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Synthesis and herbicidal activities of 2-cyano-3-benzylaminoacrylates containing thiazole moiety

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ABSTRACT

Two series of novel 2-cyano-3-benzylaminoacrylates containing long-chain thiazole ring moiety were synthesized as herbicidal inhibitors of photosystem II (PS II) electron transportation. Their structures were confirmed by ^{1}H NMR and elemental analysis. The bioassay showed that these compounds retain high herbicidal activities and especially compounds **13a** and **13h** have excellent herbicidal activities.

Cyanoacrylates have been the subject of intense interest for the past decades as one kind of herbicides. A detailed study of compounds with general structure **A** (Fig. 1) revealed that cyanoacrylates are inhibitors of photosystem II (PS II) electron transportation, which inhibits the growth of weeds by disrupting photosynthetic electron transportation at a common binding domain on the 32 kDa polypeptide (D1 protein) of the PS II reaction center.[1–3] Among these cyanoacrylates, the compound **B** (Fig. 1) has been a representative compound because of its excellent herbicidal activity and high Hill reaction inhibitory activity.[4–6] Bayer AG reported compound **C** (Fig. 1), but little information was given on its herbicidal activity.[7] Wang et al. reported that some compounds **D** (Fig. 1) modified by replacing phenyl with heterocycles (pyridine, thiazole, furan, and tetrahydrofuran) showed higher herbicidal activity than parent compounds **B** and **C**.[8–10] Then they reported that compound **E** (Fig. 1) containing arylhydrazino groups did not show herbicide activities but showed some anti-tumor activities.[11] Recently, Song et al. first reported that cyanoacrylates derivatives **F** (Fig. 1) also exhibited moderate to excellent antiviral activity against tobacco mosaic virus (TMV).[12,13] According to the bioisosterism principles, compounds **D**, **E**, and **F** were all analogues of structures **A**, **B**, and **C**. It has been reported that the D1 protein of PS II is the herbicide binding site, and the benzyl group of cyanoacrylate fits into the hydrophobic domain of the site maximizing van der Waals ring-stacking interactions with aromatic amino acids (Phe 211, Phe 255, and Tyr 262) flanking this part of the binding domain.[4,14,15] However, the complete nature and topography of this hydrophobic domain of the D1 protein are unknown. Based on the above considerations, we attempted to introduce longer-chain benzyl groups into cyanoacrylates **B** and **C** to fit into the hydrophobic domain better. Various N- or S-containing heterocyclic derivatives always display broad-spectrum biological activities,[16–18] all which encouraged us to introduce 2-chlorothiazole ring into benzylamino group of 2-cyanoacrylates and further study the relationship of structure–herbicidal activity. Herein, we are reporting the synthesis of new 2-cyano-3-benzylaminoacrylates containing thiazole moiety and evaluation of their herbicidal activities in detail.

The key intermediate 4-((2-chlorothiazol-5-yl)methoxy)benzylamine (**10**) was successfully prepared from readily available 2-chloro-5-chloromethylthiazole and 4-hydroxybenzaldehyde (**1**) as shown in Scheme 1. 4-Hydroxybenzaldehyde (**1**) was reacted with 2-chloro-5-chloromethylthiazole in the presence of potassium carbonate to obtain 4-((2-chlorothiazol-5-yl)methoxy)benzaldehyde (**3**) in 95.7% yield. Borohydride reduction of substituted benzaldehyde **3** in ethanol gave 4-((2-chlorothiazol-5-yl)methoxy)benzyl alcohol (**5**) in 91.0% yield, which was chlorinated by using thionyl chloride to obtain 4-((2-chlorothiazol-5-yl)methoxy)benzyl chloride (**7**) in 95.8% yield. The reaction of benzyl chloride **7** with potassium phthalimide (**9**) gave intermediate N-substituted phthalimide which was subsequently refluxed with hydrazine to

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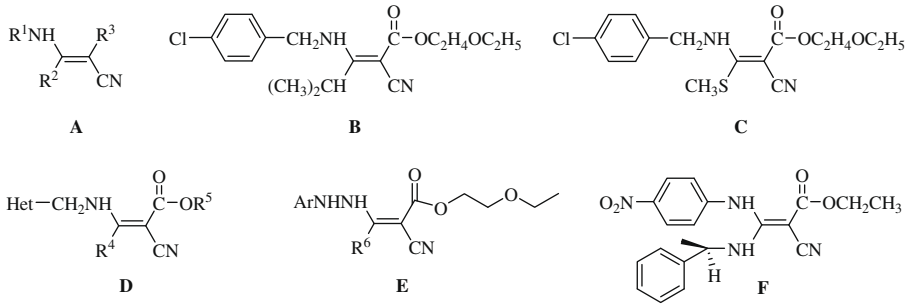
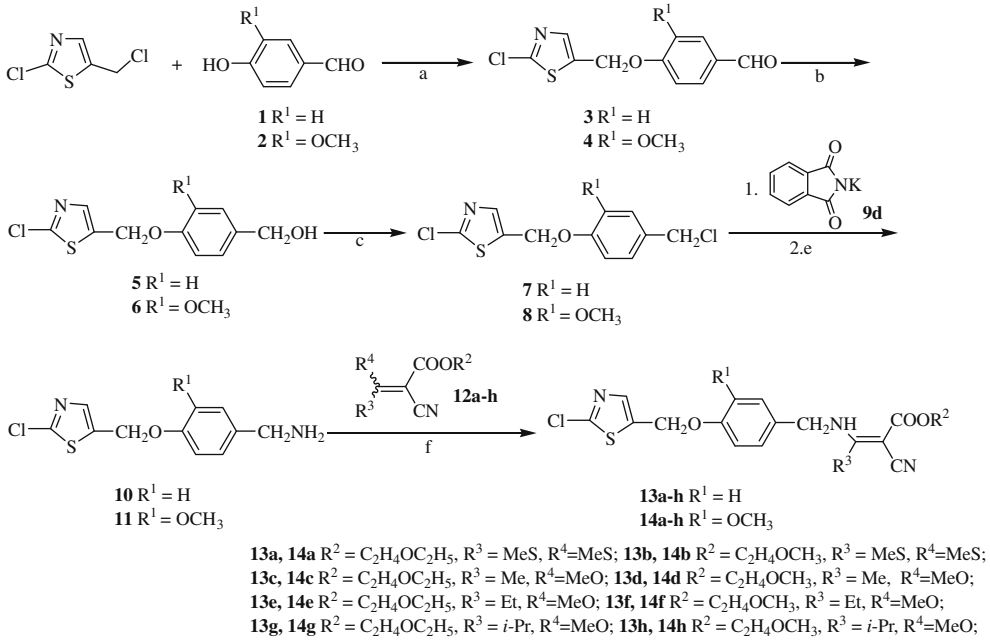


Figure 1. Structures of cyanoacrylates **A**–**F**.



Scheme 1. Reagents and conditions: (a) K_2CO_3, EtOH, reflux 6 h; (b) $NaBH_4$, EtOH, 0 °C to rt, 1 h; (c) $SOCl_2$, CH_2Cl_2, 0 °C to rt, 10 h; (d) potassium pathalimide, DMF, rt, 10 h; (e) hydrazine hydrate (85%), EtOH, reflux, 4 h; (f) EtOH, reflux, 3 h.

afford the corresponding benzylamine **10** in one step. We got benzylamine **11** in good overall yield by using the above synthetic procedure (Scheme 1). The target compounds (**13a**–**h** and **14a**–**h**) were synthesized by the nucleophilic addition and elimination reaction of substituted benzylamine **10** or **11** and **12a**–**h**.

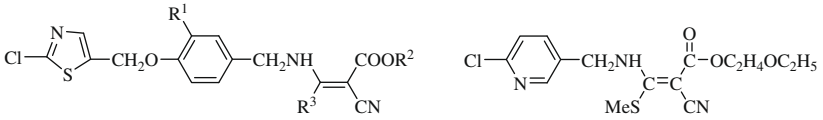
The abilities of all the target compounds **13a**–**h** and **14a**–**h** were evaluated as inhibitors of the photosynthetic electron transport by detecting their inhibiting effects on the Hill reaction at 1.0 μg/mL. Photosynthetically active thylakoid membranes were used and isolated from spinach (*S. oleracea* L.) leaves. Observed inhibitory activity data are listed in Table 1. (*Z*)-Ethoxyethyl 2-cyano-3-methylthio-3-(2-chloro-5-pyridyl)methaneaminoacrylate (**16**) was reported to display excellent herbicidal activity[8] and was used for comparison in the present Hill inhibitory and herbicidal activity study. This comparison (Table 1) clearly showed a significant enhanced activity, with compounds **13b**, **13h**, **14a**, **14g**, and **14h** having higher level of Hill inhibitory activities than compound **16**. From Table 1, the Hill inhibitory activities of most compounds bearing isopropyl group are a little higher than those of compounds bearing methyl or ethyl at R^3 position. All of these experimental results encouraged us to further evaluate their in vivo herbicidal activities in detail.

In our previous work, the cyanoacrylate structure modified by the replacement of phenyl with 4,5-dihydro-1,3,4-thiadiazol-5-one showed relatively lower herbicidal activities than the parent compound.[19] This possibly due to the relatively high polarity and the decrease in the overall lipophilicity of the molecule.

To further strengthen the interaction of these cyanoacrylates with the lipophilic binding domain of the PS II reaction center and explore the influence of aromatic ring and their substitutions on the activity, we introduced benzylamino group containing low polarity thiazole moiety into the cyanoacrylates (Schemes 1 and 2). Their herbicidal activities were evaluated as shown in Table 1. From the biological assay results in Table 1, most of the compounds synthesized showed a greater herbicidal activity in postemergence treatment than in preemergence treatment. So, we herein analyzed the structure–activity relationship mainly according to the data of biological assay in the postemergence treatment.

In postemergence treatment, most of the compounds showed greater herbicidal activities against dicotyledonous weeds (amaranth pigweed and rape) than monocotyledon weeds (alfalfa), especially rape. Compounds **13a**, **13e**, and **13g** containing methylthio, ethyl, isopropyl at the 3-position of 2-cyanocrylate (R^1 = H, R^2 = $CH_2CH_2OCH_2CH_3$), respectively, had better inhibitory effect on weed (amaranth pigweed) development as compared with compound **13c** containing methyl at the 3-position, indicating that methyl at the 3-position of 2-cyanocrylate is not a suitable group

Table 1
Hill inhibitory activity (1.0 μg/mL) and herbicidal activities of products **13a–h** and **14a–h**[b,c] (1500 g/ha,[a] percent inhibition (%))



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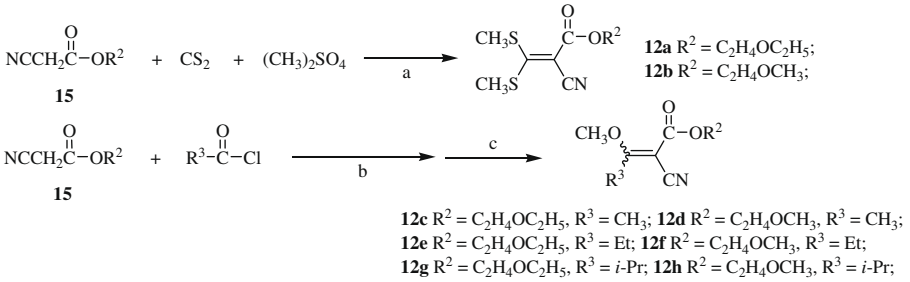
Compd	R^1	R^2	R^3	Hill activity (%)	Postemergence treatment			Preemergence treatment		
					Alfalfa	Amaranth pigweed	Rape	Alfalfa	Amaranth pigweed	Rape
13a	H	C_2H_4OEt	MeS	72.5	0	100.0	100.0	0	0	10.0
13b	H	C_2H_4OMe	MeS	80.9	30.0	71.3	100.0	0	0	0
13c	H	C_2H_4OEt	Me	56.5	0	32.6	100.0	0	0	0
13d	H	C_2H_4OMe	Me	65.2	0	0	98.5	0	0	0
13e	H	C_2H_4OEt	Et	70.2	10.0	96.3	100.0	0	0	0
13f	H	C_2H_4OMe	Et	59.6	0	0	100.0	0	0	0
13g	H	C_2H_4OEt	*i*-Pr	72.5	15.0	91.6	100.0	0	0	0
13h	H	C_2H_4OMe	*i*-Pr	82.0	30.0	91.6	100.0	0	0	0
14a	OMe	C_2H_4OEt	MeS	87.1	49.2	97.4	86.3	10.0	0	10.0
14b	OMe	C_2H_4OMe	MeS	61.2	66.1	89.6	83.6	50.6	2.7	0
14c	OMe	C_2H_4OEt	Me	68.5	30.0	89.6	94.2	30.6	5.0	0
14d	OMe	C_2H_4OMe	Me	42.7	56.5	92.2	84.6	0	0	15.0
14e	OMe	C_2H_4OEt	Et	71.3	41.9	100.0	98.3	0	10.0	5.0
14f	OMe	C_2H_4OMe	Et	70.2	46.8	100.0	96.6	2.0	0	0
14g	OMe	C_2H_4OEt	*i*-Pr	93.8	68.5	100.0	100.0	0	0	0
14h	OMe	C_2H_4OMe	*i*-Pr	80.4	71.1	100.0	100.0	42.9	0	41.7
16[d]				75.8	85.0	100.0	100.0	0	35.1	90.7

[a] g/ha means gram per hectare.
[b] Assay method and procedure were described in Supplementary data.
[c] Triplicate each treatment. Activity numbers represent percent displaying herbicidal damage as compared to control. 0 mean no activity. Error of these numbers is 2%.
[d] Compound **16** and its activity were reported in Ref. 8, while all of the data here of it came from our own work.



12a $R^2 = C_2H_4OC_2H_5$; **12b** $R^2 = C_2H_4OCH_3$;
12c $R^2 = C_2H_4OC_2H_5$, $R^3 = CH_3$; **12d** $R^2 = C_2H_4OCH_3$, $R^3 = CH_3$;
12e $R^2 = C_2H_4OC_2H_5$, $R^3 = Et$; **12f** $R^2 = C_2H_4OCH_3$, $R^3 = Et$;
12g $R^2 = C_2H_4OC_2H_5$, $R^3 = i$-Pr; **12h** $R^2 = C_2H_4OCH_3$, $R^3 = i$-Pr;

Scheme 2. Reagents and conditions: (a) KOH (2.0 equiv), CH_3CN, rt, 4 h; (b) Et_3N, $MgCl_2$, CH_3CN, −15 °C, 5 h; (c) CH_2N_2, Et_2O, rt, 12 h.

for high herbicidal activity. Compounds **13b** and **13h** containing methylthio, isopropyl at the 3-position of 2-cyanocrylate (R^1 = H, $R^2 = CH_2CH_2OCH_3$), respectively, had better inhibitory effect on weed (amaranth pigweed) development as compared with compounds **13d** and **13f** containing methyl, ethyl at the 3-position, respectively, indicating that methyl and ethyl at the 3-position of 2-cyanocrylate are not suitable groups for high herbicidal activity. So, methylthio and isopropyl are suitable groups at the 3-position for high herbicidal activity when R^1 position of benzene ring is H-atom.

The replacement of H-atom by an alkoxy (methoxy) group (**14a–h**) at the R^1 position of benzene ring affected the herbicidal activity obviously (Table 1). In general, an introduction of a methoxy into the R^1 position of benzene ring not only modified the electronic structure, greatly increased herbicidal activity both in postemergence treatment and in preemergence treatment, but also the range of substitutent groups at the 3-position of 2-cyanoacrylate was widened compared with the above compounds **13a–h**. Not only compounds **14a**, **14b**, **14g**, and **14h** with methylthio, isopropyl at the 3-position but also compounds **14c**, **14d**, **14e**, and **14f** with methyl, ethyl at the 3-position exhibited excellent herbicidal activities, indicating that introduction of an electron-donating methoxy group into benzene ring was very essential for whole herbicidal activity.

At the rate of 750 g/ha, compounds **13a**, **13e**, **13g**, **13h**, **14g**, and **14h** still exhibited excellent herbicidal activities against amaranth pigweed and rape (Table 2). Their herbicidal activities decreased when the dose was further reduced. At the rate of 375 g/ha, compound **13a** still exhibited excellent herbicidal activity to rape and compound **13h** still exhibited excellent herbicidal activities to both amaranth pigweed and rape (Table 2). The herbicidal activity assay of high active compounds **13a**, **13e–h**, **14a**, and **14e–h** (Table 1) was continued in lower concentrations. The concentrations causing 50% and 90% inhibition (LD_{50} and LD_{90}) of in vivo activity against rape were estimated utilizing the linear regression equation as shown in Table 3. From the LD_{50} and LD_{90} values in Table 3, compounds **13a** and **13h** showed greater herbicidal activity than other compounds except **16**, which is well coincident with the results judged from Table 2.

In conclusion, we have demonstrated that 2-cyano-3-benzylaminoacrylates containing thiazole moiety presented excellent herbicidal activity, and their structure–activity relationships were

Table 2
Herbicidal activities of products **13a**, **13e**, **13g**, **13h** and **14e–h**[a,b]

Compd	Rate (g/ha)	Postemergence treatment	
		Amaranth pigweed	Rape
13a	750	91.6	100.0
	375	55.6	95.1
13e	750	84.4	100.0
	375	24.5	40
13g	750	100.0	100.0
	375	47.2	51.2
13h	750	100.0	100.0
	375	98.1	92.8
14e	750	30.9	74.6
	375	21.0	41.2
14f	750	32.9	46.4
	375	0	42.9
14g	750	87.8	100.0
	375	59.3	73.5
14h	750	89.8	94.1
	375	73.6	62.4
16[c]	750	100.0	100.0
	375	100.0	100.0

[a] Assay method and procedure were described in Supplementary data.
[b] Triplicate each treatment. Activity numbers represent percent displaying herbicidal damage as compared to control. Error of these numbers is 2%.
[c] Compound **16** and its activity were reported in Ref. 8, while all of the data here of it came from our own work.

Table 3
Herbicidal activities (LD_{50} and LD_{90} values) of high active compounds against rape[a]

Compd	Correlation coefficient (r)	$y = a + bx$	LD_{50} (g/ha)	LD_{90} (g/ha)
13a	0.97	$y = 3.91 + 2.12x$	49.14	197.66
13e	0.99	$y = 3.17 + 2.36x$	83.96	311.43
13f	0.99	$y = 2.06 + 2.59x$	205.19	640.88
13g	0.99	$y = 2.82 + 3.17x$	73.01	185.40
13h	0.98	$y = 3.38 + 2.94x$	53.48	146.04
14a	0.97	$y = 2.20 + 1.83x$	507.90	2548.33
14e	0.98	$y = 2.77 + 1.99x$	196.53	862.13
14f	0.97	$y = 2.14 + 2.38x$	237.10	817.35
14g	0.98	$y = 2.87 + 2.26x$	131.42	484.40
14h	0.99	$y = 2.29 + 3.26x$	101.62	251.01
16	0.99	$y = 5.25 + 1.09x$	8.84	133.77

[a] Assay method and procedure were described in Supplementary data.

studied. In particular, (*E*)-ethoxyethyl 2-cyano-3-methylthio-3-(4-(2-chlorothiazol-5-yl)methoxy)benzylaminoacrylate (**13a**) and (*Z*)-ethoxymethyl 2-cyano-3-isopropyl-3-(4-(2-chlorothiazol-5-yl)-methoxy)benzylaminoacrylate (**13h**) showed excellent herbicidal activities even at a dose of 375 g/ha. It was found that suitable groups such as methylthio, isopropyl at the 3-position of 2-cyanoacrylates were essential for high herbicidal activities. Introduction of an electron-donating methoxy group into benzene ring of benzylamine was beneficial for the whole herbicidal activity. 2-Cyano-3-benzylaminoacrylates containing thiazole moiety have the research potency, further study is underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.027.

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