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ORIGINAL PAPER

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

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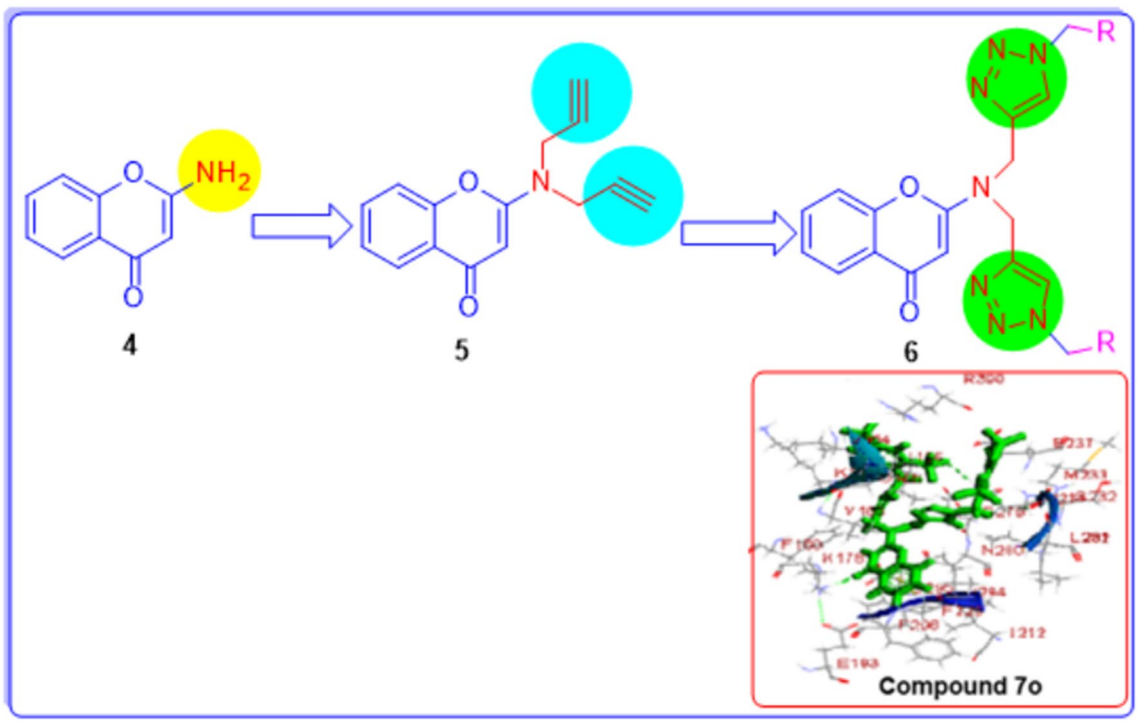
Abstract

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 ± 0.44 µM). 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 (Apurba 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 (Alaíde 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_2CO_3 (25.73 g, 0.186 mol) and Cat. Cs_2CO_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; ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{15}H_{11}NO_2$: 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 $CuSO_4{\cdot}5H_2O$ (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 CH_2Cl_2 (20 mL) was added to the reaction mass. Then, aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, 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: n-Hexane (4:6 v v^{-1})

Yield 85%, white powder, m.p: 260–262 °C; FT-IR (KBr, cm^{-1}): 2140 (N=N of triazole), 1681 (C=O), 1608, 1202; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 2H), 8.06 (q, J = 8 Hz, 1H), 7.77 (q, J = 8 Hz, 1H), 7.56–7.53 (m, 2H), 7.36–7.28 (m, 10H), 5.54 (s, 4 H), 4.98 (s, 1 H), 4.57 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{29}H_{25}N_7O_2$: 504.21480, found: 504.21425.

Dimethyl2,2'-(4,4'-(((4-oxo-4H-chromen-2-yl)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, 1193; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (q, J = 8 Hz, 1H), 8.01 (s, 2 H), 7.79–7.75 (m, 1H), 7.56–7.52 (m, 2H), 5.18 (s, 4 H), 4.98 (s, 1 H), 4.67 (s, 4 H), 3.78 (s, 6 H; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.79, 176.18, 166.92, 159.60, 142.98, 133.94, 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 $C_{21}H_{21}N_7O_6$: 468.16316, found: 468.16261.

2'-((4,4'-(((4-oxo-4H-chromen-2-yl)azanediyl) bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl)) bis(methylene))dibenzonitrile (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; ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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, 118.91, 116.60, 112.03, 82.47, 49.47, 41.22; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{31}H_{23}N_9O_2$: 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; ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.25, 164.67, 163.04, 157.31, 140.38, 132.37, 129.80, 126.01, 125.05, 121.84, 119.06, 117.78, 115.05, 111.74, 82.37, 46.29, 42.51; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{29}H_{21}F_4N_7O_2$: 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; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.06$ (q, $J = 8$ Hz, 1H), 8.02 (s, 2 H), 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, 4 H), 4.99 (s, 1 H), 4.56 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.78$, 164.39, 156.20, 141.34, 139.97, 133.46, 127.62, 126.90, 125.81, 125.21, 124.90, 123.35, 123.34, 117.02, 81.30, 53.21, 46.34; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{25}H_{21}N_7O_2S_2$: 516.12764, found: 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 (C=O), 1640, 1618; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.87$ (s, 2 H), 8.06 (q, $J = 8$ Hz, 1H), 8.02 (s, 2 H), 7.77 (q, $J = 8$ Hz, 1H), 7.56–7.53 (m, 4H), 5.44 (s, 4 H), 5.06 (s, 1 H), 4.59 (s, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 185.51$, 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 $C_{23}H_{19}N_9O_2S_2$: 518.11814, found: 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), 1660 (C=O), 1609; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.09$ (s, 2 H), 8.06 (q, $J = 8$ Hz, 1 H), 7.79–7.75 (m, 1 H), 7.56–7.52 (m, 2 H), 7.34–7.19 (m, 12 H), 7.09 (t, $J = 8$ Hz, 8 H), 6.71 (s, 2 H), 4.95 (s, 1 H), 4.59 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 185.47$, 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 $C_{41}H_{33}N_7O_2$: 656.27740, found: 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, 672; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.07$–7.85 (m, 11 H), 7.77 (q, $J = 8$ Hz, 1 H), 7.56–7.52 (m, 2 H), 5.28 (s, 4 H), 5.02 (s, 1 H), 4.52 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 198.79$, 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, 56.63, 45.58; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{31}H_{23}Br_2N_7O_4$: 716.02565, found: 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; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.07$–7.97 (m, 7H), 7.79–7.75 (m, 3H), 7.56–7.46 (m, 4H), 5.53 (s, 4 H), 5.01 (s, 1 H), 4.69 (s, 4 H), 2.69 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 181.49$, 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 $C_{35}H_{29}N_{11}O_2$: 636.25839, found: 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%, white powder, m.p: > 300 °C; FT-IR (KBr, cm^{-1}): 3480 (O–H), 2148 (N=N of triazole), 1665, 1613, 1512; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.10$–7.93 (m, 7 H), 7.79–7.75 (m, 1 H), 7.56–7.52 (m, 2 H), 6.98 (d, $J = 8$ Hz, 2 H), 5.40 (s, 4 H), 5.04 (s, 1 H), 4.48 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 183.40$, 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, 115.64, 79.70, 49.67, 43.65; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{29}H_{23}N_9O_8$: 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}): 2136 (N=N of triazole), 1743, 1670, 1618, 1182; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.10$ (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); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.89$, 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 $C_{35}H_{33}N_7O_8$: 680.24689, found: 680.24634.

2-(bis((1-((4,5-dibromo-1H-pyrrol-2-yl)(phenyl)methyl)-1H-1,2,3-triazol4yl)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; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.09$ (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); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 181.21$, 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 $C_{37}H_{27}Br_4N_9O_2$: 945.90995, found: 949.90580 $[M+H+4]^+$.

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

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

Yield 85%, Pale yellow powder, m.p: 244–246 °C; FT-IR (KBr, cm^{-1}): 2132 (N=N of triazole), 1668 (C=O), 1611, 1100; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.09$–8.04 (m, 3 H), 7.79–7.09 (m, 11 H), 6.62 (s, 2 H), 4.90–4.26 (m, 5 H), 2.55–2.47 (m, 2 H), 1.07–0.75 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 197.86$, 175.75, 166.72, 161.37, 157.46, 146.43, 133.35, 130.05, 129.12, 126.55, 125.77, 125.07, 124.12, 123.59, 118.28, 117.47, 115.20, 84.94, 63.13, 46.35, 24.65, 11.88; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{37}H_{31}F_2N_7O_4$: 676.24838, found: 676.24784.

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

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

Yield 85%, Yellow powder, m.p: 220–223 °C; FT-IR (KBr, cm^{-1}): 3382 (N–H), 2128 (N=N of triazole), 1685, 1616; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.11$–8.02 (m, 5 H), 7.80–7.74 (m, 1 H), 7.56–7.51 (m, 2 H), 7.41–7.38 (m, 2 H), 6.97–6.94 (m, 2 H), 5.34 (s, 4 H), 5.03 (s, 1 H), 4.55 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=176.48, 165.53, 158.35, 154.40, 145.73, 141.89, 136.49, 132.89, 126.34, 125.43, 122.68, 119.49, 118.38, 115.10, 114.84, 83.50, 46.99, 42.79; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{27}H_{25}N_{11}O_2$: 536.22709, found: 536.22655.

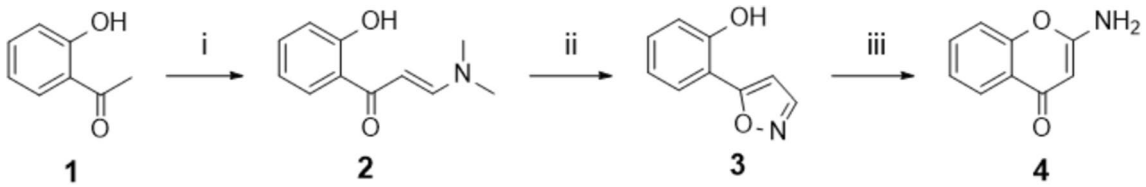
2-(bis((1-(2,4-bis(trifluoromethyl) benzyl)-1H-1,2,3-triazol-4-yl)methyl) amino)-4H-chromen-4-one (7o)

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

Yield 85%, white powder, m.p: 260–263 °C; FT-IR (KBr, cm^{-1}): 2148 (N=N of triazole), 1682, 1614, 1150; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.10–8.04 (m, 3 H), 7.80–7.52 (m, 7 H), 7.32 (d, $J = 8$ Hz, 2 H), 5.67 (s, 4 H), 5.06 (s, 1 H), 4.60 (s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 185.85$, 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 $C_{33}H_{21}F_{12}N_7O_2$: 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 MTCC (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 1.5×10^8 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 125–0.9 µg $well^{-1}$ 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 125–0.9 µg $well^{-1}$ 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



Scheme 1 Synthesis of 2-aminochromone (**4**)

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 1.5×10^8 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 3×10^3 cells in 200 µL of serum DMEM and incubated at 37 °C with 5% CO_2. 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% CO_2. 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.

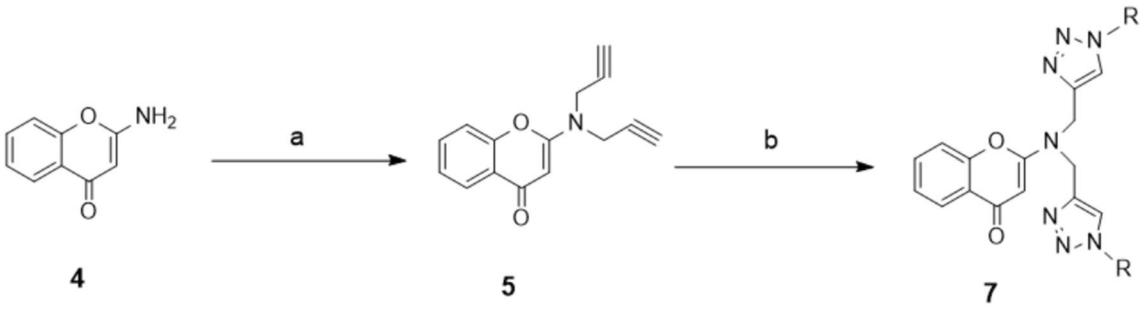
Molecular docking

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**) (Scheme1). 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 alkyne 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, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy. In the ^{1}H 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.



Scheme 2 Synthesis of 2-aminochromone-based *N,N*-bis-1,2,3-triazole analogs **(7a-o)**

Reaction conditions

(i) DMFDA, 80–90 °C, 2 h (ii) NH_2OH. HCl, Ethanol (iii) Et_3N, DMF, 140–150 °C.

2-aminochromone **(4)** was prepared from 2-hydroxy acetophenone (1) by following the reported procedure (Chandrakanta 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 $NH_2OH{\cdot}HCl$ 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 Et_3N for 8 h.

2-aminochromone **(4)** was treated with one equivalent of propargyl bromide in acetonitrile solvent in the presence of Na_2CO_3 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, ^{13}C 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*-mono propargylated 2-aminochromone readily converted into the corresponding dipropargylated 2-aminochromone **(5)** even by decreasing the moles of propargyl bromide, Na_2CO_3, 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 Cs_2CO_3 when compared with the Na_2CO_3 and K_2CO_3, due to the high cost of the Cs_2CO_3, attempted a reaction by using the stoichiometric K_2CO_3 and catalytic Cs_2CO_3, 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

Table 1 Solvent optimization

S. No	Solvent	Yield %
1	Water	0
2	Toluene	0
3	DMF	50
4	Acetonitrile	30
5	THF	5
6	MTBE	0
7	Acetone	0

*All entries were attempted by using 1.5 mol equivalent of propargyl bromide, and 3.0 mol equivalent of Na_2CO_3, at 50 °C

Table 2 Base optimization

S. No	Base	Equivalents	Yield %
1	Na_2CO_3	1.5	50
2	Na_2CO_3	3.0	65
3	$NaHCO_3$	3.0	0
4	K_2CO_3	1.5	60
5	K_2CO_3	3.0	70
6	Cs_2CO_3	1.5	70
7	Cs_2CO_3	3.0	85
8	Triethylamine	3.0	0
9	Pyridine	3.0	0
10	K_2CO_3 + Cat. Cs_2CO_3	3.0	85

*All entries were attempted by using 1.5 equivalent of propargyl bromide, in DMF solvent at 50 °C

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) (Scheme2).

Reaction conditions

(a) Propargyl bromide (3.5 eq), DMF, Cs_2CO_3 (2.5 equiv) 50 °C, 4 h. Yield-70%

b) alkyl/aryl azide (2.12 equiv), $CuSO_4{\cdot}5H_2O$ (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 $CuSO_4{\cdot}5H2O$ 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, 7 f, 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

Table 3 Physical data of the compounds 7a-o

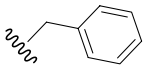
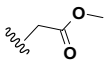
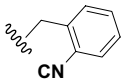
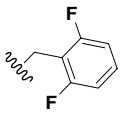
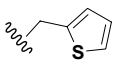
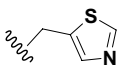
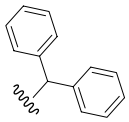
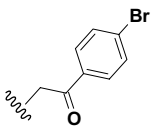
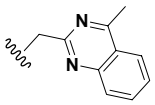
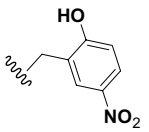
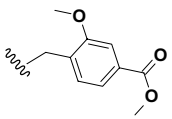
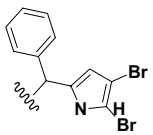
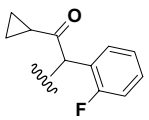
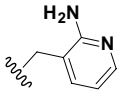
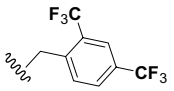
Entry	*R*	M. P. (°C)	Yield %
7a		260–262	85
7b		222–225	83
7c		285–288	80
7d		275–277	88
7e		248–250	78
7f		256–258	90
7g		288–290	89
7h		280–284	85
7i		290–293	70
7j		> 300	78
7k		288–290	84
7l		> 300	89
7m		244–246	85
7n		223–225	85
7o		260–263	85

Table 4 Anti-microbial activity (MIC in µg/mL) of novel synthesized compounds

Test compound	Minimum inhibitory concentration (µg/ml)							
	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	> 125	**3.9**	> 125	> 125
7b	> 125	> 125	> 125	> 125	> 125	**3.9**	> 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**	**3.9**	**3.9**	**3.9**
7e	**3.9**	**3.9**	**3.9**	**3.9**	> 125	**3.9**	**3.9**	> 125
7f	**3.9**	**3.9**	> 125	**3.9**	> 125	**3.9**	**3.9**	> 125
7 g	**3.9**	**3.9**	> 125	**3.9**	> 125	**3.9**	**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	> 125	> 125	**3.9**	> 125	> 125
7j	**3.9**	**3.9**	> 125	**3.9**	> 125	**3.9**	> 125	> 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 bacterial concentration (MBC in µg/mL) of novel synthesized compounds

Test compound	Minimum bactericidal concentration (µg/ml)							
	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	> 125	7.8	> 125	> 125
7b	> 125	> 125	> 125	> 125	> 125	7.8	> 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	7.8	7.8	7.8
7e	7.8	7.8	7.8	7.8	> 125	7.8	7.8	> 125
7f	7.8	7.8	> 125	7.8	> 125	7.8	7.8	> 125
7 g	7.8	7.8	> 125	7.8	> 125	7.8	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	> 125	> 125	7.8	> 125	> 125
7j	7.8	7.8	> 125	7.8	> 125	7.8	> 125	> 125
7k	7.8	> 125	7.8	7.8	> 125	7.8	> 125	> 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 IC_{50} values ranging from 0.11 to 1.04 µM than standard curcumin (IC_{50} 4.83 ± 0.44 µM) shown in Table 6. Among all the compounds, *ortho*, *para*-substituted trifluoromethane (**7o**) has shown better activity with IC_{50} 0.11 ± 0.56 µM, followed by 2,3-dibromo pyrrole methylene (**7l**) with IC_{50} 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 IC_{50} 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).

Table 6 Novel synthesis compounds (7a-o) IC_{50}

S. No	Compound	IC_{50} 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

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** IC_{50}—0.11 ± 0.56 µM) has shown better anti-cancer activity than di-ortho substituted halogen derivative (**7d** IC_{50}—0.52 ± 0.55 µM). The compound with an acetyl group (**7b** IC_{50}—1.04 ± 0.47 µM) has shown low activity in contrast to substituted acetyl groups (**7k** IC_{50}—0.16 ± 0.38 µM). A noticeable variation in IC_{50} 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

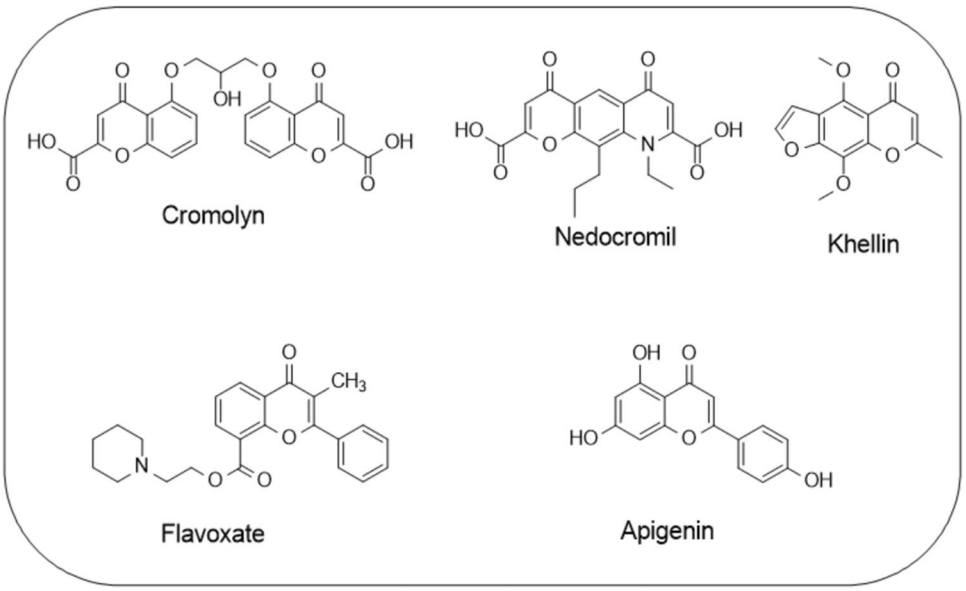


Fig. 1 Representative structures of bioactive chromone derivatives

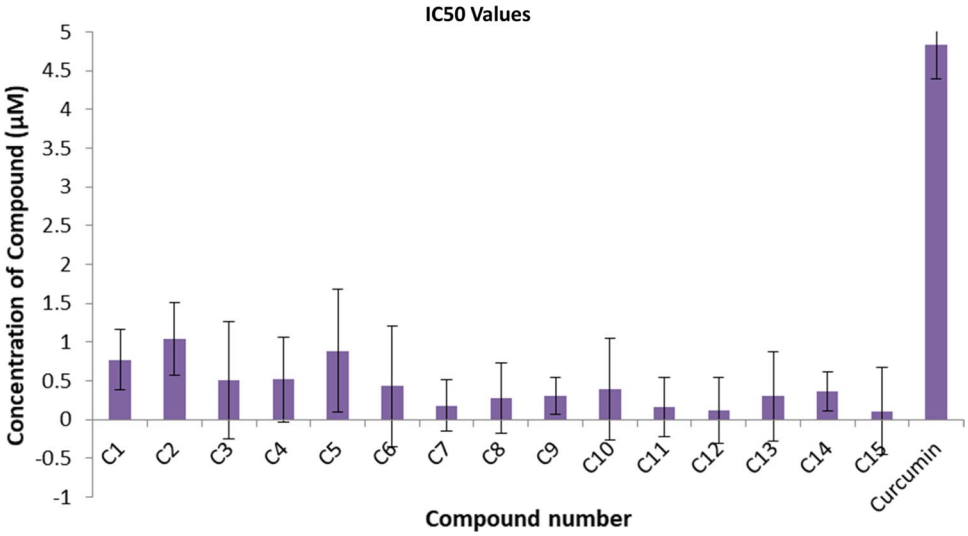


Fig. 2 Inhibitory concentration of novel synthesized derivatives (7a-o) against the HeLa cell MTT assay

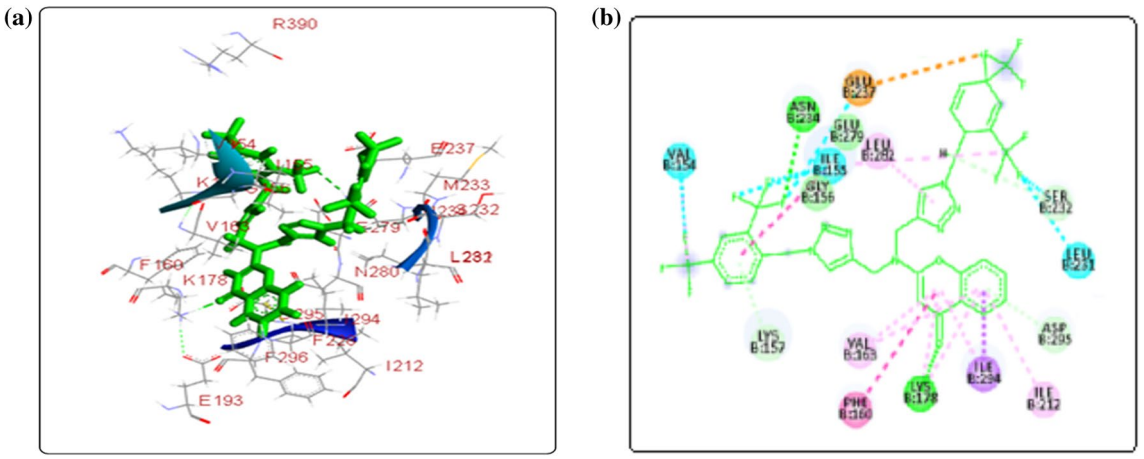


Fig. 3 **a** Doc pose of compound **7o** in DYRK2 (PDB id: 5ZTN), **b** binding interaction (H2d diagram of compound **7o**

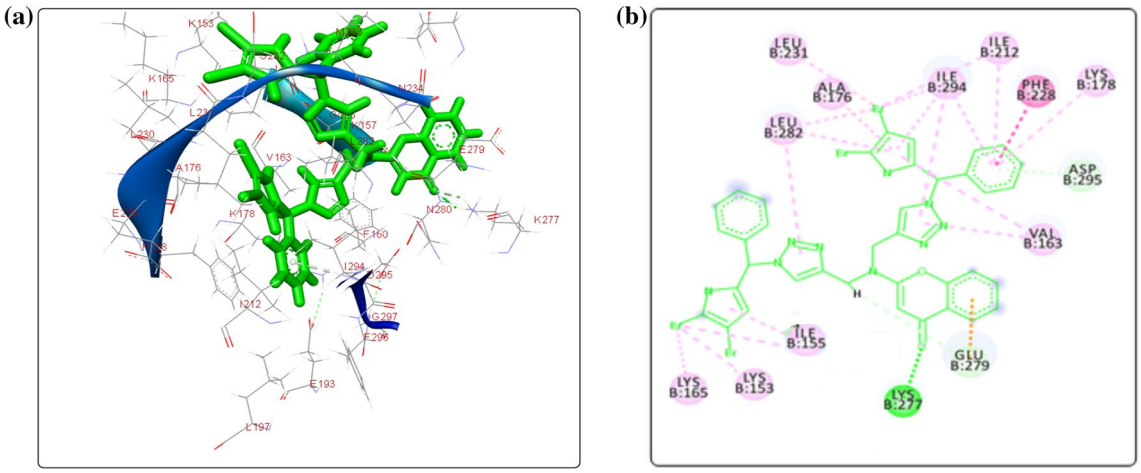


Fig. 4 **a** Doc pose of compound **7l** in DYRK2 (PDB id: 5ZTN), **b** binding interaction (Hydrogen and π-π bonding) 2d diagram of compound **7l**

(**7c**–**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_{50} 0.11 ± 0.56 µM, followed by 2,3 dibromo pyrrole methylene (**7l**) with IC_{50} 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.

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Declarations

Conflict of interest The authors declare no competing financial interest.

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