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RESEARCH ARTICLE

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Synthesis, structure and biological activity of 1-(1-methoxy-1-ferrocenyl-3-arylpropan-2-yl)-1H-1,2,4-triazole derivatives

Abstract A total of eleven new 1-(1-methoxy-1-ferrocenyl-3-arylpropan-2-yl)-1H-1,2,4-triazole derivatives have been synthesized from acetylferrocene. The structures of the title compounds have been determined by elemental analysis, ^{1}H-NMR and single crystal X-ray diffraction analysis. Bioassay showed that some of the title compounds had high plant-growth regulatory activity.

Keywords 1H-1,2,4-triazole, ferrocene, fungicidal activity, plant-growth regulatory activity

1 Introduction

Since its discovery, ferrocene and its derivatives have received extensive attention from various communities owing to their unique chemical structure. Over the past decades, biological activity research related to ferrocene and its derivatives has been promptly impelled and manifested revealing that these ferrocene-containing compounds have wide biological activities such as anti-tumor [1], antifungai [2], insecticidal [3], anti-inflammation [4] and anti-malaria [5]. A successful example is a ferrocene-chloroquine analogue, i.e., ferrochloroquine (FQ), in which one ferrocene unit was integrated into chloroquine (CQ). In vitro, for the inhibition of chloroquino-resistant strains of *Plasmodium falciparum* [6], FQ was 22 times more active than CQ. Following our continual research with respect to novel have sought to incorporate ferrocenyl unit into biological active triazole compounds. In the present study, a series 1H-1,2,4-triazole compounds with potent biological activities, we of novel ferrocene-containing 1H-1,2,4-triazole compounds were designed and synthesized (Scheme 1), and their structures were characterized by ^{1}H-NMR spectra data and crystal X-ray diffraction analysis. Bioassay revealed that some of these compounds showed predominant plant-growth regulatory activity.

2 Experimental

2.1 General comments

^{1}H-NMR spectra data were record on a Brucker AC-P 300 Ultrashield spectrometer in DMSO-d_6 solution with TMS as internal standard. Elemental analyses were determined on a Yanaco CHN Corder elemental analyzer. All melting points were determined on a Taike apparatus and thermometer was uncorrected. All reagents were of analytic pure grade and THF was distilled over Na-benzophenone system prior to use. All reactions were carried out under nitrogen and monitored by TLC.

2.2 Synthesis of the title compounds

2.2.1 Preparation of intermediates

Compounds **1** and **2** were prepared according to literature method [7, 8], and compounds **3** and **4** were synthesized according to our established procedures [9, 10].

2.2.2 General procedure for synthesis of compound **5**

To a well stirred solution of compound **4a** (0.77 g, 2.0 mmol)

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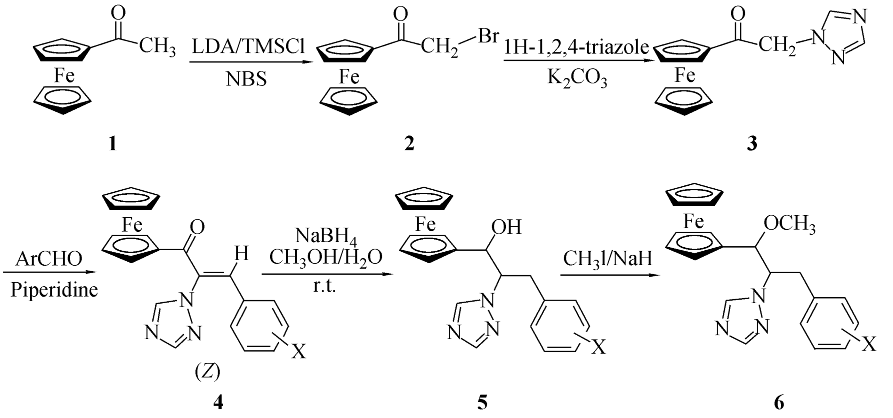

Scheme 1. Syntheses of the title compounds

in 20 mL methanol and 5 mL water was added $NaBH_4$ (0.23 g, 6.0 mmol) in small portions at ambient temperature. After stirring for 1 day at room temperature, the reaction mixture was acidified to pH 6 with 2 N hydrochloride, then was extracted with dichloromethane (30 mL × 3). The organic phase was washed once with saturated NaCl solution and dried over anhydrous MgSO4. After filtration, the solvent was removed under reduced pressure and the residue was separated by column chromatography with petroleum ether-ethyl acetate (*V*:*V* 1:1) as the eluent. Pure product **5a** was obtained as a light yellow solid, 0.49 g (yield 63.3%). Recrystallization from acetone-petroleum ether (60–90℃) gave a yellow crystal, *m.p.* 165–167℃.

2.2.3 General procedure for synthesis of compound 6

To a suspension solution of sodium hydride (1.6 mmol) in THF (2 mL) was added a solution of compound **5f** (0.16 g, 0.4 mmol) and iodomethane (0.05 mL, 0.8 mmol) in THF (2 mL) one portion at 45–50℃ by syringe. After stirring for another 40 min under this condition, the reaction mixture was cooled to room temperature and water (2 mL) was added. The mixture was extracted by ethyl ether (10 mL × 3) and the combined ether layers were washed by saturated NaCl solution. After drying over anhydrous $MgSO_4$ and filtration, the solvent was removed under reduced pressure and the residue was separated by column chromatography with petroleum ether-ethyl acetate (*V*:*V* 1:1) as the eluent. Pure product **6f** was obtained as yellow solid, 0.16 g (97 % yield). Recrystallizaiton from ether-petroleum ether (*V*:*V* 1:1) gave the pure sample, *m.p.* 112–114℃.

1-(1-methoxy-1-ferrocenyl-3-phenyl-propan-2-yl)-1H-1,2,4-triazole (**6a**)

Light yellow crystal, yield 93.0 %, *m.p.* 109–111 ℃. Anal. Calcd. for $C_{22}H_{23}N_3FeO$ C 65.85, H 5.78, N 10.47; Found. C 65.59, H 5.77, N 10.47. ^{1}H-NMR (δ) (DMSO- d_6, 300 MHz): 8.29 (s, 1H, $TrH_{C3'}$), 7.86 (s, 1H, $TrH_{C5'}$), 7.21–7.02 (m, 5H, PhH), 4.78 (m, 1H, —O—C$\underline{H}$—CH—Tr), 4.34 (d, 4H, *J* = 5 Hz, C_5H_4Fe), 4.16 (s, 5H, C_5H_5Fe), 4.14 (s, 3H, OCH_3), 3.86 (m, 1H, —O—CH—C$\underline{H}$—Tr), 3.12 (m, 2H, PhC$\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(p-methylphenyl)-propan-2-yl)-1H-1,2,4-triazole (**6b**)

Light yellow crystal, yield 93.8%, *m.p.* 86–88℃. Anal. Calcd. for $C_{23}H_{25}N_3FeO$ C 66.52, H 6.07, N 10.12; Found. C 66.49, H 5.89, N 10.38. ^{1}H-NMR (δ) (DMSO- d_6, 300 MHz): 8.28 (s, 1H, $TrH_{C3'}$), 7.86 (s, 1H, $TrH_{C5'}$), 6.99 (d, 2H, *J* = 9 Hz, PhH), 6.90 (d, 2H, *J* = 9 Hz, PhH), 4.74 (m, 1H, —O—C$\underline{H}$—CH—Tr), 4.32 (d, 4H, *J* = 5 Hz, C_5H_4Fe), 4.18 (s, 5H, C_5H_5Fe), 4.14 (s, 3H, OCH_3), 3.87 (m, 1H, —O—CH—C$\underline{H}$—Tr), 3.06 (m, 2H, PhC$\underline{H_2}$), 2.20 (s, 3H, $PhCH_3$).

1-(1-methoxy-1-ferrocenyl-3-(p-methoxylphenyl)-propan-2-yl)-1H-1,2,4-triazole (**6c**)

Light yellow crystal, yield 92.7%, *m.p.* 127–129 ℃. Anal. Calcd. for $C_{23}H_{25}N_3FeO_2$ C 64.05, H 5.84, N 9.74; Found. C 64.03, H 5.60, N 9.81. ^{1}H-NMR (δ) (DMSO- d_6, 300 MHz): 8.28 (s, 1H, TrH $_{C3'}$), 7.87 (s, 1H, TrH $_{C5'}$), 6.95 (d, 2H, *J* = 8 Hz, PhH), 6.73 (d, 2H, *J* = 8 Hz, PhH), 4.73 (m, 1H, —O—C$\underline{H}$—CH—Tr), 4.33 (d, 4H, *J* = 5 Hz, C_5H_4Fe), 4.18 (s, 5H, C_5H_5Fe), 4.14 (s, 3H, OCH_3), 3.86 (m, 1H, —O—CH—C$\underline{H}$—Tr), 3.66 (s, 3H, OCH_3), 3.06 (m, 2H, PhC$\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(o-chlorophenyl)-propan-2-yl)-1H-1,2,4-triazole (**6d**)

Light yellow oil, yield 96.3%. Anal. Calcd. for $C_{22}H_{22}ClN_3FeO$ C 60.64, H 5.09, N 9.64; Found. C 60.61, H 5.15, N 9.59. ^{1}H-NMR (δ) (DMSO-d_6, 300 MHz): 8.39 (s, 1H, TrH $_{C3'}$), 7.89 (s, 1H, TrH $_{C5'}$), 7.40–6.95 (m, 4H, PhH), 4.94 (m, 1H, —O—C$\underline{H}$—CH—Tr), 4.36 (d, 4H, *J* = 5 Hz, C_5H_4Fe), 4.20 (s, 5H, C_5H_5Fe), 4.15 (s, 3H, OCH_3), 3.77 (m, 1H, —O—CH—C$\underline{H}$—Tr), 3.28 (m, 2H, PhC$\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(m-chlorophenyl)-propan-2-yl)-1H-1,2,4-triazole (**6e**)

Orange crystal, yield 94.5%, *m.p.* 127–129℃. Anal. Calcd. for $C_{22}H_{22}ClN_3FeO$ C 60.64, H 5.09, N 9.64; Found. C

60.73, H 5.09, N 9.54. ^{1}H-NMR (δ) (DMSO- d_6, 300 MHz): 8.30 (s, 1H, $TrH_{C3'}$), 7.85 (s, 1H, $TrH_{C5'}$), 7.22–6.97 (m, 4H, PhH), 4.82 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.37 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.20 (s, 5H, C_5H_5Fe), 4.15 (s, 3H, OCH_3), 3.90 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.15 (m, 2H, $PhC\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(p-chlorophenyl)-propan-2-yl)-1H-1,2,4-triazole (**6f**)

Light yellow crystal, yield 96.8%, *m.p.* 112–114℃. Anal. Calcd. for $C_{22}H_{22}ClN_3FeO$ C 60.64, H 5.09, N 9.64; Found. C 60.51, H 5.18, N 9.56. ^{1}H-NMR (δ) (DMSO- d_6, 300 MHz): 8.29 (s, 1H, $TrH_{C3'}$), 7.85 (s, 1H, $TrH_{C5'}$), 7.23 (d, 2H, J = 8 Hz, PhH), 7.05 (d, 2H, J = 8 Hz, PhH), 4.77 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.35 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.20 (s, 5H, C_5H_5Fe), 4.14 (s, 3H, OCH_3), 3.89 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.12 (m, 2H, $PhC\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(2,4-dichlorophenyl)-*propan*-2-yl)-1H-1,2,4-triazole (**6g**)

Light yellow crystal, yield 86.8%, *m.p.* 117–119℃. Anal. Calcd. for $C_{22}H_{21}Cl_2N_3FeO$ C 56.20, H 4.50, N 8.94; Found. C 56.31, H 4.36, N 8.91. ^{1}H-NMR (δ) (DMSO-d_6, 300 MHz): 8.41 (s, 1H, $TrH_{C3'}$), 7.89 (s, 1H, $TrH_{C5'}$), 7.55 (s, 1H, PhH), 7.21 (d, 1H, J = 9 Hz, PhH), 6.98 (d, 1H, J = 9 Hz, PhH), 4.88 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.38 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.20 (s, 5H, C_5H_5Fe), 4.15 (s, 3H, OCH_3), 3.77 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.26 (m, 2H, $PhC\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(p-diethylaminophenyl)-propan-2-yl)-1H-1,2,4-triazole (**6h**)

Orange red oil, yield 96.5%, Anal. Calcd. for $C_{26}H_{32}N_4FeO$ C 66.10, H 6.83, N 11.86; Found. C 65.93, H 7.03, N 11.88. ^{1}H-NMR (δ) (DMSO-d_6, 300 MHz): 8.29 (s, 1H, $TrH_{C3'}$), 7.89 (s, 1H, $TrH_{C5'}$), 6.80 (d, 2H, J = 8 Hz, PhH), 6.48 (d, 2H, J = 8 Hz, PhH), 4.68 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.30 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.17 (s, 5H, C_5H_5Fe), 4.14 (s, 3H, OCH_3), 3.83 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.26 (q, 4H, J = 6 Hz, $NC\underline{H_2}CH_3$), 2.96 (d, 2H, J = 7 Hz, $PhC\underline{H_2}$), 1.01(t, 6H, J = 6 Hz, $NCH_2C\underline{H_3}$).

1-(1-methoxy-1-ferrocenyl-3-(m-nitroophenyl)-propan-2-yl)-1H-1,2,4-triazole (**6i**)

Orange red crystal, yield 89.6%, *m.p.* 134–136℃. Anal. Calcd. for $C_{22}H_{22}N_4FeO_3$ C 59.21, H 4.97, N 12.55; Found. C 59.20, H 4.89, N 12.62. ^{1}H-NMR (δ) (DMSO-d_6, 300 MHz): 8.30 (s, 1H, $TrH_{C3'}$), 8.00 (m, 1H, PhH), 7.95 (s, 1H, PhH), 7.83 (s, 1H, $TrH_{C5'}$), 7.48 (m, 2H, PhH), 4.89 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.42 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.20 (s, 5H, C_5H_5Fe), 4.16 (s, 3H, OCH_3), 3.93 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.33 (m, 2H, $PhC\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(p-fluorophenyl)-propan-2-yl)-1H-1,2,4-triazole (**6j**)

Light yellow crystal, yield 96.6%, *m.p.* 115–117℃. Anal. Calcd. for $C_{22}H_{22}N_3FFeO$ C 63.02, H 5.29, N 10.02; Found. C 62.95, H 5.21, N 10.03. ^{1}H-NMR (δ) (DMSO-d_6, 300 MHz): 8.29 (s, 1H, $TrH_{C3'}$), 7.86 (s, 1H, $TrH_{C5'}$), 7.09–6.96 (m, 4H, PhH), 4.77 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.35 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.20 (s, 5H, C_5H_5Fe), 4.14 (s, 3H, OCH_3), 3.88 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.12 (m, 2H, $PhC\underline{H_2}$).

1-(1-methoxy-1-ferrocenyl-3-(benzo[d]-[1,3]-dioxomethylene-5-yl)-propan-2-yl)-1H-1,2,4-triazole (**6k**)

Light yellow crystal, yield 95.4%, *m.p.* 114–116℃. Anal. Calcd. for $C_{23}H_{23}N_3FeO_3$ C 62.04, H 5.21, N 9.44; Found. C 62.05, H 5.28, N 9.44. ^{1}H-NMR (δ) (DMSO-d_6, 300 MHz): 8.29 (s, 1H, $TrH_{C3'}$), 7.86 (s, 1H, $TrH_{C5'}$), 6.71 (d, 1H, J = 2 Hz, PhH), 6.63 (s, 1H, PhH), 6.48 (d, 1H, J = 2 Hz, PhH), 5.92 (s, 2H, $-O-CH_2-O-$), 4.75 (m, 1H, $-O-C\underline{H}-CH-Tr$), 4.32 (d, 4H, J = 5 Hz, C_5H_4Fe), 4.17 (s, 5H, C_5H_5Fe), 4.13 (s, 3H, OCH_3), 3.86 (m, 1H, $-O-CH-C\underline{H}-Tr$), 3.05 (m, 2H, $PhC\underline{H_2}$).

2.3 X-ray diffraction analysis of compound 6

In order to investigate the structure-activity relationship of the compounds **6**, a single crystal of compound **6a** was obtained by recrystallization from ether-petroleum ether (60–90 ℃) (V:V 1:1) and was subjected to X-ray diffraction analysis. Crystal data for **6a**: 0.32 × 0.25 × 0.20 mm, $P2(1)/n$; a = 1.0165 (5) nm, b = 1.4205 (7) nm, c = 1.3262 (6) nm; $\alpha = \beta = \gamma = 90°$. V = 1.9150 (16) nm^3, Z = 4. D = 1.392 mg/m^3, μ = 0.804 mm^{-1}; $F(000)$= 840. $I>2\sigma(I)$; R_1= 0.0416; wR_2= 0.0830. Crystallographic structure and cell of compound **6a** were outlined in Figs 1 and 2, respectively.

2.4 Biological evaluation

In vitro fungicidal activity of the title compounds **6a**–**6k** was assayed against five selected fungi including *Pratylenchus zeae*, *A. solani*, *Cladosporium fulvum*, *P. piricola* and *C. ara*. Plant-growth regulatory activity of these novel compounds was determined by wheat gemmale elongation and cucumber cotyledon rootage methods. Their relative inhibitory ratios against these fungi and plant-growth regulatory activity are reported in Table 1.

3 Results and discussion

3.1 ^{1}H-NMR spectra

In the ^{1}H-NMR spectra of **6a**–**6k**, the chemical shifts of two triazole protons were located at δ = 8.40–8.30 and δ = 7.95–7.85, respectively as singlets. The chemical shifts of two methine groups appeared as multiplets at δ= 4.95–4.65 (CH_3O-CH) and 3.95–3.75 (triazole-CH), respectively. In

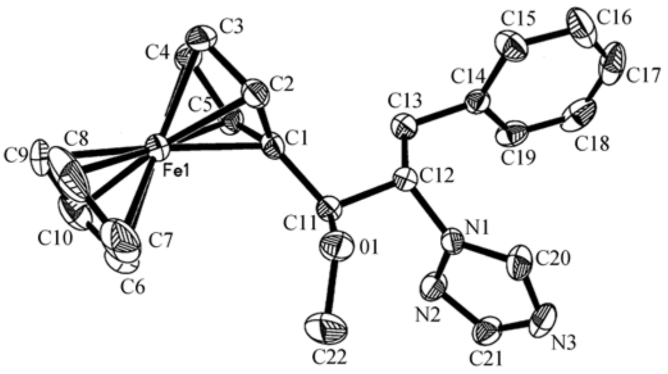

Fig. 1 Crystallographic structure for compound **6a** with hydrogen atom omitted for clarification

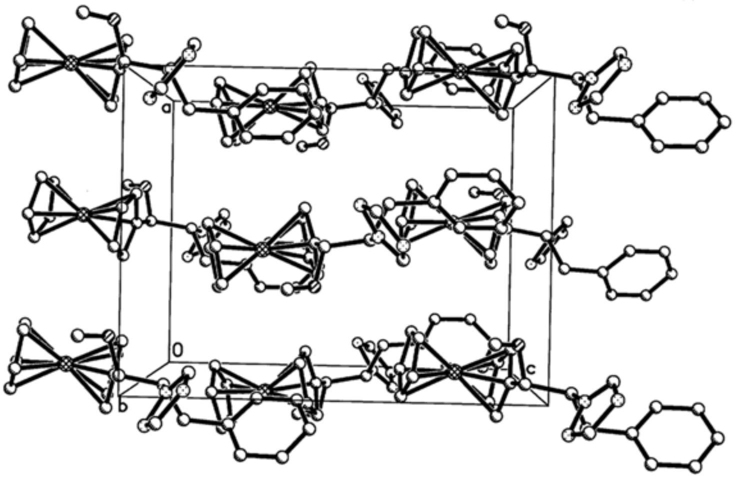

Fig. 2 Crystallographic cell for compound **6a**

Table 1 Biological activity of the title compounds **6**▽

Compound	Fungicidal activity (%) (disc paper method in vitro) ($c = 5.0 \times 10^{-5}$ mg/mL)					Plant-growth regulatory activity(%) ($c = 1.0 \times 10^{-5}$ mg/mL)	
	A	B	C	D	E	F	G
6a	20.0	25.0	33.3	0	33.3	–22.8	+10.5
6b	40.0	42.9	0	0	33.3	–22.3	+63.1
6c	0	0	0	0	20.0	–18.4	+57.8
6d	45.0	57.1	33.3	0	26.7	–20.4	+26.3
6e	0	0	33.3	0	0	–21.8	+68.4
6f	20.0	0	33.3	25.0	20.0	–20.4	+2.6
6g	30.0	28.6	25.0	0	26.7	–17.5	+34.2
6h	0	25.0	41.7	21.4	20.0	–7.8	+31.5
6i	30.0	42.9	49.9	25.0	26.7	–18.4	+73.6
6j	0	39.3	50.0	0	33.3	–12.6	+126.3
6k	35.0	28.6	25.0	21.4	33.3	–20.4	+34.2

▽A: P. zeae, B: A. Solani, C: C. fulvum, D: P. piricola, E: C. ara, F: Wheat gemmale elongation, G: Cucumber cotyledon rootage addition, the chemical shifts of Ar-CH_2 groups were located at $\delta = 2.96–3.33$ as multiplets. Chemical shifts of ferrocene were in their characteristic region, i.e. the five protons of unsubstituted ring appeared at $\delta = 4.20–4.10$ as singlets, while the four protons of the substituted ring appeared at $\delta = 4.40–4.30$ as doublets.

3.2 Structure-activity relationship

From X-ray diffraction analysis data of compound **6a**, it was found that the molecule showed a distorted shape due to bulky ferrocene group. The angles between substituted Cp-ring and triazole and between aromatic ring and triazole were 25.7° and 47.7°, respectively.

Our previous works [10] revealed that, a linking fragment consisting of a carbon-carbon single or double bond between the triazole ring and substituted aryl group was essential for their fungicidal activity. Additionally, an arrangement of the triazole ring and aryl group in an almost linear fashion possessed higher activity than one in a distorted fashion. The reduced fungicidal activity of compounds **6a**–**6k** ascertained our previous results. Because of the bulkiness of the ferrocene group, the triazole ring and the aryl group were not connected in a linear way but with a bent linkage, and thus compounds **6a**–**6k** did not display predominant fungicidal activity.

Although compounds **6a**–**6k** did not show encourageing fungicidal activity, they revealed promising plant-growth regulatory activity. All of them inhibited wheat gemmale elongation at a concentration of 5.0×10^{-5} mg/mL and improved cucumber cotyledon rootage at a concentration of 1.0×10^{-5} mg/mL, especially, the plant-growth regulatory activity of compound **6j** was +126% reaching grade B.

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