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Development of novel 2-substituted acylaminoethylsulfonamide derivatives as fungicides against *Botrytis cinerea*

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ABSTRACT

Botrytis cinerea is an economically important fungal pathogen with a host range of over 200 plant species. Unfortunately, gray mold disease caused by *B. cinerea* has not been effectively controlled because of its high risk for fungicide resistance development. As a part of our ongoing efforts to develop novel sulfonamides as agricultural fungicides against *Botrytis cinerea*, we introduced 2-aminoethanesulfonic acid (taurine) substructure, designed and synthesized a series of novel 2-substituted acylaminoethylsulfonamides. The newly synthesized sulfonamides were evaluated *in vitro* and *in vivo* for their fungicidal activity against *Botrytis cinerea*, of which the 2-ethoxyacetylamide derivative (**V-A-12**, $EC_{50} = 0.66\,mg{\cdot}L^{-1}$) exhibited the highest potency *in vitro* and superior fungicidal activity compared with procymidone ($EC_{50} = 1.06\,mg{\cdot}L^{-1}$). *In vivo* bioassay indicated that compound **V-A-12** could be effective for the control of tomato gray mold. Moreover, the structure-activity relationship of these sulfonamides was analyzed by establishing a three-dimensional quantitative structure-activity relationship (3D-QSAR) model, which can provide guidance for the development of sulfonamides as fungicides. Finally, the effeicacy of sulfonamide derivatives was again verified in the activity evaluation against resistant *Botrytis cinerea* strains. These results further enhance the development value of 2-substituted acylaminoethylsulfonamides to control the tomato gray mold.

1. Introduction

Gray mold, caused by the important phytopathogenic fungus *Botrytis cinerea*, has resulted in great yield losses in more than 200 crop species worldwide, especially for such economic crops as vegetables, grapes and flower crops [1–3]. *Botrytis cinerea* is difficult to effectively control because of its variety of attack modes and complexity of host-pathogen interaction [4]. In terms of scientific and economic importance, *Botrytis cinerea* is ranked second in dangerous phytopathogen by the international fungal pathology community [5]. Therefore, many scholars have done a lot of work to study the control measures against *Botrytis cinerea* and have formed comparatively complete systems [6–7]. Especially with deepening study on the pathogenesis of *Botrytis cinerea* and the mechanism of plant defense, some biological and genetic approaches have been developed to control *Botrytis cinerea* in an eco-friendly and sustainable manner [8–9]. Even though, chemical control still plays an irreplaceable role because of its characters of high efficiency, rapid effects and labor saving. However, intensive and continuous use of the same fungicide might increase the risk of resistance development in the *Botrytis cinerea* because of its easy acquisition of pesticide-resistance ability [2,10,11]. Lack of fungicides with new mechanisms of action, the occurrence of *Botrytis cinerea* populations which have resistance to multiple fungicides with different mechanism, including benzimidazoles, carbamates, dicarboximides, phenylpyrroles, pyrazole carboxamides, anilinepyrimidines, and hydroxyanilide fungicides, has not been effectively controlled [12–14]. The continue rise of resistant plant pathogenic fungal infections warrants the development of novel fungicides with unique modes of action. Therefore, we should use all available knowledge to discover novel fungicides with resistance-breaking mode of action.

Sulfonyl group has been widely applied in the pharmaceutical and agrochemical industry due to its unique structural properties and physicochemical properties [15]. Sulfonamides, the typical sulfonyl-containing compounds, are generally known as the first selective drugs against bacteria, and play an important role in clinical therapy [16]. A recent search in the Thomson integrity database revealed that nearly 500 compounds containing a sulfonamide moiety have been registered or have reached clinical trials [17]. Nevertheless, sulfonamides have

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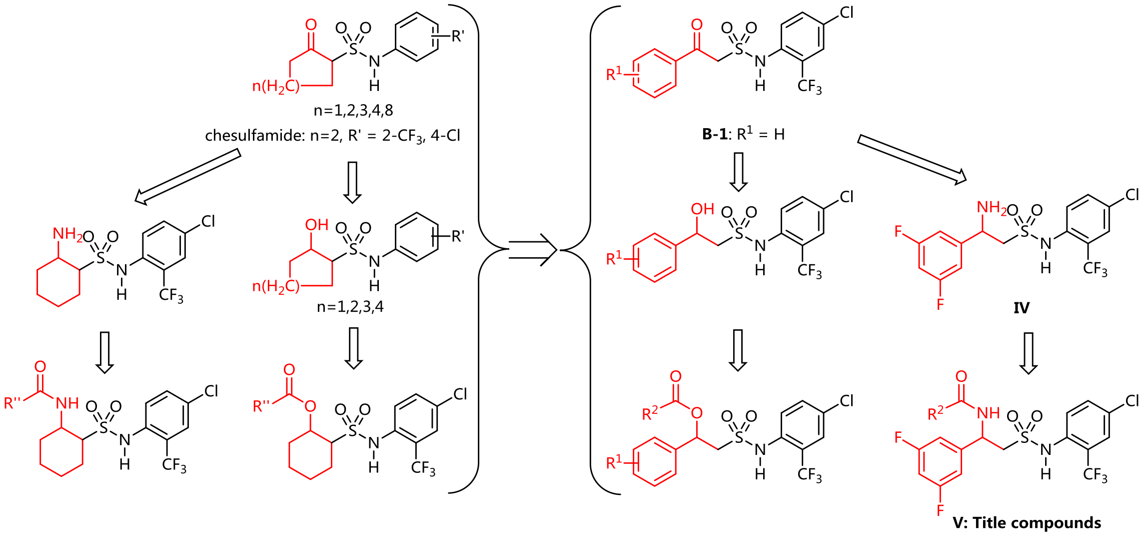


Scheme 1. Development of novel sulfonamide derivatives as agricultural fungicides in our work.

less been applied in agrochemicals, which were always used as herbicides. And as the typical function, its antibacterial activity is short of being developed and needs to be perfected.

As a part of our ongoing efforts towards developing novel sulfonamide fungicides (Scheme 1), we put emphasis on the derivation and optimization of 2-oxocycloalkylsulfonamides from such four aspects as multiple substitutions on the nitrogen, the size of naphthene base, multiple substitutions on the naphthene base and the derivation of carbonyl group. Although we screened some novel sulfonamides with good fungicidal activity, some key problems of 2-oxocycloalkylsulfonamides such as high cost and deficiency of structural variations limited their further investigations [18–21]. Then, we further reported the development of a series of 2-substituted phenyl-2-oxo-ethylsulfonamides, and discovered the lead compound (Fig. 1; the EC_{50} value of $1.58\,mg{\cdot}L^{-1}$ against *Botrytis cinerea* strain DL-11 *in vitro*) [22]. This provided theoretical reference for the further synthesis of 2-substituted phenyl-2-acyloxy ethylsulfonamides, and some compounds with outstanding activity against *Botrytis cinerea in vitro* were screened. Disappointedly, the control effect *in vivo* of these compounds was relatively modest. Moreover, the poor stability of 2-substituted phenyl-2-acyloxy ethylsulfonamides restrains their further research, application and development. Therefore, further optimization of compounds should be developed.

On the other hand, taurine (TAU, 2-aminoethanesulfonic acid) is the most abundant free amino acid in humans and plays an important role in several essential biological processes [23,24]. TAU has peculiar bioactivity such as improving hepatic metabolism [25,26], reducing triglycerides in the plasma and liver [27,28], and it also presents anti-inflammatory actions and antimicrobial activity [29,30]. Herein, we introduced the novel carbon skeleton of 2-aminoethanesulfonic acid and acylamide functional group, thus designed and synthesized 2-substituted amido ethylsulfonamides **V** on the basis of hybridization principle and bioisosterism. The biological activities of the newly synthesized compounds against *Botrytis cinerea* were evaluated *in vitro* and *in vivo*. And a three-dimensional quantitative structure–activity relationship (3D-QSAR) model was developed to research the relationship between the structural features and the activity of synthetic sulfonamides. In addition, the effeicacy of these sulfonamide derivatives against resistant *Botrytis cinerea* strains was preliminarily studied, providing valuable information for the development of novel sulfonamide fungicides.

2. Results and discussion

2.1. Chemistry of 2-substituted acylaminoethylsulfonamides

The target compounds of 2-substituted acylaminoethylsulfonamides were obtained by the route summarized in Scheme 2. Firstly, 3′,5′-difluoroacetophenone (**I**) was treated with sulfur trioxide-dioxane adduct in the presence of 1,2-dichloroethane at $-10\,^{\circ}C$ and potassium bicarbonate as a neutralizer to afford the corresponding potassium 2-(3,5-difluorophenyl)-2-oxoethylsulfonates (**II**). Next, the produced **II** was refluxed in dichloromethane with oxalyl chloride to give the corresponding 2-(3,5-difluorophenyl)-2-oxoethylsulfochloride, which became accessible with 2-trifluoromethyl-4-chlorophenylamine in the presence of triethylamine (Et_3N) to give *N*-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-oxoethylsulfonamide (**III**). The third-step reaction was a reductamination reaction to synthesize the *N*-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-aminoethylsulfonamide (**IV**), which was done using ketones with ammonia under catalysis of titanium (IV) isopropoxide in ethanol, followed by *in situ* sodium borohydride reduction. Finally, compounds **V** were obtained from compound **IV** and diverse acid chlorides as raw material by amidation reaction in 44% − 96% yield. All the target compounds were purified by silica gel column or crystallization and their structures confirmed by IR, ^1H NMR and HRMS data.

2.2. Biological activity against Botrytis cinerea

Botrytis cinerea is one of the most common phytopathogen in tomato cultivation, which can cause heavy losses not only throughout the whole growth period but also during storage. Therefore, with 50 newly synthesized 2-substituted amido ethylsulfonamide derivatives in hand, we next systematically evaluated their fungicidal activitiesagainst tomato gray mold *in vitro* and *in vivo*.

2.2.1. In vitro fungicidal activities against tomato gray mold

A mycelial growth rate method was adopted to determine the fungicidal activities of ethylsulfonamide derivatives (**IV**, **V-A-1 ~ 15**, **V-B-1 ~ 16** and **V-C-1 ~ 19**) against tomato gray mold. The lead compound **III**, procymidone and pyrimethanil were selected as positive controls. As shown in Table 1, most of the title compounds exhibited significant fungicidal activity, but there was great difference among fungicidal

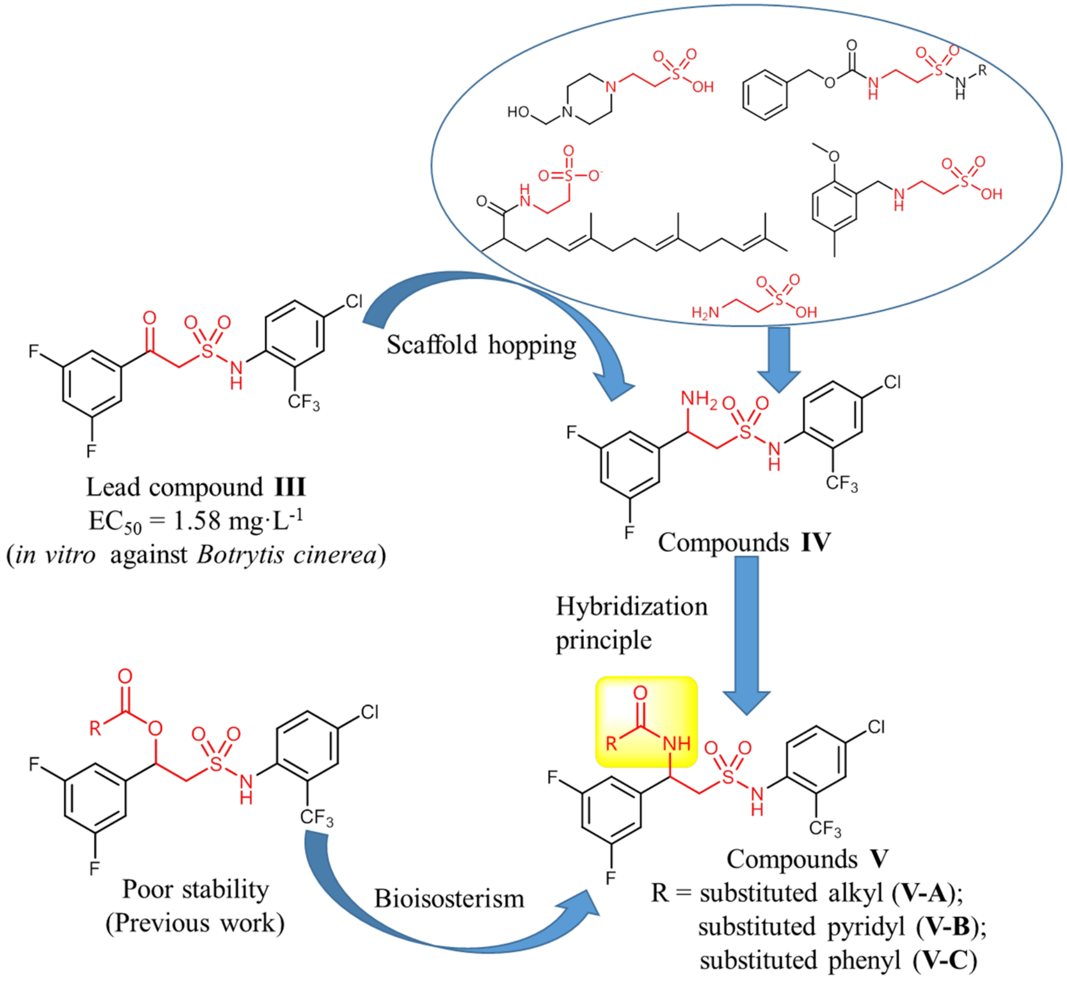
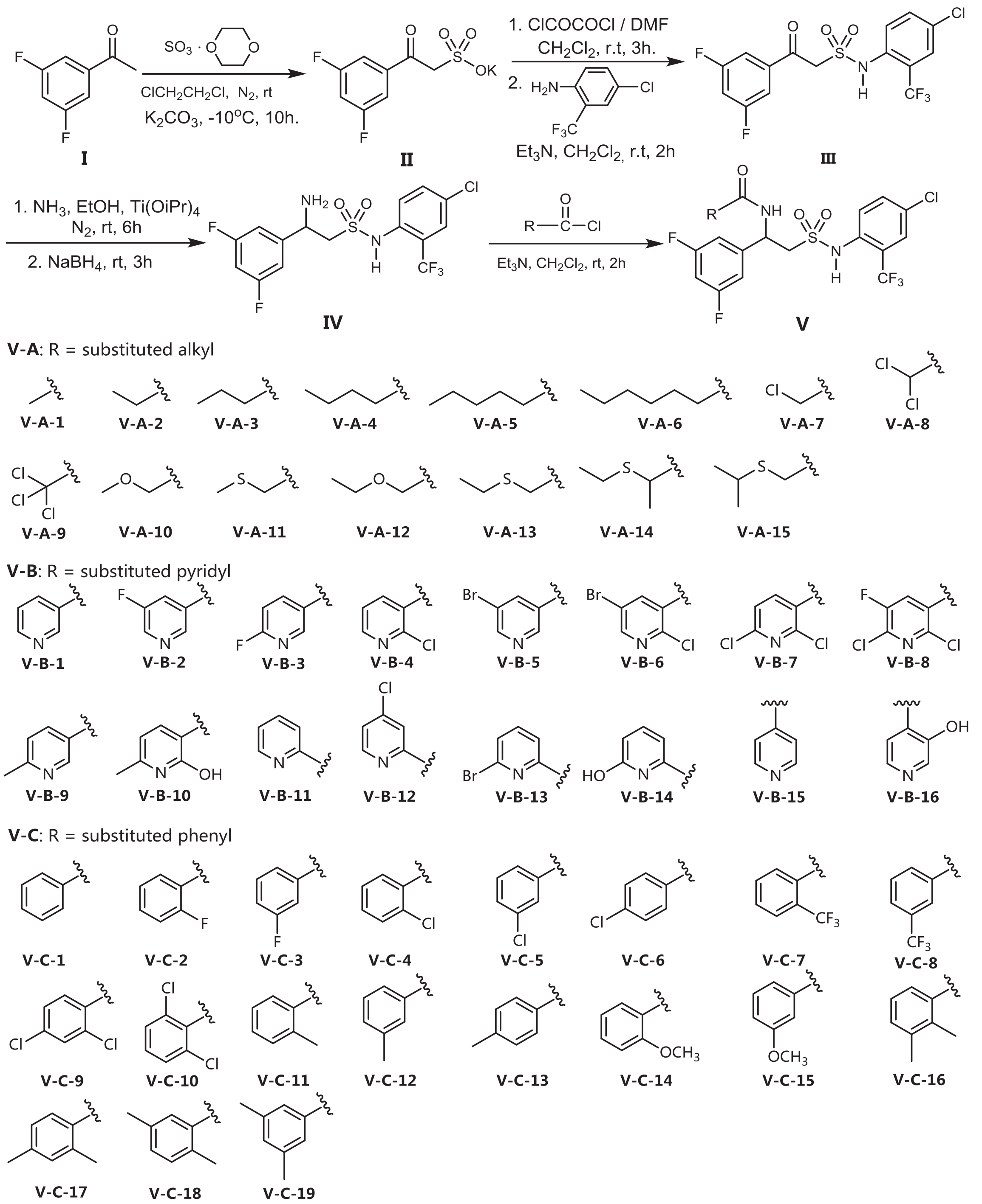


Fig. 1. Design strategy of the target compounds.

activities of the compounds **V** with EC$_{50}$ values ranging from 0.66 to 811.76 mg·L^{-1}. Among these newly synthesized ethylsulfonamides, 26 compounds were as or more potent than pyrimethanil (EC$_{50}$ = 7.71 mg·L^{-1}), of which 7 compounds showed better activity than that of the lead compound **III** (EC$_{50}$ = 2.18 mg·L^{-1}). In particular, compounds **V-A-1**, **V-A-6**, **V-A-9**, **V-A-12** and **V-B-3** showed pronounced fungicidal activities with EC$_{50}$ values of 1.89, 1.67, 1.52, 0.66 and 1.51 mg·L^{-1}, respectively. Superiorly, **V-A-12** emerged with 2-fold more potent than the standard drug procymidone (EC$_{50}$ = 1.06 mg·L^{-1}). From the fungicidal activities against tomato gray mold, we found that compounds containing a substituted alkylamide moiety (**V-A**) showed higher fungicidal activities than the corresponding 2-substituted pyridinecarboxamido ethylsulfonamides (**V-B**) and 2-substituted benzamido ethylsulfonamides (**V-C**), especially 2-substituted benzamido ethylsulfonamides (**V-C**), whose activities were much below that of the other two series. A possible explanation for lower activity of these compounds **V-C** is that their ClogPs (calculated by Chem-BioOffice 2014) are more than 5 due to the introduction of phenyl once again, and subsequently influences their absorption, ultimately causing a reduction in fungicidal activity [31].

Preliminary SAR correlations were formulated to assist in further identification of more efficient 2-substituted amido ethylsulfonamide derivatives. Among the 2-substituted alkylamide ethylsulfonamide derivatives (**V-A**), fungicidal activities were not associated with the carbon chain length of alkyl group. Interestingly, the introduction of branched alkyl groups in the main chain would improve the acitivities. For example, the EC$_{50}$ value of compound **V-A-13** was 7.49 mg·L^{-1} against *B. cinerea*, and those of compounds **V-A-14 ~ 15** were 5.17, 2.90 mg·L^{-1}, respectively. Other substituent groups of the alkyl didn't have a positive effect on the activity. However, compounds **V-A-12** bearing an ethoxymethyl group showed the greatest fungicidal activity. Otherwise, the fungicidal activity increased with the increase in number of chlorine atom bonding with the same carbon atom, such as compounds **V-A-7 ~ 9** with the EC$_{50}$ values of 27.52, 2.70 and 1.52 mg·L^{-1}, respectively.

Regarding the impact of substituted pyridyl moiety in compounds **V-B**, the obtained results highlighted that the fungicidal activity was influenced by both the locations of N atom and the kind of substrates in pyridine ring. For the 2-unsubstituted pyridinecarboxamido ethylsulfonamides, the compound **V-B-11** (EC$_{50}$ = 3.43 mg·L^{-1}) bearing a 2-pyridyl moiety exhibited the best fungicidal activity against *B. cinerea*, **V-B-1** (EC$_{50}$ = 5.36 mg·L^{-1}) bearing a 3-pyridyl moiety took second place, and **V-B-15** (EC$_{50}$ = 14.73 mg·L^{-1}) bearing a 4-pyridyl moiety was the worst. In addition, the introduction of electron-withdrawing groups was more likely to resulte in high fungicidal potency compared with the corresponding analog with an electron-donating group. And it is worth stressing that the fungicidal activity was affected the type of halogen group in pyridine ring, in which grafting of fluorine could more enhance the activity compared to those of chlorine and bromine. For example, **V-B-9** (EC$_{50}$ = 11.03 mg·L^{-1}) with a methyl substituent on the pyridyl ring had less potent fungicidal activity than analog **V-B-1** (EC$_{50}$ = 5.36 mg·L^{-1}) without any substituent, whereas the introduction of fluoro (**V-B-3**, EC$_{50}$ = 1.51 mg·L^{-1}) significantly enhanced the fungicidal activity compared with analog **V-B-1**. A possible explanation is that fluorine possesses the special nature of the inductive effect, block effect, steric effect and mimic effect, so that introduction of fluorine



Scheme 2. Synthesis route of title compounds.

may enhanced the fungicidal activities [32–34].

In an attempt to improve the potency of compound **V-C-1**, different electron–donating as well as electron–withdrawing groups were tested as substituents on the phenyl ring. The fungicidal activity against *B. cinerea* was correlated with the kinds, position and quantity of substituents in benzene ring. Analysis of the available data suggested that electron-withdrawing groups were more important than electron-donating groups in conferring fungicidal activity. For the 2-mono-substituted benzamido ethylsulfonamides, the *meta*-phenyl derivatives showed lower inhibitory activity than compound **V-C-1** while the *ortho*- and *para*-phenyl derivatives proved to be more favourable, and the *ortho*-phenyl derivatives showed the best activity. Surprisingly, the preference of the phenyl *ortho* position was also observed when both electron–withdrawing groups and electron–donating groups were explored. Altogether, it could be concluded that there was no clear correlation between the activity and the modulation of the electron density by the substituents in the benzene ring. Most probably, the influence of the substituents on potency is governed by more than one parameter, e. g. by direct interaction with the binding site, modulation of the electron density, conformational stabilizations, and potential steric interference [35]. Moreover, assuming that some of the favourable effects observed with different substituents at several ring positions could be additive, disubstitution patterns were investigated using combinations of the substituents. Biological evaluation of the resulting disubstituted compounds showed that dichlorophenyl analogues (compounds **V-C-9** and **V-C-10**) led to an increase in the activity compared with the benzamide *ortho*-chloro derivative. However, changing the nature of substituents to dimethyl (compound **V-C-11**) decreased the activity below that of the *ortho*-methyl derivative (compound **V-C-16 ~ 19**), again confirming that the introduction of electron–withdrawing groups could give an improvement in the activity.

Table 1
Fungicidal activities of the title compounds V against *B. cinerea in vitro* and *in vivo*.

Compd.	R	Mycelial growth rate method	Leaf method (500 $mg{\cdot}L^{-1}$)
		EC_{50}($mg{\cdot}L^{-1}$) (95% Cl)	Control efficacy (%)
V-A-1	CH_3-	1.89 (1.32–2.69)	26.23 ijkl[*]
V-A-2	CH_3CH_2-	7.55 (5.64–10.10)	76.51 bc
V-A-3	$CH_3CH_2CH_2$-	2.11 (1.51–2.95)	25.3 ijkl
V-A-4	$CH_3CH_2CH_2CH_2$-	2.08 (1.41–3.06)	60.33 de
V-A-5	$CH_3CH_2CH_2CH_2CH_2$-	8.37 (3.05–23.01)	51.3 efg
V-A-6	$CH_3(CH_2)_4CH_2$-	1.67 (1.16–2.39)	20.32 jkl
V-A-7	CH_2Cl-	27.52 (14.38–52.66)	−13.54o
V-A-8	$CHCl_2$-	2.70 (1.81–4.03)	66.70 cd
V-A-9	CCl_3-	1.52 (0.66–3.46)	32.54 hijk
V-A-10	CH_3OCH_2-	5.49 (3.47–8.67)	88.20 a
V-A-11	CH_3SCH_2-	2.91 (2.15–3.93)	−8.45 mno
V-A-12	$CH_3CH_2OCH_2$-	0.66 (0.21–2.11)	65.87 cd
V-A-13	$CH_3CH_2SCH_2$-	7.49 (4.02–13.95)	49.03 efgh
V-A-14	$CH_3CH_2SCH(CH_3)$-	5.17 (2.57–10.40)	11.75 lm
V-A-15	$(CH_3)_2CHSCH_2$-	2.90 (1.43–5.91)	21.55 kl
V-B-1	3-C_5H_3N-	5.36 (3.72–7.72)	41.89 ghi
V-B-2	5-F-3-C_5H_3N-	3.55 (1.54–6.29)	−34.45 pq
V-B-3	6-F-3-C_5H_3N-	1.51 (0.59–3.84)	18.67 kl
V-B-4	2-Cl-3-C_5H_3N-	5.44 (3.91–7.56)	82.02 ab
V-B-5	5-Br-3-C_5H_3N-	5.99 (4.56–7.86)	−11.83 no
V-B-6	2-Cl-5-Br-3-C_5H_3N-	3.94 (2.97–5.24)	59.19 def
V-B-7	2,6-Cl_2-3-C_5H_3N-	11.35 (8.86–14.54)	25.3 ijkl
V-B-8	2,6-Cl_2-5-F-3-C_5H_3N-	2.55 (1.95–3.34)	58.16 def
V-B-9	6-CH_3-3-C_5H_3N-	11.03 (7.42–16.40)	23.91 ijkl
V-B-10	6-CH_3-2-OH-3-C_5H_3N-	26.73 (16.35–43.69)	8.4 lmn
V-B-11	2-C_5H_3N-	3.43 (2.21–5.32)	67.32 cd
V-B-12	4-Cl-2-C_5H_3N-	4.42 (3.02–6.48)	39.41 ghij
V-B-13	6-Br-2-C_5H_3N-	77.93 (27.34–222.13)	−55.1 q
V-B-14	6-OH-2-C_5H_3N-	9.69 (7.13–13.15)	32.54 hijk
V-B-15	4-C_5H_3N-	14.73 (9.75–22.28)	19.63 jkl
V-B-16	3-OH-4-C_5H_3N-	6.56 (4.41–9.77)	−2.94 mno
V-C-1	C_6H_5-	174.92 (33.02–926.78)	21.55 ijkl
V-C-2	2-F-C_6H_5-	12.8 (2.95–55.58)	52.42 efg
V-C-3	3-F-C_6H_5-	149.44 (14.18–1574.87)	10.74 lm
V-C-4	2-Cl-C_6H_5-	56.47 (9.81–324.99)	41.07 ghi
V-C-5	3-Cl-C_6H_5-	/	33.86 hijk
V-C-6	4-Cl-C_6H_5-	14.22 (7.18–28.16)	80.15b
V-C-7	2-CF_3-C_6H_5-	39.79 (17.58–90.03)	26.23 ijkl
V-C-8	3-CF_3-C_6H_5-	535.29 (53.87–5319.01)	−14.35o
V-C-9	2,4-Cl_2-C_6H_5-	11.12 (6.30–19.63)	45.44 fgh
V-C-10	2,6-Cl_2-C_6H_5-	19.64 (6.20–62.25)	31.21 ijk
V-C-11	2-CH_3-C_6H_5-	10.68 (5.85–19.51)	33.42 hijk
V-C-12	3-CH_3-C_6H_5-	811.76 (45.22–14573.00)	−7.34 mno
V-C-13	4-CH_3-C_6H_5-	78.04 (18.34–332.05)	37.37 hij
V-C-14	2-OCH_3-C_6H_5-	39.84 (10.73–147.94)	12.76 klm
V-C-15	3-OCH_3-C_6H_5-	441.74 (9.32–20931.64)	−1.85 mn
V-C-16	2,3-$(CH_3)_2$-C_6H_5-	41.29 (10.63–160.40)	−1.31 mn
V-C-17	2,4-$(CH_3)_2$-C_6H_5-	180.22 (16.64–1951.89)	25.77 ijkl
V-C-18	2,5-$(CH_3)_2$-C_6H_5-	38.18 (14.07–103.59)	17.56 kl
V-C-19	3,5-$(CH_3)_2$-C_6H_5-	123.18 (44.35–342.16)	15.74 kl
IV		8.66 (6.63–11.33)	59.29 de
III		2.18 (1.38–3.42)	34.3 hijk
procymidone		1.06 (0.61–1.83)	72.32c
pyrimethanil		7.71 (5.70–10.42)	50.55 efg

[*] The letters a–q denoted the results of difference significance analysis. Means followed by the same letter within the same column are not significantly different ($p > 0.05$, Fisher's LSD multiple comparison test).

2.2.2. *In vivo fungicidal activities against tomato gray mold*

In order to further comprehend the whole information of all the newly synthesized compounds, the *in vivo* fungicidal activity (protective effect) was tested against *B. cinerea* on cucumber leaf in a greenhouse. As shown in Table 1, at a concentration of 500 $mg{\cdot}L^{-1}$, most of the synthesized compounds exhibited a certain degree of control efficacy, and some had greater improvement on their fungicidal activities than that of the lead compound **III**. Thereinto, 13 compounds were as or more potent than pyrimethanil (with the control efficacy of 50.55%), among which 4 compounds (**V-A-2**, **V-A-10**, **V-B-4**, **V-C-6**) showed better activity than procymidone (with the control efficacy of 72.32%). Meanwhile, we noticed that there was no direct correspondence between the fungicidal activities *in vitro* and *in vivo*, which matched past studies. Moreover, it was surprised that these compounds with high control efficacy against *B. cinerea in vivo* only exhibited moderate fungicidal activity *in vitro* with EC_{50} values of 5 $mg{\cdot}L^{-1}$ or so, and the *in vivo* control efficacy of compound **V-A-12** (65.87%, EC_{50} = 0.66 $mg{\cdot}L^{-1}$) is not satisfactory. However, it was worthy of note that compounds **V-A-10** and **V-A-12**, which performed best *in vitro* and *in vivo* respectively, were of two homologous compounds with alkoxyl groups. Therefore, the role of alkoxyl groups in the fungicidal activity against *B. cinerea* were valuable for further research.

Compound **V-A-12** had extremely excellent inhibitory effect against *B. cinerea in vitro*, but the *in vivo fungicidal activity* on cucumber leaf was not ideal. Therefore, in order to further confirm its potency, we evaluated the fungicidal activity on tomato leaves by greenhouse experiment, and the high effective botryticides procymidone and boscalid were co-assayed as positive controls under the same condition. As illustrated in Table 2 and Fig. 2, appreciable antifungal potency of compound **V-A-12** (60.96%) was observable, but less effective in comparison of those of procymidone (73.74%) and boscalid (78.97%) at a concentration of 500 $mg{\cdot}L^{-1}$. To our delight, the activity of V-A-10 (75.92%) was equal to those of positive controls. In a previous study of 2-acylaminocycloalkylsulfonamides [18], the alkoxy-containing compound also exhibited superior antifungal activity against *B. cinerea*. Therefore, it is of great necessity to focus on the alkoxyl groups in the future research.

2.3. *Quantitative structure–activity relationship (3D-QSAR) of 2-substituted acylaminoethylsulfonamides*

With the aim of clearly understanding the structure-activity relationship of 2-substituted acylaminoethylsulfonamides, a 3D-QSAR model of these novel 2-substituted acylaminoethylsulfonamides was

Table 2
In vivo fungicidal activities of compounds V-A-10 and V-A-12 against *B. cinerea* by greenhouse experiment.

Compd.	Disease Index (± SE)	Control efficacy
V-A-10	7.59 ± 0.60 a[*]	75.92
V-A-12	12.3 ± 0.72 b	60.96
procymidone	8.27 ± 0.54 a	73.74
boscalid	6.63 ± 0.44 a	78.97
CK	31.94 ± 1.07 c	/

[*] The letters a–c denoted the results of difference significance analysis. Means followed by the same letter within the same column are not significantly different ($p > 0.05$, Fisher's LSD multiple comparison test).

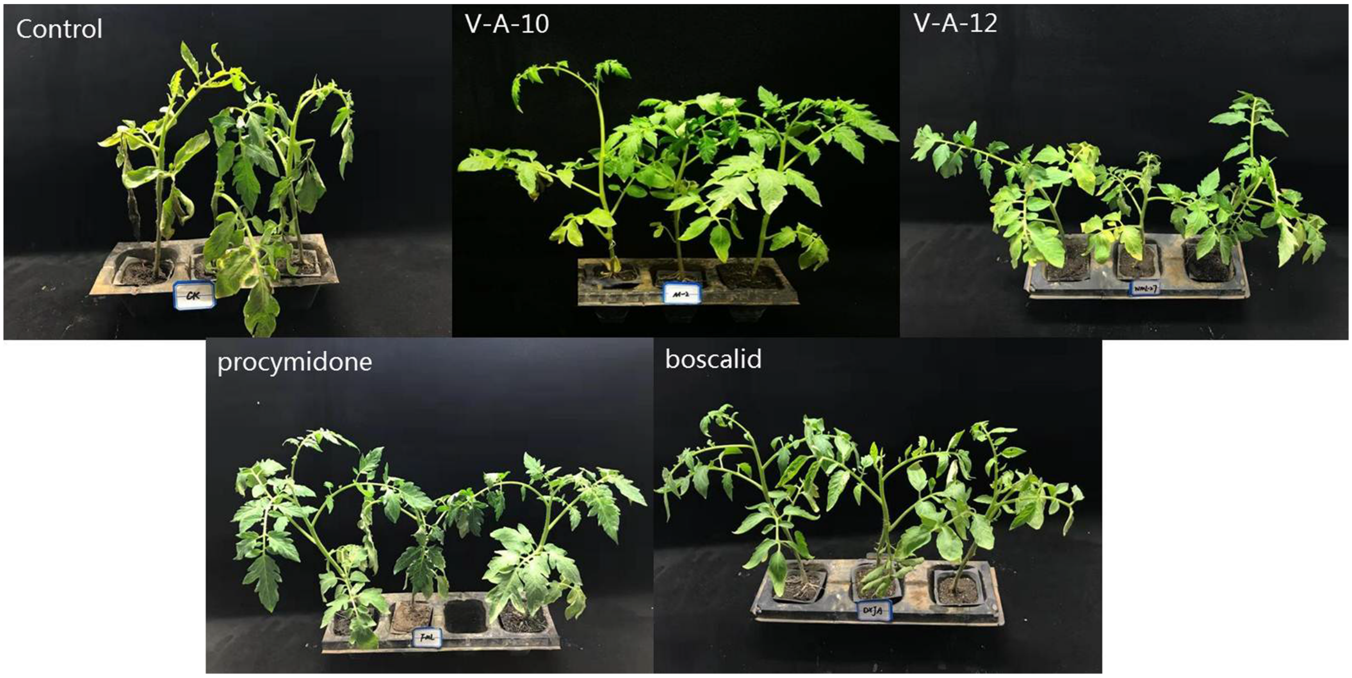


Fig. 2. *In vivo* antifungal activity of compound V-A-10 and V-A-12 against *B. cinerea* using a greenhouse experiment.

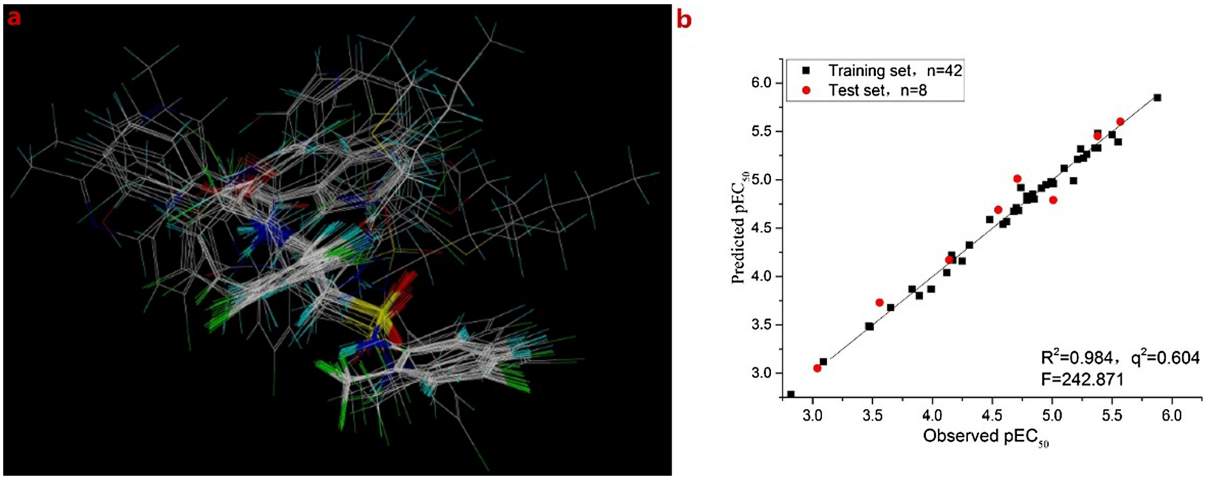


Fig. 3. Establishement of 3D-QSAR model by using CoMFA. (a) Alignment of the target compounds. (b) Plot of experimental versus predicted activities of training set and test set.

initiated by using comparative molecular field analysis (CoMFA) technique of SYBYL X2.0 base on the *in vitro* bioassay, and one of the most active compounds, **V-A-12**, was used as a template to construct the three-dimensional models of all the compounds (Fig. 3a). The initial set of compounds with the calculated pEC_{50} values ranging from 2.82 to 5.88 was divided randomly into a training set (42 compounds) and a test set (8 compounds). The squared cross-validation correlation coefficients (q^2) of the established 3D-QSAR model was 0.604, and the non-crossvalidated R^2 is 0.984, its F value was 242.871 and the standard deviation (S) was 0.104. Furthermore, the test set was used to evaluate its stability and predictive ability. The results showed that the correlation coefficient R^2 between the experimental and predicted pEC_{50} values for the the test set was 0.971, which indicates a good fit for the derived model. Comparison of experimental pEC50 versus predicted values using this QSAR model is given in Fig. 3b, which shows good prediction of the data for training and test sets. The data and residual errors are summarized in Table 3.

The final result of CoMFA model proved that the contributions of steric and electrostatic fields to the activity were 77.2% and 22.8%, respectively. This means that the steric influence plays a dominant role for the investigated compounds, which gives a brief explanation that the introduction of electron-withdrawing groups or electron-donating groups to compounds **V-B** and **V-C** has no obvious effect on the fungicidal activities. Besides, in the preliminary structure-activity relationship analysis of comopounds **V-A**, the fungicidal activity and the structures were not significantly correlated and no obvious regularity. Therefore, to highlight the steric and electrostatic contributions essential for fungicidal activity of **V-A**, contour maps were generated around **V-A-12** in the steric field (Fig. 4a) and electrostatic field (Fig. 4b). The steric map indicates areas where steric bulk is predicted to increase (green) or decrease (yellow) activity. Similarly, in the electrostaticmap, blue contours represent areas where low electron density (positive charge) is expected to increase activity, and red contours represent areas where high electron density (negative charge) is expected to increase activity. Form the Fig. 4a, we can see that there is no limit to the extension of the main alkyl chain, but the size and orientation of side

Table 3
Experimental and predicted activity (pEC_{50}, $mol \cdot L^{-1}$) by the developed QSAR model.

Compd.	Experimental activity	Predicted activity	Absolute error
IV	4.68	4.68	0.00
V-A-1	5.38	5.48	−0.10
V-A-2	4.79	4.79	0.00
V-A-3	5.36	5.33	0.03
V-A-4*	5.38	5.45	−0.07
V-A-5	4.79	4.83	−0.04
V-A-6	5.50	5.47	0.03
V-A-7	4.25	4.16	0.09
V-A-8	5.29	5.26	0.03
V-A-9*	5.57	5.60	−0.03
V-A-10	4.95	4.95	0.00
V-A-11	5.24	5.32	−0.08
V-A-12	5.88	5.85	0.03
V-A-13	4.84	4.85	−0.01
V-A-14	5.01	4.96	0.05
V-A-15	5.26	5.22	0.04
V-B-1	4.99	4.98	0.01
V-B-2	4.85	4.80	0.05
V-B-3	5.55	5.39	0.16
V-B-4*	5.01	4.79	0.22
V-B-5	5.00	4.98	0.02
V-B-6	5.21	5.21	0.00
V-B-7*	4.71	5.01	−0.30
V-B-8	5.38	5.33	0.05
V-B-9	4.68	4.67	0.01
V-B-10	4.31	4.33	−0.02
V-B-11	5.18	4.99	0.19
V-B-12	5.10	5.12	−0.02
V-B-13	3.89	3.80	0.09
V-B-14	4.74	4.92	−0.18
V-B-15*	4.55	4.69	−0.14
V-B-16	4.91	4.91	0.00
V-C-1	3.47	3.49	−0.02
V-C-2	4.62	4.57	0.05
V-C-3*	3.56	3.73	−0.17
V-C-4	3.99	3.87	0.12
V-C-6	4.59	4.54	0.05
V-C-7	4.17	4.17	0.00
V-C-8*	3.04	3.05	−0.01
V-C-9	4.72	4.68	0.04
V-C-10	4.48	4.59	−0.11
V-C-11	4.70	4.71	−0.01
V-C-12	3.83	3.87	−0.04
V-C-13	2.82	2.78	0.04
V-C-14*	4.14	4.17	−0.03
V-C-15	3.09	3.12	−0.03
V-C-16	4.12	4.04	0.08
V-C-17	3.48	3.48	0.00
V-C-18	4.16	4.22	−0.06
V-C-19	3.65	3.68	−0.03

* The compound belongs to test set.

chain groups have an important influence on the fungicidal activity of comopounds **V-A**. When side chain groups deflect in the same direction as the 2-amino ethylsulfonamide scaffold, introduction of sterically large groups is favorable for enhancing fungicidal activity. Conversely, if the side chain groups and the 2-amino ethylsulfonamide scaffold are in the opposite directions, the substituents should be sterically small. As shown in Fig. 4b, when side chain groups and the 2-amino ethylsulfonamide scaffold are on the same side, the high negative charge is the demand for the promotion of fungicidal activity, contrarily the positive charge substituents are beneficial. Altogether, the spatial conformation of substituents is an important problem that should be firstly considered in the optimization of compounds **V-A**. (see Table 4)

2.4. Biological evalution against resistant Botrytis cinerea strains

The control of gray mold relies mainly on the use of fungicides with site-specific modes of action. However, *B. cinerea,* as a classical "high-risk" pathogen, has developed resistance to most fungicide classes [2]. Early *B. cinerea* resistance studies reported cases of resistance development to one single chemical class. Nevertheless, in the recent past, the number of reports of multiple resistance to different chemical classes associated with the accumulation of different target-site mutations in the same strains has dramatically increased worldwide, representing a major threat for the successful control of the disease [1,7,10,36]. Especially anxious, there are no fungicides with novel mechanism of action for a long time from succinate dehydrogenase inhibitors (SDHIs) that represent the latest addition to the group of botryticides [37,38]. Therefore, these issues require the innovation of alternative fungicides to successfully control *B. cinerea.*

In our previous work, it is found that sulfonamides might inhibit the growth of gray mould by affecting the synthesis of the internal substance in a novel mode [39], thus the novel 2-substituted acylaminoethylsulfonamides (**V**) may effectively control resistant strains of *B. cinerea*. Therefore, three *B. cinerea* strains (**XM**, **FS-10** and **HLD-15**) with different resistant levels were selected to evaluate the fungicidal activity of synthetic compounds against resistant *B. cinerea* strains. Referring to resistant grading standards to procymidone [40], the *B. cinerea* strain **XM** was sensitive; **FS-10** with low-resistance and **HLD-15** with high-resistance. As shown in Table 3, all the selected compounds exhibited significant activity against three *B. cinerea* strains. It was worthy of note that the EC_{50} value didn't increase with the promotion of resistant level, that is to say these sulfonamides are also effective for the procymidone-resistant *B. cinerea* strains. This result further enhance the development value of 2-substituted acylaminoethylsulfonamides to control the tomato gray mold.

3. Conclusion

The current work presented three series of novel 2-substituted alkylamido, pyridylformoylamido and benzamido ethylsulfonamides with the taurine (2-aminoethanesulfonic acid) scaffold. Biological evaluation of these newly prepared sulfonamides was performed against *Botrytis cinerea in vitro* and *in vivo*, and the results showed that all the compounds exhibited fungicidal activity in various degrees. Notably, 2-ethoxyacetylamide derivative (**V-A-12**, $EC_{50} = 0.66\,mg \cdot L^{-1}$) displayed the highest potency *in vitro* and superior fungicidal activity compared with procymidone ($EC_{50} = 1.06\,mg \cdot L^{-1}$). Furthermore, the *in vivo* bioassay also indicated that compound **V-A-12** could be effective for the control of tomato gray mold caused by *Botrytis cinerea*. Moreover, a three-dimensional quantitative structureactivity relationships (3D-QSAR) model of comparative molecular field analysis (CoMFA) was developed to identify some key structural features responsible for their potency, which also rationalize the obtained activity results and provide guidance to continue the development of sulfonamides. Finally, the effeicacy of sulfonamide derivatives was verified in the activity evaluation against procymidone-resistant *Botrytis cinerea* strains. Altogether, these results further enhance the development value of 2-substituted acylaminoethylsulfonamides to control the tomato gray mold. The detailed mechanism of sulfonamides against *Botrytis cinerea* is exploring in depth to identify a possible target, thereby accelerating structural optimization and developing novel sulfonamide fungicides.

4. Materials and methods

4.1. General information

All reagents and solvents were of reagent grade or purified according to standard methods before use. The melting points were measured using an X-5 melting-point apparatus (Beijing Second Optical Instrument Factory, Beijing, China). Infrared (IR) spectra were recorded in potassium bromide disks on a Shimadzu IR Affinity-1 spectrophotometer (Shimadzu, Kyoto, Japan). Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 unless indicated otherwise

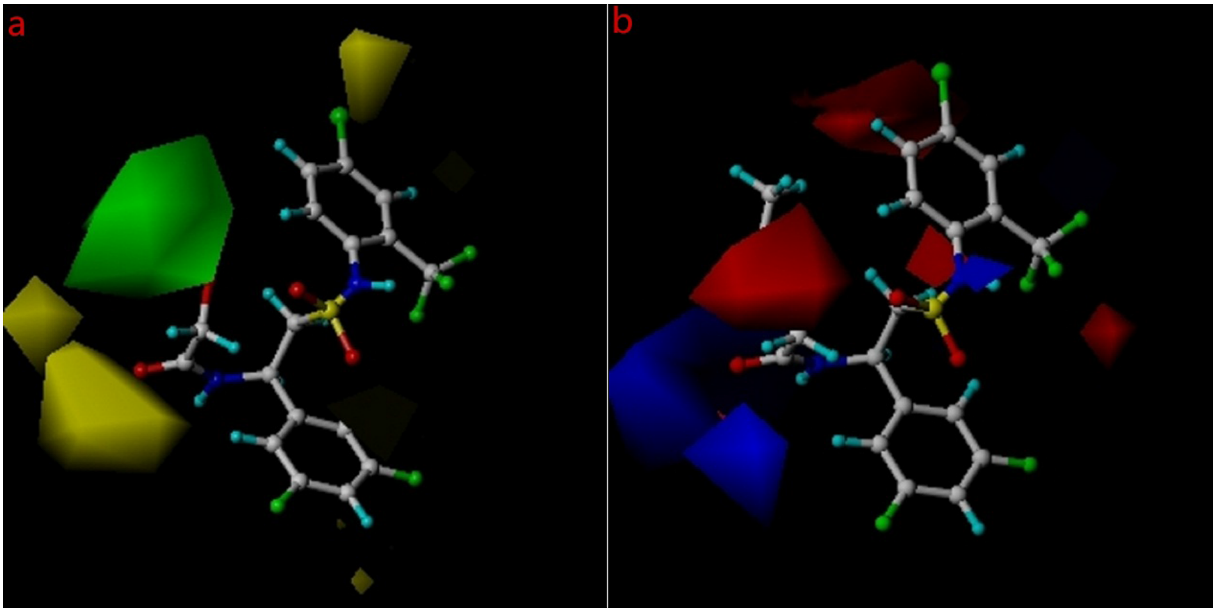


Fig. 4. Three dimensional (3D) contour plots of the CoMFA model. (a) steric field. Green represents positive coefficients; yellow represents negative coefficients. (b) electrostatic field. Blue represents positive coefficients; red represents negative coefficients.

Table 4

Biological evalution against resistant *Botrytis cinerea* strains.

Compd.	EC_{50}(mg·L^{-1}) (95% CI)		
	XM (S)*	FS-10 (LR)*	HLD-15 (HR)*
V-A-1	1.89 (1.32–2.69) a**	1.64 (1.15–2.34) a	2.40 (1.60–3.61) a
V-A-6	1.67 (1.16–2.39) a	1.40 (0.89–2.23) a	1.31 (0.38–4.54) a
V-A-9	1.52 (0.66–3.46) a	1.93 (1.19–3.15) a	3.18 (1.99–5.09) b
V-A-12	0.66 (0.21–2.11) a	1.01 (0.53–1.91) a	0.47 (0.19–1.19) a
V-B-3	1.51 (0.59–3.84) a	0.96 (0.33–2.76) a	2.61 (1.82–3.73) b
IV	8.66 (6.63–11.33) b	10.08 (7.89–12.87) b	5.40 (3.66–7.97) a
III	2.18 (1.38–3.42) a	3.06 (2.13–4.37) a	3.57 (2.48–1.54) b
procymidone	1.06 (0.61–1.83) a	3.55 (1.54–6.29) b	16.3 (9.79–29.13) c

* The *B. cinerea* strain **XM** was sensitive to procymidone (S); **FS-10** with low-resistance (LR) and **HLD-15** with high-resistance (HR).

** The letters a–c denoted the results of difference significance analysis. Means followed by the same letter within the same line are not significantly different ($p > 0.05$, Fisher's LSD multiple comparison test).

with Bruker 600 MHz spectrometers, using tetramethylsilane (TMS) as an internal standard. High resolution mass spectra (HRMS) were recorded on a G2-XS QTof Mass Spectrometry Facility (Waters, Milford, MA, USA).

4.2. Synthetic procedures of 2-substituted acylaminoethylsulfonamides

The synthetic route of the title compounds was shown in Fig. 2. Potassium *N*-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-oxoethylsulfonamide (**II**), were prepared from readily commercial available substituted acetophenone (**I**) by sulfonation with a sulfur trioxide-dioxane adduct and neutralization with potassium according to the method given in references [22]. The title compounds were synthesized by the method developed by our group shown as follows.

4.2.1. Synthesis of N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-aminoethylsulfonamide (IV)

Compound **III** were synthesized according to the method given in the Refs. [22,41].

According to the method given in the Ref. [18], a mixture of compound **III** (30 mmol) and titanium (IV) isopropoxide (17 mL, 60 mmol) in dry ethyl alcohol (150 mL) were stirred at room temperature under N_2. Then, in place of N_2, the ammonia gas was introduced into the reaction mixture with the pressure of 20 mmHg for 6 h. Next, sodium borohydride (1.7 g, 45 mmol) was added slowly to the resulting mixture and stirred for 3 h. The reaction was quenched by addition of ammonium hydroxide solution (2 M, 120 mL). The resulting inorganic precipitate was filtered off, and washed with ethyl acetate (150 mL). The filtrate was concentrated under reduced pressure to remove ethyl acetate, and then extracted with ethyl acetate (200 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and recrystallized from methanol to afford pure key intermediate **IV**. Its physical and spectra data were shown as follows.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-aminoethylsulfonamide (**IV**). White solid; yield, 92%; m.p., 157.6–158.8 °C; IR (KBr) ν_{max}: 3510 (NH), 3280 (NH), 1386, 1140 (-SO_2-); ^1H NMR (600 MHz, DMSO-d_6): 8.57 (s, 3H, NH + NH_2), 7.43 (d, J = 9.0 Hz, 1H, Ar-H), 7.35 (d, J = 2.7 Hz, 1H, Ar-H), 7.31 – 7. 23 (m, 4H, Ar-H), 4.75 (dd, J = 10.3, 2.1 Hz, 1H, CH-N), 3.49 (dd, J = 14.3, 10.5 Hz, 1H, CH-SO_2), 3.20 (dd, J = 14.3, 2.9 Hz, 1H, CH-SO_2); HRMS (ESI), m/z calcd for $C_{15}H_{13}ClF_5N_2O_2S$ $[M+H]^+$ 415.0306, found 415.0309.

4.2.2. Synthesis of 2-substituted amido ethylsulfonamides (V)

Octanoyl chlorides, halogenated octanoyl chlorides, alkoxy octanoyl chlorides, alkylthio octanoyl chlorides, substituted pyridine formyl chlorides and substituted benzoyl chlorides were synthesized according to the given method in the Ref. [21].

To a stirred solution of compound **IV** (3 mmol) and triet hylamine (Et_3N, 3.9 mmol) in dry dichloromethane (CH_2Cl_2, 40 mL), acyl chlorides (3 mmol) were dropwise added under N_2. After stirring at room temperature for 2 h,the mixture was filtered and washed with 3 M HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (40 mL). After dried by anhydrous Na_2SO_4 and concentrated in vacuo, the crude product was recrystallized with the acetone/petroleum ether to afford pure compounds **V**. Their physical data and spectra data were shown as follows.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(acetylamido) ethylsulfonamide (**V-A-1**). White solid; yield: 72%; m.p.: 195.4–196.2 °C; IR (KBr) ν_{max}: 3331 (NH), 3270 (NH), 1680 (C=O), 1340, 1165 (-SO_2-); ^1H NMR (600 MHz, DMSO-d_6): 9.65 (s, 1H, NH-SO_2), 8.52 (d, J = 8.2 Hz, 1H, NH-CO), 7.80 (d, J = 2.4 Hz, 1H, Ar-H), 7.76 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.16 – 7.12 (m, 1H, Ar-H), 7.11 – 7.09 (m, 2H, Ar-H), 5.38 (td, *J* = 8.1, 5.5 Hz, 1H, CH-N), 3.69 (dd, *J* = 14.3, 8.2 Hz, 1H, CH-SO$_2$), 3.64 (dd, *J* = 14.3, 5.4 Hz, 1H, CH-SO$_2$), 1.84 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{17}H_{15}ClF_5N_2O_3S$ [M + H]$^+$: 457.0412, found 457.0407.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(propionylamido) ethylsulfonamide (**V-A-2**). White solid; yield: 88%; m.p.: 164.2–165.4 °C; IR (KBr) ν_{max}: 3343 (NH), 3257 (NH), 1688 (C = O), 1384, 1165 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 8.60 (dd, *J* = 41.1, 8.6 Hz, 1H, NH-SO$_2$), 8.41 (d, *J* = 8.1 Hz, 1H, NH-CO), 8.01 (ddd, *J* = 10.9, 7.7, 2.4 Hz, 1H, Ar-H), 7.81 – 7.71 (m, 2H, Ar-H), 7.60 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.09 (d, *J* = 6.3 Hz, 2H, Ar-H), 5.38 (td, *J* = 8.2, 5.1 Hz, 1H, CH-N), 3.68 (dd, *J* = 14.1, 8.5 Hz, 1H, CH-SO$_2$), 3.61 (dd, *J* = 14.2, 4.9 Hz, 1H, CH-SO$_2$), 0.97 (td, *J* = 7.6, 2.5 Hz, 5H, CH$_2$CH$_3$); HRMS (ESI), *m/z* calcd for $C_{18}H_{17}ClF_5N_2O_3S$ [M + H]$^+$: 471.0569, found 471.0566.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(n-butyrylamido) ethylsulfonamide (**V-A-3**). White solid; yield: 85%; m.p.: 159.8–160.4 °C; IR (KBr) ν_{max}: 3351 (NH), 3260 (NH), 1752 (C = O), 1366, 1131 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.67 (s, 1H, NH-SO$_2$), 8.47 (d, *J* = 8.2 Hz, 1H, NH-CO), 7.82 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.77 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.15 (tt, *J* = 9.3, 2.3 Hz, 1H, Ar-H), 7.12 – 7.07 (m, 2H, Ar-H), 5.41 (td, *J* = 8.3, 5.2 Hz, 1H, CH-N), 3.71 (dd, *J* = 14.2, 8.5 Hz, 1H, CH-SO$_2$), 3.64 (dd, *J* = 14.2, 5.1 Hz, 1H, , CH-SO$_2$), 2.13–1.42 (m, 4H, 2CH$_2$), 0.82 (t, *J* = 7.4 Hz, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{19}H_{19}ClF_5N_2O_3S$ [M + H]$^+$: 485.0725, found 485.0719.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(n-valerylamido) ethylsulfonamide (**V-A-4**). White solid; yield: 92%; m.p.: 143.2–114.6 °C; IR (KBr) ν_{max}: 3351 (NH), 3248 (NH), 1750 (C = O), 1345, 1126 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.66 (s, 1H, NH-SO$_2$), 8.46 (d, *J* = 8.2 Hz, 1H, NH-CO), 7.80 (s, 1H, Ar-H), 7.76 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.61 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.14 (dd, *J* = 10.3, 8.2 Hz, 1H, Ar-H), 7.09 (d, *J* = 6.4 Hz, 2H, Ar-H), 5.39 (dd, *J* = 13.2, 8.1 Hz, 1H, CH-N), 3.65 (dd, *J* = 32.0, 8.7 Hz, 2H, CH$_2$-SO$_2$), 2.10–1.14 (m, 6H, 3CH$_2$), 0.83 (t, *J* = 7.4 Hz, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{20}H_{21}ClF_5N_2O_3S$ [M + H]$^+$: 499.0882, found 499.0873.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(n-hexanoylamido) ethylsulfonamide (**V-A-5**). White solid; yield: 72%; m.p.: 180.4–181.6 °C; IR (KBr) ν_{max}: 3353 (NH), 3240 (NH), 1686 (C = O), 1384, 1127 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.65 (s, 1H, NH-SO$_2$), 8.46 (d, *J* = 8.2 Hz, 1H, NH-CO), 7.81 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.76 (dd, *J* = 8.6, 2.5 Hz, 1H, Ar-H), 7.61 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.14 (tt, *J* = 9.2, 2.3 Hz, 1H, Ar-H), 7.09 (dd, *J* = 8.2, 2.0 Hz, 2H, Ar-H), 5.39 (td, *J* = 8.3, 5.2 Hz, 1H, CH-N), 3.70 (dd, *J* = 14.3, 8.4 Hz, 1H, CH-SO$_2$), 3.64 (dd, *J* = 14.3, 5.1 Hz, 1H, CH-SO$_2$), 2.08 (t, *J* = 7.4 Hz, 2H, CH$_2$), 1.55 – 1.35 (m, 2H, CH$_2$), 1.29 – 1.12 (m, 4H, 2 CH$_2$), 0.81 (t, *J* = 7.2 Hz, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{21}H_{23}ClF_5N_2O_3S$ [M + H]$^+$: 513.1038, found 513.1031.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(n-heptanoylamido) ethylsulfonamide (**V-A-6**). White solid; yield: 85%; m.p.: 175.9–177.0 °C; IR (KBr) ν_{max}: 3350 (NH), 3217 (NH), 1670 (C = O), 1385, 1122 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.66 (s, 1H, NH-SO$_2$), 8.47 (d, *J* = 8.2 Hz, 1H, NH-CO), 7.82 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.77 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.14 (tt, *J* = 9.3, 2.3 Hz, 1H, Ar-H), 7.09 (dd, *J* = 8.2, 1.9 Hz, 2H, Ar-H), 5.40 (td, *J* = 8.2, 5.2 Hz, 1H, CH-N), 3.71 (dd, *J* = 14.3, 8.4 Hz, 1H, 1H, CH-SO$_2$), 3.64 (dd, *J* = 14.2, 5.1 Hz, 1H, 1H, CH-SO$_2$), 2.08 (q, *J* = 7.2 Hz, 2H, CH$_2$), 1.51 – 1.42 (m, 2H, CH$_2$), 1.23 – 1.16 (m, 6H, 3CH$_2$), 0.83 (t, *J* = 7.0 Hz, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{22}H_{25}ClF_5N_2O_3S$ [M + H]$^+$: 527.1195, found 527.1194.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-chloroacetylamido) ethylsulfonamide (**V-A-7**). White solid; yield: 74%; m.p.: 143.0–144.2 °C; IR (KBr) ν_{max}: 3291 (NH), 3170 (NH), 1688 (C = O), 1386, 1127 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 8.89 (s, 1H, NH-SO$_2$), 8.88 (s, 1H, NH-CO), 7.76 (s, 1H, Ar-H), 7.72 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.19 – 7.07 (m, 3H, Ar-H), 5.39 (td, *J* = 8.2, 5.1 Hz, 1H, CH-N), 4.16 – 4.07 (m, 2H, CH$_2$-Cl), 3.77 (dd, *J* = 14.2, 8.4 Hz, 1H, CH-SO$_2$), 3.53 (dd, *J* = 14.3, 10.0 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{17}H_{14}Cl_2F_5N_2O_3S$ [M + H]$^+$: 491.0022, found 491.0025.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,2-dichloroacetylamido) ethylsulfonamide (**V-A-8**). Pale yellow solid; yield: 86%; m.p.: 153.5–154.2 °C; IR (KBr) ν_{max}: 3273 (NH), 3165 (NH), 1703 (C = O), 1385, 1120 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.72 (s, 1H, NH-SO$_2$), 9.30 (d, *J* = 7.9 Hz, 1H, NH-CO), 7.80 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.78 – 7.71 (m, 1H, Ar-H), 7.60 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.19 (tt, *J* = 9.3, 2.2 Hz, 1H, Ar-H), 7.13 (d, *J* = 6.3 Hz, 2H, Ar-H), 6.52 (s, 1H, CH-Cl), 5.37 (td, *J* = 8.3, 4.8 Hz, 1H, CH-N), 3.84 (dd, *J* = 14.3, 8.7 Hz, 1H, CH-SO$_2$), 3.71 (dd, *J* = 14.4, 4.7 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{17}H_{13}Cl_3F_5N_2O_3S$ [M + H]$^+$: 524.9633, found 491.0025.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,2,2-trichloroacetylamido) ethylsulfonamide (**V-A-9**). White solid; yield: 83%; m.p.: 153.5–154.2 °C; IR (KBr) ν_{max}: 3268 (NH), 3170 (NH), 1670 (C = O), 1384, 1127 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.84 (s, 1H, NH-SO$_2$), 9.61 (d, *J* = 7.9 Hz, 1H, NH-CO), 7.82 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.21 (tt, *J* = 9.2, 2.3 Hz, 1H, Ar-H), 7.17 (dd, *J* = 7.2, 5.3 Hz, 2H, Ar-H), 5.39 (td, *J* = 9.8, 3.6 Hz, 1H, CH-N), 4.05 (dd, *J* = 14.4, 9.8 Hz, 1H, CH-SO$_2$), 3.69 (dd, *J* = 14.4, 3.7 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{17}H_{11}Cl_4F_5N_2O_3S$ [M + NH$_4$]$^+$: 575.9508, found 575.9515.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-methoxyacetylamido) ethylsulfonamide (**V-A-10**). White solid; yield: 88%; m.p.: 154.3–155.1 °C; IR (KBr) ν_{max}: 3256 (NH), 3178 (NH), 1690 (C = O), 1390, 1130 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.70 (s, 1H, NH-SO$_2$), 8.54 (d, *J* = 8.4 Hz, 1H, NH-CO), 7.81 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.60 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.17 – 7.10 (m, 3H, Ar-H), 5.46 (td, *J* = 8.8, 4.3 Hz, 1H, CH-N), 3.96 (dd, *J* = 14.3, 9.1 Hz, 1H, CH-SO$_2$), 3.82 (q, *J* = 15.3 Hz, 2H, CH$_2$-CO), 3.63 (dd, *J* = 14.3, 4.4 Hz, 1H, CH-SO$_2$), 3.31 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{18}H_{17}ClF_5N_2O_4S$ [M + H]$^+$: 487.0518, found 487.0512.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-methylmercaptoacetylamido) ethylsulfonamide (**V-A-11**). White solid; yield: 86%; m.p.: 156.2–157.0 °C; IR (KBr) ν_{max}: 3308 (NH), 3160 (NH), 1683 (C = O), 1383, 1134 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.71 (s, 1H, NH-SO$_2$), 8.55 (d, *J* = 8.4 Hz, 1H, NH-CO), 7.85 – 7.74 (m, 2H, Ar-H), 7.61 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.18 – 7.09 (m, 3H, Ar-H), 5.47 (td, *J* = 8.7, 4.3 Hz, 1H, CH-N), 3.97 (dd, *J* = 14.3, 9.1 Hz, 1H, CH-SO$_2$), 3.83 (q, *J* = 15.3 Hz, 2H, CH$_2$-CO), 3.64 (dd, *J* = 14.3, 4.4 Hz, 1H, CH-SO$_2$), 3.33 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{18}H_{16}ClF_5N_2O_3S_2$ [M + Na]$^+$: 525.0109, found 525.0067.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-ethoxyacetylamido) ethylsulfonamide (**V-A-12**). White solid; yield: 89%; m.p.: 141.9–143.2 °C; IR (KBr) ν_{max}: 3298 (NH), 3152 (NH), 1705 (C = O), 1390, 1144 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.71 (s, 1H, NH-SO$_2$), 8.45 (d, *J* = 8.4 Hz, 1H, NH-CO), 7.82 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.18 – 7.14 (m, 2H, Ar-H), 7.13 (s, 1H, Ar-H), 5.46 (td, *J* = 8.6, 4.4 Hz, 1H, CH-N), 3.97 (dd, *J* = 14.3, 9.0 Hz, 1H, CH-SO$_2$), 3.89 – 3.82 (m, 2H, CH$_2$-CO), 3.65 (dd, *J* = 14.3, 4.4 Hz, 1H, CH-SO$_2$), 3.53 – 3.44 (m, 2H, CH$_2$-O), 1.14 (t, *J* = 7.0 Hz, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{19}H_{19}ClF_5N_2O_4S$ [M + H]$^+$: 501.0674, found 501.0672.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-ethylmercaptoacetylamido) ethylsulfonamide (**V-A-13**). White solid; yield: 85%; m.p.: 103.9–104.4 °C; IR (KBr) ν_{max}: 3249 (NH), 3168 (NH), 1688 (C = O), 1384, 1132 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.62 (s, 1H, NH-SO$_2$), 9.60 (s, 1H, NH-CO), 7.80–7.15 (m, 6H, Ar-H), 5.42 (td, *J* = 8.9, 4.1 Hz, 1H, CH-N), 3.99 (dd, *J* = 14.3, 9.3 Hz, 1H, CH-SO$_2$), 3.77 (s, 3H, CH$_3$), 3.65 (dd, *J* = 14.2, 4.0 Hz, 1H, CH-SO$_2$), 3.23 (d, *J* = 103.2 Hz, 4H, 2CH$_2$); HRMS (ESI), *m/z* calcd for

$C_{19}H_{19}ClF_5N_2O_3S_2$ [M + H]$^+$: 517.0446, found 517.0443.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-ethylmercaptopropylamido) ethylsulfonamide (**V-A-14**). White solid; yield: 75%; m.p.: 164.8–166.0 °C; IR (KBr) ν_{max}: 3349 (NH), 3240 (NH), 1690 (C = O), 1380, 1128 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.71 (s, 1H, NH-SO_2), 8.65 (dd, *J* = 45.4, 8.1 Hz, 1H, NH-CO), 7.84 – 7.73 (m, 2H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.22 – 7.08 (m, 3H, Ar-H), 5.39 (ddd, *J* = 16.3, 15.0, 6.5 Hz, 1H, CH-N), 3.80 (ddd, *J* = 33.3, 14.3, 8.6 Hz, 1H, CH-SO_2), 3.71 – 3.65 (m, 1H, CH-SO_2), 3.41 (dt, *J* = 7.1, 5.0 Hz, 1H, CH-CO), 2.53 (dd, *J* = 7.4, 5.2 Hz, 1H, CH_2-S), 2.45 (ddd, *J* = 12.7, 10.4, 6.3 Hz, 1H, CH_2-S), 1.27 (dd, *J* = 13.6, 7.1 Hz, 3H, CH_3), 1.08 (dt, *J* = 29.8, 7.4 Hz, 3H, CH_3); HRMS (ESI), *m/z* calcd for $C_{20}H_{21}ClF_5N_2O_3S_2$ [M + H]$^+$: 531.0602, found 531.0596.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-isopropylmercaptoacetylamido) ethylsulfonamide (**V-A-15**). White solid; yield: 68%; m.p.: 143.8–144.6 °C; IR (KBr) ν_{max}: 3324(NH), 3240 (NH), 1713 (C = O), 1386, 1125 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.69 (s, 1H, NH-SO_2), 8.70 (d, *J* = 8.1 Hz, 1H, NH-CO), 7.84 – 7.74 (m, 2H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.19 – 7.09 (m, 3H, Ar-H), 5.39 (td, *J* = 8.2, 5.1 Hz, 1H, CH-N), 3.79 (dd, *J* = 14.3, 8.3 Hz, 1H, CH-SO_2), 3.69 (dd, *J* = 14.3, 5.1 Hz, 1H, CH-SO_2), 3.17 (s, 2H, CH_2-CO), 2.91 (hept, *J* = 6.7 Hz, 1H, CH-S), 1.17 – 1.11 (m, 6H, 2CH_3); HRMS (ESI), *m/z* calcd for $C_{20}H_{21}ClF_5N_2O_3S_2$ [M + H]$^+$: 531.0602, found 531.0599.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-pyridyl-formoylamido) ethylsulfonamide (**V-B-1**). White solid; yield: 85%; m.p.: 199.5–200.3 °C; IR (KBr) ν_{max}: 3356 (NH + NH), 1688 (C = O), 1392, 1118 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.78 (s, 1H, NH-SO_2), 9.24 (d, *J* = 8.1 Hz, 1H, NH-CO), 8.98 (d, *J* = 1.7 Hz, 1H, Ar-H), 8.72 (dd, *J* = 4.8, 1.6 Hz, 1H, Ar-H), 8.15 (dt, *J* = 8.0, 1.9 Hz, 1H, Ar-H), 7.82 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.77 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.55 – 7.51 (m, 1H, Ar-H), 7.22 – 7.14 (m, 3H, Ar-H), 5.63 (td, *J* = 9.3, 4.2 Hz, 1H, CH-N), 3.92 (dd, *J* = 14.3, 9.6 Hz, 1H, CH-SO_2), 3.73 (dd, *J* = 14.2, 4.2 Hz, 1H, CH-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{16}ClF_5N_3O_3S$ [M + H]$^+$: 520.0521, found 520.0521.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(5-fluoro-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-2**). White solid; yield: 88%; m.p.: 195.2–196.3 °C; IR (KBr) ν_{max}: 3346 (NH), 3280 (NH), 1707 (C = O), 1386, 1122 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.80 (s, 1H, NH-SO_2), 9.35 (d, *J* = 8.1 Hz, 1H, NH-CO), 8.90 – 8.85 (m, 1H, Ar-H), 8.77 (d, *J* = 2.8 Hz, 1H, Ar-H), 8.04 (ddd, *J* = 9.4, 2.8, 1.8 Hz, 1H, Ar-H), 7.85 – 7.74 (m, 2H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.24 – 7.14 (m, 3H, Ar-H), 5.63 (td, *J* = 9.2, 4.3 Hz, 1H, CH-N), 3.92 (dd, *J* = 14.3, 9.6 Hz, 1H, CH-SO_2), 3.75 (dd, *J* = 14.3, 4.3 Hz, 1H, CH-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{15}ClF_6N_3O_3S$ [M + H]$^+$: 538.0427, found 538.0425.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(6-fluoro-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-3**). White solid; yield: 81%; m.p.: 192.4–193.1 °C; IR (KBr) ν_{max}: 3350 (NH), 3246 (NH), 1670 (C = O), 1366, 1124 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.79 (s, 1H, NH-SO_2), 9.26 (d, *J* = 8.1 Hz, 1H, NH-CO), 8.67 (d, *J* = 2.5 Hz, 1H, Ar-H), 8.34 (td, *J* = 8.2, 2.5 Hz, 1H, Ar-H), 7.89 – 7.70 (m, 2H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.33 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.24 – 7.07 (m, 3H, Ar-H), 5.62 (td, *J* = 9.2, 4.2 Hz, 1H, CH-N), 3.91 (dd, *J* = 14.2, 9.6 Hz, 1H, CH-SO_2), 3.74 (dd, *J* = 14.2, 4.3 Hz, 1H, CH-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{15}ClF_6N_3O_3S$ [M + H]$^+$: 538.0427, found 538.0423.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-chloro-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-4**). White solid; yield: 82%; m.p.: 204.5–206.4 °C; IR (KBr) ν_{max}: 3341 (NH), 3238 (NH), 1688 (C = O), 1358, 1124 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.79 (s, 1H, NH-SO_2), 9.34 (d, *J* = 8.2 Hz, 1H, NH-CO), 8.49 (dd, *J* = 4.8, 1.9 Hz, 1H, Ar-H), 7.89 (dd, *J* = 7.5, 1.9 Hz, 1H, Ar-H), 7.82 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.77 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.54 (dd, *J* = 7.5, 4.8 Hz, 1H, Ar-H), 7.23 – 7.16 (m, 3H, Ar-H), 5.60 (td, *J* = 8.3, 5.2 Hz, 1H, CH-N), 3.87 – 3.68 (m, 2H, CH-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{15}Cl_2F_5N_3O_3S$ [M + H]$^+$: 554.0131, found 554.0135.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(5-bromo-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-5**). White solid; yield: 65%; m.p.: 197.1–198.4 °C; IR (KBr) ν_{max}: 3354 (NH), 3230 (NH), 1686 (C = O), 1362, 1122 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.80 (s, 1H, NH-SO_2), 9.33 (d, *J* = 8.1 Hz, 1H, NH-CO), 8.91 (dd, *J* = 34.2, 2.0 Hz, 2H, Ar-H), 8.38 (q, *J* = 2.2 Hz, 1H, Ar-H), 7.84 – 7.74 (m, 2H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.18 (ddd, *J* = 9.2, 7.6, 4.3 Hz, 3H, Ar-H), 5.62 (td, *J* = 9.1, 4.3 Hz, 1H, CH-N), 3.90 (dd, *J* = 14.3, 9.6 Hz, 1H, CH-SO_2), 3.75 (dd, *J* = 14.3, 4.3 Hz, 1H, CH-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{15}BrClF_5N_3O_3S$ [M + H]$^+$: 597.9626, found 597.9630.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(5-bromo-2-chloro-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-6**). Pale yellow solid; yield: 81%; m.p.: 105.6–106.3 °C; IR (KBr) ν_{max}: 3309 (NH), 3218 (NH), 1703 (C = O), 1374, 1135 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.82 (s, 1H, NH-SO_2), 9.42 (d, *J* = 8.2 Hz, 1H, NH-CO), 8.69 (d, *J* = 2.5 Hz, 1H, Ar-H), 8.15 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.83 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.78 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.23 – 7.16 (m, 3H, Ar-H), 5.58 (dd, *J* = 14.1, 7.7 Hz, 1H, CH-N), 3.79 (d, *J* = 7.7 Hz, 2H, CH_2-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{13}BrCl_2F_5N_3O_3S$ [M + Na]$^+$: 653.9056, found 653.9052.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,6-dichloro-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-7**). White solid; yield: 90%; m.p.: 167.8–168.7 °C; IR (KBr) ν_{max}: 3298 (NH + NH), 1705 (C = O), 1362, 1122 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.79 (s, 1H, NH-SO_2), 9.39 (d, *J* = 8.2 Hz, 1H, NH-CO), 7.96 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.82 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.77 (dd, *J* = 8.6, 2.2 Hz, 1H, Ar-H), 7.72 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.65 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.23 – 7.16 (m, 3H, Ar-H), 5.59 (dt, *J* = 13.7, 6.8 Hz, 1H, CH-N), 3.83 – 3.71 (m, 2H, CH_2-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{14}Cl_3F_5N_3O_3S$ [M + H]$^+$: 587.9742, found 587.9739.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(5-fluoro-2,6-dichloro-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-8**). Pale yellow solid; yield: 88%; m.p.: 182.6–183.7 °C; IR (KBr) ν_{max}: 3254 (NH + NH), 1689 (C = O), 1358, 1124 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.82 (s, 1H, NH-SO_2), 9.44 (d, *J* = 8.2 Hz, 1H, NH-CO), 8.13 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.83 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 7.64 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.23 – 7.18 (m, 3H, Ar-H), 5.58 (dd, *J* = 14.6, 7.1 Hz, 1H, CH-N), 3.80 (d, *J* = 7.0 Hz, 2H, CH_2-SO_2); HRMS (ESI), *m/z* calcd for $C_{21}H_{13}Cl_3F_6N_3O_3S$ [M + H]$^+$: 605.9647, found 605.9650.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(6-methyl-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-9**). White solid; yield: 84%; m.p.: 176.3–177.8 °C; IR (KBr) ν_{max}: 3345 (NH), 3240 (NH), 1681 (C = O), 1364, 1122 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.77 (s, 1H, NH-SO_2), 9.14 (d, *J* = 8.1 Hz, 1H, NH-CO), 8.86 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.05 (dd, *J* = 8.1, 2.3 Hz, 1H, Ar-H), 7.87 – 7.71 (m, 2H, Ar-H), 7.64 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.38 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.24 – 7.10 (m, 3H, Ar-H), 5.62 (td, *J* = 9.2, 4.2 Hz, 1H, CH-N), 3.92 (dd, *J* = 14.2, 9.6 Hz, 1H, CH-SO_2), 3.72 (dd, *J* = 14.2, 4.3 Hz, 1H, CH-SO_2), 2.51 (d, *J* = 9.2 Hz, 3H, CH_3); HRMS (ESI), *m/z* calcd for $C_{22}H_{18}ClF_5N_3O_3S$ [M + H]$^+$: 534.0678, found 534.0680.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-hydroxy-6-methyl-3-pyridyl-formoylamido) ethylsulfonamide (**V-B-10**). White solid; yield: 95%; m.p.: 216.0–216.8 °C; IR (KBr) ν_{max}: 3351 (NH), 3217 (NH), 1749 (C = O), 1366, 1130 (-SO_2-); ^{1}H NMR (600 MHz, DMSO-d_6): 12.45 (s, 1H, OH-Py), 10.42 (d, *J* = 7.9 Hz, 1H, NH-SO_2), 9.65 (s, 1H, NH-CO), 8.18 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.84 – 7.70 (m, 2H, Ar-H), 7.67 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.20 (dt, *J* = 15.7, 7.8 Hz, 2H, Ar-H), 7.16 (tt, *J* = 9.2, 2.3 Hz, 1H, Ar-H), 6.30 (dd, *J* = 7.4, 0.8 Hz, 1H, Ar-H), 5.61 (td, *J* = 7.9, 5.6 Hz, 1H, CH-N), 4.06 (dt, *J* = 15.0, 7.6 Hz, 1H, CH-SO_2), 3.86 (dd, *J* = 14.4, 5.4 Hz, 1H, CH-SO_2), 2.29 (s, 3H, CH_3); HRMS (ESI), *m/z* calcd for $C_{22}H_{18}ClF_5N_3O_4S$ [M + H]$^+$:

550.0627, found 550.0624.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-pyridyl-formoylamido) ethylsulfonamide (**V-B-11**). Brown solid; yield: 83%; m.p.: 144.5–145.3 °C; IR (KBr) ν_{max}: 3318 (NH), 3180 (NH), 1690 (C = O), 1352, 1143 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.72 (s, 1H, NH-SO$_2$), 9.58 (d, J = 8.5 Hz, 1H, NH-CO), 8.67 (dt, J = 4.7, 1.2 Hz, 1H, Ar-H), 8.03 – 7.96 (m, 2H, Ar-H), 7.80 (d, J = 2.3 Hz, 1H, Ar-H), 7.76 (dd, J = 8.6, 2.3 Hz, 1H, Ar-H), 7.62 (td, J = 4.7, 2.2 Hz, 2H, Ar-H), 7.25 – 7.12 (m, 3H, Ar-H), 5.64 (td, J = 8.8, 4.2 Hz, 1H, CH-N), 4.21 (dd, J = 14.3, 9.1 Hz, 1H, CH-SO$_2$), 3.73 (dd, J = 14.3, 4.2 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{21}H_{16}ClF_5N_3O_3S$ $[M+H]^+$: 520.0521, found 520.0519.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(4-chloro-2-pyridyl-formoylamido) ethylsulfonamide (**V-B-12**). White solid; yield: 94%; m.p.: 196.4–197.2 °C; IR (KBr) ν_{max}: 3373 (NH), 3146 (NH), 1701 (C = O), 1362, 1124 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.73 (s, 1H, NH-SO$_2$), 9.64 (d, J = 8.5 Hz, 1H, NH-CO), 8.65 (d, J = 5.3 Hz, 1H, Ar-H), 8.00 (d, J = 1.9 Hz, 1H, Ar-H), 7.84 – 7.73 (m, 3H, Ar-H), 7.62 (d, J = 8.6 Hz, 1H, Ar-H), 7.26 – 7.18 (m, 2H, Ar-H), 7.15 (tt, J = 9.2, 2.3 Hz, 1H, Ar-H), 5.63 (td, J = 8.9, 4.1 Hz, 1H, CH-N), 4.20 (dd, J = 14.3, 9.3 Hz, 1H, CH-SO$_2$), 3.72 (dd, J = 14.3, 4.1 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{21}H_{15}Cl_2F_5N_3O_3S$ $[M+H]^+$: 554.0131, found 554.0137.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(6-bromo-2-pyridyl-formoylamido) ethylsulfonamide (**V-B-13**). White solid; yield: 72%; m.p.: 156.8–157.2 °C; IR (KBr) ν_{max}: 3273 (NH), 3214 (NH), 1687 (C = O), 1382, 1125 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.36 (d, J = 8.3 Hz, 1H, NH-SO$_2$), 8.01 (d, J = 7.5 Hz, 1H, NH-CO), 7.93 (t, J = 7.7 Hz, 1H, Ar-H), 7.87 (d, J = 7.6 Hz, 1H, Ar-H), 7.79 – 7.69 (m, 2H, Ar-H), 7.62 (d, J = 8.7 Hz, 1H, Ar-H), 7.27 (d, J = 6.7 Hz, 1H, Ar-H), 7.21 (d, J = 6.3 Hz, 2H, Ar-H), 7.15 (td, J = 9.3, 2.2 Hz, 1H, Ar-H), 5.62 (td, J = 8.7, 4.2 Hz, 1H, CH-N), 4.19 (dd, J = 14.3, 9.3 Hz, 1H, CH-SO$_2$), 3.71 (dd, J = 14.3, 4.0 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{21}H_{15}BrClF_5N_3O_3S$ $[M+H]^+$: 597.9626, found 597.9622.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(6-hydroxy-2-pyridyl-formoylamido) ethylsulfonamide (**V-B-14**). Brown solid; yield: 72%; m.p.: 228.1–229.0 °C; IR (KBr) ν_{max}: 3343 (NH), 3284 (NH), 1688 (C = O), 1382, 1135 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 11.09 (s, 1H, OH-Py), 9.14 (s, 1H, NH-SO$_2$), 7.78 (s, 1H, NH-CO), 7.74 (d, J = 8.4 Hz, 2H, Ar-H), 7.62 (d, J = 8.7 Hz, 1H, Ar-H), 7.44 (dd, J = 28.2, 16.3 Hz, 1H, Ar-H), 7.29 (dd, J = 10.1, 4.3 Hz, 1H, Ar-H), 7.21 (d, J = 6.3 Hz, 2H, Ar-H), 7.18 – 7.14 (m, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 5.59 (dd, J = 12.6, 8.1 Hz, 1H, CH-N), 4.03 (dd, J = 14.2, 7.1 Hz, 1H, CH-SO$_2$), 3.73 (d, J = 11.4 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{21}H_{16}ClF_5N_3O_4S$ $[M+H]^+$: 526.0470, found 536.0464.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(4-pyridyl-formoylamido) ethylsulfonamide (**V-B-15**). White solid; yield: 65%; m.p.: 201.7–203.2 °C; IR (KBr) ν_{max}: 3312 (NH), 3225 (NH), 1681 (C = O), 1384, 1126 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 9.77 (s, 1H, NH-SO$_2$), 9.31 (d, J = 8.1 Hz, 1H, NH-CO), 8.74 (dd, J = 4.4, 1.6 Hz, 2H, Ar-H), 7.80 (s, 1H, Ar-H), 7.76 (d, J = 8.6 Hz, 1H, Ar-H), 7.71 (dd, J = 4.4, 1.6 Hz, 2H, Ar-H), 7.64 (d, J = 8.7 Hz, 1H, Ar-H), 7.21 – 7.14 (m, 3H, Ar-H), 5.62 (td, J = 9.2, 4.1 Hz, 1H, CH-N), 3.91 (dd, J = 14.2, 9.7 Hz, 1H, CH-SO$_2$), 3.71 (dd, J = 14.2, 3.9 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{21}H_{16}ClF_5N_3O_4S$ $[M+H]^+$: 520.0521, found 520.0520.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-hydroxy-4-pyridyl-formoylamido) ethylsulfonamide (**V-B-16**). White solid; yield: 90%; m.p.: 143.2–144.5 °C; IR (KBr) ν_{max}: 3296 (NH), 3226 (NH), 1688 (C = O), 1382, 1144 (-SO$_2$-); ^{1}H NMR (600 MHz, DMSO-d_6): 12.51 (d, J = 6.0 Hz, 1H, OH-Py), 10.49 (d, J = 7.9 Hz, 1H, NH-SO$_2$), 9.67 (s, 1H, NH-CO), 8.29 (dd, J = 7.2, 2.2 Hz, 1H, Ar-H), 7.80 (d, J = 2.4 Hz, 1H, Ar-H), 7.77 – 7.71 (m, 2H, Ar-H), 7.67 (d, J = 8.7 Hz, 1H, Ar-H), 7.28 – 7.03 (m, 3H, Ar-H), 6.54 – 6.34 (m, 1H, Ar-H), 5.62 (td, J = 7.9, 5.6 Hz, 1H, CH-N), 4.07 (dd, J = 14.4, 8.0 Hz, 1H, CH-SO$_2$), 3.86 (dd, J = 14.4, 5.4 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{21}H_{16}ClF_5N_3O_4S$ $[M+H]^+$: 536.0470, found 536.0466.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(benzamido) ethylsulfonamide (**V-C-1**). White solid; yield: 93%; m.p.: 189.8–190.6 °C; IR (KBr) ν_{max}: 3351 (NH), 3276 (NH), 1749 (C = O), 1378, 1152 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.76 (s, 1H, NH-SO$_2$), 9.03 (d, J = 8.3 Hz, 1H, NH-CO), 7.81 (t, J = 19.1 Hz, 4H, Ar-H), 7.64 (d, J = 8.7 Hz, 1H, Ar-H), 7.56 (t, J = 7.5 Hz, 1H, Ar-H), 7.49 (t, J = 7.6 Hz, 2H, Ar-H), 7.17 (dd, J = 17.2, 9.4 Hz, 3H, Ar-H), 5.62 (s, 1H, CH-N), 3.95 (s, 1H, CH-SO$_2$), 3.71 (d, J = 11.1 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{17}ClF_5N_2O_3S$ $[M+H]^+$: 519.0569, found 519.0566.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-fluorobenzamido) ethylsulfonamide (**V-C-2**). White solid; yield: 96%; m.p.: 189.6–191.3 °C; IR (KBr) ν_{max}: 3256 (NH), 3224 (NH), 1690 (C = O), 1381, 1132 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.76 (s, 1H, NH-SO$_2$), 9.02 (d, J = 7.0 Hz, 1H, NH-CO), 7.83 (d, J = 2.4 Hz, 1H, Ar-H), 7.78 (dd, J = 8.6, 2.4 Hz, 1H, Ar-H), 7.66 – 7.60 (m, 2H, Ar-H), 7.58 – 7.53 (m, 1H, Ar-H), 7.34 – 7.26 (m, 2H, Ar-H), 7.18 (dd, J = 14.2, 5.0 Hz, 3H, Ar-H), 5.62 (td, J = 8.7, 4.3 Hz, 1H, CH-N), 3.92 (dd, J = 14.3, 9.2 Hz, 1H, CH-SO$_2$), 3.71 (dd, J = 14.3, 4.3 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{16}ClF_6N_2O_3S$ $[M+H]^+$: 537.0474, found 537.0472.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-fluorobenzamido) ethylsulfonamide (**V-C-3**). White solid; yield: 94%; m.p.: 202.4–203.8 °C; IR (KBr) ν_{max}: 3373 (NH), 3256 (NH), 1701 (C = O), 1348, 1125 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.78 (s, 1H, NH-SO$_2$), 9.12 (d, J = 8.0 Hz, 1H, NH-CO), 7.83 – 7.73 (m, 2H, Ar-H), 7.70 – 7.59 (m, 3H, Ar-H), 7.55 (td, J = 8.0, 5.9 Hz, 1H, Ar-H), 7.42 (td, J = 8.3, 2.2 Hz, 1H, Ar-H), 7.22 – 7.13 (m, 3H, Ar-H), 5.61 (td, J = 9.1, 4.1 Hz, 1H, CH-N), 3.92 (dd, J = 13.7, 9.9 Hz, 1H, CH-SO$_2$), 3.71 (dd, J = 14.1, 2.7 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{16}ClF_6N_2O_3S$ $[M+H]^+$: 537.0474, found 537.0468.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-chlorobenzamido) ethylsulfonamide (**V-C-4**). White solid; yield: 99%; m.p.: 195.2–196.8 °C; IR (KBr) ν_{max}: 3331 (NH), 3248 (NH), 1680 (C = O), 1366, 1132 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.77 (s, 1H, NH-SO$_2$), 9.17 (d, J = 8.3 Hz, 1H, NH-CO), 7.87 – 7.75 (m, 2H, Ar-H), 7.65 (d, J = 8.7 Hz, 1H, Ar-H), 7.52 – 7.39 (m, 4H, Ar-H), 7.23 – 7.15 (m, 3H, Ar-H), 5.60 (td, J = 8.6, 4.5 Hz, 1H, CH-N), 3.80 (dd, J = 14.2, 9.1 Hz, 1H, CH-SO$_2$), 3.72 (dd, J = 13.8, 4.2 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{16}Cl_2F_5N_2O_3S$ $[M+H]^+$: 553.0179, found 553.0181.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-chlorobenzamido) ethylsulfonamide (**V-C-5**). White solid; yield: 88%; m.p.: 213.4–214.6 °C; IR (KBr) ν_{max}: 3291 (NH), 3196 (NH), 1688 (C = O), 1385, 1134 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.79 (s, 1H, NH-SO$_2$), 9.16 (d, J = 8.1 Hz, 1H, NH-CO), 7.89 – 7.74 (m, 4H, Ar-H), 7.69 – 7.60 (m, 2H, Ar-H), 7.53 (t, J = 7.9 Hz, 1H, Ar-H), 7.22 – 7.15 (m, 3H, Ar-H), 5.62 (td, J = 9.3, 4.1 Hz, 1H, CH-N), 3.93 (dd, J = 14.2, 9.7 Hz, 1H, CH-SO$_2$), 3.72 (dd, J = 14.2, 4.2 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{16}Cl_2F_5N_2O_3S$ $[M+H]^+$: 553.0179, found 553.0179.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(4-chlorobenzamido) ethylsulfonamide (**V-C-6**). White solid; yield: 88%; m.p.: 222.6–223.5 °C; IR (KBr) ν_{max}: 3273 (NH), 3180 (NH), 1703 (C = O), 1367, 1124 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6) ??: 9.77 (s, 1H, NH-SO$_2$), 9.12 (d, J = 8.0 Hz, 1H, NH-CO), 7.94 – 7.90 (m, 4H, Ar-H), 7.84 (d, J = 8.3 Hz, 2H, Ar-H), 7.64 (d, J = 8.6 Hz, 1H, Ar-H), 7.17 (dd, J = 17.5, 8.3 Hz, 3H, Ar-H), 5.62 (s, 1H, CH-N), 3.93 (dd, J = 13.9, 9.6 Hz, 1H, CH-SO$_2$), 3.71 (dd, J = 13.9, 3.5 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{16}Cl_2F_5N_2O_3S$ $[M+H]^+$: 553.0179, found 553.0175.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-trifluoromethylbenzamido) ethylsulfonamide (**V-C-7**). White solid; yield: 76%; m.p.: 209.6–210.5 °C; IR (KBr) ν_{max}: 3292 (NH), 3241 (NH), 1688 (C = O), 1354, 1136 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.80

(s, 1H, NH-SO$_2$), 9.26 (d, J = 8.0 Hz, 1H, NH-CO), 7.80 (dt, J = 15.2, 4.9 Hz, 4H, Ar-H), 7.72 – 7.57 (m, 3H, Ar-H), 7.18 (ddd, J = 19.7, 9.8, 4.6 Hz, 3H, Ar-H), 5.60 (s, 1H, CH-N), 3.80 (dd, J = 13.7, 8.9 Hz, 1H, CH-SO$_2$), 3.73 (dd, J = 13.9, 3.8 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{23}H_{16}ClF_8N_2O_3S$ [M + H]$^+$: 587.0442, found 587.0443.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-trifluoromethylbenzamido) ethylsulfonamide (**V-C-8**). White solid; yield: 94%; m.p.: 204.2–205.8 °C; IR (KBr) ν_{max}: 3354 (NH), 3280 (NH), 1686 (C = O), 1347, 1122 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.80 (s, 1H, NH-SO$_2$), 9.29 (d, J = 8.1 Hz, 1H, NH-CO), 8.13 (d, J = 12.2 Hz, 2H, Ar-H), 7.95 (d, J = 7.8 Hz, 1H, Ar-H), 7.84 – 7.71 (m, 3H, Ar-H), 7.66 (d, J = 8.7 Hz, 1H, Ar-H), 7.28 – 7.12 (m, 3H, Ar-H), 5.65 (td, J = 9.3, 4.2 Hz, 1H, CH-N), 3.95 (dd, J = 14.3, 9.7 Hz, 1H, CH-SO$_2$), 3.76 (dd, J = 14.3, 4.2 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{23}H_{16}ClF_8N_2O_3S$ [M + H]$^+$: 587.0442, found 587.0439.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,4-dichlorobenzamido) ethylsulfonamide (**V-C-9**). White solid; yield: 95%; m.p.: 183.9–184.8 °C; IR (KBr) ν_{max}: 3346 (NH), 3280 (NH), 1707 (C = O), 1365, 1152 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.78 (s, 1H, NH-SO$_2$), 9.24 (d, J = 8.3 Hz, 1H, NH-CO), 7.67 (dddd, J = 44.5, 38.2, 31.1, 5.2 Hz, 6H, Ar-H), 7.19 (t, J = 8.2 Hz, 3H, Ar-H), 5.59 (td, J = 8.4, 4.4 Hz, 1H, CH-N), 3.80 (dd, J = 14.2, 9.1 Hz, 1H, CH-SO$_2$), 3.73 (dd, J = 14.2, 4.5 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{15}Cl_3F_5N_2O_3S$ [M + H]$^+$: 586.9789, found 586.9786.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,6-dichlorobenzamido) ethylsulfonamide (**V-C-10**). White solid; yield: 98%; m.p.: 177.6–179.2 °C; IR (KBr) ν_{max}: 3296 (NH), 3258 (NH), 1690 (C = O), 1364, 1143 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.77 (s, 1H, NH-SO$_2$), 9.47 (d, J = 7.8 Hz, 1H, NH-CO), 7.89 – 7.70 (m, 2H, Ar-H), 7.61 (d, J = 8.7 Hz, 1H, Ar-H), 7.56 – 7.39 (m, 3H, Ar-H), 7.19 (dd, J = 13.3, 9.0 Hz, 3H, Ar-H), 5.57 (q, J = 6.9 Hz, 1H, CH-N), 3.83 – 3.69 (m, 2H, CH$_2$-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{22}H_{15}Cl_3F_5N_2O_3S$ [M + H]$^+$: 586.9789, found 586.9784.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-methylbenzamido) ethylsulfonamide (**V-C-11**). White solid; yield: 90%; m.p.: 180.6–181.4 °C; IR (KBr) ν_{max}: 3351 (NH), 3280 (NH), 1702 (C = O), 1347, 1126 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.75 (s, 1H, NH-SO$_2$), 8.95 (d, J = 8.3 Hz, 1H, NH-CO), 7.83 (d, J = 2.4 Hz, 1H, Ar-H), 7.78 (dd, J = 8.6, 2.3 Hz, 1H, Ar-H), 7.65 (d, J = 8.7 Hz, 1H, Ar-H), 7.38 – 7.32 (m, 2H, Ar-H), 7.25 (dd, J = 12.4, 7.5 Hz, 2H, Ar-H), 7.18 (dd, J = 7.2, 2.0 Hz, 3H, Ar-H), 5.62 (td, J = 9.1, 4.1 Hz, 1H, CH-N), 3.84 (dd, J = 14.2, 9.6 Hz, 1H, CH-SO$_2$), 3.68 (dd, J = 14.2, 4.0 Hz, 1H, CH-SO$_2$), 2.26 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClF_5N_2O_3S$ [M + H]$^+$: 533.0725, found 533.0721.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-methylbenzamido) ethylsulfonamide (**V-C-12**). White solid; yield: 93%; m.p.: 216.7–218.2 °C; IR (KBr) ν_{max}: 3298 (NH), 3258 (NH), 1690 (C = O), 1348, 1152 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.76 (s, 1H, NH-SO$_2$), 8.98 (d, J = 8.1 Hz, 1H, NH-CO), 7.82 (d, J = 2.3 Hz, 1H, Ar-H), 7.78 (dd, J = 8.6, 2.3 Hz, 1H, Ar-H), 7.66 – 7.60 (m, 3H, Ar-H), 7.36 (d, J = 1.0 Hz, 2H, Ar-H), 7.21 – 7.13 (m, 3H, Ar-H), 5.62 (td, J = 9.0, 4.2 Hz, 1H, CH-N), 3.95 (dd, J = 14.2, 9.5 Hz, 1H, CH-SO$_2$), 3.71 (dd, J = 14.2, 4.2 Hz, 1H, CH-SO$_2$), 2.36 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClF_5N_2O_3S$ [M + H]$^+$: 533.0725, found 533.0728.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(4-methylbenzamido) ethylsulfonamide (**V-C-13**). White solid; yield: 98%; m.p.: 208.2–209.5 °C; IR (KBr) ν_{max}: 3345 (NH), 3286 (NH), 1681 (C = O), 1338, 1142 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.75 (s, 1H, NH-SO$_2$), 8.95 (d, J = 8.1 Hz, 1H, NH-CO), 7.82 (d, J = 2.4 Hz, 1H, Ar-H), 7.78 (dd, J = 8.6, 2.4 Hz, 1H, Ar-H), 7.74 (d, J = 8.2 Hz, 2H, Ar-H), 7.64 (d, J = 8.7 Hz, 1H, Ar-H), 7.29 (d, J = 7.9 Hz, 2H, Ar-H), 7.21 – 7.13 (m, 3H, Ar-H), 5.62 (td, J = 9.0, 4.3 Hz, 1H, CH-N), 3.95 (dd, J = 14.2, 9.5 Hz, 1H, CH-SO$_2$), 3.70 (dd, J = 14.2, 4.3 Hz, 1H, CH-SO$_2$), 2.36 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClF_5N_2O_3S$ [M + H]$^+$: 533.0725, found 533.0720.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2-methoxybenzamido) ethylsulfonamide (**V-C-14**). White solid; yield: 98%; m.p.: 174.2–175.5 °C; IR (KBr) ν_{max}: 3312 (NH), 3268 (NH), 1680 (C = O), 1361, 1122 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.75 (s, 1H, NH-SO$_2$), 8.99 (d, J = 7.8 Hz, 1H, NH-CO), 7.81 (d, J = 2.1 Hz, 1H, Ar-H), 7.77 (d, J = 8.6 Hz, 1H, Ar-H), 7.68 (dd, J = 7.7, 1.8 Hz, 1H, Ar-H), 7.63 (d, J = 8.7 Hz, 1H, Ar-H), 7.51 – 7.46 (m, 1H, Ar-H), 7.20 (d, J = 6.4 Hz, 2H, Ar-H), 7.15 (dd, J = 8.6, 3.5 Hz, 2H, Ar-H), 7.03 (t, J = 7.5 Hz, 1H, Ar-H), 5.62 (td, J = 8.2, 4.3 Hz, 1H, CH-N), 4.01 (dd, J = 14.3, 8.7 Hz, 1H, CH-SO$_2$), 3.88 (s, 3H, CH$_3$-O), 3.75 (dd, J = 14.4, 4.1 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClF_5N_2O_4S$ [M + H]$^+$: 549.0674, found 549.0672.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3-methoxybenzamido) ethylsulfonamide (**V-C-15**). White solid; yield: 96%; m.p.: 202.7–203.5 °C; IR (KBr) ν_{max}: 3343 (NH), 3246 (NH), 1688 (C = O), 1346, 1120 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.74 (s, 1H, NH-SO$_2$), 8.87 (d, J = 8.1 Hz, 1H, NH-CO), 7.86 – 7.76 (m, 6H, Ar-H), 7.64 (d, J = 8.7 Hz, 1H, Ar-H), 7.05 – 7.00 (m, 2H, Ar-H), 6.99 – 6.95 (m, 1H, Ar-H), 5.61 (td, J = 8.9, 4.3 Hz, 1H, CH-N), 3.94 (dd, J = 14.2, 9.5 Hz, 1H, CH-SO$_2$), 3.81 (s, 3H, CH$_3$-O), 3.70 (dd, J = 14.2, 4.3 Hz, 1H, CH-SO$_2$); HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClF_5N_2O_4S$ [M + H]$^+$: 549.0674, found 549.0671.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,3-dimethylbenzamido) ethylsulfonamide (**V-C-16**). White solid; yield: 98%; m.p.: 195.3–196.6 °C; IR (KBr) ν_{max}: 3351 (NH), 3274 (NH), 1719 (C = O), 1362, 1143 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.75 (s, 1H, NH-SO$_2$), 8.94 (d, J = 8.0 Hz, 1H, NH-CO), 7.80 (d, J = 34.8 Hz, 2H, Ar-H), 7.64 (d, J = 8.5 Hz, 1H, Ar-H), 7.24 – 7.13 (m, 6H, Ar-H), 5.61 (s, 1H, CH-N), 3.81 (s, 1H, CH-SO$_2$), 3.66 (d, J = 15.5 Hz, 1H, CH-SO$_2$), 2.24 (d, J = 2.7 Hz, 3H, CH$_3$), 2.11 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{24}H_{21}ClF_5N_2O_3S$ [M + H]$^+$: 547.0882, found 547.0878.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,4-dimethylbenzamido) ethylsulfonamide (**V-C-17**). White solid; yield: 97%; m.p.: 201.2–202.7 °C; IR (KBr) ν_{max}: 3331 (NH), 3228 (NH), 1680 (C = O), 1346, 1135 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.74 (s, 1H, NH-SO$_2$), 8.85 (d, J = 8.3 Hz, 1H, NH-CO), 7.86 – 7.74 (m, 2H, Ar-H), 7.65 (d, J = 8.7 Hz, 1H, Ar-H), 7.29 (d, J = 7.7 Hz, 1H, Ar-H), 7.21 – 7.14 (m, 3H, Ar-H), 7.06 (d, J = 7.6 Hz, 2H, Ar-H), 5.60 (td, J = 9.0, 4.1 Hz, 1H, CH-N), 3.84 (dd, J = 14.2, 9.5 Hz, 1H, CH-SO$_2$), 3.67 (dd, J = 14.2, 4.1 Hz, 1H, CH-SO$_2$), 2.29 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{24}H_{21}ClF_5N_2O_3S$ [M + H]$^+$: 547.0882, found 547.0875.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(2,5-dimethylbenzamido) ethylsulfonamide (**V-C-18**). White solid; yield: 95%; m.p.: 180.4–181.8 °C; IR (KBr) ν_{max}: 3349 (NH), 3268 (NH), 1690 (C = O), 1362, 1146 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.75 (s, 1H, NH-SO$_2$), 8.92 (d, J = 8.2 Hz, 1H, NH-CO), 7.86 – 7.75 (m, 2H, Ar-H), 7.65 (d, J = 8.7 Hz, 1H, Ar-H), 7.21 – 7.14 (m, 5H, Ar-H), 7.11 (d, J = 7.7 Hz, 1H, Ar-H), 5.60 (td, J = 8.9, 4.1 Hz, 1H, CH-N), 3.84 (dd, J = 14.2, 9.4 Hz, 1H, CH-SO$_2$), 3.68 (dd, J = 14.2, 4.1 Hz, 1H, CH-SO$_2$), 2.28 (s, 3H, CH$_3$), 2.20 (s, 3H, CH$_3$); HRMS (ESI), *m/z* calcd for $C_{24}H_{21}ClF_5N_2O_3S$ [M + H]$^+$: 547.0882, found 547.0880.

N-(2-trifluoromethyl-4-chlorophenyl)-2-(3,5-difluorophenyl)-2-(3,5-dimethylbenzamido) ethylsulfonamide (**V-C-19**). White solid; yield: 44%; m.p.: 190.7–192.0 °C; IR (KBr) ν_{max}: 3351 (NH), 3268 (NH), 1720 (C = O), 1374, 1168 (-SO$_2$-); ^{1}H NMR (600 M Hz, DMSO-d_6): 9.75 (s, 1H, NH-SO$_2$), 8.93 (d, J = 8.1 Hz, 1H, NH-CO), 7.79 (d, J = 30.0 Hz, 2H, Ar-H), 7.64 (d, J = 8.7 Hz, 1H, Ar-H), 7.42 (s, 2H), 7.21 – 7.11 (m, 4H, Ar-H), 5.60 (s, 1H, CH-N), 3.94 (s, 1H, CH-SO$_2$), 3.71 (s, ^{1}H, CH-SO$_2$), 2.31 (s, 6H, 2CH$_3$); HRMS (ESI), *m/z* calcd for $C_{24}H_{21}ClF_5N_2O_3S$ [M + H]$^+$: 547.0882, found 547.0875.

4.3. Bioassay of fungicidal activity against Botrytis cinerea in vitro and in vivo

The fungicidal activities of all thenewly synthesized compounds against *B. cinerea* were tested by *in vitro* mycelium growth inhibition assayand *in vivo* greenhouse pot experiments, respectively. The *B. cinerea* strains (**XM**, **FS-10**, **HLD-15**) were isolated from damaged parts of tomato in a grennhouse in different areas of Liaoning, China, and cultured on potato dextrose agar (PDA) for many generations. The commercial fungicides procymidone (with a purity of 96%), boscalid (with a purity of 96%) and pyrimethanil (with a purity of 95%) were used as positive controls, which were provided by Shenyang Research Institute of the Chemical Industry, National Pesticides Engineering Research Centre.

4.3.1. *In vitro fungicidal activity against Botrytis cinerea*

According to the Ref. [22], a mycelia growth inhibition method was used to test the *in vitro* fungicidal activity of compounds **IV** and **V**. Each compound were dissolved in acetone and mixed with sterile molten PDA to obtain five concentrations of 100, 25, 6.25, 1.56 and 0.39 mg·L^{-1}. The commercial fungicides procymidone and pyrimethanil were used as positive controls, and per treatment were repeated for three times. After an incubation period of 72 h at 23 °C, mycelia growth diameters were measured and the inhibition percentages relative to the control with 1% acetone were calculated. Then, the EC_{50} values were calculated using log-probit analysis via SPSS v.18.0 software.

4.3.2. *In vivo fungicidal activity against Botrytis cinerea*

According to the Ref. [22], the *in vivo* fungicidal activity of the title compounds against *B. cinerea* was evaluated on vital leaves of cucumber and tomato in a greenhouse. The tested compounds and commercial fungicides (procymidone and pyrimethanil) were confected to 2.5% EC formulations, which were diluted to concentration of 500 μg/mL with water to obtain the solutions. Then these solutions were sprayed with a hand spray on the surface of the seed leaves. Water sprayed seed leaves were set as the CK. After drying, the upper sides of the cucumber leaves were inoculated with 5 mm plugs of *B. cinerea*, which was maintained on PDA. This procedure was repeated three times, and nine replicates were performed per treatment. The plants were maintained at 24 ± 1 °C and above 80% relative humidity in greenhouse. Four days after *B. cinerea* inoculation, the lesion diameters were measured and the fungicidal activity was evaluated.

The tomato leaves were also used to evaluate the *in vivo* fungicidal activity. Conidia of *B. cinerea* obtained from 4-week-old cultures on PDA plates were suspensed in 0.5% (v/v) Tween 80 solution to ensure 10^6 spores per mL. When tomatoes grew to about 30 leaves, the solutions of the tested compounds and positive controls (procymidone and boscalid) at the concentration of 500 μg/mL were sprayed evenly onto tomato leaves. After dried naturally, these tomatoes were sprayed with prepared spore suspension. The plants were maintained at 24 ± 1 °C and above 80% relative humidity in greenhouse. The disease index was investigated when the untreated cucumber plant fully developed symptoms, and then the control efficacy was calculated.

4.4. *Establishment of QSAR model of 2-substituted acylaminoethylsulfonamides*

The *in vitro* fungicidal activity of 50 ethylsulfonamide compounds against *B. cinerea* was chosen to construct a 3D-QSAR model. All molecular modeling and comparative molecular field analysis (CoMFA) techniques were performed on SYBYL X. 2.0 molecular modeling software from Tripos Inc. (St. Louis, MO). For ligand preparation, the 3D structures of all the compounds were generated with Chem-BioOffice 2014 and optimized using the standard Tripos force field, including the electrostatic term calculated from Gasteiger-Hückel atomic charges. The methods of steepest descent and conjugate gradients were used successively for energy minimization until the gradient value was smaller than 0.001 kcal/mol. The search routine of Sybyl was then employed for the systematic conformational search to find the global energy-minimum conformation.

The common skeleton of newly synthesized compounds were used for rms-fitting onto the corresponding atoms of the template structure. The half-maximal effective concentration (EC_{50}; mg L^{-1}) obtained on this fungus was transformed into pEC_{50} ($-\log(EC_{50} \times MW)$) and then used as the response variable for subsequent QSAR analyses. The data set was divided randomly into a training set (42 compounds) and a test set (8 compounds). The CoMFA studies were performed with the QSAR module of SYBYL for each combination of the two molecular fields: (Ste) steric and (Ele) electrostatic. CoMFA steric and electrostatic interaction fields were calculated at each lattice intersection on a regularly spaced grid of 2.0 Å. The grid pattern was generated automatically by the SYBYL/CoMFA routine, and an sp3 carbon atom with a van der Waals radius of 1.52 Å and a + 1.0 charge was used as the probe to calculate the steric field energies and electrostatic (Coulombic potential) fields with a distance-dependent dielectric at each lattice point. Values of the steric and electrostatic fields were truncated at 30.0 kcal/mol [42]. The CoMFA steric and electrostatic fields generated were scaled by the CoMFA-STD method in SYBYL. The electrostatic fields were ignored at the lattice points with maximal steric interactions. The method of partial least squares (PLS) implemented in the QSAR module of SYBYL was used to construct and validate the models. Cross-validation was performed with the leave-one-out procedure. The optional number of components, N, retained for final PLS analyses was defined as the one that yielded the highest cross-validated q^2. The robustness of the models was internally evaluated by calculating the R^2, SD, and F test values from the training set.

4.5. *Statistical analysis*

Descriptive analysis and difference significance test of statistics method are adopted in finally result analysis. EXCEL 2007 was used to analyze bioassay data, and SPSS v.18.0 was used to analyse the difference significance using Fisher's LSD multiple comparison test. A P-value of less than 0.05 was determinated statistically significant.

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Conflicts of interest

The authors declare no conflict of interest.

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