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Synthesis and Fungicidal Activity of Novel Aminophenazine-1-carboxylate Derivatives

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A series of novel 6-aminophenazine-1-, 7-aminophenazine-1- and 8-aminophenazine-1-carboxylate derivatives were synthesized by a facile method, and their structures were characterized by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry. Some unexpected byproducts **V-7b**−**V-8d** were noticed and isolated, and their structures were identified by 2D NMR spectra including heteronuclear multiple-quantum coherence (HMQC), heteronuclear multiple-bond correlation (Hmbc) and H−H correlation spectrometry (H−H COSY) approach. Their fungicidal activities against five fungi were evaluated, which indicated that most of the title compounds showed low fungicidal activities in vitro against *Alternaria solani*, *Cercospora arachidicola*, *Fusarium omysporum*, *Gibberella zeae*, and *Physalospora piricola* at a dosage of 50 μg mL^{-1}, while compounds **IV-6a** and **IV-6b** exhibited excellent activities against *P. piricola* at that dosage. Compound **IV-6a** could be considered as a leading structure for further design of fungicides.

KEYWORDS: Aminophenazine-1-carboxylate; derivatives; synthesized; fungicidal activities; leading structure

INTRODUCTION

In the past century, many potential antibiotics containing the planar tricyclic heteroaromatic phenazine were isolated from the marine microorganism *Streptomyces antibioticus* strain Tü 2706 (*1*). The derivatives included the diphenazine antibiotics esmeraldin A and B as well as simpler monomeric structures containing 6-(1-hydroxyethyl)-1-phenazine carboxylic acid (**A**, **Figure 1**) have shown extensive antimicrobial activity toward a broad range of bacteria (*2*). Phenazine-1-carboxylic acid (**A**, **Figure 1**) isolated from *Pseudomonas* sp. had high antimicrobial activity against nine bacterial strains, inhibiting settlement of barnacle larvae, and reducing *Ulva lactuca* spore settlement and percent cover of germlings (*3*). Recently, a series of substituted (−Cl, −OCH_3, −CH_3) phenazine-1-carboxylic acids and the corresponding carboxamides (**B**, **Figure 1**) were prepared as antitumor drugs acting on electron-deficient DNA-intercalating ligands and evaluated against L1210 leukemia in vitro and against P388 leukemia and Lewis lung carcinoma in vivo (*4*).

The total synthesis of aminophenazine-1-carboxylic acid was completed in the 1960s (*5*−*7*), but few published studies reported their biological activity. Considering the other potential biological activity of phenazine structures, the derivatives of aminophenazine-1-carboxylic acid with the phenazine skeleton were synthesized and tested against fungi in vitro. In this paper, forty-six 6-aminophenazine-1-, 7-aminophenazine-1- and 8-aminophenazine-1-carboxylate derivatives, including six known compounds (**C**, **Figure 1**), were synthesized with a facile synthetic method.

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Those compounds' fungicidal activities against five fungi were evaluated, and their possible structure−activity relationships (SAR) were discussed. In order to enhance the lipophilic properties, aminophenazine-1-carboxylic acid was derivatized to its ester with corresponding $CH_3(CH_2)_nOH$ (n = 0, 1, 2, 3); The $-NH_2$ group was substituted at different positions of the phenazine ring; Different carboxamide and sulfonamide derivatives were optimized with acyl chloride or sulfonyl chloride; the phenazine rings of some carboxamide derivatives were further nitrified. All the new derivatives were designed to explore whether that might improve or decrease the fungicidal activities.

MATERIALS AND METHODS

Instruments. ^{1}H NMR, ^{13}C NMR, HMQC, HMBC, H−H COSY spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Bruker AV400 spectrometer in $CDCl_3$ or d_6-DMSO solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in ppm. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized. The reagents were all analytically or chemically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. Silica gel (200−300 mesh) was obtained from Qingdao Marine Chemical Factory, Qingdao, P. R. China. Three kinds of benzene-diamine, 2-bromo-3-nitrobenzoic acid and $NaBH_4$ were bought from the Alfa Aesar Company (Tianjin, China). Phenazine-1-carboxylic acid was synthesized according to the literature (*4*).

General Synthetic Procedures for I-a, I-b and I-c. To a solution of *o*-phenylenediamine (8.0 g, 74.0 mmol) in dry THF (50.0 mL) was added dropwise a solution of Ac_2O (8.0 mL) in dry THF (20.0 mL) under 15 °C

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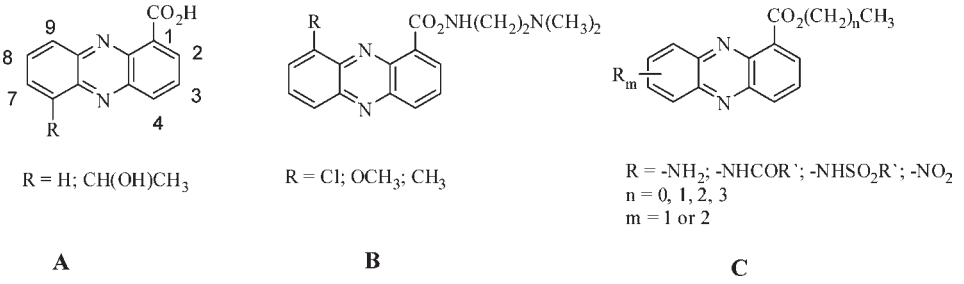
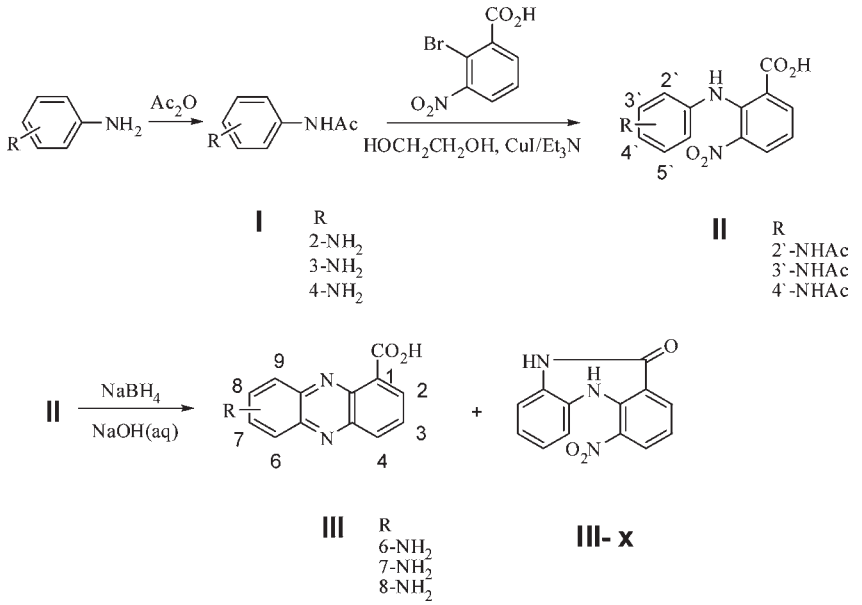


Figure 1. Chemical structure of compounds **A**−**C**.

Scheme 1. Synthetic Routes to Compounds **III**



within 2 h. The mixture was stirred for 5 h at 15 °C, and the solvent was removed, followed by cooling to get the crude product and recrystallization with ethyl acetate to give *N*-(2-aminophenyl) acetamide (**I-a**, 5.3 g, 47.7%).

To a solution of *m*-phenylenediamine (12.0 g, 111.0 mmol) in dry THF (30.0 mL) was added dropwise a solution of Ac_2O (9.0 mL) in dry THF (35.0 mL) under −10 °C within 2 h. The mixture was stirred for 3 h keeping the temperature under −10 °C, and dilute hydrochloric acid (20.0 mL, 18.5%) was added to the mixture, followed by cooling for 30 min to get the white salt. Then the salt was dissolved in dilute sodium hydroxide and extracted with ethyl acetate to give *N*-(3-aminophenyl) acetamide (**I-b**, 5.7 g, 34.2%). *N*-(4-Aminophenyl) acetamide (**I-c**) was synthesized according to the literature (*8*). All the substituents at the aromatic rings are listed in **Scheme 1**.

Data for ***I-a***. Yield: 47.7%; white crystal; mp, 129−131 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.11 (s, 1H, NHAc), 7.14 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.88 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.70 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.52 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 4.84 (s, 2H, NH_2), 2.02 (s, 3H, $COCH_3$).

Data for ***I-b***. Yield: 34.2%; white crystal; mp, 82−84 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.60 (s, 1H, NHAc), 6.92 (s, 1H, Ar−H), 6.89 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 6.65 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 6.23 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 1.2 Hz, 1H, Ar−H), 5.02 (s, 2H, NH_2), 1.99 (s, 3H, $COCH_3$).

Data for ***I-c***. Yield: 72.0%; white crystal; mp, 162−164 °C (ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, d_6-DMSO) δ: 9.46 (s, 1H, NHAc), 7.18 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 6.48 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 4.80 (s, 2H, NH_2), 1.94 (s, 3H, $COCH_3$).

General Synthetic Procedures for II-a, II-b and II-c. A mixture of N-(2-aminophenyl) acetamide (**I-a**) (4.0 g, 26.6 mmol), 2-bromo-3-nitrobenzoic acid (6.3 g, 26.6 mmol), CuI (1.3 g, 6.8 mmol) in triethylamine (12.5 mL) and ethane-1,2-diol (50.0 mL) were stirred at 80 °C for 3 h. The cooled mixture was diluted with 0.2 N aqueous NaOH, clarified with charcoal, and filtered through Celite. The resulting clear solution was acidified with dilute HCl to give 2-(2-acetamidophenylamino)-3-nitrobenzoic acid (**II-a**) (3.0 g, 35.8%) (*9*). 2-(3-acetamidophenylamino)-3-nitrobenzoic acid (**II-b**) and 2-(4-acetamidophenylamino)-3- nitrobenzoic acid (**II-c**) were given through the same process. All the substituents at the aromatic rings were listed in the **Scheme 1**.

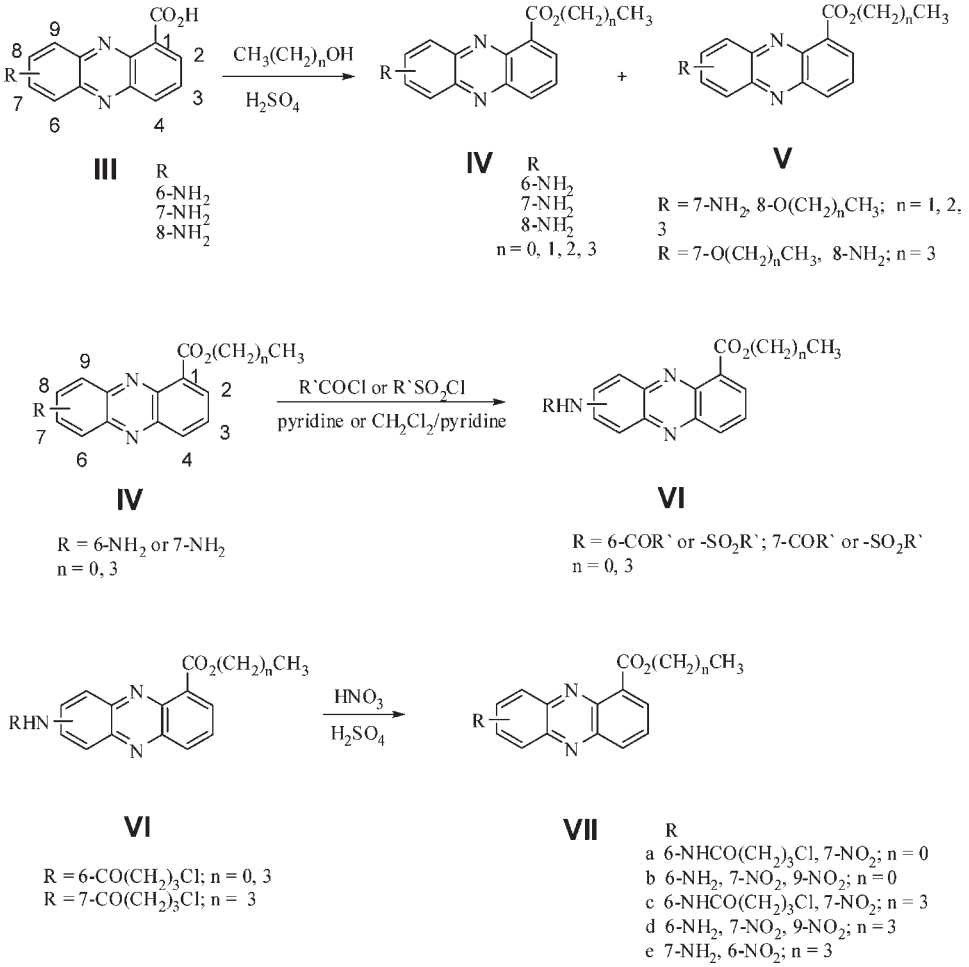
Data for ***II-a***. Yield: 35.8%; orange solid; mp, 202−204 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 13.56 (s, 1H, COOH), 9.80 (s, 1H, NHAc), 9.63 (s, 1H, Ar−NH−Ar), 8.14 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.01 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.39 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.02 (t, $^3J_{HH}$ = 8.4 Hz, 3H, Ar−H)), 6.82 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 2.07 (s, 3H, $COCH_3$).

Data for ***II-b***. Yield: 62.6%; orange solid; mp, 222−224 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.88 (s, 1H, NHAc), 9.84 (s, 1H, Ar−NH−Ar), 8.21 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 8.08 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.25 (s, 1H, Ar−H), 7.18 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.15 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.11 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 6.56 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 2.01 (s, 3H, $COCH_3$).

Data for ***II-c***. Yield: 50.6%; orange solid; mp, 218−220 °C (acetone/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.93 (s, 1H, Ar−NH−Ar), 9.87 (s, 1H, NHAc), 8.19 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 8.04 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.44 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.02 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 6.88 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 2.01 (s, 3H, $COCH_3$).

General Synthetic Procedures for III-a, III-b and III-c. A solution of 2-(3-acetamido phenylamino)-3-nitrobenzoic acid (**II-b**) (6.0 g, 19.0 mmol) and $NaBH_4$ (4.8 g, 126.0 mmol) in 2 N NaOH (500.0 mL) was refluxed for 4 h. Cooling gave the sodium salt of the phenazine acid, which was acidified to give a mixture of 6-aminophenazine-1-carboxylic acid (**III-a**) and 8-aminophenazine-1-carboxylic acid (**III-c**). The mixture consisted of 50% **III-a** and 50% **III-c**, as determined by ^{1}H NMR. A small

Scheme 2. Synthetic Routes to the Title Compounds **IV**, **VI** and **VII**



amount of the mixture was purified by flash chromatography on silica gel [elution solvent: ethyl acetate/petroleum ether (60−90 °C), 1:4, v/v]. Similar procedures were used to prepare 7-aminophenazine-1-carboxylic acid (**III-b**) by reductive cyclization of 2-(4-acetamido phenylamino)-3-nitrobenzoic acid (**II-c**). The compound **III-x** was the only product by reductive cyclization of 2-(2-acetamido phenylamino)-3-nitrobenzoic acid (**II-a**). All the substituents at the aromatic rings are listed in **Scheme 1**.

*Data for **III-a***. Yield: 59.0%; purple solid; mp, 306−308 °C (acetone/petroleum ether) (*5*). ^{1}H NMR (300 MHz, d_6-DMSO) δ: 15.27 (s, 1H, COOH), 8.62 (d, $^3J_{HH}$ = 6.6 Hz, 1H, Ar−H), 8.48 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.03 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ar−H), 7.82 (t, $^3J_{HH}$ = 7.8 Hz, 1H, Ar−H), 7.40 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 6.98 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ar−H), 6.74 (s, 2H, NH_2).

*Data for **III-b***. Yield: 69.0%; red solid; mp, beyond 340 °C (acetone/petroleum ether) (*4*). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.33 (d, $^3J_{HH}$=6.0 Hz, 1H, Ar−H), 8.23 (d, $^3J_{HH}$=8.0 Hz, 1H, Ar−H), 8.05 (d, $^3J_{HH}$=8.0 Hz, 1H, Ar−H), 7.91 (t, $^3J_{HH}$=7.2 Hz, 1H, Ar−H), 7.58 (d, $^3J_{HH}$=8.0 Hz, 1H, Ar−H), 6.95 (s, 1H, Ar−H), 6.81 (s, 2H, NH_2).

*Data for **III-c***. Yield: 59.0%; red solid; mp, beyond 340 °C (acetone/petroleum ether) (*5*). ^{1}H NMR (300 MHz, d_6-DMSO) δ: 8.41 (d, $^3J_{HH}$=6.6 Hz, 1H, Ar−H), 8.34 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar−H), 7.98 (d, $^3J_{HH}$=9.6 Hz, 1H, Ar−H), 7.78 (d, $^3J_{HH}$=7.8 Hz, 1H, Ar−H), 7.57 (d, $^3J_{HH}$=9.0 Hz, 1H, Ar−H), 7.25 (s, 2H, NH_2), 6.86 (s, 1H, Ar−H).

*Data for **III-x***. Yield: 20.0%; red solid; mp, 305−307 °C (acetone/petroleum ether) (*10*). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 10.41 (s, 1H, NHCO), 8.79 (s, 1H, Ar−NH−Ar), 8.20 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.05 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.13 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.02−7.06 (m, 4H, Ar−H).

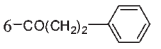
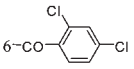
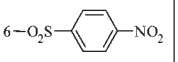
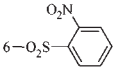
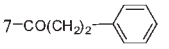
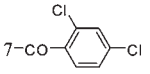
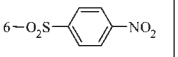
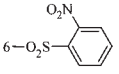
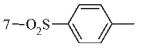
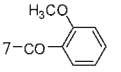
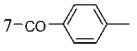
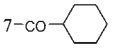
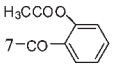
General Synthetic Procedures for Compounds IV-6a−V-8d. To a solution of the mixture 6-aminophenazine-1-carboxylic acid (**III-a**) and 8-aminophenazine-1-carboxylic acid (**III-c**) (2.0 g) in methanol (500.0 mL), H_2SO_4 (0.5 mL) was added dropwise and refluxed for 7 h. Most of the methanol was then removed by distillation, and the residue was diluted with water. The black solution was made alkaline with $NH_3 \cdot H_2O$ (*5*) and extracted with dichloromethane (2 × 50.0 mL). The extraction was evaporated and purified by flash chromatography on silica gel eluting [elution solvent: ethyl acetate/petroleum ether (60−90 °C), 1:4, v/v] to provide red solid **IV-6a** (0.52 g, Yield, 25.1%) and **IV-8a** (0.25 g, yield, 11.8%). Compounds **IV-6b−IV-8d** were prepared according to the same process. **V-7b**, **V-7c**, **V-7d**, and **V-8d** were the byproducts of **IV-7b**, **IV-7c**, **IV-7d** and **IV-8d** respectively. All the substituents at the phenazine rings are listed in **Scheme 2** and **Table 1**.

*Data for **IV-6a***. Yield: 25.1%; red solid; mp, 142−144 °C (ethyl acetate/petroleum ether) (*6*). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.06 (d, $^3J_{HH}$=6.8 Hz, 1H, Ar−H), 7.60 (t, $^3J_{HH}$=8.0 Hz, 1H, Ar−H), 7.51 (d, $^3J_{HH}$=8.4 Hz, 1H, Ar−H), 7.47 (d, $^3J_{HH}$=8.4 Hz, 1H, Ar−H), 6.74 (d, $^3J_{HH}$=6.0 Hz, 1H, Ar−H), 5.16 (s, 2H, NH_2), 3.98 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 144.3, 143.9, 141.2, 140.4, 134.9, 133.4, 132.6, 131.9, 131.0, 127.8, 117.7, 108.0, 52.6.

*Data for **IV-6b***. Yield: 41.7%; red solid; mp, 108−110 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (dd, $^3J_{HH}$=8.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 8.09 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz,1H, Ar−H), 7.65 (dd, $^3J_{HH}$=8.8 Hz, $^3J_{HH}$=7.2 Hz, 1H, Ar−H), 7.52 (d, $^3J_{HH}$= 4.4 Hz, 2H, Ar−H), 6.80 (d, $^3J_{HH}$=4.4 Hz, 1H, Ar−H), 5.16 (s, 2H, NH_2), 4.50 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 1.42 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 143.3, 142.8, 140.2, 139.4, 133.9, 132.1, 131.4, 130.5 (2C), 126.9, 116.9, 107.0, 60.5, 13.3. HRMS: *m*/*z* 268.1082. Calcd for $C_{15}H_{13}N_3O_2$: 268.1081 $[M + H]^+$.

*Data for **IV-6c***. Yield: 33.1%; red solid; mp, 98−100 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.07 (d, $^3J_{HH}$=6.4 Hz, 1H, Ar−H), 7.62 (t, $^3J_{HH}$=7.6 Hz, 1H, Ar−H), 7.50 (brd, $^4J_{HH}$ = 1.2 Hz, 2H, Ar−H), 6.76 (brs, 1H, Ar−H), 5.15 (s, 2H, NH_2), 4.41 (t, $^3J_{HH}$=6.0 Hz, 2H, OCH_2), 1.77−1.82 (m, 2H, CH_2), 1.04 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2,

Table 1. The R Group and the Value of *n* in Compounds **IV-6a**−**VII-e**

Compd.	R	n	Compd.	R	n
IV-6a	6-NH_2	0	**IV-6b**	6-NH_2	1
IV-6c	6-NH_2	2	**IV-6d**	6-NH_2	3
IV-7a	7-NH_2	0	**IV-7b**	7-NH_2	1
IV-7c	7-NH_2	2	**IV-7d**	7-NH_2	3
IV-8a	8-NH_2	0	**IV-8b**	8-NH_2	1
IV-8c	8-NH_2	2	**IV-8d**	8-NH_2	3
V-7b	7-NH_2	1	**V-7c**	7-NH_2	2
V-7d	7-NH_2	3	**V-8d**	8-NH_2	3
VI-6a	6-$COCH_3$	0	**VI-6b**	6-$COCH_2OOCCH_3$	0
VI-6c	6-$CO(CH_2)_3Cl$	0	**VI-6d**		0
VI-6e		0	**VI-6f**		0
VI-6g		0	**VI-6h**	6-$CO(CH_2)_3Cl$	3
VI-7a	7-$COCH_3$	0	**VI-7b**	7-$COCH_2OOCCH_3$	0
VI-7c	7-$CO(CH_2)_3Cl$	0	**VI-7d**		0
VI-7e		0	**VI-7f**		0
VI-7g		0	**VI-7h**	7-$CO(CH_2)_3Cl$	3
VI-7i		0	**VI-7j**		0
VI-7k		0	**VI-7l**		0
VI-7m		0	**VI-7n**	7-$COCl_3$	0
VII-a	6-$NHCO(CH_2)_3Cl$, 7-NO_2	0	**VII-b**	6-NH_2, 7-NO_2, 9-NO_2	0
VII-c	6-$NHCO(CH_2)_3Cl$, 7-NO_2	3	**VII-d**	6-NH_2, 7-NO_2, 9-NO_2	3
VII-e	7-NH_2, 6-NO_2	3			

144.3, 143.8, 141.2, 140.4, 134.9, 133.2, 132.5, 131.6 (2C), 127.9, 117.8, 108.0, 67.2, 22.2, 10.7. HRMS: *m*/*z* 282.1241. Calcd for $C_{16}H_{15}N_3O_2$: 282.1237 $[M + H]^+$.

Data for ***IV-6d***. Yield: 60.1%; brown solid; mp, 110−112 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 8.17 (dd, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.75 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.8 Hz, 1H, Ar−H), 7.63 (dt, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.61 (dt, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 6.91 (dd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 1.6 Hz, 1H, Ar−H), 5.24 (s, 2H, NH_2), 4.53 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 1.83−1.87 (m, 2H, CH_2), 1.58−1.64 (m, 2H, CH_2), 1.03 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 144.3, 143.8, 141.3, 140.5, 135.0, 133.2, 132.5, 131.7, 131.6, 128.0, 117.9, 108.1, 65.5, 30.8, 19.3, 13.8. HRMS: *m*/*z* 296.1394. Calcd for $C_{17}H_{17}N_3O_2$: 296.1393 $[M + H]^+$.

Data for ***IV-7a***. Yield: 47.6%; red solid; mp, 201−203 °C (acetone/petroleum ether) (*5*). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.11 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.90 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.86−7.87 (brd, 1H, Ar−H), 7.79 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.49 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 6.91 (s, 1H, Ar−H), 6.65 (s, 2H, NH_2), 3.96 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 167.4, 151.5, 145.8, 142.5, 139.2, 136.5, 132.0, 130.9, 130.4, 128.9, 127.4, 126.9, 100.7, 52.3.

Data for ***IV-7b***. Yield: 59.7%; red solid; mp, 190−192 °C (ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 8.07 (d, $^3J_{HH}$ = 9.3 Hz, 1H, Ar−H), 8.03 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.74 (dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.32 (dd, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.13 (s, 1H, Ar−H), 4.58 (q, $^3J_{HH}$ = 6.9 Hz, 2H, OCH_2), 4.53 (s, 2H, NH_2), 1.49 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 148.8, 145.4, 143.1, 140.4, 138.7, 132.2, 131.7 (2C), 129.2, 128.8, 125.7, 104.5, 61.5, 14.4. HRMS: *m*/*z* 290.0899. Calcd for $C_{15}H_{13}N_3O_2$: 290.0900 $[M + Na]^+$.

Data for ***IV-7c***. Yield: 29.9%; red solid; mp, 170−172 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.03 (brd, $^3J_{HH}$ = 6.8 Hz, 2H, Ar−H), 7.73 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.29 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 7.10 (s, 1H, Ar−H), 4.61 (s, 2H, NH_2), 4.47 (t, $^3J_{HH}$ = 6.0 Hz, 2H, OCH_2), 1.87−1.89 (m, 2H, CH_2), 1.12 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 148.9, 145.4, 143.1, 140.3, 138.6, 132.1, 131.8 131.5, 129.1 128.8, 125.8, 104.3, 67.1, 22.1, 10.6. HRMS: *m*/*z* 304.1059. Calcd for $C_{16}H_{15}N_3O_2$: 304.1056 $[M + Na]^+$.

Data for ***IV-7d***. Yield: 31.7%; red solid; mp, 202−204 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.07 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 8.03 (t, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.75 (t, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.33 (dd, $^3J_{HH}$ = 9.6 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.14 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 4.51 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 4.46 (s, 2H, NH_2), 1.81−1.88 (m, 2H, CH_2), 1.57−1.62 (m, 2H, CH_2), 1.02 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 148.7, 145.4, 143.1, 140.4, 138.8, 132.2, 131.9, 131.7, 129.2, 128.8, 125.7, 104.6, 65.4, 30.8, 19.3, 13.8. HRMS: *m*/*z* 296.1391. Calcd for $C_{17}H_{17}N_3O_2$: 296.1393 $[M + H]^+$.

Data for ***IV-8a***. Yield: 11.8%; red solid; mp, 185−187 °C (ethyl acetate/petroleum ether) (*6*). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.16 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.99 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.67 (dt, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.34 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.25 (s, 1H, Ar−H), 4.58 (s, 2H, NH_2), 4.08 (s, 3H, OCH_3).

Data for ***IV-8b***. Yield: 19.0%; red solid; mp, 136−138 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 8.06 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.93 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.60 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.25 (dd, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 7.17 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 4.49 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 4.37 (s, 2H, NH_2), 1.42 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.0, 147.5, 144.7, 140.5, 139.6, 138.9, 132.2, 130.5, 129.7 (2C), 125.5, 124.9, 104.7, 60.4, 13.3. HRMS: *m*/*z* 268.1082. Calcd for $C_{15}H_{13}N_3O_2$: 268.1081 $[M + H]^+$.

Data for ***IV-8c***. Yield: 21.2%; red solid; mp, 144−146 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.05 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.88 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.58 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.21 (dd, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.13 (s, 1H, Ar−H), 4.50 (s, 2H, NH_2), 4.39 (t, $^3J_{HH}$ = 6.0 Hz, 2H, OCH_2), 1.77−1.82 (m, 2H, CH_2), 1.04 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 147.7, 144.7, 140.5, 139.5, 138.8, 132.2, 130.5 129.7 129.6 125.4, 125.0, 104.4, 66.0, 21.1, 9.6. HRMS: *m*/*z* 282.1243. Calcd for $C_{16}H_{15}N_3O_2$: 282.1237 $[M + H]^+$.

Data for ***IV-8d***. Yield: 50.5%; red solid; mp, 141−143 °C (ethyl acetate/petroleum ether).^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.99 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.74 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.51 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.13 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.06 (s, 1H, Ar−H), 4.78 (s, 2H, NH_2), 4.37 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 1.67−1.70 (m, 2H, CH_2), 1.39−1.44 (m, 2H, CH_2), 0.85 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 148.2, 144.8, 140.3, 139.3, 138.7, 132.1, 130.4, 129.5, 129.4, 125.2 (2C), 103.7, 64.2, 29.7, 18.2, 12.7. HRMS: *m*/*z* 296.1392. Calcd for $C_{17}H_{17}N_3O_2$: 296.1393 $[M + H]^+$.

Data for ***V-7b***. Yield: 5.1%; red solid; mp, 159−161 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, $^3J_{HH}$ = 8.4 Hz,

1H, H-4), 8.04 (d, $^3J_{HH}$ = 6.8 Hz, 1H, H-2), 7.66−7.72 (m, 1H, H-3), 7.35 (s, 1H, H-9), 7.13 (s, 1H, H-6), 4.89 (s, 2H, NH_2), 4.56 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2-2′), 4.29 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2-1′′), 1.55 (q, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3-2′′), 1.48 (q, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3-3′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0 (s, C-1′), 152.8 (s, C-8), 143.6 (s, C-7), 142.2 (s, C-9a), 142.2 (s, C-5a), 141.2 (s, C-4a), 138.6 (s, C-10a), 131.9 (d, C-4), 130.5 (s, C-1), 129.1 (d, C-2), 127.3 (d, C-3), 105.7 (d, C-9), 103.4 (d, C-6), 64.9 (t, C-1′′), 61.3 (t, C-2′), 14.5 (q, C-2′′), 14.4 (q, C-3′). HRMS: *m*/*z* 334.1163. Calcd for $C_{17}H_{17}N_3O_3$: 334.1162 $[M + Na]^+$.

Data for ***V-7c***. Yield: 10.6%; red solid; mp, 140−142 °C (ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.97 (dd, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.61 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.28 (s, 1H, Ar−H), 7.04 (s, 1H, Ar−H), 4.72 (s, 2H, NH_2), 4.39 (t, $^3J_{HH}$ = 6.6 Hz, 2H, OCH_2), 4.13 (t, $^3J_{HH}$ = 6.6 Hz, 2H, OCH_2), 1.85−1.92 (m, 2H, CH_2), 1.77−1.85 (m, 2H, CH_2), 1.04−1.06 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 151.8, 142.3, 141.6, 141.0, 140.6, 137.7, 131.2, 129.6, 128.1, 126.1, 104.6, 102.7, 69.6, 65.9, 21.2 (2C), 9.6, 9.5. HRMS: *m*/*z* 340.1653. Calcd for $C_{19}H_{21}N_3O_3$: 340.1656 $[M + H]^+$.

Data for ***V-7d***. Yield: 30.2%; red solid; mp, 134−136 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 8.04 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.68 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.35 (s, 1H, Ar−H), 7.11 (s, 1H, Ar−H), 4.83 (s, 2H, NH_2), 4.51 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OCH_2), 4.23 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 1.82−1.92 (m, 4H, $2CH_2$), 1.54−1.60 (m, 4H, $2CH_2$), 1.00−1.03 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 152.9 143.4, 142.5, 142.0, 141.6, 138.7, 132.2, 130.7, 129.1, 127.2, 105.6, 103.7, 68.9, 65.2, 30.8 (2C), 19.3 (2C), 13.8, 13.7. HRMS: *m*/*z* 390.1786. Calcd for $C_{21}H_{25}N_3O_3$: 390.1788 $[M + Na]^+$.

Data for ***V-8d***. Yield: 14.6%; red solid; mp, 198−200 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.99 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.57 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.18 (s, 1H, Ar−H), 7.13 (s, 1H, Ar−H), 4.70 (s, 2H, NH_2), 4.43 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 4.17 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 1.83−1.86 (m, 2H, CH_2), 1.75−1.78 (m, 2H, CH_2), 1.48−1.54 (m, 4H, $2CH_2$), 0.94−0.99 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 152.0 142.1, 142.0, 140.4, 139.4, 138.9, 131.3, 129.6, 128.9, 125.2, 103.9, 103.5, 67.8, 64.2, 29.8 (2C), 18.3 (2C), 12.8 (2C). HRMS: *m*/*z* 368.1970. Calcd for $C_{21}H_{25}N_3O_3$: 368.1969 $[M + H]^+$.

General Synthetic Procedures for Target Compounds VI-6a−VI-7n. Methyl-6-aminophenazine-1-carboxylate (**IV-6a**, 50.0 mg, 0.2 mmol) was dissolved in the solution of dry CH_2Cl_2 (4.0 mL) and anhydrous pyridine (0.2 mL). Acetyl chloride (0.2 mL) diluted in CH_2Cl_2 (6.0 mL) was added dropwise to the above solution. The mixture was stirred under 15 °C for 0.5 h, and then 20 mL of CH_2Cl_2 was added, followed by washing with dilute 2 N hydrochloric acid, saturated sodium bicarbonate and water respectively. Separating the organic layer, the solvent was removed by distillation. The residue was recrystallized with ethyl acetate/petroleum ether (60−90 °C) to give methyl-6-acetamidophenazine-1-carboxylate (**VI-6a**, 23.0 mg, 40.0%). Compounds **VI-6b**−**VI-6e**, **VI-6h** and **VI-7h** were prepared with corresponding acyl chloride through the same process. Compounds **VI-6f** and **VI-6g** were prepared as follows: Methyl-6- aminophenazine-1-carboxylate (**IV-6a**, 50.0 mg, 0.2 mmol) and 4-nitrobenzene-1-sulfonyl chloride (88 mg, 0.4 mmol) were dissolved in a solution of CH_2Cl_2 (20.0 mL) and pyridine (0.2 mL). The mixture was refluxed for 1 h, and then 20 mL of CH_2Cl_2 was added, followed by washing with dilute 2 N hydrochloric acid, saturated sodium bicarbonate and water respectively. Leaving the organic layer, the solvent was removed by distillation. The residue was recrystallized with ethyl acetate/petroleum ether (60−90 °C) to give methyl 6-(4-nitrophenylsulfonamido) phenazine-1-carboxylate (**VI-6f**, 52.0 mg, 60%). To be pointed out, in the process of preparing compounds **VI-7a**−**VI-7e** and **VI-7j**−**VI-7n**, methyl-7-aminophenazine-1-carboxylate (**IV-7a**) was dissolved only in the anhydrous pyridine. The rest of the procedures were the same as preparing for compound **VI-6a**. In the process of preparing compounds **VI-7f**, **VI-7g** and **VI-7i**, compound IV-7a and the corresponding sulfonyl chloride were refluxed in anhydrous pyridine (*11*). The other procedures were the same as preparing for compound **VI-6f**. All the substituents at the phenazine rings are listed in Scheme **2** and **Table 1**.

Data for ***VI-6a***. Yield: 79.3%; yellow solid; mp, 212−214 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.66 (s, 1H, NHCO), 8.81 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 8.33 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 8.23 (dd, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.95 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.81 (dt, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, Ar−H), 4.11 (s, 3H, OCH_3), 2.43 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 166.9, 143.3, 141.2, 140.3, 134.3, 133.9, 132.7, 132.2, 132.1, 131.4, 129.1, 123.7, 116.4, 52.7, 25.1. HRMS: *m*/*z* 296.1031. Calcd for $C_{16}H_{13}N_3O_3$: 296.1030 $[M + H]^+$.

Data for ***VI-6b***. Yield: 35.7%; yellow solid; mp, 165−167 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (s, 1H, NHCO), 8.77 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 8.22 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.18 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.99 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.82 (dt, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 2.4 Hz, 2H, Ar−H),4.89 (s, 2H, OCH_2), 4.11 (s, 3H, OCH_3), 2.42 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 166.8, 165.4, 143.2, 141.2, 140.3, 134.3, 132.8, 132.6, 132.2, 132.0, 131.5, 129.3, 124.5, 116.8, 63.3, 52.7, 20.8. HRMS: *m*/*z* 376.0899. Calcd for $C_{18}H_{15}N_3O_5$: 376.0904 $[M + Na]^+$.

Data for ***VI-6c***. Yield: 80.3%; orange solid; mp, 158−160 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (s, 1H, NHCO), 8.78 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 8.32 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.22 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.96 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.82 (t, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 4.11 (s, 3H, OCH_3), 3.75 (t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2Cl), 2.85 (t, $^3J_{HH}$ = 6.8 Hz, 2H, CH_2CO), 2.29−2.35 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 166.9, 143.3, 141.2, 140.3, 134.3, 133.7, 132.8, 132.1 (2C), 131.4, 129.1, 123.9, 116.4, 52.7, 44.4, 34.5, 27.8. HRMS: *m*/*z* 380.0774. Calcd for $C_{18}H_{16}ClN_3O_3$: 380.0772 $[M + Na]^+$.

Data for ***VI-6d***. Yield: 90.1%; yellow solid; mp, 191−193 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.60 (s, 1H, NHCO), 8.82 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.25 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.20 (d, $^3J_{HH}$ = 6.0 Hz, 1H, Ar−H), 7.96 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 7.82 (t, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 7.31 (brs, 4H, Ar−H), 7.19 (brs, 1H, Ar−H), 4.10 (s, 3H, OCH_3), 3.17 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2CO), 2.96 (t, $^3J_{HH}$ = 7.2 Hz, 2H, Ar−CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 166.9, 143.3, 141.1, 140.6, 140.3, 134.3, 133.8, 132.8, 132.3, 132.2, 131.3, 129.1, 128.6 (2C), 128.4 (2C), 126.4, 123.7, 116.4, 52.8, 39.7, 31.3. HRMS: *m*/*z* 386.1501. Calcd for $C_{23}H_{19}N_3O_3$: 386.1499 $[M + H]^+$.

Data for ***VI-6e***. Yield: 92.0%; yellow solid; mp, 226−228 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.63 (s, 1H, NHCO), 8.98 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.33 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.25 (d, $^3J_{HH}$ = 6.4 Hz, 1H, Ar−H), 8.06 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.92 (t, $^3J_{HH}$ = 7.2 Hz, 2H, Ar−H), 7.85 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.56 (s, 1H, Ar−H), 7.43 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 4.11 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9, 163.6, 143.3, 141.4, 140.5, 137.6, 134.6, 133.8, 133.2, 132.9, 132.3, 132.1, 131.9 (2C), 131.4, 130.5, 129.3, 127.8, 124.6, 117.1, 52.7. HRMS: *m*/*z* 426.0408. Calcd for $C_{21}H_{13}Cl_2N_3O_3$: 426.0407 $[M + H]^+$.

Data for ***VI-6f***. Yield: 54.2%; yellow solid; mp, 226−228 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 11.12 (s, 1H, $NHSO_2$), 8.29−8.31 (brd, $^3J_{HH}$ = 8.4 Hz, 3H, Ar−H), 8.25 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.20 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 8.00−8.04 (m, 2H, Ar−H), 7.96 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.87 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 3.99 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.5, 149.7, 145.2, 142.6, 140.6, 139.9, 136.4, 133.2, 132.1, 131.8, 131.6 (2C), 130.2, 128.5 (2C), 125.9, 124.3 (2C), 121.5, 52.5. HRMS: *m*/*z* 439.0708. Calcd for $C_{20}H_{14}N_4O_6S$: 439.0707 $[M + H]^+$.

Data for ***VI-6g***. Yield: 83.3%; brown solid; mp, 192−194 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.00 (s, 1H, $NHSO_2$), 8.37 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.23 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 8.10−8.13 (m, 1H, Ar−H), 8.08 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.01 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.85 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.82 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 7.59−7.61 (m, 2H, Ar−H), 4.07 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 147.9, 143.3, 141.5, 140.9, 134.8, 134.1, 133.3, 132.9, 132.7, 132.6, 132.5, 131.3, 131.2, 131.1, 129.6, 125.7, 125.4, 116.3, 52.7. HRMS: *m*/*z* 439.0705. Calcd for $C_{20}H_{14}N_4O_6S$: 439.0707 $[M + H]^+$.

Data for ***VI-6h***. Yield: 37.0%; yellow solid; mp, 101−103 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (s, 1H, NHCO), 8.81 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.36 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.22 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.96 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.87 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.83 (d, $^3J_{HH}$ = 7.6 Hz, 1H,

Ar−H), 4.54 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OCH_2), 3.75 (t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2Cl), 2.84−2.88 (m, 2H, CH_2CO), 2.31−2.34 (m, 2H, CH_2), 1.84−1.88 (m, 2H, CH_2), 1.58−1.64 (m, 2H, CH_2), 1.04 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 166.8, 143.3, 141.3, 140.4, 134.3, 133.8, 132.6, 132.1 (2C), 131.8, 129.3, 123.8, 116.4, 65.6, 44.4, 34.5, 30.8, 27.8. 19.3, 13.7. HRMS: *m*/*z* 400.1419. Calcd for $C_{21}H_{22}ClN_3O_3$: 400.1422 $[M + H]^+$.

Data for ***VI-7a***. Yield: 34.5%; yellow solid; mp, 234−236 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (s, 1H, NHCO), 8.25 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.12−8.14 (brd, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.95 (s, 1H, Ar−H), 7.87 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.75 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.03 (s, 3H, OCH_3), 2.22 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 166.2, 143.0, 142.1, 140.3, 139.1 (2C), 132.0, 130.3, 130.2, 130.0, 128.1, 125.2, 113.9, 51.7, 23.8. HRMS: *m*/*z* 318.0847. Calcd for $C_{16}H_{13}N_3O_3$: 318.0849 $[M + Na]^+$.

Data for ***VI-7b***. Yield: 50.1%; yellow solid; mp, 206−208 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (s, 1H, NHCO), 8.28 (brs, 4H, Ar−H), 7.85−7.96 (brd, 2H, Ar−H), 4.80 (s, 2H, OCH_2), 4.11 (s, 3H, OCH_3), 2.28 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 167.1, 165.5, 150.9, 143.9, 143.2, 141.5, 140.4, 138.7, 133.2, 131.6, 131.4, 129.3, 126.0, 116.1, 63.4, 52.7, 20.8. HRMS: *m*/*z* 376.0902. Calcd for $C_{18}H_{15}N_3O_5$: 376.0904 $[M + Na]^+$.

Data for ***VI-7c***. Yield: 47.5%; brown solid; mp, 198−200 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (s, 1H, NHCO), 8.45 (s, 1H, Ar−H), 8.31 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.12 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.10 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 8.00 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.79 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.03 (s, 3H, OCH_3), 3.58 (t, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2Cl), 2.62 (t, $^3J_{HH}$ = 6.8 Hz, 2H, CH_2CO), 2.12−2.15 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 166.9, 142.3, 141.7, 141.4, 141.1, 140.0, 131.6, 131.4, 131.3, 131.1, 130.1, 126.7, 113.3, 52.8, 44.3, 34.3, 27.6. HRMS: *m*/*z* 380.0777. Calcd for $C_{18}H_{16}ClN_3O_3$: 380.0772 $[M + Na]^+$.

Data for ***VI-7d***. Yield: 65.7%; yellow solid; mp, 215−217 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H, NHCO), 8.33 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 8.28 (s, 1H, Ar−H), 8.12−8.17 (m, 2H, Ar−H), 7.95 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.81 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.20−7.26 (m, 5H, Ar−H), 4.08 (s, 3H, OCH_3), 3.06 (t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2CO), 2.80 (t, $^3J_{HH}$ = 6.4 Hz, 2H, Ar−CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 167.1, 143.3, 142.2, 141.5, 140.7, 140.3, 140.0, 132.5, 131.4, 131.2, 131.0, 129.5, 128.6 (2C), 128.4 (2C), 126.7, 126.4, 114.4, 52.8, 39.6, 31.3. HRMS: *m*/*z* 408.1322. Calcd for $C_{23}H_{19}N_3O_3$: 408.1319 $[M + Na]^+$.

Data for ***VI-7e***. Yield: 30.1%; yellow solid; mp, 246−248 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.27 (s, 1H, NHCO), 8.83 (s, 1H, Ar−H), 8.38 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.25 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 8.16 (d, $^3J_{HH}$ = 6.0 Hz, 1H, Ar−H), 8.12 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.99 (dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.85 (s, 1H, Ar−H), 7.79 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.64 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.01 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 165.0, 143.7, 142.5, 140.8, 140.5, 139.0, 135.3, 135.1, 132.0 (2C), 131.2, 130.5, 130.3 (2C), 129.9, 129.3, 127.5, 126.9, 114.4, 52.5. HRMS: *m*/*z* 426.0408. Calcd for $C_{21}H_{13}Cl_2N_3O_3$: 426.0407 $[M + H]^+$.

Data for ***VI-7f***. Yield: 38.0%; green solid; mp, 235−237 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 11.68 (s, 1H, $NHSO_2$), 8.38 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 8.29 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.19 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 8.16 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.12 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.94 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.82 (s, 1H, Ar−H), 7.78 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 3.95 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.7, 150.1, 144.2, 143.1, 142.3, 140.2, 139.7, 139.0, 131.9, 131.2, 130.5, 130.1, 128.3 (2C), 126.2, 124.9 (3C), 112.9, 52.5. HRMS: *m*/*z* 461.0528. Calcd for $C_{20}H_{14}N_4O_6S$: 461.0526 $[M + Na]^+$.

Data for ***VI-7g***. Yield: 37.1%; orange solid; mp, 199−201 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.25 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 8.20 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.99−8.01 (brd, 2H, Ar−H), 7.85−7.87 (brd, 2H, Ar−H), 7.82 (d, $^3J_{HH}$ = 10.0 Hz, 1H, Ar−H), 7.67 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 7.56 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ar−H), 4.09 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9, 148.1, 143.3, 143.1, 141.7, 140.6, 138.1, 134.5, 133.0, 132.8, 132.1, 131.9, 131.8, 131.7, 131.5, 129.7, 127.0, 125.6, 118.1, 52.8. HRMS: *m*/*z* 461.0531. Calcd for $C_{20}H_{14}N_4O_6S$: 461.0526 $[M + Na]^+$.

Data for ***VI-7h***. Yield: 40.1%; yellow solid; mp, 200−202 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H, NHCO), 8.29 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.15 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.13 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 8.11 (d, $^3J_{HH}$ = 6.0 Hz, 1H, Ar−H), 7.94 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, Ar−H), 7.82 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.53 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OCH_2), 3.67 (t, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2Cl), 2.65−2.68 (m, 2H, CH_2CO), 2.22−2.25 (m, 2H, CH_2), 1.83−1.87 (m, 2H, CH_2), 1.57−1.62 (m, 2H, CH_3), 1.03 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 167.1, 143.9, 143.1, 141.3, 140.2, 139.8, 132.9, 131.8, 131.0, 130.9, 129.2, 126.2, 115.2, 65.6, 44.3, 34.2, 30.8, 27.7. 19.3, 13.8. HRMS: *m*/*z* 400.1423. Calcd for $C_{21}H_{22}ClN_3O_3$: 400.1422 $[M + H]^+$.

Data for ***VI-7i***. Yield: 35.5%; yellow solid; mp, 183−185 °C (ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, $^3J_{HH}$ = 8.7 Hz, 1H, Ar−H), 8.09 (d, $^3J_{HH}$ = 6.3 Hz, 1H, Ar−H), 8.07 (d, $^3J_{HH}$ = 6.9 Hz, 1H, Ar−H), 7.75−7.78 (brd, 4H, Ar−H), 7.62 (d, $^3J_{HH}$ = 8.7 Hz, 1H, Ar−H), 7.13 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ar−H), 4.01 (s, 3H, OCH_3), 2.23 (s, 3H, Ar−CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.0, 143.5, 141.7, 141.0, 139.1, 134.5, 131.2, 130.8, 130.5, 130.3, 128.9 (2C), 126.4 (2C), 125.0, 123.4, 122.9, 118.0, 112.4, 51.7, 20.5. HRMS: *m*/*z* 430.0839. Calcd for $C_{21}H_{17}N_3O_4S$: 430.0832 $[M + Na]^+$.

Data for ***VI-7j***. Yield: 45.7%; yellow solid; mp, 202−204 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.22 (s, 1H, Ar−H), 8.57 (s, 1H, Ar−H), 8.21−8.26 (m, 3H, Ar−H), 8.10 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.07 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.76 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.41 (brs, 1H, Ar−H), 7.07 (brs, 1H, 1H, Ar−H), 6.95 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.09 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 163.5, 157.1, 144.2, 143.1, 141.4, 140.5, 140.0, 133.7, 133.1, 132.5, 131.3, 131.1, 130.9, 128.9, 127.0, 121.6, 120.9, 115.3, 111.4, 56.2, 52.6. HRMS: *m*/*z* 410.1111. Calcd for $C_{22}H_{17}N_3O_4$: 410.1111 $[M + Na]^+$.

Data for ***VI-7k***. Yield: 20.1%; yellow solid; mp, 238−240 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 10.88 (s, 1H, NHCO), 8.95 (s, 1H, Ar−H), 8.43 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.37 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 8.29 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.21 (d, $^3J_{HH}$ = 6.0 Hz, 1H, Ar−H), 8.02−8.04 (brd, 3H, Ar−H), 7.47 (d, $^3J_{HH}$ = 6.4 Hz, 2H, Ar−H), 4.06 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.9, 166.4, 155.0, 143.8, 142.4, 142.2, 141.5, 140.4, 138.8, 132.0, 131.5, 130.1, 129.8, 129.7, 129.0 (2C), 127.9 (2C), 127.8, 114.4, 52.5, 21.0. HRMS: *m*/*z* 394.1159. Calcd for $C_{22}H_{17}N_3O_3$: 394.1162 $[M + Na]^+$.

Data for ***VI-7l***. Yield: 41.9%; yellow solid; mp, 100−102 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (s, 1H, NHCO), 8.42 (s, 1H, Ar−H), 8.16 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.06 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.00 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.92 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 7.69 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 4.00 (s, 3H, OCH_3), 2.21−2.27 (m, 1H, cyclohexyl-CH), 1.81−1.87 (m, 2H, cyclohexyl-CH_2), 1.65−1.67 (m, 2H, cyclohexyl-CH_2), 1.41−1.52 (m, 3H, cyclohexyl-CH_2), 1.07−1.09 (m, 3H, cyclohexyl-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 166.2, 142.8, 141.7, 140.2, 139.7, 138.8, 131.9, 130.2, 130.0, 129.5, 128.0, 125.9, 113.8, 51.7, 45.4, 28.4 (2C), 24.5 (3C). HRMS: *m*/*z* 386.1482. Calcd for $C_{21}H_{21}N_3O_3$: 386.1475 $[M + Na]^+$.

Data for ***VI-7m***. Yield: 21.7%; orange solid; mp, 60−62 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (s, 1H, NHCO), 8.51 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 8.25 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.18 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 8.10 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.99 (dd, $^3J_{HH}$ = 9.2 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.79 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.75 (dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.44 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.25 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.10 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 4.02 (s, 3H, OCH_3), 2.28 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 166.1, 163.1, 146.9, 143.0, 142.1, 140.4, 139.2, 138.9, 132.1, 131.6, 130.4, 130.3, 129.9, 128.8, 128.2, 127.0, 125.5, 125.1, 122.4, 114.4, 51.7, 20.1. HRMS: *m*/*z* 416.1248. Calcd for $C_{23}H_{17}N_3O_5$: 416.1241 $[M + H]^+$.

Data for ***VI-7n***. Yield: 47.7%; yellow solid; mp, 246−248 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 11.48 (s, 1H, NHCO), 8.67 (s, 1H, Ar−H), 8.38 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.23−8.29 (m, 2H, Ar−H), 8.18 (d, $^3J_{HH}$ = 6.4 Hz, 1H, Ar−H), 7.99

(dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.00 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.7, 160.2, 143.1, 142.4, 140.6, 139.6, 139.3, 132.1, 131.9, 130.8, 130.2, 130.0, 127.2, 116.8, 51.5. HRMS: m/z 419.9688. Calcd for $C_{16}H_{10}Cl_3N_3O_3$: 419.9680 $[M + Na]^+$.

General Synthetic Procedures for Target Compounds VII-a−VII-e. At 0 °C, 65% nitric acid (0.2 mL) was dropped to the solution of **VI-6c** (80 mg, 0.22 mmol) in 98% sulfuric acid (10.0 mL). The mixture was stirred and kept at 0 °C for 2 h, then poured onto crushed ice (20 g), and extracted with dichloromethane (2 × 20 mL), followed by washing with saturated sodium bicarbonate and water respectively. The solvent of the organic layer was removed (*12*). The residue was recrystallized with ethyl acetate/petroleum ether (60−90 °C) to give methyl 6-amino-7,9-dinitrophenazine-1-carboxylate (**VII-b**, 40.0 mg, 53.3%). Two recrystallizations from ethyl acetate/petroleum ether (60−90 °C) gave methyl-6-(4-chlorobutanamido)-7-nitrophenazine-1-carboxylate (**VII-a**, 5.0 mg, 5.5%). Compounds **VII-c** and **VII-d** were gained from **VI-6h** with the same process as above. Compound **VII-e** was the only product from **VI-7h**. The structures of **VII-c**, **VII-d** and **VII-e** were testified by the 2D-NMR spectra. All the substituents at the phenazine rings are listed in **Scheme 2** and **Table 1**.

*Data for **VII-a***. Yield: 5.5%; orange solid; mp, beyond 340 °C (ethyl acetate/petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.95 (s, 1H, NHCO), 8.90 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.56 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.44 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 8.40 (d, $^3J_{HH}$ = 6.0 Hz, 1H, Ar−H), 8.02 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 4.16 (s, 3H, OCH_3), 3.77 (brs, 2H, CH_2Cl), 2.93 (brs, 2H, CH_2CO), 2.34 (brs, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 166.9, 141.8, 140.4 (2C), 138.5, 135.6, 134.4, 133.9, 133.6, 132.5, 131.3, 130.0, 113.1, 53.0, 44.2, 34.5, 27.5. HRMS: m/z 426.0620. Calcd for $C_{18}H_{15}ClN_4O_5$: 425.0623 $[M + Na]^+$.

*Data for **VII-b***. Yield: 53.3%; orange solid; mp, 257−259 °C (ethyl acetate/petroleum ether). ^1H NMR (400 MHz, d_6-DMSO) δ: 9.66−9.77 (brd, 2H, NH_2) 9.14 (s, 1H, Ar−H), 8.44 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.37 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 8.11 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 3.97 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.4, 148.7, 140.7, 138.9, 137.9, 135.3, 133.9, 132.3, 132.0, 131.7, 131.4, 127.8, 121.4, 52.4. HRMS: m/z 366.0442. Calcd for $C_{14}H_9N_5O_6$: 366.0445 $[M + Na]^+$.

*Data for **VII-c***. Yield: 18.0%; yellow solid; mp, 141−143 °C (ethyl acetate/petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H, NHCO), 8.80 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.41 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.33 (d, $^3J_{HH}$ = 8.8 Hz, 1H, Ar−H), 8.27 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ar−H), 7.92 (t, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 4.48 (t, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 3.69 (t, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2Cl), 2.85 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2CO), 2.25−2.28 (m, 2H, CH_2), 1.79−1.82 (m, 2H, CH_2), 1.41−1.46 (m, 2H, CH_2), 0.91 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 165.6, 140.8, 139.7, 139.4, 137.3, 134.6, 132.5, 132.0, 131.6, 131.2, 130.2, 128.4, 112.0, 65.3, 43.2, 33.5, 29.6, 26.5, 18.2, 12.7. HRMS: m/z 467.1100. Calcd for $C_{21}H_{21}ClN_4O_5$: 467.1093 $[M + Na]^+$.

*Data for **VII-d***. Yield: 51.9%; orange solid; mp, 176−178 °C (ethyl acetate/petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.30 (s, 1H, H-8), 9.01 (s, 1H, NH-α), 8.40 (brs, 1H, NH-β), 8.40 (brs, 1H, H-4), 8.40 (brs, 1H, H-2), 8.02 (dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, H-3), 4.54 (t, $^3J_{HH}$ = 5.6 Hz, 2H, CH_2-2′), 1.85−1.88 (m, 2H, CH_2-3′), 1.48−1.51 (m, 2H, CH_2-4′), 0.99 (t, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2 (s, C-1′), 147.2 (s, C-9), 142.5 (s, C-5a), 139.9 (s, C-4a), 138.1 (s, C-7), 135.0 (d, C-4), 134.1 (s, C-6), 133.7 (s, C-10a), 132.9 (s, C-1), 132.5 (d, C-2), 131.6 (d, C-3), 126.5 (d, C-8), 122.6 (s, C-9a), 66.4 (t, C-2′), 30.6 (t, C-3′), 19.2 (t, C-4′), 13.7 (q, C-5′). HRMS: m/z 386.1102. Calcd for $C_{17}H_{15}N_5O_6$: 386.1095 $[M + H]^+$.

*Data for **VII-e***. Yield: 50.8%; yellow solid; mp, 181−183 °C (ethyl acetate/petroleum ether).^1H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.16 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 8.08 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.84 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar−H), 7.35 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 6.91 (s, 2H, NH_2), 4.50 (t, $^3J_{HH}$ = 6.4 Hz, 2H, OCH_2), 1.82−1.85 (m, 2H, CH_2), 1.56−1.58 (m, 2H, CH_2), 1.02 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 146.8, 142.7, 139.5, 138.7, 138.5, 136.3, 133.1, 131.2, 131.1, 130.1, 125.8, 123.8, 65.5, 30.7, 19.3, 13.7. HRMS: m/z 341.1236. Calcd for $C_{17}H_{16}N_4O_4$,: 341.1244 $[M + H]^+$.

Bioassays. The fungicidal activities of the compounds **III-a−VII-e** were tested in vitro against *Alternaria solani*, *Cercospora arachidicola*, *Fusarium omysporum*, *Gibberella zeae*, *Physalospora piricola*, and their relative inhibitory ratio (%) had been determined by using the mycelium growth rate method (*13*). Phenazine-1-carboxylic acid was used as a control. After the mycelia grew completely, the diameters of the mycelia were measured and the inhibition rate was calculated according to the formula

$$I = (D1 - D2)/D1 \times 100\%$$

In the formula, I is the inhibition rate, D1 is the average diameter of mycelia in the blank test, and D2 is the average diameter of mycelia in the presence of those compounds. The inhibition ratio of those compounds at the dose of 50 μg mL^{-1} is summarized in **Table 2**. The EC_{50} of compounds **IV-6a**, **IV-6b** and phenazine-1-carboxylic acid had been experimented and calculated by the Scatchard method. The results are summarized in **Table 3**.

Table 2. Fungicidal Activity of the Compounds **III-a−VII-e** at Dosage of 50 μg mL^{-1}[a]

	inhibition (%)				
compd	*A. solani*	*C. arachidicola*	*F. omysporum*	*G. zeae*	*P. piricola*
III-a	0	7.7	13.8	12.9	19.2
III-b	5.1	11.1	2.7	1.6	4.9
III-c	5.9	11.5	6.9	33.9	9.6
IV-6a	100	26.9	40.0	36.3	100
IV-6b	51.0	32.0	33.3	41.8	100
IV-6c	46.7	30.0	36.7	43.6	57.1
IV-6d	24.2	8.3	21.4	2.7	15.6
IV-7a	33.3	0	10.8	15.1	25.0
IV-7b	29.4	7.7	31.0	11.3	44.2
IV-7c	16.7	26.1	10.0	25.5	19.6
IV-7d	43.3	17.4	13.3	7.3	29.6
IV-8a	10.0	4.0	23.3	18.2	37.1
IV-8b	20.0	12.0	16.7	20.0	51.4
IV-8c	20.2	20.0	33.3	27.3	48.6
IV-8d	23.3	24.0	26.7	23.6	34.3
V-7b	17.6	11.5	6.9	14.5	26.9
V-7c	20.0	21.7	0	20.0	26.5
V-7d	13.3	13.0	0	23.6	25.5
V-8d	17.4	16.7	20.0	42.4	34.3
VI-6a	13.8	8.3	14.3	18.2	46.4
VI-6b	10.3	0	21.4	22.7	32.1
VI-6c	13.8	0	0	25.0	41.1
VI-6d	4.3	0	28.0	30.3	31.4
VI-6e	3.4	0	7.1	27.3	10.7
VI-6f	13.8	25.0	17.9	31.8	17.9
VI-6g	3.4	0	0	43.2	28.6
VI-6h	6.1	8.3	10.7	0	0
VI-7a	3.3	0	0	12.7	3.9
VI-7b	6.5	4.0	5.3	4.8	1.8
VI-7c	37.7	7.7	0	36.8	0
VI-7d	19.1	2.6	11.1	2.4	0
VI-7e	3.0	0	7.1	0	0
VI-7f	6.5	8.0	15.8	0	18.2
VI-7g	13.3	10.9	6.7	12.7	2.0
VI-7h	6.1	8.3	3.6	0	0
VI-7i	33.3	22.2	13.5	17.5	8.0
VI-7j	6.5	24.0	2.6	13.1	23.6
VI-7k	19.1	0	0	14.6	0
VI-7l	23.4	12.8	11.1	9.8	7.4
VI-7m	17.2	4.2	10.7	36.4	33.9
VI-7n	0	12.0	5.3	4.8	21.8
VII-a	20.5	35.0	16.3	40.4	34.4
VII-b	21.7	22.2	32.0	57.6	50.0
VII-c	17.4	11.1	16.0	51.5	37.1
VII-d	17.4	5.6	24.0	53.0	42.9
VII-e	17.2	12.5	17.9	25.0	16.1
phenazine-1-carboxylic acid	100	92.3	65.4	43.1	100

[a] The data is the average of three duplicate results.

RESULTS AND DISCUSSION

Synthesis and Structural Elucidation. In the previous papers (*5*, *6*), compounds **III-a**−**III-c** and **IV-6a**−**IV-8a** were synthesized as follows: methyl-3-nitro-2-(3-nitrophenylamino) benzoate was hydrogenated over PtO_2 to give methyl 3-amino-2-(3-aminophenylamino) benzoate. The above product was refluxed in nitrobenzene for 30 h to give a mixture of **IV-6a** and **IV-8a** (1:11). Compound **III-a** was the hydrolysis product of **IV-6a**. **III-c** was the product from 3-nitro-2-(3-nitrophenylamino) benzoic acid (*6*). **III-b** and **IV-7a** were synthesized by the same author with the same process in principle (*5*). The whole procedure was rather tedious, and the total yield was low.

Compounds **III-a**−**IV-8d** were synthesized through an improved procedure referencing to the literature (*4*−*7*) (*14*−*16*): Compound **II-b** with $NaBH_4$ in 2 N NaOH was refluxed for 4−5 h, cooled, and acidified to give a mixture of **III-a** and **III-c**, which consisted of 50% **III-a** and 50% **III-c**, as determined by ^{1}H NMR. The mixture of **III-a** and **III-c** was refluxed in $CH_3(CH_2)_nOH$ (n = 0, 1, 2, 3) with a catalytic amount of H_2SO_4 to give **IV-6a**−**IV-6d** and **IV-8a**−**IV-8d**, which were easily purified by flash chromatography on silica gel [elution solvent: ethyl acetate/petroleum ether (60−90 °C)]. Similar procedures were used to prepare **III-b** and **IV-7a**−**IV-7d** from **II-c**. Regrettably, compound **III-x** was the only product from **II-a**. So the compound 9-aminophenazine-1-carboxylic acid did not come into being.

In the preparation of **IV-7a**−**IV-7d**, some unexpected byproducts (**V-7b**−**V-7d**) were isolated by flash chromatography on silica gel, and the yields increased with increasing value of n in $CH_3(CH_2)_nOH$. However, no corresponding byproduct was isolated when the n was equal to 0. **V-8d** was the only byproduct from **IV-8d**. No corresponding byproduct was isolated when n was equal to 0, 1, or 2 in the series of **IV-8**. The structures of compounds **V-7b**−**V-8d** were testified by 1D NMR and 2D NMR spectra. One typical compound (**V-7b**) was elucidated as follows: The molecular formula of **V-7b** was revealed as $C_{17}H_{17}N_3O_3$ by HRMS data $[M + Na]^+$ (found 334.1163, calcd 334.1162). The ^{1}H and ^{13}C NMR (Data for **V-7b**) spectra showed the signals of eight quaternary, five CH, two CH_2, two CH_3 carbon atoms. Considering the reagents, the HMQC spectra showed as follows: 8.22 (d, H-4), 8.04 (d, H-2), 7.66−7.72 (m, H-3), 7.35 (s, H-9) and 7.13 (s, H-6) belonged to the Ar−H, which was confirmed by $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.8 Hz and HMBC spectra; 4.89 (s, 2H) belonged to NH_2; 4.56 (t, CH_2-2′), 4.29 (t, CH_2-1″), 1.55 (q, CH_3-2″), 1.48 (q, CH_3-3′) belonged to two side chains, which was confirmed by the $^3J_{HH}$ = 7.2 Hz and HMBC spectra. The chemical shift values of C-9a and C-5a in ^{13}C NMR spectra overlapped; the chemical shift values of C-4a and C-1 in ^{13}C NMR spectra were not easily differentiated by HMBC spectra, which were mentioned by the reference data of **V-7c**, **V-7d** and known compound (*17*).

Based on the HMBC spectra, the correlations between H-4 (δ_H = 8.22) and C-2, C-10a [δ_C = 129.1 (d, C-2), 138.6 (s, C-10a)], the correlations between H-2 (δ_H = 8.04) and C-1′, C-4, C-10a [δ_C = 167.0 (s, C-1′), 131.9 (d, C-4), 138.6 (s, C-10a)], the correlations between H-3 (δ_H = 7.66−7.72) and C-1, C-4a [δ_C = 130.5 (s, C-1), 141.2 (s, C-4a)], the correlations between H-9 (δ_H = 7.35) and C-5a, C-7, C-8, C-9a [δ_C = 142.2 (s, C-5a), 143.6 (s, C-7), 152.8 (s, C-8), 142.2 (s, C-9a)], the correlations between H-6 (δ_H = 7.13) and C-8, C-9a [δ_C = 152.8 (s, C-8), 142.2 (s, C-9a)], the correlations between H-2′ (δ_H = 4.56) and C-1′, C-3′ [δ_C = 167.0 (s, C-1′), 14.4 (q, C-3′)], the correlations between H-3′ (δ_H = 1.48) and C-2′ [δ_C = 61.3 (t, C-2′)], the correlations between H-1″ (δ_H = 4.29) and C-8, C-2″ [δ_C = 152.8 (s, C-8), 14.5 (q, C-2″)], and the correlations between H-2″ (δ_H = 1.55) and C-1″ [δ_C = 64.9 (t, C-1″)] indicated the structure of **V-7b** should be as shown in **Figure 2**.

In the H−H COSY spectra, the correlations between H-3 (δ_H = 7.66−7.72) and H-4 (δ_H = 8.22), the correlations between H-3 (δ_H = 7.66−7.72) and H-2 (δ_H = 8.04) indicated H-4, H-3 and H-2 were in nearby positions. The correlations between H-2′ (δ_H = 4.56) and H-3′ (δ_H = 1.48) and the correlations between H-1″ (δ_H = 4.29) and H-2″ (δ_H = 1.55) further verified the positions of two side chains were right in the structure of **V-7b**. As the possible synthesis mechanisms to those unexpected byproducts would be further studied in the future.

Compounds **VI-7a**−**VI-7g** and **VI-7i**−**VI-7n** were given using **IV-7a** with corresponding acyl chloride or sulfonyl chloride. As the amount of **IV-6a** was limited, compounds **VI-6a**−**VI-6g** were synthesized using **IV-6a** with acyl chloride or sulfonyl chloride which were selected based on the SAR of the **VI-7** series. Considering the high activity of the **IV-6** series and the activity contribution of butan-1-ol to **IV-7d** and 4-chlorobutanoyl chloride to **VI-7c**, compounds **VI-6h** and **VI-7h** were designed and synthesized. In order to know whether the nitryl group on the phenazine ring improved the fungicidal activity or not, some nitration derivatives were given from **VI-6c**, **VI-6h** and **VI-7h**. In the nitration process of **VI-6c** and **VI-6h**, both compounds had

Table 3. EC_{50} of the Compounds **IV-6a**, **IV-6b**, and Phenazine-1-carboxylic Acid

	$Y = a + bx$	EC_{50}	R
IV-6a			
A. solani	$Y = 3.913 + 0.827x$	20.53	0.96
C. arachidicola		>50	
F. omysporum		>50	
G. zeae		>50	
P. piricola	$Y = 4.329 + 1.402x$	3.00	0.96
IV-6b			
A. solani	$Y = 3.250 + 1.0908x$	40.13	0.94
C. arachidicola		>50	
F. omysporum		>50	
G. zeae		>50	
P. piricola	$Y = 4.149 + 1.312x$	4.44	0.98
phenazine-1-carboxylic acid			
A. solani	$Y = 4.400 + 0.472x$	18.5	0.99
C. arachidicola	$Y = 3.185 + 1.615x$	13.2	0.96
F. omysporum	$Y = 4.108 + 0.758x$	14.9	0.98
G. zeae		>50	
P. piricola	$Y = 3.445 + 2.803x$	3.58	0.99

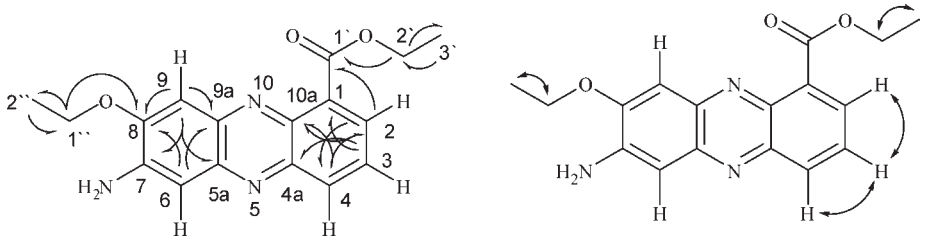


Figure 2. Key HMBC correlations (left) and key H−H COSY (right) correlations of **V-7b**.

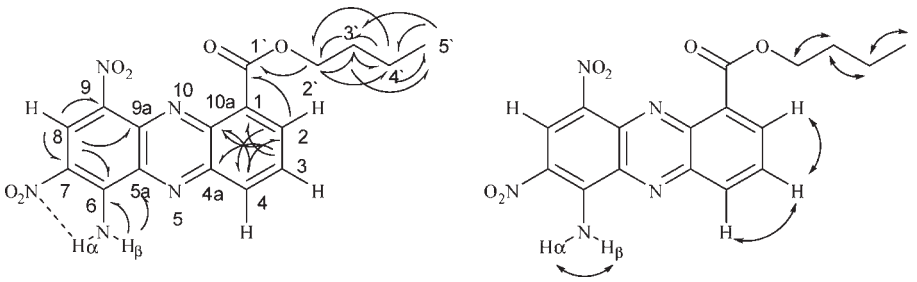


Figure 3. Key HMBC correlations (left) and key H−H COSY (right) correlations of **VII-d**.

two nitration derivatives at 0 °C. One had a single nitryl in the 7-position, and the other had two nitryls in the 7,9-position with the carboxamide bond hydrolyzed. Compound **IIV-e** was the only nitration product from **IV-7h** whenever the reaction's temperature was kept at 0 or 20 °C. The structures of compounds **VII-a**−**VII-d** were proved by 1D NMR and 2D NMR spectra. One typical compound (**VII-d**) was elucidated as follows: The molecular formula of **VII-d** was revealed as $C_{17}H_{17}N_3O_3$ by HRMS data $[M + Na]^+$ (found 334.1163, calcd 334.1162). The ^1H and ^{13}C NMR (Data for **VII-d**) spectra showed the signals of nine quaternary, four CH, three CH_2, one CH_3 carbon atoms. Considering the reagents (**VI-6h**), the HMQC spectra showed as follows: 9.30 (s, H-8), 8.40 (brs, H-4), 8.40 (brs, H-2), 8.02 (dd, H-3) belonged to the Ar−H, which was confirmed by $^3J_{HH} = 7.2$ Hz, $^3J_{HH} = 6.8$ Hz (H-3) and HMBC spectra; 9.01 (s, H-α), 8.40 (brs, H-β) belonged to NH_2; 4.54 (t, CH_2-2′), 1.85−1.88 (m, CH_2-3′), 1.48−1.51 (m, CH_2-4′), 0.99 (t, CH_3-5′) belonged to a side chain, which was confirmed by the $^3J_{HH}$ value and HMBC spectra. The chemical shift values of H-4, H-2 and NH-β in ^1H NMR spectra overlapped; the chemical shift values of C-4a and C-1 in ^{13}C NMR spectra were not easily differentiated by HMBC spectra, which were mentioned by the reference data of **VII-a**−**VII-c** and known compound (*17*).

Based on the HMBC spectra, the correlations between H-8 (δ_H = 9.03) and C-6, C-7, C-9, C-9a [δ_C = 134.1 (s, C-6), 138.1 (s, C-7), 147.2 (s, C-9), 122.6 (s, C-9a)], the correlations between NH-β (δ_H = 8.40) and C-6, C-5a [δ_C = 134.1 (s, C-6), 142.5 (s, C-5a)], the correlations between H-4 (δ_H = 8.40) and C-2, C-10a [δ_C = 132.5 (d, C-2), 133.7 (s, C-10a)], the correlations between H-2 (δ_H = 8.40) and C-1′, C-4, C-10a [δ_C = 166.2 (s, C-1′), 135.0 (d, C-4), 133.7 (s, C-10a)], the correlations between H-3 (δ_H = 8.02) and C-1, C-4a [δ_C = 132.9 (s, C-1), 139.9 (s, C-4a)], the correlations between H-2′ (δ_H = 4.54) and C-1′, C-3′, C-4′ [δ_C = 166.2 (s, C-1′), 30.6 (t, C-3′), 19.2 (t, C-4′)], the correlations between H-3′ (δ_H = 1.85−1.88) and C-2′, C-4′, C-5′ [δ_C = 66.4 (t, C-2′), 19.2 (t, C-4′), 13.7 (q, C-5′)], the correlations between H-4′ (δ_H = 1.48−1.51) and C-2′, C-3′, C-5′ [δ_C = 66.4 (t, C-2′), 30.6 (t, C-3′), 13.7 (q, C-5′)], and the correlations between H-5′ (δ_H = 0.99) and C-3′, C-4′ [δ_C = 30.6 (t, C-3′), 19.2 (t, C-4′)] indicated the structure of **VII-d** should be as shown in **Figure 3**.

In the H−H COSY spectra, the correlations between H-3 (δ_H = 8.02) and H-4 (δ_H = 8.40) and the correlations between H-3 (δ_H = 8.02) and H-2 (δ_H = 8.40) indicated H-4, H-3 and H-2 were nearby. The correlations between H-α (δ_H = 9.01) and H-β (δ_H = 8.40) further proved H-α and H-β belonged to NH_2-6. The chemical shift value of H-α in ^1H NMR spectra might be influenced by the nitryl in the 7-position. The correlations between H-2′ (δ_H = 4.54) and H-3′ (δ_H = 1.85−1.88), the correlations between H-3′ (δ_H = 1.85−1.88) and H-4′ (δ_H = 1.48−1.51), and the correlations between H-4′ (δ_H = 1.48−1.51) and H-5′ (δ_H = 0.99) indicated H-2′, H-3′, H-4′ and H-5′ were adjacent.

Biological Assay and Structure−Activity Relationship. Table 2 showed the fungicidal activities against *A. solani*, *C. arachidicola*, *F. omysporum*, *G. zeae*, and *P. piricola* of the title compounds **III-a**−**VII-e**. **Table 3** showed the EC_{50} of the high fungicidal activity compounds **IV-6a**, **IV-6b** and phenazine-1-carboxylic acid.

Fungicidal Activity against A. solani. The screening data of **Table 2** indicated that, at a dosage of 50 μg mL^{-1}, most compounds of **III-a**−**VII-e** exhibited low activities against *A. solani* except the series of compounds **IV-6**. The inhibition activity of **IV-6a** was 100%, which was equal to that of the phenazine-1-carboxylic acid. The inhibition activity of **IV-6b** was 51.0%; as the side chain prolonged, the fungicidal activities of compounds **IV-6c** and **IV-6d** evidently decreased. The series of compounds **IV-7** and **IV-8** did not show satisfactory fungicidal activity, and their activity rules seemed to be contrary to the **IV-6** series, such as the typical compounds **IV-7d** and **IV-8d** only exhibited 43.4% and 23.3% inhibition respectively. That might be due to the side chain extension. To be mentioned, compared with the biological activities of **III-a**−**III-c**, the carboxyl group substituted by the ester group in aminophenazine derivatives had a vital function for improving the fungicidal activity.

Fungicidal Activity against C. arachidicola. At a dosage of 50 μg mL^{-1}, only compounds **IV-6a**, **IV-6b** and **IV-6c** exhibited moderate activity. The fungicidal activity of **IV-6a**, **IV-6b** and **IV-6c** were 26.9%, 32.3% and 30.0% respectively, which might be attributed to the $-NH_2$ group in the 6-position of phenazine ring. Most compounds of **III-a**−**VII-e** exhibited low activities against *C. arachidicola*.

Fungicidal Activity against F. omysporum. The screening data of **Table 2** indicated that, at a dosage of 50 μg mL^{-1}, most compounds of **III-a**−**VII-e** exhibited low activities against *F. omysporum* except the compounds **IV-6a**, **IV-6b** and **IV-6c**. The fungicidal activities of **IV-6a**, **IV-6b** and **IV-6c** were 40.0%, 33.3% and 36.7% respectively, which further explained that the $-NH_2$ group in the 6-position of the phenazine ring was vital for improving their biological activity. Regrettably, the fungicidal activities of **VI-6a**−**VI-7n** against *F. omysporum* were as low as those against *C. arachidicola*. It might be concluded that the $-NH_2$ group being substituted by −NHCO− or $-NHSO_2-$ group would result in the fungicidal activity being decreased.

Fungicidal Activity against G. zeae. The biological activity rules of **III-a**−**VI-7n** against *G. zeae* were generally the same as the test against *C. arachidicola* and *F. omysporum* showed. To be pointed out, compounds **VII-a**−**VII-d** were the nitration derivatives of **VI-6c** and **VI-6h**. The fungicidal activities of **VII-a**−**VII-d** were 40.4%, 57.6%, 51.5% and 53.0% respectively. The fungicidal activities of **VII-a**−**VII-d** were higher than those of **IV-6a**−**IV-6d** or **VI-6c**, **VI-6h** (**Table 2**). It might be explained by that the nitration of the phenazine ring resulted in the activity against *G. zeae* being increased.

Fungicidal Activity against P. piricola. The screening data of **Table 2** indicated that most target compounds exhibited low activities against *P. piricola* except for **IV-6a** and **IV-6b**. At a dosage of 50 μg mL^{-1}, compounds **IV-6a**, **IV-6b** and phenazine-1-carboxylic acid exhibited 100% inhibition. The EC_{50} values of

IV-6a, **IV-6b** and phenazine-1-carboxylic acid against *F. omysporum* were 3.00 μg mL^{-1}, 4.44 μg mL^{-1}, 3.58 μg mL^{-1} (**Table 3**), which fully explained the rules as follows: The side chain of C-1 should not be too long. The $-NH_2$ group should be in the 6-position of the phenazine ring and not form the $-NHCO-$ or $-NHSO_2-$ group. The above terms were essential for high fungicidal activity of the aminophenazine derivatives.

Though the screening data of **Table 2** and **Table 3** indicated that the fungicidal activities of most target compounds were lower than that of phenazine-1-carboxylic acid, compound **IV-6a** had higher fungicidal activity than that of phenazine-1-carboxylic acid against *P. piricola*. **IV-6a** also showed excellent activity against *A. solani* at low dosage. So **IV-6a** could be developed as a leading compound for further structural optimization. In conclusion, a novel and facile procedure for preparation of derivatives of aminophenazine-1-carboxylate was developed from 2-bromo-3-nitrobenzoic acid with corresponding substituted benzene-diamine. Forty-six aminophenazine-1-carboxylate derivatives were synthesized. The results of bioassay showed that the fungicidal activities of most target compounds were lower than that of phenazine-1-carboxylic acid; a few of the title compounds exhibited moderate activities against *A. solani*, *C. arachidicola*, *F. omysporum*, *G. zeae*, *P. piricola* at a dosage of 50 μg mL^{-1}; **IV-6a** and **IV-6b** exhibited excellent activity against *A. solani* and *P. piricola* at that dosage; the EC_{50} of **IV-6a** against *P. piricola* was 3.00 μg mL^{-1}, which was lower than that of phenazine-1-carboxylic acid (**Table 3**). To our knowledge, **IV-6a** was a known compound; however, no biological activity or feasible synthesis method was reported in any literature. So **IV-6a** could be developed as a leading compound for further structural optimization. The possible SAR of aminophenazine-1-carboxylate derivatives were as follows: The $-NH_2$ group should be in the 6-position of the phenazine ring and not be substituted by the $-NHCO-$ or $-NHSO_2-$ group. The aminophenazine-1-carboxylic acid should be esterified to aminophenazine-1-carboxylate, and the side chain of C-1 should not be too long. The above terms were essential for high fungicidal activity of the aminophenazine derivatives. The nitration of the phenazine ring could increase the fungicidal activity against *G. zeae* but not for *A. solani* or *P. piricola*. The byproducts **V-7b**−**V-8d** did not show noticeable fungicidal activities.

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