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Design, synthesis and fungicidal activity of novel 2-substituted aminocycloalkylsulfonamides

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Abstract: A series of novel 2-substituted aminocycloalkylsulfonamides were designed and synthesized by highly selective *N*-alkylation reaction, whose structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Among them, the configuration of compounds **III12** and **III20** were confirmed by X-ray single crystal diffraction. Bioassays demonstrated that the title compounds had considerable effects on different strains of *Botrytis cinerea* and *Pyricularia grisea*. Comparing with positive control procymidone (EC_{50} = 10.31 mg/L), compounds **III28**, **III29**, **III30** and **III31** showed excellent fungicidal activity against a strain of *B. cinerea* (CY-09), with EC_{50} values of 3.17, 3.04, 2.54 and 1.99 mg/L respectively. Their *in vivo* fungicidal activities were also better than the positive controls cyprodinil, procymidone, boscalid and carbendazim in pot experiments. Moreover, the fungicidal activity of **III28** (EC_{50} = 4.62 mg/L) against *P. grisea* was also better than that of the positive control isoprothiolane (EC_{50} = 6.11 mg/L). Compound **III28** would be great promise as a hit compound for further study based on the structure-activity relationship.

Key words: 2-aminocycloalkylsulfonamides; *Botrytis cinerea*; fungicidal activity; structure-activity relationship

Sulfonamides with excellent bioactivity have been studied extensively and profoundly in the field of pharmaceuticals[1-5] and agrochemicals.[6-8] Taurine and its derivatives have important physiological functions in the human body, which also have good therapeutic effects as medicines.[9-13] With continuous research and structural optimization, common intermediate method (CIM) and active compound derivatization method (ADM)[14] were applied to combine the two major functional groups of sulfonamide and taurine together to form a key scaffold *β*-aminoethyl sulfonamide. Therefore, there were many reports on *β*-aminoethyl sulfonamide[15] and its acylated derivatives (Fig.1).[16-18] Synthesis of these derivatives was drawn much attention in previous studies, but their biological activity was not emphasized until recent years. However, 2-aminocycloalkylsulfonamides and alkylated derivatives at the amino group are never reported so far as we know.

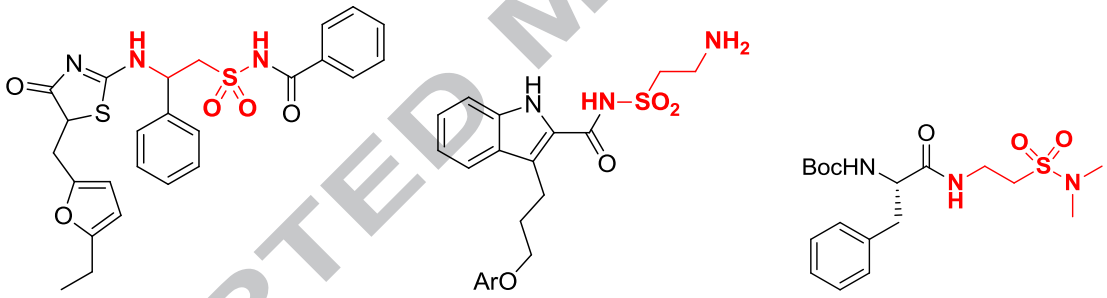


Figure 1. Chemical structures of several *β*-aminoethyl sulfonamides

Recently our group was focused on the design, synthesis and structure-activity relationship (SAR) of different 2-substituted sulfonamides **L-1** ~ **L-3**[20-22], which exhibited excellent *in vitro* and *in vivo* control efficiency on pathogenic fungus, especially against *B. cinerea* and its fungicide-resistant strains, which gave rise to the gray mold, one of the major crop and horticulture diseases[19] and there was no cross resistance with the existing fungicides.[22,23] To continue our study on these compounds and their fungicidal activity, key intermediates of 2-aminocycloalkylsulfonamides **II**

were designed and synthesis based on the compound **L-2**. Finally, a series of novel 2-substituted aminocycloalkylsulfonamides **III** were obtained and their fungicidal activities were evaluated. Meanwhile, the structure-activity relationship was summarized in this study.

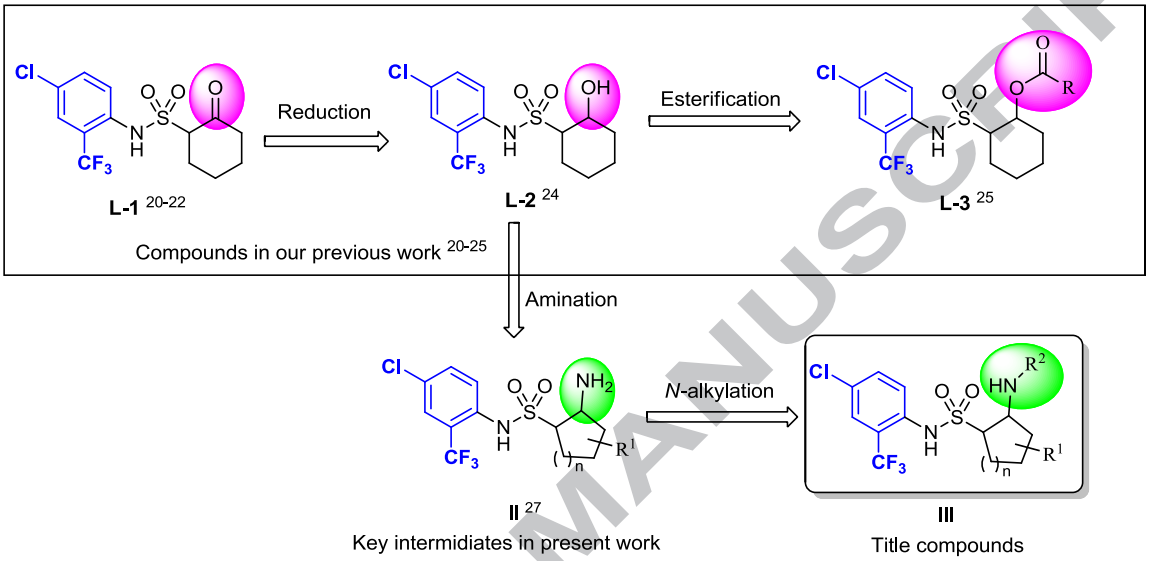
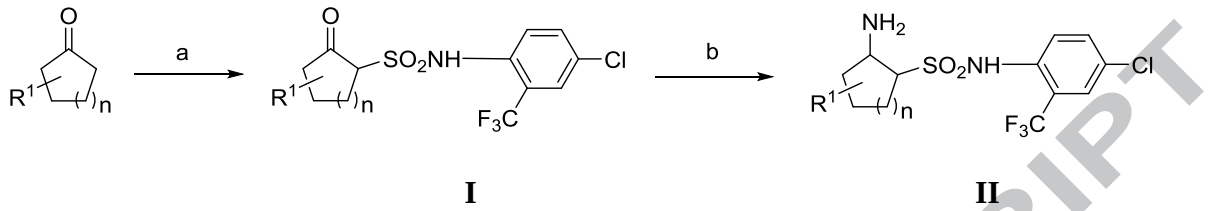


Figure 2. The designed strategy for the key intermediates **II** and title compounds **III**

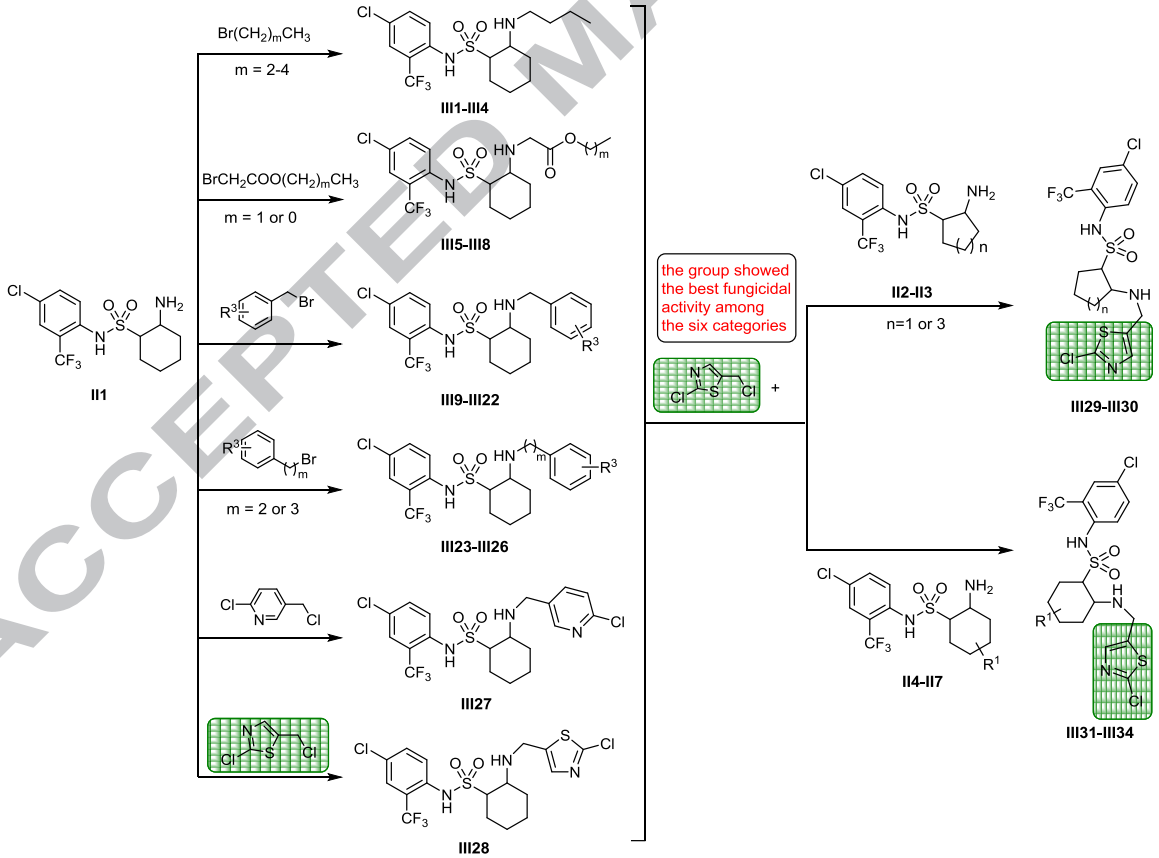
The synthetic route of **I** was illustrated in Scheme 1 according to the method given in the reference.[26,27] The key intermediates (**II**) was obtained from (**I**) by amination and reduction reaction with ammonia (under 20 mmHg pressure) and sodium borohydride (Scheme l). The title compounds **III** were obtained from the key intermediates **II** *via* nitrogen alkylation reaction[28] with corresponding halides in *N*, *N*- dimethylformamide under basic condition with cesium hydroxide as a catalyst (Scheme 2, Supplementary materials). Usually, di-substituted nitrogen alkylation reaction was occurred as a side reaction on an amino group, but the synthetic method in Scheme 2 could effectively avoid the occurrence of multi-substituted reaction and thus get a high yield of mono-alkylated

product. With this nitrogen alkylation reaction, six different groups of 2-substituted aminocycloalkylsulfonamides **III** were produced under the same conditions (Scheme 2).



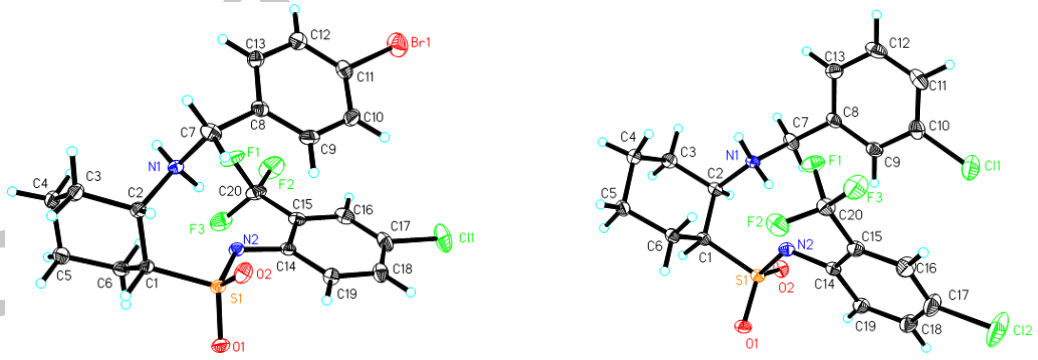
I **II**

Scheme 1. Synthesis of the key intermediates *N*-(2-trifluoromethyl-4-chlorinephenyl)-2-aminocycloalkyl-sulfonamides **II**. Reagents and conditions: (a) (i) SO_3, 1,4-dioxane, 1,2-dichloroethane; (ii) KCO_3, H_2O; (iii) $(COCl)_2$, DMF, CH_2Cl_2; (iv) 4-chloro-2-(trifluoromethyl)aniline, Et_3N; (b) (i) NH_3, EtOH, $Ti(O^iPr)_4$, 20 mmHg/25 °C, 6 h; (ii) $NaBH_4$, 25 °C, 3 h.



Scheme 2. Synthesis of 2-substituted aminocycloalkylsulfonamides **III**

The structures of all title compounds were characterized by ^{1}H NMR and HRMS (Supplementary materials). Moreover, the structures of the title compounds **III12** (CCDC No. 1496103) and **III20** (CCDC No. 1496104) were confirmed by X-ray single crystal diffraction analysis (Fig. 3). The results showed that the cyclohexane ring of **III12** and **III20** was both in a chair conformation, but the configuration of the chiral carbon atoms (C_1 and C_2) was different. For compound **III12**, the first chiral carbon atom (C_1) was *R* configuration, and the second one (C_2) was *S* configuration. The situation of compound **III20** was just the opposite, and the first chiral carbon atom (C_1) was *S* configuration, while the second one (C_2) was *R* configuration. In the two structures, the sulfonamide group occupied the equatorial position, and the amine group was in axial bond. It was clearly found from single crystal structure that two active hydrogens linked with one nitrogen atom (N_1). Because the overall performance of substituted amine (-NH) was basicity, and the amine on SO_2-NH was influenced by the strong electron withdrawing of sulfonyl, which led sulfonamide proton transferring to the substituted amine (-NH). *N*-alkylation reaction takes place at the substituted amino (-NH) because the basicity of the substituted amino (-NH) group is stronger than that of the amine on SO_2-NH.



III12 **III20**

Figure 3. Single crystal structures of compounds **III12** and **III20**.

The *in vitro* fungicidal activity of title compounds was tested against seven different kinds of pathogenic fungi, including three *B. cinerea* strains (CY-09, HLD-15 and

DL-11) which were collected from different regions (Liaoning Province, China), *Fusarium graminearum* (Fg), *Rhizoctorzia solani* (Rs), *Bipolaris sorokiniana* (Bs), *Pyricularia grisea* (Pg), *Phytophthora capsiciand* (Pc) and *Exserohilum turcicum* (Et). Commercial fungicides procymidone and carbendazim were used as positive controls. The results were shown in Table 1 - Table 4. Based on the bioassay results, the relationship between chemical structures and fungicidal activities was summarized.

The fungicidal activities of compounds **III1-III4** and **III5-III8** (Scheme 2 and Table 1) against *B. cinerea* were higher than carbendazim, but most of them were less than that of procymidone (Table 1), only **III5** exhibiting similar activity with procymidone. So, acetic acid ethyl ester group (**III5**) was considered to be the best substituted carboxylate among these compounds. Despite of low activity of these eight compounds, they also exhibited good activity against *B. cinerea* compared with other pathogens. It is noteworthy that when a substituent on nitrogen position was an alkyl group, whose fungicidal activity increased along with the extension of the carbon chain, which was not only against the *B. cinerea* but also against the other pathogens.

Table 1 *In vitro* fungicidal activities of **III1-III8** against nine pathogenic fungi at 50 mg/L

No.	Compd.			Control efficiency (%)								
	n	R^1	R^2	*Botrytis cinerea*			Fg	Rs	Bs	Pg	Pc	Et
				CY-09	HLD-15	DL-11						
III1	2	H	CH_2=$CHCH_2$-	59.34	30.45	49.57	23.36	40.62	17.48	30.61	25.22	41.32
III2	2	H	$CH_3(CH_2)_2$-	50.00	20.67	32.29	39.95	54.90	9.76	8.71	22.87	31.44
III3	2	H	$CH_3(CH_2)_3$-	55.05	32.96	44.19	34.67	34.17	58.61	34.27	33.43	44.31
III4	2	H	$CH_3(CH_2)_4$-	29.80	46.21	68.55	65.32	52.94	78.92	51.40	57.77	51.20
III5	2	H	$CH_3CH_2OCOCH_2$-	68.43	50.56	92.07	51.25	71.15	74.81	46.35	51.90	53.89
III6	2	H	CH_3OCOCH_2-	27.89	42.74	67.14	59.84	43.48	50.46	18.50	37.58	21.72
III7	2	H		19.74	74.30	89.23	46.46	60.00	41.36	23.88	15.45	19.83
III8	2	H		21.74	17.88	52.41	27.82	61.45	47.43	38.80	13.33	40.97

Procymidone	69.21	79.05	75.64	97.33	96.41	87.74	19.17	28.22	90.09
Carbendazim	33.90	10.34	10.48	100.0	98.65	93.42	100.0	42.95	68.51

Compounds **III9-III26** (Scheme 2 and Table 2) with substituted benzyl, phenylethyl and phenylpropyl groups on nitrogen position showed better activity whose inhibition rates were higher than procymidone against *B. cinerea*. Depending on specific structure-activity data showed in Table 2, it was found that (1) about the substituted benzyl group, the fungicidal activity of compounds with substituent on *ortho*- and *para*-position was better than that of the *meta*-position; (2) compared **III18** with the others, di-substituted compounds showed better activity than that of the mono-substituted ones, and the compounds containing bromide, fluoride and methyl groups also showed good activity.

With changing the length of the carbon chain between the phenyl ring and the amino group in **III9**, **III24** and **III26**, it was found that the activity varied significantly and the compound with the phenylethyl group (**III24**) gave the best activity. It could be concluded that the compounds with the substituted phenylethyl group displayed higher activity than the corresponding substituted benzyl and phenylpropyl groups. Moreover, the compounds with fluoride atom on the substituted phenylethyl group (**III23**) showed the best activity, which also exhibited the excellent activity against the other six pathogens, particularly against *B. sorokiniana*.

Table 2 *In vitro* fungicidal activities of **III9-III26** against nine pathogenic fungi at 50 mg/L

No.	Compd.			Control efficiency (%)								
	n	R^1	R^2	*Botrytis cinerea*			Fg	Rs	Bs	Pg	Pc	Et
				CY-09	HLD-15	DL-11						
III9	2	H	$C_6H_5CH_2$-	80.68	47.49	73.65	72.36	70.03	72.49	48.59	57.18	51.50
III10	2	H	4-$CH_3C_6H_4$-CH_2-	72.98	36.88	86.68	26.63	59.10	79.69	32.58	21.70	41.92
III11	2	H	3-$CH_3C_6H_4$-CH_2-	35.61	10.62	19.83	24.37	60.78	58.61	30.05	15.54	58.69
III12	2	H	4-BrC_6H_4-CH_2-	84.85	77.65	84.70	78.39	56.58	74.03	56.18	69.79	53.89
III13	2	H	3-FC_6H_4-CH_2-	60.74	74.86	92.92	72.18	58.84	69.49	37.91	41.52	53.94
III14	2	H	2-$CH_3C_6H_4$-CH_2-	77.27	54.47	86.40	70.10	53.22	80.98	57.02	53.66	64.97
III15	2	H	4-FC_6H_4-CH_2-	77.27	62.85	86.68	63.31	55.46	78.66	42.69	20.82	53.00
III16	2	H	2-FC_6H_4-CH_2-	71.72	67.04	86.40	65.83	56.58	79.18	48.03	43.69	59.88
III17	2	H	4-$CF_3OC_6H_4$-CH_2-	66.16	35.48	41.36	24.87	18.49	44.47	38.20	16.71	44.91
III18	2	H	2-Cl-5-FC_6H_3-CH_2-	82.07	86.03	81.30	72.36	62.46	81.23	57.58	69.21	66.47
III19	2	H	2-BrC_6H_4-CH_2-	54.07	84.08	86.68	71.39	57.10	54.60	38.80	38.79	48.98
III20	2	H	3-ClC_6H_4-CH_2-	5.15	17.32	41.64	29.40	62.03	52.94	19.40	5.76	54.23
III21	2	H	4-CNC_6H_4-CH_2-	44.06	71.51	85.83	59.84	50.72	50.74	33.13	31.21	71.14
III22	2	H	4-$NO_2C_6H_4$-CH_2-	56.07	75.14	79.60	67.72	71.30	33.09	58.80	34.85	51.31
III23	2	H	4-FC_6H_4-$(CH_2)_2$-	79.38	69.55	88.10	84.00	73.32	79.74	82.04	64.89	68.76
III24	2	H	$C_6H_5(CH_2)_2$-	80.79	59.22	80.74	85.33	73.99	76.58	58.39	63.01	54.39
III25	2	H	4-$NO_2C_6H_4$-$(CH_2)_2$-	67.51	67.32	70.54	70.00	54.26	73.95	74.70	41.07	49.78
III26	2	H	$C_6H_5(CH_2)_3$-	42.94	15.37	53.82	38.33	19.50	69.74	13.18	22.89	41.46
		Procymidone		69.21	79.05	75.64	97.33	96.41	87.74	19.17	28.22	90.09
		Carbendazim		33.90	10.34	10.48	100.0	98.65	93.42	100.0	42.95	68.51

The fungicidal activities of compounds **III27** and **III28** with pyridine and thiazole as substituted heterocyclic groups were tested (Scheme 2 and Table 3). The compound **III28** with 2-chlorothiazol-5-yl-methyl group as a substituent, whose inhibition rates were higher than 90% against two strains (CY-09 and DL-11) of *B. cinerea* and the EC_{50} values (Table 4) were between 1.41 and 3.17 mg/L, which was better than the positive control procymidone (EC_{50} values 3.88-10.31 mg/L). Compound **III28** also showed

broad fungicidal spectra, which exhibited excellent activities against *F. graminearum*, *B. sorokiniana* and *P. grisea*, especially agaisnt *P. grisea* (inhibition rate was 100% at a concentration of 50 mg/L). Therefore, 2-chlorothiazol-5-yl-methyl group was selected as the best bioactive group, which was linked with different 2-aminocycloalkylsulfonamides to give the title compounds **III29-III34** (Scheme 2 and Table 3), which possessed excellent fungicidal activity. According to the fungicidal activities of compounds **III28**, **III29** and **III30**, it was discovered that six-membered ring displayed higher activity than that of the five- and seven-membered ring. The length of the carbon chain and position of substituents on the cyclohexane group had significant effects on the fungicidal activity. With the length of the carbon chain increased, fungicidal activity reduced; and substituent position at 4-position expressed better activity than that of at 5-position.

Table 3 *In vitro* fungicidal activities of **III27-III34** against nine pathogenic fungi at 50 mg/L

No.	Compd.			Control efficiency (%)								
	n	R^1	R^2	*Botrytis cinerea*			Fg	Rs	Bs	Pg	Pc	Et
				CY-09	HLD-15	DL-11						
III27	2	H		71.23	62.57	86.40	82.33	68.38	65.52	85.88	61.82	59.19
III28	2	H		98.02	88.27	93.20	85.00	75.56	80.79	100.0	55.76	77.26
III29	1	H		78.81	51.40	89.23	79.00	75.11	74.47	100.0	53.61	60.25
III30	3	H		90.96	88.27	89.23	83.00	77.80	82.89	100.0	60.82	59.94
III31	2	4-CH_3		90.11	88.83	94.05	73.67	73.54	80.00	100.0	52.04	65.76
III32	2	5-C_2H_5		74.01	78.63	85.83	82.00	69.51	68.95	100.0	52.98	70.19
III33	2	5-nC_3H_7		75.42	86.31	83.29	69.00	64.80	63.16	76.35	53.92	58.37
III34	2	5-CH_3		91.53	25.42	44.47	82.00	64.12	43.15	43.12	58.00	63.45
		Procymidone		69.21	79.05	75.64	97.33	96.41	87.74	19.17	28.22	90.09
		Carbendazim		33.90	10.34	10.48	100.0	98.65	93.42	100.0	42.95	68.51

According to the preliminary bioassay results, EC_{50} values of seven title compounds (**III5, III12, III18, III28, III29, III30** and **III31**) against three strains (CY-09, HLD-15 and DL-11) of *B. cinerea* and *P. grisea* were checked for further study (Table 4). The EC_{50} values of compounds **III28, III29, III30** and **III31** against three strains of *B. cinerea* were all better than the five commercial fungicides (pyrimethanil, pyprodinil, procymidone, boscalid and carbendazim). Wherein, the *in vitro* EC_{50} value of the compound **III31** was between 0.86 mg/L and 1.99 mg/L, which were far better than the positive controls. The *in vivo* results of pot experiment showed that compound **III28** indicated better activity (EC_{50} = 11.01 mg/L) than that of the three commercial fungicides pyrimethanil (EC_{50} = 53.74 mg/L), procymidone (EC_{50} = 56.22 mg/L) and carbendazim (EC_{50} = 792.87 mg/L). The *in vitro* bioactivity of compound **III28** against *P. grisea* with EC_{50} (4.62 mg/L), which was better than the positive control isoprothiolane (EC_{50} = 6.11 mg/L), and the *in vitro* bioactivity of compound **III30** against *P. grisea* was 6.51 mg/L, which was similar with isoprothiolane.

Table 4 Fungicidal activities of compounds **III5, III12, III18, III28, III29, III30** and **III31** (EC_{50} mg/L)

No.	Compd.			*Botrytis cinerea*			Living cucumber leaves	*Pyricularia grisea*
	n	R^1	R^2	CY-09	DL-11	HLD-15		
III5	2	H	$CH_3CH_2OCOCH_2$-	25.77	15.48	21.65	/	/
III12	2	H	4-BrC_6H_4-CH_2-	10.02	8.52	7.70	/	/
III18	2	H	2-Cl-5-FC_6H_3-CH_2-	13.71	6.04	12.37	/	/
III28	2	H		3.17	2.37	1.41	11.01	4.62
III29	1	H		3.04	2.74	1.77	177.90	25.33
III30	3	H		2.54	3.03	1.13	137.12	6.51
III31	2	4-CH_3		1.99	1.26	0.86	150.08	8.05
		Pyrimethanil		7.12	11.57	15.36	53.74	/
		Cyprodinil		3.58	2.58	6.79	1.38	/
		Procymidone		10.31	3.88	6.03	56.22	/
		Boscalid		4.46	5.56	7.88	/	/
		Carbendazim		867.83	6550.50	733.72	792.87	/
		Isoprothiolane		/	/	/	/	6.11

/ means not test.

In summary, six types of 2-substituted aminocycloalkylsulfonamides were designed and synthesized by highly selective *N*-alkylation reaction with cesium hydroxide under anhydrous condition. Their fungicidal inhibitory activities were investigated against three strains of *B. cinerea* and other six kinds of pathogenic fungi. According to the results, six kinds of different substituted compounds showed varying degrees of inhibitory activities as follows: substituted heterocyclic group > substituted phenylethyl group > substituted benzyl group > substituted carboxylate group > substituted alkyl group. Finally, 2-chlorothiazol-5-yl-methyl group was selected as the best bioactive group to gain highly active compounds whose *in vitro* fungicidal activities against *B.cinerea* strains and *in*

vivo pot experiments were both higher than that of the positive control fungicides. Particularly, the *in vitro* and *in vivo* bioactivity of compound **III28** against *B.cinerea* was better than that of the three commercial anti-gray mold fungicides (pyrimethanil, procymidone, and carbendazim). Meanwhile, all the tested compounds were found safe for the plants. Among the tested compounds, some showed superiority over the commercial fungicides during the present studies. These compounds could be lead compounds for further discovery of fungicides. Further studies on structural modification and fungicidal mechanism are in progress.

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Graphical Abstract

Design, synthesis and fungicidal activity of novel 2-substituted aminocycloalkylsulfonamides

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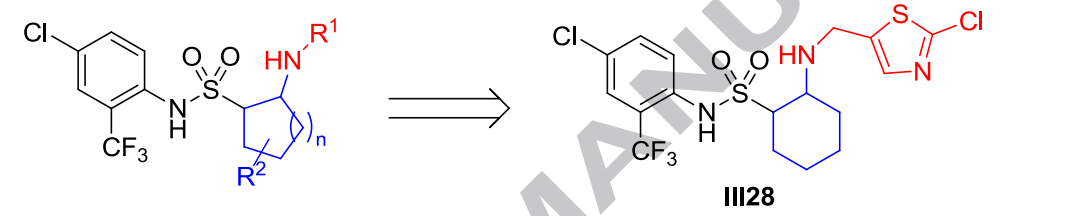

Title compounds in present work

III28

in vitro EC_{50} = 1.41 mg/L (against *Botrytis cinerea*)
in vivo EC_{50} = 11.01 mg/L (against *Botrytis cinerea*)
more active than the positive controls