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Design, Synthesis and Evaluation of Some Substituted Triazole Phenyl Methanones from Substituted Anilines

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ABSTRACT

Triazoles, a five-membered ring structure and three nitrogen atoms, are regarded as important building blocks for the synthesis of numerous organic compounds. Triazoles and their derivatives have received considerable attention over the past decade due to their chemotherapeutic value. It's been thought to be a functional core that exhibits most varieties of biological activity mainly antibiotics, antimicrobials and antifungals. In present work, a series of novel substituted triazole phenylmethanones were synthesized using Claisen-Schmidt condensation reaction of 1-(5-methyl-1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-ethan-1-one (**3a-d**) and some aromatic aldehydes. Final compounds (**5a-f**) were synthesized from compounds **4a-d**, hydrazine hydrate and benzoic acid by sequential reactions having intermolecular conjugate addition and formation of hydrazone. All the intermediate and final compounds were characterized from the mass, elemental and ^{1}H NMR spectral data.

KEYWORDS

Anilines, Acetyl acetone, Benzaldehydes, Sodium azide, Sodium nitrate, Sodium methoxide, Hydrazine hydrate, Benzoic acid.

INTRODUCTION

In all infectious diseases, tuberculosis (TB) is taken into account as one foremost dangerous chronic infections killing over 2 million people worldwide each year [1]. At the identical time, the arrival of AIDS has minimized the interest in tuberculosis control programs and contributed to the recovery of tuberculosis in developed countries [2]. Resistance of *Mycobacterium tuberculosis* (MTB) strains to antifungal agents is additionally an increasing challenge worldwide [3-5]. However, the most challenge with tuberculosis chemotherapy is not the shortage of recent development of new effective tuberculosis drugs with a replacement mechanism of action [6]. Therefore, there is an urgent need for brand new antituberculosis drugs that are efficacious against chronic MTB infection.

Reported works show that the derivatives of pyrazoline have a range of biological activities such as being antibacterial, antifungal [7], antidiabetic [8], anti-inflammatory [9] and effective against many mycobacteria [10,11]. As a result of remarkable pharmacological efficiency of 1,2,3-triazole derivatives, our research group have been focused on biological activity of 1,2,4-triazole nucleus containing substituted anilines. All

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structures were characterized by mass, CHN and ^{1}H NMR spectral data.

EXPERIMENTAL

Progress of the reaction and purity of the synthesized compounds was checked by using thin-layer chromatography (TLC) (ethyl acetate:hexane (3:7)/(6:4) mobile phase).^{1}H NMR spectra were recorded on 400 MHz (JEOL) in $CDCl_3$ solvent using TMS as an internal standard. Mass spectra were recorded on a LC-MS (Shimadzu LCMS-8030)/WATERS model Synapt G2 LCMS spectrometer. CHN was done on analyzer model Elementar Vario-EL III.

General procedure

General method for the synthesis of 1-azido substituted benzene (2a-b): Compounds **2a-b** were synthesized by the reaction between substituted anilines **1a-b** and sodium nitrate and sodium azide. In 80 mL of water, slowly conc. H_2SO_4 (0.45 mol) was charges and added to substituted aniline (0.15 mol) at > 0 ºC. Cooled the reaction mass to 0 ºC and then charged $NaNO_2$ solution (0.15 mol in 30 mL of water) at 0 ºC. The reaction mass was stirred for 20 min and then added NaN_3 solution (0.15 mol in 30 mL of water) at > 5 ºC. It was stirred at room temperature for 2 h. After completion of the reaction extract it with MDC and then remove the excess solvent under vacuum.

1-Azido-3-nitrobenzene (2a): Light brown colour solid; yield: 97%. m.p.: 80-82 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.6 (dd, 1H), 7.63 (d, 1H), 8.04 (d, 1H), 7.88 (s, 1H); Anal. analysis of $C_6H_4N_4O_2$ (*m.w.* 164.12) calcd. (found) %: C, 43.91 (43.99); H, 2.46 (2.41); N, 34.14 (34.10); O, 19.50 (19.51).

1-Azido-4-bromobenzene (2b): Black colour liquid; yield: 76%. b.p.: 65-66 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.13 (d, 2H), 7.76 (d, 2H); Anal. analysis of $C_6H_4N_3Br$ (*m.w.* 198.2) calcd. (found) %: C, 36.39 (36.49); H, 2.04 (2.15); N, 21.22 (21.30); Br, 40.35 (40.06).

General method for the synthesis of 1-(5-methyl-1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-ethan-1-one (3a-b): Compounds **3a-b** were synthesized by the reaction between 1-azido-substituted benzene **2a-b** and acetylacetone. A chilled solution of sodium methoxide (0.23 mol, in 120 mL methanol) was added to a mixture of acetylacetone (17 mL) and 1-azido-substituted benzene (0.15 mol) and stirred at 0-5 ºC for 1 h. The mixture was then refluxed in an oil-bath for 4 h. After completion of reaction, the pH of reaction mixture was acidified with concentrated hydrochloric acid. Compounds **3a-b** were isolated and crystallized from methanol.

1-(5-Methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-ethan-1-one (3a): Brown colour solid; yield: 88%. m.p.: 109-110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.1 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.57 (dd, 1H, Ar), 7.86 (s, 1H, Ar), 8.06 (d, 1H, Ar), 8.21 (d, 1H, Ar); Anal. analysis of $C_{11}H_{10}N_4O_3$ (*m.w.* 246.23) calcd. (found) %: C, 53.66 (53.33); H, 4.09 (3.89); N, 22.75 (19.72).

1-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-ethan-1-one (3b): Brown colour solid; yield: 90%. m.p.: 103-105 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.1 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.5 (d, 2H, Ar), 7.54 (d, 2H, Ar); Anal. analysis of $C_{11}H_{10}N_3OBr$ (*m.w.* 280.13) calcd. (found) %: C, 47.17 (46.55); H, 3.60 (3.12); Br, 28.52 (28.32); N, 15.01 (14.71); O, 5.71 (5.31).

General method for the synthesis of (*E*)-3-aryl-1-(5-methyl-1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-prop-2-en-1-one (4a-d): Aromatic aldehyde (0.012 mol) and compounds **3a-b** (0.01 mol) dissolved in ethanol (20 mL) followed by slowly addition of an aqueous solution of KOH (0.0128 mol). The reaction mixture was stirred in crushed ice bath for 2 h and at room temperature for 4 h. The mixture was filtered and the solid was washed with cold water and cold ethanol. The products were crystallized from ethanol to yield **4a-d**.

(*E*)-1-(5-Methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-3-(3-nitrophenyl)prop-2-en-1-one (4a): Off white colour; yield: 92%. m.p.: 188-189 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H, CH_3), 6.48 (d, 1H, CH), 7.88 (d, 1H, CH), 7.57 (dd, 1H, Ar_1), 8.06 (d, 1H, Ar_1), 7.86 (d, 1H, Ar_1), 8.21 (d, 1H, Ar_1), 7.59 (dd, 1H, Ar_2), 7.99 (d, 1H, Ar_2), 8.14 (d, 1H, Ar_2), 8.31 (d, 1H, Ar_2); Anal. analysis of $C_{18}H_{13}N_5O_5$ (*m.w.* 379.33) calcd. (found) %: C, 56.99 (56.54); H, 3.45 (3.89); N, 18.46 (17.26); O, 21.09 (22.30).

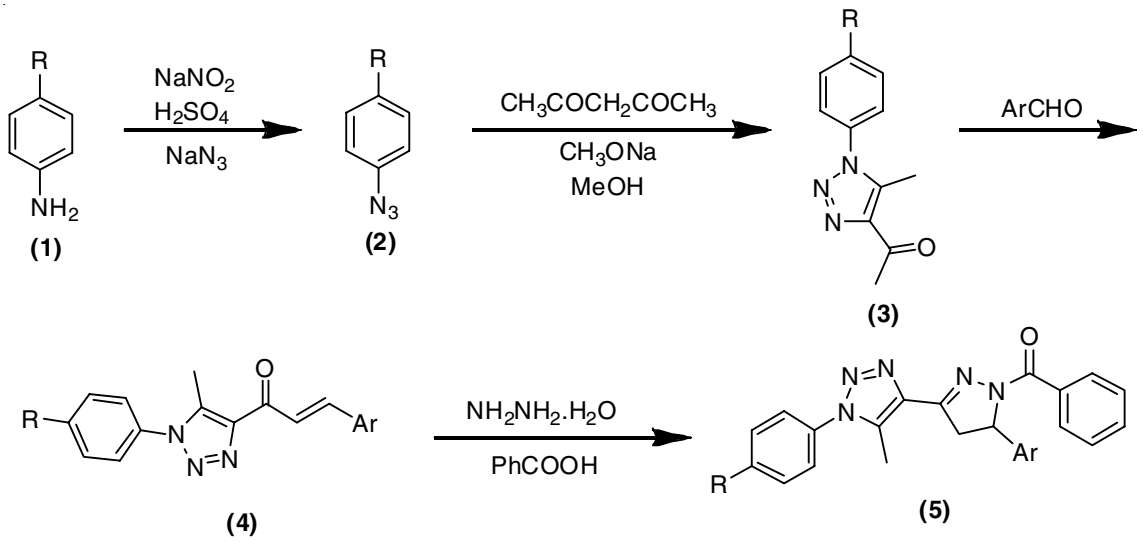
(*E*)-1-(5-Methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-3-(2-chlorophenyl)prop-2-en-1-one (4b): Off white colour; yield: 92%. m.p.: 183-185 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H, CH_3), 6.53 (d, 1H, CH), 7.97 (d, 1H, CH), 7.06 (dd, 1H, Ar_1), 7.25 (dd, 1H, Ar1), 7.28 (d, 1H, Ar_1), 7.53 (d, 1H, Ar_1), 7.57 (dd, 1H, Ar_2), 7.86 (s, 1H, Ar_2), 7.57 (d, 1H, Ar_2), 8.06 (d, 1H, Ar_2); Anal. analysis of $C_{18}H_{13}N_4O_3Cl$ (*m.w.* 368.78) calcd. (found) %: C, 58.63 (58.50); H, 3.55 (3.67); Cl, 9.61 (9.40); N, 15.19 (16.60); O, 13.02 (11.83).

(*E*)-1-(5-Methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-3-(4-chlorophenyl)prop-2-en-1-one (4c): Off white colour; yield: 92%. m.p.: 183-185 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H, CH_3), 6.24 (d, 1H, CH), 7.77 (d, 1H, CH), 7.62 (d, 2H, Ar_1), 7.68 (d, 2H, Ar_1), 7.57 (dd, 1H, Ar_2), 7.86 (s, 1H, Ar_2), 8.06 (d, 1H, Ar_2), 8.21 (d, 1H, Ar_2); Anal. analysis of $C_{18}H_{13}N_4O_3Cl$ (*m.w.* 368.78) calcd. (found) %: C, 58.63 (58.50); H, 3.55 (3.67); Cl, 9.61 (9.40); N, 15.19 (16.60); O, 13.02 (11.83).

(*E*)-1-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-3-(3-nitrophenyl)prop-2-en-1-one (4d): Off white colour; yield: 92%. m.p.: 173-175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H, CH_3), 6.95 (d, 1H, CH), 7.81 (d, 1H, CH), 7.69 (dd, 1H, Ar_1), 7.99 (d, 1H, Ar_1), 8.14 (d, 1H, Ar_1), 8.31 (d, 1H, Ar_1), 7.5 (d, 2H, Ar_2), 7.54 (d, 2H, Ar_2); Anal. analysis of $C_{18}H_{13}N_4O_3Br$ (*m.w.* 413.23) calcd. (found) %: C, 52.32 (52.15); H, 3.17 (3.03); Br, 19.34 (20.50); N, 13.56 (13.66); O, 11.62 (10.67).

(*E*)-1-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-3-(2-chlorophenyl)prop-2-en-1-one (4e): Off white colour; yield: 92%. m.p.: 146-147 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H, CH_3), 6.53 (d, 1H, CH), 7.97 (d, 1H, CH), 7.08 (dd, 1H, Ar_1), 7.25 (dd, 1H, Ar_1), 7.28 (d, 1H, Ar_1), 7.53 (d, 1H, Ar_1), 7.5 (d, 2H, Ar_2), 7.54 (d, 2H, Ar_2); Anal. analysis of $C_{18}H_{13}N_3OClBr$ (*m.w.* 402.68) calcd. (found): C 53.69 (53.50); H, 3.25 (3.67); Br, 19.84 (20.50); Cl, 8.80 (8.50); N, 10.44 (10.20); O, 3.97 (3.62).

(*E*)-1-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-3-(4-chlorophenyl)prop-2-en-1-one (4f): White colour; yield: 92%. m.p.: 144-146 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ



R = NO_2 (m), Br (p); Ar = *o*-ClC_6H_4, *p*-ClC_6H_4, *m*-$NO_2C_6H_4$

Scheme-I: Synthetic route of some substituted triazole phenyl methanones (**5**) from substituted anilines

ppm: 2.42 (s, 3H, CH_3), 6.7 (d, 1H, CH), 7.7 (d, 1H, CH), 7.62 (d, 2H, Ar_1), 7.68 (d, 2H, Ar_1), 7.5 (d, 2H, Ar_2), 7.54 (d, 2H, Ar_2); Anal. analysis of $C_{18}H_{13}N_3OClBr$ (*m.w.* 402.68) calcd. (found) %: C, 53.69 (53.55); H, 3.25 (3.20); Br, 19.84 (19.70); Cl, 8.80 (8.60); N, 10.44 (10.40); O, 3.97 (4.50).

General method for the synthesis of (5-(4-substituted phenyl)-3-(5-methyl-1-(4-substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (5a-d): Compounds **4a-d** (0.01 mol), hydrazine hydrate (0.03 mol) and benzoic acid (0.01 mol) dissolved in 50 mL ethanol were refluxed for 3 h. On completion of reaction, it was poured into crushed-ice bath and then the precipitate was separated by filtration, washed with water and crystallized from ethanol to yield **5a-f**.

(3-(5-methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-5-(3-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)-methanone (5a): Yellow colour; yield: 45%. m.p.: 180-181 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.72-2.79 (s, 3H, CH_3), 3.29-3.32 (dd, 1H, CH), 3.83-3.90 (dd, 1H, CH), 5.04-5.09 (dd, 1H, CH), 7.56-8.48 (m, 13H, Ar_1-H, Ar_2-H, Ar_3-H); Anal. analysis of $C_{25}H_{19}N_7O_5$ (*m.w.* 497.14) calcd. (found) %: C, 60.36 (60.32); H, 3.85 (3.89); N, 19.71 (19.55); O, 16.08 (16.24).

(3-(5-Methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)methanone (5b): Yellow colour; yield: 68%. m.p.: 116-118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.56-2.68 (s, 3H, CH_3), 3.22-3.24 (dd, 1H, CH), 3.85-3.92 (dd, 1H, CH), 5.30-5.35 (dd, 1H, CH), δ 7.24-8.42 (m, 13H, Ar_1-H, Ar_2-H, Ar_3-H); Anal. analysis of $C_{25}H_{19}N_6O_3Cl$ (*m.w.* 486.12) calcd. (found) %: C, 61.67 (61.58); H, 3.93 (3.90); Cl, 7.28 (7.42); N, 17.16 (17.10); O, 9.68 (9.72).

(3-(5-Methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)-methanone (5c): Yellow colour; yield: 42%. m.p.: 116-118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.68-2.77 (s, 3H, CH_3), 3.29-3.32 (dd, 1H, CH), 3.72-3.79 (dd, 1H, CH), 4.90-4.95 (dd, 1H, CH), 7.34-8.43 (m, 13H, Ar_1-H, Ar_2-H, Ar_3-H); Anal. analysis of $C_{25}H_{19}N_6O_3Cl$ (*m.w.* 486.12) calcd. (found) %: C, 61.67 (61.58); H, 3.93 (3.90); Cl, 7.28 (7.42); N, 17.16 (17.42); O, 9.68 (9.72).

(3-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-5-(3-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)-methanone (5d): Off white colour; yield: 60%. m.p.: 158-160 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.63 (s, 3H, CH_3), 3.58-3.61 (dd, 1H, CH), 3.72 (dd, 1H, CH), 5.45-5.48 (dd, 1H, CH), 7.36-8.66 (m, 14H, Ar_1-H, Ar_2-H, Ar_3-H); Anal. analysis of $C_{25}H_{19}N_6O_3Br$ (*m.w.* 530.07) calcd. (found) %: C, 56.51 (56.15); H, 3.60 (3.38); Br, 15.04 (15.02); N, 15.82 (15.72); O, 9.03 (9.75).

(3-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)methanone (5e): Off white colour; yield: 54%. m.p.: 110-112 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.70-2.79 (s, 3H, CH_3), 3.23 (dd, 1H, CH), 3.86-3.92 (dd, 1H, CH), 5.34-5.40 (dd, 1H, CH), 7.27-7.77 (m, 13H, Ar_1-H, Ar_2-H, Ar_3-H); Anal. analysis of $C_{25}H_{19}N_5OClBr$ (*m.w.* 519.05) calcd. (found) %: C, 57.65 (57.60); H, 3.68 (3.62); Br, 15.34 (15.64); Cl, 6.81 (6.91); N, 13.45 (13.15); O, 3.07 (3.08).

(3-(5-Methyl-1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) (phenyl)methanone (5f): Off white colour; yield: 59%. m.p.: 108-109 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.68-2.77 (s, 3H, CH_3), δ 3.29-3.32 (dd, 1H, CH), δ 3.72-3.79 (dd, 1H, CH), δ 4.90-4.95 (dd, 1H, CH), δ 7.34-7.83 (m, 12H, Ar_1-H, Ar_2-H, Ar_3-H); Anal. analysis of $C_{25}H_{19}N_5OClBr$ (*m.w.* 519.05) calcd. (found) %: C, 57.65 (57.60); H, 3.68 (3.62); Br, 15.34 (15.64); Cl, 6.81 (6.91); N, 13.45 (13.15); O, 3.07 (3.08).

RESULTS AND DISCUSSION

Compound (*E*)-3-aryl-1-(5-methyl-1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-prop-2-en-1-one (**4a-d**) were synthesized by the Claisen-Schmidt condensation reaction of 1-(5-methyl-1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-ethan-1-one (**3a-d**) and some aromatic aldehydes. Final molecules (5-(4-substituted phenyl)-3-(5-methyl-1-(4-substituted phenyl)-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H* -pyrazol-1-yl) phenyl

methanone (**5a-f**) were synthesized from compounds **4a-d**, hydrazine hydrate and benzoic acid by sequential reactions having intermolecular conjugate addition and formation of hydrazone (**Scheme-I**). All the intermediate and final compounds were characterized from the mass, elemental and ^{1}H NMR spectral data. Compounds **5a-f** were yellow crystalline solids, while **5d-f** are off white crystalline solids soluble in chloroform, DMSO, DMF, ethanol and acetic acid on mild heating and insoluble in water and hexane.

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