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Synthesis and plant-growth regulatory activities of novel imine derivatives containing 1*H*-1,2,4-triazole and thiazole rings

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Abstract

Eleven new imine derivatives **6** containing 1*H*-1,2,4-triazole and thiazole rings were synthesized by the condensation of 5-((1*H*-1,2,4-triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-amine with various substituted benzaldehydes. The structures of the title compounds were characterized by ^{1}H NMR, MS and elemental analysis. The plant-growth regulatory activities of these compounds were evaluated. The primary bioassay results indicated that these target compounds exhibited promising plant-growth regulatory activities.

Keywords: 1*H*-1,2,4-Triazole; Thiazole; Synthesis; Imine; Plant-growth regulatory activity

Molecules containing thiazole ring systems are widely studied because of its low toxicity, excellent biological activity as well as readily access of diverse derivatives. Thiazole moiety is the key pharmacophore and intermediate for synthesizing pharmaceuticals and it is extensively found in the field of agrochemicals [1–6]. On the other hand, 1*H*-1,2,4-triazole-containing derivatives plays a vital role in many biological activities [7]. Compounds containing the 1*H*-1,2,4-triazole ring system have been found to show significant plant-growth regulatory activity such as uniconazole and paclobutrazol [8]. We also know that imine derivatives possess potent activities including antibacterial, antifungal, and antitumor activities [9,10]. Promoted by the above observations and in continuation of our study on the biological activities of thiazole derivatives, we designed and synthesized some new thiazole derivatives by incorporating the 1*H*-1,2,4-triazole unit into the title compounds (Scheme 1). Compounds **2**–**4** were synthesized according to the literature methods [11,12].

Synthesis of 5-((1*H*-1,2,4-triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-amine (**5**). Thiourea was added to the solution of compound **4** (9.92 mmol) in ethanol (15 mL), the mixture was heated to 50 °C and stirred for 8 h to form the hydrobromide salt of **5** which precipitated out. The mixture was then cooled and vacuum filtered. The solid was then stirred for 1 h in the solution of sodium bicarbonate. The precipitated product was collected by filtration, and dried to give compound **5** as a white crystalline solid with yield 75%, m.p. 187–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30

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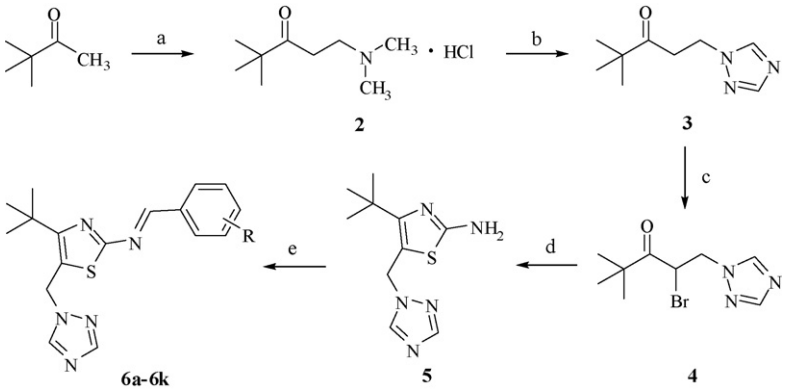

Scheme 1. Synthesis of the title compounds **6**. (a) $(CH_2O)n/Me_2NH{\cdot}HCl$, C_2H_5OH; (b) 1*H*-1,2,4-triazole/H_2O; (c) Br_2/CH_3COOH, CH_3COONa; (d) thiourea/C_2H_5OH; (e) substituted benzaldehyde/toluene/piperidine.

(s, 9H, *t*-butyl), 5.49 (s, 2H, CH_2), 6.82 (s, 2H, NH_2), 7.97 (s, 1H, TrH), 8.49 (s, 1H, TrH). Anal. calcd. (%) for $C_{10}H_{15}N_5S$: C, 50.61; H, 6.37; N, 29.51. Found: C, 50.45; H, 6.30; N, 29.78.

General preparation of the title compounds **6a**–**k**. To the solution of compound **5** (2 mmol) in toluene (20 mL) was added appropriate substituted benzaldehyde (2.2 mmol) and piperidine (3 drops). The reaction mixture was stirred and refluxed for 20 h. The solvent was evaporated under the reduced pressure the residue was purified by flash chromatography to afford the title compounds **6a**–**k** in high purity.

Data for **6a**: yellow solid, yield 53%, m.p. 87–89 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H, *t*-butyl), 5.67 (s, 2H, CH_2), 7.52 (q, 3H, J = 6.6 Hz, ArH), 7.97 (d, 2H, J = 6.8 Hz, ArH), 8.00 (s, 1H, TrH), 8.09 (s, 1H, TrH), 8.86 (s, 1H, N=CH). Anal. calcd. for $C_{17}H_{19}N_5S$: C 62.74, H 5.88, N 21.52; found C 62.55, H 6.01, N 21.61.

Data for **6b**: yellow solid, yield 51%, m.p. 94–95 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.47 (s, 9H, *t*-butyl), 5.68 (s, 2H, CH_2), 7.12–7.27 (m, 2H, ArH), 7.50–7.54 (m, 1H, ArH), 8.01 (s, 1H, TrH), 8.09 (s, 1H, TrH), 8.21–8.27 (m, 1H, ArH), 9.17(s, 1H, N=CH). MS (ESI), *m*/*z* 344.49 ([M+1]$^+$, 100). Anal. calcd. for $C_{17}H_{18}FN_5S$: C 59.46, H 5.28, N 20.39; found C 59.21, H 5.44, N 20.44.

Data for **6c**: yellow solid, yield 14%, m.p. 83–85 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.47 (s, 9H, *t*-butyl), 5.59 (s, 2H, CH_2), 7.68–7.72 (m, 2H, ArH), 8.00 (s, 1H, TrH), 8.10 (d, 1H, J = 8.5 Hz, ArH), 8.11 (s, 1H, TrH), 8.37 (d, 1H, J = 7.7 Hz, ArH), 8.40 (s, 1H, N=CH). MS (ESI), *m*/*z* 370.97 ([M+1]$^+$, 100). Anal. calcd. for $C_{17}H_{18}N_6O_2S$: C 55.12, H 4.90, N 22.69; found C 55.34, H 5.13, N 22.58.

Data for **6d**: yellow solid, yield 62%, m.p. 130–131 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.48 (s, 9H, *t*-butyl), 3.92(s, 3H, CH_3), 5.67 (s, 2H, CH_2), 6.93–7.04 (m, 2H, ArH), 7.44–7.53 (m, 1H, ArH), 8.00 (s, 1H, TrH), 8.09 (s, 1H, TrH), 8.23 (q, 1H, J = 7.8 Hz, ArH), 9.23 (s, 1H, N=CH). MS (ESI), *m*/*z* 356.36 ([M+1]$^+$, 100). Anal. calcd. for $C_{18}H_{21}N_5OS$: C 60.82, H 5.95, N 19.70; found C 60.72, H 6.12, N 19.74.

Data for **6e**: yellow solid, yield 42%, m.p. 87–89 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H, *t*-butyl), 2.42(s, 3H, CH_3), 5.67 (s, 2H, CH_2), 7.28 (d, 2H, J = 8.0 Hz, ArH), 7.86 (d, 2H, J = 8.1 Hz, ArH), 8.00 (s, 1H, TrH), 8.08 (s, 1H, TrH), 8.80 (s, 1H, N=CH). MS (ESI), *m*/*z* 340.40 ([M+1]$^+$, 100). Anal. calcd. for $C_{18}H_{21}N_5S$: C 63.69, H 6.24, N 20.63; found C 63.49, H 6.49, N 20.78.

Data for 6**f**: yellow solid, yield 55%, m.p. 136–137 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.45 (s, 9H, *t*-butyl), 5.67 (s, 2H, CH_2), 7.46 (d, 2H, J = 8.5 Hz, ArH), 7.90 (d, 2H, J = 8.5 Hz, ArH), 8.00 (s, 1H, TrH), 8.09 (s, 1H, TrH), 8.84 (s, 1H, N=CH). MS (ESI), *m*/*z* 359.96 ([M+1]$^+$, 100). Anal. calcd. for $C_{17}H_{18}ClN_5S$: C 56.74, H 5.04, N 19.46; found C 56.40, H 5.14, N 19.45.

Data for **6g**: yellow solid, yield 73%, m.p. 122–123 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H, *t*-butyl), 5.66 (s, 2H, CH_2), 7.17 (t, 2H, J = 8.6 Hz, ArH), 7.98 (t, 2H, J = 8.6 Hz, ArH), 8.00 (s, 1H, TrH), 8.10 (s, 1H, TrH), 8.83 (s, 1H, N=CH). MS (ESI), *m*/*z* 344.36 ([M+1]$^+$, 100). Anal. calcd. for $C_{17}H_{18}FN_5S$: C 59.46, H 5.28, N 20.39; found C 59.25, H 5.37, N 20.54.

Data for **6h**: yellow solid, yield 57%, m.p. 113–114 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H, *t*-butyl), 3.88 (s, 3H, CH_3), 5.65 (s, 2H, CH_2), 6.98 (d, 2H, J = 8.8 Hz, ArH), 7.92 (d, 2H, J = 8.8 Hz, ArH), 8.00 (s, 1H, TrH), 8.07 (s,

Table 1
Plant-growth regulatory activity of title compounds **6a–k** (c = 10 mg/L).

Compound	R	Plant-growth regulatory activity (relative ratio, %)	Active grade[a]
6a	H	72.2	+
6b	2-F	116.6	++
6c	2-NO_2	100.0	++
6d	2-OMe	116.6	++
6e	4-Me	66.6	+
6f	4-Cl	83.3	+
6g	4-F	100.0	++
6h	4-OMe	23.2	−
6i	2,4-Me_2	50.0	+
6j	3,4-Me_2	88.8	+
6k	2-F-4-Br	26.7	−
Triadimefon		80.7	+
Triadimenol		120.6	++

[a] Active grade: +++ ≥150%, ++ ≥100%, + ≥50%, and − <50%.

1H, TrH), 8.74 (s, 1H, N=CH). MS (ESI), m/z 356.46 ([M+1]$^+$, 100). Anal. calcd. for $C_{18}H_{21}N_5OS$: C 60.82, H 5.95, N 19.70; found C 60.66, H 6.14, N 19.98.

Data for **6i**: yellow solid, yield 37%, m.p. 125–127 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H, t-butyl), 2.37 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 5.66 (s, 2H, CH_2), 7.05 (s, 1H, ArH), 7.10 (d, 1H, J = 8.1 Hz, ArH), 8.00 (s, 1H, TrH), 8.06 (s, 1H, ArH), 8.07 (d, 1H, J = 9.2 Hz, ArH), 8.09 (s, 1H, TrH), 9.10 (s, 1H, N=CH). MS (ESI), m/z 354.33 ([M+1]$^+$, 100). Anal. calcd. for $C_{19}H_{23}N_5S$: C 64.56, H 6.56, N 19.81; found C 64.30, H 6.59, N 19.99.

Data for **6j**: yellow solid, yield 35%, m.p. 82–83 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.48 (s, 9H, t-butyl), 2.32 (d, 6H, J = 3.7 Hz, 2CH_3), 5.67 (s, 2H, CH_2), 7.22–7.25 (m, 1H, ArH), 7.64–7.67 (m, 1H, ArH), 7.79 (s, 1H, ArH), 8.00 (s, 1H, TrH),8.09 (s, 1H, TrH), 8.77 (s, 1H, N=CH). MS (ESI), m/z 354.47 ([M+1]$^+$, 100). Anal. calcd. for $C_{19}H_{23}N_5S$: C 64.56, H 6.56, N 19.81; found C 64.39, H 6.81, N 20.04.

Data for **6k**: yellow solid, yield 24%, m.p. 107–109 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H, t-butyl), 5.67 (s, 2H, CH_2), 7.34–7.42 (m, 2H, ArH), 8.00 (s, 1H, TrH), 8.08 (s, 1H, TrH), 8.13 (d, 1H, J = 7.9 Hz, ArH), 9.11 (s, 1H, N=CH). MS (ESI), m/z 423.86 ([M+1]$^+$, 100). Anal. calcd. for $C_{17}H_{17}BrFN_5S$: C 48.35, H 4.06, N 16.58; found C 48.17, H 4.31, N 16.78.

The plant-growth regulatory activity of title compounds **6a–k** was screened using cucumber cotyledon rhizogenesis method according to procedures described previously [13]. At the concentration of 10 mg/L, the plant-growth regulatory activity results for compounds **6a–k** are shown in Table 1. In comparison with triadimefon and triadimenol [14,15], some of the target compounds showed promising plant-growth regulatory activity. For example, **6b** and **d** showed obvious plant regulatory activities as the same as triadimenol. And **6f**, **g**, **j** exhibited higher plant-growth regulatory activities than triadimefon. These data show that efficacy is strongly influenced by the nature of the substitutes and their position on the benzene ring. In general, the presence of halo group such as fluorine and chlorine atom at position 2 or 4 of phenyl ring may increase their plant-growth regulatory activity while electronic-donating group, such as methyl and methoxy will cause the decrease of biological activity.

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