Discovery of Novel 3 -(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfonyl) methyl) benzo[d]isoxazole analogs as Promising Very long chain fatty acids Inhibitors

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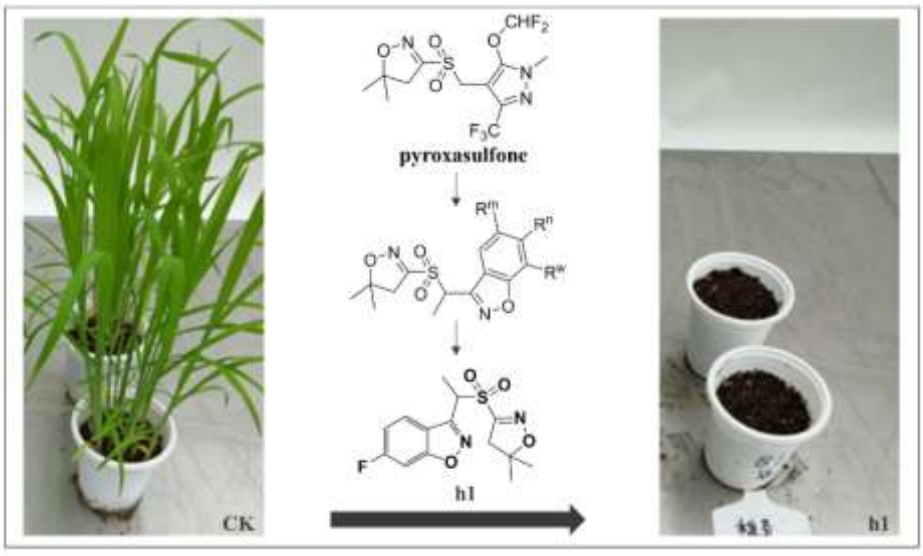

Abstract: Very long chain fatty acids (VLCFAs) are one of the most principal and promising targets for herbicides discovery. In order to explore and find novel VLCFAs inhibitors with higher herbicidal activity and improved crop safety, a variety of new 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)benzo[d]isoxazole derivatives were reasonably designed and synthesized. The results of greenhouse experiments indicated that several compounds exhibited good herbicidal activity against *Digitaria sanguinalis*, *Echinochloa crus-galli* and *Setaria faberii* at rates of 150 g ai /ha. Compounds **g4** and **h1** displayed promising herbicidal activity against *D. sanguinalis* and *E. crus-galli* at rates of 75 g ai/ha, which is better than commercial pyroxasulfone and S-metolachlor. Moreover, compound **h1** displayed higher activity against *E. crus-galli*, *D. sanguinalis* and *S. faberii* than pyroxasulfone and S-metolachlor even at a rate of 37.5 g ai/ha and 18.75 g ai/ha. Furthermore, both of the compounds **g4** and **h1** were much safer to these tested crops, especially to rice, wheat and rape, at the rate of 150 g ai/ha than pyroxasulfone. Therefore, **h1** may act as a new lead structure for novel herbicides discovery.

Keywords: Very long chain fatty acids, herbicidal activity, benzoisoxazole derivatives, heterocyclic compounds.

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1 INTRODUCTION

In global agriculture, weeds control can significantly avoid crop losses in many crop protection strategies [1]. Thus, herbicides are particularly important in weeds control and the discovery of new environmentally friendly and crop safety herbicides becomes imminent [2-4]. Very long chain fatty acids (VLCFAs) are important components for plants, invertebrates and vertebrates. In higher plants, VLCFAs are involved in sphingolipids and phospholipids as membrane components and signal molecules, which can regulate cell size, division and differentiation [5, 6]. They are also prerequisite for the production of suberin and cuticular waxes, which can protect plants from desiccation or external aggressions [7-9]. Therefore, inhibiting the synthesis of VLCFAs can effectively destroy the cuticular waxes of the plant and reduce the defense ability of the plant to achieve the purpose of weeds control [10].

The application of VLCFAs herbicides to extirpate weeds in crop fields can be traced back to the 1950s. With more than 60 years of developments, a lot of different types of VLCFAs inhibitors have been discovered [11]. They are mainly divided into Acetamides, Chloroacetamides, Oxyacetamides, Tetrazolinones and others [12-14]. As an early herbicide of chloroacetamide, acetochlor occupies a large market, and metolachlor is the same as acetochlor [15-19]. Subsequently, Syngenta developed the optically active isomer S- metolachlor [20-24]. In 2016, worldwide sales of S- metolachlor reached $590 million, making it the largest acetamide herbicide, surpassing acetochlor. At present, with the exposure of acetochlor and isopromethachlor potential hazards to human and the forbiddance of acetochlor in European Union, the herbicides containing the structural type of 3-sulfonylisooxazole, such as pyroxasulfone and fenoxasulfone were commercialized by Japanese companies in 2011 and 2014, respectively [25]. Pyroxasulfone was mainly used for pre-emergence grass and broadleaf weeds control at 125 ~ 250 g ai /ha in various crops such as corn, soybean, cotton, peanut, wheat, etc [26-28]. However, pyroxasulfone is less safe to rice. The extended exposure of some VLCFAs herbicides and improper use may lead to the rapid development of herbicide-resistant biotypes [29-31]. Therefore, it is still very essential to find novel environmentally friendly VLCFAs inhibitors with a unique structure.

Due to the broad spectrum and high efficiency of heterocyclic compounds, it has become the mainstream of pesticide discovery in recent years [32,33]. More than 90% of the world's pesticide patents are about heterocyclic compounds [32-34]. Benzo-heterocyclic compounds are an important branch of heterocyclic compounds, and they occupy an important position in the research and development of pesticides and medicines [35,36]. There are many benzo five-membered heterocyclic herbicides on the market, all of which have good herbicidal activity, such as fenoxaprop-p-ethyl and metamifop [37-39]. Benfuresate and ethofumesate are both benzofuran ring herbicides that can control annual or perennial grass weeds [40,41]. Benzoisoxazole, as an important biomedical molecular skeleton, has extremely high biological activity and pharmaceutical properties and is abundantly applied in drugs [42,43]. In agriculture, benzoisoxazole is mainly used in fungicides as a molecular active fragment, and less in herbicides [44]. Therefore, benzoisoxazole might be a promising pharmacophore moiety to integrate with a five-membered ring pharmacophore of pyroxasulfone. In this paper, we designed and synthesized a series of 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)benzo[d]isoxazole compounds by regarding pyroxasulfone as the lead compound

to obtain novel molecules with better herbicidal effects. S-metolachlor was used as a positive control. In this paper, the synthesis of these compounds, herbicidal activities against three weeds and their structure-activity relationships were reported in details.

2 RESULTS AND DISCUSSION

2.1 Chemistry.

Synthesis of the target compounds were revealed in Scheme **1** and **2**, respectivly. Synthetic route of target compound (g) and compound (h) are shown in scheme **1**, R^m, R^n, R^v and R^w represent different substitutions. Compound (a) can react with acetylchloride to give compound (b); compound (b) can react with hydroxylamine hydrochloride under a base condition (*i.e.*, sodium acetate, *etc*.) to give compound (c); compound (c) can undergo cyclization to give compound (d); compound (d) can undergo bromination reaction to give compound (e); compound (e) with 5,5-dimethyl-4,5-dihydroisoxazol-3-yl carbamimidothioate can undergo condensation reaction to give compound (f); compound (f) can further be oxidized to give objective compound (g); objective compound (g) can react with iodomethane to give objective compound (h). Synthetic route of target compound(s) is shown in Scheme **2**, R^c is diffirent substitutions. Compound (n1) with R^c-C(=O)-Cl can undergo nucleophilic substitution under a base condition (*i.e.*, K_2CO_3, TEA, Py, *etc.*) to give objective compound (s).

2.2 Herbicidal activities

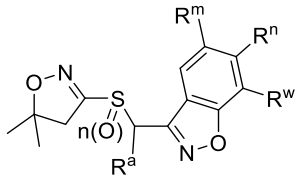
The pre-emergence herbicidal activities of these newly synthesized compounds **f1**, **f2**, **g1-g8**, **h1-h3**, **m1-m3**, **n1** and **s1-s15** were tested against *D. sanguinalis*, *E. crus-galli* and *S. faberii* at rates of 150 g ai/ha in the greenhouse experiments. The commercial herbicide pyroxasulfone and S-metolachlor were selected as positive controls (table **1** and **2**). The treated weeds didn't germinate, which demonstrated the typical features of herbicides that inhibit VLCFAs. Several compounds had good herbicidal activity to three weeds at the concentration of 150 g ai/ha. Such as, compounds **g3**, **g4**, **g7**, **s14**, **h1** and **h2** showed a 100% herbicidal activity against at least two weeds in *D. sanguinalis*, *E. crus-galli* and *S. faberii* at a concentration of 150 g ai/ha which is much better than pyroxasulfone and S-metolachlor. Therefore, compounds with a weed inhibition rate of 100% against at least two weeds were selected for further herbicidal testing.

Figure 1 Comparison of greenhouse pot experiment

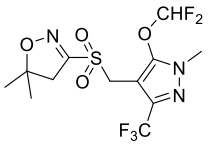
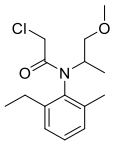
Compounds **g3**, **g4**, **g7**, **s14**, **h1** and **h2** were choosed to detect herbicidal activity before emergence against three species at lower concentrations. As shown in table **3**, compounds **g4** and **h1** exhibited promising herbicide activity against *D. sanguinalis* and *E. crus-galli* (**Figure 1**), with ≥80% inhibition at rates of 75 g ai/ha, which is better than pyroxasulfone and S-metolachlor. Moreover, compound **g4** and **h1** displayed excellent activity against *E. crus-galli*

even at rates of 37.5 g ai/ha, which was better than pyroxasulfone and S-metolachlor. The other compounds, **g3** and **h2**, had good activity against *E. crus-galli*, but displayed poor activity against *D. sanguinalis* and *S. faberii* at rates of 75 g ai/ha. It can be concluded from table **1**, **2** and **3** that the herbicide actidivity of compounds with substituents R^m –F or –H and R^n –H or –F was better than compounds with substituents on benzoisoxazole is -Br. At the same time, most of compounds **s** have poor herbicidal activity against three weeds except **s1**, **s4** and **s14**, which indicated that substituent R^c on N was not conducive to herbicidal activity except for ester group. Finally, compounds **g4** and **h1** were selected for further crop selectivity testing.

Table 1 Herbicidal activity of compounds under pre-emergence at 150 g ai ha^{-1}

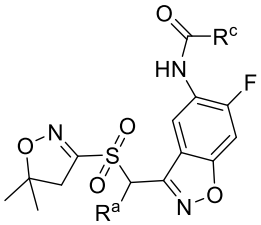


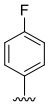
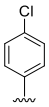
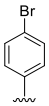
Compound	R^m	R^n	R^w	R^a	n	SF	EC	DS
f1	-H	-F	-H	-H	0	0	30	0
f2	-H	-H	-F	-H	0	0	20	0
g1	-H	-F	-H	-H	2	80	95	90
g2	-H	-F	-H	-H	1	20	70	70
g3	-H	-H	-F	-H	2	100	90	100
g4	-F	-H	-H	-H	2	100	100	100
g5	-H	-Br	-H	-H	2	90	100	80
g6	-H	-H	-Br	-H	2	40	0	0
g7	-H	-Cl	-H	-H	2	100	90	100
g8	-H	-Cl	-H	-H	1	90	100	90
h1	-H	-F	-H	$-CH_3$	2	100	100	100
h2	-F	-H	-H	$-CH_3$	2	100	100	90
h3	$-NH_2$	-F	-H	$-CH_3$	2	0	0	0
m1	$-NO_2$	-F	-H	-H	2	0	0	30
m2	-H	$-NO_2$	-Br	-H	2	40	0	0
m3	$-NO_2$	-Cl	-H	-H	2	0	0	0
n1	$-NH_2$	-F	-H	-H	2	0	0	0

pyroxasulfone		70	70	70
960 g/L S-Metolachlor		85	90	75

SF-*Setaria faberii*, EC-*Echinochloa crus-galli*, DS-*Digitaria sanguinalis*

Table 2 Herbicidal activity of compounds under pre-emergence at 150 g ai ha^{-1}



Compound	**R^c**	**R^a**	**SF**	**EC**	**DS**
s1	$-OC_2H_5$	-H	90	90	80
s2		-H	0	0	0
s3	$-C(CH_3)_3$	-H	25	30	45
s4	$-OCH_2CH{=}CH_2$	-H	100	80	90
s5		-H	60	25	45
s6		-H	0	0	0
s7		-H	0	0	0
s8		-H	20	30	15
s9		$-CH_3$	80	80	80
s10		-H	0	0	0
s11	$-CH_2CH_2Cl$	-H	20	30	15
s12	$-(CH_2)_4CH_3$	-H	25	15	30
s13	$-CH_2Br$	-H	40	50	25
s14	$-OCH(CH_3)_2$	-H	100	100	100

s15		-H	45	60	70
pyroxasulfone			70	70	70
960 g/L			85	90	75
S-Metolachlor					

SF-*Setaria faberii*, EC-*Echinochloa crus-galli*, DS-*Digitaria sanguinalis*

Table 3 Further herbicidal activity of six compounds under pre-emergence conditions at different concentrations

Compound	Dosage g ai /ha	SF	EC	DS
g3	18.75	15	20	15
	37.5	30	45	25
	75	60	85	65
g4	18.75	55	55	25
	37.5	70	80	60
	75	75	90	80
g7	18.75	40	35	55
	37.5	55	50	65
	75	75	70	80
h1	18.75	65	60	65
	37.5	75	80	75
	75	90	90	85
h2	18.75	55	40	20
	37.5	60	55	50
	75	65	85	75
s14	18.75	20	10	20
	37.5	65	45	45
	75	75	55	70
Pyroxasulfone	18.75	50	50	50
	37.5	60	65	65
	75	65	70	70
960 g/L	18.75	25	45	20
S-Metolachlor	37.5	55	70	35
	75	75	80	65

SF-*Setaria faberii*, EC-*Echinochloa crus-galli*, DS-*Digitaria sanguinalis*

2.3 Crop selectivity

Crop selectivity and safety is one of the main difficulties in herbicides discovery. The crop selectivity of **h1**, **g4** and pyroxasulfone were also tested at rates of 37.5, 75, 150, 300 and 600 g ai/ha, respectively (Table **4**). Among seven of the tested crops, soybean, cotton and maize displayed high tolerance to compounds **h1** by pre-emergence application even at rates of 600 g ai/ha (injury ≤10%). Compound **g4** displayed high safety to soybean, cotton and sunflower after pre-emergence application at a dosage of 600 g ai/ha. However, the commercial pyroxasulfone was safe only to soybean at concentrations of 600 g ai/ha and 300 g ai/ha, whereas compound **h1** was quite safe to these seven crops at a dosage of 300 g ai/ha (injury ≤10%). Moreover, the compound **h1** show

almost no harm to seven crops at a rate of 150 g ai/ha, whereas the commercial pyroxasulfone was found to show damage (injury >10%) to most of tested crops at the same rate. These results indicate that compound **h1** might develop as a promising and potential herbicidal for rice, wheat and others fields.

Table 4 Crop selectivity (injury rating 0–100) of compounds h1 and g4 (pre-emergence 37.5, 75, 150, 300 and 600 g ai/ha)

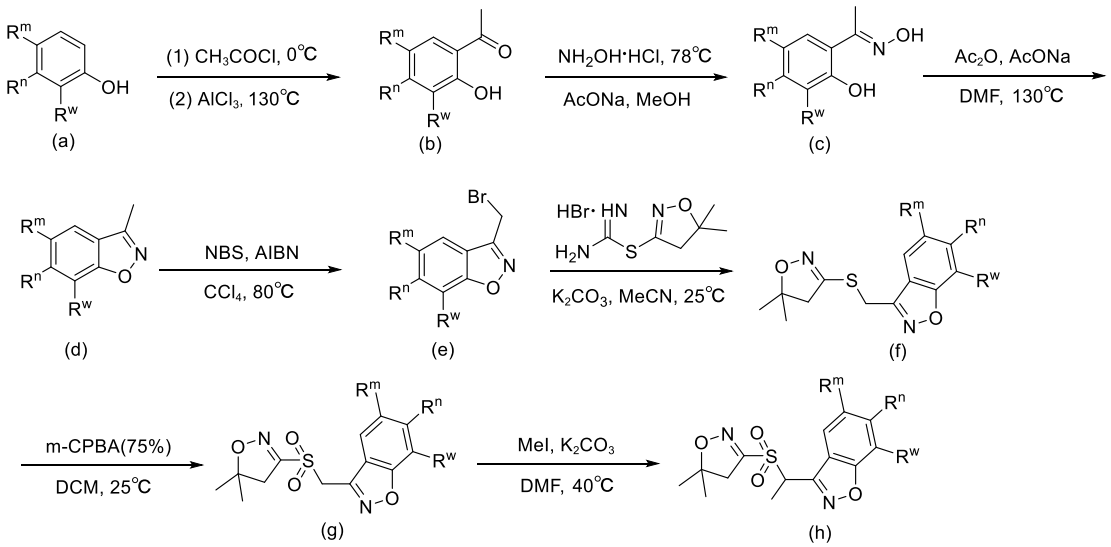
Compound	Dosage (g ai/ha)	maize	soybean	cotton	rape	wheat	rice	sunflower
	37.5	0	0	0	0	0	0	0
	75	0	0	0	0	0	0	0
h1	150	0	0	0	2	0	0	0
	300	0	0	0	5	10	10	10
	600	0	10	5	15	30	20	15
	37.5	0	0	0	0	0	0	0
	75	0	0	0	0	0	0	0
g4	150	0	0	0	2	10	10	0
	300	10	0	0	8	30	30	5
	600	30	0	3	15	50	50	10
	37.5	0	0	15	25	0	0	5
	75	0	0	25	45	20	20	15
Pyroxasulfone	150	10	0	40	50	30	40	25
	300	50	0	55	75	40	70	50
	600	80	0	85	90	50	90	60

3 EXPERIMENTALS

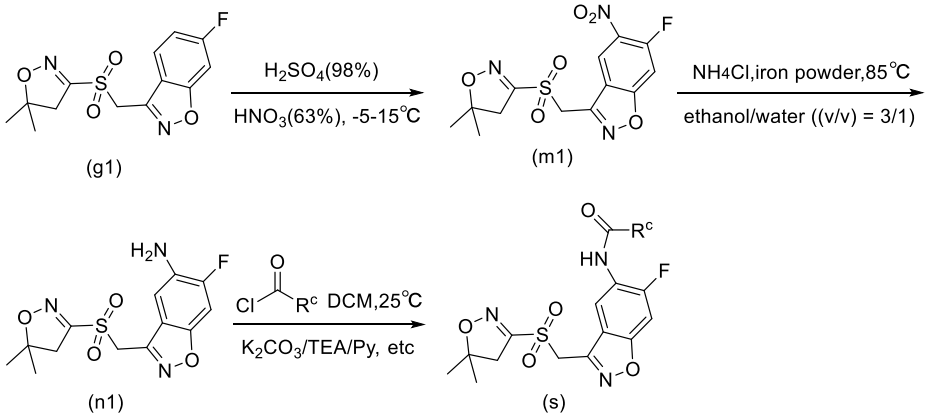
3.1 Materials and methods

All reagents have been purchased commercially and can be used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a VARIAN Mercury-Plus 400 or 600 spectrometer (varian Inc., Palo Alto, California, USA) and TMS was regarded as the internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on the VARIAN Mercury-Plus 400 or 600 spectrometer, and chemical shifts (δ) are given in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$. Multiplicities are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

3.2 Synthetic procedures



Scheme 1. Synthetic route of compound (g) and compound (h). R^m, R^n and R^w represent different substitutions.



Scheme 2. Synthetic route of compound (s). R^c is diffirent substitutions.

synthesis of 1-(4-fluoro-2-hydroxyphenyl) ethanone

In a three-neck flask, 3-Fluorophenol (31.36 g, 280 mmol) was added and stirred at 0 °C, then acetyl chloride (24.22 g, 308 mmol) was added slowly into the flask drop by drop. After dropwise addition, the mixture was stirred at 25 °C for 2 hours, then heated to 130 °C, and anhydrous aluminium trichloride (52.00 g, 389 mmol) was added slowly into the mixture. After addition, stirring the mixture for 2 hours at 130 °C, then water (500 mL) to was added the mixture. Ethyl acetate (300 mL) was used to extract the mixture for three times, and the combined organic layers were concentrated *in vacuo* to remove the solvent. Column chromatography (eluent: petroleum ether/EtOAc (v/v) = 10/1) was used to purify the residue to give a brown solid (30.20 g), yeild: 70%.

synthesis of 1-(4-fluoro-2-hydroxyphenyl) ethanone oxime

1-(4-Fluoro-2-hydroxyphenyl)ethanone (6.3 g, 41 mmol), hydroxylamine hydrochloride (5.70 g, 82 mmol) and anhydrous sodium acetate (7.73 g, 94 mmol) were added in anhydrous methanol (60 mL). The mixture was refluxed in an oil-bath at 70 °C for 4 hours, then the reaction was stopped. Water (200 mL) was added to the

mixture when it cooled to 25 °C. The resulting mixture was stirred for 0.5 h, and then filtered. The residue was washed with water (300 mL) for three times to give a gray solid (6.60 g), yield: 95%.

synthesis of 6-fluoro-3-methylbenzo [*d*]isoxazole

1-(4-Fluoro-2-hydroxyphenyl)ethanone oxime (6.60 g, 39 mmol), acetic anhydride (28.00 g, 273 mmol) and anhydrous sodium acetate (7.40 g, 90 mmol) were mixed in DMF (100 mL). An oil-bath was used to reflux the mixture for 12 hours at 136 °C, then the reaction was stopped. Water (200 mL) was added to the mixture when it cooled to 25 °C, then the mixture was stirred. Ethyl acetate (300 mL) was used to extract the mixture for three times. The combined organic layers were concentrated *in vacuo* to remove the solvent. Column chromatography (eluent: petroleum ether/EtOAc (v/v) = 10/1) was used to purify the residue to give a white solid (4.35 g), yield: 74%.

synthesis of 3-(bromomethyl)-6-fluorobenzo [*d*]isoxazole

6-Fluoro-3-methylbenzo[*d*]isoxazole (2.10 g, 13.9 mmol) and NBS (7.42 g, 41.7 mmol) was added in CCl_4 (30 mL) and was heated to 75 °C under nitrogen protection, then azodiisobutyronitrile (0.92 g, 5.6 mmol) was added to the mixture and stirred for 18 h. The reaction was stopped, and the mixture was filtered when it cooled to 25 °C. CCl_4 (30 mL) was used to wash the filtrate for three times, and the organic layer was concentrated to remove solvent in vacuo. Column chromatography (eluent: petroleum ether/EtOAc (v/v) = 10/1) was used to purify the residue to give a white solid (1.10 g), yield: 34.4%.

synthesis of 3-chloro-5,5-dimethyl-4,5 -dihydroisoxazole

To a 250 mL dried four-neck flask was added anhydrous methanol (100 mL), then potassium methoxide solid (21 g, 0.3 mol) was added slowly into the flask, and the mixture was stirred till the solid was dissolved. Hydroxyurea (15.2 g, 0.2 mol) was added to the solution and ethyl 3,3-dimethylacrylate (25.6 g, 0.2 mol) was added drop by drop. After stirring the mixture for 120 min at room temperature, it was filtered and the filtrate was concentrated by rotary evaporation in vacuo to remove the methanol. Water (100 mL) was added into the residue and the mixture was stirred until the residue was dissolved completely at room temperature, then the mixture was adjusted with concentrated HCl (2 mol/L) to pH 2. Dichloromethane (60 mL) was used to extract the mixture and the obtained organic layer was concentrated by rotary evaporation in vacuo to remove dichloromethane.

5,5-dimethylisoxazolidin-3-one as a white solid (18 g) was obtained, yield: 78.3%.

To a 250 mL dried four-neck flask was added dichloromethane (100 mL), phosphorus oxychloride (24.5 g, 0.16 mol) and *N*, *N*-dimethylformamide (3.7 g, 0.05 mol) under nitrogen protection. Stir the mixture for 30 minutes at room temperature. The mixture of 5, 5-dimethylisoxazolidine-3-ketone (12.1g, 0.1mol) and dichloromethane (30mL) was added to the reaction flask drop by drop. After the additon, stir the mixture until 2 hours later at room temperature and the mixture was concentrated by vacuum distillation to give 3-chloro-5,5-dimethyl-4,5-dihydroisoxazole as light yellow liquid (12.8 g), yield: 95.5%.

synthesis of 5,5-dimethyl-4,5-dihydroisoxazol-3-yl carbamimidothioate hydrobromide

Thiourea (6 g, 79 mmol) was dissolved in acetonitrile (65 mL) and hydrobromic acid (48%, 10 mL) was added to the solution dropwise. Then, stirr the mixture for 60 min at room

temperature.3-chloro-5,5-dimethyl-4,5-dihydrois oxazole (12.6 g, 95 mmol) was added drop by drop to the mixture, which was stirred overnight at 40 °C. The solid was obtained by evaporating

the solvent in the mixture under reduced pressure and recrystallizing from ethyl acetate to get a white crystaline (19.2 g), yield: 96.0%.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)thio)methyl)-6-fluorobenzo[*d*]isoxazole (compound f1)

3-(Bromomethyl)-6-fluorobenzo[*d*]isoxazole (1.2 g, 5.2 mmol) and 5,5-dimethyl-4,5-dihydroisoxazol-3-yl carbamimidothioate hydrobromide (1.59 g, 6.3 mmol) was dissolved in acetonitrile (30 mL). After stirring the mixture for 20 minutes, potassium carbonate (2.88g, 21.0mmol) was added to the mixture and stirred at 25 ℃ for 8 hours before stopping. To the reaction mixture was added water (30 mL) with stirring. Ethyl acetate (50 mL) was used to extract the mixture for three times. To remove the solvent, the organic layers were concentrated in vacuo. Column chromatography (eluent: petroleum ether/EtOAc (v/v) = 15/1) was used to purify the residue to obtain brown liquid (1.04 g), yield: 71.2%. The compounds of **f2** was obtained according to this method.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazole (compound g1) and 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfinyl)methyl) -6-fluorobenzo[*d*]isoxazole (g2)

3-(((5,5-Dimethyl-4,5-dihydroisoxazol-3-yl)thio)methyl)-6-fluorobenzo[d]isoxazole (0.32 g, 1.1 mmol) and metachloroperbenzoic acid (0.46 g, 2.3 mmol) were dissolved in dichloromethane (10 mL). The mixture was stirred for 4 hours before stopping the reaction at 25 °C. Water (50 mL), saturated aqueous sodium sulphite (50 mL), saturated brine (50 mL), saturated aqueous sodium bicarbonate (50 mL) and saturated brine (50 mL) were used to wash the mixture in turn. Ethyl acetate (50 mL) was used to extract the solution for three times. Rotary evaporation and column chromatography (eluent: petroleum ether/EtOAc (v/v) = 15/1) were used to get a white solid product (0.26 g): 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazole (**g1**), yield: 73.3%; and a white solid product (50mg): 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfinyl)methyl)-6-fluorobenzo[d]isoxazole (**g2**), yield: 14.5%. The compounds of **g3-g8** was obtained according to this method.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluoro-5-nitrobenzo[*d*]isoxazoe (commpound m1)

To a three-neck flask equipped with thermometer was dissolved 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfonyl) methyl)-6-fluorobenzo[d]isoxazole (0.84 g, 2.7 mmol) in concentrated sulfuric acid (98%, 10 mL). Stir the mixture at -5 ° C, then slowly add concentrated nitric acid (63%, 0.42 g, 4.0 mmol) while the temperature of the mixture was maintained below 0 °C. After addition, the mixture was stirred below 15 °C for 4 h, then the reaction was stopped. To the reaction mixture was added ice-water (30 mL) with stirring, then the mixture was filtered. Ice-water (20 mL) was used to wash the solid for three times, then column chromatography (eluent: petroleum ether/EtOAc (v/v) = 4/1) was also used to purify the residue to give a brown solid (0.3 g), yield: 31%. The compounds of **m2** and **m3** was obtained according to this method.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol -5-amine (compound n1)

3-(((5,5-Dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluoro-5-nitrobenzo[*d*]isoxazole (0.26 g, 0.73 mmol), NH_4Cl (0.078 g, 1.5 mmol) and iron powder (0.16 g, 2.9 mmol) were dissolved in a mixture of ethanol and water ((v/v) = 3/1, 13 mL). Before stopping the reaction, the mixture was refluxed for 8 hours at 85 °C. Celite pad and ethanol (30 mL) were used to filter and wash the mixture respectively. Rotary evaporation and column chromatography

(eluent: petroleum ether/EtOAc (v/v) = 4/1) were used to dry and purify the residue to obtain a light yellow solid (0.088 g), yield: 36.8%.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)thio)methyl)-7-fluorobenzo[*d*]isoxazole (compound s1)

3-(((5,5-Dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-amine (100 mg, 0.31 mmol) and pyridine (48 mg, 0.62 mmol) were added in dichloromethane (10 mL). Ethyl carbonochloridate (33.6 mg, 0.31 mmol) was then put in the mixture and stirred at 25 °C for 2 h. Water (20 mL) was added to the mixtureand then extracted with ethyl acetate (30 mL) for three times. Rotary evaporation and column chromatography (eluent: petroleum ether/EtOAc (v/v) = 6/1) were used to remove the solvent and purify the residue to give a light yellow solid (68 mg), yield:55%. The compounds of **s2 - s15** was obtained according to this method.

3-(1-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)ethyl)-6-fluorobenzo[*d*]isoxazole (compound h1)

3-(((5,5-Dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazole (7.00 g, 22.4 mmol) and K_2CO_3 (6.20 g, 44.8 mmol) were dissolved in N,N-dimethylformamide (100 mL). Iodomethane (3.82 g, 26.9 mmol) was added to the reaction mixture at 25 °C and then stirr the mixture at 40 °C for 8 hours. Saturated brine (300 mL) and ethyl acetate (150 mL) were used to wash and extract the mixture for three times. The solvent in organic layer was removed by rotary evaporation. Column chromatography (eluent: petroleum ether/EtOAc (v/v) = 8/1) was used to purify the residue to obtain a white solid: 3-(2-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)propan-2-yl)-6-fluorobenzo[d]isoxazole (1.3 g), yield: 17.1%. The compounds of **h2** was obtained according to this method.

3-(1-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)ethyl)-6-fluorobenzo[*d*]isoxazol-5-amine (compound h3)

3-(((5,5-Dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazol-5-amine (100 mg, 0.31 mmol) and K_2CO_3 (85.6 mg, 0.62 mmol) were put in DMF (10 mL). Iodomethane (52 mg, 0.37 mmol) was added in the mixture when it was stirred at 25 °C. Then, stirr the mixture at 40 °C for 4 h befor stopping the reaction. To the mixture was added water (20 mL), and ethyl acetate (30 mL) was used to extract the resulting mixture for 3 times. The solvent in combined organic layers was romoved by concentration in vacuo. Column chromatography (eluent: petroleum ether/EtOAc (v/v) = 8/1) was used to purify the residue to give a white solid (80 mg), yield: 77%.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)thio)methyl)-6- fluorobenzo[*d*]isoxazole (f1)

Brown liquid (71.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.7, 5.1 Hz, 1H), 7.26 (dd, J = 7.5, 2.5 Hz, 1H), 7.10 (td, J = 8.9, 2.0 Hz, 1H), 4.61 (s, 2H), 2.83 (s, 2H), 1.43 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.25 (s), 164.16 (d, *J* = 13.7 Hz), 163.58 (s), 155.08 (s), 153.61 (s), 123.09 (d, *J* = 11.1 Hz), 117.16 (s), 113.17 (s), 113.00 (s), 97.44 (s), 97.26 (s), 85.49 (s), 49.88 (s), 26.84 (s), 24.54 (s). MS (ESI): $C_{13}H_{13}FN_2O_2S$ m/z 280.1 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)thio)methyl) -7-fluorobenzo[d]isoxazole (f2)

Brown liquid (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 1H), 7.32 – 7.27 (m, 2H), 4.63 (s, 2H), 2.84 (s, 2H), 1.43 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.42 (s), 153.47 (s), 151.35 (d, *J* = 13.2 Hz), 147.79 (s), 145.28 (s), 124.80 (d, *J* = 5.0 Hz), 117.44 (d, *J* = 4.7 Hz), 115.85 (d, *J* = 15.6 Hz), 85.49 (s), 49.85 (s), 26.80 (s), 24.57 (s). MS (ESI): $C_{13}H_{13}FN_2O_2S$ m/z 280.1 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl) -6-fluorobenzo[*d*]isoxazole (g1)

White solid (73.3%). Melting points: 127.1～127.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.8, 5.0 Hz, 1H), 7.32 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.18 (td, *J* = 8.9, 2.0 Hz, 1H), 4.99 (s, 2H), 2.99 (s, 2H), 1.48 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.90 (s), 164.63 (d, *J* = 13.8 Hz), 163.38 (s), 157.34 (s), 147.76 (s), 123.51 (d, *J* = 11.2 Hz), 117.31 (s), 114.13 (d, *J* = 25.4 Hz), 97.53 (d, *J* = 29.1 Hz), 90.95 (s), 51.04 (s), 44.22 (s), 27.03 (s). MS (ESI): $C_{13}H_{13}FN_2O_4S$ m/z 313.0 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfinyl)methyl) -6-fluorobenzo[*d*]isoxazole (g2)

White solid (14.5%). Melting points: 133.5～134.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.7, 5.1 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.16 (td, *J* = 8.9, 1.9 Hz, 1H), 4.64 (dd, *J* = 42.6, 13.6 Hz, 2H), 2.98 (dd, *J* = 79.2, 17.0 Hz, 2H), 1.45 (d, *J* = 12.8 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.34 (s), 164.78 (d, *J* = 13.6 Hz), 163.66 (s), 156.63 (s), 151.35 (s), 130.90 (s), 123.94 (d, *J* = 11.0 Hz), 120.13 (s), 97.62 (d, *J* = 26.3 Hz), 62.07 (s), 45.02 (s), 30.47 (s), 27.04 (d, *J* = 14.9 Hz). MS (ESI): $C_{13}H_{13}FN_2O_3S$ m/z 297.0 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl) -7-fluorobenzo[*d*]isoxazole (g3)

White solid (42.3%). Melting points:125.6～126.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 5.9 Hz, 1H), 7.35 (d, J = 6.6 Hz, 2H), 5.01 (s, 2H), 3.00 (s, 2H), 1.49 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.49 (s), 153.58 (s), 147.53 (s), 145.85 (s), 125.03 (d, *J* = 4.9 Hz), 117.75 (d, *J* = 4.6 Hz), 116.09 (d, *J* = 15.6 Hz), 85.64 (s), 50.08 (s), 32.32 (s), 27.15 (s), 24.88 (s). MS (ESI): $C_{13}H_{13}FN_2O_4S$ m/z 313.0 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl) -5-fluorobenzo[d]isoxazole (g4)

White solid (50.3%). Melting points:122.5～123.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 9.9, 8.3, 3.1 Hz, 2H), 7.36 (td, *J* = 8.7, 2.2 Hz, 1H), 5.00 (s, 2H), 3.01 (s, 2H), 1.48 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.82 (s), 160.59 (s), 158.40 (s), 157.39 (s), 148.09 (d, *J* = 4.7 Hz), 121.46 (d, *J* = 11.0 Hz), 119.73 (d, *J* = 27.6 Hz) , 111.26 (d, *J* = 9.4 Hz), 107.21 (d, *J* = 25.1 Hz), 90.98 (s), 51.09 (s), 44.19 (s), 27.00 (s). MS (ESI): $C_{13}H_{13}FN_2O_4S$ m/z 313.1 $[M+H]^+$.

6-bromo-3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfonyl)methyl)benzo[*d*]isoxazole (g5)

White solid (53.6%). Melting points: 126.0～127.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.83 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 4.99 (s, 2H), 2.99 (s, 2H), 1.47 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.82 (s), 159.46 (s), 146.80 (s), 127.37 (s), 124.65 (s), 124.45 (s), 119.29 (s), 111.14 (s), 88.23 (s), 48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{13}H_{13}BrN_2O_4S$ m/z 372.9 $[M+H]^+$.

7-bromo-3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfonyl)methyl)benzo[*d*]isoxazole (g6)

White solid (67.9%). Melting points: 122.0～123.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.84 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 5.01 (s, 2H), 3.01 (s, 2H), 1.48 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.38 (s), 157.33 (s), 148.80 (s), 133.67 (s), 126.02 (s), 121.91 (s), 121.41 (s), 102.85 (s), 91.12 (s), 51.19 (s), 44.23 (s), 27.07 (s). MS (ESI): $C_{13}H_{13}BrN_2O_4S$ m/z 372.9 $[M+H]^+$.

6-chloro-3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfonyl)methyl)benzo[*d*]isoxazole (g7)

White solid (55.0%). Melting points: 124.0～125.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.82 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 1.2 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.5 Hz, 1H), 5.00 (s, 2H), 2.99 (s, 2H), 1.47 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.14 (s), 157.30 (s), 147.83 (s), 137.61 (s), 125.82 (s), 122.97 (s), 119.49 (s), 110.59 (s), 91.03 (s), 51.00 (s), 44.18 (s), 27.05 (s). MS (ESI): $C_{13}H_{13}ClN_2O_4S$ m/z 328.8 $[M+H]^+$.

6-chloro-3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfinyl)methyl)benzo[*d*]isoxazole (g8)

White solid (37.9%). Melting points: 130.2～131.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ ppm

7.75 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.37 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.65 (dd, *J* = 39.1, 13.6 Hz, 2H), 2.97 (dd, *J* = 80.2, 17.1 Hz, 2H), 1.44 (d, *J* = 12.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.92 (s), 161.59 (s), 149.71 (s), 137.56 (s), 125.59 (s), 122.78 (s), 119.95 (s), 110.60 (s), 88.37 (s), 48.78 (s), 43.00 (s), 27.20 (s), 26.98 (s). MS (ESI): $C_{13}H_{13}ClN_2O_3S$ m/z 312.8 $[M+H]^+$.

3-(1-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl) ethyl)-6-fluorobenzo[*d*]isoxazole (h1)

White solid (17.1%). Melting points: 134.7～135.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ ppm 7.92 (dd, *J* = 8.8, 5.1 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.16 (td, *J* = 8.9, 2.0 Hz, 1H), 5.08 (q, *J* = 7.2 Hz, 1H), 2.85 (dd, *J* = 53.8, 17.2 Hz, 2H), 2.04 (d, *J* = 7.3 Hz, 3H), 1.42 (d, *J* = 27.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.75 (s), 164.72 (d, *J* = 13.7 Hz), 163.24 (s), 156.45 (s), 152.61 (s), 124.12 (d, *J* = 11.1 Hz), 116.59 (s), 114.11 (s), 113.85 (s), 97.49 (d, *J* = 26.9 Hz), 90.73 (s), 57.80 (s), 45.15 (s), 26.99 (d, *J* = 8.9 Hz), 12.39 (s). MS (ESI): $C_{14}H_{15}FN_2O_4S$ m/z 327.1 $[M+H]^+$.

3-(1-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl) ethyl)-5-fluorobenzo[*d*]isoxazole (h2)

White solid (65.0%). Melting points: 129.1～129.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.59 (dd, *J* = 14.3, 5.4 Hz, 2H), 7.36 (t, *J* = 8.6 Hz, 1H), 5.08 (q, *J* = 7.0 Hz, 1H), 2.86 (dd, *J* = 50.7, 17.1 Hz, 2H), 2.04 (d, *J* = 7.1 Hz, 3H), 1.43 (d, *J* = 26.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.69 (d, *J* = 7.2 Hz), 158.23 (s), 156.46 (s), 152.87 (d, *J* = 4.7 Hz), 120.69 (d, *J* = 11.0 Hz), 119.67 (d, *J* = 27.4 Hz), 111.24 (d, *J* = 9.3 Hz), 107.82 (d, *J* = 27.4 Hz), 90.70 (s), 57.84 (s), 45.11 (s), 27.00 (d, *J* = 9.0 Hz), 12.27 (s). MS (ESI): $C_{14}H_{15}FN_2O_4S$ m/z 327.1 $[M+H]^+$.

3-(1-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)ethyl)-6-fluorobenzo[*d*]isoxazol-5-amine (h3)

White solid (77%). Melting points:142.0～143.0 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ ppm 7.65 (d, *J* = 10.6 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 5.53 (q, *J* = 7.1 Hz, 1H), 5.38 (s, 2H), 2.98 (q, *J* = 17.5 Hz, 2H), 1.83 (d, *J* = 7.1 Hz, 3H), 1.36 (d, *J* = 10.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.75 (s), 165.71 (d, *J* = 13.7 Hz), 163.28 (s), 156.75 (s), 152.91 (s), 124.72 (d, *J* = 11.1 Hz), 116.79 (s), 114.41 (s), 113.89 (s), 97.59 (d, *J* = 27.1 Hz), 90.79 (s), 57.90 (s), 45.15 (s), 26.99 (d, *J* = 8.9 Hz), 12.49 (s). MS (ESI): $C_{14}H_{16}FN_3O_4S$ m/z 342.1 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluoro-5-nitrobenzo[d]isoxazole (m1)

Brown solid (31%). Melting points:141.1 ～141.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 6.9 Hz, 1H), 7.55 (d, J = 9.5 Hz, 1H), 5.07 (s, 2H), 3.08 (s, 2H), 1.51 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.35 (d, *J* = 13.0 Hz), 157.59 (s), 155.89 (s), 154.33 (s), 147.06 (s), 133.86 (d, *J* = 15.3 Hz), 116.95 (s), 105.53 (d, *J* = 5.3 Hz), 97.47 (d, *J* = 24.8 Hz), 91.02(s), 51.34 (s), 44.46 (s), 27.06 (s). MS (ESI): $C_{13}H_{12}FN_3O_6S$ m/z 358.1 $[M+H]^+$.

7-bromo-3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-nitrobenzo[*d*]isoxazole (m2)

Yellow solid (43.6%). Melting points: 130.0～131.2 °C.^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.11 (d, *J* = 1.8 Hz, 1H), 8.79 (d, *J* = 1.8 Hz, 1H), 5.78 (s, 2H), 3.26 (s, 2H), 1.44 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.11 (s), 151.48 (s), 147.14 (s), 127.40 (s), 122.03 (s), 119.73 (s), 106.42 (s), 88.23 (s), 48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{13}H_{12}BrN_3O_6S$ m/z 419.9 $[M+H]^+$.

6-chloro-3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-5-nitrobenzo[*d*]isoxazole (m3)

Yellow solid (57.9%). Melting points: 135.9～137.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.50 (s, 1H), 7.85 (s, 1H), 5.06 (s, 2H), 3.06 (s, 2H), 1.51 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.10 (s), 159.45 (s), 138.42 (s), 135.72 (s), 121.15 (s), 119.17 (s), 110.38 (s), 88.23 (s),

48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{13}H_{12}ClN_3O_6S$ m/z 373.9 $[M+H]^+$.

3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-amine (n1)

Light yellow solid (36.8%). Melting points:135.2～135.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 10.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 4.91 (s, 2H), 3.92 (s, 2H), 2.96 (s, 2H), 1.46 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.05 (d, *J* = 13.0 Hz), 157.29 (s), 155.69 (s), 154.03 (s), 146.96 (s), 133.80 (d, *J* = 15.3 Hz), 116.92 (s), 105.13 (d, *J* = 5.3 Hz), 97.37 (d, *J* = 24.8 Hz), 91.01 (s), 51.32 (s), 44.44 (s), 27.04 (s). MS (ESI): $C_{13}H_{14}FN_3O_4S$ m/z 328.2 $[M+H]^+$.

ethyl (3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazol-5-yl)carbamate (s1)

Light yellow solid (55%). Melting points: 145.1～145.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.38 (d, *J* = 9.9 Hz, 1H), 6.90 (s, 1H), 4.99 (s, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.02 (s, 2H), 1.49 (s, 6H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.07 (d, *J* = 13.0 Hz), 157.39 (s), 155.59 (s), 154.18 (s), 153.08 (s), 146.86 (s), 133.83 (d, *J* = 15.3 Hz), 116.96 (s), 105.16 (d, *J* = 5.3 Hz), 97.37 (d, *J* = 24.8 Hz), 91.01 (s), 61.04 (s) 51.32 (s), 44.44 (s), 27.04 (s), 22.04 (s). MS (ESI): $C_{16}H_{18}FN_3O_6S$ m/z 400.2 $[M+H]^+$.

N-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazol-5-yl)-3-(trifluoromethyl)benzamide (s2)

Light yellow solid (65%). Melting points: 160.7～170.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 7.0 Hz, 1H), 8.19 (s, 1H), 8.09 (d, *J* = 7.1 Hz, 2H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 9.9 Hz, 1H), 5.04 (s, 2H), 3.06 (s, 2H), 1.51 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.61 (s), 159.45 (s), 158.93 (s), 154.25 (s), 134.87 (s), 134.87 (s), 144.37 – 128.69 (m), 131.72 (dd, *J* = 434.3, 354.0 Hz), 144.37 – 127.22 (m), 144.37 – 123.22 (m), 122.57 (s), 117.71 (d, *J* = 19.1 Hz), 98.08 (s), 88.23 (s), 48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{21}H_{17}F_4N_3O_5S$ m/z 500.2 $[M+H]^+$.

N-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazol-5-yl)pivalamide (s3)

Light yellow solid (55.8%). Melting points: 138.9～140.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 7.3 Hz, 1H), 7.69 (s, 1H), 7.39 (d, *J* = 9.9 Hz, 1H), 4.98 (s, 2H), 3.04 (s, 2H), 1.50 (s, 6H), 1.35 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.75(d, *J* = 13.7 Hz), 157.42 (s), 156.14 (s), 154.48 (s), 148.11 (s), 125.03 (d, *J* = 12.0 Hz), 117.16 (s), 113.67 (s),97.18 (d, *J* = 25.3Hz), 90.84 (s), 50.63 (s), 44.15 (s), 40.06(s),27.53 (s) ,27.15 (s). MS (ESI): $C_{18}H_{22}FN_3O_5S$ m/z 412.2 $[M+H]^+$.

allyl(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)carbamate (s4)

Light yellow solid (65.2%). Melting points: 137.1～138.6 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.60 (s, 1H), 7.38 (d, J = 9.9 Hz, 1H), 6.97 (s, 1H), 5.99 (ddd, J = 16.3, 11.0, 5.8 Hz, 1H), 5.40 (dd, J = 17.2, 1.3 Hz, 1H), 5.30 (dd, J = 10.4, 1.0 Hz, 1H), 4.99 (s, 2H), 4.72 (d, J = 5.8 Hz, 2H), 3.02 (s, 2H), 1.49 (s, 6H). ^{13}C NMR (151 MHz, CDCl3) δ 159.49 (d, J = 13.5 Hz), 155.15 (d, J = 678.2 Hz), 148.02 (s), 131.95 (s), 127.10 (s), 125.05 (d, J = 12.8 Hz), 121.53 (dd, J = 1060.2, 136.3 Hz), 97.40 (s), 97.23 (s), 90.84 (s), 66.50 (s), 50.75 (s), 44.16 (s), 27.08 (s). MS (ESI): $C_{17}H_{18}FN_3O_6S$ m/z 412.2 $[M+H]^+$.

***N*-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)-4-fluorobenzamide (s5)**

Light yellow solid (53.6%). Melting points: 160.9 ～ 171.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.23 (d, *J* = 7.2 Hz, 1H), 8.10 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.98 (d, *J* = 9.6 Hz, 1H), 7.40 (t, *J* = 8.7 Hz, 2H), 5.61 (s, 2H), 3.22 (s, 2H), 1.43 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.90 (d, *J* = 204.6 Hz),

181.00 – 159.37 (m), 181.00 – 143.22 (m), 131.45 (d, *J* = 33.8 Hz), 122.57 (s), 117.71 (d, *J* = 19.1 Hz), 116.12 (s), 98.08 (s), 88.23 (s), 48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{20}H_{17}F_2N_3O_5S$ m/z 450.1 $[M+H]^+$.

4-chloro-N-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazol-5-yl)benzamide (s6)

Light yellow solid (44.6%). Melting points: 165.0～166.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 7.0 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 24.8, 8.3 Hz, 4H), 5.03 (s, 2H), 3.05 (s, 2H), 1.51 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.72 (s), 159.45 (s), 158.93 (s), 154.25 (s), 138.09 (s), 133.21 (s), 129.09 (s), 128.61 (s), 122.57 (s), 117.71 (d, *J* = 19.1 Hz), 98.08 (s), 88.23 (s), 48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{20}H_{17}ClFN_3O_5S$ m/z 466.1 $[M+H]^+$.

4-bromo-*N*-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)benzamide (s7)

Light yellow solid (75.2%). Melting points: 158.1～159.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.97 (d, *J* = 7.3 Hz, 1H), 8.05 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 12.9 Hz, 1H), 5.03 (s, 2H), 3.05 (s, 2H), 1.50 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.72 (s), 159.45 (s), 158.93 (s), 154.25 (s), 134.82 (s), 131.60 (s), 130.42 (s), 127.93 (s), 122.57 (s), 117.71 (d, *J* = 19.1 Hz), 98.08 (s), 88.23 (s), 48.66 (s), 38.26 (s), 27.71 (s). MS (ESI): $C_{20}H_{17}BrFN_3O_5S$ m/z 510.0 $[M+H]^+$.

***N*-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)thiophene-2-carboxamide (s8)**

Light yellow solid (60.2%). Melting points: 149.0 ～ 150.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) :δ ppm 10.42 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 3.6 Hz, 1H), 7.98 (d, *J* = 9.6 Hz, 1H), 7.90 (d, *J* = 4.9 Hz, 1H), 7.29 – 7.23 (m, 1H), 5.61 (s, 2H), 3.22 (s, 2H), 1.43 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.44(d, *J* = 14.6 Hz), 160.85 (s), 158.28 (s), 149.53(s), 139.07 (s), 132.76 (s), 130.26 (s), 128.74 (s), 123.95 (d, *J* = 15.5Hz), 121.33 (s), 117.60 (s), 98.63 (s), 98.45 (s), 91.43 (s), 49.86 (s), 44.49 (s),27.02(s). MS (ESI): $C_{18}H_{16}FN_3O_5S_2$ m/z 438.0 $[M+H]^+$.

***N*-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)cyclopropanecarboxamide (s9)**

Light yellow solid (65.8%). Melting points: 148.0～148.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm (d, *J* = 7.1 Hz, 1H), 7.74 (s, 1H), 7.38 (d, *J* = 9.9 Hz, 1H), 5.07 (q, *J* = 7.3 Hz, 1H), 2.89 (q, *J* = 17.1 Hz, 2H), 2.04 (d, *J* = 7.2 Hz, 3H), 1.45 (d, *J* = 13.8 Hz, 6H), 1.16 – 1.14 (m, 1H), 0.95 – 0.84 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.41 (s), 162.59 (s), 159.27 (d, *J* = 18.4 Hz), 120.86 (s), 117.96 (d, *J* = 11.2 Hz), 98.66 (s), 88.23 (s), 62.05 (s), 39.15 (s), 27.71 (s), 16.24 (s), 14.93 (s), 12.50 (s). MS (ESI): $C_{18}H_{20}FN_3O_5S$ m/z 396.1 $[M+H]^+$.

***N*-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)adamantane-1-carboxamide (s10)**

Light yellow solid (48.8%). Melting points: 172.0 ～ 174.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.25 (s, 1H), 8.08 (d, *J* = 7.1 Hz, 1H), 7.88 (d, *J* = 9.4 Hz, 1H), 5.57 (s, 2H), 3.21 (s, 2H), 2.03 (s, 3H), 1.94 (s, 6H), 1.72 (s, 6H), 1.43 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.96 (s), 161.19 (s), 159.84 (s), 158.29 (s), 158.16 (s), 149.41 (s), 124.86 (d, J=15.6Hz), 121.06 (s),117.41 (s), 98.16 (d, J=13.2Hz), 91.41 (s), 49.82 (s), 44.50 (s), 41.09 (s), 38.95 (s), 36.50 (s), 28.11 (s), 27.02 (s). MS (ESI): $C_{24}H_{28}FN_3O_5S$ m/z 490.1 $[M+H]^+$.

3-chloro-*N*-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)propanamide (s11)

Light yellow solid (56.3%). Melting points: 140.1 ～ 140.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.08 (s, 1H), 8.49 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 10.0 Hz, 1H), 5.59 (s, 2H), 3.91 (t, *J* = 6.0 Hz, 2H), 3.21 (s, 2H), 2.96 (t, *J* =

6.0 Hz, 2H), 1.43 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.17(s), 160.30 (d, *J* = 13.7 Hz), 158.31 (s), 157.83 (s), 156.15 (s), 149.51 (s), 124.57 (d, *J* = 14.4Hz), 117.81 (s), 117.43 (s)98.29(d, *J* = 27.2Hz), 91.40 (s), 49.89 (s), 44.49 (s), 41.11 (s), 38.99 (s), 27.01 (s). MS (ESI): $C_{16}H_{17}ClFN_3O_5S$ m/z 418.1 $[M+H]^+$.

_N_-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl) sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)heptanamide (s12)

Light yellow solid (45.9%). Melting points: 135.0 ～ 136.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) :δ ppm 9.84 (s, 1H), 8.42 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 10.0 Hz, 1H), 5.57 (s, 2H), 3.21 (s, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.67 – 1.56 (m, 2H), 1.42 (s, 6H), 1.30 (m, 6H), 0.87 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.37 (s), 160.26 (d, *J* = 13.1 Hz), 158.31 (s), 149.45 (s), 124.90 (d, *J* = 14.9 Hz),117.97 (s), 117.40 (s), 98.17 (d, *J* = 27.0 Hz), 91.54 (s), 49.90 (s), 44.50 (s), 36.08 (s), 31.51 (s), 28.74 (s), 27.00 (s), 25.54 (s), 22.48 (s), 14.40 (s). MS (ESI): $C_{20}H_{26}FN_3O_5S$ m/z 440.2 $[M+H]^+$.

2-bromo-_N_-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)acetamide (s13)

Light yellow solid (75.3%). Melting points: 145.0 ～ 146.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.47 (t, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 10.0 Hz, 1H), 5.59 (s, 2H), 4.19 (s, 2H), 3.20 (s, 2H), 1.42 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.87(s), 160.70 (d, *J* = 14.7 Hz), 158.37 (s), 157.87 (s), 156.45 (s), 149.56 (s), 124.57 (d, *J* = 14.4Hz), 117.81 (s), 117.48 (s)98.29(d, *J* = 27.2Hz), 91.48 (s), 49.89 (s), 44.49(s), 38.99 (s), 27.01 (s). MS (ESI): $C_{20}H_{17}BrFN_3O_5S$ m/z 448.0 $[M+H]^+$.

Isopropyl(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[*d*]isoxazol-5-yl)carbamate (s14)

Light yellow solid (80.2%). Melting points: 133.0～135.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ ppm 8.60 (d, *J* = 6.7 Hz, 1H), 7.37 (d, *J* = 9.9 Hz, 1H), 6.85 (s, 1H), 5.07 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.98 (s, 2H), 3.02 (s, 2H), 1.49 (s, 6H), 1.33 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.67(s), 160.38 (d, *J* = 13.7 Hz), 158.39(s), 157.43 (s), 156.17 (s), 149.56 (s), 124.59 (d, *J* = 14.4Hz), 117.86 (s), 117.53 (s)98.39(d, *J* = 27.2Hz), 91.46 (s), 49.89 (s), 44.49 (s), 41.11 (s), 28.99 (s), 24.01 (s). MS (ESI): $C_{17}H_{20}FN_3O_6S$ m/z 414.0 $[M+H]^+$.

6-chloro-N-(3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)-6-fluorobenzo[d]isoxazol-5-yl)nicotinamide (s15)

Light yellow solid (66.2%). Melting points: 160.1 ～ 160.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.74 (s, 1H), 8.54 (dd, *J* = 13.0, 5.2 Hz, 2H), 8.11 (d, *J* = 7.4 Hz, 1H), 7.99 (d, *J* = 9.8 Hz, 1H), 7.59 (dd, *J* = 7.3, 4.9 Hz, 1H), 5.64 (s, 2H), 3.22 (s, 2H), 1.44 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ164.82(s), 160.92 (d, J=13.5Hz), 158.31(s), 156.76(s), 151.19 (s), 149.63 (s),147.00 (s), 138.82 (s), 133.00 (s), 123.83 (d, J=13.9 Hz),123.65 (s), 118.92 (s), 117.56(s), 98.60 (d, J=25.9 Hz), 91.43 (s), 49.88 (s), 44.50 (s), 27.03 (s). MS (ESI): $C_{19}H_{16}ClFN_4O_5S$ m/z 467.0 $[M+H]^+$.

3.3 Herbicidal activities

The pre-emergence herbicidal activities of 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl)benzo[d]isoxazole derivatives against *Setaria faberii*(SF), *Digitaria sanguinalis*(DS) and *Echinochloa crus-galli*(EC) were tested according to methods reported previously, the commercial VLCFAs inhibitor S-metolachlor acted as a positive control. All the experimental compounds were prepared into 1.0% emulsified concentrates with DMF as solvent and 1.0% Tween 80 as emulsifier. The concentrate is then diluted with water to the needed concentration and applied to potted plants. These test targets were sown in a 7.5 cm diameter flower pot filled with composite soil (vegetable garden soil: seedling substrate, 1: 2, v / v), covered with 0.2 cm soil, and water was added to keep the soil moist for 24 hours before use. Each test compound was sprayed on the soil

surface by an automatic spray tower (model: 3WPSH-700E) at a dose of 150, 75, 37.5or 18.75 g ai / ha. After the soil surface liquid was dried, it was placed in a greenhouse. The control effect (%) of weeds was investigated and evaluated after 25 days. The results of herbicidal activities are shown in Table **1**, **2** and **3**.

3.4 Crop selectivity

Conventional rape, soybean, maize, cotton sunflower, wheat and rice were sown in a 7.5 cm diameter flower pot filled with composite soil (vegetable garden soil: seedling substrate, 1: 2, v / v), covered with 0.2 cm soil, and water was added to keep the soil moist for 24 hours before use. Each test compound was sprayed on the soil surface by an automatic spray tower (model: 3WPSH-700E) at a dose of 600, 300, 150, 75 and 37.5 g ai / ha. After the soil surface liquid was dried, it was placed in a greenhouse. The final results for crop safety of compound h1, g4 and pyroxasulfone were dectected by visual observation and the damage to the crops was investigated and evaluated after 20 days (%). The results are shown in Table **4**.

4 Conclusion

In summary, many new 3-(((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl)methyl) benzo[d]isoxazole derivatives were rationally designed and synthesized as promising VLCFAs inhibitors. According to the results of greenhouse experiments, several analogues exhibited good herbicidal activity against tested weeds and showed crop safety to tested crops. It is worth mentioning that compounds **g4** and **h1** have excellent herbicidal activity against *E. crus-galli* at a dosage as low as 37.5 g ai/ha, and they are safe to these tested crops at a concentration of 150 g ai/ha. Especially, compound **h1** is safer than commercial pyroxasulfone even at the rate of 600 g ai/ha and showed no harm to crops such as rice, wheat and rape at rates of 150 g ai/ha. These results suggested that compound **h1** may be a promising VLCFAs inhibitor.

SUPPORTING INFORMATION

The structural characterizations (^{1}H NMR and ^{13}C NMR) of synthesized compounds were collected in Supporting Information.

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