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Design and Synthesis of Novel 1,2,3-Triazole-Based 2-Amino-4H-Chromene-3-Carbonitrile Derivatives: Molecular Docking and Antimicrobial Evaluation

Manne Subhash[1], Doma. Anitha Rangasree[1], E Samarpana[1], Kathi Hareesh[1],
[1]Research Scholar, Department of chemistry, Osmania University, Hyderabad, 500007.
Jagadeshwar Vannada[1*]
[1*]Associate Professor, Department of chemistry, Osmania University, Hyderabad, 500007.

Mail id: mannesubhashphd@gmail.com[1]
Corresponding author mail: oujagan@gmail.com[1*]

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1,2,3-Triazole, Multicomponent reaction, Click chemistry, antimicrobial activity, Molecular Docking.

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Abstract

A series of novel 1,2,3-triazole-based 2-amino-4H-chromene-3-carbonitrile derivatives (7a–7o) were synthesized through a combination of copper-catalysed azide–alkyne cycloaddition (CuAAC) and multicomponent reaction strategies. The synthesized compounds were characterized by FT-IR, NMR, and mass spectroscopic analyses, confirming their proposed structures. The antimicrobial potential of all synthesized derivatives was evaluated against selected bacterial and fungal strains. Biological screening revealed that several compounds exhibited significant antimicrobial activity, with some derivatives showing comparable or superior potency relative to the standard drugs. These findings suggest that the synthesized 1,2,3-triazole-linked 2-amino-4H-chromene-3-carbonitrile derivatives represent promising candidates for the development of new antimicrobial agents. Among all the synthesized molecules, compound 7i emerged as the most promising candidate, exhibiting a Glide score of -7.94 kcal/mol, Glide Emodel of -74.88 kcal/mol.

1. INTRODUCTION

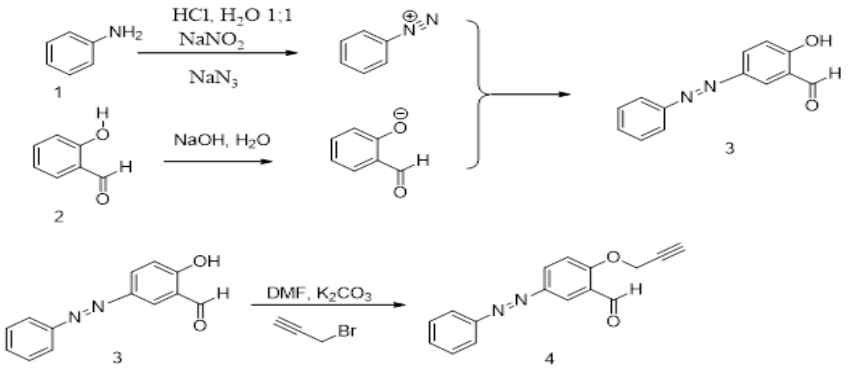
Because of their many uses in pharmaceutical chemistry, materials science of 1,2,3-triazoles have attracted a lot of attention lately [1-2]. Among the several synthetic approaches, the cupper(I)-catalysed azide–alkyne cycloaddition (CuAAC), a classic "click" reaction, provides a mildly regioselective and effective pathway to 1,4-disubstituted 1,2,3-triazoles [3-4]. Triazoles are useful scaffolds in drug development and functional material design because of their distinct physicochemical and electrical characteristics, including their stability, hydrogen-bonding ability, and bio isosteric resemblance to amide bonds [5-8]. The chemical and functional variety of organic frameworks is further increased by the incorporation of azo functionalities [9]. Azo compounds are widely recognized for their reversible photoisomerization behaviour, bright chromophores, and prospective use in dyes, sensitive materials, and molecular switches [10]. In addition to improving molecular stiffness and planarity, the conjugation of azo-linked aromatic moieties with triazole rings via ether linkages creates p-conjugated routes that are advantageous for optoelectronic applications [11]. An important class of oxygen-containing bioactive scaffolds [12], chromene-based heterocycles have garnered a lot of attention because of their various pharmacological characteristics [13], which include antioxidant [14], antibacterial [15], anti-inflammatory [16], and anticancer effects [17]. Because of their synthetic accessibility and diverse biological characteristics, 2-amino-4H-chromenes have become a preferred structural motif in medicinal chemistry and drug development programs [18]. Significant

changes in biological activity are frequently the result of adding different electron-donating or electron-withdrawing groups at particular locations within the chromene structure [19]. A valuable molecular hybrid that combines a highly functionalized chromene core with essential substituents like a cyano group at C-3, an amino group at C-2, and a phenyl ring at C-4 all of which are further stabilized by gem-dimethyl substitution at C-7 is 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile [20]. It is well recognized that these structural components increase molecular stiffness, promote receptor binding, and affect the molecule's bioavailability and lipophilicity. Additionally, this compound's effective synthesis by multicomponent reactions (MCRs) [21-22] including active methylene compounds, aldehydes, and malononitrile in a safe environment is in line with contemporary green chemistry trends. This chromene derivative is a good option for additional research as a pharmacophore or synthetic intermediary in the creation of more intricate heterocyclic systems due to its strategic molecular design and ease of manufacture. Here, we present the synthesis and characterisation of novel 1,2,3-triazole-based 2-amino-4H-Chromene-3-carbonitrile, a novel hybrid molecule created by combining a 1,4-disubstituted triazole core with a diazenyl-substituted aromatic ether, and 2-amino-4H-chromenes-3 carbonitrileFurthermoreall the synthesised compounds screened for antimicrobial activity and in silico Molecular Docking studies.

1 EXPERIMENTAL

Synthetic reagents, catalysts, and solvents were sourced from industrial suppliers including Merck, Sigma-Aldrich, TCI, Spectrochem, and Avra Chemicals. These materials were used as received, without any further purification. The reaction's progress was tracked through thin-layer chromatography (TLC) employing Merck 60F254 silica gel plates. Melting points of the final products were recorded using the Stuart SMP3 melting point apparatus, and these values were uncorrected. Purification of the mixtures was achieved through recrystallization and column chromatography utilizing silica gel with a mesh size of 60–120. The composition of the mixtures was established by analysing the IR spectra of the compounds with a Shimadzu FTIR 8400 S spectrometer using KBr pellets. Nuclear magnetic resonance (NMR) spectroscopy for both ^{1}H and ^{13}C was conducted using a Bruker 400 spectrometer operating at frequencies of 400 and 100 MHz, respectively. The solvents employed were $CDCl_3$ and DMSO-d_6, with TMS serving as the internal standard. Mass spectrometry was performed utilizing a Shimadzu GC-MS QP 1000 spectrometer.

1.1 Synthesis: The synthetic scheme for the designed substituted 2-amino-7,7-dimethyl-5-oxo-4-(2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6a-o) is depicted in Scheme-1, 2 and the detailed procedure for the synthesis enumerated below:



Scheme 1. Synthesis of 5-(phenyldiazenyl)-2-(prop-2-yn-1-yloxy)benzaldehyde.

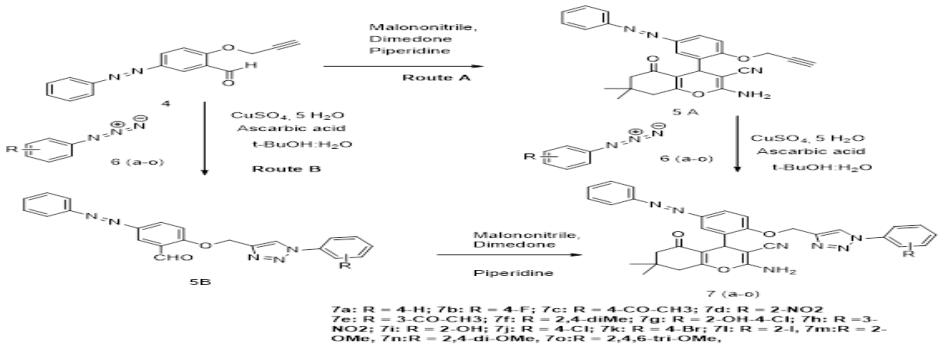
1.2 Synthesis of 2-hydroxy-5-(phenyldiazenyl)benzaldehyde (3):

In a 100 mL round-bottom flask, aniline (0.93 g, 10 mmol) was dissolved in concentrated HCl (5 mL) and water (5 mL). The solution was cooled to 0–5 °C in an ice bath. A cold solution of $NaNO_2$ (0.70 g, 10.1 mmol) in 5 mL water was added dropwise over 10 minutes with stirring to form the diazonium salt. After stirring for 15 minutes, a cold alkaline solution of 2-hydroxy benzaldehyde (1.09 g, 10 mmol) in 10 mL

NaOH (10%, w/v) was added slowly. The mixture was stirred for an additional 30 minutes at 0–5 °C and then for 2 h at room temperature. The precipitated 2-hydroxy-5-(phenyldiazenyl)benzaldehyde was filtered, washed with cold water, and dried under vacuum to afford a red solid (Yield: 80%).

1.3 Synthesis of 5-(phenyldiazenyl)-2-(prop-2-yn-1-yloxy)benzaldehyde (4):

To a stirred solution of 2-hydroxy-5-(phenyldiazenyl)benzaldehyde (1.00 g, 4.5 mmol) and K_2CO_3 (1.24 g, 9 mmol) in DMF (20 mL), 3-bromoprop-1-yne (0.90 g, 5 mmol) was added dropwise. The reaction mixture was refluxed for 8 h under nitrogen. After completion (monitored by TLC), the mixture was cooled to room temperature, filtered to remove inorganic salts, and the solvent evaporated. The crude residue was purified by column chromatography (hexane/ethyl acetate, 8:2) to afford the intermediate compound (**4**).



Scheme-2: Synthetic routes for the preparation of compounds 7a–l. Route A and Route B represent two alternative methods employed for the synthesis of the target compounds.

1.4 Synthesis of 2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy) 5(phenyldiazenyl)benzaldehyde: (5B) To a solution of compound (4) (0.55 g, 5.4 mmol) in t-BuOH:H_2O (1:1, 10 mL), the azide compound (1.2 g, 4.5 mmol) was added. To this mixture, CuSO4·5H_2O (0.05 g, 0.2 mmol) and sodium ascorbate (0.10 g, 0.5 mmol) were added sequentially. The reaction was stirred at room temperature for 12 h. After completion, the mixture was extracted with ethyl acetate (3 × 25 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane:ethyl acetate (5:5) as eluent to obtain the target triazole compound as a red-orange solid.

1.5 Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-(2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl) -5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile 7(a-0): mL of ethanol containing a catalytic amount of piperidine (2–3 drops) was mixed with benzaldehyde(5A) (1.0 mmol, 0.106 g), malononitrile (1.0 mmol, 0.066 g), and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (1.0 mmol, 0.140 g) either at room temperature or under reflux for 30–90 minutes. Using ethyl acetate:hexane (3:7) as the eluent, thin-layer chromatography (TLC) was used to track the reaction's development. The title chemical was obtained as a white to off-white crystalline solid after the final solid product was filtered, cleaned with cold ethanol, and recrystallized from ethanol.

2 SPECTRAL DATA: SPECTRAL DATA:

2.1 7a:(E)-2-amino-7,7-dimethyl-5-oxo-4-(2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Yellow solid215–216 °C; mp. 85%1H NMR (400 MHz, cdcl3) δ 8.49 (s, 1H), 7.89 -7.78(m, 5H), 7.75 (s, 1H), 7.54-7.74 (m, 5H), 7.16-7.14 (d,J=8Hz 2H), 5.59(s, 2H), 5.04(s, 1H), 4.56(s, 2H), 2.50 (s, 2H), 2.27 (s, 2H), 1.18 (s, 3H), 1.17 (s, 3H)3C NMR (126 MHz, CDCl3) δ 195.90, 162.69, 158.00, 157.63, 152.81, 151.74, 138.36, 137.46, 130.59, 130.38, 129.02, 124.82, 124.15, 123.47, 122.53, 121.58, 118.89, 117.69, 112.26, 62.56, 50.70, 40.66, 32.27, 29.13, 27.71, 27.55. ; IR (KBr, cm−1): 3444, 3331, 2956, 1674, 1480, 1483, 1366, 1253; HRMS (ESI) m/z calcd for C33H29N7O3 [M + H+], 571.641; Found 572.236.

2.2 7b:(E)-2-amino-4-(2-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5 (phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Yellow solid214–215 °C; mp 90%.; 1H NMR (400 MHz, cdcl3) δ 8.61 (s, 1H), 7.93-7.86 (m, 5H), 7.64-7.54 (m, 6H), 7.23-7.20(d,J=12Hz, 3H), 5.68(s, 2H), 5.15(s, 1H), 4.65(s, 2H), 2.61(s, 2H), 2.36 **(s**, 2H), 1.27(s, 3H), 1.25(s, 3H).13C NMR (101 MHz, $CDCl_3$) δ 196.11, 163.69, 163.07, 161.21, 158.14, 157.33, 152.81, 147.30, 133.50, 132.90, 130.55, 129.13, 124.17, 123.15, 122.61, 122.50, 122.42, 116.87, 116.64, 113.14, 112.38, 62.56, 50.77, 40.76, 32.38, 29.21, 29.02, 27.81. ; IR (KBr, cm^{-1}): 3481, 3375, 2964, 1688,1654,1543,1580, 1365; **HRMS (ESI)** m/z calcd for $C_{33}H_{28}FN_7O_3$, [M + H^+], 589.631; Found 590.227.

2.3 7c:(E)-4-(2-((1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5(phenyldiazenyl)phenyl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Yellow solid214–215 °C; mp 92%.;. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.65(s,1H), 8.11-8.08(d, J=12Hz, 1H), 7.97 -7.95(d, J=8 Hz,1H), 7.82-7.73 (m, 3H), 7.66 (s, 1H), 7,55-7.36(m,5H),7.11-7.08(d, J=12Hz), 5.59(s, 2H), 5.06(s, 1H), 4.52(s, 2H), 2.63(s, 3H), 2.50(s, 2H),2.26(s,2H),1.16 (s, 3H), 1.15 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.53, 174.52, 162.37, 162.29, 148.52, 146.05, 142.36, 139.77, 137.34, 136.85, 135.45, 134.58, 133.05, 129.99, 128.99, 127.45, 125.50, 123.31, 122.02, 120.04, 118.82, 117.44, 60.07, 50.75, 40.65, 32.71, 31.47, 30.81, 27.93, 26.68. ; **IR (KBr, cm^{-1}):** 3453, 3381, 2929, 2148, 16755, 1644,1560,1488, 1356 ; **HRMS (ESI)** m/z calcd for $C_{35}H_{31}N_7O_4$, [M + H^+], 613.243; Found 614.247.

2.4 7d:(E)-2-amino-7,7-dimethyl-4-(2-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Brown solid212–213 °C; mp.; 88%**^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.19 (s, 1H), 8.06-8.04 (d, *J* = 6 Hz, 1H), 7.91-7.72 (m, 5H), 7.54 – 7.37(m, 4H), 7.13-7,11 (d, J=6Hz,1H), 5.44(s, 2H), 4.84(s, 1H), 4.58(s, 2H), 2.44(s, 2H), 2.21(s, 2H), 1.11 (s, 6H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.09, 162.90, 158.33, 157.82, 152.79, 147.11, 144.42, 144.13, 133.88, 132.13, 130.73, 130.41, 130.17, 129.03, 127.88, 125.57, 125.14, 124.13, 122.57, 119.32, 112.53, 112.17, 105.21, 61.94, 50.72, 40.60, 32.27, 29.72, 29.11, 27.62. ; **IR (KBr, cm^{-1}):** 3438, 2930, 2116, 1648, 1604, 1506, 1530, 1367; **HRMS (ESI)** m/z calcd for $C_{33}H_{28}N_8O_5$, [M + H^+], 616.218; Found 617.221.

2.5 7e:(E)-4-(2-((1-(3-acetylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Yellow solid214–223 °C; mp **89%^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.61 (s, 1H), 8.38(s, 1H), 8.09-7.98(m, 3H), 7.83 – 7.76(m, 3H), 7.51-7.40 (m, 4H), 7.10(s, 1H), 5,53 (s, 2H), 5.03(s, 1H), 4.60(s, 2H), 2.66(s, 3H), 2.45(s, 2H), 2,25 (s, 2H), 1.13 (s, 6H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.68, 174.68, 162.52, 162.44, 148.67, 146.20, 142.51, 139.92, 137.49, 137.00, 135.60, 134.74, 133.89, 133.

Molecular Weight: 613..20, 131.84, 130.15, 129.14, 127.60, 125.65, 123.46, 122.17, 120.19, 118.97, 117.59, 60.22, 50.91, 40.80, 32.86, 31.62, 30.96, 28.08, 26.83. ; **IR (KBr, cm^{-1}):** 3460, 3320, 2916, 219248, 1671,1602, 1478 ,1366, ; **HRMS (ESI)** m/z calcd for $C_{35}H_{31}N_7O_4$ [M + H^+], 613.243; Found 614.247

2.6 7f:(E)-2-amino-4-(2-((1-(2,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Yellow solid210–223 °C; m p.91%**^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.37 (s, 1H), 7.87-7.74 (m, 4H), 7.72 (s, 1H), 7.59(s, 1H), 7.51-7.40 (m, 5H), 7.13-7.11(d,J=6Hz,1H), 5,48(s, 2H), 4.96(s, 1H), 4.43(s, 2H), 2.33(s, 3H), 2.30(s, 3H), 2,23 (s, 2H), 1.57 (s, 2H), 1.13(s, 3H), 1.12(s, 3H)**^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.09, 162.90, 158.33, 157.82, 152.79, 147.11, 144.42, 144.13, 133.88, 132.13, 130.73, 130.41, 130.17, 129.03, 127.88,127.08, 125.57, 125.14, 124.13, 122.57, 112.53, 112.17, 61.94, 50.72, 40.55, 32.27, 30.89, 29.72, 29.11, 27.62. ; **IR (KBr, cm^{-1}):** 3445, 3378, 2916, 2148, 1659, 1582, 1549 1362; ; **HRMS (ESI)** m/z calcd for $C_{35}H_{33}N_7O_3$ [M + H^+], 599.264; Found 600.267.

2.7 7g:(E)-2-amino-4-(2-((1-(4-chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile

Black solid210–223 °C; m p.84%**^{1}H NMR (300 MHz, $CDCl_3$)** δ 10.02 (s, 1H), 8.85 (s, 1H), 7.85-7.79 (m, 5H), 7.57–– 7.46(m, 5H), 7.11(s, 1H), 5,67 (s, 2H), 5.13(s, 1H), 4.61(s, 2H), 2.56(s, 2H), 2,34 (s, 2H), 1.21 (s, 3H), 1.20(s, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 196.16, 162.96, 158.27, 157.89, 153.07, 152.00, 138.62, 137.72, 136.76, 135.29, 132.68, 131.29, 130.86, 130.64, 129.28, 125.08, 124.41, 123.73, 122.80, 121.84, 119.16, 117.95, 112.52, 62.82, 50.97, 40.93, 32.54, 29.39, 27.98,

27.81. ; **IR (KBr, cm^{-1}):** 3640,3445, 3340, 2933, 2191, 1675, 1659, 1540,1493, 982, 858; **HRMS (ESI)** m/z calcd for $C_{33}H_{28}N_7O_4$ [M + H^+], 621.189; Found 622.192.

2.8 7h:(E)-2-amino-7,7-dimethyl-4-(2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile

Yellow solid210–223 °C; m p.88%**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.86 (s, 1H), 8.77 (s, 1H), 8.31-8.21(m, 2H), 7.77-7.63(m, 5H), 7.49-7.42 (m, 3H), 7.09-7.06(d J=12Hz, 1H), 5.67(s, 2H),5.13(s, 1H), 4.54(s, 2H), 2.54(s, 2H), 2,32 (s, 2H), 1.17 (s, 6H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.15, 162.95, 158.38, 157.87, 152.84, 147.16, 144.47, 144.18, 133.93, 132.19, 130.78, 130.47, 130.23, 129.08, 127.93, 125.62, 125.19, 124.18, 122.63, 119.38, 112.58, 112.22, 105.26, 62.00, 50.77, 40.65, 32.32, 29.78, 29.16, 27.68. ; **IR (KBr, cm^{-1}):** 3504, 3330, 2916, 2191, 1659, 1520, 1450,1212, ; **HRMS (ESI)** m/z calcd for $C_{33}H_{28}N_7O_5$ [M + H^+], 616.218; Found 617.221.

2.9 7i:(E)-2-amino-4-(2-((1-(2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile

Black solid215–220°C; mp.86%;**^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.97(s,1H) 8.81(s, 1H), 7.85-7.74(m, 4H), 7.68-7.66(d, J=6Hz, 2H), 7.52-7.39 (m, 6H), 5.57(s, 2H),5.08(s, 1H), 4.56(s, 2H), 2.52(s, 2H), 2,29 (s, 2H), 1.16(s, 3H), 1.15(s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 196.22, 163.02, 158.45, 157.94, 152.91, 147.23, 144.54, 144.25, 142.44, 134.00, 132.26, 130.85, 130.54, 130.29, 129.15, 128.00, 127.20, 125.69, 125.26, 124.25, 122.70, 112.65, 112.29, 62.06, 50.84, 40.67, 32.39, 29.80, 29.23, 27.74. ; **IR (KBr, cm^{-1}):** 3337, 3130, 2146, 1620 1548, 1450, 1259, **HRMS (ESI)** m/z calcd for $C_{33}H_{29}N_7O_4$ [M + H^+], 587.228; Found 588.231.

2.10 7j;(E)-2-amino-4-(2-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile

yellow solid215–220°C; mp.83%**^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.49 (s, 1H), 7.80-7.75(m, 4H), 7.67-7.66(d, J=3Hz, 1H), 7.49-7.42 (m, 6H),7.11-7.09(d,J=6Hz,1H), 5.56(s, 2H),5.03(s, 1H), 4.53(s, 2H), 2.49(s, 2H), 2,24 (s, 2H), 1.15(s, 3H), 1.13(s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.60, 163.41, 158.84, 158.33, 153.30, 147.62, 144.93, 144.64, 134.39, 132.64, 131.24, 130.92, 129.54, 128.39, 126.08, 125.65, 124.64, 123.08, 113.04, 112.68, 62.45, 62.22, 51.23, 41.06, 32.78, 31.40, 29.62, 28.13. ; **IR (KBr, cm^{-1}):** 3537, 3130, 2116, 1648, 1459, 1230; **HRMS (ESI)** m/z calcd for $C_{33}H_{28}ClN_7O_3$ [M + H^+], 605.194; Found 606.197.

2.11 7k:(E)-2-amino-4-(2-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:

Yellow solid210–225 °C; mp. 88%**^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.28 (s, 1H), 8.09(s, 1H), 7.92-7.90(d, J=3Hz,4H), 7.64-7.50 (m, 6H), 7.26-7.24(d, J=6Hz 1H), 5.61(s, 2H),5.01(s, 1H), 4.60(s, 2H), 2.56(s, 2H), 2,31(s, 2H), 1.22(s, 3H), 1.20(s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 195.87, 162.83, 160.98, 157.91, 157.09, 152.57, 147.06, 133.26, 132.67, 130.31, 128.89, 125.85, 123.93, 122.91, 122.37, 122.26, 122.18, 116.63, 116.40, 112.90, 112.14, 62.32, 50.53, 40.53, 32.15, 28.97, 28.78,

27.57. ; **IR (KBr, cm^{-1}):** 3537, 3230, 2916, 2148, 1659, 1470, 1230; **HRMS(ESI)** m/z calcd for $C_{33}H_{28}BrN_7O_3$ [M + H$^+$], 649.143; Found 650.537.

2.12 7l:(E)-2-amino-4-(2-((1-(2-iodophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:
Yellow solid214–225 °C; mp.77%**^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.19 (s, 1H), 7.99-7.97(d,J=6Hz, 1H), 7.87-7.76(m, 3H), 7.73(s, 1H), 7.54-7.39 (m, 6H), 7.16-7.14(d, J=6Hz 1H), 5.52(s, 2H),4.92(s, 1H), 4.51(s, 2H), 2.63(s, 2H), 2,22 (s, 2H), 1.13 (s, 3H), 1,11(s, 3H).**^{13}C NMR (101 MHz, CDCl$_3$)** δ 195.92, 162.79, 158.12, 157.78, 152.78, 147.15, 140.32, 140.04, 132.42, 131.53, 130.41, 129.27, 129.03, 127.89, 124.22, 124.02, 123.47, 122.56, 120.81, 112.81, 112.50, 100.25, 96.55, 93.94, 62.50, 50.67, 40.69, 32.28, 30.01, 29.13, 27.74. ; **IR (KBr, cm^{-1}):** 3527, 3240, 2956, 2168, 1649, 1460, 1240; **HRMS (ESI)** m/z calcd for $C_{33}H_{28}IN_7O_3$ [M + H$^+$], 697.129; Found 698.133.

2.13 7m:(E)-2-amino-4-(2-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:
Yellow solid213–224°C; mp.92%**^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.37 (s, 1H), 7.89-7.80(m, 4H), 7.50-7.38(m, 5H), 7.18-7.08(m, 3H), 5.38(s, 2H),4.79(s, 1H), 4.47(s, 2H), 3.38(s, 3H), 2,19 (s, 2H),1.64(s, 2H) 1.10(s, 3H), 1,09(s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 196.00, 162.68, 158.40, 156.25, 152.85, 151.30, 147.51, 146.97, 138.64, 138.43, 132.19, 131.08, 130.36, 129.03, 126.33, 125.70, 124.28, 122.59, 121.40, 115.34, 112.49, 112.42, 112.14, 65.93, 60.43, 56.12, 50.70, 40.54, 32.24, 29.16, 27.57. ; **IR (KBr, cm^{-1}):** 3537, 3330, 2916, 2148, 1659, 1648, 1520,1365; ; **HRMS (ESI)** m/z calcd for $C_{34}H_{31}IN_7O_4$ [M + H$^+$], 601.243; Found 602.247..

2.14 7n:(E)-2-amino-4-(2-((1-(2,3-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile:
Yellow solid 215–226 °C; mp.91%**^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.44 (s, 1H), 7.83-7.70(m, 4H), 7.69(s, 1H), 7.49-7.40(m, 4H),7.11-7.09(d, J=8Hz,1H) 5.52(s, 2H),4.99(s, 1H), 4.51(s, 2H), 3.84(s, 6H), 2,45 (s, 2H),2,22(s, 2H) 1.13(s, 3H), 1,12(s, 3H).**^{13}C NMR (126 MHz, CDCl$_3$)** δ 195.98, 162.66, 160.56, 158.38, 155.54, 152.83, 151.28, 146.95, 140.30, 135.64, 131.73, 130.36, 129.01, 127.05, 125.68, 124.26, 122.57, 121.38, 119.26, 116.65, 115.32, 112.47, 112.12, 62.21, 56.10, 53.45, 50.68, 40.52, 33.99, 32.22, 29.14, 27.55; **IR (KBr, cm^{-1}):** 3347, 3230, 2916,2192 1548, 1520 1259, ; **HRMS (ESI)** m/z calcd for $C_{35}H_{33}IN_7O_5$ [M + H$^+$], 631.254; Found 632.257.

2.15 7o:(E)-2-amino-7,7-dimethyl-5-oxo-4-(5-(phenyldiazenyl)-2-((1-(2,4,6-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile
Yellow solid 210–216 °C; mp.92%**^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.49 (s, 1H), 7.82-7.71(m, 3H), 7.66(s, 1H), 7.53-7.38(m, 4H),7.12-7.02(m, 3H) 5.57(s, 2H),5.30(s, 1H),5.07(s, 2H), 3.91(s, 6H), 3.86(s, 3H), 2,22 (s, 2H),1,63(s, 2H) 1.15(s, 3H), 1,13(s, 3H).**^{13}C NMR (126 MHz, CDCl$_3$)** δ 196.06, 162.75, 160.64, 158.44,

152.91, 151.36, 147.04, 140.39, 133.17, 131.82, 130.44, 129.09, 125.76, 124.34, 122.65, 121.46, 112.56, 112.48, 112.20, 100.48, 88.99, 56.18, 50.76, 40.60, 35.98, 32.30, 31.59, 29.23, 27.63. ; **IR (KBr, cm^{-1}):** 3437, 3230, 2985, 2116, 1648, 1459, 1258; **HRMS (ESI)** m/z calcd for $C_{36}H_{35}N_7O6$, [M + H^+], 651.264; Found 662.268.

3 BIOLOGICAL ACTIVITIES

3.1 Antibacterial activity:

The synthesized compounds **7(a–o)** were evaluated for their antibacterial activity against a panel of bacterial strains, including Gram-negative Klebsiella pneumoniae, Escherichia coli, and Gram-positive Bacillus subtilis and Staphylococcus aureus.

The antibacterial assays were conducted using the agar disc diffusion method [23] at two concentrations: 10 µg/mL and 20 µg/mL. Bacterial cultures were freshly prepared and diluted in 5% sterile saline, adjusted to an inoculum density of approximately 10^5–10^6 CFU/mL. The test compounds were dissolved in dimethyl sulfoxide (DMSO) to prepare the required concentrations for biological testing. Sterile discs (6 mm diameter) were impregnated with 20 µL of each test solution and allowed to air-dry to ensure full saturation. These discs were then placed on the surface of Muller–Hinton agar plates that had been uniformly seeded with the respective bacterial strains. The plates were incubated at 37 °C for 24–48 h, and the zones of inhibition (in mm) were measured after incubation. All experiments were conducted in triplicate, and the antibacterial efficacy of the synthesized compounds was compared to that of the standard antibiotic gatifloxacin at the same concentrations (10 and 20 µg/mL). The average zone of inhibition values was recorded and tabulated.

3.2 Results of Antibacterial activity:

Table 1. Antibacterial activity of compounds 7(a-o).

Compound	Zone of inhibition (mm)							
	Gram positive bacteria				Gram negative bacteria			
	s.aureus		***B. subtilis***		***K. pneumoniae***		***E. coli***	
	10 µg/mL	20 µg/mL	10 µg/mL	20 µg/mL	10 µg/mL	20 µg/mL	10 µg/mL	20 µg/mL
7a	11.2	19.4	9.8	19.7	6.7	11.4	7.9	11.4
7b	9.2	15.7	6.3	15.4	10.4	18.1	10.2	16.6
7c	11.5	16.3	10.1	18.2	8.5	9.5	8.6	7.4
7d	10.9	15.9	11.0	18.1	12.6	10.4	9.8	8.8
7e	14.8	24.8	13.9	26.1	13.1	22.5	14.1	22.1
7f	14.5	23.9	12.9	27.0	13.8	21.4	15.1	23.0
7g	14.6	25.1	13.8	25.8	13.1	22.0	14.9	21.5
7h	12.2	17.7	11.5	20.5	9.8	18.2	9.5	16.4
7i	11.8	16.5	10.1	18.1	8.6	19.0	8.6	7.8
7j	9.5	15.1	7.9	16.6	10.4	16.1	11.4	18.2
7k	10.1	14.5	8.1	13.9	11.5	15.2	11.7	16.5

7l	9.8	13.7	8.4	14.5	11.5	14.2	11.9	12.4
7m	9.2	15.7	6.3	15.4	10.4	18.1	10.2	16.6
7n	9.6	15.1	7.9	16.6	10.4	16.1	12.4	18.2
7o	9.7	13.7	8.4	16.5	13.5	14.2	10.9	13.4
Gatifloxacin	13.9	23.5	12.4	25.4	12.8	20.4	13.9	21.4

The newly synthesized title compounds **7(a-o)** were evaluated for their *in-vitro* antibacterial activity against Gram-positive strains (such as *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 96)) and Gram-negative strains (such as *Escherichia coli*, (MTCC 43), *Klebsiella pneumonia* (MTCC 530)) at various concentration10µg/mL and 20µg/mL. The zone of inhibition was measured in mm and Gatifloxacin was used as the standard drug and are shown (**Table 1**). Among the synthesized derivatives, compound 7g exhibited the most potent antibacterial activity against Staphylococcus aureus and Bacillus subtilis, surpassing the activity of the reference drug Gatifloxacin. Compound 7e also demonstrated significant antibacterial potency, particularly against B. subtilis.

In the case of Gram-negative bacteria, compound 7f exhibited excellent inhibitory activity against Escherichia coli and Klebsiella pneumoniae. Likewise, compound 7e showed appreciable activity against both organisms. Compounds containing halogen substituents at the para position (7b–7d) generally displayed moderate antibacterial activity when compared with nitro- and methoxy-substituted analogues. Notably, compounds 7e, 7f, and 7g exhibited antibacterial activities comparable to or greater than that of Gatifloxacin, highlighting their potential as promising antibacterial candidates.

3.3 Antifungal activity:

Using the poison plate technique, the antifungal activity of synthesized compounds 7(a-o) was evaluated at a concentration of 50 µg/mL against three pathogenic fungi: Aspergillus niger, Aspergilus flavus, and Fusarium oxysporum. To get fresh mycelium for the antifungal test, three different types of fungus were incubated in PDA for five days at 25 ± 1 ^{0}C. After that, a mycelium disc of about 0.45 cm in diameter was removed from the culture medium using a sterile inoculation needle, and it was injected in the middle of the PDA plate [24]. The test chemicals were added to the Potato Dextrose Agar medium (PDA, 20 mL) after being dissolved in 5 mL of DMSO. 50µg/mL was the final concentration of chemicals added to the medium. For five days, the inoculation plates were incubated at 25 ± 1ºC. Three experimental duplicates were conducted for each treatment, using acetone diluted with sterile distilled water as the control and clotrimazole (50µg/mL) as the standard control. On the fifth day, the fungal colonies' radial growth was measured.

3.4 Results of Antifungal activity

Table 2. Antifungal activity of compounds **7(a-l)**

Compound	Zone of Inhibition (mm)		
Conc. (50µg/mL)	***A. niger***	***A. flavus***	***F.oxysporum***
7a	16.8	14.2	11.4
7b	17.5	16.7	18.5
7c	16.5	16.5	17.8
7d	14.9	15.1	16.6
7e	18.4	17.8	19.5

7f	18.8	17.5	19.8
7g	12.7	16.3	17.1
7h	13.5	15.9	16.0
7i	12.1	14.1	13.9
7j	13.1	13.9	14.1
7k	12.8	14.1	17.4
7l	16.6	12.9	14.1
7m	12.7	12.3	11.1
7n	12.5	15.1	12.0
7o	12.7	11.1	11.9
Clotrimazole	17.3	16.7	18.2

All the synthesized compounds 7a–7o were evaluated for their in vitro antifungal activity against Aspergillus niger, Aspergillus flavus, and Fusarium oxysporum at a concentration of 50 µg/mL. The antifungal activity results are presented in Table 2 and were compared with the standard antifungal drug Clotrimazole. Analysis of the antifungal activity data revealed that compound 7f exhibited the highest inhibitory activity against A. niger, followed closely by 7e and 7b. In contrast, compound 7g showed the lowest activity against A. niger. A similar trend was observed against A. flavus, where 7f displayed the strongest antifungal activity, marginally outperforming 7e and 7b, whereas 7l exhibited the weakest inhibition. Against F. oxysporum, compounds 7f and 7e demonstrated superior antifungal activity, exceeding that of the reference drug Clotrimazole. The remaining derivatives showed moderate levels of inhibition against this fungal strain. Notably, compounds 7e and 7f exhibited antifungal activities comparable to or greater than that of Clotrimazole, highlighting their potential as promising antifungal agents.

3.5 Molecular Docking:

The X-ray crystal structure of BTK (PDB ID: 5VFI) was retrieved from the Protein Data Bank [25]. Protein was refined, and energy minimization was performed using the Protein Preparation Wizard implemented in the Schrodinger suite with the OPLS2005 force field [26]. The co-crystallized protein-ligand complex was chosen, and the native ligand was removed before receptor grid generation. A grid box of dimensions 10 Å × 10 Å × 10 Å is generated around the active site. For non-polar atoms, the receptor van der Waals scaling factor was set to 0.8 [27, 28]. The synthesized molecules (1-12) were sketched using the 2D Sketcher module in the Maestro Build Panel and subsequently converted into three-dimensional structures using LigPrep. Low-energy conformers of all compounds were generated through the LigPrep module of the Schrodinger Suite [29, 30]. Molecular docking studies were carried out using the Glide docking module to investigate the binding interactions of synthesized molecules within the active site of BTK.

3.6 Results of Molecules Docking:

The synthesized molecules 7 (a-o), together with the reference drug doxorubicin, were ranked based on the Glide score and Glide Emodel. Analysis of the docking poses revealed consistent interactions with key amino acid residues within the BTK active site, including Lys406, Leu408, Ala428, Tyr476, Met477, Ala478, and Leu528. These residues were considered crucial for effective BTK inhibition. Comparative docking analysis demonstrated that doxorubicin exhibited less favorable Glide score and Glide Emodel, 7i and 7e. These findings suggest comparatively weaker binding affinities of the currently available therapeutics towards the BTK target.

Among all the synthesized molecules, compound 7i emerged as the most promising candidate, exhibiting a Glide score of -7.94 kcal/mol, Glide Emodel of -74.88 kcal/mol. Figure 1 depicts the three-dimensional binding poses of molecule7i, doxorubicin drug, within the BTK binding pocket, visualized using BIOVIA Discovery Studio (BIOVIA, Dassault Systèmes, 2020). Overall, the docking analyses indicate that molecule 7i possesses superior binding properties compared with the reference inhibitors. These results suggest that molecule 7i may serve as a promising lead molecule for the development of novel BTK-targeted anticancer therapeutics.

Table 3: Interacting amino acid residues of BTK protein with synthesized molecules, the reference drug, along with Glide Score and Glide Emodel values.

Compound ID	Glide Score	Glide Emodel	Interactions
7a	-6.957	-68.452	Lys406, Leu408, Val416, Ala428, Tyr476, Met477, Ala478, Leu528
7b	-5.675	-65.730	Leu408, Ala428, Met477, Ala478, Gly480, Leu528
7c	-5.659	-64.703	Leu408, Ala428, Met477, Ala478, Leu528
7d	-4.595	-44.425	Lys406, Leu528
7e	**-7.492**	**-79.897**	Lys406, Leu408, Val416, Ala428, Tyr476, Met477, Ala478, Leu528
7f	-6.752	-67.556	Lys406, Leu408, Val416, Ala428, Val458, Tyr476, Met477, Ala478, Gly488, Leu528
7g	-6.371	-66.305	Lys406, Leu408, Val416, Ala428, Tyr476, Met477, Ala478, Leu528
7h	-7.379	-77.605	Lys406, Leu408, Val416, Ala428, Lys430, Tyr476, Met477, Ala478, Leu528
7i	**-7.949**	**-74.889**	Lys406, Leu408, Val416, Ala428, Tyr476, Met477, Ala478, Leu528
7j	-6.136	-66.878	Lys406, Leu408, Ala428, Met477, Ala478, Gly480, Leu528
7k	-5.67	-67.024	Leu408, Ala428, Met477, Ala478, Leu528

7l	-5345	-68.056	Leu409, Ala430, Met477, Ala479,Leu530
7m	-7.238	-72.398	Lys406, Leu408, Val416, Ala428, Glu475, Tyr476, Met477, Ala478,
7n	-7.349	-72.998	Gly480, Leu528 Lys408, Leu409, Val423, Ala430, Glu480, Tyr479, Met472, Ala488, Gly492, Leu532
7o	-7.539	-73.421	Lys410, Leu408, Val433, Ala442, Glu492, Tyr481, Met486, Ala489, Gly494, Leu538
Doxorubicin	-5.34	-58.24	Lys406, Glu407, Asn479, Glu488, Arg490

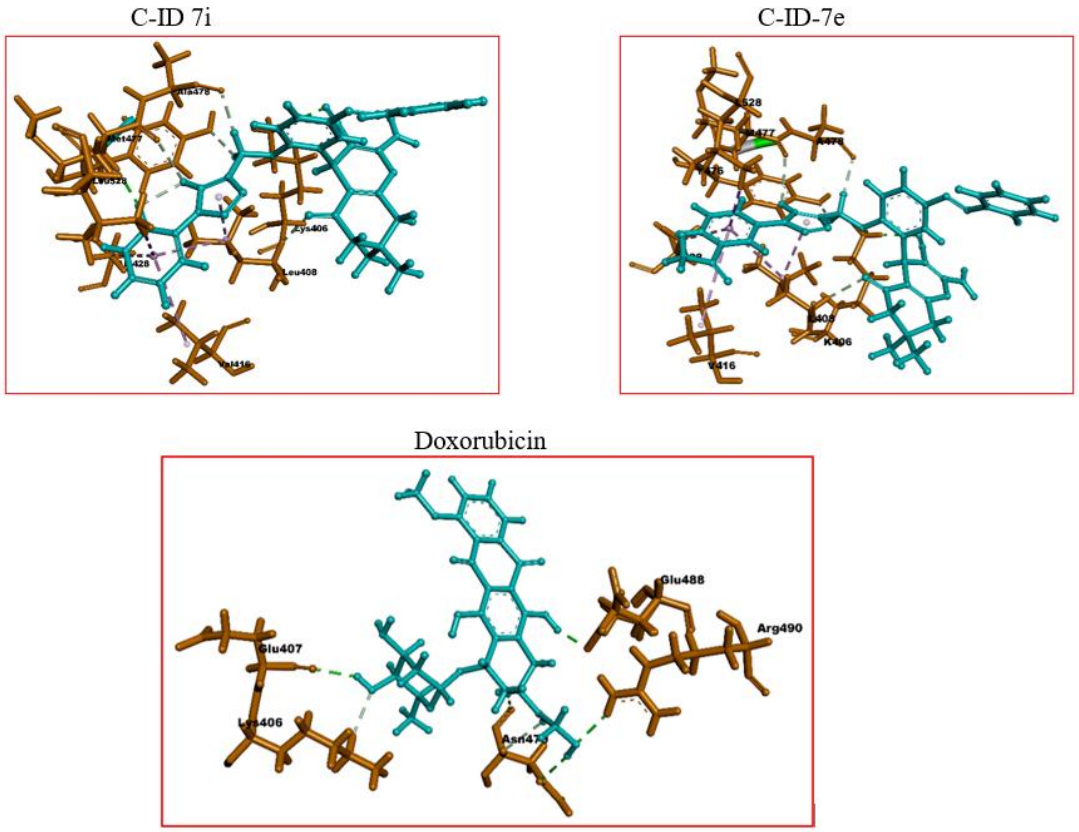


Figure 1: The molecules 7i, 7e and reference doxorubicin drug docked into the active region of the BTK protein are exhibited in a 3-dimensional representation.

4 RESULTS AND DISCUSSION

As illustrated in Scheme 1, the synthesis of the key alkyne intermediate (4) commenced with the diazotization of aniline (1) using sodium nitrite and hydrochloric acid under ice-cold conditions to generate the corresponding diazonium salt. The freshly prepared diazonium intermediate was then subjected to azo-coupling with

salicylaldehyde (2) in an alkaline medium, affording the azo-linked aldehyde intermediate 3. Subsequently, compound 3 underwent O-propargylation with propargyl bromide in the presence of potassium carbonate in DMF, leading to the formation of 5-(phenyldiazenyl)-2-(prop-2-yn-1-yloxy)benzaldehyde (4). The introduction of the terminal alkyne functionality in compound 4 provided a versatile synthetic handle for further derivatization through click chemistry and multicomponent reactions.

Scheme 2 describes two complementary synthetic approaches for the preparation of the target triazole-linked chromene derivatives 7a-7l from the common alkyne intermediate 4. In Route A, compound 4 was first subjected to a one-pot multicomponent reaction with malononitrile and dimedone in the presence of piperidine as a catalyst. The reaction proceeds through a sequence of Knoevenagel condensation, Michael addition, and intramolecular cyclization steps to furnish the chromene intermediate 5A, namely 2-amino-7,7-dimethyl-5-oxo-4-(5-(phenyldiazenyl)-2-(prop-2-yn-1-yloxy)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. The terminal alkyne group present in 5A was subsequently reacted with various aryl azides (R-N_3) under copper-catalyzed azide-alkyne cycloaddition (CuAAC) conditions using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in a t-BuOH/H_2O solvent system. This click reaction efficiently generated the corresponding 1,2,3-triazole derivatives, yielding the final compounds 7a-7l.

In Route B, the sequence of reactions was reversed. Initially, the alkyne intermediate 4 underwent CuAAC reaction with substituted aryl azides (R-N_3) in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate to afford the triazole-containing aldehyde intermediates 5B. These intermediates were then subjected to the one-pot multicomponent reaction with malononitrile and dimedone in the presence of piperidine. Through the same Knoevenagel condensation, Michael addition, and cyclization sequence, the desired chromene derivatives 7a-7l were obtained.

Both routes successfully furnished the target compounds **7a–7o**; however, they differ in the order of the key transformations. Route A involves multicomponent chromene formation followed by click cycloaddition, whereas Route B employs click cycloaddition prior to chromene ring construction. These alternative pathways demonstrate the synthetic flexibility of intermediate **4** and provide efficient access to a diverse library of triazole-functionalized chromene derivatives.

5 CONCLUSIONS

A series of novel 1,2,3-triazole-based 2-amino-3-carbonitrile derivatives (7a–7o) were successfully synthesized and evaluated for their antimicrobial activities. The biological screening results demonstrated that several compounds exhibited promising antibacterial and antifungal activities against the tested microbial strains. Among the synthesized derivatives, compound 7g and compound 7e displayed enhanced antibacterial activity, Furthermore, the antifungal evaluation demonstrated compound 7e, and compounds 7b and 7f exhibited superior antifungal activity. Notably, compound 7f emerged as the most active antifungal derivative against the tested fungal strains. Overall, the present study highlights the potential of triazole-linked 2-amino-3-carbonitrile hybrids as promising antimicrobial agents and provides valuable insights for the future design and development of more potent antibacterial and antifungal compounds. Among all the synthesized molecules, compound 7i emerged as the most promising candidate, exhibiting a Glide score of -7.94 kcal/mol, Glide Emodel of -74.88 kcal/mol.

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7 CONFLICT OF INTEREST

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

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