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Synthesis and Antimicrobial Activity of 3-(1-Aryl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)propan-1-ones[1]

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Abstract—A number of novel 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)propan-1-ones has been synthesized from 2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)ethanone by its propargylation followed by the click reaction. Structures of all the newly synthesized compounds were characterized by ^{1}H and ^{13}C NMR, and Mass spectra. Their antimicrobial activity was evaluated.

Keywords: fluorinated organic molecule, propargylation, click reaction, 1,2,3-triazole, antimicrobial activity

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INTRODUCTION

Fluorinated compounds are highly lipophilic which allows their molecules to be easily delivered to the active sites across the living body. Since there is only a limited number of naturally occurring fluorine-containing compounds, there is a certain demand in developing synthetic approaches to fluorinated organic compounds with biological potential. 1,2,3-Triazole and its derivatives demonstrate diverse biological activities such as antimicrobial [1], antiproliferative [2], antibacterial [3], anti-HIV [4], antifungal [5], anticancer [6], and antitubercular [7]. Based on the above, we have synthesized 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)propan-1-ones (Scheme 1).

RESULTS AND DISCUSSION

A number of novel 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-propan-1-ones (**3a**–**3h**) has been synthesized from 2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)ethanone (**1**) by its propargylation in the presence of K_2CO_3 in dry acetone to afford 2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)pent-4-yn-1-one (**2**). Upon treatment of the compound **2** by various aryl azides in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in *t*-BuOH–H_2O media the title compounds were accumulated with high yields.

Spectral analysis, ^{1}H and ^{13}C NMR, and mass spectra, supported the structures of all synthesised compounds.

Antimicrobial activity. All synthesized compounds were screened for antibacterial activity against five gram positive and five gram negative bacterial strains: *M. Tuberculosis, M. Luteus, MRSA, B. Subtilis, B. Cereus, P. Aerginosa, K. Pneumonia, E. Coli, P. Vulgaris,* and *S. Typhi* using Gentamycin as a standard drug [8–10]. Among all compounds **3b** and **3d** demonstrated the highest activity against *K. Pneumonia* and *E. Coli*. The compounds **3a** and **3d** were most active against *K. pneumonia* and *E. coli.* The compounds **3a** and **3f** demonstrated the pronounced activity against *B. Subtilis* and *B. Cereus.*

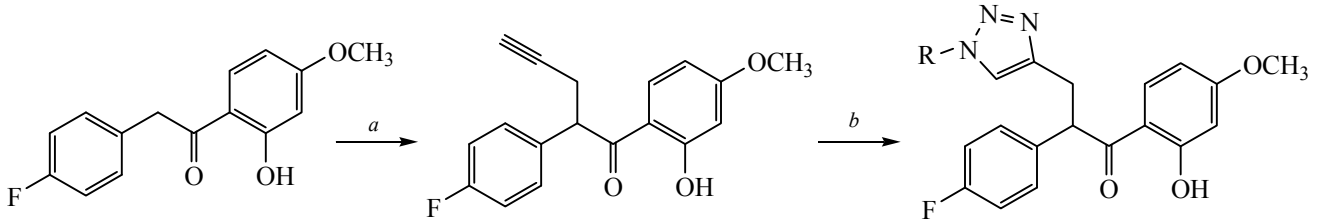
Antifungal activity. The synthesized compounds were also screened for antifungal activity against five fungal strains, including *T. Interdigitale, E. Floccosum, M. Canis, M. Gypseums,* and *Rubrum* using Nystatin as a standard drug [8–10]. The compound **3b** inhibited completely *M. Canis* and *M. Gypseums* and demonstrated the moderate activity against *T. Interdigitale*.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was tested by TLC using precoated silica gel plates 60_{254} (Merck). ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance II 400 MHz spectrometer using

[1] The text was submitted by the authors in English.

Scheme 1. Synthetic pathway to 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)propan-1-ones.



1 **2** **3a–3h**

a: propargyl bromide, K_2CO_3, dry acetone; *b:* R–N_3, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-butanol, water.

TMS as an internal standard. Mass spectra were measured on a GCMS-QP 1000 EX mass spectrometer. Elemental analysis was carried out on a Thermo Finnigan CHNS analyzer.

Synthesis of 2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)pent-4-yn-1-one (2). A mixture of 2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-ethanone (**1**) (1 mmol) with propargyl bromide (1.2 mmol) and potassium corbonate in dry acetone was refluxed for 8 h under TLC control. Upon completion of the process, the was mixture cooled down to room temperature and poured in ice cold water The precipitated solid was filtered off, washed with water and purified by column chromatography using ethyl acetate: heaxane as an eluent. Yield 55%, mp 164–166°C. ^{1}H NMR spectrum, δ, ppm: 1.94–1.96 t (1H, CH), 2.64–2.71 d.d (1H, CH_2), 2.94–3.01 d.d (1H, CH_2), 3.80 s (3H, OCH_3), 4.67–4.71 d.d (1H, CH), 6.35–6.40 m (2H, ArH), 6.99–7.03 m (2H, ArH), 7.28–7.31 m (2H, ArH), 7.61–7.63 d (1H, ArH), 12.68 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.7, 55.5, 61.6, 77.2, 101.0, 107.6, 108.0, 115.9, 116.1, 128.8, 129.5, 130.5, 132.2, 167.69, 189.4. MS 299 $[M - H]^+$.

Synthesis of 3-(1-Aryl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-propan-1-ones (3a–3h). A mixture of 2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)pent-4-yn-1-one (**2**) (1 mmol) with a certain azide (1 mmol), $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in *t*-BuOH–H_2O (2 : 1) was stirred at room temperature until completion of the reaction according to TLC (15–20 h). Then it was poured into ice cold water. The precipitated solid was filtered off and purified by column chromatography using ethyl acetate: heaxane as an eluent.

2-(4-Fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)propan-1-one (3a). Yield 84%, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 3.18–3.24 d.d (1H, CH_2), 3.62–3.68 d.d (1H, CH_2), 3.76 s (3H, OCH_3), 5.11–5.15 d.d (1H, CH), 6.32–6.35 m (2H, ArH), 7.01–7.06 m (2H, ArH), 7.27–7.34 m (3H, ArH), 7.37–7.40 m (2H, ArH), 7.45–7.54 m (2H, ArH), 7.58–7.73 m (2H, ArH), 12.76 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.8, 51.6, 55.6, 66.6, 101.0, 107.8, 112.8, 115.9, 116.4, 120.2, 120.4, 128.6, 128.8, 129.5, 129.6, 129.7, 130.9, 132.0, 132.2, 134.8, 134.8, 136.9, 166.1, 166.2, 167.6, 202.7. MS 418 $[M - H]^+$.

3-[1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-propan-1-one (3b). Yield 77%, mp 202–204°C. ^{1}H NMR spectrum, δ, ppm: 3.24–3.29 d.d (1H, CH_2), 3.62–3.68 d.d (1H, CH_2), 3.78 s (3H, OCH_3), 5.08–5.12 d.d (1H, CH), 6.34–6.46 m (2H, ArH), 6.98–7.01 m (2H, ArH), 7.27–7.32 m (2H, ArH), 7.39–7.42 m (2H, ArH), 7.50–7.55 m (2H, ArH), 7.68–7.73 m (2H, ArH), 12.77 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.6, 51.6, 55.5, 61.6, 101.0, 107.8, 112.8, 115.8, 116.1, 127.6, 127.8, 128.8, 129.5, 129.6, 130.6, 130.9, 132.0, 132.2, 166.1, 166.2, 167.6, 202.7. MS 452 $[M - H]^+$.

3-[1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-2-(4-fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-propan-1-one (3c). Yield 80%, mp 191–193°C. ^{1}H NMR spectrum, δ, ppm: 3.17–3.22 d.d (1H, CH_2), 3.61–3.67 d.d (1H, CH_2), 3.75 s (3H, OCH_3), 5.12–5.19 d.d (1H, CH), 6.32–6.35 m (2H, ArH), 6.86–7.01 m (2H, ArH), 7.28–7.46 m (5H, ArH), 7.63–7.68 m (2H, ArH), 7.81–7.83 m (1H, ArH), 12.77 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.6, 51.6, 55.5, 61.6, 101.0, 107.8, 112.8, 115.8, 116.1, 127.6, 127.8, 128.8, 129.5, 129.6, 130.6, 130.9, 132.0, 132.2, 166.1, 166.2, 167.6, 202.7. MS 452 $[M - H]^+$.

2-(4-Fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-3-[1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl]propan-1-one (3d). Yield 86%, mp 175–177°C. ^{1}H NMR spectrum, δ, ppm: 1.85 s (1H, CH_3), 3.10–3.16 d.d (1H, CH_2), 3.45–3.51 d.d (1H, CH_2), 3.72 s (3H, OCH_3), 5.01–5.08 d.d (1H, CH), 6.33–6.35 m (2H, ArH), 6.82–6.88 m (2H, ArH), 7.13–7.20 m (2H,

ArH), 7.28–7.32 m (2H, ArH), 7.49–7.56 m (2H, ArH), 7.60–7.65 m (2H, ArH), 12.58 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 25.5, 29.8, 55.8, 61.2, 100.4, 102.8, 120.4.1, 124.5, 127.2, 128.4, 129.5, 130.0, 131.6, 134.8, 155.1, 161.7, 166.3, 166.7, 167.0, 202.8. MS 433 $[M - H]^+$.

2-(4-Fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-3-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]propan-1-one (3e). Yield 79%, mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 3.20–3.26 d.d (1H, CH_2), 3.52–3.58 d.d (1H, CH_2), 3.77 s (3H, OCH_3), 3.80 s (1H, OCH_3), 5.08–5.15 d.d (1H, CH), 6.34–6.36 m (2H, ArH), 6.88–6.94 m (4H, ArH), 7.27–7.38 m (4H, ArH), 7.56–7.63 m (2H, ArH), 12.71 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 30.2, 52.1, 55.8, 56.3, 61.5, 99.3, 100.6, 112.4, 116.8, 118.9, 122.3, 126.5, 128.7, 129.5, 129.6, 130.4, 1314, 135.6, 155.5, 161.2, 166.7, 167.1, 167.5, 202.4. MS 447 $[M - H]^+$.

2-(4-Fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-3-{1-[4-(trifluoromethoxy)phenyl]-1*H*-1,2,3-triazol-4-y})propan-1-one (3f). Yield 75%, mp 212–214°C. ^{1}H NMR spectrum, δ, ppm: 3.19–3.23 d.d (1H, CH_2), 3.58–3.64 d.d (1H, CH_2), 3.765 s (3H, OCH_3), 5.08–5.12 d.d (1H, CH), 6.34–6.37 m (2H, ArH), 6.99–7.04 m (2H, ArH), 7.24–7.30 m (2H, ArH), 7.38–7.40 m (2H, ArH), 7.54–7.65 m (2H, ArH), 12.76 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.5, 51.5, 55.5, 66.4, 96.5, 100.8, 107.6, 111.2, 112.2, 120.2, 126.5, 127.6, 128.8, 129.5, 130.1, 130.7, 131.4, 133.2, 135.7, 160.4, 166.2, 167.6, 202.3. MS 502 $[M - H]^+$.

2-(4-Fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-3-[1-(2,4,6-trimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl]propan-1-one (3g). Yield 82%, mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 3.16–3.22 d.d (1H, CH_2), 3.59–3.65 d.d (1H, CH_2), 3.88 s (3H, OCH_3), 3.92 s (9H, OCH_3), 5.14–5.18 d.d (1H, CH), 6.33–6.35 m (2H, ArH), 6.84–6.88 m (2H, ArH), 6.95–7.01 m (2H, ArH), 7.30–7.33 m (2H, ArH), 7.55–7.83 m (2H, ArH), 12.76 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.6, 52.1, 56.3, 61.5, 98.2, 101.0, 117.4, 119.1, 129.5, 129.6, 129.8, 128.7, 130.9, 132.2, 135.6, 155.5, 161.5, 166.0, 166.2, 167.5, 170.5, 202.5. MS 508 $[M - H]^+$.

2-(4-Fluorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-3-[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]-propan-1-one (3h). Yield 85%, mp 196–198°C. ^{1}H NMR spectrum, δ, ppm: 3.19–3.24 d.d (1H, CH_2), 3.63–3.69 d.d (1H, CH_2), 3.77 s (3H, OCH_3), 5.13–5.17 d.d (1H, CH), 6.33–6.40 m (2H, ArH), 6.98–7.03 m (2H, ArH), 7.28–7.36 m (2H, ArH), 7.62–7.73(m, 2H, ArH), 7.88–7.90 m (2H, ArH), 8.35-8.37 m (2H, ArH), 12.72 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 30.1, 51.4, 55.5, 61.6, 101.0, 107.9, 116.0, 116.2, 119.0, 120.1, 120.3, 123.9, 124.4, 125.4, 128.8, 129.4, 129.5, 130.9, 132.0, 132.2, 147.0, 166.1, 166.3, 167.6, 202.4. MS 463 $[M - H]^+$.

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