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Synthesis, characterization, and biological evaluation of novel ferrocene-triadimefon analogues

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Abstract

In order to improve biological behavior of the 1*H*-1,2,4-triazole derivatives, a series of new ferrocene-analogues of commercial triadimefon were synthesized and their antifungal and plant growth regulatory activities evaluated. These organometallic analogues showed lower antifungal activity than parent triadimefon, but exhibited promising plant growth regulatory activity.

Keywords: Ferrocene; Triadimefon; Antifungal activity; Plant growth regulatory activity

1. Introduction

Nowadays, invasive fungal infections, ranking alongside bacterial infections, have become a major cause of morbidity and mortality in seriously debilitated and immunocompromised patients [1]. Relatively, seriously insuppressible mildews and rusts have arose from invasive fungal infections on all kinds of agricultural and horticultural species [2]. 1*H*-1,2,4-Triazole derivatives (Chart 1), such as agrochemicals triadimefon (**1**), triadimenol (**2**), flusilazole, bitertanol, cyproconazole, etc. [3] and clinical drugs fluconazole (**3**) and itraconazole (**4**) [4], are a class of biologically significant compounds which were widely used as antifungal agents against mildews and rusts of cereal grains, fruits, vegetables, and ornamentals, or clinically against topical or disseminated *Candida* spp. and *Aspergillus* spp. These compounds inhibit fungal proliferation by their interference with steroid biosynthesis and fungal cell-wall formation mediated by cytochrome P450-dependent 14α-sterol demethylase ($P450_{DM}$), an important enzyme in ergosterol biosynthesis in fungi and cholesterol synthesis in mammalian cells [5].

However, with extensive application in agriculture and horticulture, triadimefon and triadimenol are suspected of having teratogenic potential such as craniofacial and axial skeletal defects on the basis of developmental toxicity studies on rodent mammals [6]. It has also been ascertained that triadimefon and triadimenol can produce a neurotoxic syndrome in rats characterized by increased motor activity, stereotyped behaviors, and altered monoamine metabolism due to inhibition of dopamine uptake [7]. And besides, triadimefon had a significant stimulating side effect on respiration at a concentration of 1–100 mg/kg and on inhibition of nitrification in soil at a concentration of 100 mg/kg [8]. Although few data are available on the effect of agrochemical triazoles on human pregnancy, the effect of the clinical drug fluconazole on newborns has been well documented. Long-term or high-dose maternal fluconazole therapy is probably related to an increased teratological risk, reported craniofacial and limb abnormalities in newborns [9].

Recently, increasing interests have been focused on developing structural variations of established drugs by

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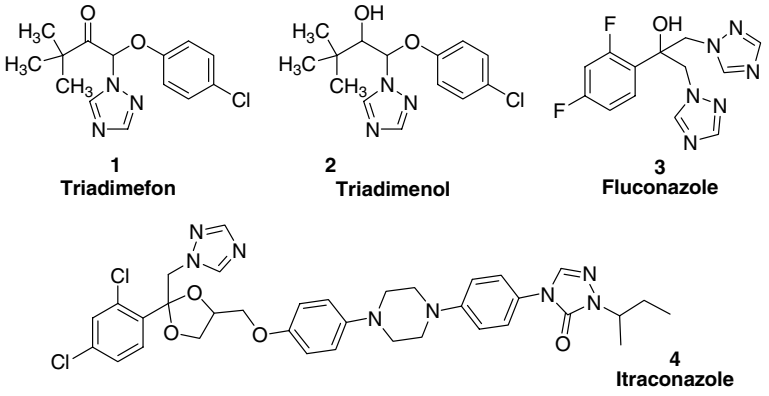


Chart 1.

metallocenic organometallic compounds as alternatives of the chemotherapy of drug-resistance in cancer and tropical diseases [10]. The stability, non-toxicity and readily membrane-permeation of the ferrocenyl group, the accessibility of a large variety of derivatives, as well as its favorable electrochemical properties have made ferrocene and its derivatives very suitable for biological applications and for conjugation with biomolecules [11]. Several structural modification of established drugs with ferrocenyl moiety have been reported, such as ferrocene fluconazole [12], ferrocene aspirin [13], the anti-malarial drugs chloroquine (termed ferroquine), quinine, mefloquine, and artemisinin [14], and the anti-cancer drug tamixofen (termed ferrocifen) [15].

As part of our continual program in pursuit of novel biological molecules containing 1*H*-1,2,4-triazole moiety, a class of novel triadimefon analogues **10a**–**j** structurally modified by ferrocenyl group was designed and synthesized for improving biological behavior (Chart 2). We herein reported their chemistry and biological screening results involving antifungal and plant growth regulatory activity.

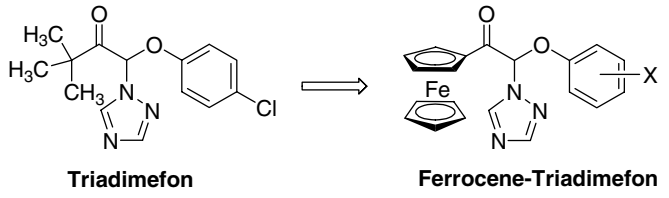


Chart 2.

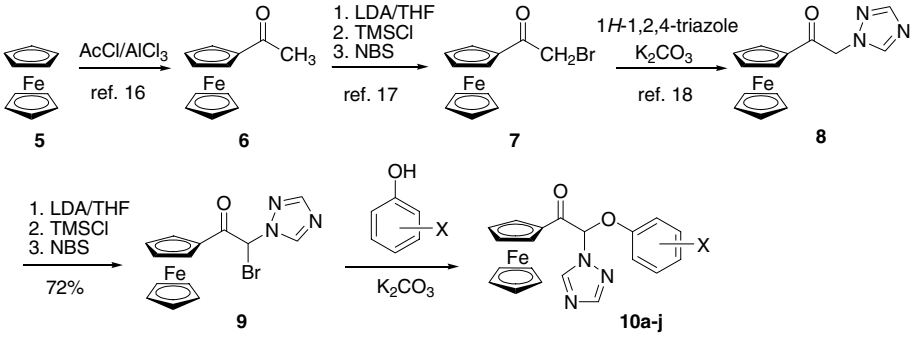
2. Results and discussion

2.1. Synthesis of ferrocene-triadimefon analogues

As shown in Scheme 1, our synthesis of the title compounds **10a**–**j** was started from commercial ferrocene **5**. The intermediates, acetylferrocene (**6**), α-bromoacetylferrocene (**7**), and α-(1*H*-1,2,4-triazol-1-yl)acetylferrocene (**8**) were prepared according to the previous literatures' methods in a yield of 93%, 80%, and 95%, respectively [16–18].

Attempt to direct bromination of α-(1*H*-1,2,4-triazol-1-yl)acetylferrocene (**8**) under conventional conditions, such as Br_2/HOAc, NBS in CH_3CN or CS_2, NBS/azobis(isobutyronitrile) (AIBN), and etc., caused a decomposed mixture of original materials. Thus, the key intermediate **9** was prepared utilizing similar bromination method described by Tarraga and co-workers [17].

Originally, substitution reactions of bromide **9** by various phenols were conducted utilizing sodium hydride as base in anhydrous tetrahydrofuran (THF), and low yields were reached because of insolubility of sodium phenoxyl in THF. Thus, anhydrous potassium carbonate was used as base instead of sodium hydride and reactions were carried out in anhydrous acetonitrile under elevated temperature. After conventional workup, the target ferrocene-



Scheme 1.

triadimefon analogues **10a–j** were readily obtained in good to excellent yields.

2.2. Single crystalline X-ray diffraction analysis of ferrocene-triadimefon analogues

To confirm their structures and explore steady conformation of this type of ferrocene-triadimefon derivatives, the structure of compound **10f** was investigated by a single crystalline X-ray diffraction analysis (Fig. 1). In the crystal cell, due to the bulkiness of ferrocenyl group, the substituted aryl group was spatially repulsed and swerved to nearby triazole group.

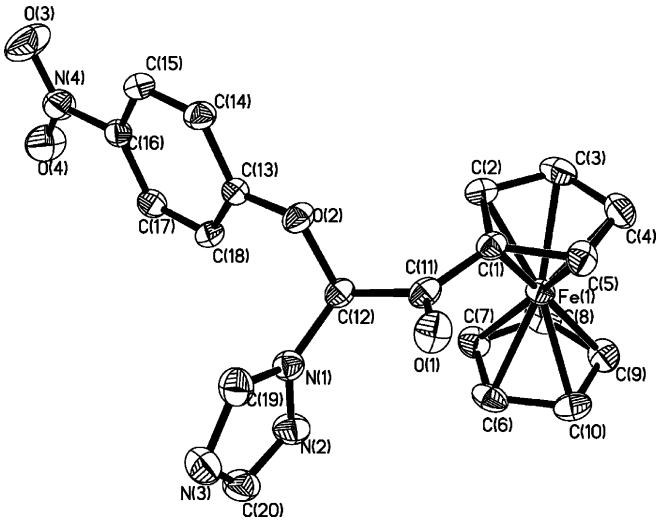


Fig. 1. Molecular structure and crystallographic numbering scheme for compound **10f** (Hydrogen atoms were omitted for clarification). Selected bond lengths (Å): Fe1–C1 2.028(2); Fe1–C2 2.027(2); Fe1–C5 2.043(2); Fe1–C6 2.042(2); C1–C11 1.450(3); O1–C11 1.211(3); O2–C12 1.413(3); O2–C13 1.383(3): C11–C12 1.543(3); N1–C12 1.441(3); N1–N2 1.356(3); N3–C19 1.314(3); N2–C20 1.313(3); N3–C19 1.314(3); N3–20 1.342(4). Selected bond angles (°): C2–Fe1–C1 41.41(9); C2–Fe1–C7 108.28(11); C1–Fe1–C7 122.39(10); C2–Fe1–C8 120.97(11); C7–Fe1–C8 40.35(10); C5–C1–C2 107.5(2); C5–C1–C11 124.7(2); C2–C1–C11 127.4(2); C13–O2–C12 118.13(17); C19–N1–N2 109.6(2); C19–N1–C12 130.9(2); N3–C19–N1 110.5(2); N2–C20–N3 115.8(2).

2.3. Biological evaluation

2.3.1. Antifungal activity

Compounds **10a–j** were assayed for antifungal activities against mildew and rusts on intravital wheat plants, including five selected fungi *Isariopsis clavispora*, *Bremia lactucae*, *Cladosporium fulvum*, *Erysiphe graminis*, and *Alternaria mali*, according to procedures described previously [19]. The screening results were outlined in Table 1.

To our disappointment, all the tested compounds showed lower antifungal activity against all fungi than parent triadimefon. As far as we know, a linkage between the triazole ring and substituted aryl group via no more than two atoms is essential for their fungicidal activity. Besides, we have proved that an extended backbone linking the triazole group and aryl group in an almost linear fashion possesses higher antifungal activity than a distorted backbone [20]. It is the bulkiness of ferrocenyl group that make a distorted backbone linking the triazole group and aryl group adopted. In addition, it is well known that the antifungal activities of the triazole derivatives are related to their interference with steroid biosynthesis and fungal cell-wall formation mediated by ferrous cytochrome-P450 enzymes [5]. It was also hypothesized that binding of the triazole to ferrous atom of cytochrome-P450 enzymes was replaced with binding of the triazole to ferrous atom of ferrocene group by intramolecular or intermolecular interaction, as a result, the antifungal activities of title compounds **10a–j** was depressed.

2.3.2. Plant growth regulatory activity

Plant growth regulatory activities of new ferrocene-triadimefon derivatives **10a–j** were tested using cucumber cotyledon rhizogenesis method (see Section 4.3.). The plant growth regulatory activity data for compounds **10a–j** were shown in Table 1.

Table 1
Antifungal and plant growth regulatory activity of compounds **10a–j**

Compound	Substituted X	Antifungal activity (relative inhibitory ratio, %)[a]					Plant growth regulatory activity (%)[b]
		I. clavispora	*B. lactucae*	*C. fulvum*	*E. graminis*	*A. mali*	
10a	4-Cl	15.6	26.7	13.0	11.9	20.0	+60.0
10b	2,4-Cl_2	15.6	26.7	13.0	14.3	20.0	+50.0
10c	2,5-Cl_2	15.6	26.7	0	11.9	30.0	+40.0
10d	2,4,5-Cl_3	15.6	26.7	0	11.9	20.0	+40.0
10e	2,4,6-Cl_3	15.6	26.7	13.0	11.9	20.0	+16.6
10f	4-NO_2	23.3	26.7	0	16.6	20.0	+68.1
10g	3-CH_3-6-Cl	23.3	33.3	13.0	16.6	30.0	+16.3
10h	2,4-Br_2	15.6	26.7	13.0	11.9	20.0	+93.9
10i	1-Naphthoxy	15.6	33.3	0	14.3	30.0	+76.7
10j	2-Naphthoxy	15.6	26.7	0	11.9	20.0	+98.2
Triadimefon	–	92.8	76.2	42.8	56.6	96.6	+57.1

[a] Antifungal activity was assayed on intravital wheat plants at a concentration of 50 mg/L.
[b] Plant growth regulatory activity was assayed using cucumber cotyledon rhizogenesis method at a concentration of 10 mg/L.

To our surprise, although these novel triadimefon analogues exhibited lower antifungal activities against various fungi than parent triadimefon, screening data displayed that all of them had excellent plant growth regulatory activity. The target compounds **10a**–**j** obvious promoted cotyledon rhizogenesis of cucumber seed at a concentration of 10 mg/L. In comparison with parent triadimefon, compounds **10e** and **10g** showed lower activity than the parent triadimefon, the ferrocenee analogue **10a**, **10f** and **10i** had a comparative activity while compounds **10h** and **10j** displayed more highly promoting activity.

With respect to ineffective antifungal activity and promising plant growth regulatory activity of these ferrocene-triadimefon derivatives, it could be inferred that these triazole derivatives might share different action mechanism between fungicidal activity and plant growth regulator activity. However, to prove this possibility, further chemical and biological investigation is needed to clarify action modes of these novel ferrocene-triadimefon analogues.

3. Conclusion

In search of potentially biological molecules containing 1*H*-1,2,4-triazole moiety, a series of new ferrocene-triadimefon analogues were synthesized and their antifungal and plant growth regulatory activity assayed. These ferrocenyl-substituted derivatives showed lower antifungal activity than parent triadimefon, while exhibited unexpectedly promising plant growth regulatory activity.

4. Experimental

All reactions were carried out under nitrogen atmosphere and monitored by conventional TLC method. THF was distilled on CaH_2 and acetonitrile was distilled on anhydrous $CaCl_2$ prior to use. All melting points were determined on a Taike hotplate melting apparatus and thermometer was uncorrected. The ^{1}H NMR spectra were measured on a Bruker Ultra-300 spectrometer in d_6-DMSO solution with TMS as internal standard. Elemental analyses were determined on an MT-3 elemental analyzer within $\pm 5‰$ of the theoretical values. Mass spectra were recorded on a HP-5988A GC–MS instrument at 70 eV, and the temperature of ionization was 200 °C. Acetylferrocene (**6**), α-bromoacetylferrocene (**7**), and α-(1*H*-1,2,4-triazol-1-yl)acetylferrocene (**8**) were prepared according to the literatures' methods in a yield of 93%, 80%, and 95%, respectively [16–18].

4.1. 2-Bromo-2-(1H-1,2,4-triazol-1-yl)acetylferrocene (9)

To a well stirred LDA (72.3 mmol) solution in THF (20 mL) was dropwise added a solution of α-(1*H*-1,2,4-triazol-1-yl)acetylferrocene (**8**) in THF (20 mL) at −78 °C during a period of 30 min. After stirred at that temperature for 2 h, trimethylchlorosilane (57 mmol) was run into the mixture in one portion. The reaction mixture was stirred for another 4 h at −78 °C and *N*-bromosuccinimide (57 mmol) was added in small portions. The cool bath was then removed and the reaction was not quenched until room temperature was reached. After conventional workup and separation by flash column chromatography, 2-bromo-2-(1*H*-1,2,4-triazol-1-yl)acetylferrocene (**9**) was obtained as deep red crystal in 72.7% yield, m.p. 114–116 °C (after recrystallization from acetone-petroleum ether (V/V 1:1)), ^{1}H NMR δ (300 MHz, d_6-DMSO): 8.24 (1H, s, C3′, triazole), 8.08 (1H, s, C5′, triazole), 6.48 (1H, s, CHBr), 4.30 (2H, s, metallocene), 4.22 (2H, s, metallocene), 4.14 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 373. Anal. Calc. for $C_{14}H_{12}BrFeN_3O$: C 44.96, H 3.23, N 11.23. Found: C 44.70, H 3.19, N 11.10%.

4.2. General procedure for synthesis of 2-aryloxy-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanones (10a–j)

To a suspension solution of 2-bromo-2-(1*H*-1,2,4-triazol-1-yl)acetylferrocene (**9**) (2.7 mmol) and anhydrous potassium carbonate (2.835 mmol) in dry acetonitrile (10 mL) was added substituted phenols (2.835 mmol) in one portion at room temperature. The mixture was stirred and warmed to reflux for 2 h. The cooled mixture was run into a 10% aqueous NaOH solution (50 mL) and resulting precipitate was collected by filtration. Recrystallization from ethyl acetate-petroleum ether (v/v 1:1) gave title compounds, 2-aryloxy-1-ferrocenyl-2-(1*H*-1,2,4-triazol-1-yl) ethanone derivatives (**10a**–**j**).

4.2.1. 2-(4-Chlorophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (10a)

Orange yellow solid; yield 88.1%; m.p. 165–167 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 9.00 (1H, s, C3′, triazole), 8.18 (1H, s, C5′, triazole), 7.48–7.23 (4H, m, aryl), 7.42 (1H, s, CHTr), 4.97 (2H, s, metallocene), 4.86 (1H, s, metallocene), 4.77 (1H, s, metallocene), 4.30 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 422. Anal. Calc. for $C_{20}H_{16}ClFeN_3O_2$: C 56.97, H 3.82, N 9.97. Found: C 56.88, H 3.79, N 10.02%.

4.2.2. 2-(2,4-Dichlorophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (10b)

Red solid; yield 86.6%; m.p. 151–152 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 8.94 (1H, s, C3′, triazole), 8.18 (1H, s, C5′, triazole), 7.71–7.32 (3H, m, aryl), 7.50 (1H, s, CHTr), 5.01 (1H, s, metallocene), 4.92 (1H, s, metallocene), 4.88 (1H, s, metallocene), 4.74 (1H, s, metallocene), 4.29 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 456. Anal. Calc. for $C_{20}H_{15}Cl_2FeN_3O_2$: C 52.67, H 3.31, N 9.21. Found: C 52.78, H 3.48, N 9.41%.

4.2.3. 2-(2,5-Dichlorophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (10c)

Deep red solid; yield 63.0%; m.p. 173–175 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 9.19 (1H, s, C3′, triazole), 8.25 (1H, s, C5′, triazole), 7.71–6.46 (3H, m, aryl), 7.57 (1H,

s, CHTr), 5.02 (1H, s, metallocene), 4.93 (1H, s, metallocene), 4.89 (1H, s, metallocene), 4.75 (1H, s, metallocene), 4.31 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 456. Anal. Calc. for $C_{20}H_{15}Cl_2FeN_3O_2$: C 52.67, H 3.31, N 9.21. Found: C 52.69, H 3.38, N 9.35%.

4.2.4. 2-(2,4,5-Trichlorophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10d**)

Yellow solid; yield 81.3%; m.p. 175–177 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 8.95 (1H, s, C3′, triazole), 8.18 (1H, s, C5′, triazole), 7.95 (1H, s, aryl), 7.78 (1H, s, aryl), 7.67 (1H, s, CHTr), 5.00 (1H, s, metallocene), 4.92 (1H, s, metallocene), 4.75 (2H, s, metallocene), 4.30 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 490. Anal. Calc. for $C_{20}H_{14}Cl_3FeN_3O_2$: C 48.97, H 2.88, N 8.57. Found: C 49.09, H 3.04, N 8.73%.

4.2.5. 2-(2,4,6-Trichlorophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10e**)

Orange yellow solid; yield 80.5%; m.p. 196–198 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 8.85 (1H, s, C3′, triazole), 8.15 (1H, s, C5′, triazole), 7.81 (2H, s, aryl), 7.20 (1H, s, CHTr), 5.03 (1H, s, metallocene), 4.82 (1H, s, metallocene), 4.71 (1H, s, metallocene), 4.48 (1H, s, metallocene), 4.29 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 490. Anal. Calc. for $C_{20}H_{14}Cl_3FeN_3O_2$: C 48.97, H 2.88, N 8.57. Found: C 49.07, H 2.78, N 8.58%.

4.2.6. 2-(4-Nitrophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10f**)

Red solid; yield 75.0%; m.p. 159–160 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 9.04 (1H, s, C3′, triazole), 8.18 (1H, s, C5′, triazole), 7.31–7.43 (4H, m, aryl), 7.76 (1H, s, CHTr), 4.97 (2H, s, metallocene), 4.86 (1H, s, metallocene), 4.77 (1H, s, metallocene), 4.31 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 432. Anal. Calc. for $C_{20}H_{16}FeN_4O_4$: C 55.58, H 3.73, N 12.96. Found: C 55.50, H 3.70, N 13.05%.

4.2.7. 2-(3-Methyl-6-chlorophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10g**)

Pale red solid; yield 50.3%; m.p. 140–142 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 8.95 (1H, s, C3′, triazole), 8.14 (1H, s, C5′, triazole), 7.46–7.08 (3H, m, aryl), 7.26 (1H, s, CHTr), 4.96 (2H, s, metallocene), 4.85 (1H, s, metallocene), 4.77 (1H, s, metallocene), 4.30 (5H, s, metallocene), 2.31 (3H, s, CH_3); EIMS (M^+) *m*/*z*: 436. Anal. Calc. for $C_{21}H_{18}ClFeN_3O_2$: C 57.89, H 4.16, N 9.64. Found: C 58.06, H 4.29, N 9.43%.

4.2.8. 2-(2,4-Dibromophenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10h**)

Red solid; yield 83.2%; m.p. 140–142 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 8.92 (1H, s, C3′, triazole), 8.18 (1H, s, C5′, triazole), 7.92–7.24 (3H, m, aryl), 7.51 (1H, s, CHTr), 4.99 (1H, s, metallocene), 4.92 (1H, s, metallocene), 4.86 (1H, s, metallocene), 4.75 (1H, s, metallocene), 4.29 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 545. Anal. Calc. for $C_{20}H_{15}Br_2FeN_3O_2$: C 44.08, H 2.77, N 7.71. Found: C 44.07, H 2.66, N 7.61%.

4.2.9. 2-(1-Naphthenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10i**)

Red solid; yield 82.0%; m.p. 173–175 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 9.03 (1H, s, C3′, triazole), 8.19 (1H, s, C5′, triazole), 7.94–7.39 (7H, m, aryl), 7.92 (1H, s, CHTr), 4.96 (2H, s, metallocene), 4.75 (2H, s, metallocene), 4.30 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 437. Anal. Calc. for $C_{24}H_{19}FeN_3O_2$: C 65.92, H 4.38, N 9.61. Found: C 65.91, H 4.39, N 9.70%.

4.2.10. 2-(2-Naphthenoxy)-1-ferrocenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**10j**)

Purple red solid; yield 81.6%; m.p. 152–154 °C; ^{1}H NMR δ(300 MHz, d_6-DMSO): 8.95 (1H, s, C3′, triazole), 8.16 (1H, s, C5′, triazole), 7.97–7.40 (7H, m, aryl), 7.70 (1H, s, CHTr), 4.99 (2H, s, metallocene), 4.77 (2H, s, metallocene), 4.30 (5H, s, metallocene); EIMS (M^+) *m*/*z*: 437. Anal. Calc. for $C_{24}H_{19}FeN_3O_2$: C 65.92, H 4.38, N 9.61. Found: C 65.90, H 4.37, N 9.74%.

4.3. Biological evaluation

4.3.1. Antifungal activity

Antifungal activity of the title compounds **10a**–**j** were assayed against powdery mildew and brown rust on intravital wheat plants at the Biological Assay Centre, Nankai University according to procedures described previously [19]. The five selected fungi included *I. clavispora*, *B. lactucae*, *C. fulvum*, *E. graminis*, and *A. mali*.

4.3.2. Plant growth regulatory activity

Plant growth regulatory activity of compounds **10a**–**j** was screened using cucumber cotyledon rhizogenesis method at the same department as above. The detailed procedure was described as following:

After dipped in distilled water for 1 h at 23 °C, the cucumber seed (JINKE, No. 4, commercial availably) was then sowed into soil with 0.7% agar at a covered porcelain enamel plate and incubated at 26 °C in a darkroom for 3 days. The same size cotyledons were carefully selected to subsequent biological assay. The tested compound (3 mg) was resolved in *N*,*N*-dimethylformamide (3 mL) and this solution was then diluted to 10% concentration with distilled water. A sample solution (0.3 mL) was sprayed over a 6-cm diameter filter paper and solvent was volatilized to dryness on air. The filter paper thus prepared was placed into a 6-cm diameter incubation vessel and soaked with 10 mL distilled water. Finally, ten pieces of the same size cotyledons were added into incubation vessel. These cotyledons were incubated at 26 °C in a darkroom for 5 days. At that moment, the rhizogenesis numbers of every ten pieces of hypocotyls were measured. Each sample was repeated twice. In contrast, the distilled water was used as control experiment.

The relative ratios of cucumber cotyledon rhizogenesis were calculated according to the following formula:

Relative ratio $\% = (N_S - N_C)/N_C \times 100\,\%$, where N_S and N_C are the numbers of cucumber cotyledon rhizogenesis of tested compound and control experiment, respectively.

5. Supplementary material

Crystallographic data for compound **10f** has been deposited with the Cambridge Crystallographic Data Center, CCDC No. 279 272. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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