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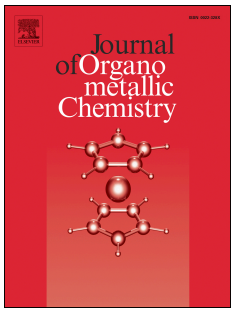

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Design, Synthesis and Fungicidal Activity Studies of 3-Ferrocenyl-*N*-Acryloylmorpholine

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ABSTRACT

Ferrocene and its derivatives have been widely used in many fields and also used to modify and improve the performance. Particularly, their low toxicity also attract much attention in medical and pesticide fields. In order to get fungicides with higher biological activity, ferrocenyl were introduced into the skeleton of dimethomorph instead of phenyl and a series of 3-ferrocenyl-*N*-acryloylmorpholine were sythesized. The fungicidal bioassay results indicated that most of compounds showed moderate fungicidal activities against 14 kinds of agricultural pathogenic fungi and some compounds displayed higher fungicidal activities than that of dimethomorph. Intrestlingly, compounds **5(Z)** exhbited better fungicdal activity against *Sclerotinia sclerotiorum* than that of compound **5(*E*)**.

1. Introduction

The emergence of resistance against commercial drugs in current use necessitates the search for new classes of drugs. Since the discovery of ferrocene in 1951,[1] its distinctive "sandwich" structure, reversible change of the valency state and low toxicity have attracted tremendous attention of chemists as a backbone for the design of new drugs.[2-10] Therefore, ferrocenyl compounds have been explored in medicinal chemistry as antibacterial[11], antimalarial[12] and anticancer[13] agents in the recent years. For example, compound **A** (Figure 1) displayed higher or the equivalent antibacterial activities compared with commercial antibiotics (amoxicillin and cephalosporin).[4] Ferroquine (Figure 1, compound **B**), which is a ferrocenyl derivative of the antimalarial drug chloroquine, is also active on *Plasmodium falciparum* strains which are resistant to chloroquine.[7] Hydroxyferrocifen (Figure 1, compound **C**) is a new and promising class of ferrocifen-type breast-cancer drug candidates, which exhibits strong antiproliferative effects on hormone-dependent breast cancer cells (MCF-7) and hormone-independent ones (MDA-MB-231) as well.[14] Compound **D** (Figure 1) exhibits excellent antiproliferative effect on hormone-independent MDA-MB-231 breast and PC-3 prostate cancer cell lines with IC_{50} values of 90 nM and 94 nM respectively.[15] Ferrocenylseleno-dopamine derivative **E** (Figure 1) exhibited better *in vivo* antitumor activity in mice bearing HepG2 tumor xenograft in comparison to free dopamine.[13e] Compound **F** (Figure 1) displayed selectivity for cancer-associated isozymes CA IX and CA XII with K_is of 5.9 and 6.8 nM respectively.[16]

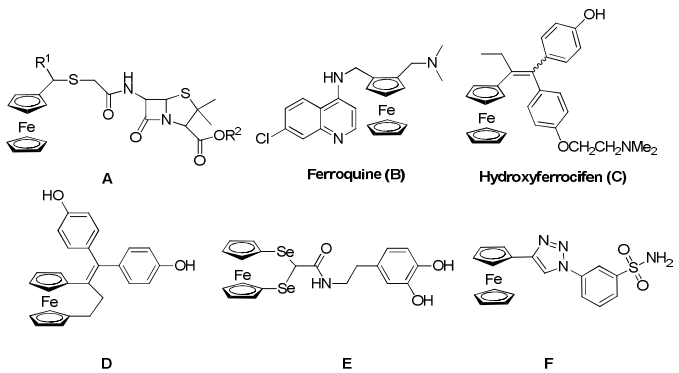


Figure 1. Chemical structure of medicinal molecules containing ferrocenyl groups.

Ferrocene can participate in the metabolic activity of organisms due to its special properties of lipophilicity and redox reversibility, so many pesticides were modified by introducing ferrocenyl groups. In a search for new insect growth regulators, Wang and coworkers replaced the phenyl moiety by ferrocenyl group in *N-tert*-butyl-*N,N´*-dibenzoylhydrazine to obtain the novel acylhydrazines containing the ferrocenyl moiety

(compound **G**, Figure 2) and the results of bioassay showed that some of the title compounds exhibited excellent larvicidal activities against Southern armyworm.[17] Then they replaced the benzoyl moiety by ferrocenoyl in benzoylphenylurea, and synthesized a series of new benzoylphenylureas containing a ferrocenyl moiety (compound **H**, Figure 2), however, these compounds showed poor larvicdial activities against Oriental armyworm at 500 ppm.[18] In order to extend their research work of cyanoacrylates as herbicides, they designed and synthesized some novel cyanoacrylates by the replacement of the phenyl group with a ferrocenyl group and compound **I** (Figure 2) exhibit 100% herbicidal activities for rape weed at 1.5 kg ha^{-1}.[19] In order to improve biological behavior of the 1*H*-1,2,4-triazole derivatives, a series of triadimefon analogues containing ferrocenyl moiety (compounds **J**-**L**, Figure 2) were synthesized and their antifungal and plant growth regulatory activities were evaluated by Fang and coworkers.[20] The bioassay results revealed that these novel ferrocenyl triadimefon derivatives lost their antifungal activities of the parent compound, while compounds **J** and **K** exhibited excellent plant growth regulatory activity unexpectedly.[20]

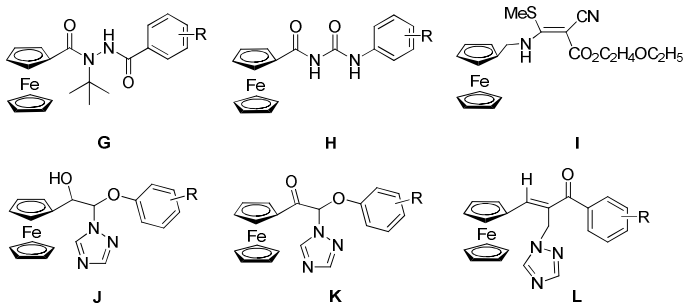


Figure 2. Chemical structure of pesticides containing ferrocenyl groups.

Dimethomorph (Figure 3) was discovered as a specific Oomycete fungicide during 1980s by the pharmaceutical research group at Celamerck, and it was described in detail by Alber et al. in 1988.[22] The results of cytological studies have implied that dimethomorph inhibit process involved in cell-wall biosynthesis and assembly.[23-25] In order to broaden the fungicidal spectrum, flumorph[26] (Figure 3) and pyrimorph[27] (Figure 3) were discovered successively. To obtain acryloylmorpholine analogues with high activity against plant pathogens, ferrocenyl groups were introduced into the skeleton of *N*-acryloylmorpholine fungicides instead of phenyl groups and a series of 3-ferrocenyl *N*-acryloylmorpholine were synthesized and their fungicidal activities were evaluated (Figure 3).

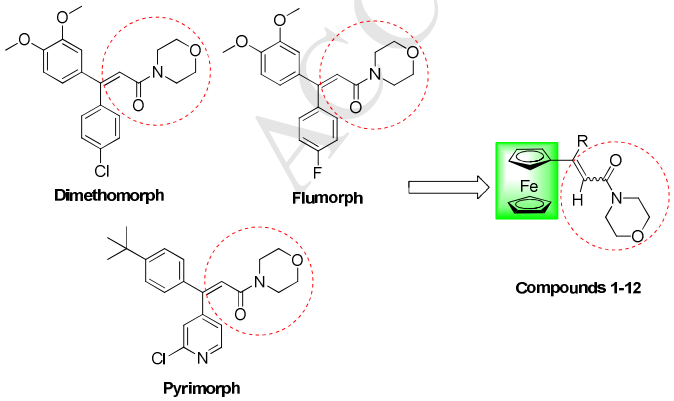


Figure 3. Design strategy of 3-ferrocenyl *N*-acryloylmorpholine.

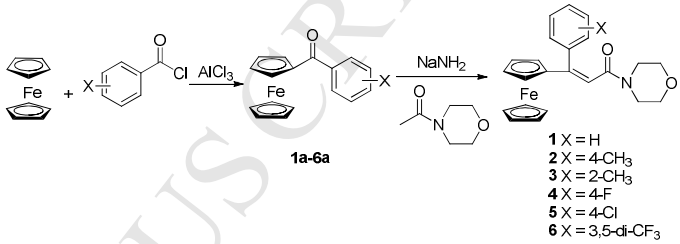
2. Materials and methods

2.1. General experimental methods.

All NMR experiments were carried out on a 500 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. HRMS data were obtained on a Bruker ultrafleXtreme MALDI-TOF/TOF mass spectrometer (Bruker Daltonik GmbH, Leipzig, Germany) equipped with a smart beam II laser (1000 Hz). The X-ray crystallographic data were collected on a Bruker Smart APEX II CCD area detector with a MoKα radiation (λ = 0.71073 Å) at 294 K in the φ–ω scan mode. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. CH_3CN, dioxane, toluene, and DMF were dried according to literature techniques.

2.2. Synthetic Procedures

*2.2.1 General Synthetic Procedure for Compounds **1**–**12** (Scheme 1)*



Scheme 1. Synthetic procedure of compound **1-6**

*Synthesis of Benzoylferrocene (**1a**)*[13]

A 100 mL 3-neck round-bottom flask was charged with anhydrous $AlCl_3$ (1.3 g, 10.0 mmol) and CH_2Cl_2 (10.0 mL). The mixture was cooled to -5 °C and benzoyl chloride (1.4 g, 10.0 mmol) in CH_2Cl_2 was added dropwisely. The above mixture was added dropwisely to a solution of ferrocene (1.5 g, 8.3 mmol) in CH_2Cl_2 (20.0 mL) at 0 °C, then the reaction mixture was warmed to room temperature and stood for 2 h. The mixture was poured to ice-water (100.0 mL) and the organic phase was separated. The organic phase was successively washed with 1N HCl solution, water and 5% aqueous Na_2CO_3, dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure to give a crude product. The product was purified by recrystallization from petroleum ether (60-90 °C) to give compound **1a** as an orange-red solid (67.5%).

*Synthesis of (E)-3-ferrocenyl-1-morpholino-3-phenylprop-2-en-1-one (**1**)*[14]

A solution of *N*-acetylmorpholine (230.8 μL, 2.0 mmol) and sodium amide (85.8 mg, 2.2 mmol) in toluene (2.5 mL) was stirred at 110 °C for 30 min. Then compound **1a** (372.0 mg, 2.0 mmol) in toluene (2 mL) was added to the reaction solution. The mixture was stirred at 110 °C for 12 h and washed with water (3 × 5 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel to give compound **1** as an orange-red solid (77.0%): mp 152-154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 5H, Ph), 6.30 (s, 1H, CH), 4.36–4.33 (m, 2H, C_5H_4), 4.32–4.28 (m, 2H, C_5H_4), 4.13 (s, 5H, C_5H_5), 3.41 (dd, J = 22.4, 3.1 Hz, 4H, OC_2H_4), 3.18 (s, 2H, CH_2N), 3.01 (s, 2H, CH_2N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 146.3, 138.5, 128.7, 128.3,128.2, 116.4, 83.8, 77.4 , 77.1 , 76.8 , 69.7, 67.8, 66.4, 46.8 , 41.6; HRMS (ESI): m/z calcd for $C_{23}H_{23}FeNO_2$ $[M+H]^+$: 401.1078, found 401.1073.

*(E)-3-ferrocenyl-1-morpholino- 3-(p-tolyl)prop -2-en-1-one (**2**)*

The synthetic procedure was similar to that of compound **1**, and compound **2** was obtained as an orange-red solid (82%): mp 151-153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.0 Hz, 2H, Ph), 7.19 (d, J = 7.9 Hz, 2H, Ph), 6.27 (s, 1H, CH), 4.36–4.33 (m, 2H, C_5H_4), 4.31-4.28 (m, 2H, C_5H_4), 4.13 (s, 5H, C_5H_5), 3.43 (dd, J = 14.7, 3.8 Hz, 4H, OC_2H_4), 3.17 (d, J = 4.1 Hz, 2H, CH_2N), 3.05 (d, J = 4.2 Hz, 2H, CH_2N), 2.39 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 144.9, 139.1, 137.5, 128.7, 128.0 , 119.4, 81.9, 77.4, 77.1, 76.9, 69.6, 68.8, 66.5,66.5, 46.7, 41.5, 21.2; HRMS (ESI): m/z calcd for $C_{24}H_{25}FeNO_2$ $[M+H]^+$: 415.1235, found 415.1229.

*(E)-3-ferrocenyl -1-morpholino-3-(o-tolyl)prop-2-en-1-one (**3**)*

The synthetic procedure was similar to that of compound **1**, and compound **3** was obtained as an orange-red solid (64.0%): mp 128-129° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 7.3 Hz, 1H, Ph), 7.22 (dd, J = 20.4, 7.4 Hz, 3H, Ph), 6.44 (s, 1H, CH), 4.58 (s, 1H, C_5H_4), 4.35 (s, 1H, C_5H_4), 4.20 (s, 1H, C_5H_4), 4.15 (s, 5H, C_5H_5), 3.84 (s, 1H, C_5H_4), 3.51–3.13 (m, 8H, C_4H_8NO), 2.12 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 148.4, 138.1, 135.5, 130.1, 129.0, 128.0, 125.3, 116.4, 84.1, 77.4, 77.1, 76.8, 69.7 , 66.6, 65.6, 46.6, 41.7, 19.9; HRMS (ESI): m/z calcd for $C_{24}H_{25}FeNO_2$ $[M+H]^+$: 415.1235, found 415.1229.

*(E)- 3-ferrocenyl-3-(p-fluorophenyl)- 1-morpholinoprop-2-en-1-one (**4**)*

The synthetic procedure was similar to that of compound **1** , and compound **4** was obtained as an orange-red solid (65.0%): mp 135-136° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.31 (m, 2H, Ph), 7.09 (t, J = 8.4 Hz, 2H, Ph), 6.31 (s, 1H, CH), 4.31 (s, 4H, C_5H_4), 4.13 (s, 5H, C_5H_5), 3.44 (s, 4H, OC_2H_4), 3.20 (d, J = 20.5 Hz, 4H, C_2H_4N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 163.5, 161.6, 145.8, 134.4,v130.4, 130.3, 116.5 , 115.2, 837, 77.3, 77.1, 76.8, 69.7, 67.6, 66.5, 46.7, 41.5; HRMS (ESI): m/z calcd for $C_{23}H_{22}FeNFO_2$ $[M+H]^+$: 419.0984, found 419.0979.

*(E)-3-(p-chlorophenyl)-3-ferrocenyl-1-morpholinoprop-2-en-1-one **5** **(E)***

The synthetic procedure was similar to that of compound **1**, and compound **5** ***(E)*** was obtained as an orange-red solid (54.0%): mp 179-180° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 25.1, 7.9 Hz, 4H, Ph), 6.33 (s, 1H, CH), 4.31 (d, J = 9.8 Hz, 4H, C_5H_4), 4.13 (s, 5H, C_5H_5), 3.45 (s, 4H, OC_2H_4), 3.23 (s, 4H, C_2H_4N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 146.1, 136.9, 134.1, 130.0, 128.4, 116.5, 83.5, 77.4, 77.1, 76.8, 69.7, 67.6, 66.5, 46.7, 41.6; HRMS (ESI): m/z calcd for $C_{23}H_{22}FeNClO_2$ $[M]^+$: 433.0179, found 433.0171.

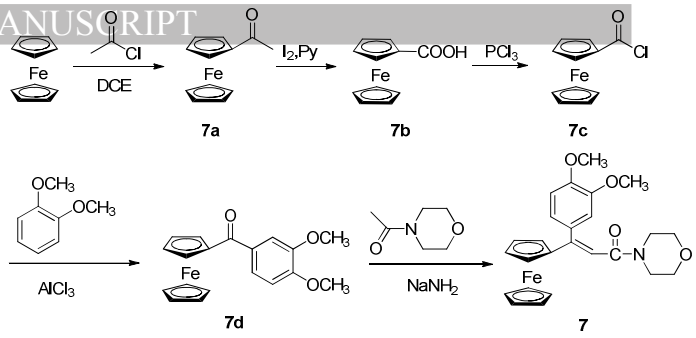
*(Z)-3-(p-chlorophenyl)-3-ferrocenyl-1-morpholinoprop-2-en-1-one **5** **(Z)***

The synthetic procedure was similar to that of compound **1**, and compound **5** ***(Z)*** was obtained as an orange-red solid (13.0%):^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.2 Hz, 2H, Ph), 7.39 (d, J = 8.2 Hz, 2H, Ph), 5.81 (s, 1H, CH), 4.32 (s, 2H, C_5H_4), 4.30 (s, 2H, C_5H_4), 4.09 (s, 5H, C_5H_5), 3.69 (s, 4H, OC_2H_4), 3.46 (d, J = 4.2 Hz, 2H, CH_2N), 3.39 (d, J = 4.4 Hz, 2H, CH_2N).

*(E)-3-ferrocenyl-1-morpholino-3-(3,5-bis(trifluoromethyl)phenyl)prop-2-en-1-one(**6**)*

The synthetic procedure was similar to that of compound **1**, and compound **6** was obtained as an orange-red solid (35.0%): mp 139-142° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 3H, Ph), 6.48 (s, 1H, CH), 4.41–4.38 (m, 2H, C_5H_4), 4.23–4.17 (m, 7H, C_5H_4, C_5H_5), 3.51 (s, 2H, OCH_2), 3.47 (s, 2H, OCH_2), 3.40 (d, J = 8.3 Hz, 4H, C_2H_4N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 146.6, 140.9, 128.9, 124.4, 121.8, 117.2, 83.1, 77.4, 77.1, 76.9, 70.4, 69.8, 67.5, 66.6, 46.6, 41.7; HRMS (ESI): m/z calcd for $C_{25}H_{21}FeF_6NO_2$ $[M+H]^+$: 537.0826, found 537.0821*2.2.2*

*Synthetic Procedure for Compound **7**(Scheme 2)*



Scheme 2. Synthetic procedure of compound **7**

*Synthesis of Acetylferrocene (**7a**)*[26]

To a solution of anhydrous $AlCl_3$ (1.6 g, 12.0 mmol) in CH_2Cl_2 (20 mL) acetyl chloride (935.8 mg, 12.0 mmol) in CH_2Cl_2 (10 mL) was added at -5 °C. The above mixture was dropwisely added to the solution of ferrocene (1.86 g, 10 mmol) and CH_2Cl_2 (20 mL) at 0 °C and the solution color changed from orange to bluish violet. Then the reaction mixture was warmed to room temperature and stood for 2 h. The mixture was poured to ice-water and the organic phase was successively washed with 1N HCl solution, water and 5% aqueous Na_2CO_3. The organic layer was dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure to give a crude product. The crude product was purified by recrystallization from petroleum ether (60-90 °C) to give compound **7a** (77.1%).

*Synthesis of Ferrocenecarboxylic acid (**7b**)*[27]

Compound **7a** (2.3g, 10 mmol) was dissolved in anhydrous pyridine (5.0 mL) and I_2 (2.5g, 20 mmol) was added slowly. The mixture was stirred at room temperature for 1 h and heated at 90 °C for 1 h. After standing overnight at room temperature, the solution of NaOH (2.5 g) in water (10 mL) was added and the reaction mixture was stirred at room temperature for 24 h. Then the mixture was neutralized to pH 3 with 10% aqueous HCl and brown precipitate formed. The precipitate was filtered off and washed with water until the filtrate is neutral. The product was dried under high vacuum to obtained compound **7b** (56.0%).

*Synthesis of Chlorocarbonyl ferrocene (**7c**)*[28]

Compound **7b** (1.38g, 6.0mmol) was dissolved in anhydrous toluene (30 mL) and phosphorus trichloride (892.8mg, 6.6mmol) was added. The reaction mixture was stirred at the temperature range of 55-60 °C for 3h until the reaction was completed. The solvent was removed under reduced pressure to give a crude residue and the residue was extracted by petroleum ether (10 mL). The layer of petroleum ether was concentrated in vacuum to give compound **7c** as a dark red crystal (94.0%).

*Synthesis of (3, 4-dimethoxy) benzoyl-ferrocene (**7d**)*[29]

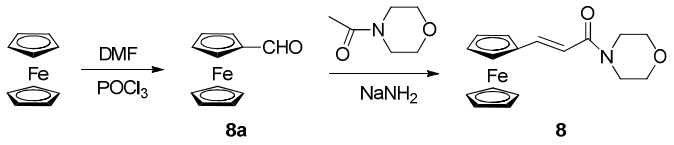
The synthetic procedure was similar to that of compound **1a** and compound **7d** was obtained as an orange-red solid (57.2%).

*Synthesis of (E,Z)- 3-ferrocenyl-3-(3,4-dimethoxyphenyl)-1-morpholinopro-2-en-1-one(**7**)*

The synthetic procedure was similar to that of compound **1** and compound **7** was synthesized from compound **7d** as an orange solid (63.0%): mp 147-149° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, J = 8.2 Hz, 1H, Ph), 6.94 (s, 1H, Ph), 6.88 (d, J = 8.2 Hz, 1H, Ph), 6.27 (s, 1H, CH), 4.37 (s, 2H, C_5H_4), 4.30 (s, 2H, C_5H_4), 4.14 (s, 5H, C_5H_5), 3.92 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.45 (d, J = 11.6 Hz, 4H, OC_2H_4), 3.19 (s, 2H, CH_2N), 3.10 (s, 2H, CH_2N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 149.1, 148.6, 145.9, 131.0, 121.2, 116.3, 112.2, 110.6, 83.9, 77.4, 77.1, 76.9,

69.7, 69.6, 67.9, 56. 2, 56.0, 46.8, 41.5; HRMS (ESI): m/z calcd for $C_{25}H_{27}FeNO_4$ $[M+H]^+$: 461.1290, found 461.1287.

*2.2.3 Synthetic Procedure for Compound **8**(Scheme 3)*



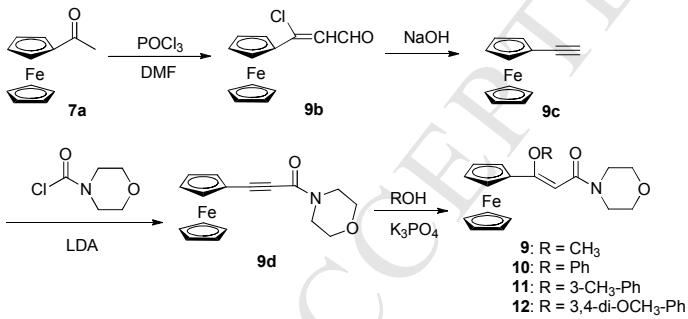
Scheme 3. Synthetic procedure of compound **8**

*Synthesis of Ferrocenylcarbaldehyde(**8a**)*[30]

The mixture of ferrocene (2.79 g, 15 mmol), DMF (2.19 g, 30 mmol) and chloroform (11 mL) was stirred at 0 °C under N_2 atmosphere. Phosphorus oxychloroide (4.59 g, 30 mmol) was added slowly over a period of 30 min at 0 °C and stirred at the temperature range of 55-60 °C for 24 h until the reaction was completed. The mixture was poured into ice-water (100 mL) and neutralized with 5% aqueous Na_2CO_3 accompanying the precipitate formation. The precipitate was filtered off and the filtrate was extracted with 100 mL of toluene. Then the organic phase was washed three times with water, dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on silica gel to give compound **8a** as a crimson solid (75.7%).

*Synthesis of (E)- 3-ferrocenyl-1-morpholinoprop-2-en-1-one(**8**)*
The synthetic procedure was similar to that of compound **1** and compound **8** was obtained as an orange solid from compound **8a** (64%): mp 121-123° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 15.1 Hz, 1H, CH), 6.41 (d, J = 15.1 Hz, 1H, CH), 4.46 (s, 2H, C_5H_4), 4.37 (s, 2H, C_5H_4), 4.15 (s, 5H, C_5H_5), 3.66 (d, J = 51.7 Hz, 8H, C_4H_8NO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 144.0, 112.9, 79.8, 77.4, 77.1, 76.8, 70.5, 69.6, 68.3, 46.1, 42.4; HRMS (ESI): m/z calcd for $C_{18}H_{21}FeNO_3$ $[M+H]^+$: 355.0871, found 355.0866.

*2.2.4 General Synthetic Procedure for Compounds **9-12**(Scheme 4)*



Scheme 4. Synthetic procedure of compounds **9-12**

*Synthesis of 3-chloro-3-ferrocenylacrylaldehyde (**9b**)*[31]

Compound **7a** (2.3 g, 10 mmol) was dissolved in DMF (30 mL) and then phosphorus oxychloroide (6.1 mL) in DMF (20 mL) was added dropwisely at 0 °C under N_2. The reaction mixture was stirred at 0 ° C for 15 min and then warmed to room temperature for 2 h. The mixture was poured to 20% sodium acetate trihydrate (150 mL) solution under N_2 and stirred for 1.5 h. The mixture was extracted with dichloromethane and washed with water. The organic phase was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a crude product. The product was purified by recrystallization from petroleum ether (60-90 °C) and ethyl ether to give compound **9b** (87%).

*Synthesis of Ethynylferrocene (**9c**)*[32]

To a solution of compound **9b** (473.9 mg, 1.73 mmol) in 1,4-dioxane (15 mL) was refluxed under N_2 and 0.5 M NaOH (10mL) solution was added to the system. Then the reaction mixture was refluxed for 5 min and poured to ice-water (50 mL). The mixture was subsequently neutralized by 1M HCl solution and extracted with ethyl ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography on silica gel to give compound **9c** (88%).

*Synthesis of 1-morpholine-3-phenylprop-2-yn-1-one (**9d**)*[33]

Compound **9c** (95.8 mg, 0.456 mmol) was dissolved in THF (2.28 mL) and 1M LDA in THF/hexanes (0.456 mL, 0.456 mmol) was added dropwisely at -78 °C. and then stirred for 10 min. Subsequently, morpholine-4-carbonyl chloride (136 mg, 0.912 mmol) was added and kept for 30 min at -78 °C. The reaction was warmed to room temperature for 1 h and quenched with saturated $NaHCO_3$ solution. Then the mixture was extracted with dichloromethane. The organic layer was successively washed with water, saturated NaCl solution, dried over anhydrous magnesium sulfate, filtered and the filtrate was removed under reduced pressure to give a crude product. The crude product was purified by column chromatography on silica gel to give compound 9d as an orange-red solid (94%): m.p113-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 – 4.48 (m, 2H, C_5H_4), 4.30 – 4.25 (m, 2H, C_5H_4), 4.20 (s, 5H, C_5H_5), 3.74 (d, J = 5.1 Hz, 2H, OCH_2), 3.70 (d, J = 5.1 Hz, 2H, OCH_2), 3.64 (s, 4H, C_2H_4N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 92.5, 78.0, 77.4, 77.1, 76.9, 72.3, 70.2, 77.0 66.8 , 66.4, 60.9, 47.1, 41.8; HRMS (ESI): m/z calcd for $C_{17}H_{17}FeNO_2$ $[M+H]^+$: 323.0609, found 323.0606.

*Synthesis of (E)-3-ferrocenyl-3-methoxy-1-morpholinopro-2-en-1-one (**9**)*

A mixture of compound **9d** (161.5 mg, 0.5 mmol), methanol (16 mg, 0.5 mmol), K_3PO_4 (105.9 mg, 0.5 mmol) and acetonitrile (3 mL) was stirred at 90 °C for 12 h. After the reaction was completed water was added and extracted with dichloromethane. The organic layer was washed with saturated NaCl, dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on silica gel to obtain a khaki solid (82%): m.p 114-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1H, CH), 4.43 (s, 2H, C_5H_4), 4.23 (s, 2H, C_5H_4), 4.14 (s, 5H, C_5H_5), 3.71 (s, 3H, OCH_3), 3.58 (s, 4H, OCH_2), 3.28 (s, 2H, CH_2N), 3.21 (s, 2H, CH_2N); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 160.9, 91.9, 79.1, 77.4, 77.1, 76.9, 69.6, 69.2, 68.3, 55.4, 47.2, 41.9; HRMS (ESI): m/z calcd for $C_{18}H_{21}FeNO_3$ $[M+H]^+$: 355.0871, found 355.0866.

*Synthesis of (E)-3-ferrocenyl-1-morpholinopro-3-phenoxyprop-2-en-1-one (**10**)*

The synthetic procedure was similar to that of compound **9** and compound **10** was obtained as a khaki solid (83%): mp 110-112° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H, Ph), 7.07–6.96 (m, 3H, Ph), 5.92 (s, 1H, CH), 4.49–4.41 (m, 2H, C_5H_4), 4.32–4.25 (m, 2H, C_5H_4), 4.15 (s, 5H, C_5H_5), 3.65 (s, 2H, C_4H_8NO), 3.53 (d, J = 26.6 Hz, 4H, C_4H_8NO), 3.42 (s, 2H, C_4H_8NO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 157.1, 156.4, 129.5, 122.5, 116.2, 104.7, 79.0, 77.4, 77.1, 76.8, 69.9, 69.8, 67.3, 47.2, 41.7; HRMS (ESI): m/z calcd for $C_{23}H_{23}FeNO_3$ $[M+H]^+$: 417.1027, found 417.1020.

*Synthesis of (E)-3-ferroceny-1-morpholino-3-(m-tolyloxy)prop-2-en-1-one(**11**)*

The synthetic procedure was similar to that of compound **9** and compound **11** was obtained as a khaki solid (89%): mp 135-137°

C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, J = 8.3 Hz, 2H, Ph), 6.92 (d, J = 8.5 Hz, 2H, Ph), 5.90 (s, 1H, CH), 4.46 – 4.40 (m, 2H, C_5H_4), 4.31 – 4.25 (m, 2H, C_5H_4), 4.15 (s, 5H, C_5H_5), 3.66 (s, 2H, C_4H_8NO), 3.54 (d, J = 21.2 Hz, 4H, C_4H_8NO), 3.42 (s, 2H, C_4H_8NO), 2.27 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 156.5, 155.0, 131.8, 129.9, 116.0, 104.5, 79.1, 77.4, 77.1, 76.8, 69.8, 67.3, 66.9, 47.3, 41.7, 20.6; HRMS (ESI): m/z calcd for $C_{24}H_{25}FeNO_3$ $[M+H]^+$: 431.1184, found 431.1179.

Synthesis of (Z)-3-ferrocenyl- 3-(3,4-dimethooxyphenoxy)-1-morpholinoprop-2-en-1-one ***12 (Z)***

The synthetic procedure was similar to that of compound **9** and compound **12*(Z)*** was obtained as a khaki solid (68%): mp 192-194^o C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, J = 8.8 Hz, 1H, Ph), 6.66 (d, J = 2.8 Hz, 1H, Ph), 6.51 (dd, J = 8.8, 2.8 Hz, 1H, Ph), 5.89 (s, 1H, CH), 4.46 – 4.41 (m, 2H, C_5H_4) 4.30 – 4.26 (m, 2H, C_5H_4), 4.14 (s, 5H, C_5H_5), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.65 (s, 2H, C_4H_8NO), 3.54 (d, J = 16.1 Hz, 4H, C_4H_8NO), 3.43 (s, 2H, C_4H_8NO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 156.5, 151.2, 149.6, 144.5, 111.6, 106.9, 104.5, 101.4, 79.0, 77.4, 77.1, 76.8, 69.8, 69.8, 67.3, 56.3, 56.1, 47.3, 41.8; HRMS (ESI): m/z calcd for $C_{25}H_{27}FeNO_5$ $[M+H]^+$: 477.1239, found 477.123.

Synthesis of (E)-3-ferrocenyl- 3-(3,4-dimethooxyphenoxy)-1-morpholinoprop-2-en-1-one ***12 (E)***

The synthetic procedure was similar to that of compound **9** and compound **12*(E)*** was obtained as a khaki solid (17%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, J = 9.1 Hz, 1H, Ph), 6.69 – 6.59 (m, 2H, Ph), 4.96 (s, 1H, CH), 4.63 – 4.55 (m, 2H, C_5H_4), 4.34 – 4.28 (m, 2H, C_5H_4), 4.23 (s, 5H, C_5H_5), 3.87 (d, J = 2.5 Hz, 6H, OCH_3), 3.57 (s, 4H, OCH_2), 3.36 (s, 2H, CH_2N), 3.23 (s, 2H, CH_2N).

2.3. Fungicidal Activity Assay

The fungicidal activity determination was conducted by fungi growth inhibition method according to the reference using potato dextrose agar (PDA) as the cultivation medium at 50 μg/mL.[34] Fungi used in this study included *Alternaria solani*, *Fusarium graminearum*, *Phytophthora infestans*, *Phytophthora capsici*, *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Rhizoctonia solani*, *Fusarium oxysporium f. sp. Cucumeris*, *Cercospora arachidicola Hori*, *Physalospora piricola*, *Rhizoctonia cerealis*, *Bipolaris maydis*, *Colletotrichum lagenarium*, *Fusarium moniliforme*. The solution of each compound was prepared at a concentration of 500 μg/mL. Then the above solution (1 mL) was injected into glass Petri dishes, followed by the addition of agar culture medium (9 mL), and then formed some plates of samples (50 μg/mL). An inoculum (4 mm diameter) was diverted from the fringes of active mycelium, and then put in the center of the above plates and incubated at 24±1 ºC. Three replicates were performed. Distilled water containing acetone alone was as a negative control. Dimethmorph and flumorph were used as a positive control. After the mycelia grew completely, the diameter of the mycelia was measured and the inhibition rate calculated according to the formula

$$I = (\bar{D}_1 - \bar{D}_{0\,0})/\bar{D}_1 \times 100\%$$

in which I is the inhibition rate, $\bar{D}_1$ is the average diameter of mycelia in the negative control, and $\bar{D}_0$ is the average diameter of mycelia in the presence of tested compounds.

3. Results and discussion

3.1. Synthesis

The synthetic procedure of compounds **1–6** was shown in scheme 1. Using ferrocene as the starting material compound **1a-6a** was constructed through Friedel-Crafts acylation. Then compound **1-6** was obtained from N-acetylmorpholine through aldol condensation.

The target compound **7** was synthesized from ferrocene as shown in scheme 2. The synthesis of compound **7a** was commenced with ferrocene through Friedel-Crafts acylation. Compounds **7d** were prepared from compound **7a** via haloform reaction, acylation reaction and friedel-crafts acylation. Further aldol condensation using *N*-acetylmorpholine provided compound **7**.

As shown in scheme 3, the compound **8a** was synthesized from ferrocene, and constructed through vilsmeier reaction. Further aldol condensation using *N*-acetylmorpholine provided compound **8**.

The synthesis of compound **9–12** was shown in scheme 4. Treatment of compound **7a** with phosphorus oxychloride gave compound **9a** which was combined with sodium hydroxide to afford compound **9c**. Compound **9** was prepared from compound **9b** via corresponding substitution reaction and addition reaction.

The *Z* configuration products were also obtained during the separation of compounds **1**, **2** and **5**. These *Z* configuration products were characterized by ^{1}H NMR.

3.2. Crystal structure

The molecular structure of compound **3** was determined by single crystal X-ray analysis (Figure 4). The X-ray quality crystal was grown from the solution of chloroform and *n*-hexane.

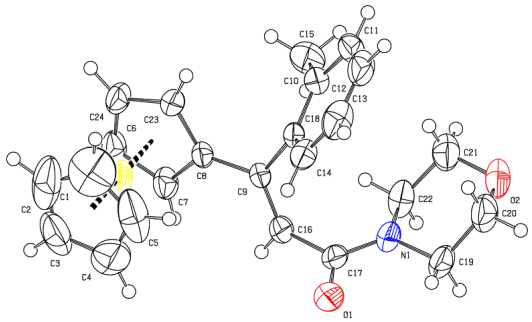


Figure 4. Molecular structure of compound **3**

3.3. Fungicidal activity

The target compounds 1-12 were evaluated for their in vitro antifungal activity on 14 kings of plant fungi at 50mg/kg. The commercial fungicides dimethomorph and flumorph as the controls.

As shown in Table 1, most of compounds displayed moderate fungicidal activity against 14 kinds of phytopathogens at 50 μg/mL. For compounds **1-7**, the fungicidal activities were affected by the substituent on the phenyl ring. The phenyl ring with substituents (compounds **1-7**) exhibited higher activities than the phenyl ring with hydrogen (compound **8**). Compound **6** containing two trifluoromethyl groups at the 3-position and 5-position of phenyl ring exhibited broad-spectrum and good fungicidal activity against 14 kinds of agricultural pathogenic fungi. Compound **8** containing a hydrogen group at the β-position of acryloylmorpholine exhibited much lower activities than compound **1-7**. The compounds with alkoxy or aryloxy at the β-position of acryloylmorpholine exhibited relatively poor activities, for example, compounds **9-12** exhibited worse fungicidal activities than compounds **1-8**. The designed compound **7** gave more than 80% inhibition against *Phytophthora capsici* and compound **5 (Z)** gave more than 70%

inhibition against *Sclerotinia sclerotiorum*. Furthermore, most of the designed compounds exhibited higher activities than two commercial fungicides against 14 kinds of phytopathogens. Two commercial fungicides exhibited specific fungicidal activity against *Phytophthora capsici*, however, both of them had poor fungicidal activities against other plant fungi. On the contrary, the target compounds exhibited a broad-spectrum fungicidal activity in comparison with the two commercial fungicides (Dimethmorph and flumorph) (Table 1). Compounds **7**, **2(*Z*)** and **5(*Z*)** with excellent fungicidal activities were further evaluated for their EC_{50} values (Table 2). As shown in Table 2, the EC_{50} values of Dimethomorph against *Phytophthora capsici* was better then compound 7. The result indicates that the specific fungicidal activity of Dimethomorph against *Phytophthora capsici* was better than compound 7, but compound 7 exhibited more than 60% inhibition rate against five kinds of fungus, which exhibited wider fungicidal spectrum than Dimethomoroh. Dimethomoroh exhibited more than 60% inhibition rate agains only two plant fungus.

Table 1. Fungicidal activities of compounds **1**-**12**, dimethomorph and flumorph against 14 kinds of fungi at 50 μg/mL

compd	Inhibition ratio (%)						
	A. s.[a]	*F. g.*	*P. i.*	*P. c.*	*S. s.*	*B. c.*	*R. s.*
1	31.3	13.9	22.2	25.8	14.0	13.9	21.7
1(*Z*)	25.0	13.9	11.1	35.5	26.0	22.2	19.6
2	31.3	11.1	11.1	32.3	16.0	16.7	15.2
2(*Z*)	31.3	22.2	16.7	41.9	58.0	36.1	39.1
3	31.3	27.8	27.8	48.4	38.0	27.8	41.3
4	25.0	11.1	16.7	41.9	14.0	22.2	34.8
5	25.0	44.4	11.1	29.0	12.0	22.2	10.9
5(*Z*)	31.3	41.7	41.7	38.7	78.0	41.7	26.1
6	43.8	38.9	44.4	45.2	50.0	33.3	41.3
7	18.8	38.9	11.1	80.6	38.0	22.2	32.6
8	12.5	19.4	11.1	29.0	16.0	27.8	32.6
9	31.6	22.2	20.0	24.1	49.3	10.8	32.9
10	42.1	41.7	36.0	34.5	57.7	13.5	39.5
11	31.6	25.0	36.0	27.6	47.9	27.0	39.5
12	15.8	8.3	24.0	20.7	31.0	5.4	6.6
12(*E*)	21.1	8.3	28.0	17.2	35.2	16.2	18.4
DM[b]	18.8	19.4	16.7	100.0	40.0	22.2	17.4
FM[b]	12.5	13.9	11.1	100.0	14.0	13.9	15.2

[a] *A. s.* = *Alternaria solani*, *F. g.* = *Fusarium graminearum*, *P. i.* = *Phytophthora infestans*, *P. c.* = *Phytophthora capsici*, *S. s.* = *Sclerotinia sclerotiorum*, *B. c.* = *Botrytis cinerea*, *R. s.*= *Rhizoctonia solani*. [b] DM = Dimethomorph, FM = Flumorph

Table 1-continued

compd	Inhibition ratio (%)						
	F. o[a].	*C. a.*	*P. p.*	*R. c.*	*B. m.*	*C. l.*	*F. m.*
1	32.3	35.0	37.2	44.6	30.3	26.9	35.0
1(*Z*)	29.0	30.0	53.5	44.6	30.3	38.5	35.0
2	25.8	30.0	60.5	53.6	33.3	26.9	40.0
2(*Z*)	32.3	30.0	53.5	60.7	33.3	38.5	40.0
3	38.7	40.0	58.1	58.9	39.4	38.5	45.0
4	35.5	40.0	25.6	60.7	42.4	38.5	45.0
5(*E*)	29.0	40.0	67.4	53.6	42.4	38.5	40.0
5(*Z*)	25.8	50.0	44.2	46.4	42.4	42.3	40.0
6	16.1	20.0	48.8	50.0	42.4	30.8	40.0
7	45.2	60.0	51.2	66.1	63.6	53.8	60.0
8	25.8	20.0	51.2	17.9	36.4	26.9	30.0
9	16.7	9.5	27.3	5.6	10.5	10.7	3.7
10	16.7	23.8	43.6	33.3	26.3	32.1	25.9
11	13.9	14.3	34.5	33.3	15.8	17.9	18.5
12	8.3	9.5	27.3	29.6	13.2	17.9	7.4
12(*E*)	16.7	14.3	38.2	42.6	31.6	25.0	18.5
DM[b]	22.6	50.0	62.8	39.3	33.3	26.9	30.0
FM[b]	32.3	25.0	58.1	30.4	27.3	34.6	20.0

[a] *F. o.* = *Fusarium oxysporium* f. sp. *Cucumeris*, *C. a.*= *Cercospora arachidicola Hori*, *P. p.*= *Physalospora piricola*, *R. c.*= *Rhizoctonia cerealis*, *B. m.* = *Bipolaris maydi*, *C. l.* = *Colletotrichum lagenarium*, *F. m.* = *Fusarium moniliforme*. [b] DM = Dimethomorph, FM = Flumorph.

Table 2. EC_{50} Values of **7**, **2(*Z*)** and **5(*Z*)** against *Phytophthora capsici* and *Sclerotinia sclerotiorum*,

compd	EC_{50} (μg/mL)		Toxicity equation
	P. c.[a]	*S. s.*	
2(*Z*)	-[b]	40.55	y = 1.3707x + 2.7959, r = 0.9938
5(*Z*)	-	30.24	y = 2.0539x +1.9590, r = 0.9859
7	14.76	-	y = 1.7099x + 3.0010, r = 0.9866,
Dimethomorph	0.11	-	y = 1.6550x + 6.5558, r = 0.9930

[a] *P. c.* = *Phytophthora capsici*, *S. s.* = *Sclerotinia sclerotiorum*, [b] "–": not tested, EC_{50}: concentration for 50% of maximal effect.

4. Conclusions

In conclusion, on the basis of the structure of dimethomorph, a series ferrocenyl dimethomorph derivatives were synthesized and valued for their fungicidal activity against 14 kinds of phytopathogens. The bioassay results indicated that most of compounds showed moderate fungicidal activities, and certain compounds displayed fungicidal activities higher than that of commercial dimethomorph. When ferrocenyl was employed into the skeleton of dimethomorph, the fungicidal activities were enhanced, and the fungicidal spectrum was broadened. As the unique biological activity of ferrocene, the development of ferrocene fungicides has been promoted, and the fungicidal activities of the designed compounds should be useful for future new active compound design and development.

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Highlights

·Twelve novel 3-Ferrocenyl-*N*-Acryloylmorpholine compounds were synthesized and characterized.

·Single crystal X-ray characterization of novel compound 3.

·Compound 7 exhibited a broad- spectrum fungicidal activity.

·Compound 5(*Z*) exhibited better fungicidal activity against *Sclerotinia sclerotiorum* than that of 5(*E*).