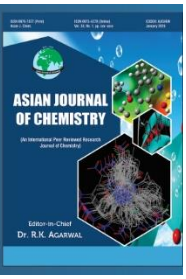
Asian Journal of Chemistry; Vol. 38, No. 7 (2026), 1795-1804

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2026.36100



Synthesis, Characterisation, Cytotoxicity, Antimicrobial and Docking Studies of (2,4-*Bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone Derivatives

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Received: 29 March 2026 *Accepted*: 29 May 2026 *Published online*: 3 July 2026 AJC-22405

Using a copper(I)-catalysed azide-alkyne (CuAAC) cycloaddition method, a new series of 2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)(phenyl)methanone analogues (**7a-o**) were synthesised, characterised by ^{1}H and ^{13}C NMR, FT-IR, mass and elemental analysis and evaluated for the biological activities. Cell viability method on MCF-7, HeLa and PC-3 cells revealed compounds **7d**, **7j** and **7f** exhibited potent cytotoxicity, while other compounds displayed moderate to weak effects, indicating promising anticancer potential for selected derivatives. Antibacterial and antifungal activities were tested using disc diffusion method, among the tested compounds **7d**, **7f** and **7k** showed strong activity, outperforming streptomycin and amphotericin B. Molecular docking against 17β-HSD1 demonstrated high binding affinities for **7j** (-12.4 kcal/mol) and **7d** (-12.3 kcal/mol), superior to doxorubicin (-8.9 kcal/mol), forming interactions with key residues like ILE14 and SER142. These findings suggest the synthesised compounds are promising anticancer and antimicrobial agents.

Keywords: CuAAC reaction, 1,2,3-Triazole hybrids, Anticancer agents, Antifungal evaluation, VEGFR2 inhibition.

INTRODUCTION

1,2,3-Triazole heterocyclic ring-fused analogues are currently high valuable in medicinal chemistry since they can form strong hydrogen bonds and are chemically stable, versatile and applicable in a wide range of industries [1,2] and biological fields, including antitumor [3], antimicrobial [4], antiviral [5], anti-Alzheimer's [6], antitubercular [7], antioxidant [8], antidiabetic [9], anti-inflammatory [10], antihypertensive [11], anticonvulsant [12], antimalarial [13], anti-HIV [14] and anti-obesity activity [15].

Cu(I)-catalyzed click chemistry represents a powerful and selective synthetic strategy for the preparation of novel molecular derivatives, particularly those containing the 1,2,3-triazole heterocyclic motif [16,17]. The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction enables the regioselective formation of 1,4-disubstituted 1,2,3-triazoles, which are widely recognized for their chemical stability, hydro-gen bonding capability and diverse biological activities. These characteristics have facilitated the development of numerous 1,2,3-triazole ring-fused heterocyclic analogues, exhibiting enhanced pharmacological, electronic and structural properties [18]. Consequently, CuAAC-derived triazole frameworks have found extensive applications in materials science [19], drug discovery [20], biosynthesis [21], polymer chemistry [22], supramolecular chemistry [23], amino acid synthesis [24], DNA labelling and the construction of glycoclusters and glycodendrimers [25]. The incorporation of fused 1,2,3-triazole systems has further expanded the utility of these compounds in medicinal and functional-material applications [18,26].

Chemotherapy remains a cornerstone of cancer treatment; however, its clinical efficacy is often limited by poor selectivity, severe side effects and the emergence of drug resistance, as highlighted by previous workers [27,28]. Simultaneously, antimicrobial resistance has become a major global health concern, significantly compromising the effectiveness of existing therapies against infectious diseases [29-31]. Cancer patients undergoing chemotherapy are particularly vulnerable to microbial infections because of treatment-induced immunosuppression [32,33]. Therefore, the development of single molecular entities possessing both anticancer and antimicrobial activities represents an attractive strategy to reduce treatment costs, minimize adverse effects, limit antimicrobial resistance and decrease the frequency of drug administration. Furthermore, the high toxicity associated with many conventional

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anticancer agents has accelerated efforts to discover safer and more effective therapeutic candidates [34-36].

The rapid emergence of multidrug-resistant pathogens, driven by genetic mutations, horizontal gene transfer and the indiscriminate use of antibiotics, further underscores the urgent need for novel bioactive compounds [37-41]. Notably, resistant strains of *Staphylococcus aureus* have developed defense mechanisms against several classes of antibiotics, including β-lactams, aminoglycosides, glycopeptides and fluoroquinolones [42,43]. In this context, heterocyclic scaffolds containing the 1,2,3-triazole moiety have attracted considerable attention owing to their diverse pharmacological properties. Accordingly, the present study describes the design and synthesis of a novel series of 15 substituted (2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone derivatives (**7a-o**). The synthesized compounds were structurally characterized using various spectroscopic techniques and subsequently evaluated for their anticancer, antibacterial, antifungal and molecular docking properties.

EXPERIMENTAL

All the reactions were conducted in an oven-dried apparatus. TLC on silica gel plates (60 F_{254}) was used to monitor the progress of the reaction, while iodine vapour and UV light were used for visualisation. Distilled hexane and ethyl acetate mixtures were used in column chromatography on silica gel (60-120 mesh) for purification. $CDCl_3$/DMSO-d_6 solvents were used to record the ^1H and ^{13}C NMR spectra on 400 MHz spectrometers, mostly Varian 400 MHz equipment. A Shimadzu FT-IR-8400s was used to record infrared spectra and a QSTAR XL GCMS mass spectrometer was used to obtain mass spectra. An DbkProg device with an open glass capillary tube was used to measure melting points and are uncorrected.

Synthesis of (2,4-dinitrophenyl)(phenyl)methanone (2): (2,4-Dichlorophenyl)(phenyl)methanone (**1**) (6 g, 0.0239 mol) was dissolved in sulphuric acid (12 mL). Cool to 0-5 ºC, then added the nitrating mixture (1:2 ratio of HNO_3 and H_2SO_4) dropwise over a duration of 20 min and agitated the reaction mixture for 2-3 h at the same temperature. After the complete disappearance of the starting material, the reaction mass was quenched with crushed ice. The resulting light-yellow solid was filtered, washed with cold water and dried in an oven. Yield: 85%.

Synthesis of (2,4-diaminophenyl)(phenyl)methanone (3): Compound **2** (5.5 g, 0.0202 mol), 10% Pd/C (0.55 g) catalyst and methanol (27 mL) were charged into a clean and dry autoclave. The mixture was hydrogenated for 7 h at lab temperature under a hydrogen atmosphere with continuous stirring. After completion of the reaction, the reaction mass was filtered through a celite pad. The methanol solvent was distilled under reduced pressure. The resulting crude product was recrystallised using methanol to obtain an off-white pure solid compound. Yield: 96%.

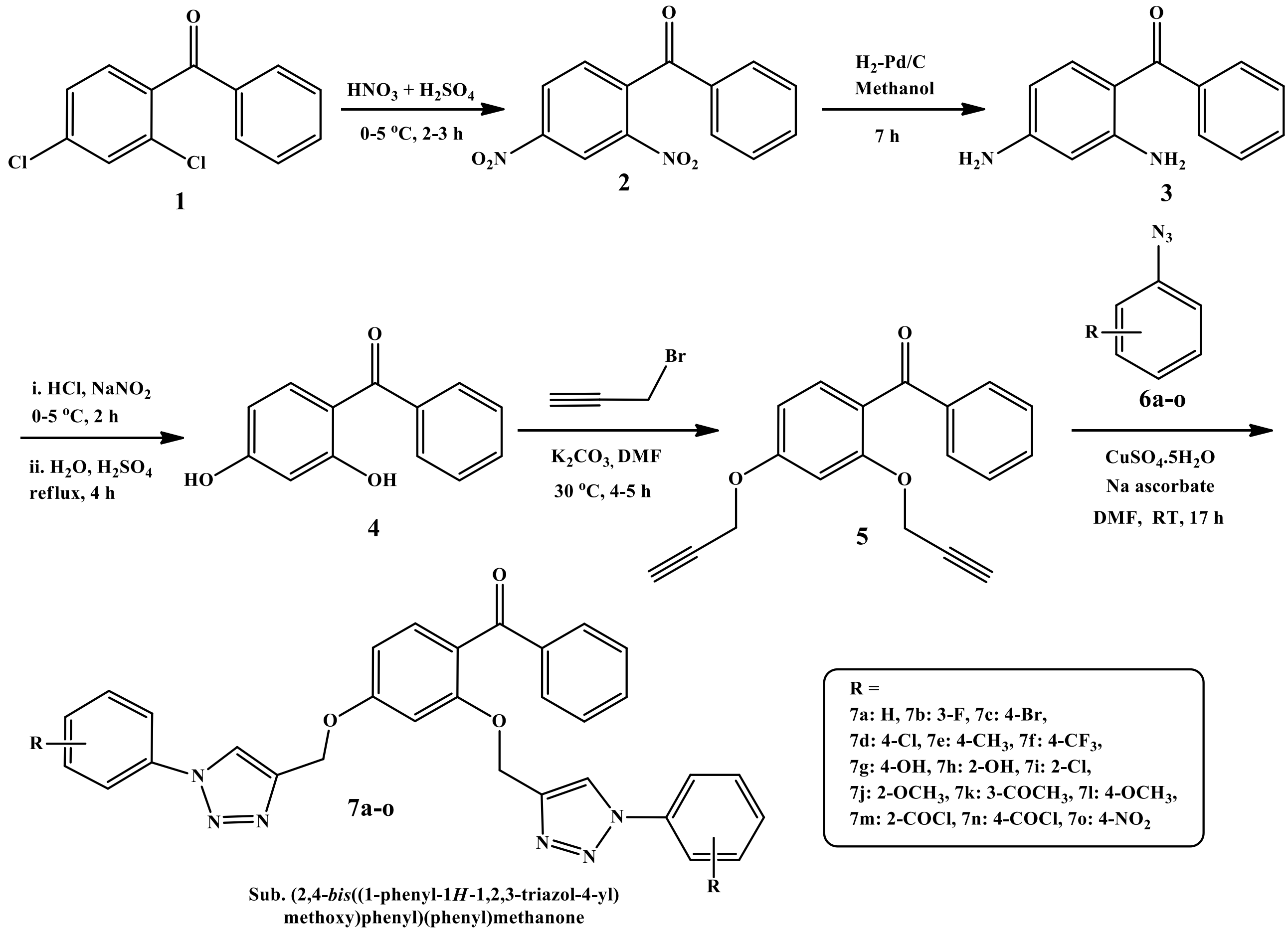
Synthesis of (2,4-dihydroxyphenyl)(phenyl)methanone (4): An amine compound **3** (4 g, 1 equiv., 0.0188 mol) was dissolved in conc. HCl (4 g, 6 equiv., 0.1132 mol) and cooled to 0-5 ºC. A solution of $NaNO_2$ (1.56 g, 1.2 equiv., 0.0226 mol) in water (12 mL) was added dropwise and stirred for 2 h at 0-5 ºC. Subsequently, aqueous H_2SO_4 (30%, 3 vol., 12 mL) was added and the reaction mixture was refluxed for 2-4 h to obtain the corresponding dihydroxy derivative. The crude product obtained was isolated by using column chromatography with 10% ethyl acetate and hexane. Yield: 89%. Colour: Off white solid.

Synthesis of (2,4-bis(prop-2-yn-1-yloxy)phenyl)(phenyl)-methanone (5): Compound **4** (3.5 g, 0.0163 mol) dissolved in DMF (10 mL) was added to K_2CO_3 solution (11.28 g, 0.0817 mol) and then the reaction mixture was cooled to 0 ºC. 3-Bromoprop-1-yne (5.83 g, 0.0490 mol) was added slowly dropwise at 0 ºC. The reaction was then allowed to proceed at room temperature for 4-5 h. TLC was used to monitor the reaction progress. After the complete consumption of the starting material, the reaction mass was quenched with crushed ice. The resulting off-white solid was filtered and washed with cold water. Yield: 82%.

Substituted aryl azide derivatives (6a-o): A 50 mL portion of 5 N HCl was placed in a round-bottom flask and cooled to 0 ºC. Substituted aryl amines (0.02 mol) were added, followed by the slow dropwise addition of aqueous NaN_3 (24 mmol, 50 mL). An additional 50 mL of aqueous NaN_3 (24 mmol) was then added while maintaining the temperature at 0 ºC. The reaction mixture was stirred for 2 h at room temperature. After completion, the mixture was extracted with DCM (2 × 50 mL). The combined organic extracts were washed successively with saturated $NaHCO_3$ solution and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure at room temperature. The resulting aryl azides (**6a-o**) were obtained and used directly in the subsequent reactions without further purification.

Synthesis of title 1,2,3-triazole derivatives (7a-o): Compound **5** (0.25 g, 0.00086 mol) dissolved in DMF solvent (2 mL) was mixed to sodium ascorbate (1 mL) and $CuSO_4 \cdot 5H_2O$ (1 mL) as catalyst and stirred for 5 min, followed by the addition of substituted aryl azides (0.001 mol) under N_2 gas conditions. The reaction mixture was stirred at room temperature for 17 h. Upon completion, the reaction was quenched with crushed ice, resulting in the precipitation of various coloured solid products (**Scheme-I**). The solids were collected by filtration, washed successively with cold water and hexane, and dried to afford the desired 1,2,3-triazole derivatives in good yields (66-84%).

(2,4-*Bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-(phenyl)methanone (7a): Colour: off white, yield: 72%, m.p.: 199-201 ºC, m.f.: $C_{31}H_{24}N_6O_3$; Elemental analysis: calcd. (found) %: C, 70.44 (70.41); H, 4.58 (4.54); N, 15.90 (15.93); O, 9.08 (9.05); IR (KBr, ν_{max}, cm^{-1}): 3096 (C-H, Ar), 2932 (C-H, aliph.), 1682 (C=O), 1505 (C=C, Ar), 1338 (N-N), 1231 (C-O-C, Ar-O-CH_2); ^1H NMR (DMSO, 400 MHz, δ ppm): 9.04 (1H, s, triazole ring-CH), 8.03 (1H, s, triazole ring-CH), 7.93-7.95 (2H, d, Ar, *J* = 8 MHz), 7.74-7.76 (2H, d, Ar, *J* = 8 MHz), 7.61-7.63 (6H, m, Ar), 7.51-7.53 (4H, m, Ar), 7.41-7.42 (3H, m, Ar), 7.16 (1H, s, Ar), 5.40 (2H, CH_2), 5.23 (2H, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 190.54 (C=O), 166.54, 164.32, 143.62, 143.16, 137.60, 130.98, 130.92, 130.67, 129.91, 129.85, 124.30, 123.99, 122.51, 121.32, 121.20, 119.69 (trizole-CH), 109.21, 101.01, 72.82 (CH_2), 72.61 (CH_2). Mass: 528 $[M+1]^+$.



Scheme-I: Synthetic approaches to synthesise novel 1,2,3-Triazole derivatives (**7a-o**)

(2,4-*bis*((1-(3-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)(phenyl)methanone (7b): Colour: ash, yield: 72%, m.p.: 216-218 °C; m.f.: $C_{31}H_{22}F_2N_6O_3$; Elemental analysis: calcd. (found) %: C, 65.95 (65.91); H, 3.93 (3.96); F, 6.73 (6.70); N, 14.89 (14.87); O, 8.50 (8.54); IR (KBr, ν_{max}, cm^{-1}): 3038 (C-H, Ar), 2975 (C-H, aliph.), 1688 (C=O), 1505 (C=C, Ar), 1319 (N-N), 1249 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.93 (1H, s, triazole ring-CH), 7.93 (1H, s, triazole ring-CH), 7.81 (2H, d, Ar, *J* = 8 MHz), 7.62 (2H, d, Ar, *J* = 8 MHz), 7.57-7.59 (4H, d, Ar, *J* = 8 MHz), 7.41-7.45 (2H, m, Ar), 7.39 (3H, m, Ar), 7.09 (1H, s, Ar), 6.82 (1H, s, Ar), 5.39 (2H, s, CH_2), 5.21 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 189.62 (C=O), 165.45, 163.23, 150.32, 148.02, 136.67, 136.56, 131.87, 130.78, 125.20, 122.52, 118.12 (triazole-CH), 116.07, 115.91, 114.59, 114.41, 113.64, 112.43, 106.80, 106.53, 102.17, 72.33 (CH_2). Mass: 565 [M+1]$^+$.

(2,4-*bis*((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)(phenyl)methanone (7c): Colour: light brown, yield: 66%, m.f.: $C_{31}H_{22}Br_2N_6O_3$, m.p.: 208-210 °C; Elemental analysis: calcd. (found) %: C, 54.25 (54.21); H, 3.23 (3.20); Br, 23.28 (23.30); N, 12.24 (12.20); O, 6.99 (6.96); IR (KBr, ν_{max}, cm^{-1}): 3066 (C-H, Ar), 2973 (C-H, aliph.), 1687 (C=O), 1506 (C=C, Ar), 1336 (N-N), 1233 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 9.09 (1H, s, triazole ring-CH), 8.04 (1H, s, triazole ring-CH), 7.97-7.99 (2H, d, Ar, *J* = 8 MHz), 7.78-7.80 (2H, d, Ar, *J* = 8 MHz), 7.68-7.70 (6H, d, Ar, *J* = 8 MHz), 7.56-7.58 (4H, m, Ar), 7.41-7.43 (3H, m, Ar), 7.04 (1H, s, Ar), 5.40 (2H, s, CH_2), 5.24 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 186.74 (C=O), 166.54, 164.32, 152.33, 146.29, 139.99, 138.60, 137.48, 133.04, 130.36, 129.54, 128.90, 128.72, 128.56, 128.24, 128.06, 126.62, 124.85, 120.96, 119.15 (triazole-CH), 117.34, 112.34, 111.24, 103.73, 72.24 (CH_2). Mass: 686 [M+2]$^+$.

(2,4-*bis*((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)(phenyl)methanone (7d): Colour: off white, yield: 70%, m.f.: $C_{31}H_{22}Cl_2N_6O_3$, 194-196 °C; Elemental analysis: calcd. (found) %: C, 62.32 (62.29); H, 3.71 (3.73); Cl, 11.87 (11.84); N, 14.07 (14.03); O, 8.03 (8.06); IR (KBr, ν_{max}, cm^{-1}): 3051 (C-H, Ar), 2939 (C-H, aliph.), 1679 (C=O), 1511 (C=C, Ar), 1337 (N-N), 1249 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.98 (1H, s, triazole ring-CH), 8.01 (1H, s, triazole ring-CH), 7.94-7.96 (2H, d, Ar, *J* = 8 MHz), 7.69-7.71 (2H, d, Ar, *J* = 8 MHz), 7.60-7.62 (6H, d, Ar, *J* = 8 MHz), 7.49-7.55 (4H, m, Ar), 7.36-7.38 (3H, m, Ar), 6.89 (1H, s, Ar), 5.32 (2H, s, CH_2), 5.22 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 184.32 (C=O), 165.44, 163.78, 150.22, 145.83, 138.79, 138.44, 137.31, 132.98, 130.12, 128.49, 128.22, 127.83, 127.63, 127.44, 127.16, 126.58, 124.65, 120.74, 119.22 (triazole-CH), 116.66, 112.29, 110.42, 105.70, 72.09 (CH_2). Mass: 599 [M+2]$^+$.

(2,4-*bis*((1-*p*-Tolyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7e): Colour: light yellow, yield: 84%, m.f.: $C_{33}H_{28}N_6O_3$, m.p.: 188-190 ºC; Elemental analysis: calcd. (found) %: C, 71.21 (71.21; H, 5.07 (5.07); N, 15.10 (15.10); O, 8.62 (8.62); IR (KBr, ν_{max}, cm^{-1}): 3055 (C-H, Ar), 2923 (C-H, aliph.), 1686 (C=O), 1503 (C=C, Ar), 1342 (N-N), 1245 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.92 (1H, s, triazole ring-CH), 8.12 (1H, s, triazole ring-CH), 8.01-7.98 (4H, d, Ar, *J* = 8 MHz), 7.78-7.80 (4H, d, Ar, *J* = 8 MHz), 7.59-7.61 (2H, d, Ar, *J* = 8 MHz), 7.40-7.43 (3H, m, Ar), 7.35-7.37 (2H, m, Ar), 6.81 (1H, s, Ar), 5.36 (2H, s, CH_2), 5.18 (2H, s, CH_2), 2.34 (6H, s, 2×CH_3); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 186.54 (C=O), 165.34, 162.67, 152.27, 145.98, 141.05, 140.94, 137.92, 134.03, 131.18, 130.55, 129.91, 129.70, 129.21, 129.04, 127.59, 126.77, 124.13, 120.32, 119.12, 118.31, 117.34, 112.34, 111.24, 102.73, 72.06 (CH_2), 26.78 (CH_3). Mass: 556 [M+1]$^+$.

(2,4-*bis*((1-(4-(Trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7f): Colour: silvery, yield: 77%, m.f.: $C_{33}H_{22}F_6N_6O_3$, m.p.: 210-212 ºC. Elemental analysis: calcd. (found) %: C, 59.64 (59.61); H, 3.34 (3.30); F, 17.15 (17.18); N, 12.65 (12.61); O, 7.22 (7.27); IR (KBr, ν_{max}, cm^{-1}): 3057 (C-H, Ar), 2947 (C-H, aliph.), 1674 (C=O), 1515 (C=C, Ar), 1343 (N-N), 1242 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.89 (1H, s, triazole ring-CH), 8.09 (1H, s, triazole ring-CH), 7.95-7.97 (4H, d, Ar, *J* = 8 MHz), 7.71-7.73 (4H, d, Ar, *J* = 8 MHz), 7.54-7.56 (2H, d, Ar, *J* = 8 MHz), 7.36-7.40 (3H, m, Ar), 7.29-7.32 (2H, m, Ar), 6.78 (1H, s, Ar), 5.33 (2H, s, CH_2), 5.17 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 185.42 (C=O), 164.29, 161.58, 152.17, 145.77, 139.84, 139.80, 136.76, 131.86, 130.07, 129.44, 128.80, 128.59, 128.10, 127.93, 126.48, 125.66, 123.02, 119.21 (triazole-C), 118.11, 117.23, 116.26, 111.24, 110.17, 101.66, 70.91 (CH_2), 25.63 (CH_3). Mass: 666 [M+1]$^+$.

(2,4-*bis*((1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7g): Colour: maroon, yield: 65%, m.f.: $C_{31}H_{24}N_6O_5$, m.p.: 205-207 ºC; Elemental analysis: calcd. (found) %: C, 66.42 (66.39); H, 4.32 (4.30); N, 14.99 (14.96); O, 14.27 (14.31). IR (KBr, ν_{max}, cm^{-1}): 3412 (OH), 3052 (C-H, Ar), 2940 (C-H, aliph.), 1669 (C=O), 1511 (C=C, Ar), 1337 (N-N), 1232 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 10. 17 (1H, s, OH), 8.84 (1H, s, triazole ring-CH), 7.94 (1H, s, triazole ring-CH), 7.81 (2H, d, Ar, *J* = 8 MHz), 7.67-7.69 (2H, d, Ar, *J* = 8 MHz), 7.58-7.61(2H, m, Ar), 7.45-7.47 (1H, m, Ar), 7.35-7.37 (4H, d, Ar, *J* = 8 MHz), 7.22-7.24 (2H, d, Ar, *J* = 8 MHz), 6.84 (1H, s, Ar, *J* = 8 MHz), 5.35 (2H, s, CH_2), 5.18 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 185.42 (C=O), 166.23, 162.66, 152.34, 151.19, 144.40, 140.03, 133.04, 130.23, 129.51, 128.99, 128.65, 128.12, 128.04, 126.53, 126.34, 125.57, 125.13, 121.31, 119.14 (triazole-C), 117.50, 112.31, 108.23, 104.06, 72.32 (CH_2). Mass: 561 [M+1]$^+$.

(2,4-*bis*((1-(2-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7h): Colour: light red, yield: 81%, m.f.: $C_{31}H_{24}N_6O_5$, m.p.: 216-218 ºC; Elemental analysis: calcd. (found) %: C, 66.42 (66.38); H, 4.32 (4.29); N, 14.99 (14.94); O, 14.27 (14.30); IR (KBr, ν_{max}, cm^{-1}): 3431 (OH), 3039 (C-H, Ar), 2946 (C-H, aliph.), 1663 (C=O), 1517 (C=C, Ar), 1333 (N-N), 1242 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 10. 21 (1H, s, OH), 8.91 (1H, s, triazole ring-CH), 7.94 (1H, s, triazole ring-CH), 7.86-7.88 (2H, d, Ar, *J* = 8 MHz), 7.72.7.74 (2H, d, Ar, *J* = 8 MHz), 7.65-7.67 (4H, m, Ar), 7.53-7.55 (3H, m, Ar), 7.47-7.49 (2H, d, Ar, *J* = 8 MHz), 7.07 (1H, s, Ar), 5.43 (2H, s, CH_2), 5.26 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 184.76 (C=O), 166.09, 161.43, 151.62, 150.22, 143.53, 140.21, 132.56, 130.09, 129.47, 129.09, 128.72, 128.51, 128.24, 126.42, 126.11, 125.48, 125.02, 121.29, 119.23 (triazole-C), 117.62, 112.39, 108.31, 105.13, 72.28 (CH_2). Mass: 561 [M+1]$^+$.

(2,4-*bis*((1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7i): Colour: off white, yield: 77%, m.f.: $C_{31}H_{22}Cl_2N_6O_3$, m.p.: 202-204 ºC; Elemental analysis: calcd. (found) %: C, 62.32 (62.28); H, 3.71 (3.74); Cl, 11.87 (11.84); N, 14.07 (14.06); O, 8.03 (8.07); IR (KBr, ν_{max}, cm^{-1}): 3033 (C-H, Ar), 2951 (C-H, aliph.), 1672 (C=O), 1527 (C=C, Ar), 1341 (N-N), 1234 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.91 (1H, s, triazole ring-CH), 8.01 (1H, s, triazole ring-CH), 7.96-7.98 (2H, d, Ar, *J* = 8 MHz), 7.77.7.79 (2H, d, Ar, *J* = 8 MHz), 7.59-7.61 (4H, m, Ar), 7.41-7.43(3H, m, Ar), 7.37-7.39 (2H, d, Ar, *J* = 8 MHz), 7.01 (1H, s, Ar), 5.41 (2H, s, CH_2), 5.24 (2H, s, CH_2). ^{13}C NMR (DMSO, 400 MHz, δ ppm): 185.76 (C=O), 165.73, 163.33, 152.76, 143.03, 142.53, 138.87, 130.91, 129.78, 126.99, 126.83, 125.87, 125.57, 120.92, 119.01 (triazole-CH), 113.03, 108.11, 101.02, 72.19 (CH_2). Mass: 596 [M]$^+$.

(2,4-*bis*((1-(2-Bethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7j): Colour: cream, yield: 73%, m.f.: $C_{33}H_{28}N_6O_5$, m.p.: 195-197 ºC; Elemental analysis: calcd. (found) %: C, 67.34 (67.30); H, 4.79 (4.76); N, 14.28 (14.31); O, 13.59 (13.56); IR (KBr, ν_{max}, cm^{-1}): 3041 (C-H, Ar), 2956 (C-H, aliph.), 1662 (C=O), 1524 (C=C, Ar), 1345 (N-N), 1236 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.92 (1H, s, triazole ring-CH), 8.18 (1H, s, triazole ring-CH), 7.97-7.99 (2H, d, Ar, *J* = 8 MHz), 7.71-7.73 (2H, d, Ar, *J* = 8 MHz), 7.51-7.53 (4H, m, Ar), 7.37-7.39 (4H, m, Ar), 7.29-7.31 (3H, m, Ar), 6.91 (1H, s, Ar), 5.38 (2H, s, CH_2), 5.21 (2H, s, CH_2), 3.81 (6H, s, 2×CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 186.13 (C=O), 164.60, 162.23, 145.84, 145.81, 138.49, 138.44, 134.28, 130.24, 129.63, 123.12, 122.66, 120.06, 119.99 (triazole-C), 118.76, 108.23, 104.28, 102.34, 72.35 (CH_2), 56.41(OCH_3). Mass: 588 [M+1]$^+$.

(2,4-*bis*((1-(3-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7k): Colour: white, yield: 69%, m.f.: $C_{35}H_{28}N_6O_5$, m.p.: 214-216 ºC; Elemental analysis: calcd. (found) %: C, 68.62 (68.59); H, 4.61 (4.64); N, 13.72 (13.69); O, 13.06 (13.04); IR (KBr, ν_{max}, cm^{-1}): 3047 (C-H, Ar), 2951 (C-H, aliph.), 1670 (C=O), 1529 (C=C, Ar), 1338 (N-N), 1238 (C-O-C, Ar-O-CH_2); ^{1}H NMR (DMSO, 400 MHz, δ ppm): 8.74 (1H, s, triazole ring-CH), 8.36-8.38 (4H, m, Ar), 8.21-8.23 (4H, m, Ar), 8.07 (1H, s, triazole ring-CH), 7.91-7.93 (2H, d, Ar, *J* = 8 MHz), 7.76-7.78 (2H, d, Ar, *J* = 8 MHz), 7.56-7.58 (3H, m, Ar), 5.41 (2H, s, CH_2), 5.22 (2H, s, CH_2), 2.78 (6H, s, 2×$COCH_3$); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 199.33 ($COCH_3$), 195.45 (C=O), 163.40, 159.21, 153.23, 134.76, 131.12, 130.03, 129.81, 127.61, 127.51, 127.03, 126.97, 126.83, 126.79, 124.96, 124.17, 123.46, 121.46, 120.92 (triazole-CH), 108.78, 101.03, 72.74 (CH_2), 29.23 (CH_3). Mass: 513 $[M+1]^+$.

(2,4-*bis*((1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7l): Colour: green, yield: 66%, m.f.: $C_{33}H_{28}N_6O_5$, m.p.: 221-223 ºC; Elemental analysis: calcd. (found) %: C, 67.34 (67.29); H, 4.79 (4.76); N, 14.28 (14.33); O, 13.59 (13.56); IR (KBr, ν_{max}, cm^{-1}): 3058 (C-H, Ar), 2955 (C-H, aliph.), 1668 (C=O), 1535 (C=C, Ar), 1346 (N-N), 1235 (C-O-C, Ar-O-CH_2); ^1H NMR (DMSO, 400 MHz, δ ppm): 8.79 (1H, s, triazole ring-CH), 7.86 (1H, s, triazole ring-CH), 7.76-7.78 (2H, d, Ar, *J* = 8 MHz), 7.61-7.63 (2H, d, Ar, *J* = 8 MHz), 7.53-7.55(2H, m, Ar), 7.39-7.41 (1H, m, Ar), 7.30-7.32 (4H, d, Ar, *J* = 8 MHz), 7.17-7.19 (2H, d, Ar, *J* = 8 MHz), 6.81 (1H, s, Ar, *J* = 8 MHz), 5.31 (2H, s, CH_2), 5.16 (2H, s, CH_2), 3.72 ((6H, s, 2×CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 185.16 (C=O), 162.62, 158.33, 152.27, 133.68, 131.26, 129.74, 129.31, 128.56, 127.89, 127.49, 126.91, 126.73, 125.79, 124.87, 124.26, 123.51, 121.39, 120.92, 119.23 (triazole-CH), 108.49, 105.03, 72.62 (CH_2), 28.12 (CH_3). Mass: 588 $[M+1]^+$.

(2,4-*bis*((1-(2-Chloroacetylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7m): Colour: Off white, yield: 70%, m.f.: $C_{33}H_{22}Cl_2N_6O_5$, m.p.: 229-227 ºC; Elemental analysis: calcd. (found) %: C, 60.65 (60.62); H, 3.39 (3.34); Cl, 10.85 (10.88); N, 12.86 (12.81); O, 12.24 (12.27); IR (KBr, ν_{max}, cm^{-1}): 3053 (C-H, Ar), 2950 (C-H, aliph.), 1662 (C=O), 1546 (C=C, Ar), 1334 (N-N), 1232 (C-O-C, Ar-O-CH_2); ^1H NMR (DMSO, 400 MHz, δ ppm): 9.03 (1H, s, triazole ring-CH), 8.60-8.62 (2H, d, Ar, *J* = 8 MHz) 8.39 (1H, s, triazole ring-CH), 8.19-8.21 (2H, d, Ar, *J* = 8 MHz), 7.89-7.91 (2H, m, Ar), 7.80-7.82 (4H, d, Ar, *J* = 8 MHz), 7.62-7.64 (2H, d, Ar, *J* = 8 MHz), 7.55-7.57 (3H, m, Ar,), 7.19 (1H, s, Ar,), 5.43 (2H, s, CH_2), 5.24 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 187.26 (COCl), 178.10 (C=O), 167.06, 162.66, 152.34, 151.19, 144.40, 140.03, 133.04, 130.23, 129.51, 128.99, 128.65, 128.12, 128.04, 126.53, 126.34, 125.57, 125.13, 121.31, 119.14 (triazole-C), 117.50, 112.31, 103.21, 101.01, 72.38 (CH_2). Mass: 652 $[M+1]^+$.

(2,4-*bis*((1-(4-Chloroacetylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7n): Colour: off white, yield: 75%, m.f.: $C_{33}H_{22}Cl_2N_6O_5$, m.p.: 233-235 ºC; Elemental analysis: calcd. (found) %: C, 60.65 (60.61); H, 3.39 (3.36); Cl, 10.85 (10.81); N, 12.86 (12.88); O, 12.24 (12.21); IR (KBr, ν_{max}, cm^{-1}): 3051 (C-H, Ar), 2936 (C-H, aliph.), 1680 (C=O), 1513 (C=C, Ar), 1340 (N-N), 1237 (C-O-C, Ar-O-CH_2); ^1H NMR (DMSO, 400 MHz, δ ppm): 8.92 (1H, s, triazole ring-CH), 7.94 (1H, s, triazole ring-CH), 7.89-7.91 (2H, d, Ar, *J* = 8 MHz), 7.61-7.62 (2H, d, Ar, *J* = 8 MHz), 7.54-7.56 (6H, d, Ar, *J* = 8 MHz), 7.42-7.46 (4H, m, Ar), 7.31-7.34 (3H, m, Ar), 6.82 (1H, s, Ar), 5.29 (2H, s, CH_2), 5.20 (2H, s, CH_2). ^{13}C NMR (DMSO, 400 MHz, δ ppm): 183.25 (C=O), 165.36, 162.71, 149.22, 144.75, 137.71, 137.39, 136.27, 131.86, 129.04, 128.43, 128.17, 126.75, 126.55, 126.39, 126.08, 125.50, 123.57, 119.66 (triazole-CH), 118.14, 115.58, 111.21, 109.34, 104.62, 71.99 (CH_2). Mass: 562 $[M+1]^+$.

(2,4-*bis*((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone (7o): Colour: pale yellow, yield: 76%, m.f.: $C_{31}H_{22}N_8O_7$, m.p.: 223-225 ºC; Elemental analysis: calcd. (found) %: C, 60.19 (60.15); H, 3.58 (3.55); N, 18.12 (18.16); O, 18.11 (18.08); IR (KBr, ν_{max}, cm^{-1}): 3047 (C-H, Ar), 2954 (C-H, aliph.), 1672 (C=O), 1543 (C=C, Ar), 1349 (N-N), 1241 (C-O-C, Ar-O-CH_2); ^1H NMR (DMSO, 400 MHz, δ ppm): 8.81 (1H, s, triazole ring-CH), 8.22-8.24 (4H, d, Ar, *J* = 8 MHz), 7.98 (1H, s, triazole ring-CH), 7.86-7.88 (4H, d, Ar, *J* = 8 MHz), 7.66-7.68 (2H, d, Ar, *J* = 8 MHz), 7.40-7.43(3H, m, Ar), 7.31-7.33 (2H, d, Ar, *J* = 8 MHz), 6.92 (1H, s, Ar,), 5.29 (2H, s, CH_2), 5.12 (2H, s, CH_2); ^{13}C NMR (DMSO, 400 MHz, δ ppm): 186.52 (C=O), 166.43, 163.42, 142.62, 142.21, 134.47, 131.91, 130.66, 129.89, 128.59, 128.61, 127.30, 126.88, 119.01 (trizole-C), 108.36, 106.56, 101.51, 72.30 (CH_2). Mass: 618 $[M+1]^+$.

Biological assays

Cell culture: MCF-7 cells were cultured in MEM with 10% FBS, while PC-3, HeLa and additional MCF-7 cells were maintained in RPMI-1640 with 10% FBS. All cells were incubated at 37 ºC in a 5% CO_2 humidified atmosphere. Stock solutions of synthesised compounds were prepared in DMSO and added to the cultures, ensuring the final DMSO concentration remained below 0.1%.

MTT assay: MTT assay was used to assess the cytotoxicity of synthesised **7a-o** derivatives. Stock solutions were prepared in culture medium and cells (5 × 10^4 per well) were seeded in 96-well plates until 90-95% confluence. Treated with 100 μL of compound-containing medium, the cells were incubated for 48 h. Afterward, 20 μL of MTT (5 mg/mL) was added for 4 h. Formazan crystals were dissolved in 200 μL of DMSO and absorbance at 490 and 630 nm was measured. The percentage of growth inhibition was calculated.

$$\text{Inhibition (\%)} = \left(1 - \frac{\text{Sample group OD490} - \text{Sample group OD630}}{\text{Control group OD490} - \text{Control group OD630}}\right) \times 100$$

Using GraphPad Prism, IC_{50} values were calculated, with standard deviations obtained from at least three separate experiments.

Antibacterial assay: Using the disc diffusion method, **7a-o** compounds were evaluated for antibacterial activity against six bacterial strains *viz.* three Gram-negative (*P. aeruginosa* MTCC 741, *K. aerogenes* MTCC 39, MTCC 2656) and three Gram-positive (*B. subtilis* MTCC 441, *B. sphaericus* MTCC 11, *S. aureus* MTCC 96). Agar plates with 1-2 × 10^7 cfu/mL inoculums were prepared and sterile Whatman No. 1 filter paper discs (6.26 mm diameter) containing the synthesized compounds were aseptically placed onto the agar surface.

Antifungal assay: The antifungal efficacy of synthesised **7a-o** derivatives was determined using the disc diffusion method against *C. albicans* (ATCC 10231), *A. fumigatus* (HIC 6094), *T. rubrum* (IFO 9185) and *T. mentagrophytes* (IFO 40996). Dissolved in DMSO, compounds were compared to amphotericin B, with MZI values alongside controls.

Molecular docking analysis: The three-dimensional structure of the target protein was retrieved from the RCSB Protein Data Bank (PDB). Prior to docking, water molecules and other co-crystallized entities were removed using Discovery Studio Visualizer. The chemical structures of the synthesized compounds (**7a-o**) and the reference drug doxorubicin were drawn using ChemDraw software. Molecular docking studies were performed using the PyRx virtual screening platform. The binding interactions between the ligands and target protein were subsequently analyzed and visualized using PyMOL and Discovery Studio Visualizer. The docking results were evaluated based on binding affinity and interaction profiles [44,45].

RESULTS AND DISCUSSION

A series of 1,2,3-triazole derivatives (**7a-o**) were synthesised through a sequential multi-step approach starting from (2,4-dichlorophenyl)(phenyl)methanone. The synthetic pathway involved nitration, reduction, hydroxylation, propargylation, azidation and Cu(I)-catalysed click chemistry. The process began with nitration, where (2,4-dichlorophenyl)-(phenyl)methanone was treated with nitric and sulphuric acid at 0-5 ºC to obtain 2,4-dinitrophenyl ketone (**2**). This was followed by catalytic hydrogenation using Pd/C under a H_2 atmosphere, converting the nitro groups into amines and yielding 2,4-diaminophenyl ketone (**3**). The next step involved hydroxylation, where the diamine was refluxed in methanol for 16 h to obtain 2,4-dihydroxyphenyl ketone (**4**). For propargylation, compound **4** was reacted with 3-bromoprop-1-yne in DMF using K_2CO_3 as a base, forming the alkyne-functionalised intermediate **5**. The azidation step involved the diazotisation of substituted aromatic amines in DCM, followed by treatment with sodium azide to yield aryl azides (**6a-o**). Finally, the Cu(I)-catalysed click reaction between propargylated compound **5** and aryl azides (**6a-o**) under mild conditions furnished the desired 1,2,3-triazole derivatives (**7a-o**) in 66-84% yields.

Cytotoxicity: Table-1 presents the *in vitro* cytotoxic activity of novel synthesised hybrids **7a-o** and standard drug doxorubicin drug against MCF-7 (breast cancer), PC-3 (prostate cancer) and HeLa (cervical cancer) cell lines at increasing concentrations (5-100 μM), showing a clear concentration-dependent decrease in cell viability for all synthesised molecules. Among the tested compounds, compounds **7d**, **7j** and **7f** revealed the strongest anticancer potency, with very low cell viability values at 100 μM, indicating high potency and low IC_{50} values, whereas compounds **7k**, **7o**, **7i**, **7e**, **7h** and **7g** demonstrated moderate anticancer effects with intermediate cell viability values. In addition, compounds **7n**, **7c**, **7l**, **7m**, **7b** and **7a** showed weak anticancer potential with higher cell survival even at the higher doses. Thus, MCF-7 cells appear slightly more sensitive to treatment than PC-3 and HeLa cells, which show relatively higher resistance in several cases. The standard compound doxorubicin also demonstrates strong cytotoxicity comparable to the most active derivatives, confirming the reliability of the assay and highlighting **7d** and related analogues as promising lead candidates for further anticancer evaluation.

The IC_{50} results (Table-2) shows that all the tested compounds exhibit moderate to strong anticancer activity against MCF-7, PC-3 and HeLa cell lines, with clear variations in potency. Compound **7d** is the most active derivative (IC_{50}: 17.6 ± 1.6 – 20.1 ± 1.7 μM), showing activity comparable to doxorubicin (IC_{50}: 17.1 ± 1.2 – 19.3 ± 0.9 μM), followed by **7j** and **7f** with low IC_{50} values. Compounds **7a** and **7b** are the least active, with higher IC_{50} values (> 60 μM). Thus, based on these results, if is found that MCF-7 cells are slightly more sensitive than PC-3 and HeLa, indicating mild cell-line selectivity across the series.

Antibacterial studies: Compounds **7d**, **7f**, **7g** and **7l** demonstrate consistently higher MZI values across all bacterial strains, highlighting their potent antibacterial activity (Table-3). These compounds exhibit efficacy comparable to the standard anti-biotic streptomycin. Compounds **7b**, **7e**, **7h** and **7j** show moderate antibacterial activity, with MZI values generally lower than those of the high-activity compounds but still significant higher than those of the low-activity group. Conversely compounds **7a**, **7c**, **7i** and **7k** exhibit low antibacterial activity, as indicated by their significantly reduced

TABLE-1
PERCENTAGE CELL VIABILITY DATA OF THREE CANCER CELL LINES TREATED WITH SYNTHESISED COMPOUNDS (**7a-o**)

Compd.	Human breast (MCF-7)						Prostate (PC-3)						Cervical (HeLa)					
	Concentrations (μM)						Concentrations (μM)						Concentrations (μM)					
	5	10	25	50	75	100	5	10	25	50	75	100	5	10	25	50	75	100
7a	94	89	72	61	43	30	96	93	82	67	57	38	95	91	75	64	46	37
7b	93	87	69	58	41	27	95	92	79	64	53	36	94	90	73	61	44	35
7c	89	81	63	51	34	24	93	89	69	55	42	28	92	87	66	53	40	26
7d	65	56	33	17	10	4	75	62	41	25	16	7	72	60	38	23	13	5
7e	82	74	53	39	25	18	88	80	59	44	33	22	86	79	55	41	29	19
7f	71	62	42	26	15	6	77	68	47	31	20	10	75	66	45	28	17	7
7g	84	77	57	44	29	20	91	85	63	49	37	23	89	83	61	52	33	22
7h	83	76	55	42	27	19	90	83	61	47	35	22	88	81	58	44	31	20
7i	80	71	51	36	23	15	86	78	56	42	31	20	84	76	53	39	28	18
7j	68	60	39	21	12	5	76	67	45	27	18	9	74	64	43	25	15	8
7k	73	65	45	29	17	9	79	69	49	33	22	11	82	77	49	31	22	10
7l	91	84	65	53	36	26	94	90	71	58	47	31	93	88	67	55	41	29
7m	92	85	66	55	38	27	95	91	73	61	49	33	94	89	69	58	43	31
7n	86	79	60	47	31	22	92	87	66	51	40	26	91	85	64	53	34	23
7o	76	68	47	33	20	11	82	73	51	36	24	13	84	79	53	33	24	12
Doxorubicin	62	48	34	23	15	6	67	53	39	27	19	8	65	49	36	25	18	7

TABLE-2
ANTICANCER POTENCY DATA OF SYNTHESISED COMPOUNDS **7a-o**

Compd.	IC_{50} values (μM ± SEM)		
	MCF-7	PC-3	HeLa
7a	69.6 ± 1.9	74.3 ± 2.5	71.3 ± 1.4
7b	64.3 ± 2.4	69.4 ± 2.5	66.7 ± 2.2
7c	46.6 ± 1.8	50.1 ± 1.3	48.9 ± 1.8
7d	17.6 ± 1.6	20.1 ± 1.7	19.5 ± 1.4
7e	31.1 ± 2.1	34.7 ± 1.9	32.8 ± 2.3
7f	23.2 ± 1.7	25.8 ± 2.0	24.3 ± 2.2
7g	36.6 ± 1.6	39.7 ± 1.9	37.8 ± 2.4
7h	34.4 ± 1.7	37.3 ± 2.0	35.8 ± 2.3
7i	29.3 ± 2.3	31.9 ± 1.7	30.5 ± 2.1
7j	21.5 ± 1.9	24.7 ± 2.1	22.8 ± 1.8
7k	25.8 ± 1.5	28.81 ± 2.2	26.5 ± 2.1
7l	50.5 ± 1.6	55.1 ± 1.4	53.1 ± 2.6
7m	58.6 ± 2.3	63.5 ± 2.5	60.4 ± 1.9
7n	39.5 ± 2.1	43.8 ± 1.7	41.0 ± 2.2
7o	27.4 ± 1.6	30.7 ± 1.8	28.6 ± 2.3
Doxorubicin	17.1 ± 1.2	19.3 ± 0.9	18.5 ± 1.4

MZI values compared to both the high- and moderate-activity groups, reflecting limited effectiveness against the tested bacterial strains.

Antifungal assay: Compounds **7d**, **7e**, **7f** and **7k** were highly effective antifungal agents, outperforming standard amphotericin B (Table-4). This broad-spectrum efficacy against diverse fungal pathogens suggests that these compounds may possess unique structural features that disrupt critical fungal cell processes, such as membrane integrity or metabolic pathways. Conversely, compounds **7g**, **7h** and **7j** exhibited moderate antifungal activity, indicating a less potent inhibitory effect on fungal growth. While these compounds may have some therapeutic potential, further optimisation of their structure and properties may be necessary to enhance their efficacy. On the other hand, compounds **7a**, **7b**, **7c**, **7i** and **7l** demonstrated weak antifungal activity, suggesting that their structural features are insufficient to effectively target and inhibit fungal growth.

TABLE-4
ANTIFUNGAL ACTIVITY DATA OF SYNTHESISED COMPOUNDS **7a-o**

Compd.	Mean zone inhibition (MZI) in 100 μg/mL			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagropytes*
7a	16	13	14	15
7b	15	12	13	14
7c	17	14	15	16
7d	27	24	25	26
7e	24	21	22	23
7f	26	23	24	25
7g	21	18	19	20
7h	20	17	18	19
7i	18	15	16	17
7j	22	19	20	21
7k	25	22	23	24
7l	19	16	17	18
7m	15	13	14	15
7n	16	12	13	15
7o	23	20	21	22
Amphotericin B	28	25	26	27

Docking studies: In the molecular docking studies, the binding interactions between novel derivatives **7a-o** and the crystal structure of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1), a key enzyme in estrogen biosynthesis, has been determined (PDB ID: 3HB5). This enzyme catalyses the conversion of estrone (E1) into estradiol (E2), the most potent estrogen. Increased levels of E2 drive the proliferation of estrogen receptor-positive (ER^+) breast cancer cells, making 17β-HSD1 a critical target for hormone-dependent breast cancer therapy. Given its role in estrogen-dependent tumours, 17β-HSD1 is an attractive candidate for drug development. Moreover, the standard chemotherapeutic agent doxorubicin is widely used in breast cancer treatment, though it targets cancer cells through a different mechanism.

The findings of the docking study revealed diverse binding affinities and modes for the derivatives compared to the refer-

TABLE-3
ANTIBACTERIAL DATA OF SYNTHESISED COMPOUNDS **7a-o**

Compd.	Mean zone inhibition (MZI) in 100 μg/mL					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
7a	19	18	20	17	14	16
7b	24	23	25	22	19	21
7c	18	17	19	16	13	15
7d	29	28	30	27	24	26
7e	20	18	21	17	15	16
7f	27	26	28	25	22	24
7g	28	27	29	26	23	25
7h	22	21	23	20	17	19
7i	17	16	18	15	13	15
7j	21	20	22	19	16	17
7k	17	16	18	15	12	14
7l	26	25	27	24	21	23
7m	16	15	17	14	12	14
7n	15	14	16	13	12	13
7o	25	24	26	23	20	22
Streptomycin	30	29	31	28	25	27

ence compounds. Derivatives **7j** and **7d** exhibited superior binding energies (-12.4 and -12.3 Kcal/mol, respectively) compared to all the derivatives and the reference compound doxorubicin (-8.9 kcal/mol). The good binding affinities can be attributed to hydrogen bonding interactions and other interactions including pi-sigma, amide-pi stacked, alkyl, pi-alkyl, pi-sulphur, pi-anion and pi-cation interactions of the compounds with the target protein 17β-HSD1 (Figs. 1 and 2).

Compound **7j** exhibited multiple hydrogen bond interactions with ILE14, GLY141, SER142 and CYS185 residues along with strong hydrophobic interactions in the active site which indicated the stable and well-oriented binding of the compound. Similarly, compound **7d** formed a hydrogen bond with SER12 and was stabilised by several hydrophobic interactions with key active-site residues, such as ARG37, ASP65, VAL66, TYR155 and PHE192. The large number of interactions and good binding energies suggest that both **7d** and **7j** fit well into the receptor pocket (Fig. 3).

Hydrophobic residues contribute significantly to binding by stabilizing ligand-protein complexes. The most frequently interacting residues across the synthesised compounds include GLY 9, SER 12, GLY 13, ILE 14, ASP 65, VAL 66, ASN 90, ALA 91, GLY 92, LEU 93, GLY 94, THR 140, TYR 155, PRO 187, VAL 188, PHE 192, MET 193, LYS 195, VAL 196 and PHE 226**.** The presence of TYR 155, PHE 226 and MET 193 in multiple compounds suggests their importance in hydrophobic stabilisation. Compounds such as **7e**, **7j** and **7n** exhibit extensive hydrophobic interactions, correlating with their strong binding affinities.

Conclusion

In conclusion, the design and synthesis of a novel series of 15 substituted final title compounds 2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)(phenyl)methanone derivatives (**7a-o**) were synthesised *via* click chemistry. The structural characterisation validated using various spectral methods. The products were tested for *in vitro* cytotoxicity against MCF-7, PC-3 and HeLa cell lines using MTT assay. Compounds **7d**, **7j** and **7f** showed substantial activity, with cell viability and low IC$_{50}$ values at 100 μM. Antibacterial screening against six strains revealed that **7d**, **7f**, **7g**, **7l** and **7o** products exhibited good bacterial activity. In antifungal investigations, **7d**, **7e**, **7f** and **7k** products showed more antifungal activity compared to other derivatives. Molecular docking against 17β-HSD1 showed that **7j** (-12.4 kcal/mol) and **7d** (-12.3 kcal/mol) had substantial binding affinities that were higher than doxorubicin (-8.9 kcal/mol), with ILE14, GLY141, SER142 and CYS185 exhibiting favourable interactions.

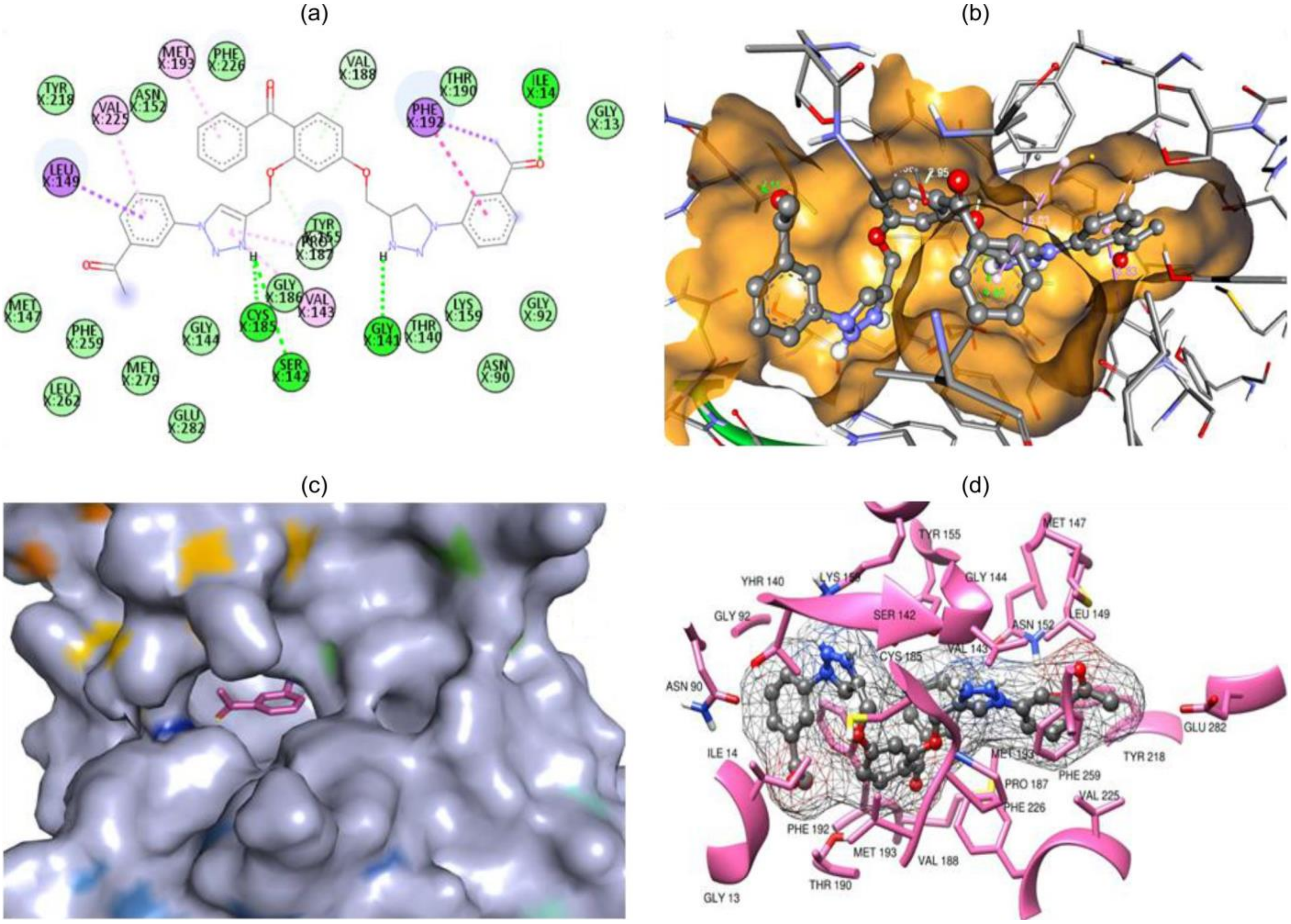


Fig. 1. 2D, 3D interaction, binding pocket and residues within 4 Å of '**7j**' with 17β-HSD

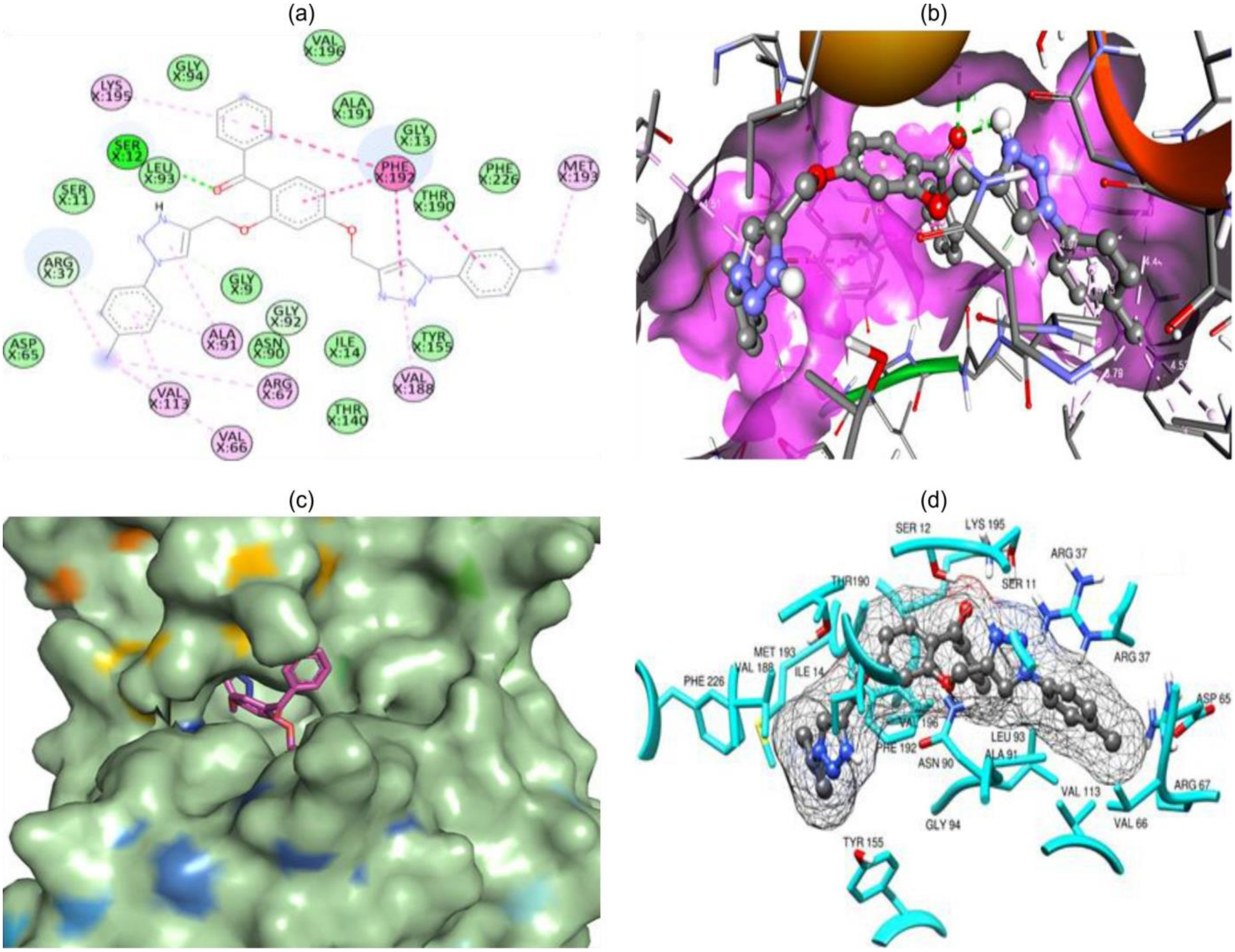


Fig. 2. 2D, 3D interaction, binding pocket and residues within 4 Å of '**7d**' with 17β-HSD

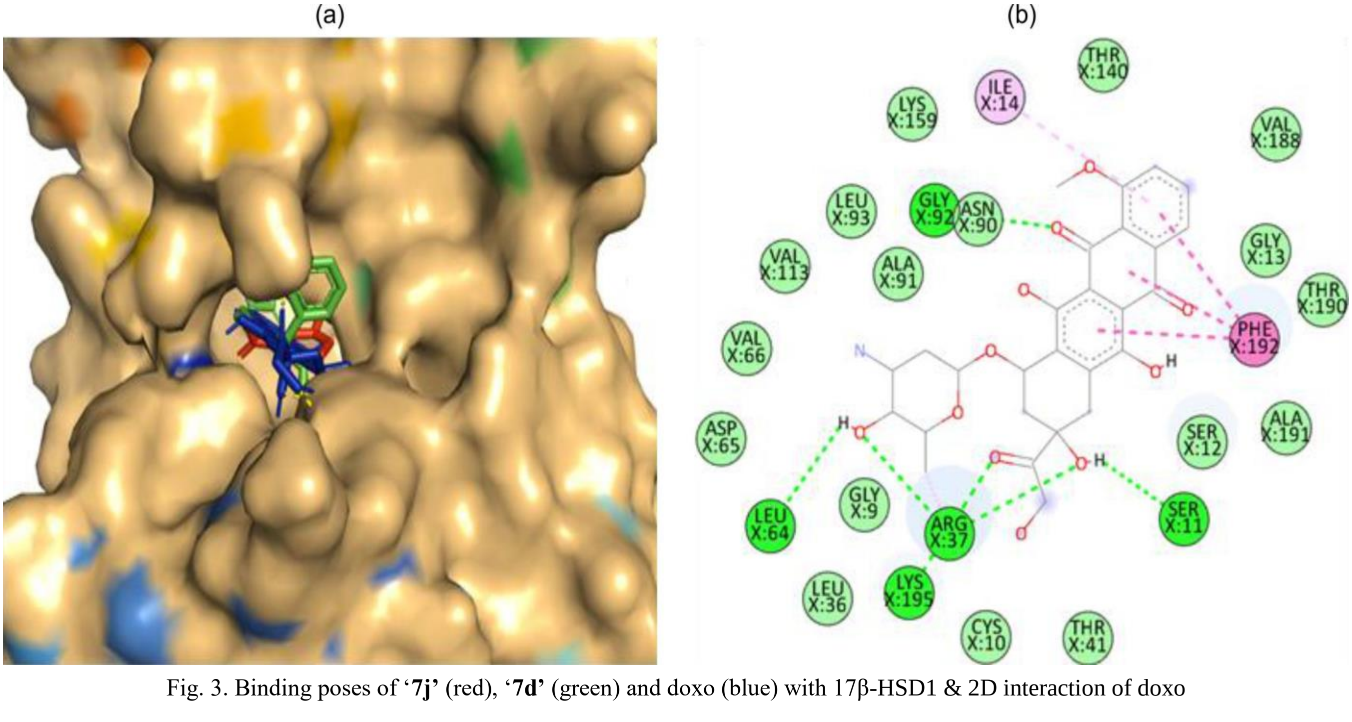


Fig. 3. Binding poses of '**7j**' (red), '**7d**' (green) and doxo (blue) with 17β-HSD1 & 2D interaction of doxo

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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