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Synthesis and antifungal activity of new 1-(2,4-dichloro phenyl)-3-aryl-2-(1*H*-1,2,4-triazol-1-yl) prop-2-en-1-one derivatives

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A series of novel 1-(2,4-dichlorophenyl)-3-aryl-2-(1*H*-1,2,4-triazol-1-yl) prop-2- en-1-one derivatives were synthesized in good yields by an aldol condensation between 1-(2,4-dichlorophenyl)-2-(1*H*-1,2, 4-triazol-1-yl) ethanone and an aryl aldehyde. The structures were established through ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis. All compounds 4a-l at a concentration of 50 mg/L showed inhibition against the growth of *Gibberella zeae*, *Fusarium oxysporium*, *Cytospora mandshurica*. The title compound 4a displayed high antifungal activities against *G. zeae*, *F. oxysporium*, *C. mandshurica* comparable to hymexazol.

Key words: 1*H*-1,2,4-triazol derivative, prop-2-en-1-one moiety, antifungal activity.

INTRODUCTION

Since resistance of pathogens towards currently available drug therapies is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant fungus has become one of the most important areas of antibacterial research today. Traditionally, small heterocyclic molecules have been a reliable source for discovering novel biologically active molecules. Among the family of heterocyclic compounds, 1, 2, 4-triazole derivatives represent one of the most interesting and important classes of compounds, which have been the subject of extensive study in the recent past. Diverse biological activities, such as antibacterial (Arafa, 2010; Güzeldemirci et al., 2010), antifungal (Krimer et al., 1994; Arnoldi et al., 2007; Cao et al., 2008), anti-inflammatory (Abdel-Megeed et al., 2009; Kumar et al., 2008; Sun et al., 2008), insecticidal (Cudworth et al., 2007), herbicidal (Ma et al., 2006), antitumor (Lesyk et al., 2007; Sztanke et al., 2008; Hu et al., 2007), antiviral (Al-Soud et al., 2004; Akhtar et al., 2007) and plant growth regulatory activities (Liu et al., 2006, 2007) have been associated with 1, 2, 4-triazole derivatives. In the present work, we studied herein the effect of some novel 1-(2,4-dichlorophenyl)-3-aryl-2-(1H-1,2,4-triazol-1-yl)prop-2-en-1-one derivatives in the design of new antifungal compounds. The basis for the design of target compounds and the synthetic route through an aldol condensation between 1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazole-1-yl) ethanone and an aryl aldehyde are shown in Scheme 1. Preliminary bioassay results showed that some of these compounds possess a certain degree of antifungal activity against fungus at 0.05 mg/ml *in vitro* as shown in Table 2. According to the bioassay, compounds 4a displayed more potent antifungal activity against *Gibberella zeae*, *Fusarium oxysporium*, *Cytospora mandshurica* than hymexazol. To the best of our knowledge, this is the first report on the synthesis and antifungal activity of 1-(2,4-dichlorophenyl)-3-aryl-2-(1*H*-1,2,4-triazol-1-yl) prop-2-en-1-one analogue.

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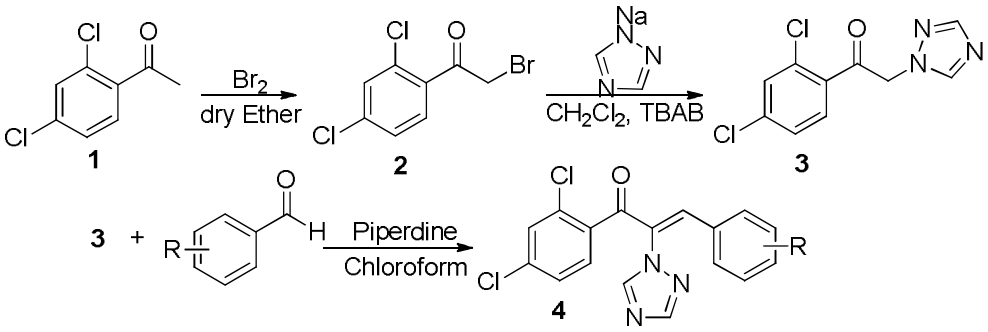
MATERIALS AND METHODS

General experimental part

Melting points of the products were determined on a XT-4 binocular



Scheme 1. Synthesis of 1-(2,4- dichloro phenyl)-3-aryl-2-(1H-1,2,4-triazol-1-yl) prop-2-en-1one.

microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in KBr disk. The ^{1}H, ^{13}C NMR (solvent $CDCl_3$, DMSO-d_6) spectral analyses were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Analytical thin layer chromatography (TLC) was performed on silica gel GF_{254}. Column chromatographic purification was carried out using silica gel. All reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated, and redistilled before use; 2-bromo-1-(2,4-dichlorophenyl) ethanone, intermediate 2 and sodium-1,2,4-triazolide were prepared according to the reported methods (Hill and Kropa, 1933; Abdul-Ghani and Tipping, 1995) and used without further purifications.

1-(2, 4-Dichlorophenyl)-2-(1H-1, 2, 4-triazol-1-yl) ethanone (3)

To a stirred suspension of the intermediate 2 (590 mg, 6.50 mmol) in 20 ml dichloromethane, TBAB (0.04 g, 0.13 mmol) was added in a single portion. The mixture was refluxed for 0.5 h, and then cooled to room temperature. After cooling to 0 to -5°C in an ice bath, the intermediate compound 1 (1150 mg, 4.32 mmol) was added in portions. The mixture was stirred for another 0.5 h, and then refluxed for 2.0 h. The reaction mixture was cooled to room temperature and filtered, and the solvent was removed by evaporation. Then, 20 ml of ice water was added with stirring and the mixture was acidified with 2 M hydrochloric acid, removed the undissolved substance and then neutralized with a 10% aqueous NaOH solution. The resulting precipitate was filtered, washed with water, and recrystallized from ethanol to afford a white solid 3 (1100 mg), Yield 80%; m.p. 115-116°C lit.(Helumut et al., 1988) m.p. 117°C); IR (KBr): ν_{max} 3126, 3098, 1713 (C=O), 1583 (C=N), 876, 817, 723 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.24 (s, 1H, triazole-H), 7.99 (s, 1H, triazole-H), 7.65 (d, *J*=8.6 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.39 (d, *J*=8.6 Hz, 1H, Ar-H), 5.60 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) : δ 192.2, 152.3, 145.0, 139.6, 133.7, 132.8, 131.7, 130.9, 128.1, 58.0. Anal. Calcd. for $C_{10}H_7Cl_2N_3O$: C, 46.90; H, 2.76; N, 16.41; Found: C, 46.94; H, 2.49; N, 16.44.

General procedure for the preparation of compounds 4a–l

To a well-stirred solution of 1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (255 mg, 1.00 mmol), 1.10 mmol of aryl aldehyde and 20 ml of dry chloroform, 3 drops of piperdine were added at room temperature. Then, the mixture was heated to reflux and the reaction was allowed to continue till its completion. The solvent was evaporated off in vacuum and the residue was purified by chromatography on silica gel to get desired compounds 4a–l in 33 to 70% yields. The physical and spectral data for 4a–l are provided below.

1-(2,4-Dichorophenyl)-3-(2-hydroxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propen-one (4a)

The crude residue was purified by chromatography on silica gel (Acetone/Petroleum ether, 2:1) to yield 4a as a white solide (162 mg). Yield 45%; m.p. 154-155°C; IR (KBr): ν_{max} 3125, 3066, 3036, 1630 (C=O), 1587 (C=N), 1545 (C=C), 804, 779, 761 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H, triazole-H), 7.97 (s, 1H, triazole-H), 7.95 (s, 1H, =CH), 7.37-7.34 (m, 1H, Ar-H), 7.29-7.27 (m, 2H, Ar-H), 7.26 (s, 1H, Ar-H), 7.11-7.02 (m, 3H, Ar-H), 5.30 (br s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 151.8, 150.3, 143.1, 136.3, 135.1, 133.9, 131.4, 130.0, 129.9, 128.8, 128.0, 127.0, 122.6, 120.8, 117.6, 116.8. Anal. Calcd. for $C_{17}H_{11}Cl_2N_3O_2$: C, 56.69; H, 2.76; N, 16.41; Found: C, 56.87; H, 3.00; N, 16.45.

1-(2,4-dichorophenyl)-3-(3-hydroxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4b)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4b as a straw yellow solid (118 mg). Yield 33%; m.p. 164-165°C; IR (KBr): ν_{max} 3487, 3144, 3125, 3090, 2922, 1661 (C=O), 1584 (C=N), 1551 (C=C), 808, 763, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H, triazole-H), 8.16 (s, 1H, triazole-H), 7.85 (s, 1H, =CH), 7.50 (d, *J*=1.8 Hz, 1H, Ar-H), 7.45 (d, *J*=8 Hz, 2H, Ar-H), 7.41-7.34 (m, 1H, Ar-H), 6.95-6.80 (m, 1H, Ar-H) , 6.69 (d, *J*=8 Hz, 1H, Ar-H), 6.21 (s, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.4, 157.2, 152.5, 145.2, 144.1, 137.7, 135.1, 132.3, 132.1, 131.5, 130.6, 130.3, 130.2, 127.7, 124.8, 120.8, 115.0. Anal. Calcd. for $C_{17}H_{11}Cl_2N_3O_2$: C, 56.69; H, 3.08; N, 11.67; Found: C, 56.76; H, 3.18; N, 11.29.

1-(2,4-Dichorophenyl)-3-(4-hydroxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4c)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4c as a straw yellow solid (151 mg). Yield 42%; m.p. 202-203°C; IR (KBr): ν_{max} 3445, 3148, 3080, 2939, 2621, 1659 (C=O), 1589 (C=N), 1540 (C=C), 831, 804, 779 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.72 (s, 1H, triazole-H), 8.32 (s, 1H, triazole-H), 7.82 (s, 1H, =CH), 7.65-7.58 (m, 3H, Ar-H),

6.74 (d, *J*=8.6 Hz, 2H, Ar-H), 6.70 (d, *J*=8.6 Hz, 2H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 190.0, 162.2, 153.3, 146.5, 145.7, 136.5, 136.1, 134.3, 134.3, 131.7, 130.9, 130.2, 130.0, 128.2, 122.3, 116.7, 116.7. Anal. Calcd for $C_{17}H_{11}Cl_2N_3O_2$: C, 56.69; H, 3.08; N, 11.67; Found: C, 56.55; H, 3.45; N, 11.90.

1-(2,4-Dichorophenyl)-3-(3-nitrophenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4d)

The crude residue was purified by chromatography on silica gel (EtOAc/ Petroleum ether, 2:1) to yield 4d as a yellow solid (217 mg). Yield 56%; m.p. 164-165°C lit.(Krimer et al., 1994) m.p. 165-166°C); IR (KBr): ν_{max} 3122, 3092, 1676 (C=O), 1595 (C=N), 1550 (C=C), 864, 831, 814 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H, triazole-H), 8.18 (s, 1H, triazole-H), 7.91 (s, 1H, =CH), 7.52 (s, 1H, Ar-H), 7.50 (d, *J*=5.2 Hz, 2H, Ar-H), 7.47-7.42 (m, 3H, Ar-H), 7.15 (d, *J*=7.5 Hz, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.1, 153.2, 148.4, 145.1, 139.7, 138.1, 135.2, 134.54, 134.52, 132.2, 130.4, 130.19, 130.16, 127.8, 125.9, 125.5. Anal. Calcd. for $C_{17}H_{10}Cl_2N_4O_3$: C, 52.46; H, 2.59; N, 14.40; Found: C, 52.46; H, 2.63; N, 14.59.

1-(2,4-Dichorophenyl)-3-(3-methoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propen- one (4e)

The crude residue was purified by chromatography on silica gel (EtOAc/ Petroleum ether, 1:1) to yield 4e as a white solid (119 mg). Yield 32%; m.p. 101-102°C; IR (KBr): ν_{max} 3110, 1663 (C=O), 1610 (C=N), 1557 (C=C), 833, 792, 750, 690 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (s, 1H, triazole-H), 8.33 (s, 1H, triazole-H), 7.85 (s, 1H, =CH), 7.73 (s, 1H, Ar-H), 7.70-7.62 (m, 2H, Ar-H), 7.26 (t, *J*=8.1 Hz, 1H, Ar-H), 7.03-7.01 (m, 1H, Ar-H), 6.57 (d, *J*=8.1 Hz, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 3.61 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.6, 158.8, 152.8, 146.5, 145.2, 138.6, 137.3, 135.6, 133.7, 132.5, 131.4, 130.3, 130.2, 129.6, 127.5, 121.1, 119.9, 111.1, 55.8. Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C, 57.77; H, 3.50; N, 11.23; Found: C, 57.70; H, 3.45; N, 11.35.

1-(2,4-Dichorophenyl)-3-(4-hydroxy-3-methoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4f)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 2:1) to yield 4f as a straw yellow solid (191 mg). Yield 49%; m.p. 186-187°C; IR (KBr): ν_{max} 3420, 3120, 3075, 2964, 1643 (C=O), 1595 (C=N), 1554 (C=C), 812, 750, 671 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.73 (s, 1H, triazole-H), 8.35 (s, 1H, triazole-H), 7.83 (s, 1H, =CH), 7.65-7.59 (m, 3H, Ar-H), 6.72 (d, *J*=8.1 Hz, 1H, Ar-H), 6.55 (d, *J*=6.9 Hz, 1H, Ar-H), 6.27 (s, 1H, Ar-H), 3.52 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.9, 153.3, 152.0, 150.2, 148.2, 146.6, 146.0, 136.5, 136.1, 131.7, 131.0, 130.2, 130.1, 128.3, 127.6, 122.6, 116.3, 114.1, 55.7. Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_3$: C, 55.40; H, 3.36; N, 10.77; Found: C, 55.26; H, 3.35; N, 10.43.

1-(2,4-Dichorophenyl)-3-(3-hydroxy-4-methoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4g)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4g as a straw yellow solid (121 mg). Yield 31%; m.p. 161-162°C; IR (KBr): ν_{max} 3130, 3084, 2940, 1663 (C=O), 1597 (C=N), 1550 (C=C), 858, 732, 671 cm^{-1}. "1H NMR (500 MHz, DMSO-d6): δ 8.70 (s, 1H, triazole-H), 8.31 (s, 1H, triazole-H), 7.81 (s, 1H, =CH), 7.64-7.55 (m, 3H, Ar-H), 6.92 (d, J=8.6 Hz, 1H, Ar-H), 6.61 (d, J=8.6 Hz, 1H, Ar-H), 6.18 (s, 1H, Ar-H), 3.79 (s, 3H, OCH3)". ^{13}C NMR (125 MHz, DMSO-d_6): δ 190.0, 153.3, 152.3, 136.4, 136.2, 131.7, 131.0, 130.6, 130.2, 128.2, 126.0, 124.0, 117.2, 112.4, 56.22. Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_3$: C, 55.40; H, 3.36; N, 10.77; Found: C, 55.19; H, 3.48; N, 10.91.

1-(2,4-Dichorophenyl)-3-(2-hydroxy-3-methoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4h)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4h as a yellow solid (195 mg). Yield 50%; m.p. 112-113°C; IR (KBr): ν_{max} 3130, 3084, 2940, 2938, 1662 (C=O), 1585 (C=N), 1558 (C=C), 732, 671 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H, triazole-H), 8.14 (s, 1H, triazole-H), 7.91 (s, 1H, =CH), 7.49-7.37 (m, 3H, Ar-H), 6.64 (t, *J*=8.0 Hz, 1H, Ar-H), 6.13 (s, 1H, Ar-H), 5.95 (d, *J*=8.6 Hz, 1H, Ar-H), 3.88 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.9, 153.1, 152.0, 150.1, 148.3, 146.7, 146.0, 136.5, 136.3, 131.7, 131.0, 130.2, 130.1, 128.2, 127.6, 122.5, 116.3, 114.1, 55.9. Anal. Calcd for $C_{18}H_{13}Cl_2N_3O_3$: C, 55.40; H, 3.36; N, 10.77; Found: C,55.45; H, 3.72; N, 10.91.

1-(2,4-Dichorophenyl)-3-(2,3-dimethoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4i)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4i as a straw yellow solid (242 mg). Yield 60%; m.p. 168-169°C; IR (KBr): ν_{max} 3115, 3078, 2970, 2938, 1684 (C=O), 1600 (C=N), 1549 (C=C), 833, 791, 739, 686 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.16 (s, 1H, triazole-H), 8.14 (s, 1H, triazole-H), 7.89 (s, 1H, =CH), 7.49-7.38 (m, 3H, Ar-H), 6.94 (d, *J*=8.1 Hz, 1H, Ar-H), 6.85 (t, *J*=8.1 Hz, 1H, Ar-H), 6.00 (d, *J*=7.5 Hz, 1H, Ar-H), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.7, 152.9, 152.8, 149.5, 145.1, 138.5, 137.5, 135.5, 133.2, 132.2, 130.2, 130.1, 127.6, 125.2, 124.6, 120.4, 116.0, 61.8, 56.0. Anal. Calcd. for $C_{19}H_{15}Cl_2N_3O_3$: C, 56.45; H, 3.74; N, 10.39; Found: C, 56.43; H, 3.95; N, 10.56.

1-(2,4-Dichorophenyl)-3-(2,4-dimethoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4j)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4j as a yellow solid (197 mg). Yield 49%; m.p. 161-162°C; IR (KBr): ν_{max} 3401, 3323, 3113, 3080, 1680 (C=O), 1591 (C=N), 1558 (C=C), 825, 751, 673 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (1H, s, triazole-H), 8.16 (1H, s, triazole C-H), 7.92 (1H, s, =CH), 7.47 (d, J=2.3 Hz, 1H, Ar-H), 7.42 (d, J=8.6 Hz, 1H, Ar-H), 7.37-7.35 (m, 1H, Ar-H), 6.37-6.29 (m, 3H, Ar-H), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.6, 164.8, 160.9, 152.9, 145.2, 138.8, 136.9, 136.0, 132.3, 131.2, 130.1, 127.4, 119.5, 117.4, 112.9, 106.1, 98.3, 55.9, 55.7. Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_3$: C, 56.45; H, 3.74; N, 10.39; Found: C, 56.47; H, 3.84; N, 10.60.

1-(2,4-Dichorophenyl)-3-(2,5-dimethoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4k)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4k as a yellow solid (282 mg). Yield 70%; m.p. 163-164°C; IR (KBr): ν_{max} 3123, 3069, 2951, 2833, 1668 (C=O), 1583 (C=N), 1558 (C=C), 817, 768, 673 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H, triazole- H), 8.16 (s, 1H, triazole-H), 7.92 (s, 1H, =CH), 7.48 (d, *J*=1.8 Hz, 1H, Ar-H), 7.45 (d, *J*=8.6

Table 1. Preparation of compound 3 under different conditions.

Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield (%)[a]
1	TBAB	Acetone	40	7	55
2	TBAB	CH_3CN	40	5.5	62
3	TBAB	CH_2Cl_2	r.t.	5	70
4	TBAB	CH_2Cl_2	40	3	80
5	TEBA	Acetone	40	8	53
6	TEBA	CH_3CN	40	6	59
7	TEBA	CH_2Cl_2	r.t.	4	65
8	TEBA	CH_2Cl_2	40	3.5	77

[a]isolated yields.

Hz, 1H, Ar-H), 7.39-7.37 (m, 1H, Ar-H), 6.93 (q, *J*=2.9 Hz, 1H, Ar-H), 6.80 (d, *J*=9.2 Hz, 1H, Ar-H), 5.95 (d, *J*=2.9 Hz, 1H, Ar-H), 3.76 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 153.4, 153.3, 152.8, 145.3, 138.5, 137.2, 135.5, 132.3, 132.2, 130.1, 127.4, 121.0, 119.8, 117.5, 113.8, 112.3, 56.2, 55.4. Anal. Calcd. for $C_{19}H_{15}Cl_2N_3O_3$: C, 56.45; H, 3.74; N, 10.39; Found: C, 56.19; H, 3.99; N, 10.58.

1-(2,4-Dichorophenyl)-3-(2-hydroxy-5-methoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)-2-propenone (4l)

The crude residue was purified by chromatography on silica gel (EtOAc/Petroleum ether, 1:1) to yield 4l as a yellow solid (210 mg). Yield 54%; m.p. 193-194°C; IR (KBr): ν_{max} 3121, 3085, 2940, 2948, 1662 (C=O), 1592 (C=N), 1559 (C=C), 732, 675 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (s, 1H, triazole-H), 8.22 (s, 1H, triazole-H), 7.72 (s, 1H, =CH), 7.53-7.48 (m, 3H, Ar-H), 7.21 (s, 1H, Ar- H), 6.46 (d, *J*=8 Hz, 1H, Ar-H), 6.22 (d, *J*=8.6 Hz, 1H, Ar-H), 5.57 (s, 1H, OH), 3.64 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.8, 154.9, 152.0, 144.2, 143.1, 136.3, 135.1, 133.8, 130.9, 129.8, 129.6, 127.0, 120.5, 118.0, 117.4, 117.3, 112.0, 55.9. Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_3$: C, 55.40; H, 3.36; N, 10.77; Found: C, 55.40; H, 3.23; N, 11.52.

Antifungal activity assay

The antifungal activity of all synthesized compounds was tested against three pathogenic fungi, *G. zeae*, *F. oxysporium*, and *C. mandshurica* by the poison plate technique (Boué et al., 2005).

Compounds were dissolved in 1 ml dimethyl sulfoxide before mixing with 90 ml potato dextrose agar (PDA). The compounds were tested at a concentration of 50 µg/ml. All kinds of fungi were incubated in PDA at 27±1°C for 4 days to get new mycelium for antifungal assay. Then mycelia dishes of approximately 4 mm diameter were cut from culture medium and one of them was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate aseptically. The inoculated plates were incubated at 27±1°C for 5 days. Acetone in sterile distilled water served as control, while hymexazol acted as positive controls. For each treatment, three replicates were conducted. The radial growth of the fungal colonies was measured and the data were statistically analyzed. The inhibiting effects of the test compounds *in vitro* on these fungi were calculated by the formula: I(%) = [(*C*-*T*)/(C-0.4)]*100, where *C* represents the diameter of fungi growth on untreated PDA, and *T* represents the diameter of fungi on treated PDA while I means the inhibition rate.

RESULTS AND DISCUSSION

Chemistry

The synthetic protocol leading to the title compounds is outlined in Scheme 1. The key intermediate 1-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (3) was earlier accessed in poor yield (40%) from α-bromo-2,4-dichloroacetophenone (2) and 1*H*-1,2,4-triazole in acetone in the presence of triethylamine (TEA) as a base. Several attempts to improve the yield by changing the solvent or the base were subsequently undertaken but with little success. It appears that the rate of the one-step N-alkylation reaction was adversely affected by the weak nucleophilicity of 1*H*-1,2,4-triazole and poor electrophilicity of the intermediate 2.

In order to enhance the reactivity of nucleophilic component of the reaction, we converted 1*H*-1,2,4-triazole into its corresponding sodium salt and then reacted with 2 in the presence of different solvents and catalysts to obtain 3 in much higher yield under relatively mild conditions as shown in Table 1. The optimal result was obtained in CH_2Cl_2 using tetrabutylammonium bromide (TBAB) as the catalyst. It is worth noting here that the compound 3, being basic in character, may easily be converted into a water-soluble salt under acidic conditions thus avoiding the need of separation and purification by chromatography on silica. Finally, the title compounds 4a–l were obtained through an aldol condensation reaction between 1-(2,4- dichloro-phenyl)-2-(1*H*-1,2,4-triazol-1-yl) ethanone and a dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone and a substituted aryl aldehyde.

The IR spectrum of compounds 4a-l showed characteristic absorption bands of carbonyl and C=C group of α, β-unsaturated carbonyl skeleton at 1690 to 1630 cm^{-1} and 1530 to 1560 cm^{-1} respectively. The absorption band observed at 1611 to 1580 cm^{-1} could be attributed to =CHN stretching in the ring. In the ^1H NMR spectra of title compounds, the two protons of triazole ring appeared as 8.07 to 8.74 ppm and 7.97 to 8.35 ppm respectively.

Table 2. Fungicidal activity of the title compounds 4a-l at concentration of 50 µg/ml

Compound	Inhibition rate[a] (%)		
	G. zeae	*F. oxysporum*	*C. mandshurica*
Hymexazol[b]	63.6±3.26	58.9±2.12	49.6±1.27
4a	62.4±0.82	49.6±3.28	54.0±2.24
4b	51.8±1.63	44.1±1.62	36.0±1.68
4c	40.5±1.06	27.4±1.76	37.3±1.70
4d	46.4±1.51	28.2±1.35	27.8±0.98
4e	58.0±1.68	41.6±1.64	43.2±1.26
4f	12.1±0.54	6.58±1.35	16.5±0.99
4g	39.9±0.82	43.8±1.74	43.4±0.92
4h	29.6±0.79	26.8±1.71	22.9±1.57
4i	58.0±1.68	56.2±1.98	33.7±1.09
4j	15.1±0.67	12.9±1.67	17.0±1.23
4k	24.6±0.77	13.7±1.83	19.0±1.12
4l	33.7±1.35	20.3±1.92	32.6±3.13

[a]Average of three replicates, [b]The commercial agricultural fungicide Hymexazol was used for the comparison of activity.

Pharmacology

All the compounds 4a-l were tested for *in vitro* antifungal activity using mycelial growth rate method (Boué et al., 2005). The antifungal activity was evaluated against three different fungal strains *G. zeae*, *F. oxysporium* and *C. mandshurica*. The results of preliminary bioassays were compared with the experimental data of a commercial agricultural fungicide, Hymexazol (Table 2). It is evident that the antifungal activity of the products depended to some extent on the nature of substituent R attached to the phenyl ring. Thus, among the synthesized compounds, 4a (R=2-OH) was found to be more potent against *G. zeae*, *F. oxysporum*, and *C. mandshurica* compared to the rest. Under laboratory conditions, at the concentration of 50 µg/ml, 4a could inhibit the growth of *G. zeae*, *F. oxysporum*, and *C. mandshurica* at 62.4, 49.6 and 54.0%, respectively. These figures were in the same range as those exhibited by Hymexazol (63.6% against *G. zeae*, 58.9% against *F. oxysporum*, 49.6% against *C. mandshurica* at 50 µg/ml). In particular, compounds 4b, 4e and 4i inhibited growth of a couple of pathogens but at a slightly lower level (4b, 4e and 4i against *G. zeae* at 51.8, 58.0 and 58.0%, respectively; 4i against *F. oxysporum* at 56.2%). As stated before, the remaining compounds were associated with weak antifungal activities. Out of the three selected fungal strains, *G. zeae* was more sensitive followed by *C. mandshurica* and *F. oxysporum* to all the compounds.

Conclusion

In summary, a series of novel 1-(2,4-dichlorophenyl)-3-aryl-2-(1H-1,2,4- triazol-1-yl) prop-2-en-1-one derivatives were obtained through aldol condensation. Amongst the tested products, compound 4a showed an antifungal activity level similar to that displayed by Hymexazol against *G. zeae*, *F. oxysporum*, and *C. mandshurica*.

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