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Design, Synthesis and Antifungal Activities of Novel 1,2,4-Triazole Schiff Base Derivatives

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Abstract: With the aim to find new compounds with high antifungal activity, 21 4-amino-5-substitute-1,2,4-triazole Schiff bases (2a-2g, 3a-3g and 4a-4g) were designed and synthesized. Their antifungal activities against *Pythium solani*, *Gibberlla nicotiancola*, *Fusarium oxysporium f. sp. niveum*, *Gibberlla saubinetii*, *Alternaria iycopersici*, *Phytophthora capsici*, *Physalospora piricola*, *Cercospora arachidicola hori*, and *Fusarium oxysporium f. sp. cucumber* were tested, parts of the compounds exhibited excellent antifungal activity. This research provides useful information for further study of antifungal agents.

Keywords: synthesis; 1,2,4-triazole; Schiff base; antifungal activity

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1. Introduction

1,2,4-Triazole derivatives due to their broad-spectrum activities have potential applications in the fields of pesticides and medicines possessing antifungal[1], antibacterial[2], antitumor[3] antitrypanosomal[4], antiproliferative[5] and antibiotics[6] properties. In recent years, 1,2,4-triazole Schiff bases were found with good pharmacological activity[7-9] as well. In our previous research, a large number of 4-amino-5-substitute-1,2,4-triazole Schiff bases were designed and synthesized. Their biological activity showed parts of the compounds have excellent antifungal activity compared with triadimefon[10-12], this result inspires us with passion to synthesize more 1,2,4-triazole Schiff bases. Some research reported introducing heterocyclic skeleton into structure can enhance the biological activity[13-15], on the basis of the above information, we designed and synthesized series of 1,2,4-triazole Schiff bases containing pyridine ring, imidazole ring and halogenated benzene ring, respectively, expecting to find lead compound with higher antifungal

activity. Target compounds were synthesized via 4-amino-5-substitute-1,2,4-triazolethione with

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substituted benzaldehyde using glacial acetic acid as catalyst and solvent. Their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, melting point, elemental analysis and mass spectra. In addition, their antifungal activity against *Pythium solani*, *Gibberlla nicotiancola*, *Fusarium oxysporium f. sp. niveum*, *Gibberlla saubinetii*, *Alternaria iycopersici*, *Phytophthora capsici*, *Physalospora piricola*, *Cercospora arachidicola hori*, and *Fusarium oxysporium f. sp*. *cucumber* were tested.

2. Results and Discussion

2.1 Synthesis and Characterization

The synthesis of compounds 2a-2g, 3a-3g, and 4a-4g were outlined in Scheme 1 and Scheme 2, all the target compounds were first reported. The structure of title compounds was confirmed on the basis of their spectral data. All spectral and analytical data were consistent with the assigned structure. The bands observed near 2950 and 3050 cm^{-1} in the IR spectrum are assigned to the C–H and N–H stretching modes, respectively. The strong peaks around 1560 cm^{-1} are ascribed to the C=N group of Schiff base. The characteristic stretching vibrations v (C=S) appeared at around 1254 cm^{-1}, and there is no absorption at 2565-2550 cm-1 (S–H), manifesting title compounds are mainly exist in keto configuration, and this result is in agreement with the previous research[11].

2.2 Antifungal activities

The tested fungi and antifungal activity results were listed in Table 1 and Table 2, respectively. From Table 2, title compounds showed good, moderate, and week acticity, respectively. The bioassay indicated the inhibition ratio of triadimefon to the fungi *Pythium solani*, *Gibberlla nicotiancola*, *Fusarium oxysporium f. sp. niveum*, *Gibberlla saubinetii*, and *Alternaria iycopersici*, are greater than 50 %. No matter triadimefon or title compounds, their antifungal activities against *Phytophthora capsici*, *Physalospora piricola*, *Cercospora arachidicola hori*, and *Fusarium oxysporium f. sp*. *Cucumber* are moderate or week. Then the title compounds against *Pythium solani*, *Gibberlla nicotiancola*, *Fusarium oxysporium f. sp. niveum*, *Gibberlla saubinetii*, and *Alternaria iycopersici* were listed separately in Fig.1. Compounds 2b, 2c, 2f, 2g, 3a, 4a, 4b, and 4e showed excellent activity

against *Pythium solani*; compound 4a showed good activity against *Gibberlla nicotiancola*; compounds 3a, 3b, 4a, 4b, and 4e showed good activty against *Gibberlla saubinetii*; compounds 2a and 2f showed good activity against *Alternaria iycopersici*.

Generally, parts of the compounds exhibited excellent antifungal activity, the results showed compounds 3a, 3b, 4a and 4b exhibited good activity against *gibberlla nicotiancola*, *pythium solani* and *fusarium oxysporium f. sp. niveum*. Only compound 4a showed broad-spectrum antifungal activity, which has the potential to be further researched as antifungal agent.

3. Conclusions

From the above results, it is concluded that, a series of novel 4-amino-5-substitute -1,2,4-triazole Schiff bases have been prepared and evaluated antifungal activity. The activity test showed compound 4a showed broad-spectrum antifungal activity, which has the potential to be further researched as antifungal agent. This research provides a basic data for further investigation of antifungal drugs.

4. Experimental

4.1 Chemistry

Elemental analysis was performed with a Vario ELШ CHNOS analyzer; IR (KBr) spectra was recorded on an IR-400 spectrophotomete; ^{1}H NMR and ^{13}C NMR spectra was measured with a Varian unity INOVA-400 nuclear magnetic resonance using $CDCl_3$ or DMSO as the solvent and TMS as an internal standard; mass spectra was obtained from micrOTOF-Q II mass spectrometer; the melting point was determined on MP3 melting point apparatus.

4.2 Synthesis

Compounds 1a-1g were prepared according to the literatures[10, 13-15]. Compounds 2a-2g, 3a-3g, and 4a-4g were synthesized by compounds 1a-g and solution of absolute ethanol with 4-pyridine benzaldehyde (5 mL), 3-bromo-6-hydroxy-2-methoxybenzaldehyde (5 mL) and 4-(1*H*-imidazol -1-yl) benzaldehyde (5 mL) in the presence of glacial acetic acid (2 mL), the mixture was refluxed about 4 h, TLC monitors the reaction until all raw material disappeared, the crude products were purified by DMF and Water (1:1).

(E)-5H-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2a)**: yield 75.3 %; yellow solid; mp: 233.4-234.3 °C; IR (KBr) v/cm^{-1}: 3112, 2931, 1550, 1490, 1291, 925, 846, 685, 560; ^{1}H NMR (400 MHz, (D_6)DMSO) δ 9.58 (s, 1H); 9.00 (s, 1H); 8.79-8.80 (m, 2H); 7.79-7.80 (m, 2H); ESI–MS m/z: 206.0423 (M+H); Elemental Anal. $C_8H_7N_5S$, Found (Calcd) %: C 46.99 (46.82), H 3.21 (3.44), N 34.09 (34.12).

(E)-5-ethyl-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2b)**: yield 81.9 %; yellow solid; mp: 250.5-252.0 °C; IR (KBr) v/cm^{-1}: 3050, 2940, 1548, 1487, 1254, 901, 788, 653, 562; ^{1}H NMR (400 MHz, (D) $CDCl_3$) δ 10.85 (s , 1H); 10.57 (s, 1H); 8.79-8.81 (m, 2H), 7.71-7.72 (m, 2H), 2.88-2.90 (q, 2H), 1.36-1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400MHz, (D6) DMSO) δ 11.2, 25.6, 120.1, 142.3, 148.7, 154.8, 157.9, 182.3; ESI–MS m/z: 234.2927 (M+H); Elemental Anal. $C_{10}H_{11}N_5S$, Found (Calcd) %: C 51.49 (51.48), H 4.73 (4.75), N 30.03 (30.02).

(E)-5-propyl-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2c)**: yield 78.3 %; yellow solid; mp: 234.0-236.0 °C; IR (KBr) v/cm^{-1}: 3130, 2960, 1561, 1481, 1240, 953, 842, 683; ^{1}H NMR (400 MHz, (D) $CDCl_3$) δ 11.02 (s, 1H), 10.85 (s, 1H), 8.79-8.82 (t, *J* = 8.0 Hz, 2H), 7.72-7.74 (m, 2H), 2.83-2.85 (t, *J* = 7.2 Hz, 2H), 1.81-1.82 (m, 2H), 1.04-1.06 (t, *J* = 7.2 Hz, 3H); ESI–MS m/z: 248.3195 (M+H); Elemental Anal. $C_{11}H_{13}N_5S$, Found (Calcd) %: C 53.43 (53.42), H 5.31 (5.30), N 25.23 (25.25).

(E)-5-benzy-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2d)**: yield 80 %; yellow solid; mp: 238.7-240.2 °C; IR (KBr) v/cm^{-1}: 3064, 2953, 1587, 1499, 1221, 967, 859, 693; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.35 (s, 1H), 8.77-8.79 (d, *J* = 7.2 Hz, 2H), 7.80-7.81 (m, 2H), 7.31 (m, 5H), 4.19 (s, 2H); ESI–MS m/z: 296.3623 (M+H); Elemental Anal. $C_{15}H_{13}N_5S$, Found (Calcd) %: C 61.01 (61.00), H 4.41 (4.44), N 23.73 (23.71).

(E)-5-(4-pridyl)-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2e)**: yield 77 %; yellow solid; mp: > 275 °C; IR (KBr) v/cm^{-1}: 3056, 2932, 1583, 1454, 1280, 965, 841, 689; ^{1}H NMR (400 MHz, (D6) DMSO) 8.78 (s, 4H), 7.81 (s, 4H); ESI–MS m/z: 283.3236 (M+H); Elemental Anal. $C_{13}H_{10}N_6S$, Found (Calcd) %: C 55.29 (55.30), H 3.58 (3.57), N 29.76 (29.77).

(E)-5-(4-methylphenyl)-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2f)**: yield 84 %; yellow solid; mp: 254.4-256.2 °C; IR (KBr) v/cm^{-1}: 3102, 2927, 1581, 1460, 1271, 1007, 839, 647. ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.01 (s, 1H), 8.79-8.80 (m, 2H), 7.81-7.82 (m, 2H), 7.74-7.46 (d, *J* =

8.0 Hz, 2H), 7.35-7.37 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H); ESI–MS m/z: 296.3624 (M+H); Elemental Anal. $C_{15}H_{13}N_5S$, Found (Calcd) %: C 60.99 (61.00), H 4.45 (4.44), N 23.70 (23.71).

(E)-5-(2-methoxylphenyl)-4-[(4-pyridyl)methyleneamino]-1,2,4-triazole-3-thione **(2g)**: yield 74.3 %; yellow solid; mp: 240.6-242.4 ℃IR (KBr) v/cm^{-1}: 3103, 2920, 1576, 1456, 1281, 1017, 840, 695, 581; ^{1}H NMR (400 MHz, (D6) DMSO) δ 9.96 (s, 1H), 8.72-8.73 (m, 2H), 7.66-7.67 (m, 2H), 7.52-7.58 (m, 2H), 7.15-7.17 (m, 2H), 3.65 (s, 3H); ESI–MS m/z: 312.3618 (M+H); Elemental Anal. $C_{15}H_{15}N_5OS$, Found (Calcd) %: C 57.86 (57.86), H 4.20 (4.21), N 22.50 (22.49).

(E)-5H-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3a)**: yield 71.8 %; light brown solid; mp: 276.2-277.8 ℃; IR (KBr) v/cm^{-1}: 3424, 3139, 2998, 1618, 1569, 1439, 1226, 1128, 897, 656; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.37 (s, 1H), 10.12 (s, 1H), 7.59 (s, 1H), 7.31(s, 1H) 3.89 (s, 3H); ESI–MS m/z: 328.9612 (M+H); Elemental Anal. $C_{10}H_9BrN_4O_2S$, Found (Calcd) %: C 36.81 (36.49), H 2.33 (2.76), N 17.46 (17.02).

(E)-5-ethyl-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3b)**: yield 74.5 %; light brown solid, mp: 269.5-270.3℃; IR (KBr) v/cm^{-1}: 3425, 3135, 2994, 1618, 1569, 1439, 1226, 1128, 897, 655; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.31(s, 1H), 10.06 (s, 1H), 7.52 (s, 1H), 7.25 (s, 1H), 3.83 (s, 3H), 2.67-2.71 (q, 2H), 1.14-1.18 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (400 MHz, (D6) DMSO) δ 10.8, 23.9, 103.9, 111.7, 116.8, 136.4, 144.2, 157.8, 162.5, 163.5, 182.1; ESI–MS m/z: 356.9903 (M+H); Elemental Anal. $C_{12}H_{13}BrN_4O_2S$, Found (Calcd) %: C 40.11 (40.35), H 3.42 (3.67), N 15.76 (15.68).

(E)-5-propyl-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3c)**: yield 73.3 %; light brown solid; mp: 266.7-268.4 ℃; IR (KBr) v/cm^{-1}: 3425, 3131, 2994, 1618, 1565, 1482, 1228, 1129, 898, 653; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.43 (1H, s), 10.17 (1H, s), 7.64 (s, 1H), 7.38 (s, 1H), 3.96 (s, 3H), 2.79-2.81 (t, *J* = 8.0 Hz, 2H), 1.71-1.71 (m, 2H), 1.00-1.04 (t, *J* = 8.0

Hz, 3H); ESI–MS m/z: 371.0054 (M+H); Elemental Anal. $C_{13}H_{15}BrN_4O_2S$, Found (Calcd) %: C 42.33 (42.06), H 4.22 (4.27), N 15.36 (15.09).

(E)-5-benzy-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3d)**: yield 71.4 %; light brown solid; mp: 272.4-274.5 ℃; IR (KBr) v/cm^{-1}: 3425, 3131, 2994, 1618, 1565, 1482, 1228, 1129, 898, 653; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.40 (s, 1H), 10.04 (s, 1H), 7.49(s, 1H), 7.28-7.34 (m, 6H), 4.16 (s, 3H), 3.88 (s, 3H); ESI–MS m/z: 419.0063 (M+H); Elemental Anal. $C_{17}H_{15}BrN_4O_2S$, Found (Calcd) %: C 48.35 (48.70), H 3.78 (3.61), N 13.56 (13.36).

(E)-5-(4-pridyl)-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3e)**: yield 62.3 %; light brown solid; mp: 161.5-162.3 ℃. IR (KBr) v/cm^{-1}: 3424, 3131, 2993, 1617, 1566, 1483, 1224, 1129, 898, 653; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.26 (s, 1H), 10.11 (s, 1H), 8.82-8.83 (m, 2H), 7.89-7.90(m, 2H), 7.56-7.58 (m, 1H), 7.41 (m, 1H), 3.95 (s, 3H); ESI–MS m/z: 405.9854 (M+H); Elemental Anal. $C_{15}H_{12}BrN_5O_2S$, Found (Calcd) %: C 44.65 (44.35), H 2.78 (2.98), N 17.46 (17.24).

(E)-5-(4-methylphenyl)-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3f)**: yield 75.3 %; light brown solid; mp: 266.2-267.8 ℃; IR (KBr) v/cm^{-1}: 3423, 3132, 2990, 1615, 1568, 1486, 1223, 1128, 899, 653; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.19 (s, 1H), 10.03 (s, 1H), 7.72-7.73 (m, 2H), 7.46-7.48 (m, 1H), 7.33-7.36 (m, 3H), 3.89 (s, 3H), 2.37 (s, 3H); ESI–MS m/z: 419.0067 (M+H); Elemental Anal. $C_{17}H_{15}BrN_4O_2S$, Found (Calcd) %: C 44.65 (44.35), H 2.78 (2.98), N 17.46 (17.24).

(E)-5-(2-methoxylphenyl)-4-[(3-bromo-6-hydroxy-2-methoxyphenyl)methyleneamino]-1,2,4-triazole-3-thione **(3g)**: yield 63.5 %; light brown solid; mp: 248.2-250.1 ℃. IR (KBr) v/cm^{-1}: 3424, 3131, 2993, 1617, 1566, 1483, 1224, 1129, 898, 653; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.18 (s, 1H), 9.95 (s, 1H), 7.56-7.60 (m, 1H), 7.48-7.50 (d, *J* = 8 Hz, 1H), 7.25-7.27 (d, *J* = 8 Hz, 2H), 7.16-7.18 (d, *J* = 8 Hz, 1H), 7.08-7.12 (m, 1H), 3.86 (s, 3H), 3.68 (s, 3H); ESI–MS m/z: 435.0050 (M+H); Elemental Anal. $C_{17}H_{15}BrN_4O_3S$, Found (Calcd) %: C 46.75 (46.91), H 3.42 (3.47), N 12.54 (12.87).

(E)-5-H-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4a)**: yield 65.5 %; light yellow solid; mp: 259.4-261.3 ℃; IR (KBr) v/cm^{-1}: 3119, 2905, 1578, 1472, 1263, 1018, 865, 637; ^{1}H NMR (400 MHz, (D6) DMSO) δ 14.06 (s, 1H), 9.60 (s, 1H), 9.03 (s, 1H), 8.81-8.83 (d, *J* = 8.0 Hz, 2H), 7.81-7.83 (d, *J* = 8.0 Hz, 2H); ESI–MS m/z: 271.0689 (M+H); Elemental Anal. $C_{12}H_{10}N_6S$, Found (Calcd) %: C 53.63 (53.32), H 3.53 (3.33), N 31.33 (31.09).

(E)-5-ethyl-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4b)**: yield 64.5 %; light yellow solid; mp: 228.5-230.2 ℃; IR (KBr) v/cm^{-1}: 3198, 2964, 1578, 1463, 1281, 1018, 849, 663; ^{1}H NMR (400 MHz, (D6) DMSO) δ 10.02 (s, 1H), 8.44 (s, 1H), 8.04-8.06 (d, *J*=8.0 Hz, 2H), 8.87-8.89(d, *J* = 8.0 Hz, 2H), 7.16 (s, 1H), 2.75-2.77 (q, 2H), 1.21-1.25 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.2, 25.1, 118.4, 130.2, 130.5, 130.6, 133.5, 135.9, 139.6, 154.6, 157.2, 181.4; ESI–MS m/z: 299.1022 (M+H); Elemental Anal. $C_{14}H_{14}N_6S$, Found (Calcd) %: C 56.43 (56.36), H 4.94 (4.73), N 28.32 (28.33).

(E)-5-propyl-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4c)**: yield 67.1 %; light yellow solid; mp: 241.2-242.1 ℃; IR (KBr) v/cm^{-1}: 3109, 2934, 1587, 1483, 1229, 1010, 840, 689; ^{1}H NMR (400MHz, (D6) DMSO) δ 10.03 (s, 1H), 8.45 (s, 1H), 8.05-8.06 (m, 2H), 7.89-7.91 (m, 3H), 7.18 (s, 1H), 2.72-2.76 (t, *J* = 8.0 Hz, 2H), 1.68-1.72 (m, 2H), 0.93-0.95 (t, *J*=7.2 Hz, 3H); ESI–MS m/z: 313.1143 (M+H); Elemental Anal. $C_{15}H_{16}N_6S$, Found (Calcd) %: C 57.43 (57.67), H 5.34 (5.16), N 26.56 (26.90).

(E)-5-benzy-2,4-dihydro-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4d)**: yield 73.3 %; light yellow solid; mp: 260.1-261.5 ℃. IR (KBr) v/cm^{-1}: 3237, 2965, 1598, 1479, 1282, 1017, 858, 698; ^{1}H NMR (400MHz, (D6) DMSO) δ 14.01 (s, 1H), 10.35 (s, 1H), 8.77-8.79 (d, *J* = 8.0 Hz, 2H), 7.80-7.81 (d, *J* = 7.4 Hz, 2H), 7.32-7.31(d, *J* = 7.2 Hz, 4H), 7.22-7.26 (m, 1H), 4.20 (2H, s); ESI–MS m/z: 361.1137 (M+H); Elemental Anal. $C_{19}H_{16}N_6S$, Found (Calcd) %: C 63.56 (63.31), H 4.32 (4.47), N 23.55 (23.32).

(E)-5-(4-pridyl)-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4e)**: yield 79.3 %; light yellow solid; mp: 260.1-261.5 ℃; IR (KBr) v/cm^{-1}: 3031, 2965, 1600, 1476, 1283, 1027, 848, 688 ; ^{1}H NMR (400MHz, (D6) DMSO) δ 8.77 (3H, s), 8.03 (3H, s), 5.86(3H, s); ESI–MS m/z: 348.0934 (M+H); Elemental Anal. $C_{17}H_{13}N_7S$, Found (Calcd) %: C 58.56 (58.77), H 3.63 (3.77), N 28.76 (28.22).

(E)-5-(4-methylphenyl)-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4f)**: yield 74.1 %; light yellow solid; mp: 236.2-238.1℃; IR (KBr) v/cm^{-1}: 3033, 2965, 1598, 1476, 1282, 1017, 848, 687; ^{1}H NMR (400MHz, (D6) DMSO) δ 10.01 (s, 1H), 8.79-8.80 (d, *J* = 7.2 Hz, 2H), 7.81-7.82 (m, 3H), 7.74-7.76 (m, 3H), 7.35-7.37 (d, *J* = 8.0 Hz, 3H), 2.37 (3H, s); ESI–MS m/z: 361.1133 (M+H); Elemental Anal. $C_{19}H_{16}N_6S$, Found (Calcd) %: C 63.16 (63.31), H 4.29 (4.47), N 23.18 (23.32).

(E)-5-(2-methoxylphenyl)-4-[(4-(1H-imidazol)phenyl)methyleneamino]-1,2,4-triazole-3-thione **(4g)**: yield 71.4 %; light yellow solid; mp: 250.2-251.3 ℃; IR (KBr) v/cm^{-1}: 3056, 2965, 1597, 1474, 1283, 1017, 848, 688, 642; ^{1}H NMR (400MHz, (D6) DMSO) δ 9.65 (s, 1H), 8.40 (s, 2H), 7.86-7.89 (m, 2H), 7.81-7.83 (m, 3H), 7.50-7.56 (m, 2H), 7.13-7.15 (m, 4H), 3.66 (s, 3H); ESI–MS m/z: 337.1109 (M+H); Elemental Anal. $C_{19}H_{16}N_6OS$, Found (Calcd) %: C 60.45 (60.62), H 4.54 (4.28), N 22.56 (22.33).

4.3 Antifungal activities

The antifungal activities of all target compounds were evaluated against pathogenic fungi, containing *pythium solani*, *gibberlla nicotiancola*, *fusarium oxysporium f. sp. niveum*, *gibberlla saubinetii*, *alternaria iycopersici*, *phytophthora capsici*, *physalospora piricola*, *cercospora arachidicola hori*, and *fusarium oxysporium f. sp*. *cucumber*, which are often encountered in plants. Triadimefon was used as positive control. The plants pathogenic fungi were provided by Microbiology Institute of

Shaanxi and triadimefon was purchased from Jiangsu Sevencontinent Green Chemical Co., Ltd.,. The antifungal activity test method and data-processing method were according to the literature[16-17].

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Author Contribution Statement

Jingli Liu, Guanghui Zhang, Jiajia Li and Shuan Zhang performed the experiments, Hui Guo contributed reagents and analysis tools. Ruyi Jin designed the experiments, analyzed the data, and wrote the paper.

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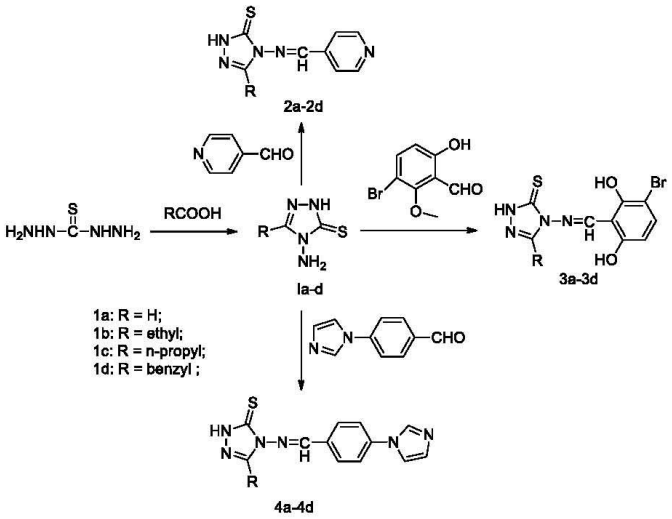
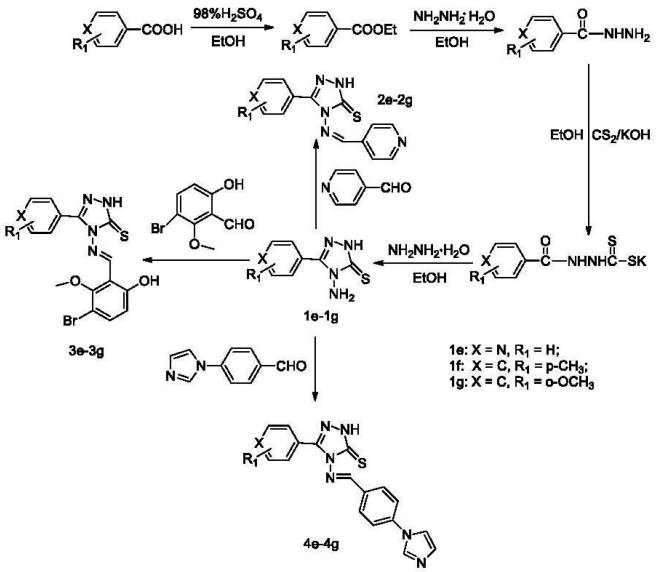


Scheme 1. Synthesis procedure of compounds 2a-d, 3a-d and 4a-d.



Scheme 2. Synthesis procedure of compounds 2e-3g, 3e-3g and 4e-4g.

Table 1. Pathogens fungi for test

Number	Pathogens fungi
A	*Gibberlla nicotiancola*
B	*Pythium solani*
C	*Gibberlla saubinetii*
D	*Fusarium oxysporium f.sp. niveum*
E	*Alternaria iycopersici*
F	*Phytophthora capsici*
G	*Fusarium oxysporium f.sp. cucumber*
H	*Cercospora arachidicola hori*
I	*Physalospora piricola*

Table 2. The antifungal results of the compounds II_{33-48} to nine pathogens at 50 ug·mL^{-1} (%)

Compounds	A	B	C	D	E	F	G	H	I
2a	42.6	10.2	3.4	31.2	57.3	52.3	33.1	28.9	42.1
2b	68.3	58.7	38.5	53.6	46.5	46.1	34.5	43.2	33.9
2c	70.1	65.7	25.6	60.2	33.7	38.2	32.9	33.2	32.1
2d	58.5	60.3	57.9	56.2	34.6	36.9	28.9	24.5	28.9
2e	28.2	34.5	36.3	40.2	44.7	32.1	26.8	26.8	20.9
2f	68.1	69.5	56.3	69.2	56.3	48.2	33.9	31.2	38.3
2g	63.4	72.8	32.3	73.9	48.2	46.3	35.5	34.8	40.8

3a	59.2	67.8	28.1	79.4	29.4	38.7	9.5	14.3	38.5
3b	56.1	65.2	18.8	77.3	23.5	35.5	9.5	35.7	30.8
3c	45.2	56.3	12.5	54.2	17.6	35.5	9.5	0.0	26.9
3d	33.8	48.9	46.9	56.1	23.5	32.3	0.0	0.0	23.1
3e	38.9	63.2	46.9	60.4	23.5	38.7	0.0	14.3	26.9
3f	45.3	78.2	43.8	70.3	23.5	32.3	9.5	14.3	26.9
3g	46.7	67.1	46.9	77.6	35.3	41.9	4.8	14.3	19.2
4a	66.8	82.8	27.5	83.6	15.7	36.7	9.5	7.1	19.2
4b	62.3	76.4	18.8	80.9	23.5	41.9	9.5	0.0	19.2
4c	45.3	65.2	12.5	62.3	29.4	45.2	4.8	0.0	19.2
4d	38.9	54.6	12.5	50.1	29.4	45.2	4.8	0.0	46.2
4e	60.5	76.3	18.8	60.7	11.8	29.0	19.0	28.6	50.0
4f	72.1	69.9	25.0	78.3	23.5	41.9	33.3	57.1	69.2
4g	30.7	40.2	12.5	50.3	35.3	45.2	9.5	14.3	30.8
Triadimefon	56.2	80.3	71.9	82.5	52.9	41.9	47.6	21.4	34.6

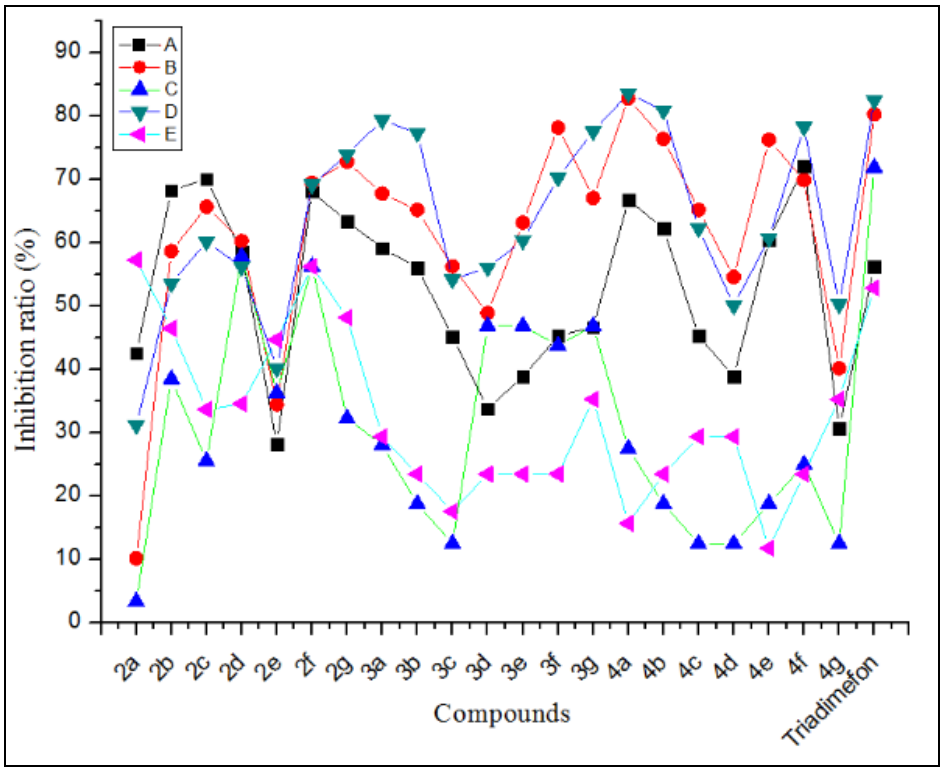


Fig.1 The inhibition ratio of title compounds against fungi A, B, C, D, and E at 50 ug•mL^{-1} (%)