3(2H)-pyridazinone derivatives: a new scaffold for novel plant activators

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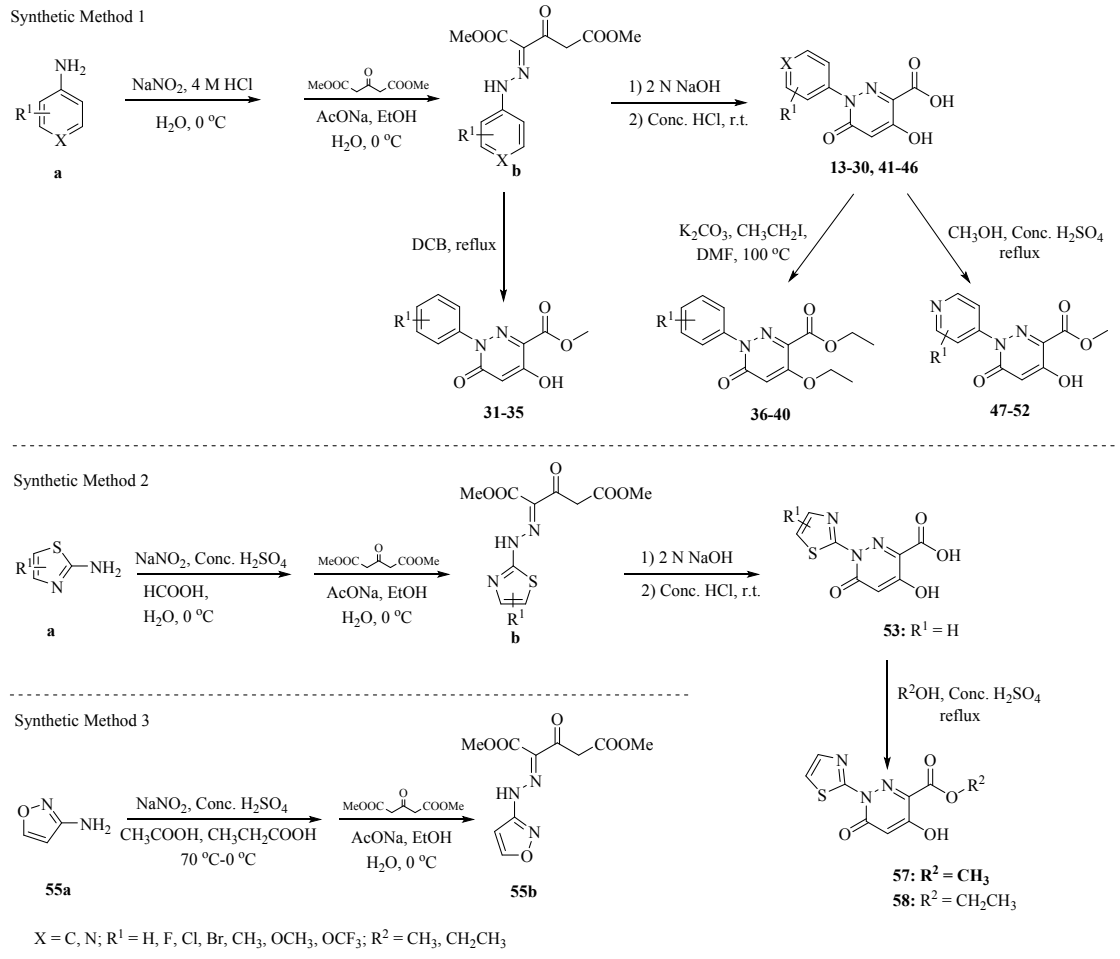
1. Experimental procedures

1.1 Materials and methods:

The NMR spectra were recorded on a Brucker AM-400 (400 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. The MS spectra were measured with an HRMS Micromass GCT CA 055 spectrometer. Melting points were recorded on a Buchi B540 apparatus (Buchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. Solvents and chemicals were of reagent grade and used without further purification. BTH was synthesized in our lab.[1]

1.2 Synthesis and characterization of compounds

The general method for the preparation of the target compounds was shown in Scheme S1.[2] Target compounds were synthesized via a simple route, which is starting from various amines, through diazotization, coupling reaction, cyclization, and esterification. Most compounds were diazotized with 4 M hydrochloric acid (Method 1), and several others were diazotized with concentrated sulfuric acid/formic acid or concentrated sulfuric acid/acetic acid/propionic acid (Method 2, 3). All compounds were separated and purified by recrystallization or silica gel chromatography, and their structures were determined by ^{1}H NMR, ^{13}C NMR, and HRMS, and compounds containing fluorine atoms were also identified by ^{19}F NMR.



Scheme S1 The general method for the preparation of the target compounds

The synthesis of compounds **14**, **21**, **38** was presented as an example (Scheme S1, Method 1).

Step 1: To a solution of 4-fluoroaniline (**14a**, 555 mg, 5 mmol) in 4 M HCl (7.5 mL) in an ice bath was slowly added a solution of sodium nitrite (400 mg, 5.8 mmol) in 4 mL of water for 15 min. When the solution was clear and the result of the potassium iodide-starch test paper was blue, the diazotization was finished. Then this solution was slowly added into a mixture of dimethyl acetonedicarboxylate (870 mg, 5 mmol) in 3 mL of ethanol and sodium acetate (3 g, 36 mmol) in 10 mL of water with vigorous stirring in an ice bath. The precipitate appeared almost immediately, and the mixture was stirred for another 30 minutes until it was finished by detection of thin-layer chromatography (TLC). The precipitate was filtered, washed with water, collected, and dried under vacuum. Crude was purified by silica gel column chromatography on silica gel with PE/EtOAc (8:1, v/v) as the eluent to give dimethyl 1-(4-fluorophenyl)hydrazono-2-oxopropane-1,3-dicarboxylates (**14b**) with 80% yield as a yellow solid. Mp: 89-91°C.[2]

Step 2: The hydrazone **14b** (1.2 g, 4 mmol) was dissolved in 2 N sodium hydroxide (22 mL) and the mixture was stirred until clear. The solution was acidified by slow addition of concentrated hydrochloric acid with vigorous stirring. The precipitate was filtered, washed with water, collected, dried under vacuum and recrystallized in methanol to give compound 5-hydroxy-2-(4-fluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**14**).
Data for **14**: Yellow crystal. Yield, 75%. Mp: 242-245°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.52 (dd, J_1 = 5.2 Hz, J_2 = 8.8 Hz, 2H), 7.27-7.32 (m, 2H), 5.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.5, 162.9, 161.7, 161.0, 160.4, 138.0, 133.8, 128.7, 128.6, 115.9, 115.7, 105.3. HRMS (ESI) calcd for $C_{11}H_7N_2O_4F$ $[M+H]^+$ 251.0463, found 251.0466.

Step 3: The hydrazone **14b** (1.3 g, 4.3 mmol) was dissolved in 8 mL o-dichlorobenzene, refluxed till the end of the reaction and cooled down to room temperature. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography on silica gel with PE/EtOAc (1:1, v/v) as the eluent to give compound Methyl 5-hydroxy-2-(4-fluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**31**).
Data for **31**: White crystal. Yield, 70%. Mp: 145-146°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.42 (s, 1H), 7.58 (dd, J_1 = 5.2 Hz, J_2 = 8.8 Hz, 2H), 7.17-7.22 (m, 2H), 6.41 (s, 1H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.0, 163.7, 161.8, 161.2, 159.4, 136.7, 136.7, 127.6, 127.5, 116.0, 115.8, 107.6, 53.7. HRMS (ESI) calcd for $C_{12}H_9N_2O_4F$ $[M+H]^+$ 265.0619, found 265.0622.

Step 4: The mixture of compound **14** (1 g, 4 mmol), ethyl iodide (1.55 g, 10 mmol) and potassium carbonate (1.4 g, 10 mmol) was dissolved in dimethylformamide (10 mL) and reacted at 100°C until finished and cooled down to room temperature. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography on silica gel with PE/EtOAc (5:1, v/v) as the eluent to give compound Ethyl 5-ethyoxyl-2-(4-fluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**38**).
Data for **38**: White crystal. Yield, 49%. Mp: 132.5-133.7°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.58(dd, J_1 = J_2 = 4.8 Hz, 2H), 7.13-7.17 (m, 2H), 6.27 (s, 1H), 4.38-4.43 (m, 2H), 4.09-4.14 (m, 2 H), 1.49 (t, J = 6.8 Hz, 3H), 1.37-1.40 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 161.1, 160.4, 157.5, 137.0, 134.1, 128.1, 115.6, 115.4, 105.0, 65.4, 61.8, 13.9, 13.7. HRMS (ESI) calcd for $C_{15}H_{15}FN_2O_4$ $[M+H]^+$ 307.1089, found 307.1091.

Compounds **13**, **15-30**, **32-37**, **39-52** were prepared similarly by the variation of aniline.

For the thiazole ring substituted compounds, method 2 was adopted. The synthesis of compounds **53**, **57** was presented as an example (Scheme S1, Method 2).
Step 1: To a round-bottom flask charged with thiazol-2-amine (**53a**, 400 mg, 4 mmol) was added concentrated H_2SO_4 (2 mL), formic acid (1 mL) and water (4 mL) and stirred in an ice bath. Then the mixture added a solution of sodium nitrite (280 mg, 4 mmol) in 4 mL of water very slowly. When the diazotization was finished, this solution was slowly added into a mixture of dimethyl acetonedicarboxylate (696 mg, 4 mmol) in 2 mL of ethanol and sodium acetate (3 g, 36 mmol) in 10 mL of water with vigorous stirring in an ice bath. Until the reaction was finished by detection of TLC, the precipitate was filtered, washed with water, collected, and dried under vacuum. Crude was purified by silica gel column chromatography on silica gel with PE/EtOAc (4:1, v/v) as the eluent to give compound Dimethyl 1-(2-(thiazol-2-yl))hydrazono-2-oxopropane-1,3-dicarboxylates (**53b**).
Data for 53b: Yellow solid. Yield, 44%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32 (d, J=4.4 Hz, 1H), 6.90 (d, J=3.6 Hz, 1H), 3.83 (s, 2H), 3.74 (s, 3H), 3.64 (s, 3H).

Step 2: Compound **53** was synthesized successfully following Method 1.
Data for 5-hydroxy-2-(thiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**53**): Yellow crystal. Yield, 47%. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.72 (d, J=3.6 Hz, 1H), 7.59 (d, J=3.6 Hz，1H), 5.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.2, 160.8, 156.9, 138.3, 135.1, 118.9, 102.3. HRMS (ESI) calcd for $C_8H_5N_3O_4S$ $[M-H]^-$ 237.9923, found 237.9917.

Step 3: A mixture of 53 (100 mg, 0.42 mmol) in methane (10 mL) was added 5 drops concentrated H_2SO_4 and refluxed until it was finished. The solvent was cooling to room temperature and removed under vacuum and the crude product was purified by silica gel column chromatography on silica gel with PE/EtOAc (1:1, v/v) as the eluent to give compound Methyl 5-hydroxy-2-(thiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**57**).
Data for **57**: Yellow crystal. Yield, 50%. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.63 (s, 1H), 7.86 (d, J=3.6 Hz, 1H), 7.37 (d, J=3.6 Hz，1H), 6.53 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 160.3, 159.1, 156.2, 139.6, 128.3, 119.4, 107.5, 54.4. HRMS (ESI) calcd for $C_9H_7N_3O_4S$ $[M+H]^+$ 254.0236, found 254.0228.

Compounds **54**, **56**, **58**, **59**, **61** were prepared according to a similar manipulation.

For the isoxazole ring substituted compounds **55** and **60**, method 3 was adopted (Scheme 1, Method 3).
Step 1: A mixture of sodium nitrite (350 mg, 5 mmol) in concentrated H_2SO_4 (3.5 mL) was stirred at 70°C for 1 h and cooled below 5°C. To a flask charged with isoxazol-3-amine (**55a**, 420 mg, 5 mmol) was added into a solution of acetic acid (5 mL) and propionic acid (1 mL) in an ice bath and then dropped the nitrile solution until the reaction was finished. When the diazotization was finished, this solution was slowly added into a mixture of dimethyl acetonedicarboxylate (870 mg, 5 mmol) in 3 mL of ethanol and sodium acetate (3 g, 36 mmol) in 10 mL of water with vigorous stirring in an ice bath. Until the reaction was finished by detection of TLC, the precipitate was filtered, washed with water, collected, and dried under vacuum. Crude was purified by silica gel column chromatography on silica gel with PE/EtOAc (4:1, v/v) as the eluent to give compound

Dimethyl 3-oxo-2-(2-(isoxazol-3-yl)hydrazono)pentanedioate (**55b**).
Data for **55b**: Yellow solid. Yield, 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 (d, J=4.4 Hz, 1H), 6.86 (d, J=3.6 Hz, 1H), 3.81 (s, 2H), 3.72 (s, 3H), 3.62 (s, 3H).

Step 2: Compounds **55** was obtained according to Method 2 as described for **53**.
Data for 5-hydroxy-2-(isoxazol-3-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**55**): Faint yellow crystal. Yield, 78%. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.06 (d, J=1.6 Hz, 1H), 6.98 (d, J=1.6 Hz, 1H), 6.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 161.6, 160.1, 160.1, 159.3, 136.2, 105.0, 102.7. HRMS (ESI) calcd for $C_8H_5N_3O_5$ [M-H]$^-$ 222.0151, found 222.0150.

Step 3: Compound **60** was conducted according to Method 2 as described for **57**.
Data for Methyl 5-hydroxy-2-(isoxazol-3-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**60**): White crystal. Yield, 75%. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.49 (s, 1 H), 8.50 (d, J=1.6 Hz, 1 H), 7.02 (d, J=1.6 Hz, 1 H), 6.39 (s, 1 H), 4.07 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6，160.5，160.0，159.7，159.3，128.4，107.6，102.0, 54.0. HRMS (ESI) calcd for $C_9H_7N_3O_5$ [M-H]$^-$ 236.0307, found 222.0310.

Data for 5-hydroxy-2-phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**13**): Yellow crystal. Yield, 80%. Mp: 246-247°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.42-7.51 (m, 5H), 6.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 161.4, 159.7, 141.5, 133.4, 129.1, 128.7, 126.4, 106.2. HRMS (ESI) calcd for $C_{11}H_8N_2O_4$ [M+H]$^+$ 233.0562, found 233.0577.

Data for 5-hydroxy-2-(4-chloro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**15**): Yellow crystal. Yield, 75%. Mp: 242-245°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.57 (m, 4H), 6.15 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 161.2, 140.2, 133.8, 133.0, 129.0, 128.1, 106.2. HRMS (ESI) calcd for $C_{11}H_7N_2O_4Cl$ [M+H]$^+$ 267.0173, found 267.0184.

Data for 5-hydroxy-2-(4-trifluoromethyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**16**): Yellow crystal. Yield, 87%. Mp: 255-256°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.88 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 6.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 161.3, 159.6, 144.6, 134.7, 127.0, 126.3, 123.1, 106.1. HRMS (ESI) calcd for $C_{12}H_9N_3O_6$ [M+H]$^+$ 301.0431, found 301.0427.

Data for 5-hydroxy-2-(4-methoxy)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**17**): Yellow crystal. Yield, 80%. Mp: 232-234°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.41 (d, J = 8.8 Hz, 1H), 7.03(d, J = 8.8 Hz, 1H), 6.18 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 161.5, 159.3, 159.2, 134.5, 133.2, 127.6, 114.2, 106.1, 55.9. HRMS (ESI) calcd for $C_{12}H_7N_2O_5$ [M+H]$^+$ 263.0662, found 263.0666.

Data for 5-hydroxy-2-(4-trifluoromethoxy)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**18**): Yellow crystal. Yield, 83%. Mp: 256-257°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.67 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.17 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.0, 166.0, 164.0, 152.7, 145.0, 138.6, 133.1, 126.5, 124.0, 111.0. MS (ESI) calcd for $C_{12}H_7F_3N_2O_5$ [M+H]$^+$ 316.0, found 316.0.

Data for 5-hydroxy-2-(2-fluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**19**): Yellow crystal. Yield, 78%. Mp: 235-236°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.34-7.57 (m, 4H), 6.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 161.0, 159.4, 158.3, 134.5, 131.7, 131.6, 129.8, 129.2, 125.5, 125.4, 116.8, 116.6, 105.8. HRMS (ESI) calcd for $C_{11}H_7N_2O_4F$ [M+H]$^+$ 251.0463, found 251.0466.

Data for 5-hydroxy-2-(2-trifluoromethyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**20**): Yellow crystal. Yield, 85%. Mp: 258-259°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.93 (d, J = 7.6 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 6.19 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9, 161.7, 159.5, 139.0, 134.3, 130.9, 130.7, 127.8, 127.7, 127.6, 127.0, 126.7, 126.4, 126.1, 124.9, 122.2, 105.9. HRMS (ESI) calcd for $C_{12}H_7F_3N_2O_4$ [M+H]$^+$ 301.0436, found 301.0437.

Data for 5-hydroxy-2-(2-methoxy)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**21**): Yellow crystal. Yield, 86%. Mp: 232-233°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.46 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.20 (d, J =7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.14 (s, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.5, 161.3, 159.3, 154.9, 132.9, 131.0, 130.4, 129.1, 120.9, 112.9, 105.9, 56.2. HRMS (ESI) calcd for $C_{12}H_7N_2O_5$ [M+H]$^+$ 263.0662, found 263.0666.

Data for 5-hydroxy-2-(3-fluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**22**): Yellow crystal. Yield, 79%. Mp: 270-271°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.52-7.59 (m, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.31 (dt, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 6.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.1, 163.2, 161.2, 160.8, 159.2, 142.7, 142.6, 134.0, 130.8, 130.7, 122.5, 122.5, 115.7, 115.5, 113.9, 113.7, 106.2. HRMS (ESI) calcd for $C_{11}H_7N_2O_4F$ [M+H]$^+$ 251.0463, found 251.0466.

Data for 5-hydroxy-2-(3-trifluoromethyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**23**): Yellow crystal. Yield, 81%. Mp: 263-264°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.95 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 6.22 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 161.3, 159.6, 159.4, 157.1, 137.8, 137.8, 134.3, 133.4, 133.3, 125.5, 125.5, 124.0, 121.3, 118.3, 118.1, 117.0, 117.2, 117.0. 116.9, 106.2. HRMS (ESI) calcd for $C_{12}H_7F_3N_2O_4$ [M+H]$^+$

301.0436, found 301.0437.

Data for 5-hydroxy-2-(3-methoxy)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**24**): Yellow crystal. Yield, 82%. Mp: 235-236°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.41 (t, J = 8.0Hz, 1H), 7.01-7.08 (m, 3H), 6.17 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165, 161.3, 159.7, 159.2, 142.5, 133.2, 129.9, 118.7, 114.4, 112.2, 106.2. HRMS (ESI) calcd for $C_{12}H_7N_2O_5$ [M-H]$^-$ 261.0511, found 261.0516.

Data for 5-hydroxy-2-(3,5-dichloro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**25**): Yellow crystal. Yield, 74%. Mp: 263-264°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.71 (s, 1H), 7.7 (s, 2H), 6.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 161.1, 159.6, 143.2, 134.7, 134.2, 128.2, 125.3, 106.1. HRMS (ESI) calcd for $C_{11}H_6N_2O_4Cl_2$ [M+H]$^+$ 300.9777, found 300.9778

Data for 5-hydroxy-2-(2,4-dichloro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**26**): Yellow crystal. Yield, 72%. M: 236-237°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.87 (s, 1H, 7.61 (s, 2H), 6.13 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 161.0, 159.7, 138.1, 135.1, 134.7, 132.6, 131.6, 130.0, 128.9, 105.9. HRMS (ESI) calcd for $C_{11}H_6N_2O_4Cl_2$ [M+H]$^+$ 300.9777, found 300.9773.

Data for 5-hydroxy-2-(3,4-dichloro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**27**): Yellow crystal. Yield, 77%. Mp: 268-269°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.89 (d, J = 2.4 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.59 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9, 161.2, 159.4, 141.0, 134.5, 131.3, 131.1, 131.0, 128.3, 126.6, 106.1. HRMS (ESI) calcd for $C_{11}H_6N_2O_4Cl_2$ [M+H]$^+$ 300.9777, found 300.9774.

Data for 5-hydroxy-2-(3,4-difluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (28**):** Yellow crystal. Yield, 78%. Mp: 273-274°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.39-7.46 (m, 3H), 6.17 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 161.2, 159.3, 150.7, 150.6, 150.4, 150.3, 148.2, 148.1, 147.9, 147.8, 137.9, 137.8, 137.8, 137.7, 134.1, 123.7, 123.6, 123.5, 123.5, 117.9, 117.7, 116.4, 116.2, 106.2. HRMS (ESI) calcd for $C_{11}H_6F_2N_2O_4$ [M+H]$^+$ 267.0217, found 267.0218.

Data for 5-hydroxy-2-(4-fluoro-3-trifluoromethyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**29**): Yellow crystal. Yield, 74%. Mp: 265-266°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.65-8.02 (m, 3H), 6.18 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 161.3, 159.6, 159.3, 157.1, 137.8, 134.4, 134.3, 134.2, 133.4, 133.3, 125.5, 124.0, 121.3, 118.3, 118.1, 117.3, 117.2, 117.0, 117.8, 106.2. HRMS (ESI) calcd for $C_{12}H_6F_4N_2O_4$ [M+H]$^+$ 318.0264, found 318.3499.

Data for 5-hydroxy-2-(3,5-dimethoxyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**30**): Yellow crystal. Yield, 77%. Mp: 251-253°C. ^{1}H NMR (400MHz, DMSO-d_6): δ 6.66 (d, J = 1.0 Hz, 2H), 6.60 (d, J = 1.0 Hz, 1H), 6.17 (s, 1H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 161.2, 160.7, 159.1, 143.1, 133.0, 106.3, 105.2, 100.7, 56.0. HRMS (ESI) calcd for $C_{13}H_{12}N_2O_6$ [M+H]$^+$ 291.0617, found 291.0616.

Data for Methyl 5-hydroxy-2-(4-methoxy)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**32**): White crystal. Yield, 67%. Mp: 184-186°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.40 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.40 (s, 1H), 4.04 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 162.0, 159.8, 159.3, 133.9, 126.8, 126.4, 114.1, 107.4, 55.6, 53.6. HRMS (ESI) calcd for $C_{13}H_{12}N_2O_5$ [M+H]$^+$ 277.0819, found 277.0822.

Data for Methyl 5-hydroxy-2-(2-methoxy)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**33**): White crystal. Yield, 66%. Mp: 171-173°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.44 (s, 1H), 7.46 (t, J = 7.6Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.05-7.11 (m, 2H), 6.41 (s, 1H), 4.02 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 161.8, 159.6, 131.1, 129.8, 128.1, 126.9, 120.9, 112.4,107.2, 56.0, 53.6. HRMS (ESI) calcd for $C_{13}H_{12}N_2O_5$ [M-H]$^-$ 275.0668, found 275.0664.

Data for Methyl 5-hydroxy-2-(3-fluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**34**): White crystal. Yield, 66%. Mp: 135-137°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.43 (s, 1H), 7.42-7.51 (m, 2H), 7.36-7.39 (m, 1H), 7.13-7.19 (m, 1H), 6.41 (s, 1H), 4.06 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 163.7, 161.5, 161.2, 159.3, 141.9, 141.8, 130.2, 130.1, 127.0, 121.3, 121.2, 116.0,115.9, 113.5, 113.2, 107.6, 53.8. HRMS (ESI) calcd for $C_{12}H_9N_2O_4F$ [M+H]$^+$ 265.0619, found 265.0622.

Data for Methyl 5-hydroxy-2-(3,4-dichloro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**35**)*:* White crystal. Yield, 81%. Mp: 179-180°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.41 (s, 1H), 7.76 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.39 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1, 156.7, 154.6, 134.9, 128.4, 128.2, 125.7, 122.8, 120.1, 102.9, 49.1. HRMS (ESI) calcd for $C_{12}H_8N_2O_4Cl_2$ [M+H]$^+$ 314.9934, found 314.9940.

Data for Ethyl 5-ethyoxyl-2-(4-trifluoro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**36**): White crystal. Yield, 45.39%. Mp: 137.9-139.2°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H), 6.27 (s, 1 H), 4.36-4.41 (m, 2 H), 4.10-4.15 (m, 2 H), 1.48-1.52 (m, 3 H), 1.34-1.38 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 160.3, 157.5, 143.8, 134.8, 126.6, 125.9, 125.8, 105.1, 65.5, 61.9, 13.9, 13.7. HRMS (ESI) calcd for $C_{16}H_{15}F_3N_2O_4$ [M+H]$^+$ 357.1057, found 357.1064.

Data for Ethyl 5-ethyoxyl-2-(4-trimethyoxyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**37**): White crystal. Yield, 54.45%. Mp: 122.4-123.3°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.27 (s, 1H), 4.40

(q, *J* = 7.2 Hz, 2 H), 4. 80-4.13 (m, 2 H), 3.84 (s, 3 H), 1.47-1.50 (m, 3 H), 1.36-1.39 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 161.5, 159.4, 158.2, 134.2, 133.8, 126.8, 114.0, 104.7, 65.3, 62.1, 55.5, 14.1, 13.9. HRMS (ESI) calcd for $C_{16}H_{18}N_2O_5$ $[M+H]^+$ 319.1288, found 319.1299.

Data for Ethyl 5-ethyoxyl-2-(3,5-dimethyoxyl)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**39**): White crystal. Yield, 60%. Mp: 119.2-121.3°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 2 H), 6.52 (s, 1 H), 6.28 (s, 1 H), 4.39-4.45 (m, 2 H), 4.11-4.16 (m, 2 H), 3.83 (s, 6 H), 149-1.53 (m, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 161.2, 160.8, 158.1, 142.2, 134.4, 104.8, 104.2, 101.1, 65.3, 62.2, 55.6, 14.1, 13.9. HRMS (ESI) calcd for $C_{17}H_{20}N_2O_6$ $[M+H]^+$ 349.1394, found 349.1401.

Data for Ethyl 5-ethyoxyl-2-(3,5-dichloro)phenyl-3-oxo-2,3-dihydropyridazine-6-carboxylate (**40**): White crystal. Yield, 68.95%. Mp: 195.5-196.4°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 2 H), 7.40 (s, 1 H), 6.27 (s, 1 H), 4.41-4.47 (m, 2 H), 4.11-4.17(m, 2 H), 1.50-1.53 (m, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ161.3, 160.8, 158.2, 142.0, 135.4, 134.9, 128.4, 124.1, 104.8, 65.6, 62.5, 14.1, 13.9. HRMS (ESI) calcd for $C_{15}H_{14}C_{l2}N_2O_4$ $[M+H]^+$ 357.0403, found 357.0408.

Data for 5-hydroxy-2-(2-fluoropyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**41**): Yellow crystal. Yield, 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, *J* = 5.6 Hz, 1H), 7.70 (d, *J* =5.6 Hz, 1H), 7.54 (s, 1H), 6.24 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.4, 163.8, 162.1, 160.7, 159.3, 151.9, 148.1, 135.9, 117.4, 105.4. HRMS (ESI) cacld for $C_{10}H_5N_3O_4F$ $[M-H]^-$ 250.0264, found 250.0268.

Data for 5-hydroxy-2-(2-chloropyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**42**): Yellow crystal. Yield, 70%. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.54 (d, *J*=5.6 Hz, 1H), 7.88 (d, *J*=1.6 Hz, 1H), 7.78 (dd, J_1=2.0 Hz, J_2=1.6 Hz, 1H), 6.26 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 160.6, 158.8, 150.5, 150.4, 149.8, 135.6, 119.3, 118.5, 105.6. HRMS (ESI) calcd for $C_{10}H_6ClN_3O_4$ $[M+Na]^+$ 265.9969, found 265.9965.

Data for 5-hydroxy-2-(2-bromopyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**43**): Yellow crystal. Yield, 65%. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.51 (d, *J* = 5.2 Hz, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 5.2 Hz, 1H), 6.19 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 160.8, 159.9, 150.9, 149.5, 141.1, 135.9, 122.8, 118.8, 105.0. HRMS (ESI) calcd for $C_{10}H_6BrN_3O_4$ $[M-H]^-$ 309.0463, found 309.9464.

Data for 5-hydroxy-2-(2-trifluoromethylpyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**44**): White crystal. Yield, 65%. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.90 (d, *J* = 5.6 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 8.07 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz，1H), 6.21 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 160.9, 159.7, 151.3, 149.1, 136.1, 122.7, 122.1, 119.9, 116.0, 105.2. HRMS (ESI) calcd for $C_{11}H_6F_3N_3O_4$ $[M-H]^-$ 300.0232, found 300.0236.

Data for 5-hydroxy-2-(2-methoxypyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**45**): White crystal. Yield, 50%. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.27 (d, *J* = 5.6 Hz, 1H), 7.27 (dd, J_1 =2.0 Hz, J_2 = 2.0 Hz, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 6.23 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 164.1, 160.7, 158.9, 150.0, 147.3, 134.8, 113.3, 106.2, 105.5, 53.7. HRMS (ESI) calcd for $C_{11}H_9N_3O_5$ $[M-H]^-$ 262.0464, found 262.0457.

Data for 5-hydroxy-2-(2,6-dichloropyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**46**): Yellow crystal. Yield, 70%. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.94 (s, 2H), 6.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 160.7, 159.3, 151.6, 149.4, 136.2, 118.4, 105.3. HRMS (ESI) cacld for $C_{10}H_5N_3O_4Cl_2$ $[M-H]^-$ 299.9679, found 299.9580.

Data for Methyl 5-hydroxy-2-(2-fluoropyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**47**): White crystal. Yield, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 8.34 (d, *J* = 5.6 Hz, 1H), 7.69 (d, *J* = 5.6 Hz, 1H), 7.45 (s, 1H), 6.40 (s, 1H), 4.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.0, 161.8, 160.2, 157.8, 151.6, 148.2, 135.4, 117.6, 106.1, 52.9. HRMS (ESI) cacld for $C_{11}H_8N_3O_4F$ $[M-H]^-$ 264.0421, found 264.0425.

Data for Methyl 5-hydroxy-2-(2-chloropyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**48**): White crystal. Yield, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 8.50 (d, *J*=5.2 Hz, 1H), 7.79 (s, 1H), 7.72 (d, *J*=4.4 Hz, 1H), 6.38 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 161.3, 159.2, 152.3, 150.4, 149.4, 128.2, 119.7, 117.9, 108.0, 54.2. HRMS (ESI) calcd for $C_{11}H_8ClN_3O_4$ $[M-H]^-$ 280.0131, found 280.0120.

Data for Methyl 5-hydroxy-2-(2-bromopyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**49**): White crystal. Yield, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.50 (d, *J*=4.8 Hz, 1H), 7.95 (s, 1H), 7.76 (d, *J*=3.6 Hz, 1H), 6.39 (s, 1H), 4.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 161.1, 159.1, 150.7, 148.9, 142.5, 128.1, 123.2, 118.2, 107.9 54.1. HRMS (ESI) calcd for $C_{11}H_8BrN_3O_4$ $[M+H]^+$ 325.9776, found 325.9777.

Data for Methyl 5-hydroxy-2-(2-trifluoromethylpyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**50**): White crystal. Yield, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (s, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 8.00 (dd, J_1 = 1.6 Hz, J_2 = 2.0 Hz, 1H), 6.41 (s, 1H), 4.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 161.2, 159.2, 151.1, 148.6, 128.3, 122.5, 121.3, 119.8, 116.0, 107.9, 53.9. HRMS (ESI) calcd for $C_{12}H_8F_3N_3O_4$ $[M-H]^-$ 314.0389, found 314.0390.

Data for Methyl 5-hydroxy-2-(2-methoxypyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**51**): White crystal. Yield, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 5.6 Hz, 1H), 7.27 (dd, J_1 = 2.0 Hz, J_2 = 2.0 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 6.23 (s, 1H), 4.11 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 161.9, 160.2, 157.7, 149.8, 147.5, 134.5, 113.3, 106.3, 106.1, 53.6, 52.8. HRMS (ESI) calcd for $C_{12}H_{11}N_3O_5$ $[M+H]^+$ 278.0777, found 278.0772.

Data for Methyl 5-hydroxy-2-(2,6-dichloropyridin-4-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**52**): White crystal. Yield, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (s, 1H), 7.81 (s, 2H), 6.39 (s, 1H), 4.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 160.2, 158.0, 151.4, 149.4, 136.2, 118.6, 105.9, 52.9. HRMS (ESI) calcd for $C_{11}H_7Cl_2N_3O_4$ $[M-H]^-$ 313.9735, found 313.9734.

Data for 5-hydroxy-2-(5-bromothiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**54**): Yellow crystal. Yield, 30%. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.82 (s, 1H), 5.91 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 164.2, 161.1, 156.0, 139.2, 135.6, 107.1, 101.1. HRMS (ESI) calcd for $C_8H_4BrN_3O_4S$ $[M-H]^-$ 315.9028, found 315.9034.

Data for 5-hydroxy-2-(benzo[d]thiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**56**): Yellow crystal. Yield, 40%. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.10（d, J=8 Hz, 1H），8.02（d，J = 8 Hz，1H），7.53-7.58 (m, 1H), 7.42-7.46 (m, 1H), 6.09 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 160.6, 159.9, 156.5, 147.8, 138.0, 133.6, 126.5, 125.1, 122.2, 121.9, 104.1. HRMS (ESI) calcd for $C_{12}H_7N_3O_4$ $[M-H]^-$ 288.0079, found 288.0079.

Data for Ethyl 5-hydroxy-2-(thiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**58**): Yellow crystal. Yield, 35%. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.76 (s, 1H) , 7.84 (d, J=3.6 Hz, 1H), 7.36 (d, J=3.6 Hz，1H), 6.50 (s, 1H), 4.60 (q, J=7.2 Hz, 2H), 1.50 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 160.3, 159.2, 156.3, 139.4, 128.5, 119.3, 107.2, 64.3, 54.3. HRMS (ESI) calcd for $C_{10}H_9N_3O_4S$ $[M+Na]^+$ 290.0211, found 290.0244.

Data for Methyl 5-hydroxy-2-(5-bromothiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**59**): White crystal. Yield, 30%. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.67 (s, 1H), 7.78 (s, 1H), 6.53 (s, 1H), 4.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 160.3, 159.3, 155.4, 140.3, 128.5, 110.1, 107.3, 54.6. HRMS (ESI) calcd for $C_9H_6BrN_3O_4S$ $[M-H]^-$ 329.9184, found 329.9189.

Data for Methyl 5-hydroxy-2-(benzo[d]thiazol-2-yl)-3-oxo-2,3-dihydropyridazine-6-carboxylate (**61**): Yellow crystal. Yield, 40%. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.12（d, J=8 Hz, 1H），8.02（d，J = 8 Hz，1H），7.55 (t, J=8 Hz, 1H), 7.46 (t, J=7.6 Hz, 1H), 6.33 (s, 1H), 3,94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 160.1, 157.6, 156.1, 147.9, 137.5, 133.7, 126.6, 125.2, 122.4, 121.9, 105.3, 53.2. HRMS (ESI) calcd for $C_{13}H_9N_3O_4$ $[M+H]^+$ 304.0392, found 304.0390.

1.3 Biological assay Screening

The *in vivo* induced resistance activity and the *in vitro* antimicrobial activity of the target compounds were evaluated according to the following procedures.

***In vivo* induced resistance activity screening**

For *in vivo* screening, the cucumber variety of 'zhongnong five' was used at a growing season in which two leaves have spread and the heart leaves have not. The tomato variety of 'var. validum Bailey' was used at a growing season in which four leaves have spread. And the chili variety of 'zhongnong seven' was used also at a growing season in which four leaves have spread.

The inducing activity of the target compounds was evaluated according to the protocol referred to the work we did before.[1, 3, 4]

First, four pathogens including *Corynespora cassiicola*, *Cladosporium cucumerinum*, *Fusarium oxysporum*, and *Pseudoperonospron cubensis* were used to screen the lead compound (Table S1). Then nine pathogens (Table S2) were tested for the screening of the target compounds. Each pathogen had a commercialized fungicide as a control which was elaborated in Table S2. Additionally, BTH was chosen as a positive control. All test compounds were dissolved in acetone and diluted with water to a concentration of 100 mg/L. The inducing resistance activity of each test compound was measured using the backward method: plants were treated with test compounds for four times separately at 7, 5, 3, and 1 day before inoculation. Then the plants were inoculated with conidial suspension (10^6 spores/mL), and cultured in a greenhouse with 90–100% RH at 26°C. Three repeated tests were performed for each compound. In every repeated test, five plants were used for the test of each compound. The experiment was set up in a randomized complete block design and performed twice to ensure reproducibility. No other germicide or insecticide was used during the screening. Disease severities on individual plants were assessed seven days after inoculation[5] using a modified disease rating system based on the standardized grading system.[6-8] The disease index (DSI) is calculated as DSI = [∑(number of plants in each severity class × class number)] × 100/(total number of plants × the highest number of disease classes). The variability of the isolates in aggressiveness on plants was analyzed with ANOVA. All statistical analyses were performed with SPSS (IBM SPSS Statistics 19, IBM Corp., Armonk, NY, USA) at the significance level of P = 0.05.

***In vitro* antimicrobial activity screening**

During the *in vitro* assay, *M. melonis*, *C. cassiicola*, *R. solani*, *P. infestans* were used. All test compounds were dissolved in N, N-dimethylformamide (DMF) to prepare a stock solution with a concentration of 1000 mg/L. Preparation of potato dextrose agar (PDA) medium: adding 200 g potato, 20 g glucose, and 20 g agar into 1000 mL water and boiling until clarified and filtering. Then the hot culture medium cooled to 50℃, and a working solution of 100 mg/L was prepared by mixing 1 mL of the stock solution with 9 mL of the PDA culture medium thoroughly in a Petri dish under aseptic condition, three replicates per concentration. After solidification, the micro-organism was inoculated on the plate and incubated in the culture tank at 26-28°C, and the ditilled water was used as the control or check (CK). The radial growth was measured perpendicularly and averaged to calculate the growth inhibition rates to evaluate the inhibition efficacy of the tested compounds on the target fungus. The mycelial growth inhibition rate was calculated based on the following formula:[9]

Averaged colony net diameter = averaged diameter of the colony - diameter of inoculum

Inhibition rate（%）=

$$\frac{Averaged\ colony\ net\ diameter\ of\ the\ control - Averaged\ colony\ net\ diameter\ of\ the\ \ treated}{Averaged\ colony\ diameter\ of\ the\ control} \times 100$$

Results and discussion

Table S1. *In-vivo* induced resistance activity of the lead compound

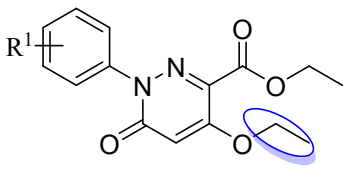
Compd[a]	*Efficacy (%)*[b]			
	Corynespora cassiicola	*Cladosporium cucumerinum*	*Fusarium oxysporum*	*Pseudoperonospron cubensis*
5 (PBZ-13)	31.87	31.48	23.94	18.52
6 (JAD1-20)	**81.06**	47.43	-[c]	30.72
7 (TDL-28)	**77.34**	27.35	-	5.19
8 (RJC02830)	**67.82**	**84.29**	-	40.97
50 % Chlorothalonil (WP)	**64.06**		**84.51**	
40 % flusilazole (EC)		**100.00**		
50 % dimethomorph (WP)				**93.46**

[a]The concentration of compounds is 100 mg/L; [b]Efficacy is given as the mean of triplicate experiments. Inducing activity > 50% are shown in bold; [c]Means not detected.

Table S2. Commercialized fungicide as a control for each plant disease used in the present study

Fungicide	Plant disease	Abbreviations	Strain
50% Dimethomorph (WP)	*Phytophthora infestans*	PI	oomycete
	Phytophthora capsici	PC	
20% bismerthlazol (WP)	*Pseudomonas syringae* PV. *lachrymans*	PL	bacteria
	Pseudomonas syringae PV. *tomato*	PT	
50% kresoxim-methyl (WG)	*Mycosphaerella melonis*	MM	fungi
75% chlorothalonil (WP)	*Corynespora cassiicola*	CC	
5% validamycin A (WP)	*Rhizoctonia solani*	RS	
50% procymidone (WP)	*Botrytis cinerea*	BC	
70% Mildothane (WP)	*Fusarium oxysporum*	FO	

Table S3. Structure and *in vivo* induced resistance activity of compounds **36-40**

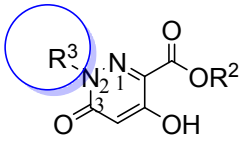


36-40

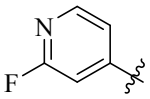
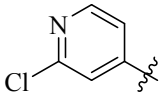
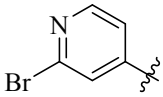
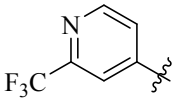
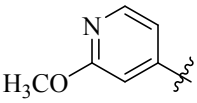
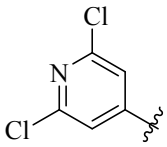
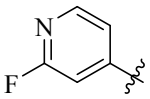
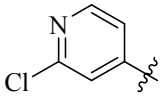
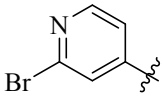
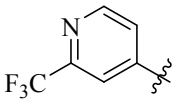
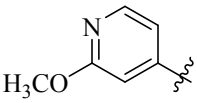
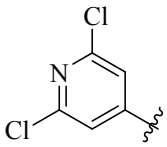
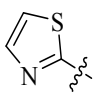
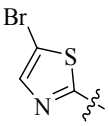
Compd	*R*[1]	*Efficacy (%)*				
		PC	*CC*	*RS*	*BC*	*PI*
36	4-CF_3	40.14	48.71	38.48	**53.27**	-0.13
37	4-OCH_3	46.94	-60.35	4.45	**78.45**	-3.98
38	4-F	26.30	-40.83	25.54	**64.18**	-0.43
39	3,5-di-OCH_3	37.41	-7.13	12.12	**76.37**	-2.44
40	3,5-di-Cl	**80.95**	-21.62	16.15	33.18	-0.13
BTH	□	**52.38**				**99.71**
50%dimethomorph(WP)			**60.18**			
75%chlorothalonil (WP)				**58.76**		
5%validamycin A(WP)					**72.85**	
50%procymidone(WP)						

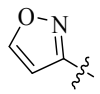
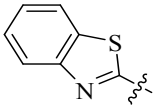
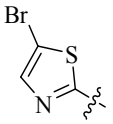
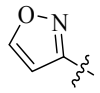
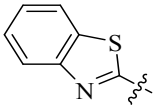
ND-not detected; Inducing activity > 50% are shown in bold.

Table S4. Structure and *in-vivo* induced resistance activity of compounds **41-61**



41-61

Compd	*R^1*	*R^3*	*Efficacy (%)*				
			PC	*CC*	*RS*	*BC*	*PI*
41	H		26.53	36.51	-7.98	**56.67**	39.42
42	H		**52.38**	-36.8	3.74	**60.30**	11.19
43	H		**72.79**	-16.5	5.45	**69.25**	14.50
44	H		34.69	**53.37**	**93.25**	**68.14**	46.85
45	H		**56.46**	42.52	25.26	39.10	14.50
46	H		**65.09**	38.14	9.06	32.32	54.70
47	CH_3		44.22	38.74	**62.51**	**68.76**	15.08
48	CH_3		**53.74**	3.20	27.67	**52.34**	15.06
49	CH_3		**59.18**	45.50	**67.84**	36.99	36.26
50	CH_3		36.05	33.64	**86.55**	**56.54**	41.65
51	CH_3		**59.18**	41.14	1.97	43.18	16.24
52	CH_3		48.30	45.65	17.42	44.44	39.73
53	H		44.22	42.89	**63.78**	**54.00**	-3.98
54	H		**53.74**	-9.12	21.35	**55.23**	-2.06

55	H		**63.27**	45.95	-10.4	**81.48**	22.40
56	H		**53.74**	23.35	-12.5	**88.72**	24.71
57	CH_3		26.53	44.75	9.02	**63.51**	-3.98
58	CH_2CH_3		**59.18**	9.23	4.11	**75.79**	-2.44
59	CH_3		45.58	-14.7	-11.0	**66.13**	2.76
60	CH_3		48.30	35.14	**61.36**	**76.66**	15.27
61	CH_3		**65.99**	42.72	26.92	**81.12**	13.16
50%dimethomorph(WP)			**52.38**				**99.71**
75%chlorothalonil (WP)				**60.18**			
5%validamycin A(WP)					**58.76**		
50%procymidone(WP)						**72.85**	

2. ^{1}H NMR, ^{13}C NMR, HRMS-ESI spectra

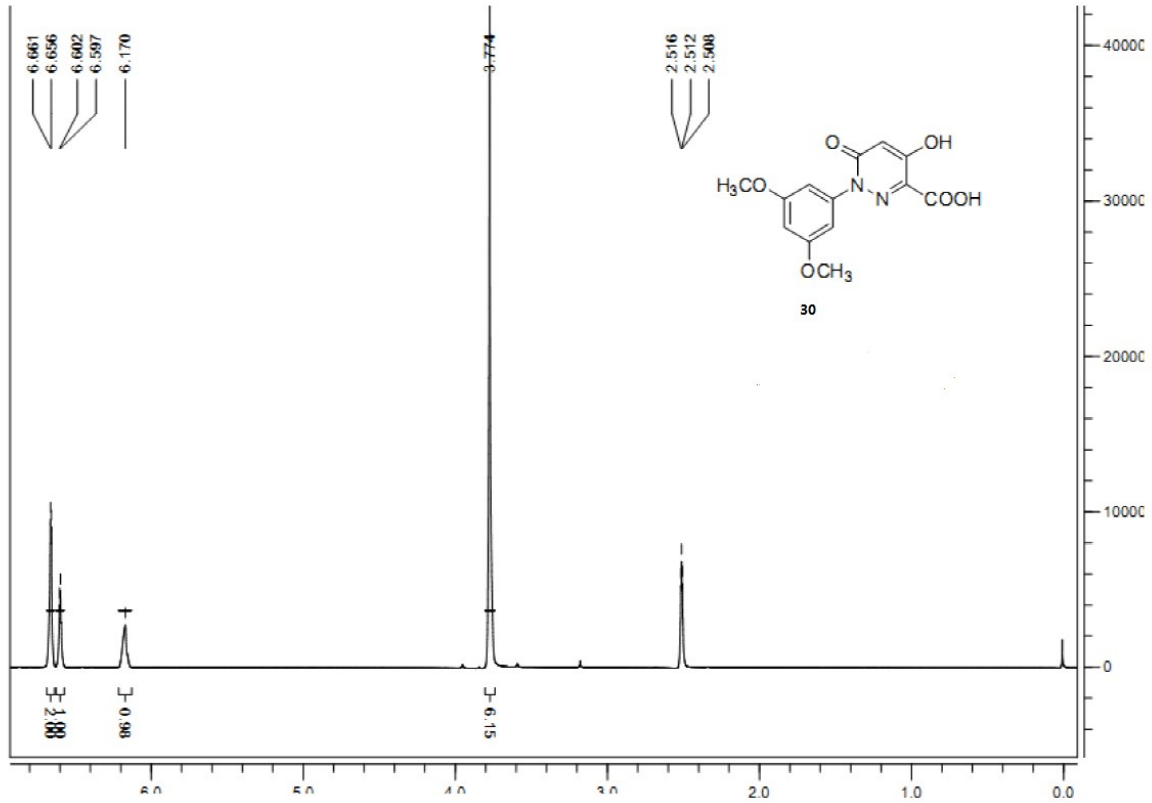


Fig. S1 ^{1}H NMR spectra of **30** in DMSO-d_6

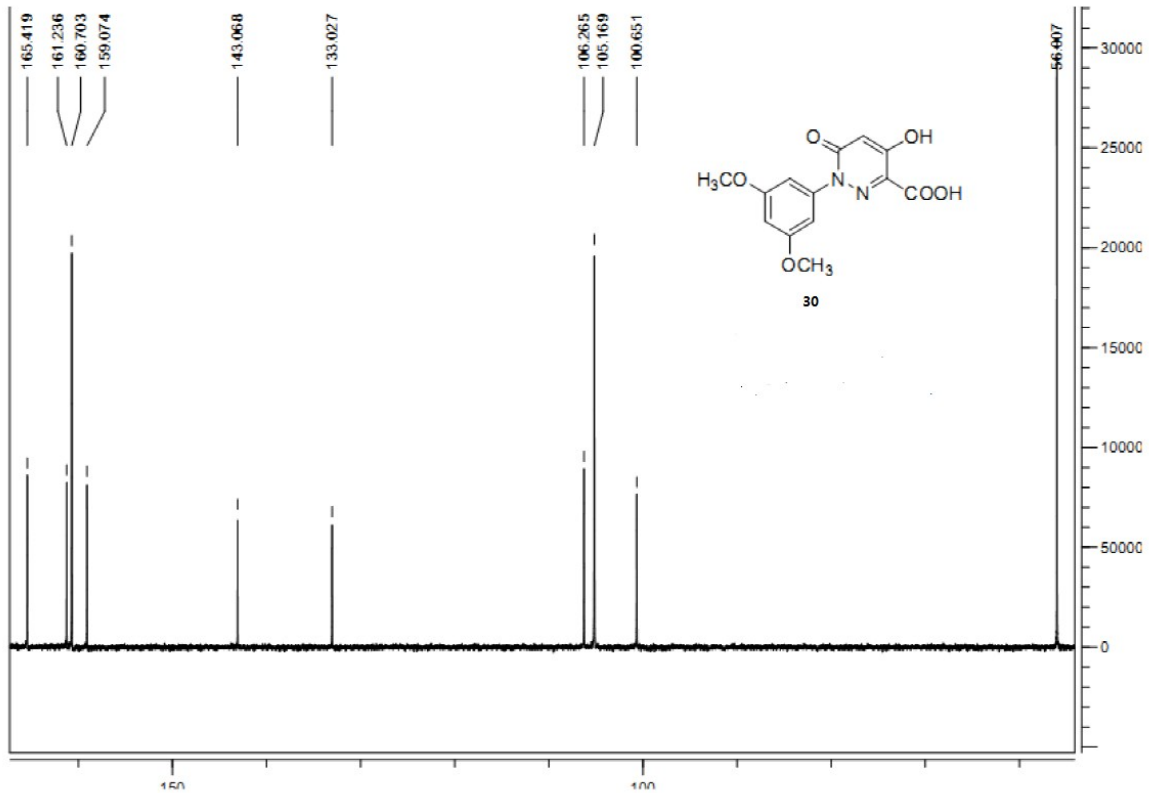


Fig. S2 ^{13}C NMR spectra of **30** in DMSO-d_6

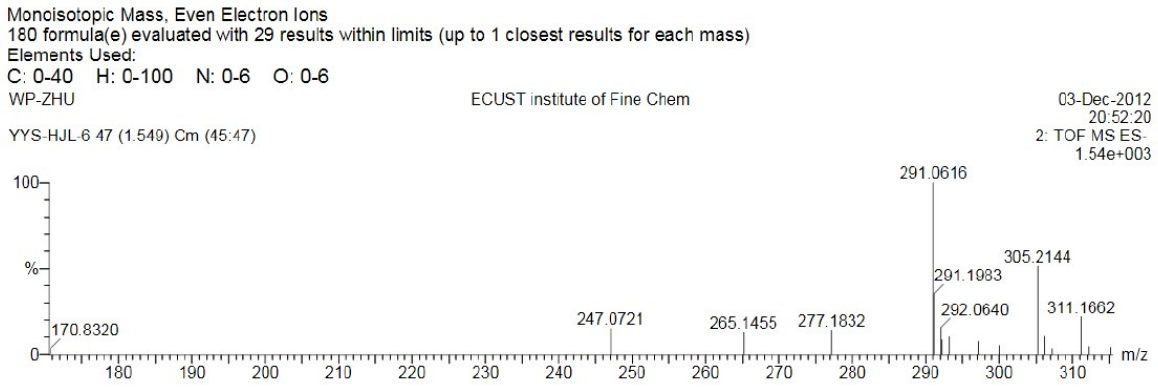


Fig. S3 HRMS spectra of **30**

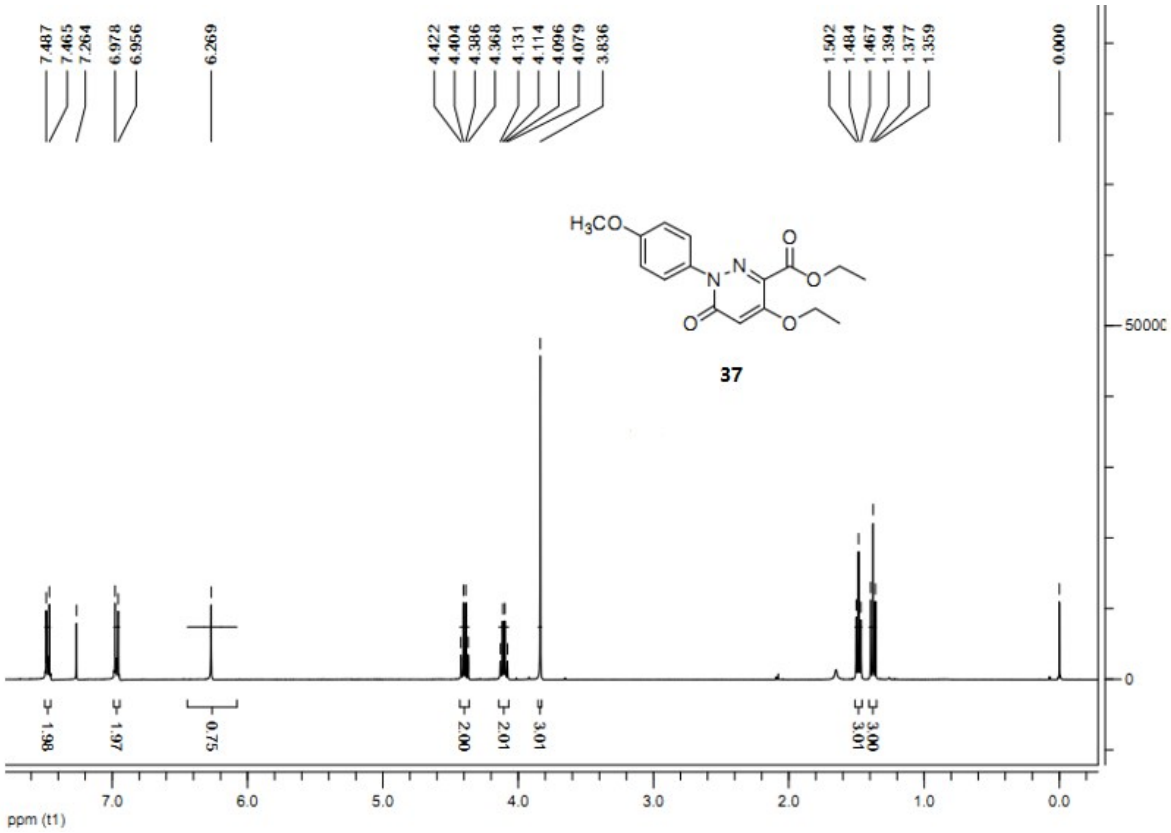


Fig. S4 ^{1}H NMR spectra of **37** in $CDCl_3$

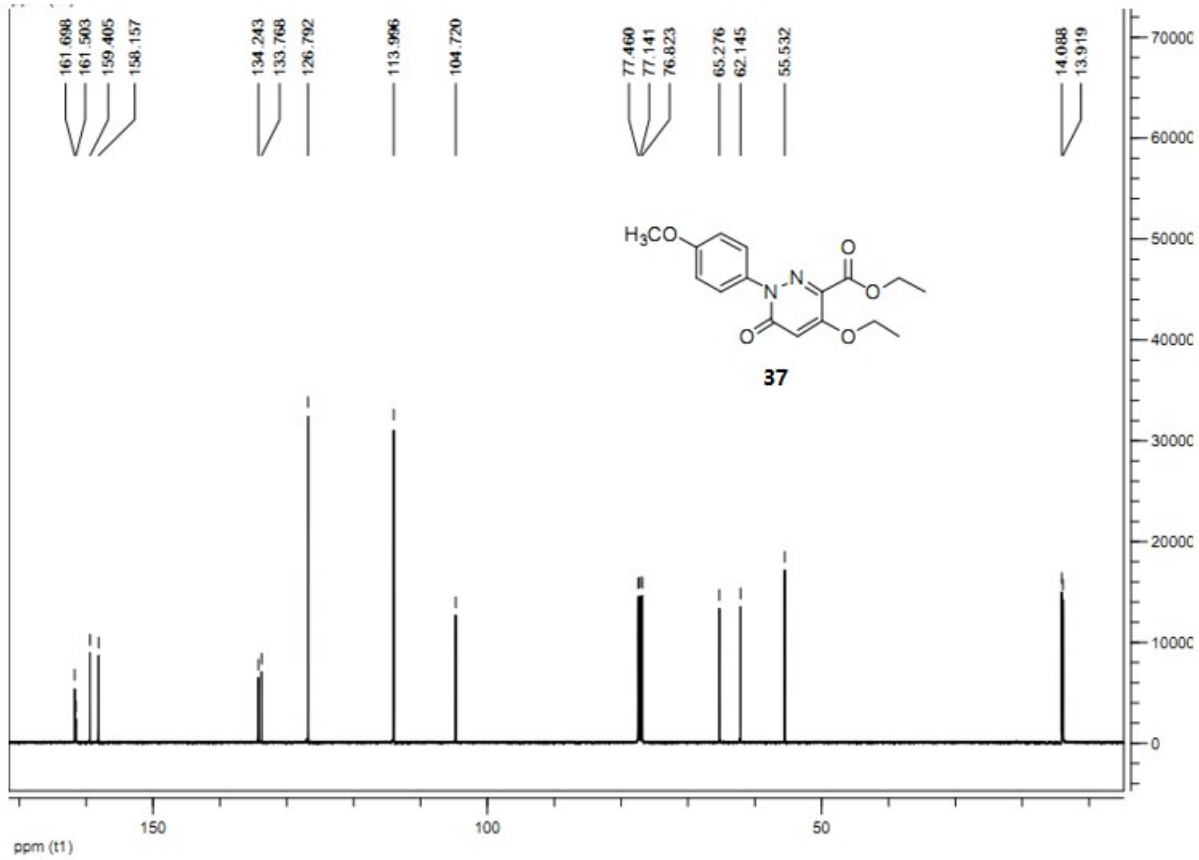


Fig. S5 ^{13}C NMR spectra of **37** in $CDCl_3$

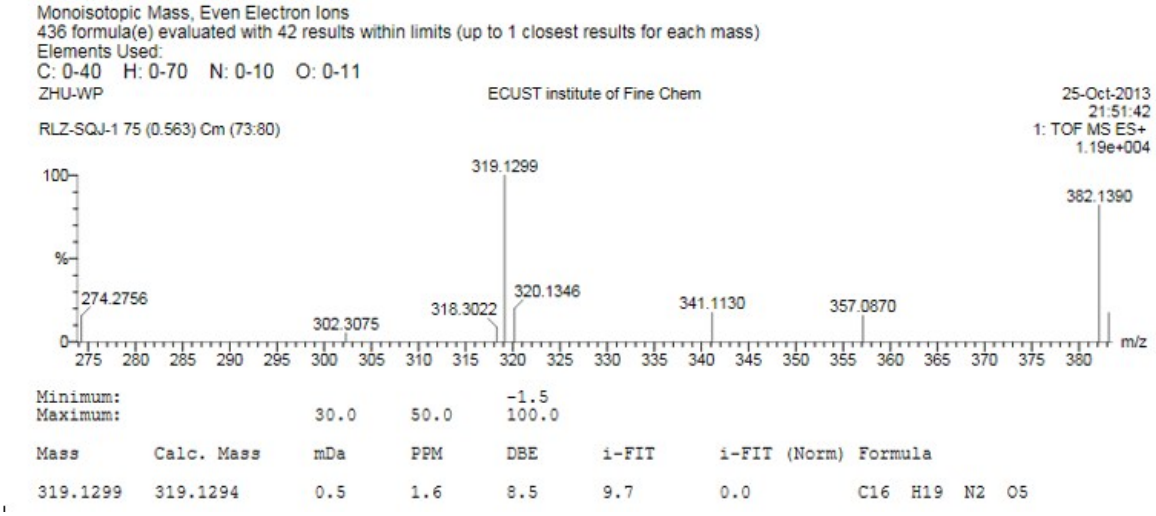


Fig. S6 HRMS spectra of **37**

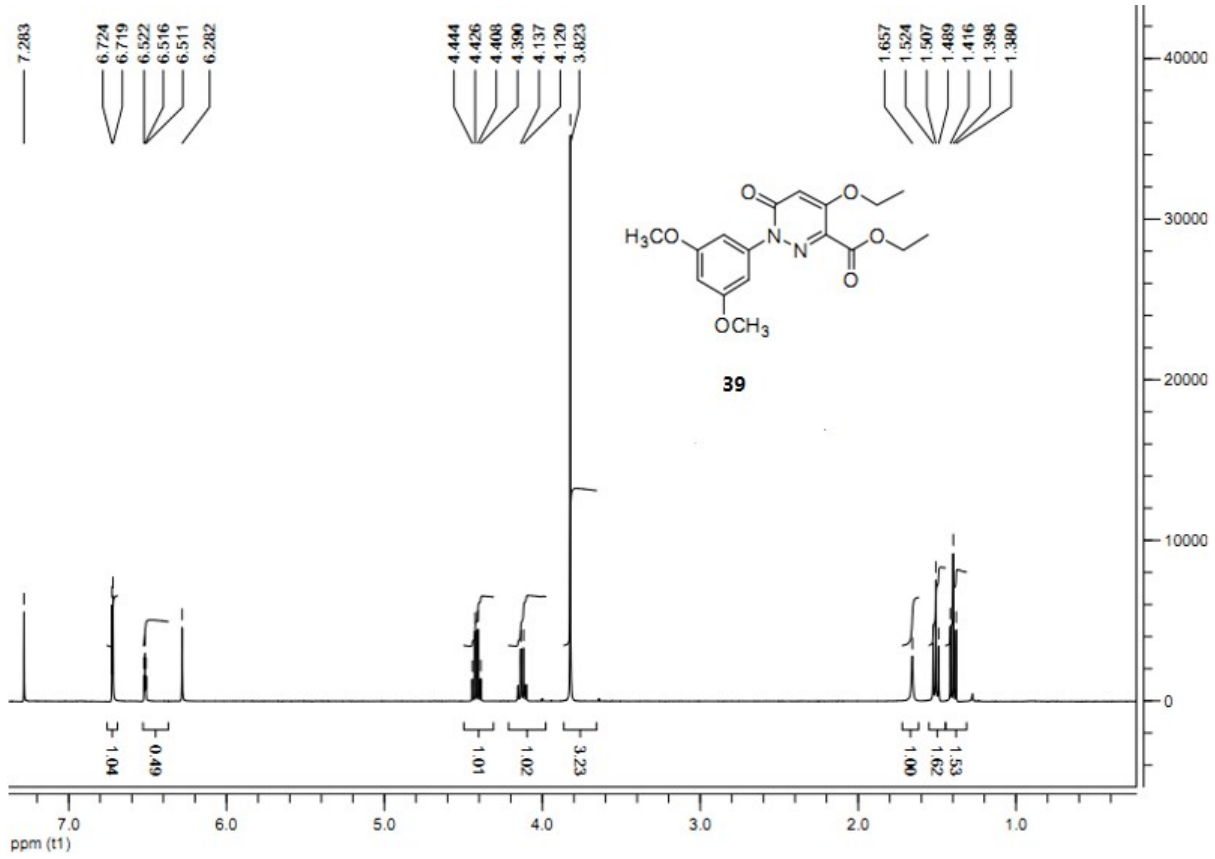


Fig. S7 ^{1}H NMR spectra of **39** in $CDCl_3$

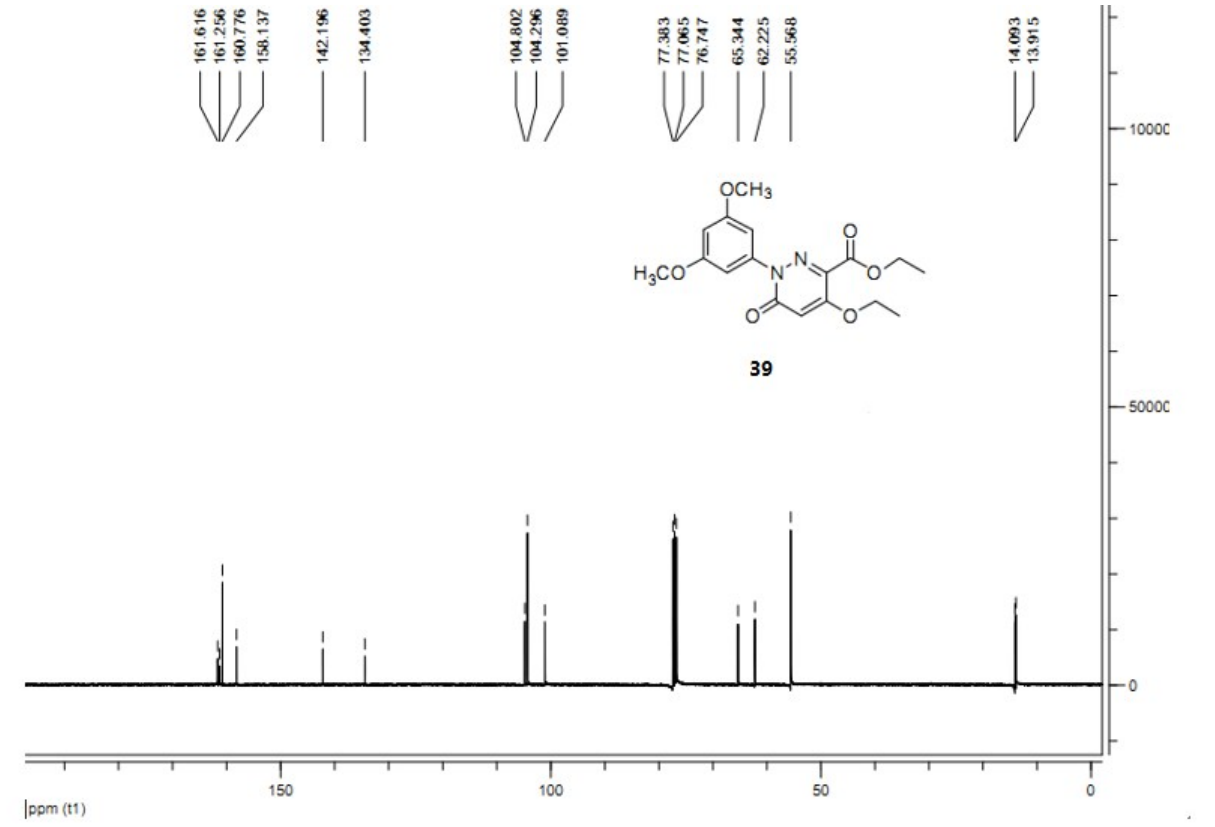


Fig. S8 ^{13}C NMR spectra of **39** in $CDCl_3$

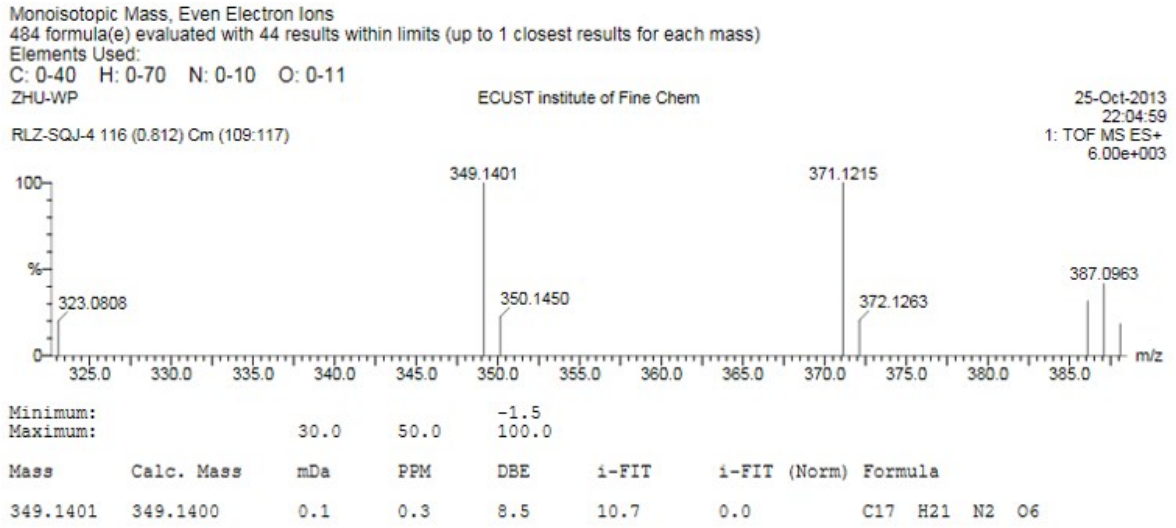


Fig. S9 HRMS spectra of **39**

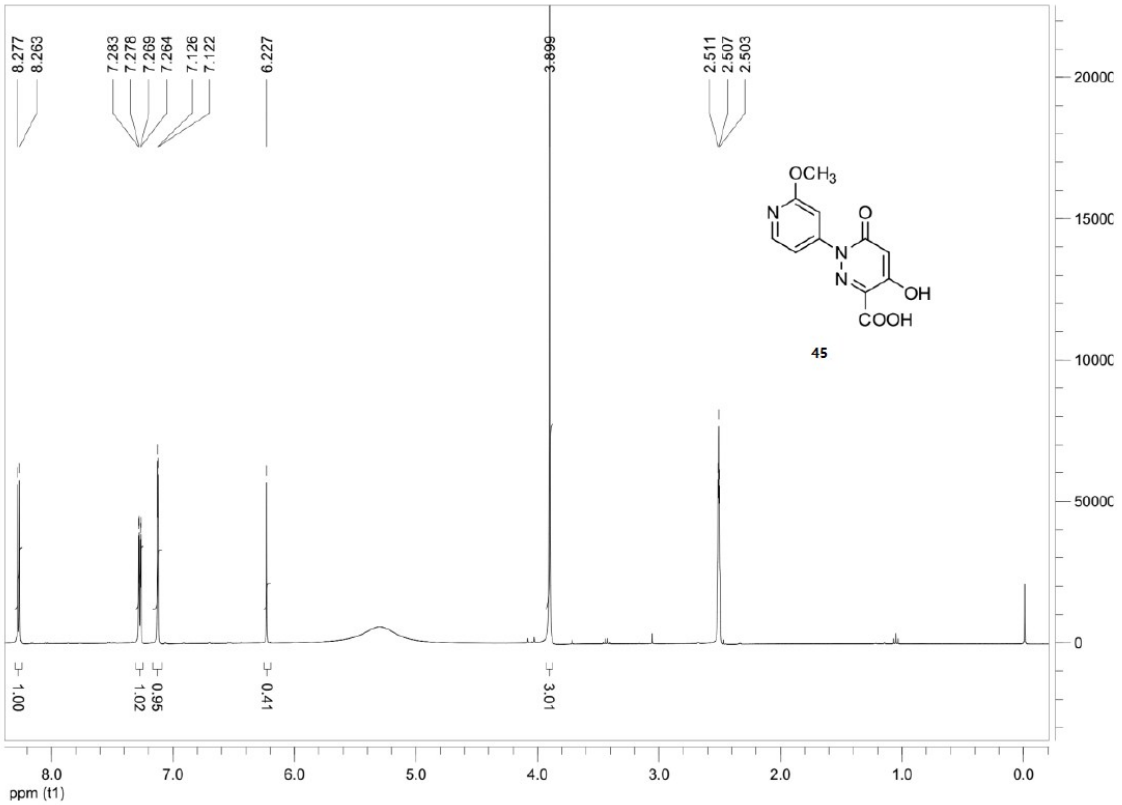


Fig. S10 ^{1}H NMR spectra of **45** in DMSO-d_6

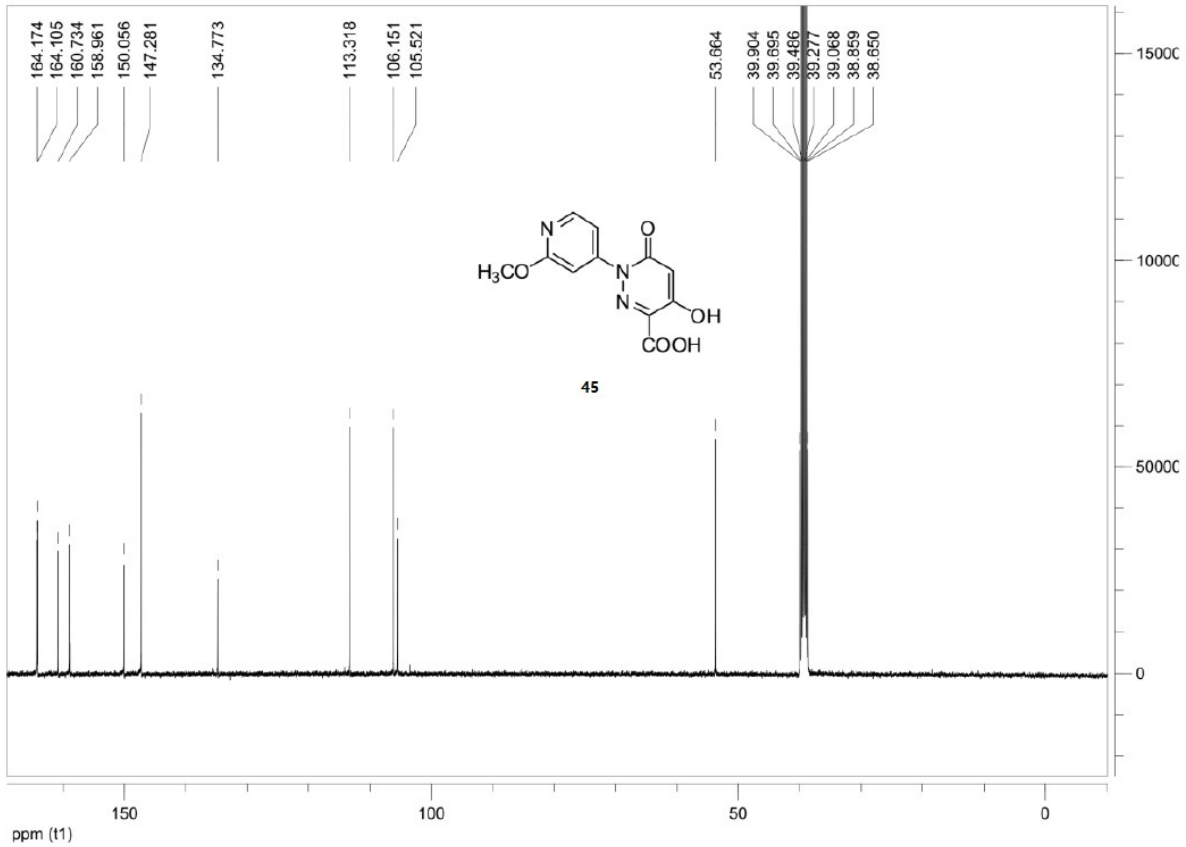


Fig. S11 ^{13}C NMR spectra of **45** in DMSO-d_6

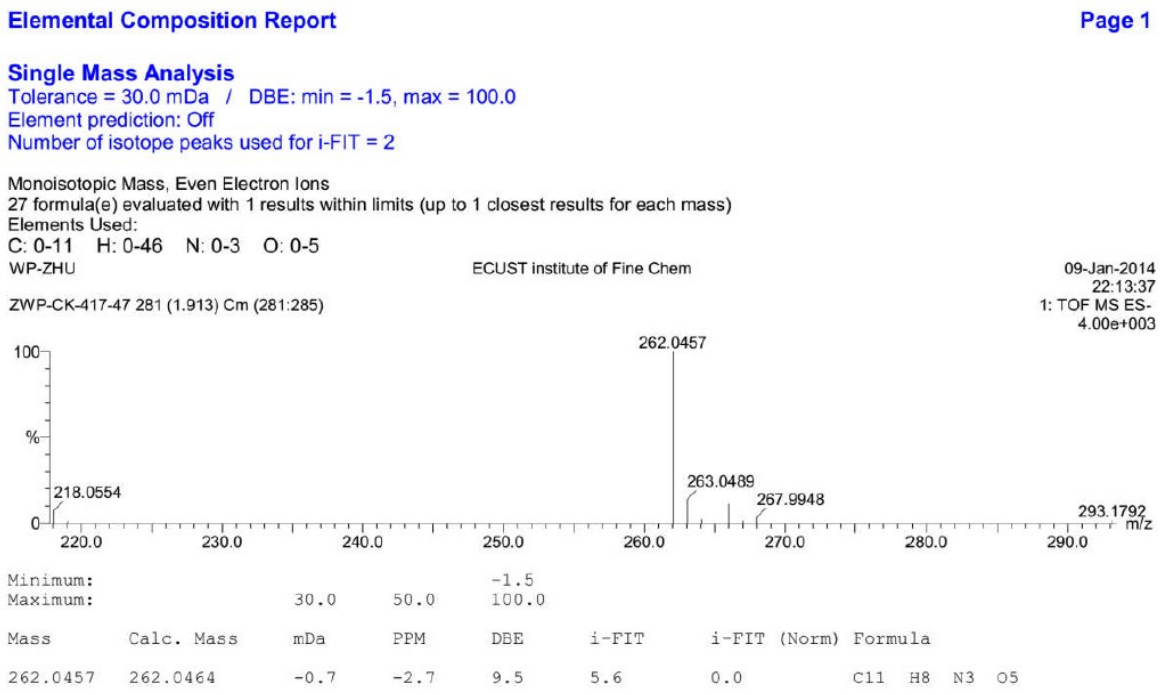


Fig. S12 HRMS spectra of **45**

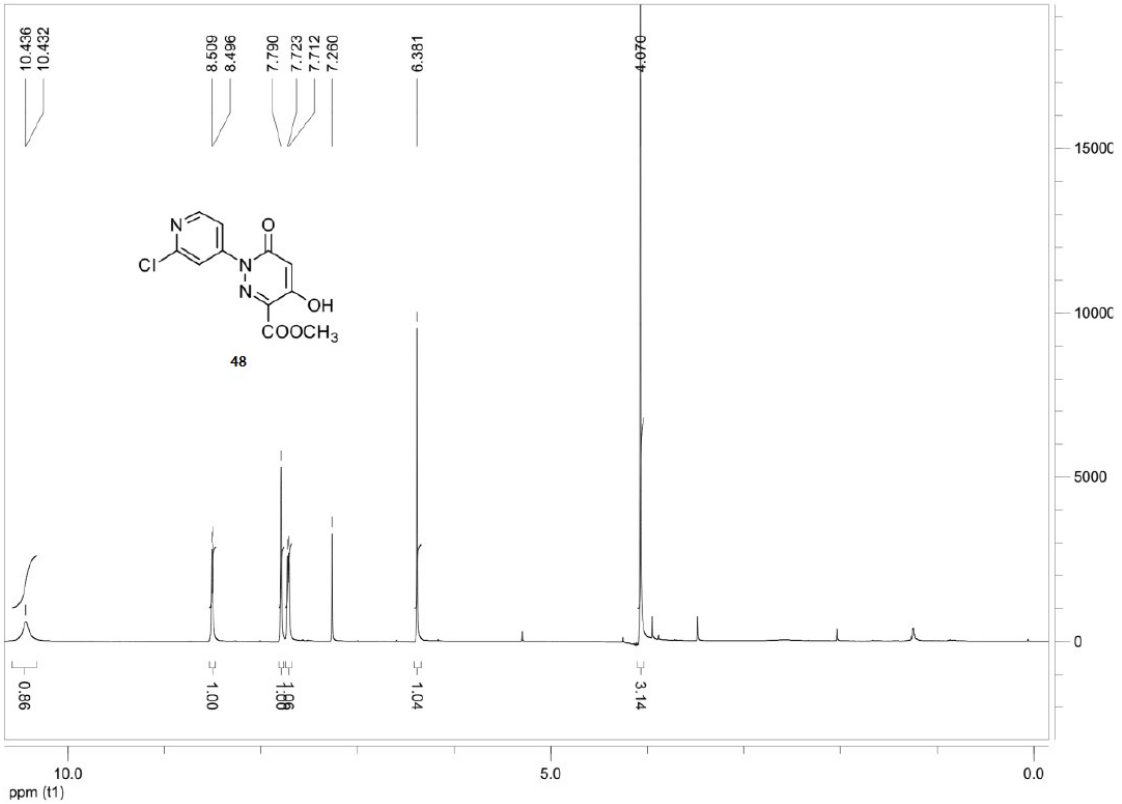


Fig. S13 ^{1}H NMR spectra of **48** in $CDCl_3$

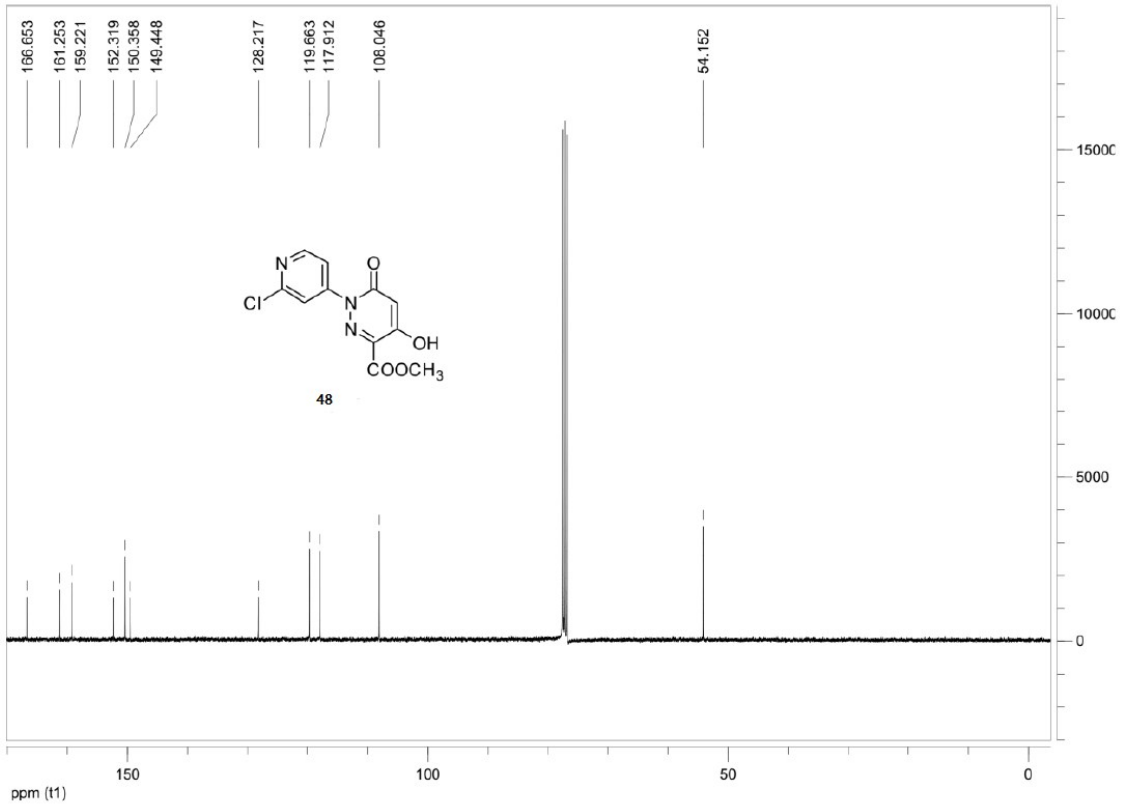


Fig. S14 ^{13}C NMR spectra of **48** in $CDCl_3$

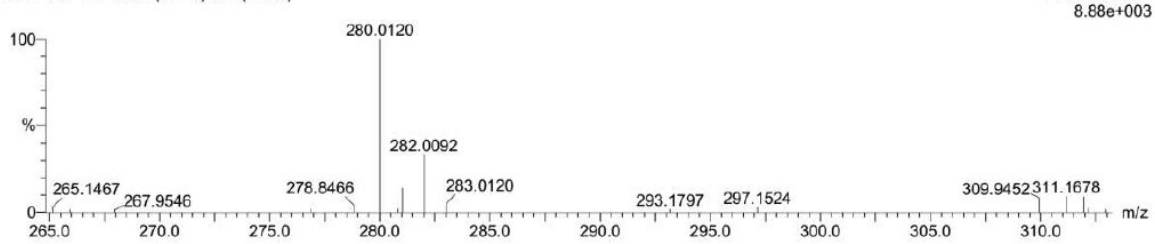
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 30.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 10 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-10 N: 0-3 O: 0-4 Cl: 0-1

WP-ZHU ECUST institute of Fine Chem 19-Dec-2013 20:22:40

ZWP-CK-417-13 51 (0.423) Cm (47:56) 1: TOF MS ES- 8.88e+003



Minimum:				-1.5			
Maximum:		30.0	50.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
280.0120	280.0125	-0.5	-1.8	9.5	16.4	0.0	C11 H7 N3 O4 Cl

Fig. S15 HRMS spectra of **48**

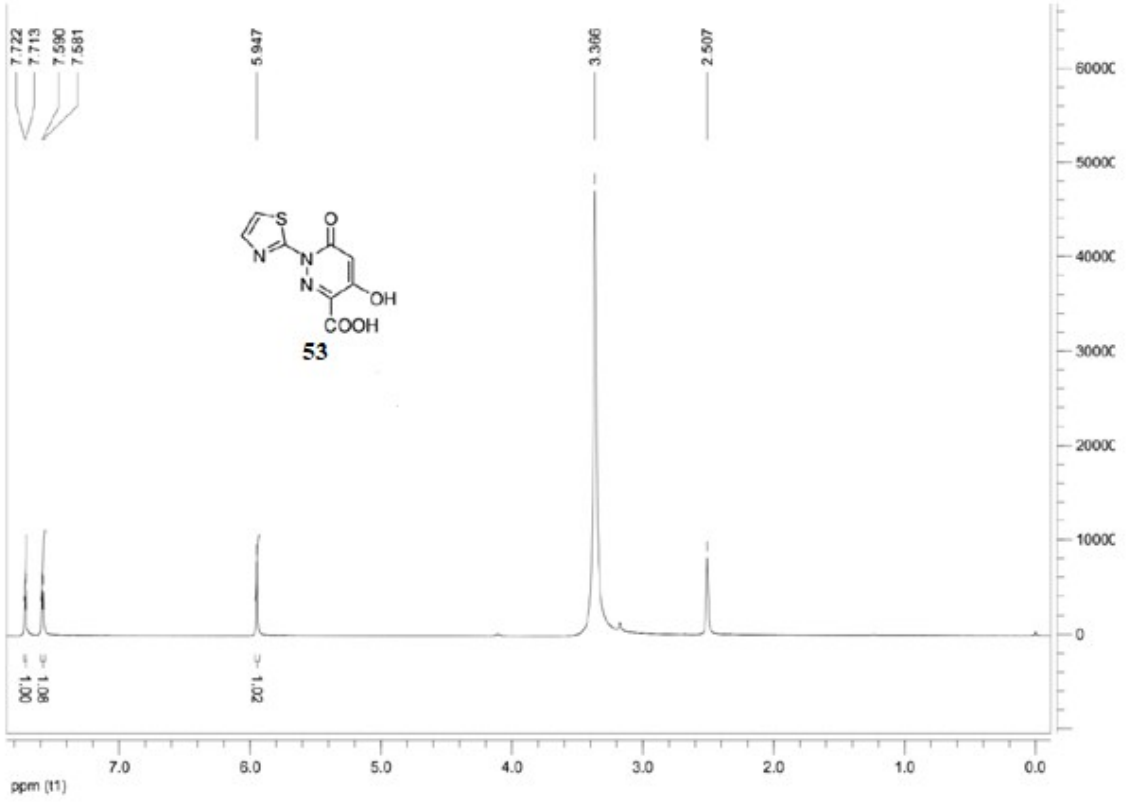


Fig. S16 ^{1}H NMR spectra of **53** in DMSO-d_6

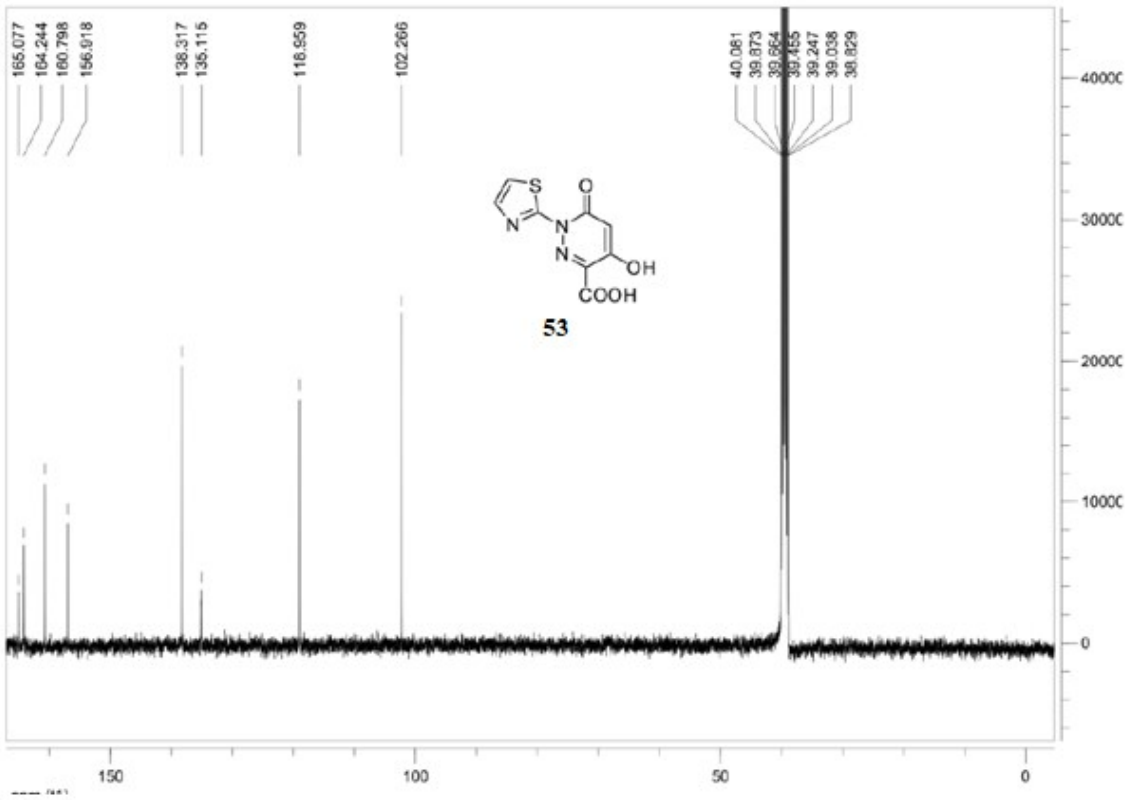


Fig. S17 ^{13}C NMR spectra of **53** in DMSO-d_6

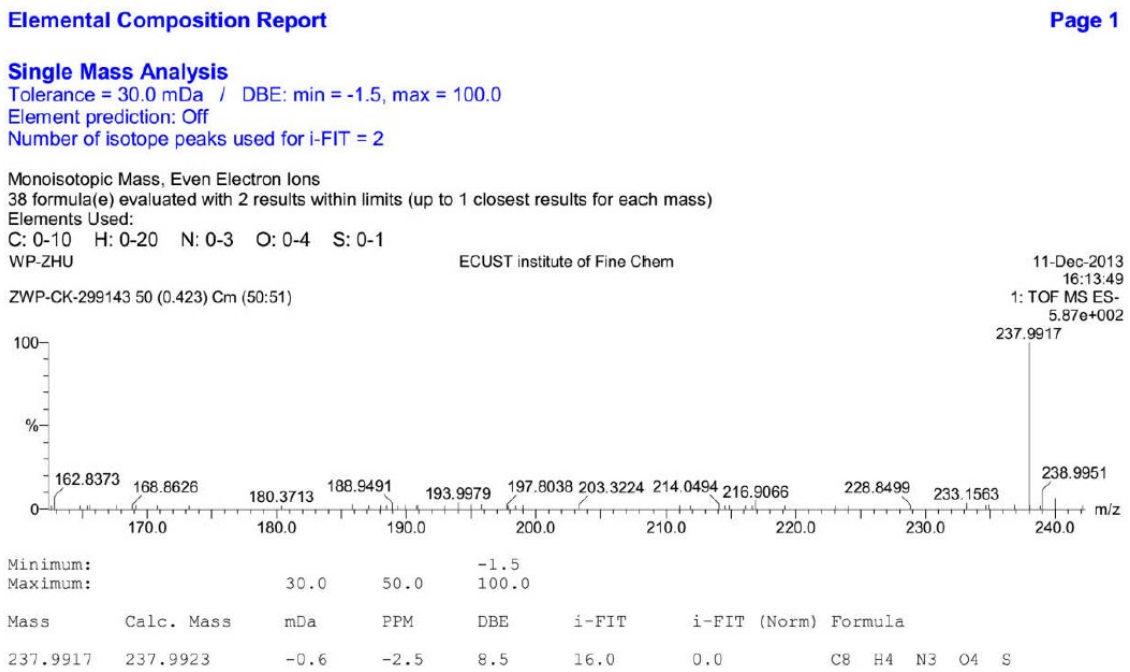


Fig. S18 HRMS spectra of **53**

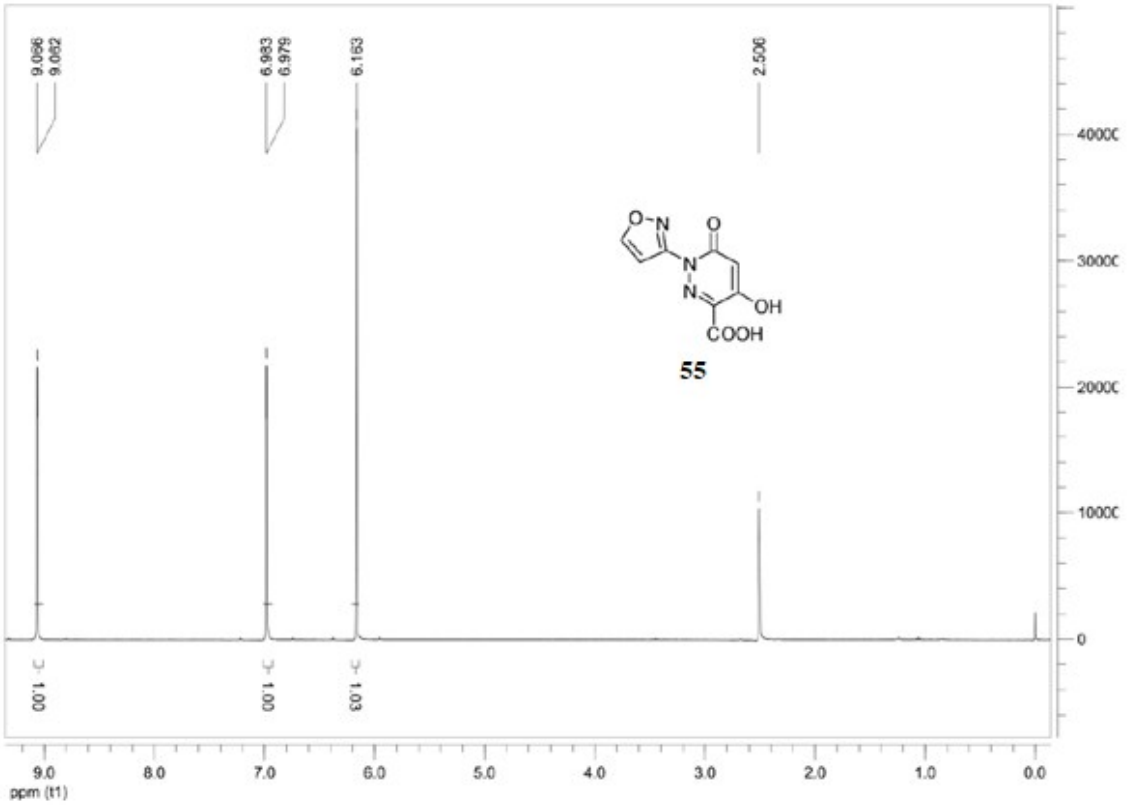


Fig. S19 ^{1}H NMR spectra of **55** in DMSO-d_6

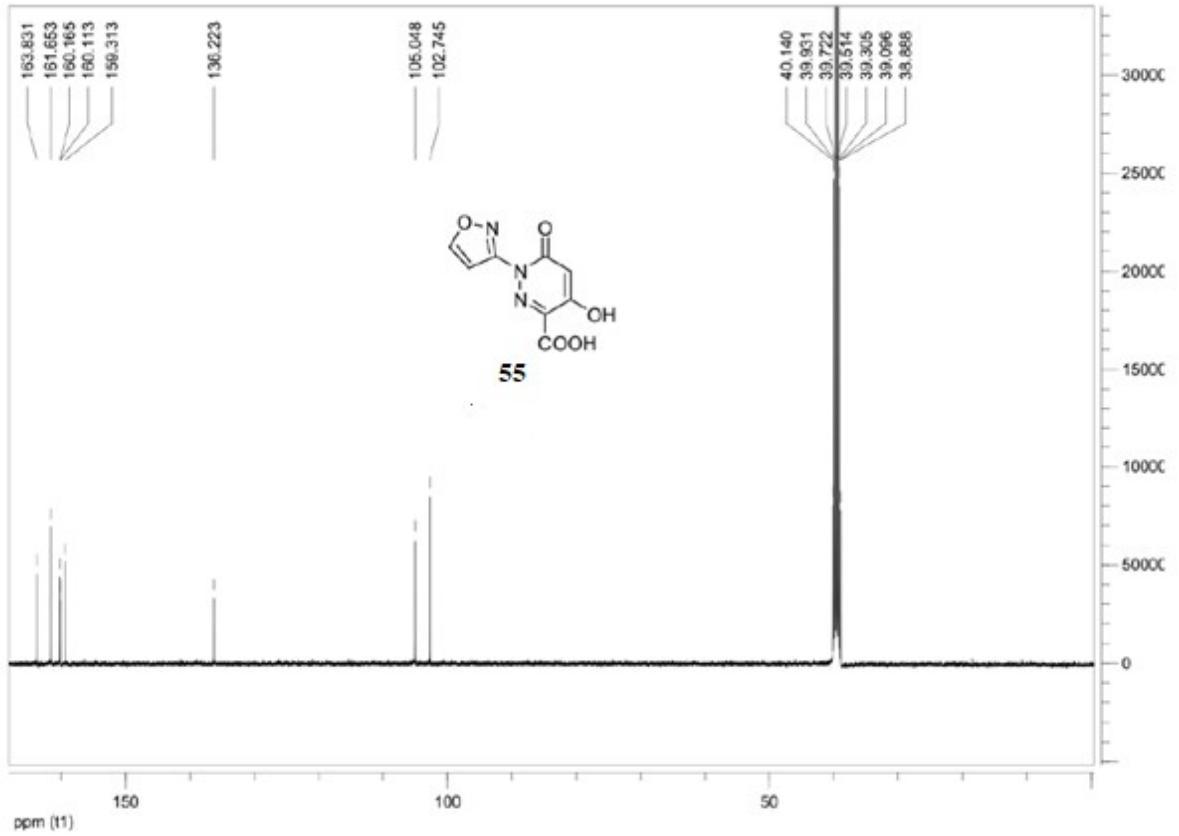


Fig. S20 ^{13}C NMR spectra of **55** in DMSO-d_6

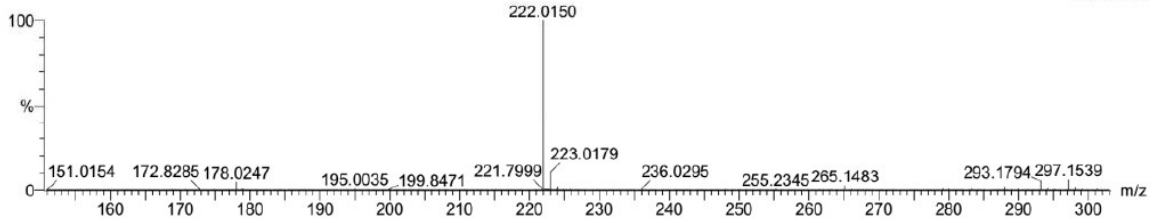
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 30.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
62 formula(e) evaluated with 8 results within limits (up to 1 best isotopic matches for each mass)
Elements Used:
C: 0-20 H: 0-30 N: 0-3 O: 0-5

ZHU-WP ECUST institute of Fine Chem 26-Jun-2014 19:51:08

ZWP-CK-417-119 94 (0.698) Cm (84:95) 1: TOF MS ES- 2.67e+004



Minimum:				-1.5			
Maximum:		30.0	50.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
222.0150	222.0151	-0.1	-0.5	8.5	264.5	0.0	C8 H4 N3 O5

Fig. S21 HRMS spectra of **55**

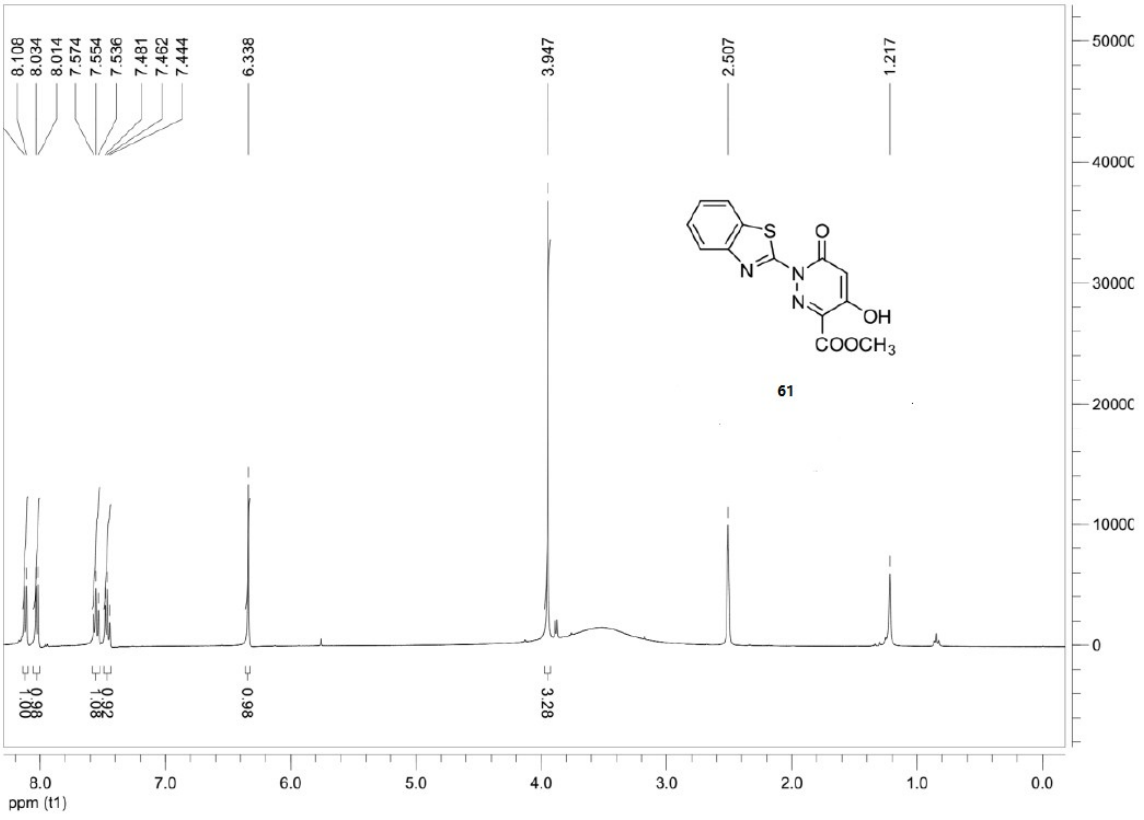


Fig. S22 ^{1}H NMR spectra of **61** in $CDCl_3$

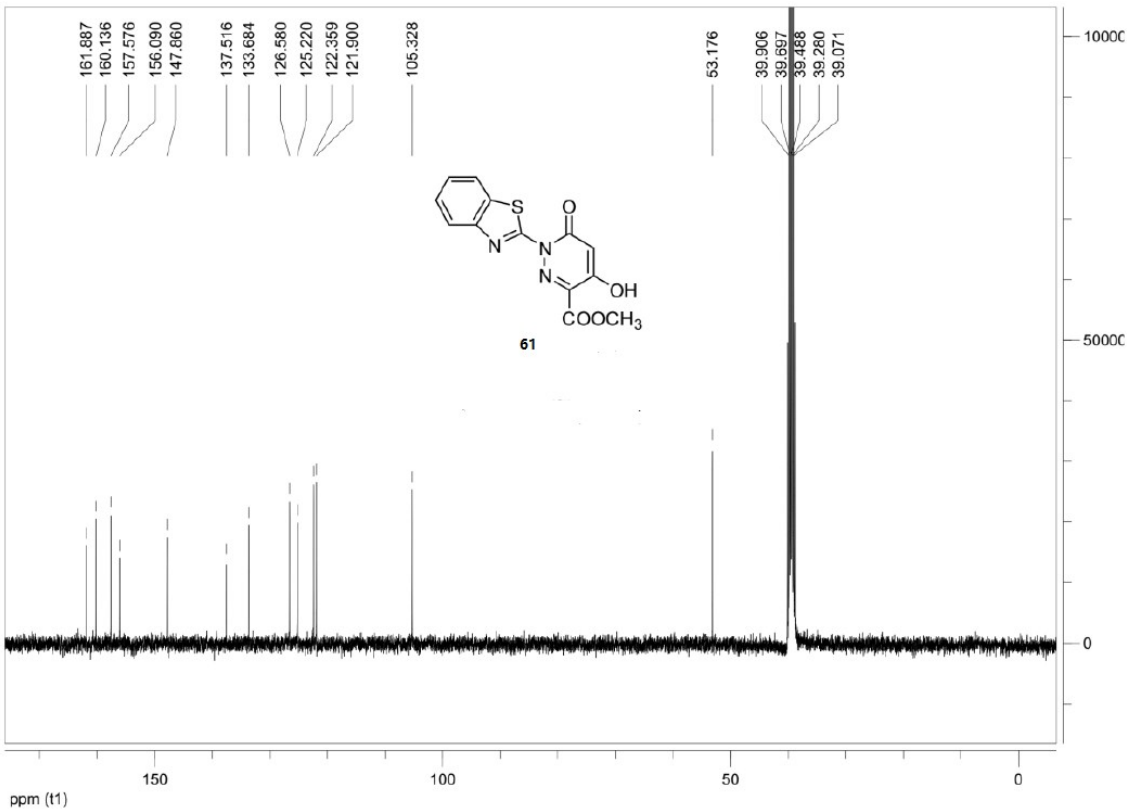


Fig. S23 ^{13}C NMR spectra of **61** in $CDCl_3$

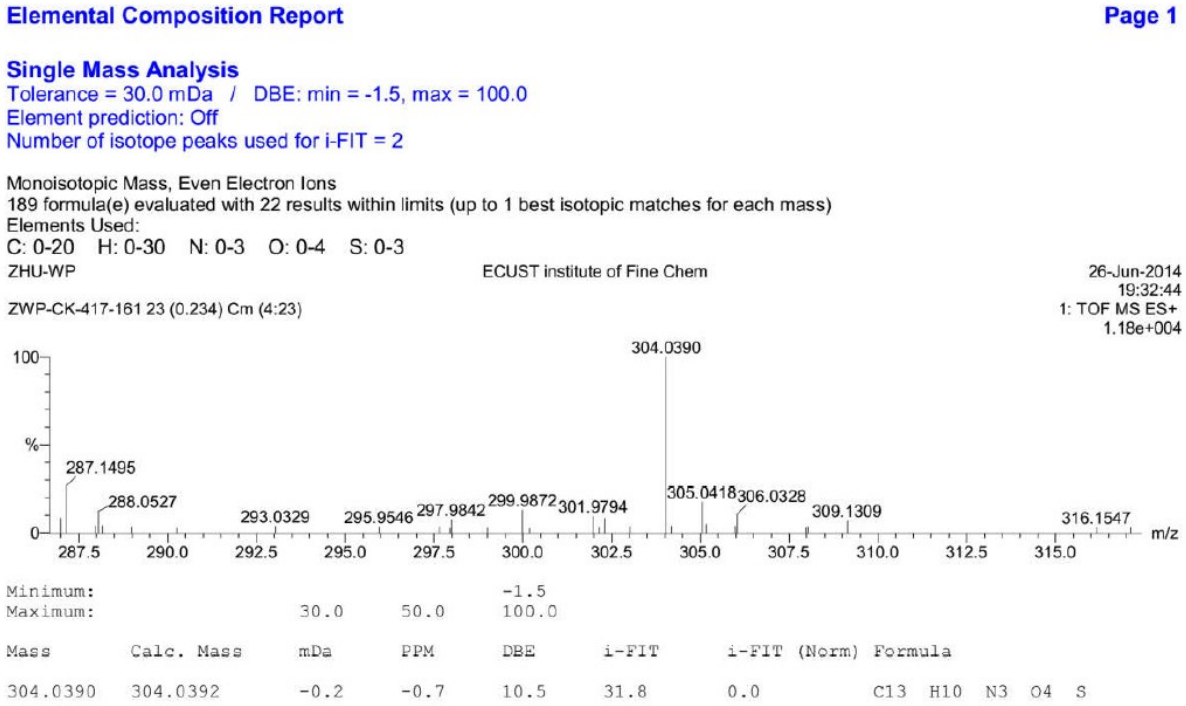


Fig. S24 HRMS spectra of **61**

3. References

1. Q. Du, W. Zhu, Z. Zhao, X. Qian and Y. Xu, *J. Agric. Food Chem.*, 2012, **60**, 346-353.
2. G. M. B. D. Schober, Th. Kappe, *J. Heterocyclic Che.*, 1989, **26**, 169-176.
3. K. Chang, Y. Shi, J. Chen, Z. He, Z. Xu, Z. Zhao, W. Zhu, H. Li, Y. Xu, B. Li and X. Qian, *MedChemComm*, 2016, **7**, 1849-1857.
4. X. Liu, H. Jiang and H. Li, *J. Chem. Inf. Model.*, 2011, **51**, 2372-2385.
5. C. Robert, M. O. Bancal, P. Nicolas, C. Lannou and B. Ney, *Journal of Experimental Botany*, 2004, **55**, 1079-1094.

6. Pesticide: Guidelines for the field efficacy trials(Ⅰ). GB/T 17980.27-2000 [S]. Beijing: Standard Press of China, **2000**.

7. Pesticide: Guidelines for the field efficacy trials(Ⅰ). GB/T 17980.28-2000 [S]. Beijing: Standard Press of China, **2000**.

8. Pesticide: Guidelines for the field efficacy trials(Ⅰ). GB/T 17980.32-2000 [S]. Beijing: Standard Press of China, **2000**.

9. Pesticides guidelines for laboratory bioactivity tests, Part 2: Petri plate test for determining fungicide inhibition of mycelial growth. NY/T 1156.2-2006[S].Beijing: China Agricultural Press, **2006**.