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Synthesis, Characterization, Antibacterial and Anticancer Activity of Some Novel Triazolyl Chromenone Derivatives

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ABSTRACT

A series of newer seventeen coumarin linked 1,2,3-triazole derivatives have been synthesised by utilising the approach of click chemistry. All of the synthesised compounds have been well characterized by an array of spectroscopic techniques such as ^{1}H, ^{13}C-NMR and MS. These compounds have been screened for antibacterial activity against Gram-positive and Gram-negative strains. In addition 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to determine cytotoxicity against two cell lines e.g., HOP-62 and Colo-205. Among the tested compounds 3a and 3k displayed promising activity.

Keywords: Coumarin, Click chemistry, 1,2,3-Triazole, Antibacterial activity, Anticancer activity

INTRODUCTION

Substituted coumarins, benzofused six membered oxygen containing heterocyclic ring, exhibit a broad pharmacological profile either isolated from natural sources [1] or synthesized (e.g., Umbelliferone, warfarin). Many coumarin derivatives have been reported to have antibacterial [2], antimicrobial [3], anticancer [4], antialzheimer's [5], CNS disorders [6], antihuman monoamine oxidase [7,8], antioxidant [9], anti-AD activities [10], antiviral [11], antimoraxella catarrhalis activity [12], anti-inflammatory [13] and antifungal activity [14]. On the other hand compounds containing substituted triazoles exhibit a wide range of medicinal properties e.g., Tazobactam [15,16]. In light of these knowledge, as a part of ongoing programme in our laboratory, in search of new antibacterial and anticancer agents [17] we purportedly designed the new molecules by combining the structural features of both coumarin and 1,2,3-triazole moiety. The designed compounds were synthesized by applying CuAAC strategy [18] as the key step combining coumarin based azide and aliphatic/ aromatic terminal alkynes.

MATERIALS AND METHODS

Melting points were determined by open glass capillary method on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker-Alpha t spectrometer using KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer using $CDCl_3$, with reference to Tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a Jeol JMC D-300 instrument by using Electron ionization at 70 eV. All reactions were monitored by Thin Layer Chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed by using silica gel (100-200 mesh, SRL, India) (10-20 times (by weight)) of the crude product.

Synthesis

Preparation of azides (1): Azides have been prepared by following the earlier reported procedure [19].

Preparation of alkyne (2): Alkynes have been prepared by following the earlier reported procedure [20].

Preparation of title compounds (3): A mixture of azide 1 (2 mmol), an appropriate terminal alkyne 2 (2 mmol), copper sulphate (62.5 mg, 0.5 mmol) and sodium ascorbate (49.5 mg, 0.5 mmol) in dry Dimethyl Fluoride (DMF) (5 ml) was stirred vigorously for 5-10 min. The progress of the reaction was monitored by checking TLC at a regular interval. After completion of the reaction the mixture was poured into crushed ice (30 g). The solid separated was filtered, dried and purified by column chromatography on silica gel (100-200 mesh) using dichloro methane and ethyl acetate to isolate pure desired products.

(1) 4-Methyl-7-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3a): White solid; Yield: 93%; M.P. 98-100°C; R_f: 0.5 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3053, 2928, 2425, 1715, 1626, 1587, 1435, 1314, 1246, 924, 735; ^{1}H-NMR ($CDCl_3$, δ

ppm): 7.93 (s, 1H), 7.74 (d, 2H, *J*=8.5 Hz), 7.64 (d, 1H, *J*=9.6 Hz), 7.40 (d, 1H, *J*=9.3 Hz), 7.29 (s, 1H), 6.84 (m, 2H), 6.29 (d, 1H, *J*=9.8 Hz), 6.17 (s, 1H), 4.87 (t, 2H, *J*=5.3 Hz), 4.49 (t, 2H, *J*=5.5 Hz), 2.40 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): =160.8, 155.7, 143.1, 138.1, 129.5, 129.0, 127.5, 125.6, 113.8, 113.3, 112.3, 101.8, 66.8, 49.5, 21.3; MS *m/z* 347.1 (M+1, 100%).

(2) 4-Methyl-7-(2-(4-propyl-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3b): Off white solid; Yield: 93%; M.P. 80-82°C; R_f: 0.46 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3054, 2932, 2431, 1713, 1624, 1584, 1433, 1313, 1242, 929, 736; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.51 (d, 1H, *J*=8.5 Hz), 7.46 (s, 1H), 6.82 (m, 2H), 6.17 (s, 1H), 4.77 (t, 2H, *J*=4.8 Hz), 4.43 (t, 2H, *J*=5.0 Hz), 2.70 (t, 2H, *J*=7.3 Hz), 2.40 (s, 3H), 1.67 (m, 2H), 0.97 (m, 3H);^{13}C-NMR ($CDCl_3$, δ ppm): 160.5, 160.2, 155.5, 153.5, 130.3, 126.5, 121.0, 113.1, 111.4, 103.5, 68.3, 46.2, 36.1, 23.4, 17.3, 14.6; MS *m/z* 313.1 (M+1, 100%).

(3) 7-(2-(4-Heptyl-1*H*-1,2,3-triazol-1-yl)ethoxy)-4-methyl-2*H*-chromen-2-one (3c): Pale yellow solid; Yield: 93%; M.P. 84-86 ºC; R_f: 0.43 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3054, 2934, 2432, 1715, 1623, 1583, 1432, 1312, 1246, 921, 739; ^{1}H NMR ($CDCl_3$, δ ppm): 7.51 (d, 1H, *J*=7.3 Hz), 7.45 (s, 1H), 6.82 (m, 2H), 6.16 (s, 1H), 4.77 (t, 2H, *J*=4.8 Hz), 4.43 (t, 2H, *J*=5.0 Hz), 2.72 (t, 2H, *J*=7.3 Hz), 2.42 (s, 3H), 1.66 (m, 2H), 1.27 (m, 8H), 0.87 (t, 3H, *J*=6.5 Hz); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.3, 159.9, 155.2, 153.4, 131.2, 124.6, 123.1, 112.0, 110.9, 110.7, 104.3, 67.2, 45.4, 32.4, 32.0, 30.0, 29.5, 28.9, 23.1, 18.3, 15.4.; MS *m/z* 369.2 (M+1, 100%).

(4) 4-Methyl-7-(2-(4-octyl-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3d): Light yellow solid; Yield: 93%; M.P. 86-88°C; R_f: 0.43 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3055, 2932, 2430, 1710, 1624, 1584, 1434, 1314, 1244, 924, 734; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.52 (d, 1H, *J*=8.5 Hz), 7.47 (s, 1H), 7.29 (s, 1H), 6.85 (d, 1H, *J*=10.1 Hz), 6.19 (s, 1H), 4.79 (t, 2H, *J*=4.8 Hz), 4.44 (t, 2H, *J*=4.5 Hz), 2.74 (t, 2H, *J*=8.0 Hz), 2.42 (s, 3H), 1.28 (m, 12H), 0.89 (t, 3H, *J*=5.0 Hz); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.5, 159.7, 155.3, 153.6, 131.4, 124.5, 123.1, 112.5, 111.1, 110.7, 104.2, 66.8, 46.5, 32.3, 29.7, 29.5, 23.3, 18.6, 14.8; MS *m/z* 369.1 (M+1, 100%).

(5) 4-Methyl-7-(2-(4-((o-tolyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3e): White solid; Yield: 93%; M.P. 86-88°C; R_f: 0.5 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3052, 2924, 2428, 1714, 1625, 1584, 1432, 1312, 1244, 925, 736; ^{1}H NMR ($CDCl_3$, δ ppm): 7.80 (s, 1H), 7.52 (d, 1H, *J*=8.0 Hz), 7.29 (d, 2H, *J*=5.3 Hz), 7.18 (m, 2H), 6.97 (m, 1H), 6.91 (m, 1H), 6.19 (s, 1H), 5.26 (s, 2H), 4.84 (t, 2H, *J*=4.8 Hz), 4.47 (t, 2H, *J*=5.0 Hz), 2.42 (s, 3H), 2.26 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.8, 156.5, 155.6, 153.4, 143.3, 130.7, 129.3, 126.8, 121.2, 113.5, 113.2, 112.8, 111.6, 101.9, 66.5, 62.4, 49.4, 18.3, 16.2; MS *m/z* 391.1 (M+1, 100%).

(6) 4-((1-(2-((4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy) benzaldehyde (3f): White solid; Yield: 93%; M.P. 146-148°C; R_f: 0.5 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3055, 2924, 2423, 1720, 1630, 1590, 1428, 1313, 1250, 925, 738; ^{1}H-NMR ($CDCl_3$, δ ppm): 9.12 (s, 1H), 9.02 (s, 1H), 8.11 (d, 2H, *J*=5.3 Hz), 8.01 (d, 2H, *J*=5.3 Hz), 7.64 (s, 1H), 7.16 (d, 2H, *J*=7.3 Hz), 7.01 (d, 2H, *J*=9.34 Hz), 5.20 (s, 2H), 4.22 (t, 2H, *J*=4.5 Hz), 3.98 (t, 2H, *J*=4.5 Hz), 2.22 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 190.7, 163.1, 160.3, 155.8, 143.4, 131.9, 130.5, 128.8, 124.3, 114.9, 113.7, 113.1, 112.3, 111.0, 66.4, 62.3, 49.6, 18.2; MS *m/z* 405.5 (M+1, 100%).

(7) 4-Methyl-7-(2-(4-((naphthalen-2-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3g): Pale yellow solid; Yield: 93%; M.P. 160-162°C; R_f: 0.7 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3051, 2926, 1715, 1621, 1510, 1460, 1391, 1274, 1207, 11465, 1105, 840, 766; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.84 (s, 1H), 7.71(m, 3H), 7.42-7.30 (m, 4H), 7.16 (d, 1H, *J*=11.4 Hz), 6.73-6.69 (m, 2H), 6.10 (s, 1H), 5.32 (s, 2H), 4.78 (t, 2H, *J*=4.8 Hz), 4.39 (t, 2H, *J*=4.8 Hz), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.9, 160.5, 156.0, 154.9, 152.3, 144.2, 134.3, 129.5, 127.5, 126.8, 126.4, 125.7, 124.0, 123.8, 118.7, 114.2, 112.4, 112.0, 107.2, 101.6, 66.6, 61.8, 49.5, 18.6; MS *m/z* 427.1 (M+1, 100%).

(8) 7-(2-(4-((4-Chloro-3-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-4-methyl-2*H*-chromen-2-one (3h): Off white solid; Yield: 93%; M.P. 150-152°C; R_f: 0.7 (1:1 Dichloro methane: Ethyl acetate). FTIR **(**KBr, υ in cm^{-1}**):** 3052, 2923, 2430, 1717, 1623, 1580, 1436, 1314, 1245, 920, 737; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.49 (s, 1H), 7.25 (s, 1H), 6.86-6.7 (m, 5H), 6.16 (s, 1H), 5.29 (s, 2H), 5.23 (t, 2H, *J*=4.8 Hz), 4.51 (t, 2H, *J*=4.8 Hz), 2.39 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.5, 160.2, 158.3, 154.2, 152.6, 141.8, 133.7, 130.5, 129.3, 128.4, 124.9, 113.8, 113.6, 112.3, 111.6, 111.4, 104.7, 72.5, 68.6, 46.3, 19.4, 18.6; MS *m/z* 425.11 (M+1, 100%).

(9) 4-Methyl-7-(2-(4-((naphthalen-1-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3i): Off white solid; Yield: 93%; M.P. 130-132°C; R_f: 0.7 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3051, 2925, 1715, 1611, 1508, 1458, 1390, 1270, 1204, 1145, 1101, 839, 760; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.82 (s, 1H), 7.78 (m, 3H), 7.60 (d, 1H, *J*=9.3 Hz), 7.40 (dd, 1H, *J*=8.5 Hz, 2.5 Hz), 7.34 (t, 1H, *J*=7.8 Hz), 7.29 (d, 1H, *J*=8.5 Hz), 7.25 (m, 1H), 7.18 (dd, 1H, *J*=8.8 Hz, 2.5 Hz), 6.75 (d, 1H, *J*=2.0 Hz), 6.71 (dd, 1H, *J*=8.5 Hz, 2.5 Hz), 6.26 (s, 1H), 5.39 (s, 2H), 4.84 (t, 2H, *J*=5.0 Hz), 4.44 (t, 2H, *J*=5.3 Hz), 2.38 (s, 3H); ^{13}C=NMR ($CDCl_3$, δ ppm): 160.9, 156.4, 155.2, 143.9, 143.5, 133.6, 131.1, 130.0, 128.6, 127.9, 126.5, 123.4, 118.7, 113.7, 113.1, 112.2, 108.2, 101.8, 66.2, 62.0, 50.3, 19.2; MS *m/z* 427.15 (M+1, 100%).

(10) 4-Methyl-7-(2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3j): White solid; Yield: 93%; M.P. 130-132°C; Rf: 0.43 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3055, 2930, 2430, 1716, 1628, 1589, 1435, 1313, 1240, 925, 740; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.80 (s, 1H), 7.48 (d, 1H, *J*=8.3 Hz), 7.30-7.28 (m, 2H), 6.98 (m, 3H), 6.80-6.78 (m, 2H), 6.15 (s, 1H), 5.22 (s, 2H), 4.81 (t, 2H, *J*=4.8 Hz), 4.44 (t, 2H, *J*=4.8 Hz), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 160.9, 160.5, 158.1, 155.0, 152.2, 129.5, 125.8, 123.7, 121.2, 114.7, 114.4, 112.5, 112.0, 101.8, 66.6, 61.8, 45.5, 18.6; MS *m/z* 377.14 (M+1, 100%).

(11) 4-Methyl-7-(2-(4-((m-tolyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3k): Off white solid; Yield: 93%; M.P. 130-132°C; Rf: 0.43 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3051, 2925, 2427, 1715, 1627, 1586, 1430, 1310, 1247, 921, 739; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.80 (s, 1H), 7.49 (d, 1H, *J*=7.5 Hz), 7.08 (d, 2H, *J*=7.5 Hz), 6.85 (m, 4H), 6.16 (s, 1H), 5.20 (s, 2H), 4.81 (t, 2H, *J*=6.5 Hz), 4.44 (t, 2H, *J*=6.5 Hz), 2.39 (s, 3H), 2.28 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.5, 158.1, 155.0, 142.9, 130.4, 129.5, 125.8, 120.8, 113.7, 113.4, 112.5, 111.5, 101.6, 66.5, 62.8, 49.7, 18.6, 16.1; MS *m/z* 391.1 (M+1, 100%).

(12) 7-(2-(4-((4-chloro-3-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3l): Pale yellow solid; Yield: 93%; M.P. 148-150°C; R_f: 0.43 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3054, 2927, 2435, 1715, 1626, 1597, 1442, 1321, 1236, 935, 740; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.64 (d, 1H, *J*=9.3 Hz), 7.50 (s, 1H), 7.23 (s, 1H), 6.76-6.73 (m, 5H), 6.14 (d, 1H, *J*=9.3 Hz), 5.32 (s, 2H), 5.21(t, 2H, *J*=4.8 Hz), 4.65 (t, 2H, *J*=4.8 Hz), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 160.8, 160.4, 158.7, 153.9, 151.9, 142.0, 133.9, 131.5, 130.3, 128.4, 125.9, 113.8, 113.7, 112.4, 111.4, 111.2, 104.3, 72.2, 68.4, 46.8, 19.8; MS *m/z* 411.1 (M+1, 100%).

(13) 7-(2-(4-(p-Tolyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3m): Pale yellow solid; Yield: 93%; M.P. 90-92°C; R_f: 0.5 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3055, 2929, 2424, 1715, 1628, 1585, 1438, 1317, 1250, 924, 739; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.65 (d, 1H, *J*=9.3 Hz), 7.61 (d, 2H, *J*=8.2 Hz), 7.51 (d, 1H, *J*=8.5 Hz), 7.46 (s, 1H), 7.22 (d, 2H, *J*=8.2 Hz), 6.82 (m, 2H), 6.17 (d, 1H, *J*=9.3 Hz), 4.82 (t, 2H, *J*=5.0 Hz), 4.45 (t, 2H, *J*=5.0 Hz), 2.26 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.4, 159.2, 155.6, 148.0, 143.2, 131.4,

130.3, 129.0, 126.9, 125.3, 112.9, 111.6, 110.9, 104.5, 66.5, 48.4, 20.9; MS *m/z* 347.1 (M+1, 100%).

(14) 4-((1-(2-((2-Oxo-2*H*-chromen-7-yl)oxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy) benzaldehyde (3n): Light yellow solid; Yield: 93%; M.P. 140-142°C; Rf: 0.33 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3054, 2925, 2424, 1718, 1627, 1594, 1429, 1314, 1253, 929, 736; ^{1}H-NMR ($CDCl_3$, δ ppm): 9.89 (s, 1H), 7.86 (d, 3H, *J*=5.3 Hz), 7.83 (s, 1H), 7.65 (d, 1H, *J*=9.3 Hz), 7.38 (d, 1H, *J*=9.0 Hz), 7.29 (s, 1H), 7.10 (d, 1H, *J*=7.3 Hz), 6.79 (s, 1H), 6.29 (d, 1H, *J*=9.3 Hz), 5.33 (s, 2H), 4.85 (t, 2H, *J*=4.5 Hz), 4.47 (t, 2H, *J*=4.5 Hz); ^{13}C-NMR ($CDCl_3$, δ ppm): (175) 192.1, 190.7, 163.0, 160.6, 155.6, 143.1, 131.9, 130.3, 129.0, 124.1, 115.1, 113.8, 113.3, 112.3, 101.8, 66.7, 62.0, 49.6; MS *m/z* 391.1 (M+1, 100%).

(15) 7-(2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3o): Off white solid; Yield: 93%; M.P. 160-162°C; R_f: 0.45 (1:1 Dichloro methane: Ethyl acetate). FTIR **(**KBr, υ in cm^{-1}): 3051, 2929, 2426, 1715, 1626, 1587, 1436, 1316, 1245, 927, 739; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.95 (s, 1H), 7.83 (d, 2H, *J*=7.0 Hz), 7.61 (d, 1H, *J*=9.6 Hz), 7.42 (t, 2H, *J*=7.4 Hz), 7.35 (t, 2H, *J*=8.6 Hz), 6.82–6.80 (m, 2H), 6.26 (d, 1H, *J*=7.2 Hz), 4.85 (t, 2H, *J*=5.2 Hz), 4.47 (t, 2H, *J*=4.8 Hz); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.8, 155.6, 148.0, 143.1, 130.3, 129.0, 128.8, 128.2, 125.7, 120.6, 113.8, 113.3, 112.9, 112.3, 101.8, 66.8, 49.5; MS *m/z* 333.1 (M+1, 100%).

(16) 7-(2-(4-((Naphthalen-2-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3p): Off white solid; Yield: 93%; M.P. 140-142°C; R_f: 0.5 (1:1 Dichloro methane: Ethyl acetate). FTIR **(**KBr, υ in cm^{-1}): 3055, 2926, 1716, 1616, 1511, 1459, 1396, 1280, 1214, 1135, 1115, 834, 765; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.82 (s, 1H), 7.76 (m, 3H), 7.59 (d, 1H, *J*=9.3 Hz), 7.43 (t, 1H, *J*=7.0 Hz), 7.34 (t, 1H, *J*=7.8 Hz), 7.29 (d, 1H, *J*=8.5 Hz), 7.25 (m, 1H), 7.18 (d, 1H, *J*=8.8 Hz), 6.75 (s, 1H), 6.71 (d, 1H, *J*=8.5 Hz), 6.26 (d, 1H, *J*=9.3 Hz), 5.35 (s, 2H), 4.80 (t, 2H, *J*=5.0 Hz), 4.42 (t, 2H, *J*=5.3 Hz); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.7, 156.0, 155.6, 144.4, 143.1, 134.3, 129.5, 129.0, 127.6, 126.9, 126.5, 123.9, 118.7, 113.8, 113.2, 112.3, 107.2, 101.7, 66.7, 61.9, 49.5; MS *m/z* 413.1 (M+1, 100%).

(17) 7-(2-(4-((*o*-Tolyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)-2*H*-chromen-2-one (3q): Pale yellow solid; Yield: 93%; M.P. 110-112°C; R_f: 0.5 (1:1 Dichloro methane: Ethyl acetate). FTIR (KBr, υ in cm^{-1}): 3061, 2935, 2447, 1715, 1628, 1596, 1439, 1314, 1246, 923, 741;^{1}H NMR ($CDCl_3$, δ ppm): 7.81 (s, 1H), 7.65 (d, 1H, *J*=9.6 Hz), 7.39 (d, 1H, *J*=9.0 Hz), 7.16 (d, 2H, *J*=6.3 Hz), 6.97 (d, 1H, *J*=8.0 Hz), 6.91 (t, 1H, *J*=7.5 Hz), 6.80 (s, 2H), 6.30 (d, 1H, *J*=9.6 Hz), 5.26 (s, 2H), 4.84 (t, 2H, *J*=5.0 Hz), 4.47 (t, 2H, *J*=4.8 Hz), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 160.8, 156.3, 155.7, 143.1, 130.8, 129.0, 126.8, 121.0, 113.8, 113.3, 112.3, 111.5, 101.8, 66.7, 62.2, 49.5, 16.3; MS *m/z* 377.1 (M+1, 100%).

Pharmacology

Antibacterial activity

Test organisms and culture condition: A collection of four organisms including two Gram-positive and two Gram-negative organisms were used for this study. *Escherichia coli* (MTCC 1563) and *Pseudomonas aeruginosa* (MTCC 6642) were obtained from Microbial Type Culture Collection, IMTECH, and Chandigarh, India. Clinical isolates such as *Staphylococcus aureus, Klebsiella pneumonia* were obtained from Microbiology Laboratory of Global Hospital, Hyderabad. All strains were tested for purity by standard microbiological methods. The bacterial stock cultures were maintained on Mueller Hinton Agar (MHA) slants and stored at 4°C.

Determination of antibacterial activity

An agar-well diffusion method was employed for evaluation of antibacterial activity. The bacterial strains were reactivated from stock cultures by transferring into MHB and incubating at 37°C for 18 h. A final inoculum containing 106 colony forming units (1 × 106 CFU/ml) was added aseptically to MHA medium and poured into sterile petri dishes. Different test compounds at a concentration of 0.5 mg/50 µl were added to wells (8 mm in diameter) punched on agar surface. Plates were incubated overnight at 37°C and Diameter of Inhibition Zone (DIZ) around each well was measured in mm. Experiments were performed in triplicates. Antibiotic such as pefloxacin at a concentration of 0.05 mg/50 µl were used as positive reference to determine sensitivity of microorganisms tested. Dimethyl Sulfoxide (DMSO) was used as a negative control.

***In vitro* cytotoxicity assay**

The human tumor cell lines are grown in RPMI-1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. Cells are inoculated into 96-well microtiter plates in 100 µl at plating densities ranging from 5000-40000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37°C, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to addition of test compounds.

After 24 h, two plates of each cell line are fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of addition of test compound (Tz). Test compounds are dissolved in DMSO at 400-fold the desired final maximum test concentration and 17 stored frozen prior to use. At the time of compound addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10-fold or ½log serial dilutions are made to provide a total of five drug (test compound) concentrations plus control. Aliquots of 100 µl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37°C, 5% CO_2, 95% air and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed *in situ* by the gentle addition of 50 µl of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4°C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4% (w/v) in 1% acetic acid is added to each well, and plates are incubated for 10 min at room temperature. After staining, unbound dye is removed by washing five times with 1% acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. Using the 7 absorbance measurements (Time zero, (Tz), Control growth, (C) and test growth in the presence of drug at the five concentration levels (Ti)), the percentage control growth is calculated at each of the drug concentrations levels. Three dose response parameters are calculated for each test compound.

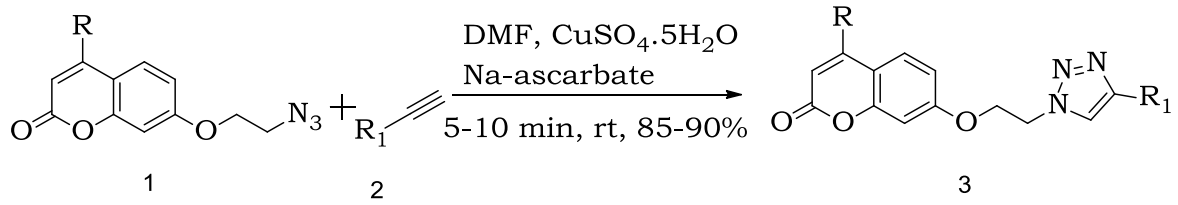
GI_{50}: Growth inhibition of 50% (GI_{50}) is calculated from [(Ti-Tz)/(C-Tz)] × 100=50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation.

TGI: The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti=Tz.

LC_{50}: The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti-Tz)/Tz] × 100=-50.

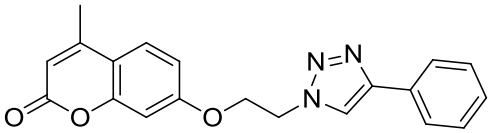
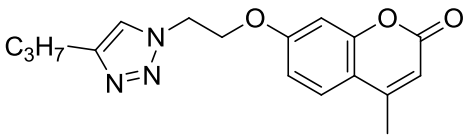
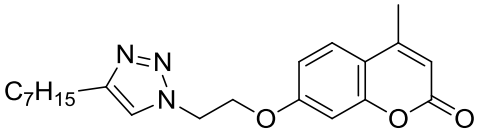
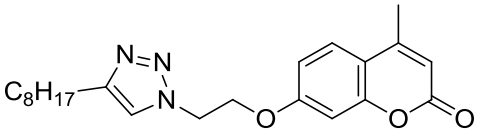
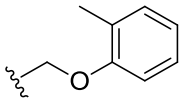
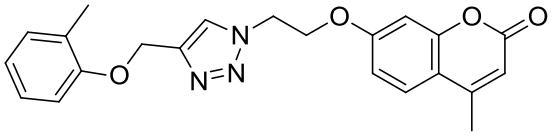
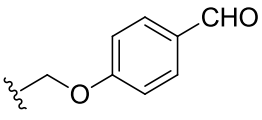
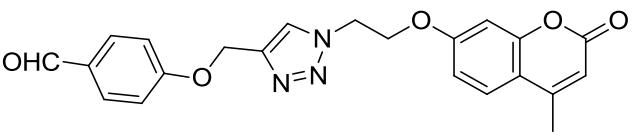
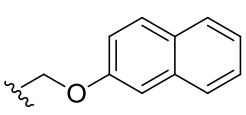
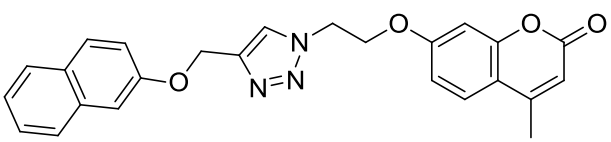
RESULTS AND DISCUSSIONS

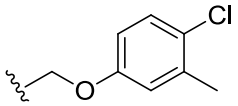
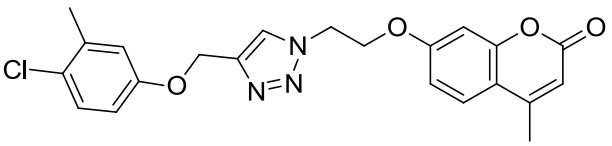
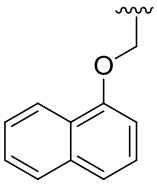
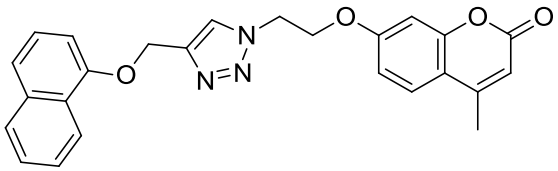
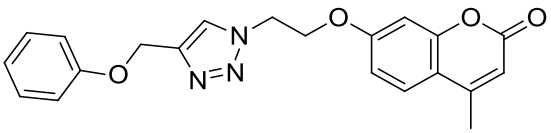
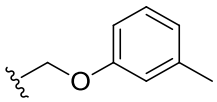
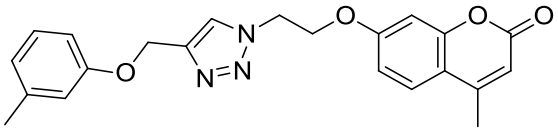
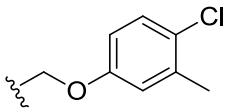
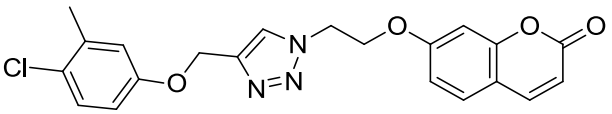
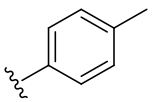
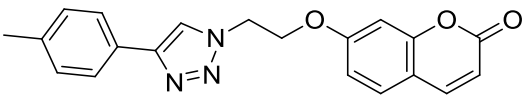
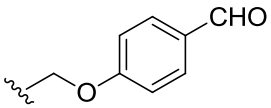
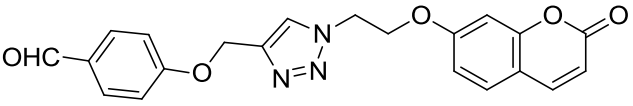
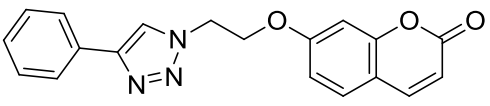
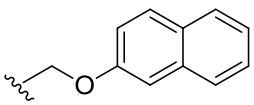
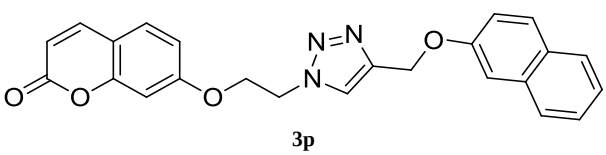
In the present communication, we hereby report the synthesis of triazolyl chromenone derivatives as per the reported Scheme 1.

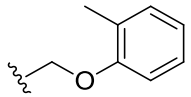
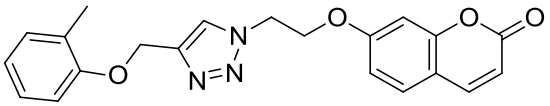


Scheme 1: Triazolyl chromenone derivatives

Table 1: List of the derivatives 3(a-q)

S. No.	R	R_1	3 (a-q)
1	CH_3	Ph-	 **3a**
2	CH_3	Propyl	 **3b**
3	CH_3	Heptyl	 **3c**
4	CH_3	Octyl	 **3d**
5	CH_3		 **3e**
6	CH_3		 **3f**
7	CH_3		 **3g**

8	CH_3		 **3h**
9	CH_3		 **3i**
10	CH_3	$PhOCH_2$-	 **3j**
11	CH_3		 **3k**
12	H		 **3l**
13	H		 **3m**
14	H		 **3n**
15	H	Ph-	 **3o**
16	H		 **3p**

17	H		 **3q**

The targets 3(a-q) (Table 1) were synthesized using CuAAC method as shown above in Scheme 1, were obtained as solid in 88-90% yield. The titled compounds in IR spectrum exhibited a band in the region 3050 for aromatic C-H stretching, 1710-1720 for conjugated C=O stretching of lactone, 1240-1280 for C-O stretching. In the ^{1}H-NMR spectra, the compound exhibited a singlet at δ=7.8 ppm due to CH proton of triazole ring, two doublets each of 1H appeared at δ=7.6 and 6.3 due to olefinic hydrogens of unsubstituted coumarin ring (12-17). One olefinic hydrogen at C-3 of 4-methylcoumarin derivatives appeared at δ=6.16 ppm. Methyl group at C-4 gave signal at δ=2.3 ppm. Appearance of two triplets at around δ=4.8, 4.4 ppm confirmed the presence of two methylene groups in final compounds.

Antibacterial activity

All the synthesized compounds exhibited mediocre antibacterial activity against both Gram-positive, Gram-negative bacteria and the results are summarised in Table 2. Compounds 3a, 3k and 3p displayed best activity against all the Gram-positive and Gram-negative bacterial strains. Compounds 3b, 3i and 3k displayed good activity against all the bacterial strains tested. Compound 3c, 3e and 3i exhibited significant activity against *S. aureus*.

Table 2: Antibacterial activities of the targets 3

S. No.	Compound	Zone of inhibition (mm) tested at 0.5 mg/100 µl			
		P. aeruginosa	***S. aureus***	***K. pneumoniae***	***Escherichia coli***
1	3a	18	15	16	16
2	3b	12	14	14	12
3	3c	11	15	13	14
4	3e	11	15	12	13
5	3i	13	13	15	12
6	3k	13	14	13	17
7	3l	11	13	12	11
8	3m	12	11	12	13
9	3o	12	12	13	12
10	3p	16	15	14	15
11	3q	13	13	11	15
12	Pefloxacin	28	36	35	31

Anticancer activity

Most of the synthesized compounds were evaluated for *in vitro* cytotoxic properties. Some of the compounds 3e, 3g, 3k, 3l, 3o, 3p and 3q were tested for their cytotoxicity against two cancer cell lines, e.g., colon cancer cell line Colo-205 (Table 2) and lung cancer cell line HOP-62 were summarized (Table 3). 3p is good against lung cancer, 3g, 3i, 3p and 3q are good for colon cancer (Figure 1).

Table 2: Anticancer activities of compound against colon cancer

	Human colon cancer cell line (Colo-205)															
	%Control growth															
	Molar Drug concentrations															
	Experiment 1				**Experiment 2**				**Experiment 3**				**Average values**			
	10^{-7} M	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**
3e	63.0	56.2	78.5	63.9	74.6	83.8	71.9	55.5	79.5	56.2	66.3	55.2	72.4	65.4	72.2	58.2
3g	68.5	59.7	75.1	62.1	70.6	74.1	63.8	48.1	65.0	56.5	59.1	32.7	68.0	63.4	66.0	47.7
3k	69.8	68.7	76.2	77.4	79.9	76.4	73.7	59.9	62.0	47.9	59.1	44.1	70.6	64.3	69.7	60.5
3l	106.3	81.9	89.0	69.2	81.2	72.3	67.7	53.8	92.6	59.0	61.2	24.8	93.4	71.1	72.7	49.3
3o	78.5	68.4	68.8	52.8	78.9	67.6	62.0	53.2	80.8	52.5	60.2	64.1	79.4	62.8	63.7	56.7
3p	79.2	83.8	70.8	50.6	89.6	76.6	67.0	58.7	75.6	38.1	57.1	46.6	81.5	66.2	65.0	52.0
3q	86.0	80.7	74.8	47.5	76.9	75.6	73.7	50.9	82.5	68.5	73.3	54.4	81.8	74.9	73.9	50.9

Table 3: Anticancer activities of compound against lung cancer

	Human lung cancer cell line (HOP-205)															
	%Control growth															
	Molar drug concentrations															
	Experiment 1				**Experiment 2**				**Experiment 3**				**Average values**			
	10^{-7} M	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**	**10^{-4} M**
3e	97.6	100.7	87.1	59.5	95.3	91.9	86.7	67.8	96.9	96.9	87.3	71.4	96.6	96.5	87.1	66.2
3g	87.5	93.3	86.3	69.1	98.6	94.5	83.3	66.6	93.8	90.9	85.0	66.2	93.3	92.9	84.9	67.3
3k	96.8	105.9	92.0	53.3	103.6	101.4	89.6	61.9	99.6	99.1	88.3	76.8	100.0	102.1	90.0	64.0
3l	96.1	106.	01.3	81.4	106.7	101.8	98.7	83.8	107.8	95.9	95.2	86.4	103.5	101.2	98.4	83.9
3o	103.4	104.2	94.1	77.6	103.6	98.6	87.9	81.6	94.6	98.1	90.5	82.3	100.5	100.3	90.8	80.5
3p	103.0	100.2	88.6	54.0	107.0	99.3	88.0	48.2	95.5	99.4	83.6	48.6	101.8	99.6	86.7	50.3
3q	97.2	97.0	86.5	66.6	108.0	98.4	90.2	66.1	103.4	99.9	94.8	68.6	102.9	98.4	90.5	67.1

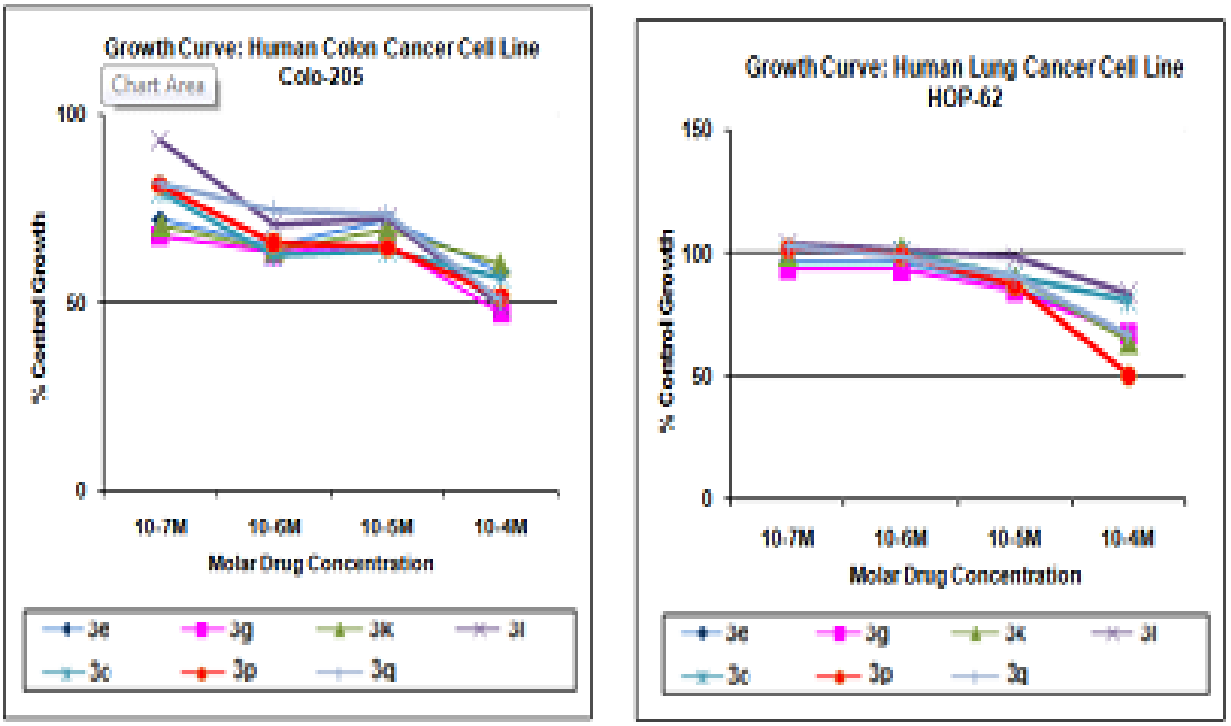


Figure 1: %Control growth curve of against two cancer cell lines

CONCLUSION

Substituted 7-(2-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2H-chromen-2-ones 3(a-q) were prepared by employing click reaction in excellent yields and are evaluated for antibacterial and anticancer activity against a panel of human cancer cell lines. Among the screened, compounds 3a, 3p demonstrated good activity. Product 3p has come out to be the best anti-bacterial as well as anti-cancer agent. Compound 3a is promising candidate for a broad spectrum antibacterial while 3c and 3e have the potential to be developed. Since 3g, 3i, 3p and 3q compounds showed activity against colon cancer, they can be considered good lead compounds for anticancer agents.

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