, long reaction time, tedious synthetic procedures, or low yields of the products. In recent years, solvent-free organic synthesis has become a popular method and attracted immense interest as an environmental benign methodology. It leads to good yields, clean reactions, and shorter reaction times [17]. In view of the facts mentioned above, a series of novel sulfonylurea benzothiazoline were designed and synthesised with *o*-aminothiophenol and ketone as the starting materials in the presence of neutral alumina *via* solvent-free procedure (Scheme 3)[18].



Scheme 3. Route for synthesis of the target compounds **3**

2 Results and Discussion

2.1 Chemistry

1,3-Benzothiazoline derivatives **2** were synthesized with *o*-aminothiophenol and ketone **1** smoothly in the presence of neutral alumina. All compounds were synthesized under solvent-free conditions and further purified by column chromatography (silica gel, petroleum ether(PE): ethyl acetate; 20:1) to give the pure product.

The yields of compounds **2** were 56-92% (Table 1). The substituent group affected the yields significantly. When the substituents were cyclopentyl or cyclohexyl, the formation of spirocompounds made the structure more stable than others. Thus the yields of **2l**, **2m** were better, which were 91% and 92%, respectively. The bulk substituent reduced the stability of the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 September 2017 doi:10.20944/preprints201709.0056.v1

Peer-reviewed version available at Molecules 2017, 22, 1601; doi:10.3390/molecules22101601

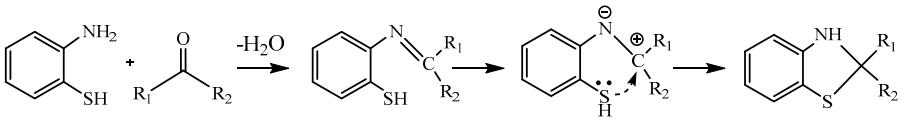
benzothiazoline. The yield of **2k** was only 56% which might be caused by the R_1 and R_2 being two *n*-propyl groups. The yields were similar for**2f** and **2g**.

Table 1. Characterization data, reaction condition and yields for product **2** and **3**

Entry	R_1	R_2	Compound 2			Compound 3		
			T (℃)	Time(h)	Yield (%)#	*T* (℃)	Time(h)	Yield (%)#
a	CH_3	CH_3	rt	0.5	82	12	12	96
b	CH_3	CH_2CH_3	rt	0.5	83	rt	5	65
c	CH_3	$CH_2CH_2CH_3$	rt	0.5	92	rt	5	78
d	CH_3	$CH(CH_3)_2$	80	1	84	rt	12	70
e	CH_3	CH_2COCH_3	50	3	78	rt	10	55
f	CH_3	$CH_2CH_2CH_2CH_3$	rt	2	76	rt	10	50
g	CH_3	$CH_2CH(CH_3)_2$	rt	0.5	76	rt	12	36
h	CH_3	$C(CH_3)_3$	88	1	80	36	2	59
i	CH_3	$PhCH_2CH_2$	rt	0.5	86	12	12	95
j	CH_2CH_3	CH_2CH_3	rt	0.5	82	5	5	40
k	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	80	0.5	56	4	4	82
l		$(CH_2)_4$	rt	0.5	91	12	12	95
m		$(CH_2)_5$	rt	0.5	92	12	12	99

Refers to yields of crude products only

The proposed mechanism for the cyclization was outlined in Scheme 4. First, *o*-aminothiophenolwas treated with ketone to generate schiff base. The resulting C-N double bond would easily broke and produce carbenium ion to receive attack from nearby S atom nucleophile to give the intermediate **2**.



Scheme 4. Proposed mechanism for cyclization reaction.

The target compounds **3** were synthesized by direct carbamylation with 1,3-benzothiazoline derivatives **2**and tosyl isocyanate. All compounds were obtained by washing the mixture with the solution (anhydrous benzene: anhydrous *n*-hexane; 1:1) to get white powder.

The yields of compounds **3** were 36%-99% (Table 1). When the substituents are symmetric small groups or cyclic structures, the yield was good. Compounds **3a, 3l**, **3m** were over 90% yields.

In general, there was no significant effect on the yields of the target products caused by steric hindrance, because the substituents at the 2-position were almost perpendicular to the plane of benzothiazoline ring. Comparing the **3f** and **3g**, it is also noticeable that the presence of a straight-chain at 2-position of benzothiazoline increased the yield. In contrast, the yields were decreased when there was a branch-chain with the same carbon atom number.

The peaks at 1708, 1341, and 1152 cm^{-1} in the IR for compound **3a** confirmed the presence of the carbonyl, and sulfonyl groups, respectively. The ^{1}H-NMR spectrum also confirmed the proposed structure, the three hydrogens at δ 2.37-2.41 ppm show the methyl of benzene ring. The signals at δ 6.48-7.85 ppm related to benzene ring. The single signal observed at δ 11.86 ppm was characteristic of hydrogen linked to nitrogen atom.

2.2 Biological activity

All the novel sulfonylurea benzothiazoline derivatives **3** were evaluated for their protection of maize against the injury of chlorsulfuron (2 μg/kg) (Table 2). After a preliminary screening, the concentration of the safener and compounds applied in the bioassay was determined. Chlorsulfuron could provoke an obvious decrease on the growth of maize, but significant differences were observed after the introduction of compounds. The recovery rates of the root length were attained over 25% except for compounds **3e**, **3j**. Recovery rates of plant weight were over 40% except for compound **3e**.

Among all the test compounds, compound **3c** showed the best safener activity against the injury of chlorsulfuron, better than the commercialized safener AD-67. A good protection activity may be due to the introduction of a sulfonyl group, making the compound bind with the herbicide target site competitively and reduce the injury of chlorsulfuron.

Table 2. Effect of detoxification of compounds **3a-m** to growth index of maize [i,ii,iii,iv]

Compound	Root length recovery rate (%)	Plant height recovery rate (%)	Root fresh weight recovery rate (%)	Plant fresh weight recovery rate (%)
AD-67	32.66^{efg}	81.62^{de}	81.25^{b}	89.47^{c}
3a	38.05^{cde}	68.57^{f}	37.50^{h}	57.89^{ef}
3b	35.02^{def}	54.41^{g}	43.75^{g}	21.05^{h}
3c	55.89^{a}	109.56^{a}	87.50^{b}	126.31^{a}
3d	42.76^{bc}	100.92^{ab}	6.25^{m}	52.63^{f}
3e	19.87^{i}	20.59^{i}	56.25^{e}	42.11^{g}
3f	56.23^{a}	91.73b^{cd}	12.50^{l}	73.68^{d}
3g	27.95^{gh}	81.86^{de}	37.50^{h}	84.21^{c}
3h	45.12^{b}	72.24^{ef}	87.50^{b}	105.26^{b}
3i	32.66^{efg}	84.01^{cd}	31.25^{i}	110.53^{b}
3j	18.18^{ij}	73.35^{ef}	156.25^{a}	57.89^{ef}
3k	31.31^{fg}	40.26^{h}	37.50^{h}	57.89^{ef}
3l	33.00^{efg}	89.34^{cd}	18.75^{k}	84.21^{c}
3m	25.93^{h}	92.65^{bc}	12.50^{l}	110.53^{b}

[i] Data are means of three replicates

[ii] $$\text{Recovery Rate (\%)} = \frac{\text{Treated with compounds - Treated with chlorsulfuron}}{\text{Contrast - Treated with chlorsulfuron}}$$

[iii] Water treated was used as contrast

[iv] Small letter is significant at the 0.05 level

Comparing the chemical properties of compound **3c** and chlorsulfuron, such as log *p*, pK_a, molecular weight (MW) and electronegativity, with a view to improving the hypothesis that safener may act as competitive antagonists of herbicides at the herbicide target site (Table 3). It was observed that pK_a, MW and electronegativity of compound **3c** were all similar to the herbicide chlorsulfuron. which indicated that in terms of the investigated features the safener/herbicide combinations are quite similar at the molecular level. The visual evaluations of the superimposed molecular structures was shown in Figure 1. Chlorsulfuron and **3c** were perfectly aligned in a common skeleton.

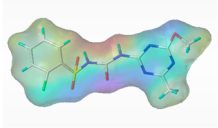
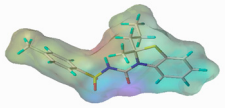
Sulfonylurea herbicides are a kind of acetolactate synthase (ALS) inhibitors. The three-dimensional structure of compound **3c** and Chlorsulfuron was constructed by the Sketch module of SYBYL-X 2.0. Subsequently, the molecule was optimized and Gasteiger−Huckel charges were calculated. The crystal structure of ALS was taken from the Protein Data Bank (PDB ID 1YHY). Docking modeling used the "CDOCKER" method in Accelrys Discovery Studio 2.5. Before docking, the protein structure was gave the CHARMm force field and remove the water and some other co-crystallized small molecules. After the protein preparation, the docking studies active site was defined, with a subset region of 13.0Å from the centre of the known ligand. The Top Hits set to 100, the remaining parameters were used "CDOCKER" the default value. The binding energy of the small molecule-receptor protein complex was used as an evaluation index, with the largest negative representation of the most stable conformation. The molecular docking result showed that both compound **3c** and chlorosulfuron could bind well to the herbicide target active site of ALS (Figure 2). In the docking modeling, the phenyl moiety of chlorsulfuron rotated to the right side in the active site, effectively blocking the entrance of channel and preventing the substrate binding with active site, played a herbicidal activity. In contrast, the phenyl moiety of compound 3c turned left in the active site，partially blocked the entrance of the channel. While preventing the combination of chlorosulfuron with active site, the small substrate would have more opportunity to thrust itself into this channel and catalyze active site.

When compound **3c** was applied before or simultaneously with chlorosulfuron, it might compete with chlorosulfuron at the target site by preventing the herbicide from reaching or acting on

Peer-reviewed version available at *Molecules* **2017**, *22*, 1601; doi:10.3390/molecules22101601

the ALS active pocket leading to counter action of the herbicide. That might be the detoxification mechanism of the novel compound.

Table 3. Chemical property comparisons of chlorsulfuron with **3c**

Compounds	log *p*[a]	p*K*a[b]	MW	Electronegativity[c]
Chlorsulfuron	**2.63**	**4.1±0.4**	**357.77**	
3c	**4.85**	**4.6±0.4**	**390.52**	

[a] The log *p* was predicted by ChemBioOffice 2014

[b] The p*K*awas predicted by ACD/lab

[c]The Electronegativity was predicted by Sybyl-X 2.0

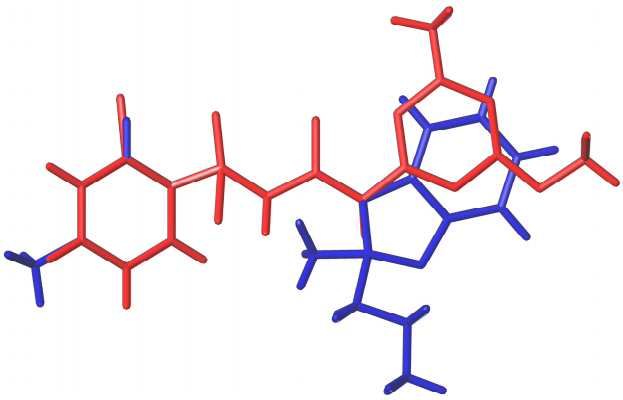


Figure 1. Superimposed molecular structures modeling. The structure of chlorsulfuron was shown in red, and compound 3c was shown in blue

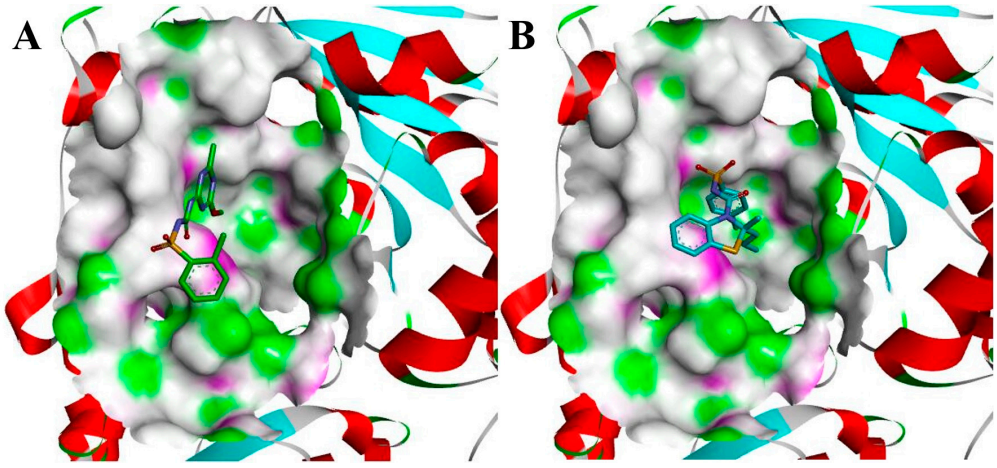


Figure 2. The docking modeling of Chlorsulfuron (A) and **3c** (B) with ALS

3 Materials and Methods

3.1 Reagents and Analysis

All the reagents were analytical grade and used without further purification. The IR spectra were recorded on a Bruker ALPHA-T spectrometer (KBr). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AVANVE 300 MHz using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal

standard. The melting points was measured on a Beijing Taike melting point apparatus (X-4) and was uncorrected. The high-resolution mass spectrometry was recorded on a FT-ICR MS spectrometer.

3.2 General procedure for the preparation of 1,3-benzothiazoline derivatives **2**

o-Aminothiophenol (0.03 mol) and ketone (0.02 mol) were mixed ina round bottomed flask in the presence of neutral alumina (3 g). The reaction mixture was stirred under nitrogen atmosphere at appropriate temperature for a period of time. The reaction mixture was extracted with chloroform and filtered. The organic layer was dried over anhydrous Na_2SO_4 and chloroform was evaporated under vacuum. The pure products were obtained by recrystallization (**2a**, **2e**, **2i**, **2l**-**2m**) or column chromatography on silica gel eluting with PE and EtOAc (20:1) (**2b-2d**, **2f-2h**, **2j-2k**).

2,2-Dimethylbenzothiazoline(**2a**): White solid, Yield 82%. IR (KBr, $\bar{\nu}$/cm^{-1})3334 (N-H), 2961-2917 (C-H), 1581-1363 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ(ppm) 6.67-7.10 (m, 4H), 3.97 (s, 1H), 1.74 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ(ppm) 145.9, 128.5, 125.1, 122.2, 121.1, 111.5, 74.8, 31.7, 31.7.

2-Ethyl-2-methyldihydro-benzothiazoline (***2b***):Yellow liquid, Yield 83%. IR (KBr, $\bar{\nu}$/cm^{-1}) 3353 (N-H), 3086-2875 (C-H), 1581-1375 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.60-7.05 (m, 4H), 3.89 (s, 1H), 1.80-2.02 (m, 2H), 1.66 (s, 3H), 1.02 -1.06 (t, *J*=7.5Hz ,3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.2, 127.7, 125.0, 122.0, 129.5, 110.8, 78.9, 38.9, 29.6, 9.8.

2-Methyl-2-propylbenzothiazoline (***2c***):Yellow liquid, Yield 92%. IR (KBr, $\bar{\nu}$/cm^{-1})3353 (N-H), 3067-2871 (C-H), 1583-1395 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.62-7.06 (m, 4H,), 3.85 (s, 1H), 1.80-1.98 (m, 2H), 1.68 (s, 3H), 1.44-1.58 (m, 2H), 0.94-0.99 (t, *J*=7.5Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.0, 127.9, 124.9, 121.9, 120.6, 110.9, 78.2, 46.4, 30.0, 18.8, 14.2.

2-Isopropyl-2-methylbenzothiazoline(***2d***):Yellow liquid, Yield 84%. IR (KBr, $\bar{\nu}$/cm^{-1})3348 (N-H), 3068-2869 (C-H), 1583-1373 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.61-7.07 (m, 4H,), 3.95 (s, 1H), 2.13-2.22 (m, 1H), 1.66 (s, 3H), 1.05-1.11 (q, *J*=6.6Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.4, 127.0, 124.9, 121.8, 120.1, 110.2, 82.6, 39.9, 27.1, 19.0, 18.2.

2-(Acetonyl)-2-methylbenzothiazoline(***2e***):Transparent crystal, Yield 78%. IR (KBr, $\bar{\nu}$/cm^{-1})3334 (N-H), 3070-2969 (C-H), 1580-1338, 1706 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.52-6.95 (m, 4H), 6.42 (s, 1H), 3.14-3.21 (q, *J*=17.4Hz , 2H), 2.12 (S, 3H), 1.619 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 206.1, 145.9, 125.2, 124.9, 121.1, 118.2, 108.8, 74.3, 55.8, 30.8, 29.5.

2-Butyl-2-methylbenzothiazoline(***2f***):Yellow liquid, Yield 76%. IR (KBr, $\bar{\nu}$/cm^{-1}): 3349 (N-H), 3068-2859 (C-H), 1583-1374 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.64-7.08 (m, 4H,), 4.02 (s, 1H), 1.83-1.98 (m, 2H), 1.70 (s, 3H,), 1.31-1.54 (m, 4H), 0.92-0.96 (t, *J*=7.2Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 145.9, 127.8, 125.0, 122.0, 120.7, 110.9, 78.4, 73.8, 30.0, 27.7, 22.9, 14.1.

2-Isobutyl-2-methylbenzothiazoline (***2g***):Yellow liquid, Yield 76%. IR (KBr, $\bar{\nu}$/cm^{-1})3357 (N-H), 2967 (C-H), 1582-1391 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.64-7.08 (m, 4H), 3.88 (s, 1H), 1.84-1.98 (m, 3H), 1.70 (s,3H), 1.02-1.04 (d, *J*=6.3Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 145.7, 128.1, 125.0, 122.0, 120.6, 111.0, 78.4, 52.1, 30.5, 25.6, 21.5, 21.0.

2-tert-Butyl-2-methyl benzothiazoline (***2h***): Yellow liquid,Yield 80%. IR (KBr, $\bar{\nu}$/cm^{-1})3362 (N-H), 3068-2871(C-H), 1582-1385 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.59-7.06 (m, 4H), 3.96 (s, 1H), 1.74 (s,3H), 1.14 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.7, 126.5, 124.8, 121.5, 119.7, 109.5, 85.7, 39.9, 27.1, 26.3, 26.3, 26.3.

2-Methyl-2-phenethylbenzothiazoline (***2i***):Transparent crystal, Yield 86%. IR (KBr, $\bar{\nu}$/cm^{-1})3353 (N-H), 3060-2856 (C-H), 1602-1375 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.66-7.38 (m, 9H), 3.90 (s, 1H), 2.89-2.94 (t, *J*=6.6Hz ,2H), 2.22-2.30 (m, 2H), 1.82 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.1,141.7, 128.5, 128.5, 128.5, 128.5, 127.5, 126.0, 125.1, 122.0, 120.7, 110.8, 76.7, 45.9, 31.9, 30.3.

2,2-Diethylbenzothiazoline(***2j***):Yellow liquid, Yield 82%. IR (KBr, $\bar{\nu}$/cm^{-1})3371 (N-H), 3068-2930 (C-H), 1583-1398 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.59-7.05 (m, 4H), 3.89 (s, 1H), 1.88-1.95 (q, *J*=7.5Hz ,4H), 1.01-1.06 (t, *J*=7.5Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.7, 127.1, 124.8, 121.7, 120.0, 109.9, 82.7, 34.5, 34.5, 9.2, 9.2.

2,2-Dipropylbenzothiazoline(***2k***):Yellow liquid, Yield 56%. IR (KBr, $\bar{\nu}$/cm^{-1})3370 (N-H), 3068-2871 (C-H), 1583-1397 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.59-7.05 (m, 4H), 3.94 (s, 1H), 1.85-1.90

(t, *J*=7.8Hz ,3H), 1.41-1.63 (m, 4H), 0.95-1.00 (t, *J*=7.5Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$):δ (ppm) 146.5, 127.3, 124.9, 121.7, 120.1, 110.0, 81.5, 44.7, 44.7, 18.2, 18.2, 14.3, 14.3.

3H-spiro [1,3-benzothiazoline-2,1'-cyclopentane](***2l***):Transparent crystal, Yield 91%. IR (KBr, $\bar{\nu}$/cm^{-1})3354 (N-H), 3066-2871 (C-H), 1581-1320 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.64-7.08 (m, 4H), 4.00 (s, 1H), 2.16-2.25 (m, 2H), 1.99-2.08 (m, 2H), 1.77-1.82 (m, 4H,). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 145.9, 128.1, 125.0, 121.8, 129.7, 110.9, 84.2, 42.5, 42.5, 22.9, 21.9.

3H-spiro[1,3-benzothiazoline-2,1'-cyclohexane](***2m***): (KBr, $\bar{\nu}$/cm^{-1})Transparent crystal, Yield 92%. IR (KBr)3329 (N-H), 3063-2863 (C-H), 1579-1443 (C=C).^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.64-7.06 (m, 4H), 3.94 (s, 1H), 2.20-2.24 (d, *J*=12.6Hz, 2H), 1.53-1.81 (m, 7H), 1.23-1.36 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 145.9, 127.1, 125.0, 121.9,120.5, 110.9, 80.0, 40.9, 40.9, 25.0, 24.0, 24.0.

3.3 General procedure for the preparation of Sulfonylurea benzothiazoline derivatives ***3***

The intermediate **2** (5 mmol) was mixed with tosyl isocyanate (5 mmol) in round bottomed flask. The mixture was vigorously stirred at 10℃ for 12 h. At the end of the reaction a solid precipitated. Then the solid was washed with the mixed solution of anhydrous benzene and n-hexane to get compounds **3**.

2,2-Dimethyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide (***3a***):White solid, Yield 96%, m.p. 129-131 ℃. IR (KBr,$\bar{\nu}$/cm^{-1})3242 (N-H), 3071-2928 (C-H), 1708 (C=O), 1341, 1152 (O=S=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 11.86 (s, 1H), 6.48-7.85 (m, 8H), 2.37-2.41 (d, *J*=10.5Hz ,3H), 1.61-1.70 (d, *J*=24.9Hz ,6H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) 147.3, 142.3, 141.9, 129.7, 127.8, 126.1, 125.4, 124.3, 123.5, 121.9, 118.8, 116.4, 109.4, 75.3, 31.9, 23.0, 21.4. HR-MS (ESI): m/z calcd for $C_{17}H_{19}N_2O_3S_2$ ([M+H]$^+$) 363.0832 found 363.0827.

2-Ethyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide(***3b***):White solid, Yield 65%, m.p. 91-93℃. IR (KBr,$\bar{\nu}$/cm^{-1})3234 (N-H), 3064-2934 (C-H), 1704 (C=O), 1350, 1155 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.97-7.98 (m, 8H), 2.43-2.45 (d, *J*=6.3Hz, 3H), 2.18-2.28 (m, 1H), 1.86-1.98 (m, 1H), 1.77 (s, 3H), 0.78-0.83 (t, *J*=7.2Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.9, 122.9, 138.1, 136.0, 129.6, 129.6, 128.4, 128.4, 126.5, 125.6, 124.8, 123.5, 115.4, 82.8, 32.6, 26.7, 21.7, 9.3. HR-MS (ESI): m/z calcd for $C_{18}H_{21}N_2O_3S_2$ ([M+H]$^+$) 377.0988 found 377.0984.

2-Propyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide(***3c***):White solid, Yield 78%, m.p. 91-94℃. IR (KBr,$\bar{\nu}$/cm^{-1}) 3380 (N-H), 3057-2872 (C-H), 1715 (C=O), 1349, 1162 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.97-7.98 (m, 8H), 2.44-2.45 (d, *J*=4.5Hz, 3H), 2.13-2.23 (m, 1H), 1.82-1.88 (m, 1H), 1.77 (s, 3H,), 1.34-1.46 (m, 1H),0.93-1.03 (m, 1H), 0.70-0.74 (t, *J*=6.6Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.9, 144.9, 138.0, 135.9, 129.5, 129.5, 128.4, 128.4, 126.5, 125.6, 124.8, 123.5, 115.4, 81.9, 41.6, 27.3, 21.7, 18.4, 13.7. HR-MS (ESI): m/z calcd for $C_{19}H_{23}N_2O_3S_2$ ([M+H]$^+$) 391.1145 found 391.1144.

2-Isopropyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide(***3d***):White solid, Yield 70%, m.p. 105-109℃. IR (KBr,$\bar{\nu}$/cm^{-1}) 3347 (N-H), 3056-2973 (C-H), 1706 (C=O), 1357, 1164 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.96-7.97 (m, 8H), 2.60-2.69 (m, 1H), 2.45 (s, 3H), 1.79 (s, 3H), 0.92-0.95 (d, *J*=6.9Hz, 3H), 0.76-0.78 (d, *J*=6.6Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 147.2, 144.8, 138.9, 136.1, 129.5, 129.5, 128.4, 128.4, 126.5, 125.5, 124.7, 123.1, 115.3, 87.1, 36.4, 25.4, 21.7,18.4,17.9. HR-MS (ESI): m/z calcd for $C_{19}H_{23}N_2O_3S_2$ ([M+H]$^+$) 391.1145 found 391.1149.

2-Acetonyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide(***3e***):White solid, Yield 55%, m.p. 128-130℃. IR (KBr,$\bar{\nu}$/cm^{-1})3175 (N-H), 1714 (C=O), 1350, 1164 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.52-7.71 (m, 8H), 6.43 (s, 1H), 3.14-3.21 (q, *J*=17.4Hz, 4H), 2.37 (s, 3H), 2.12 (s, 3H), 1.61 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 206.1, 145.9, 141.8, 141.4, 129.2, 129.2, 128.3, 125.6, 125.6, 125.2, 124.9, 121.1, 118.2, 108.8, 74.3, 55.8, 30.8, 29.5, 20.8. HR-MS (ESI): m/z calcd for $C_{19}H_{20}N_2NaO_4S_2$ ([M+Na]$^+$) 427.0756 found 427.0754.

2-Butyl-2-methyl-N-butyl-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3-(2H)-formamide(***3f***):White solid, Yield 50%, IR (KBr,$\bar{\nu}$/cm^{-1})3245 (N-H), 3068-2871 (C-H), 1702 (C=O), 1352, 1166 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.97-7.97 (m, 8H), 2.45 (s, 3H), 1.77 (s, 3H), 0.87-1.42 (m, 6H), 0.69-0.74 (t, *J*=7.2Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 144.8, 129.5, 129.5, 128.3,

128.3, 126.4, 125.5, 124.7, 123.4, 121.9, 120.5, 115.4, 110.8, 82.1, 43.8, 38.9, 30.0, 27.2, 22.4, 13.8. HR-MS (ESI): m/z calcd for $C_{20}H_{25}N_2O_3S_2$ ([M+H]$^+$) 405.1301 found 405.1306.

2-Isobutyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3-(2H)-formamide(***3g***):White solid, Yield 36%, m.p. 96-98℃. IR (KBr,$\bar{\nu}$/cm^{-1})3248 (N-H), 2976-2864 (C-H), 1697 (C=O), 1345, 1163 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.98-7.98 (m, 8H), 2.45 (s, 3H), 2.07-2.13 (q, *J*=5.1Hz, 1H), 1.83-1.89 (q, *J*=5.7Hz, 1H), 1.80 (s, 3H), 1.64-1.72 (m, 1H), 0.87-0.90 (d, *J*=6.6Hz, 3H), 0.70-0.72 (d, *J*=6.9Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 147.0, 144.9, 138.0, 136.1, 129.5, 129.5, 128.4, 128.4, 126.5, 125.6, 124.9, 123.5, 115.6, 82.0, 47.7, 27.3, 25.3, 24.3, 23.9, 21.7. HR-MS (ESI): m/z calcd for $C_{20}H_{25}N_2O_3S_2$ ([M+H]$^+$) 405.1301 found 405.1307.

2-Tert-butyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3benzothiazoline-3(2H)-formamide(***3h***): White solid, Yield 59%, m.p. 126-129℃. IR (KBr,$\bar{\nu}$/cm^{-1})3256 (N-H), 2972 (C-H), 1701 (C=O), 1349, 1167 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.03-7.97 (m, 8H), 2.45 (s, 3H), 1.79 (s, 3H), 0.96 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 147.9, 144.7, 140.9, 136.2, 133.1, 129.5, 129.5, 128.3, 128.3, 126.5, 125.6, 122.1, 117.3, 89.4, 43.7, 25.6, 25.6, 25.6, 23.0, 21.7. HR-MS (ESI): m/z calcd for $C_{20}H_{25}N_2O_3S_2$ ([M+H]$^+$) 405.1301 found 405.1305.

2-Phenylethyl-2-methyl-N-[(4-methylphenyl)sulfonyl]-1,3–benzothiazoline-3(2H)-formamide(***3i***):White solid, Yield 95%, m.p. 126-129℃. IR KBr,$\bar{\nu}$/cm^{-1})3333 (N-H), 3070-2892 (C-H), 1706 (C=O), 1364, 1118 (O=S=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 12.03 (s,1H), 6.72-7.92 (m, 13H), 2.70-2.82 (m, 1H), 2.48 (s, 1H), 2.42 (s, 3H), 1.99-2.14 (m, 2H), 1.68-1.72 (s, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) 149.0, 147.6, 144.2, 142.2, 141.3, 138.9, 137.8, 129.9, 128.5, 128.1, 127.2, 126.2, 125.5, 124.2, 123.5, 121.7, 118.5, 116.3, 108.9, 80.9, 46.1, 31.7, 29.0, 21.6. HR-MS (ESI): m/z calcd for $C_{24}H_{24}N_2NaO_3S_2$ ([M+Na]$^+$) 475.1120 found 475.1113.

2,2,-Diethyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide(***3j***):White solid, Yield 40%, m.p. 103-105℃. IR (KBr,$\bar{\nu}$/cm^{-1})3280 (N-H), 2959-2934 (C-H), 1715 (C=O), 1349, 1163 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.98-7.98 (m, 8H), 2.46 (s, 3H), 2.13-2.24 (m, 1H), 1.83-1.88 (m, 1H), 1.77 (s, 3H), 1.34-1.46 (m, 1H), 0.93-1.03 (m, 1H), 0.70-0.74 (t, *J*=7.2Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 146.9, 144.9, 138.0, 135.9, 129.5, 129.5, 128.4,128.4, 126.5, 125.6, 124.8, 123.5, 115.3, 81.9, 41.6, 27.3, 21.7, 18.4, 13.7. HR-MS (APCI): m/z calcd for $C_{19}H_{23}N_2O_3S_2$ ([M+H]$^+$) 391.1145 found 391.1140.

2,2,-Dipropyl-N-[(4-methylphenyl)sulfonyl]-1,3-benzothiazoline-3(2H)-formamide (***3k***):White solid, Yield 82%, m.p. 101-104℃. IR (KBr,$\bar{\nu}$/cm^{-1})3187 (N-H), 3066-2871 (C-H), 1700 (C=O), 1344, 1167 (O=S=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 6.94-7.96 (m, 8H), 2.44 (s, 3H), 2.15-2.25 (m, 2H), 1.67-1.77 (m, 2H), 1.35-1.47 (m, 2H), 0.81-0.98 (m, 2H), 0.66-0.71 (t, *J*=7.2Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 147.0, 144.9, 138.5, 135.7, 129.4, 129.4, 128.6, 128.6, 126.5, 125.4, 124.6, 123.1, 114.8, 85.7, 41.4, 41.4, 21.6, 17.9, 17.9, 13.7,13.7. HR-MS (ESI): m/z calcd for $C_{21}H_{27}N_2O_3S_2$ ([M+H]$^+$) 419.1458 found 419.1461.

N-[(4-methylphenyl)sulfonyl]-3h-screw[1,3-benzothiazoline-2,1′-cyclopentane]-3-formamide(***3l***):White solid, Yield 95%, m.p. 120-121℃. IR (KBr,$\bar{\nu}$/cm^{-1})3286 (N-H), 3066-2869 (C-H), 1602 (C=O), 1343, 1153 (O=S=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 6.99-7.99 (m, 8H), 2.53-2.63 (m, 2H), 2.46 (s, 3H), 1.65-2.02 (m, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) 146.8, 144.9, 138.5, 136.1, 129.6, 129.6, 128.4, 128.4, 126.5, 125.7, 124.9, 123.5, 115.5, 87.2, 38.1, 38.1, 23.7, 23.7, 21.7. HR-MS (ESI): m/z calcd for $C_{19}H_{21}N_2O_3S_2$ ([M+H]$^+$) 389.0988 found 389.0982.

N-[(4-methyl-phenyl)sulfonyl]-3h-screw[1,3-benzothiazoline-2,1′-cyclohexane]-3-formamide(***3m***):White solid, Yield 99%, m.p. 149-152℃. IR (KBr,$\bar{\nu}$/cm^{-1})3287 (N-H), 3071-2849 (C-H), 1692 (C=O), 1346, 1160 (O=S=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 11.95 (s,1H), 6.96-7.89 (m, 8H), 2.44 (s, 3H), 1.09-2.38 (m, 10H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) 149.0, 144.2, 140.0, 137.9, 129.9, 127.8, 126.9, 124.1, 123.3, 121.7, 118.4, 116.4, 109.1, 84.9, 35.1, 25.0, 24.7, 24.3, 24.0, 21.6. HR-MS (ESI): m/z calcd for $C_{20}H_{23}N_2O_3S_2$ ([M+H]$^+$) 403.1145 found 403.1149.

4 Conclusion

In conclusion, a series of novel sulfonylurea benzothiazoline derivatives were rationally designed and synthesized by solvent-free method and identified as potential herbicide safener for

sulfonylurea herbicides. All the synthesized compounds displayed safener activity to chlorsulfuron to some extents, and compound **3c** was even superior to the commercial safenerAD-67. The results suggested that compound **3c** might be a novel candidate for potential safener.

Supplementary Materials: Supplementary data associated with this article can be found in the online version.

Acknowledgments: This work was supported by the National Nature Science Foundation of China(31572042), the National Nature Science Foundation of Heilongjiang Province(ZD2017002), and the Research Science Foundation in Technology Innovation of Harbin(2015RAYXJ010). The authors are grateful to Prof. Jia-Zhong Li (Lanzhou University) for assistance with molecular docking analyses.

Author contributions: Y. Fu and F. Ye developed the concept of the work. J. Y. Wang carried out the synthetic work. Y. F. Chen developed the molecular docking and comparison. S. Gao conducted the bioactivity assay. D. Zhang contributed to the discussed and analyzed the results. Y. Fu wrote the paper.

Conflict of interest: The authors have no conflicts of interest to declare.

Reference

1. Berrade, L.; Aisa, B.; Ramirez, M. J.; Galiano, S.; Guccione, S.; Moltzau, L. R.; Levy, F. O.; Nicoletti, F.; Battaglia, G.; Molinaro, G.; Aldana, I.; Monge, A.; Perez-Silanes, S. Novel benzo [b] thiophene derivatives as new potential antidepressants with rapid onset of action. *J. Med. Chem.* **2011**, *54*, 3086-3090.
2. Venturelli, A.; Tondi, D.; Cancian, L.; Morandi, F.; Cannazza, G.; Segatore, B.; Prati, F.; Amicosante, G.; Shoichet, B. K.; Costi, M. P. Optimizing cell permeation of an antibiotic resistance inhibitor for improved efficacy. *J. Med. Chem.* **2007**, *50*, 5644-5654.
3. Mahran, M.; El-Nassry, S.; Allam, S. Synthesis of some new benzothiazole derivatives as potential antimicrobial and antiparasitic agents. *Pharmazie*. **2003**, *58*, 527-530.
4. Collier, P.; Ramsey, A.; Austin, P. Growth inhibitory and biocidal activity of some isothiazolone biocides. *J. Appl. Microbiology*. **1990**, *69*, 569-577.
5. Sacher, R.M.; Lee, L.F.; Schafer, D.E.; Howe, R.K. *Pesticide Chemistry: Human Welfare and Environment: Synthesis and structure-activity relationships. International Union of Pure and Applied Chemistry. Published by Elsevier Ltd.***1983**, 165-168.
6. Rendina, A.; Campopiano, O.; Marsilii, E.; Hixon, M.; Chi, H.; Taylor, W.; Hagenah, J. Overlap between herbicidal inhibitors of acetyl-coenzyme A carboxylase: Enhanced binding of cyclic triketones, a novel class of graminicide. *Pestic. Sci*. **1995**, *43*,368-371.
7. (a) Chen, J.L.; Tang, W.; Che, J.Y.; Chen, K.; Yan, G.; Gu, Y.C.; Shi, D.Q. Synthesis and biological activity evaluation of novel α-amino phosphonate derivatives containing a pyrimidinyl moiety as potential herbicidal agents. *J. Agric. Food Chem.* **2015**, *63*, 7219-7229. (b) Xie, Y.; Chi, H.W.; Guan, A.Y.; Liu, C.L.; Ma, H.J.; Cui, D.L. Design, synthesis, and herbicidal activity of novel substituted 3-(pyridin-2-yl) benzenesulfonamide derivatives. *J. Agric. Food Chem.* **2014**, *62*, 12491-12496.
8. Hatzios, K.K. Herbicide antidotes: development, chemistry, and mode of action. *AdvAgron.***1983**, *36*, 265-316.
9. Komives, T.; Hatzios, K.K. Chemistry and structure-activity relationships of herbicide safeners. *Z. Naturforsch. C: Biosci*. **1991**, *46*, 798-804.
10. Fu, Y.; Qu, L.H.; Zhang, S.S.; Ye, F.; Zhao, L.X.; Gao, S.; Xing, Z.Y. Simple and efficient synthesis of novel N-dichloroacetyl-3, 4-dihydro-2H-1, 4-benzoxazines. *Heterocycl. Commun.* **2012**, *18*, 143-146.
11. Fu, Y.; Kang, J.X.; Wang, Y.K.; Liu, J.; Zhao, L.X.; Gao, S.; Ye, F. Design, synthesis and biological activity of novel sulfonylurea oxazolidines. *Heterocycles*. **2016**, *92*, 740-750.
12. Ye, F.; Wu, S.L.; Zhao, L.X.; Qu, H.T.; Gao, S.; Fu, Y. Synthesis and safener activity of novel substituted 4-phenoxyacetyl-1, 4-benzoxazines. *Heterocycles*. **2015**, *91*, 1256-1268.
13. Liso, G.; Trapani, G.; Latrofa, A.; Marchini, P. Oxidative ring-expansion of benzothiazolines into 1, 4-benzothiazines *J. Heterocyclic. Chem.* **1981**, *18*, 279-282.
14. Prakash, G.S.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G.A. Efficient one-pot synthesis of fluorinated benzimidazolines, benzothiazolines, benzoxazolines, and dihydrobenzoxazinones using gallium(III) triflate as a catalyst. *Org. Lett.* **2007**, *9*, 179-182.
15. Zhong, W.; Chen, X.; Zhang, Y. Low-valent titanium induced simultaneous reduction of nitro group and SS bond in nitrodisulfides: A novel method for the synthesis of benzothiazoline, benzothiazoles and 2, 3-dihydro-1, 5-benzothiazepines. *Synth. Commun.***2000**, *30*, 4451-4460.

16. Chen, X.Y.; Zhong, W.H.; Zhang, Y.M. Simultaneous reduction of nitro group and S-S bond in nitrodisulfides by samarium diiodide: A new approach to benzothiazolines. *Chin. Chem. Lett*. **2000**, *11*, 387-388.
17. Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, 2003.
18. Kodomari, M.; Satoh, A.; Nakano, R. Aoyama, T. Solvent-Free Synthesis of benzothiazolines in the presence of alumina. *Synthetic Communications*. **2007**, *37* 3329-3335.