Design, synthesis, and activity of 2-aminochromone core \(N,N\)-bis-1,2,3-triazole derivatives using click chemistry

Jayaprakash Rao Yerrabelly\(^1\) · Subbanarasimhulu Porala\(^{1,2,4}\) · Venkateshwar Reddy Kasireddy\(^3\) · Earrawandla Janapiya Sony\(^5\) · Someshwar Rao Sagurthi\(^5\)

Received: 25 April 2022 / Accepted: 22 August 2022 / Published online: 5 September 2022
© Institute of Chemistry, Slovak Academy of Sciences 2022

Abstract
A new series of 2-aminochromone-based \(N,N\)-di-1,2,3-triazole hybrid heterocycles were synthesized in one pot from \(N,N\)-terminal dialkyne 2-aminochromone with various organo azides by following the click strategy using classical Cu(I)-catalyzed azide-alkyne \([3 + 2]\) annulation reaction. The synthesized compounds were well characterized by using various spectral analyses such as IR, \(^1\)H NMR, \(^{13}\)C NMR, and HRMS data for their structural elucidation. All newly synthesized compounds have been investigated for anti-microbial activity against Gram-positive, Gram-negative bacteria, and fungal strains and exhibited high activity against microbial growth when compared with standard anti-bacterial agents. These derivatives were tested for anti-cancer activity against HeLa cell lines and found that all compounds exhibit good activity with \(IC_{50}\) values ranging from 0.11 to 1.04 µM than standard curcumin \((IC_{50} 4.83 \pm 0.44 \mu M)\). The molecular docking studies of the synthesized compounds with the affinity of ligands toward the target protein dual-specificity tyrosine-regulated kinase 2, DYRK2 (PDB id: 5ZTN) molecular docking were shown a better Moldock score performed compared to standard.

Graphic abstract

Extended author information available on the last page of the article
Keywords Chromone N,N-di-1,2,3-triazole · Click reaction · Anti-microbial activity · Anti-cancer activity · Molecular docking · SAR studies

Introduction

Chromones are a distinct class of heterocycles and are secondary metabolites produced by plants (Robin et al. 2012). Chromone scaffold was found in nature as well as in synthetic compounds and exhibits a broad spectrum of biological activities including anti-viral (Anil et al. 2013), anti-microbial (Harpreet et al. 2013), anti-inflammatory (An-Rong et al. 2016), anti-convulsant (Ahmed et al. 2010), anti-oxidant (Arpad et al. 2017), anti-cancer (Bo et al. 2016), anti-tubercular (Aypurba et al. 2021), and many more. Chromone moiety serves as an important structural unit in medicinal chemistry due to extensive utilization in the synthesis of various drugs with distinct pharmacological activities including cromolyn was used to treat mastocytosis (Cem et al. 2013), nedocromil was used for the prevention of asthma as an inhaled anti-inflammatory (Keenan et al. 1994), apigenin derived from plant material is used for treating cancer therapy (Huanjie et al. 2017). Flavoxate is a muscle relaxant and also treats the bladder and urinary tracts (Alan et al. 2012). Khellin treats different maladies such as kidney stones, psoriasis, vitiligo, bronchial asthma, coronary disease, and renal colic (Asad et al. 2014).

In addition, 1,2,3-triazole derivatives are highly focused five-membered heterocyclic molecules due to more likely to be water-soluble than normal aromatic compounds and stable in biological systems and are associated with various applications in different fields such as agrochemicals (fungicides) (Joseph-Alexander et al. 2007), anti-microbial (Sandip et al. 2011), anti-cancer (Nazariy et al. 2014) and anti-HIV (Barascut et al. 2001), anti-malarial (Alaide et al. 2016; Ashima et al. 2018), anti-bacterial and anti-fungal (Cheng-He et al. 2010, 2015; Aiyalu et al. 2006; Tejshri et al. 2021), anti-coronavirus agent (Christine et al. 2018), anti-diabetic (Ashwani et al. 2020), anti-allergic (Barbara et al. 1984), anti-tuberculosis (Anirban et al. 2020; Abdul et al. 2017; Tejshri et al. 2020a, b, 2019a, 2020a), anti-proliferative agents (Tejshri et al. 2019a, b) as fluorescent whiteners (Rangnekar et al. 1986). In view of the above biological importance, we are encouraged to synthesize 2-aminochromone-based N,N-bis-1,2,3-triazole analogs.

In this work, 2-aminochromone-based 1,2,3-triazole derivatives (7a-o) were developed by using classical copper(I)-catalyzed double azide-alkyne cycloaddition reaction between the N,N-dipropargylated 2-aminochromone (5) and different alkyl/aryl azides (6a-o) with pharmacophore moieties with a target of designing new heterocyclic entities with enhanced biological activity.

These newly synthesized hybrid molecules are screened for anti-microbial activity against Gram-positive, Gram-negative bacteria and fungal strains found to exhibit potent and active against microbial growth when compared with standard anti-bacterial agents, and all these derivatives were tested for in vitro anti-cell proliferation activity against human cervical (HeLa) cancer cell lines, the experimental results revealed that all the compounds exhibit the good activity with IC$_{50}$ values ranging from 0.11 to 1.04 µM than standard curcumin (IC$_{50}$ 4.83±0.44 µM). All the molecules were docked against dual-specificity tyrosine-regulated kinase 2, DYRK2, and the results show that all the molecules have a better Moldock score when compared to the standard curcumin.

Experimental

Material and methods

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, Bangalore, India) and Alfa-Aesar (Johnson Matthey Company, India). Reactions were monitored by TLC, performed on Merck silica gel 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. Melting points were taken on a hot-plate microscope apparatus. IR spectra were obtained with a Bruker Tensor 27 spectrometer (KBr disk). NMR spectra were recorded with a Varian 500 spectrometer with CDCl$_3$ as solvent and TMS as internal standard (500 and 125 MHz for $^1$H NMR and $^{13}$C NMR spectra, respectively). High-resolution mass (ESI) was obtained with a Bruker Micro-TOF spectrometer.

General procedure for synthesis of 2-[di(prop-2-yn-1-yl)amino]-4H-chromen-4-one (5)

A magnetically stirred solution of 2-aminochromone (4) (10 g, 0.062 mol) dissolved in the DMF (80 mL), then K$_2$CO$_3$ (25.73 g, 0.186 mol) and Cat. Cs$_2$CO$_3$ (2.02 g, 0.006 mol) was added. The resulting suspension was heated in a water bath at 50 °C for 2 h and then cooled the reaction mixture to 30 °C. Slowly added propargyl bromide (25.85 g,
0.217 mol) then heated the reaction mixture at 50 °C for 4 h. Added water and ethyl acetate into the reaction mixture, extracted the product with ethyl acetate, dried the ethyl acetate solution with sodium sulfate, and distilled at 50 °C under vacuum to get the brown color solid (slightly gummy solid). Isolated the product in methyl tertiary butyl ether (50 mL) to get the pure slight yellow color product 5 with 80% yield (M. P: 215 °C). FT-IR (KBr, cm⁻¹): 3280 (≡C-H), 2215, 1680 (C=O), 1602, 1210; ¹H NMR (500 MHz, CDCl₃): δ=8.22–8.20 (m, 1 H), 7.72 (d, J = 8 Hz, 1 H), 7.39–7.34 (m, 2 H), 5.42 (s, 1 H), 4.12 (s, 4H), 3.17 (s, 2H); ¹³C NMR (125 MHz, CDCl₃): δ=175.98, 168.89, 158.47, 133.49, 125.78, 125.76, 121.33, 118.32, 89.05, 77.80, 74.15, 38.25; HRMS (ESI) m/z [M + H]⁺ calculated for C₁₅H₁₁NO₂: 238.08680, found: 238.08626.

**General procedure for the synthesis of 2-aminochromone-based N,N-bis-1,2,3-triazole (7a-o)**

In a round-bottom flask equipped with a magnetic stirring bar, compound 5 (3.3 mmol), aryl/alkyl azide derivatives (6a-o) (7.0 mmol) in water (20 mL), and t-butanol (10 mL) were added CuSO₄·5H₂O (1 mol %) and sodium ascorbate (5 mol %). The resulting suspension was stirred at room temperature for 8 h. After completion of the reaction, as indicated by the TLC, the CH₂Cl₂ (20 mL) was added to the reaction mass. Then, aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel afforded chromone-based N,N-bis triazoles (7a-o) with good yield.

**2-(bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7a)**

Solvent system for purification: n-Propanol: THF (5:5 v v⁻¹)

Yield 85%, white powder, m.p: 222–225 °C; FT-IR (KBr, cm⁻¹): 2140 (N=N of triazole), 1681 (C=O), 1603, 1413; ¹H NMR (500 MHz, CDCl₃): δ=8.10 (s, 2H), 8.06 (q, J = 8 Hz, 1 H), 7.77 (q, J = 8 Hz, 1 H), 7.62–7.44 (m, 10 H), 5.50 (s, 4 H), 4.98 (s, 1 H), 4.56 (s, 4 H); ¹³C NMR (125 MHz, CDCl₃): δ=176.48, 165.53, 158.35, 141.89, 136.45, 132.89, 128.32, 127.77, 126.34, 125.43, 122.55, 119.49, 118.38, 83.50, 52.74, 42.79; HRMS (ESI) m/z [M + H]⁺ calculated for C₂₉H₂₅N₇O₂: 504.21480, found: 504.21425.

**2'-((4,4'-(4-oxo-4H-chromen-2-y)azanediyl)bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))diacetate (7b)**

Solvent system for purification: n-propanol: THF (5:5 v v⁻¹)

Yield 83%, Off white powder, m.p: 222–225 °C; FT-IR (KBr, cm⁻¹): 2120 (N=N of triazole), 1750 (C=O), 1678, 1605, 1210; ¹H NMR (500 MHz, CDCl₃): δ=8.06 (q, J = 8 Hz, 1 H), 7.97–7.75 (m, 2H), 5.18 (s, 4 H), 4.98 (s, 1 H), 4.76 (s, 4 H), 3.78 (s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ=177.79, 176.18, 166.92, 159.60, 134.04, 127.30, 126.28, 122.37, 118.49, 117.11, 85.17, 52.79, 49.40, 43.79; HRMS (ESI) m/z [M + H]⁺ calculated for C₁₅H₁₁NO₂: 468.16316, found: 468.16261.

**2'-((4,4'-(4-oxo-4H-chromen-2-y)azanediyl)bis(methylene))bis(benzonitrile) (7c)**

Solvent system for purification: n-Butanol: THF (5:5 v v⁻¹)

Yield 80%, white crystals, m.p: 285–288 °C; FT-IR (KBr, cm⁻¹): 2258 (C≡N), 2125 (N=N of triazole), 1666 (C=O), 1613; ¹H NMR (500 MHz, CDCl₃): δ=8.10 (s, 2H), 8.06 (q, J = 8 Hz, 1 H), 7.77 (q, J = 8 Hz, 1 H), 7.62–7.44 (m, 10 H), 5.05 (s, 4 H), 4.98 (s, 1 H), 4.56 (s, 4 H); ¹³C NMR (125 MHz, CDCl₃): δ=178.91, 168.34, 160.91, 145.33, 138.72, 134.04, 132.41, 130.59, 128.85, 128.05, 126.03, 125.01, 122.41, 119.86, 116.91, 116.60, 112.03, 82.47, 49.47, 41.22; HRMS (ESI) m/z [M + H]⁺ calculated for C₃₅H₂₅N₉O₂: 554.20530, found: 554.20475.

**2-(bis((1-(2,6-difluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7d)**

Solvent system for purification: ethanol:THF (3:7 v v⁻¹)

Yield 88%, Pale yellow powder, m.p: 275–277 °C; FT-IR (KBr, cm⁻¹): 2150 (N=N of triazole), 1675 (C=O), 1615, 620; ¹H NMR (500 MHz, CDCl₃): δ=8.10 (s, 2 H), 8.06 (q, J = 8 Hz, 1 H), 7.77 (q, J = 8 Hz, 1 H), 7.66–7.53 (m, 4 H), 6.96 (t, J = 8 Hz, 4 H), 5.58 (s, 4 H), 5.02 (s, 1 H), 4.59 (s, 4 H); ¹³C NMR (125 MHz, CDCl₃): δ=175.25, 164.67, 163.04, 157.31, 140.38, 132.37, 129.80, 126.01, 125.01, 122.84, 119.06, 116.86, 116.60, 112.03, 82.47, 49.47, 41.22; HRMS (ESI) m/z [M + H]⁺ calculated for C₁₉H₁₁F₂N₇O₂: 576.17711, found: 576.17656.
2-(bis((1-thiophen-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7e)

Solvent system for purification: ethanol: THF (2:8 v:v-1)

Yield 78%, Yellow powder, mp: 248–250 °C; FT-IR (KBr, cm⁻¹): 2158 (N=N of triazole), 1677 (C=O), 1620, 1226; ¹H NMR (500 MHz, CDCl₃): δ = 8.06 (q, J = 8 Hz, 1H), 8.02 (s, 2H), 7.77 (q, J = 8 Hz, 1H), 7.56–7.53 (m, 2H), 7.27 (d, J = 8 Hz, 2H), 6.97–6.87 (m, 4H), 5.59 (s, 4H), 4.99 (s, 1H), 4.56 (s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 174.78, 164.39, 156.20, 141.34, 139.97, 133.46, 127.62, 126.90, 125.81, 125.21, 124.90, 123.34, 117.02, 81.30, 53.21, 46.34; HRMS (ESI) m/z [M + H]+ calculated for C₂₅H₂₁N₇O₂S₂: 516.12709.

2-(bis((1-thiazol-5-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7f)

Solvent system for purification: ethanol: MTBE (3:7 v:v-1)

Yield 90%, Pale yellow powder, m.p: 256–258 °C; FT-IR (KBr, cm⁻¹): 2148 (N=N of triazole), 1669, 1640, 1618; ¹H NMR (500 MHz, CDCl₃): δ = 8.87 (s, 2H), 8.06 (q, J = 8 Hz, 1H), 8.02 (s, 2H), 7.77 (q, J = 8 Hz, 1H), 7.56–7.53 (m, 4H), 5.44 (s, 4H), 5.06 (s, 1H), 4.59 (s, 4H). ¹³C NMR (125 MHz, CDCl₃): δ = 185.51, 174.06, 165.10, 157.35, 146.08, 142.59, 136.67, 130.47, 129.17, 127.41, 121.21, 119.29, 117.05, 91.86, 48.11, 43.83; HRMS (ESI) m/z [M + H]+ calculated for C₂₃H₁₉N₉O₂S₂: 518.11759.

2-(bis((1-benzhydryl-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7g)

Solvent system for purification: methanol: MTBE (3:7 v:v-1)

Yield 89%, White powder, m.p: 288–290 °C; FT-IR (KBr, cm⁻¹): 2128 (N=N of triazole), 1669 (C=O), 1640, 1618; ¹H NMR (500 MHz, CDCl₃): δ = 8.09 (s, 2H), 8.06 (q, J = 8 Hz, 1H), 7.79–7.75 (m, 1H), 7.56–7.52 (m, 2H), 7.34–7.19 (m, 12H), 7.09 (t, J = 8 Hz, 8H), 6.71 (s, 2H), 4.95 (s, 1H), 4.59 (s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 185.47, 165.53, 160.37, 149.98, 139.89, 134.64, 130.94, 128.18, 127.19, 124.89, 124.38, 124.33, 117.53, 116.73, 76.16, 58.58, 39.72; HRMS (ESI) m/z [M + H]^+ calculated for C₄₁H₃₃N₇O₂: 656.27685.

2'-((4,4'-(4-oxo-4H-chromen-2-yl)azanediyl)bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(1-(4-bromophenyl)ethanone) (7h)

Solvent system for purification: isopropyl alcohol: ether (3:7 v:v-1)

Yield 85%, Off white powder, m.p: 280–284 °C; FT-IR (KBr, cm⁻¹): 2129 (N=N of triazole), 1685 (C=O), 1613, 1672; ¹H NMR (500 MHz, CDCl₃): δ = 8.07–8.85 (m, 11H), 7.77 (q, J = 8 Hz, 1H), 7.56–7.52 (m, 2H), 5.28 (s, 4H), 5.02 (s, 1H), 4.52 (s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 198.79, 179.51, 168.69, 161.07, 141.11, 133.10, 132.44, 131.59, 130.94, 128.86, 125.88, 124.90, 123.01, 118.74, 117.79, 83.50, 56.35, 45.58; HRMS (ESI) m/z [M + H]^+ calculated for C₃₁H₂₃Br₂N₇O₄: 716.02510, 718.02334 [M + H + 2]^+.

2-(bis((1-((4-methylquinazolin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7i)

Solvent system for purification: methanol: MTBE (5:5 v:v-1)

Yield 70%, Pale yellow powder, m.p: 290–293 °C; FT-IR (KBr, cm⁻¹): 2138 (N=N of triazole), 1680 (C=O), 1642, 1622; ¹H NMR (500 MHz, CDCl₃): δ = 8.07–8.75 (m, 7H), 7.79–7.75 (m, 3H), 7.56–7.46 (m, 4H), 5.53 (s, 4H), 5.01 (s, 1H), 4.69 (s, 4H), 2.69 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ = 181.49, 167.54, 164.78, 160.15, 152.09, 144.25, 144.19, 135.73, 132.31, 129.66, 127.11, 126.47, 125.04, 123.42, 122.06, 119.96, 117.51, 116.43, 77.67, 61.47, 47.07, 34.07; HRMS (ESI) m/z [M + H]^+ calculated for C₃₅H₂₉N₁₁O₂: 636.25785.

2-(bis((1-(2-hydroxy-5-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-4H-chromen-4-one (7j)

Solvent system for purification: methanol: MTBE (5:5 v:v-1)

Yield 78%, Off white powder, m.p: > 300 °C; FT-IR (KBr, cm⁻¹): 3480 (O–H), 2148 (N=N of triazole), 1665, 1613, 1512; ¹H NMR (500 MHz, CDCl₃): δ = 8.10–7.93 (m, 11H), 7.79–7.75 (m, 2H), 6.98 (d, J = 8 Hz, 2H), 5.40 (s, 4H), 5.04 (s, 1H), 4.48 (s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 183.40, 173.35, 158.00, 154.72, 144.61, 138.48, 129.38, 126.75, 126.17, 125.43, 124.91, 124.51, 122.96, 121.48, 117.18, 115.73, 79.70, 49.67, 43.65; HRMS (ESI) m/z [M + H]^+ calculated for C₂₉H₂₅N₉O₆: 626.17478, found: 626.17424.
Dimethyl4,4'-(4,4'-(((4-oxo-4H-chromen-2-yl)azanediyl)bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl)) bis(methylene)bis(3-methoxybenzoate) (7k)

Solvent system for purification: n-Butanol: n-Hexane (5:5 v v-1)

Yield 84%, white crystal, m.p: 288–290 °C; FT-IR (KBr, cm⁻¹): 3136, 2924, 1743, 1670, 1618, 1182; ¹H NMR (500 MHz, CDCl₃): δ = 8.10 (s, 2 H), 8.07–8.05 (m, 1 H), 7.79–7.75 (m, 1 H), 7.56–7.46 (m, 6 H), 7.26 (d, J = 8 Hz, 2 H), 5.33 (s, 4 H), 4.98 (s, 1 H), 4.54 (s, 4 H), 3.87 (s, 6 H), 3.80 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃): δ = 171.89, 165.72, 162.98, 157.10, 165.72, 162.98, 157.83, 154.37, 143.14, 131.50, 129.03, 128.57, 127.55, 126.49, 124.06, 124.03, 122.68, 117.18, 115.41, 112.10, 81.82, 55.32, 52.48, 48.24, 43.28; HRMS (ESI) m/z [M + H]⁺ calculated for C₃₅H₃₃N₇O₈ 680.24689, found: 680.24634.

2-(bis(1-(4,5-dibromo-1H-pyrrol-2-yl)(phenyl)methyl)-1H-1,2,3-triazol4y1)methyl)amino)-4H-chromen-4-one (7l)

Solvent system for purification: methanol: MTBE (4:6 v v-1)

Yield 89%, yellow powder, m.p: > 300 °C; FT-IR (KBr, cm⁻¹): 2129 (N=N of triazole), 1688 (C=O), 1602, 682; ¹H NMR (500 MHz, CDCl₃): δ = 8.09 (s, 2 H), 8.07–8.05 (m, 1 H), 7.79–7.75 (m, 1 H), 7.57–7.19 (m, 12 H), 6.94 (s, 2 H), 6.64 (s, 2 H), 5.33 (s, 4 H), 5.06 (s, 1 H), 4.86 (d, J = 8 Hz, 2 H), 4.37 (d, J = 8 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃): δ = 181.21, 169.76, 162.63, 147.04, 139.20, 134.06, 130.04, 129.27, 128.73, 128.21, 126.20, 125.31, 123.73, 119.49, 118.38, 109.07, 104.05, 95.59, 86.14, 59.74, 42.26; HRMS (ESI) m/z [M + H]⁺ calculated for C₂₇H₂₅N₇Br₄O₂ 1100; ¹H NMR (500 MHz, CDCl₃): δ = 7.32 (d, J = 8 Hz, 2 H), 5.67 (s, 4 H), 5.06 (s, 1 H), 4.60 (s, 4 H); ¹³C NMR (125 MHz, CDCl₃): δ = 185.85, 175.47, 160.09, 146.21, 136.52, 133.31, 131.94, 130.73, 129.39, 126.72, 125.86, 125.02, 124.63, 123.81, 122.86, 121.99, 120.05, 119.03, 92.32; HRMS (ESI) m/z [M + H]⁺ calculated for C₂₇H₂₁F₂₁Br₄N₂O₂ 776.16434, found: 776.16379.

Anti-microbial activity assay

The anti-microbial activity of the chromone-based bis triazole conjugates was determined using the well diffusion method. (Amsterdam et al. 1996; Hussaini et al. 2015) against different pathogenic reference strains procured from the MTTC (Microbial type culture collection), CSIR-Institute of Microbial Technology, Chandigarh, India. The pathogenic reference strains were seeded on the surface of the media Petri plates, containing Mueller –Hinton agar with 0.1 mL of previously prepared microbial suspensions individually containing 1.5 x 10⁶ cfu mL⁻¹ (equal to 0.5 McFarland). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer, and the synthesized chromone-based bis triazole conjugates at a dose range of 125–0.9μg well⁻¹ were added to each well under sterile conditions in a laminar airflow chamber. Standard anti-biotic solution of ciprofloxacin and miconazole at a dose range of 125–0.9μg well⁻¹ and the well-containing methanol served as positive and negative controls, respectively. The plates were incubated for 24 h at 37 °C for bacterial and 30 °C
for candida albicans and the well containing the list concentration showing the inhibition zone was considered as the minimum inhibitory concentration. All the experiments were carried out in triplicates and the mean values were determined and values are represented as mean ± S.D.

**Minimum bactericidal concentration assay**

Bactericidal assay (NCCL, 2000) was performed in 1000 sterile 2.0 mL microfuge tubes against a panel of above-mentioned various pathogenic bacterial strains which were cultured overnight in Muller–Hinton broth. Serial dilution of test compounds was prepared in Mueller–Hinton broth with different concentrations ranging from 0 to 125 μg mL⁻¹. To the test compounds, 100 μL of overnight cultured bacterial suspension was added to reach a final concentration of 1.5 × 10⁸ cfu mL⁻¹ (equal to 0.5 Mc Farland) and incubate at 37 °C for 24 h. After 24 h of incubation, the minimum bacterial concentration (MBC) was determined by sampling 10 μL of suspension from the tubes into Mueller–Hinton agar plates and was incubated for 24 h at 37 °C to observe the growth of test organisms. MBC is the lowest concentration of compound required to kill a particular bacterium. All the experiments were carried in triplicates values represented as a mean ± S.D.

**Anti-cancer activity assays**

**Material and methods**

Dulbecco’s modified Eagle’s medium (DMEM), fetal bovine serum (FBS), 1xPBS, anti-biotic and anti-mycotic, dimethyl sulfoxide (DMSO), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and all the chemicals were procured from HiMedia laboratories.

**MTT assay protocol**

HeLa cells were grown in DMEM containing 10% fetal bovine serum in the presence of 100 U/mL of anti-biotic and anti-mycotic. Each well was seeded with 3 × 10⁵ cells in 200 μL of serum DMEM and incubated at 37 °C with 5% CO₂. After 12–14 h of incubation, DMEM was discarded and washed with 1XPBS. Later, the cells were treated with curcumin and chromone triazole analogs with concentrations ranging from 1 μM to 100 μM in plain DMEM at 37 °C for 24 h with 5% CO₂. In the next step, 100 μL of 0.5 mg/mL of MTT was added to each well. After 3 h of incubation discard the good contents and wash the cells with 1 × PBS followed by DMSO treatment and absorbance readings were taken by ELISA plate reader at 595 nm.

**Molecular docking**

Molecular docking studies were performed by using Molegro Virtual Docker, MVD 2010.4.0.0. to predict the protein–ligand interactions at the molecular level. The crystal structure of human dual specificity tyrosine phosphorylation regulated Kinase-2, DYRK2 (PDB id: 5ZTN) was downloaded from Protein Data Bank. The ligand molecules and protein were imported in PDB format. The imported protein was prepared by assigning missing bond orders, bonds, and charges. Docking was performed at the CUR_501 site of the DYRK2 site. Molecules with the lowest Moldock score have the best protein–ligand interaction. Moldock scoring function is based on piecewise linear potential (PLP). In the last step, 2D and 3D interactions of protein–ligands with the best score were imaged by using Discovery Studio, 2019.

**Results and discussion**

**Chemistry**

The 2-aminochromone (4) was used as an intermediate for the construction of 1,2,3-triazole derivatives (7a-o) (Scheme 1). Then, the 2-aminochromone (4) was converted to a series of fifteen bis-1,2,3-triazole derivatives (7a-o) via key intermediate N,N-di-terminal alkylene amino chromone (5) in excellent yields by involving in Cu(I)-catalyzed azide-alkyne [3 + 2] annulation (Scheme 2). All the synthesized compounds were well characterized by IR, ¹H NMR, ¹³C NMR, and HRMS spectroscopy. In the ¹H NMR spectrum of the compound, 7a showed two singlets at 4.57 and 4.98 ppm integrated for each four protons, which corresponds to four N-methylene groups, and showed another singlet at 8.10 ppm integrated for two protons belonging to two triazole ring protons.
Reaction conditions

(i) DMFDA, 80–90 °C, 2 h (ii) NH₂OH. HCl, Ethanol (iii) Et₃N, DMF, 140–150 °C.

2-aminochromone (4) was prepared from 2-hydroxy acetophenone (1) by following the reported procedure (Chandrakanta et al. 2005) (Scheme 1). 1-(2-Hydroxyphenyl)-3-N,N-dimethylamino propenone (2), obtained by heating the 2-hydroxy acetophenone (1) and dimethyl formamide dimethyl acetal (DMFDA), was heated with NH₂OH·HCl in ethanol under reflux for 30 min to give isoxazole (3) (yield 60–70%). Then, isoxazole (3) was converted to 2-aminochromone (4) by heating in DMF under reflux in the presence of Et₃N for 8 h.

2-aminochromone (4) was treated with one equivalent of propargyl bromide in acetonitrile solvent in the presence of Na₂CO₃ at 50 °C, we anticipated the formation of mono propargylated product but surprisingly we observed the formation of N,N-Dipropargyl 2-aminochromone (4), which was confirmed by the ¹H NMR, ¹³C NMR, and mass spectra, the targeted mono N-propargyl 2-amino chromone not found even in traces. Probably due to the more basic nature of N-monopropargylated 2-aminochromone readily converted into the corresponding dipropargylated 2-aminochromone (5) even by decreasing the moles of propargyl bromide, Na₂CO₃, and at low temperatures also.

Later we tried to optimize the reaction conditions to get a better yield and quality of the N,N-dipropargylated 2-aminochromone (5). For the selection of a suitable solvent, attempted the reaction between 2-aminochromone (4) and propargyl bromide in different solvents. In water, toluene, acetone, and MTBE solvents, no reaction has been observed. In THF, only 5% product formation was observed, in acetonitrile and DMF good reaction progress was observed but in DMF better yield was observed, in all the solvents mono propargylated 2-aminochromone not observed (Table 1). After the selection of DMF as a suitable solvent, we tried to select the base. For this, attempted different bases, no progress in the reaction was observed by using the organic bases like triethylamine and pyridine. The better results were observed by using the Cs₂CO₃ when compared with the Na₂CO₃ and K₂CO₃, due to the high cost of the Cs₂CO₃, attempted a reaction by using the stoichiometric K₂CO₃ and catalytic Cs₂CO₃, the reaction was completed successfully with good yield. Comparatively, excellent yield is observed in excess quantities of base conditions than in lower quantities (Table 2).

Based on the above optimization condition, successfully prepared the N,N-dipropargyl 2-amino chromone (5) with

---

**Scheme 2** Synthesis of 2-aminochromone-based N,N-bis-1,2,3-triazole analogs (7a-o)
excellent yield. Later in view of the huge pharmacological activity of triazoles, we intended to prepare the 2-aminochromone-based bis 1,2,3-triazoles (7a-o) (Scheme 2).

**Reaction conditions**

(a) Propargyl bromide (3.5 eq), DMF, Cs₂CO₃ (2.5 equiv) 50 °C, 4 h. Yield-70%

(b) alkyl/aryl azide (2.12 equiv), CuSO₄·5H₂O (1 mol%), Sodium ascorbate (5 mol%), Water:t-butyl alcohol (1: 1 v v⁻¹), rt, 8 h.

The N,N-dipropargyl 2-aminochromone (5) was reacted with 2 equivalents of alkyl/aryl azides (6a-o) in the presence of the catalytic amount of CuSO₄·5H₂O and sodium ascorbate in the t-butyl alcohol: water medium at room temperature to obtain the desired product 2-aminochromone-based N,N-bis-1,2,3-triazole (7a-o) with excellent yields (Table 3).

**Anti-microbial activity**

The novel synthesized 2-aminochromone-based N,N-bis-1,2,3-triazole (7a-o) analogs were screened in vitro for anti-microbial activity against Gram-positive bacteria Micrococcus luteus (MTCC-2470), Staphylococcus aureus (MLS-96 MTCC-2940), Bacillus subtilis (MTCC-121) and Gram-negative bacteria Escherichia coli (MTCC-739), Pseudomonas aeruginosa (MTCC-2453), Klebsiella planticola (MTCC-530), and fungal strain Candida albicans (MTCC-3017) used with agar well diffusion method. The result was obtained as minimum inhibitory concentration (MIC) in μg/mL, and the results are shown in Table 4. Some of the active compounds were compared with the standard drugs miconazole and ciprofloxacin. Most of the 7c, 7d, 7e, 7f, 7g, 7l, and 7m compounds showed good activity against the Gram-positive and Gram-negative bacteria. The compounds 7c, 7d, 7h, 7l, and 7m showed promising activity against Candida albicans (MTCC 3017) with MIC values ranging between 3.9 and 7.8 μg/mL with standard drug miconazole. The remaining compounds exhibited moderate anti-microbial activity.

**Minimum bacterial concentration**

Novel 2-aminochromone-based N,N-bis-1,2,3-triazole (7a-o) derivatives based on the good anti-microbial activity results further tested the minimum bacterial concentration (MBC) against various strains of Micrococcus luteus MTCC 2470, Staphylococcus aureus MTCC 96, Staphylococcus aureus MLS-16 MTCC 2940, Bacillus subtilis MTCC 121, Escherichia coli MTCC 739, Pseudomonas aeruginosa MTCC 2453, Klebsiella planticola MTCC 530, and the results are showed in Table 5. The compounds 7c, 7d, 7g, 7h, 7l, and 7m showed good activity against

| Entry | R | M. P. (°C) | Yield % |
|-------|---|------------|---------|
| 7a    |   | 260–262    | 85      |
| 7b    |   | 222–225    | 83      |
| 7c    |   | 285–288    | 80      |
| 7d    |   | 275–277    | 88      |
| 7e    |   | 248–250    | 78      |
| 7f    |   | 256–258    | 90      |
| 7g    |   | 288–290    | 89      |
| 7h    |   | 280–284    | 85      |
| 7i    |   | 290–293    | 70      |
| 7j    |   | > 300      | 78      |
| 7k    |   | 288–290    | 84      |
| 7l    |   | > 300      | 89      |
| 7m    |   | 244–246    | 85      |
| 7n    |   | 223–225    | 85      |
| 7o    |   | 260–263    | 85      |
Table 4  Anti-microbial activity (MIC in µg/mL) of novel synthesized compounds

| Test compound | M. luteus MTCC 2470 | S. aureus MTCC 96 | S. aureus MLS-16 MTCC 2940 | B. subtilis MTCC 121 | E. coli MTCC 739 | P. aeruginosa MTCC 2453 | K. planticola MTCC 530 | C. albicans MTCC 3017 |
|---------------|---------------------|------------------|-----------------------------|----------------------|------------------|--------------------------|------------------------|-------------------------|
| 7a            | > 125               | > 125            | > 125                       | > 125                | 3.9              | > 125                    | > 125                  | > 125                   |
| 7b            | > 125               | > 125            | > 125                       | > 125                | 3.9              | > 125                    | > 125                  | > 125                   |
| 7c            | 3.9                 | 3.9              | 3.9                         | 3.9                  | 3.9              | 3.9                      | 3.9                    | 3.9                     |
| 7d            | 3.9                 | 3.9              | > 125                       | 3.9                  | 3.9              | > 125                    | 3.9                    | > 125                   |
| 7e            | 3.9                 | 3.9              | 3.9                         | 3.9                  | 3.9              | > 125                    | 3.9                    | > 125                   |
| 7f            | 3.9                 | 3.9              | > 125                       | 3.9                  | 3.9              | > 125                    | 3.9                    | > 125                   |
| 7g            | 3.9                 | 3.9              | > 125                       | 3.9                  | 3.9              | > 125                    | 3.9                    | > 125                   |
| 7h            | 3.9                 | 3.9              | 3.9                         | 3.9                  | 3.9              | 3.9                      | 3.9                    | 3.9                     |
| 7i            | 3.9                 | 3.9              | > 125                       | 3.9                  | 3.9              | > 125                    | 3.9                    | > 125                   |
| 7j            | 3.9                 | 3.9              | > 125                       | 3.9                  | 3.9              | > 125                    | 3.9                    | > 125                   |
| 7k            | 3.9                 | > 125            | 3.9                         | 3.9                  | > 125            | 3.9                      | > 125                  | > 125                   |
| 7l            | 3.9                 | 3.9              | 3.9                         | 3.9                  | 3.9              | 3.9                      | 3.9                    | 3.9                     |
| 7m            | 3.9                 | 3.9              | 3.9                         | 3.9                  | 3.9              | 3.9                      | 3.9                    | 3.9                     |
| 7n            | > 125               | > 125            | > 125                       | > 125                | > 125            | > 125                    | > 125                  | > 125                   |
| 7o            | 7.8                 | 7.8              | 7.8                         | 7.8                  | 7.8              | 7.8                      | 7.8                    | 7.8                     |
| Miconazole (Standard) | NA               | NA              | NA                          | NA                   | NA              | NA                      | NA                    | 7.8                     |
| Ciprofloxacin (Standard) | 0.9           | 0.9              | 0.9                         | 0.9                  | 0.9              | 0.9                      | 0.9                   | NA                     |

Bold values are related to the high activity and showing good IC50

M. luteus (Micrococcus luteus), S. aureus: (Staphylococcus aureus), B. subtilis (Bacillus subtilis), E. coli: (Escherichia coli), P. aeruginosa (Pseudomonas aeruginosa), K. planticola (Klebsiella planticola), C. albicans: (Candida albicans), NA (not applicable)

Table 5  Minimum bactericidal concentration (MBC in µg/mL) of novel synthesized compounds

| Test compound | M. luteus MTCC 2470 | S. aureus MTCC 96 | S. aureus MLS-16 MTCC 2940 | B. subtilis MTCC 121 | E. coli MTCC 739 | P. aeruginosa MTCC 2453 | K. planticola MTCC 530 | C. albicans MTCC 3017 |
|---------------|---------------------|------------------|-----------------------------|----------------------|------------------|--------------------------|------------------------|-------------------------|
| 7a            | > 125               | > 125            | > 125                       | > 125                | 7.8              | > 125                    | > 125                  | > 125                   |
| 7b            | > 125               | > 125            | > 125                       | > 125                | 7.8              | > 125                    | > 125                  | > 125                   |
| 7c            | 7.8                 | 7.8              | 7.8                         | 7.8                  | 7.8              | 7.8                      | 7.8                    | 7.8                     |
| 7d            | 7.8                 | 7.8              | > 125                       | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7e            | 7.8                 | 7.8              | 7.8                         | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7f            | 7.8                 | 7.8              | > 125                       | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7g            | 7.8                 | 7.8              | > 125                       | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7h            | 7.8                 | 7.8              | 7.8                         | 7.8                  | 7.8              | 7.8                      | 7.8                    | 7.8                     |
| 7i            | 7.8                 | 7.8              | > 125                       | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7j            | 7.8                 | 7.8              | > 125                       | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7k            | 7.8                 | > 125            | 7.8                         | 7.8                  | 7.8              | > 125                    | 7.8                    | > 125                   |
| 7l            | 7.8                 | 7.8              | 7.8                         | 7.8                  | 7.8              | 7.8                      | 7.8                    | 7.8                     |
| 7m            | 7.8                 | 7.8              | 7.8                         | 7.8                  | 7.8              | 7.8                      | 7.8                    | 7.8                     |
| 7n            | > 125               | > 125            | > 125                       | > 125                | > 125            | > 125                    | > 125                  | > 125                   |
| 7o            | 15.6                | 15.6             | 15.6                        | 15.6                 | 15.6             | 15.6                     | 15.6                   | 15.6                    |
| Miconazole (Standard) | –                 | –               | –                           | –                    | –               | –                        | –                      | 7.8                     |
| Ciprofloxacin (Standard) | 1.9            | 1.9              | 1.9                         | 1.9                  | 1.9              | 1.9                      | 1.9                   | –                      |

Bold values are related to the high activity and showing good IC50

M. luteus (Micrococcus luteus), S. aureus: (Staphylococcus aureus), B. subtilis (Bacillus subtilis), E. coli: (Escherichia coli), P. aeruginosa (Pseudomonas aeruginosa), K. planticola (Klebsiella planticola), C. albicans: (Candida albicans), NA (not applicable)
the Gram-positive and Gram-negative bacterial strains with MBC values ranging from 3.9–31.2 μg/mL.

**Evaluation of anti-cancer activity**

Chromone is an important scaffold in the medicinal chemistry field with a wide spectrum of activities like anti-cancer, anti-diabetic, anti-microbial, and anti-inflammatory. In the present study, the synthesized chromone derivatives were tested for anti-cancer activity on HeLa cell lines and all the molecules exhibited good activity with IC₅₀ values ranging from 0.11 to 1.04 μM than standard curcumin (IC₅₀ 4.83 ± 0.44 μM) shown in Table 6. Among all the compounds, ortho, para-substituted trifluoromethane (7o) has shown better activity with IC₅₀ 0.11 ± 0.56 μM, followed by 2,3-dibromo pyrrole methylene (7l) with IC₅₀ 0.12 ± 0.43 μM. The molecules have shown better activity when substituted with aryl or heteryl groups when compared to its counter molecule with alkyl group substitution (7b) which is having the highest IC₅₀ value (1.04 ± 0.47 μM) among all the synthesized compounds. The higher activity of 7o might be due to heteryl substitution at the ortho, para position, and in particular the presence of halogens.

**Molecular docking studies**

Molecular docking studies provide ligand binding interactions of molecules against target protein at the molecular level which is directly proportional to affinity. All the molecules were docked against dual-specificity tyrosine-regulated kinase 2, (DYRK2) (PDB id: 5ZTN). Docking results show that all the molecules have shown a better Moldock score when compared to the standard curcumin shown in Table 7. The compounds 7o and 7l have the highest Moldock scores with values -229.95 and -214.32. In 7o, higher binding scores are due to the interaction of ortho and para-substituted trifluoro derivatives, in which the fluorine atoms are interacting with B-VAL 154, B-ILE 155, B-LEU 231, B-SER 232, B-ASN 234, and B-GLU237, whereas in 7l, the Bromo diaryl substituted methylene plays a key role in high binding scores with interactions at B-LYS 153, B-ILE 155, B-LYS 165, and B-LEU 231. The compound 7b with the lowest binding score (-169.11) is also exhibiting better activity and moldock score when compared to the standard curcumin (-147.20).

**Structural–activity relationship**

All the synthesized compounds have exhibited good anti-cancer and better moldock scores against the target protein when compared to the standard curcumin. Among all the compounds, ortho, para halogen-substituted triazole derivative (7o IC₅₀—0.11 ± 0.56 μM) has shown better anti-cancer activity than di-ortho substituted halogen derivative (7d IC₅₀—0.52 ± 0.55 μM). The compound with an acetyl group (7b IC₅₀—1.04 ± 0.47 μM) has shown low activity in contrast to substituted acetyl groups (7k IC₅₀—0.16 ± 0.38 μM). A noticeable variation in IC₅₀ values was seen with triazole substituted acetyl (7b) in contrast to aryl derivatives (7a, 7c – 7o) (Figs. 1, 2).

Ligand with only phenyl ring (7a) manifested least activity than substituted aryl or heterocyclic aryl derivatives

---

**Table 6** Novel synthesis compounds (7a-o) IC₅₀ values (μM)

| S. No | Compound | IC₅₀ values (μM) |
|-------|----------|-----------------|
| 1     | 7a       | 0.77 ± 0.39     |
| 2     | 7b       | 1.04 ± 0.47     |
| 3     | 7c       | 0.51 ± 0.55     |
| 4     | 7d       | 0.52 ± 0.55     |
| 5     | 7e       | 0.89 ± 0.79     |
| 6     | 7f       | 0.43 ± 0.78     |
| 7     | 7g       | 0.18 ± 0.33     |
| 8     | 7h       | 0.28 ± 0.45     |
| 9     | 7i       | 0.31 ± 0.24     |
| 10    | 7j       | 0.39 ± 0.66     |
| 11    | 7k       | 0.16 ± 0.38     |
| 12    | 7l       | 0.12 ± 0.43     |
| 13    | 7m       | 0.30 ± 0.58     |
| 14    | 7n       | 0.36 ± 0.25     |
| 15    | 7o       | 0.11 ± 0.44     |
| 16    | Curcumin | 4.83 ± 0.44     |

Bold values are related to the high activity and showing good IC₅₀

**Table 7** Novel synthesis compounds (7a-o) molecular docking scores

| S. No | Compounds | Rerank score | Moldock score |
|-------|-----------|--------------|---------------|
| 1     | 7a        | -183.22      | 139.15        |
| 2     | 7b        | -169.11      | 122.36        |
| 3     | 7c        | -189.06      | 145.35        |
| 4     | 7d        | -182.94      | 134.42        |
| 5     | 7e        | -186.05      | 195.45        |
| 6     | 7f        | -196.03      | 145.73        |
| 7     | 7g        | -223.52      | 169.86        |
| 8     | 7h        | -205.12      | 151.19        |
| 9     | 7i        | -202.95      | 143.79        |
| 10    | 7j        | -212.8       | 165.71        |
| 11    | 7k        | -220.63      | 170.76        |
| 12    | 7l        | -214.32      | -159.94       |
| 13    | 7m        | -200.47      | 145.47        |
| 14    | 7n        | -193.57      | 147.58        |
| 15    | 7o        | -229.95      | -151.72       |
| 16    | Curcumin  | -147.20      | -126.616      |

Bold values are related to the high activity and showing good IC₅₀
Fig. 1 Representative structures of bioactive chromone derivatives

Fig. 2 Inhibitory concentration of novel synthesized derivatives (7a-o) against the HeLa cell MTT assay

Fig. 3 a Doc pose of compound 7o in DYRK2 (PDB id: 5ZTN), b binding interaction (H2d diagram of compound 7o)
After 7o, ligand 7l has evidenced the highest activity with better ligand affinity which might be due to halogen substitution and di-substituted methylene derivative, molecular docking studies also supported B-ILE 155, B-VAL 163, and B-ILE 294 (Fig. 3 2d image). In conclusion, halogen-substituted aryl or heteroaryl derivatives specifically bulk derivatives evidenced better activity and affinity toward DYRK2.

**Conclusions**

In conclusion, we have successfully applied the click strategy using Cu(I)-catalyzed azide-alkyne [3 + 2] annulation reaction for the synthesis of 2-aminochromone core N,N-bis-1,2,3-triazole derivatives (7a-o) and were evaluated for the anti-microbial and anti-cancer activities (Fig. 4). Some of the compounds from the present series, 7c, 7d, 7h, 7l, and 7m, exhibit promising activity against *Candida albicans* (MTCC 3017) with MIC values ranging between 3.9 and 7.8 µg/mL. The compounds 7c, 7d, 7g, 7h, 7l, and 7m showed good activity against the Gram-positive and Gram-negative bacterial strain with MBC values ranging from 3.9–31.2 µg/mL. Among the newly synthesized series, *ortho para*-substituted trifluoromethane (7o) has shown better activity with IC<sub>50</sub> 0.11 ± 0.56 µM, followed by 2,3 dibromo pyrrole methylene (7l) with IC<sub>50</sub> 0.12 ± 0.43 µM and also 7o and 7l have the highest moldock scores with values -229.95 and -214.32, respectively. From the above observations, it can be concluded that newly synthesized 2-aminochromone core N,N-bis-1,2,3-triazole derivatives (7a-o) offer an attractive lead series for the discovery of novel anti-microbial and anti-cancer agents.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11696-022-02449-w.

**Acknowledgements** We thank the HOD’s Osmania University, Telangana University, and JNTU Hyderabad for the opportunity to pursue his Ph.D. Our sincere thanks to Dr. M. S. N. Reddy for providing infrastructural facilities to carry out the research work, and we are also indebted to S. Eswaraiah and S. T. Rajan for their continuous guidance and support.

**Declarations**

**Conflict of interest** The authors declare no competing financial interest.

**References**

Abdul AA, Dhrubajyoti G, Amrita KC, Alak KB, Priyanka T, Prakash JS, Praveen SG, Avind K, Vinita C, Diganta S (2017) Synthesis and biological evaluation of novel 1,2,3-triazole derivatives as anti-tubercular agents. Bioorg Med Chem Lett 27:3698–3703

Ahmed MEK, Amal AHME, Fatma AFR, Nehad AME (2010) Synthesis and anticonvulsant activity of certain substituted furochromone benzofuran and flavone derivatives. Chem Pharm Bull 58:1148–1156. https://doi.org/10.1248/cpb.58.1148

Aiyalu R, Kalasalingam A, Sankaranarayanan M (2006) Antibacterial, antifungal and anticonvulsant evaluation of novel newly synthesized 1-[2-(1H-Tetrazol-5-yl)ethyl]-1 H-benzo[d][1,2,3] triazoles. Arch Pharm Res 29:535–540. https://doi.org/10.1007/BF02969261

Alaíde BDO, Alex GT, Fernando PV, Geraldo CB, Guilherme RP, Juliana DO, Lucas MA, Luciana FS, Maria FADN, Márila RCF, Renata CDP, Santos Tatiane FB (2016) Synthesis, in vitro antimalarial activity and in silico studies of hybrid kauranoid 1,2,3-triazoles derived from naturally occurring diterpenes. J. Braz. Chem. Soc. 27:551–565. https://doi.org/10.5935/0103-5053.20150287

Alan JW, Karl-Erik A (2012) Pharmacologic management of lower urinary tract storage and emptying failure. Campbell-Walsh-Wein
Cheng-He Z, Hui-Zhen Z, Jin-Jian W, Kannekanti VK, Syed R (2015) Synthesis and biological evaluation of novel D-glucose-derivered 1,2,3-triazoles as potential antibacterial and antifungal agents. Med Chem Rev 24:182–196. https://doi.org/10.1007/s00044-014-1123-9

Christine H, Christophe P, Frank C, Konstantina K, Leenjte P, Mario AQ, Sergio RR, Wim D (2018) Synthesis, biological evaluation and molecular modeling of a novel series of fused 1,2,3-triazoles as potential anti-coronavirus agents. Bioorg Med Chem Lett 28:3472–3476. https://doi.org/10.1016/j.bmcl.2018.09.019

Harpreet K, Mohan PSI, Naureen A, Vishal S (2013) Synthesis and evaluation of some novel chrome based dithiazoles as antimicrobial agents. J Med Chem Int. https://doi.org/10.1155/2013/7845

Huanjie S, Miao Q, Pengfei L, Xiaohui Y, Yihong Z (2017) Apigenin in cancer therapy: anti-cancer effects and mechanisms of action. Cell Biosci 7:1–16. https://doi.org/10.1186/s13578-017-0179-x

Hussaini SM, Kamal A, Kumar CG, Machiraju PK, Moku B, Poornachandra Y, Rahim A, Riyaz S, Shridhar B (2015) Regioselective synthesis, antimicrobial evaluation and theoretical studies of 2-styryl quinolines. Org. Biomol. Chem. 13:1347–1357. https://doi.org/10.1039/C4OB02277G

Joseph-Alexander V, Marco B, Melanie BK (2007) Comparison of the declining triazole sensitivity of Gibberellazaeae and increased sensitivity achieved by advances in triazole fungicide development. Crop Prot 26:683–690. https://doi.org/10.1016/j.cropro.2006.06.006

Keenan JM (1994) Nedocromil: a new agent for the treatment of asthma. Am Fam Physician 50:1059–1064. https://doi.org/10.1517/14656566.2013.824424

Nazariv P, Olga S, Vasyl M (2014) Synthesis and anticanicer activity evaluation of new 1,2,3-triazole-4-carboxamide derivatives. Med Chem Res 23:2426–2438. https://doi.org/10.1007/s00044-013-0841-8

Rangnekar DW, Tagdiwala PV (1986) Synthesis of 2,4-Dihydro-6-methyl-4-phenyl-3-[4,3,1,2,3-triazole Derivatives and Their Use as fluorescent whiteners for polyester Fibres. Dyes Pigm 7:289–298. https://doi.org/10.1016/0039-7911(86)80014-8

Robin JM, Shahrir K (2012) Chromone and flavonoid alkaloids: occurrence and bioactivity. Molecules 17:191–216. https://doi.org/10.3390/molecules17010191

Sandip GA, Sulikaran RM, Vandana SP (2011) Click chemistry: 1,2,3-triazoles as pharmacophores. Chem Asian J 6:2696–2718. https://doi.org/10.1002/asia.201100432

Tejshri RD, Smita PK, Vagoluk SK, Dharmarajan S, Jaiprakash NS, Omprakash B, Vijay MK, Bapuraos BS (2019a) Design and synthesis of new arlyoxy-linked dimeric 1,2,3-Triazoles via click chemistry approach: biological evaluation and molecular docking study. J Heterocyclic Chem 56:2144–2162. https://doi.org/10.1002/jhet.3608

Tejshri RD, Aniket PS, Deepak KL, Shailee VT, Rajaram A, Bapuraos BS (2019b) New amide linked dimeric 1,2,3-triazoles bearing arlyoxy scaffolds as a potent antiproliferative agents and EGFR tyrosine kinase phosphorylation inhibitors. Bioorg Med Chem Lett 29:126618–126625. https://doi.org/10.1016/j.bmcl.2019.08.022

Tejshri RD, Vagoluk SK, Dharmarajan S, Jaiprakash NS, Bapuraos BS (2020a) Synthesis and bioevaluation of a α-β(1H-1,2,3-triazol-5-ylmethylene) ketones. Chem Pap 74:809–820. https://doi.org/10.1002/cpap.201900908-5

Tejshri RD, Smita PK, Vagoluk SK, Dharmarajan S, Jaiprakash NS, Vijay MK, Bapuraos BS (2020b) Synthesis, bioevaluation and molecular docking study of new piperazine and amide linked dimeric 1,2,3-triazoles. Synth Commun 50:271–288. https://doi.org/10.1080/00397911.2019.1695275
Tejshri RD, Vijay MK, Rohit GJ, Aniket PS, Jaiprakash NS, Shailee VT, Bapurao BS (2021) A copper-catalyzed synthesis of aryloxy-tethered symmetrical 1,2,3-triazoles as potential antifungal agents targeting 14 α-demethylase. New J Chem 45:13104–13118. https://doi.org/10.1039/D1NJ01758D

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Jayaprakash Rao Yerrabelly1 · Subbanarasimhulu Porala1,2,4 · Venkateshwar Reddy Kasireddy3 · Earrawandla Janapiya Sony5 · Someshswar Rao Sagurthi5

1 Department of Chemistry, University College of Science, Saifabad, Osmania University, Hyderabad, Telangana 500004, India
2 Department of Chemistry, Jawaharlal Nehru Technological University College of Engineering, Hyderabad, Telangana 500085, India
3 CMR Engineering College, Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad, Telangana 501401, India
4 MSN R&D Center, Department of Research and Development, Medak, Telangana 502307, India
5 Molecular Medicine Lab, Department of Genetics, Osmania University, Hyderabad, Telangana, India