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Cu(I) Catalyzed Coumarin-1,2,3-Triazole Hybrids: Click Chemistry

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A series of novel coumarin-1,2,3-triazole derivatives were synthesized in good yield *via* click chemistry using Cu(I) catalyzed intermolecular Huisgen [3+2] cycloaddition reaction. All the synthesized compounds were characterized spectroscopically. This piece of work could be helpful to develop biologically relevant coumarin analogs.

Keywords: Coumarin, 1,2,3-Triazoles, Hybrid molecules, Click chemistry.

INTRODUCTION

Coumarin (benzopyran-2-one or chromen-2-one) ring system is imperative and exhibits interesting pharmacological properties and has intrigued chemists for decades to explore its synthetic analogs for their activities. Pharmacologically, it falls in the class of flavonoids [1] and has widespread biological activities, affecting many mammalian cell functions, including inhibition of mitochondrial enzyme systems [2]. They have a reputation for anti-inflammatory [3,4], antiallergic, antimicrobial [5], anticancer [6] and antihemorrhagic activities [7], novobiocin [8] and clorobiocin [9] are coumarin antibiotics of natural origin, which are known inhibitors of DNA gyrase and exhibit activity against Gram-positive bacteria, including methicillin-resistant strains of *Staphylococci* species [10,11].

Novobiocin has also been developed for anti-proliferative activity against various cancer cell lines [12]. Geiparvarin has been isolated from the leaves of *Geijera parviflora* Lindl [13] and exhibit potent *in vitro* cytostatic activity [14]. Warfarin exhibits anticoagulant activity and possess significant pharmacokinetic profile [15]. Phenprocoumon and substituted 4-hydroxy-2-pyrone derivatives are considered to be the first generation HIV-PR inhibitors [16]. Dicoumarol is another well-known molecule developed for the management of myocardial infarction.

Triazole is a five-membered heterocyclic compound with three nitrogen atoms at position 1, 2 and 3. The molecule is capable of binding with various enzymes and receptors *via* hydrogen bonds, diverse non-covalent interactions and thus shows potential biological activity such as anti-HIV [17,18], antimicrobial [19] and selective ω-3 adrenergic receptor agonist [20] activities. Triazoles are part of many biologically active natural product such as vancomycin [21], syn-TZ2PA6. Triazole is a rigid linking unit, which cannot be oxidized or reduced and cannot be easily cleaved hydrolytically. Examples of ligation of two different pharmacophores by 1,2,3-triazole ring are linezolid-macrolide [22] and vancomycin-cephalosporin [23] conjugates.

Coumarin 1,2,4 triazoles have displayed comparable or even better antibacterial and antifungal efficacy in comparison with reference drugs enoxacin, chloromycin and fluconazole [24]. Few coumarin-1,2,3-triazole derivatives have been recently reported to exhibit antimicrobial activity [25]. Owing to the importance of hybrid molecules, we tried to incorporate both coumarin and 1,2,3-triazole in one pharmacophore. To synthesize a hybrid molecule click chemistry is a powerful strategy, which relies mainly upon the construction of carbon-heteroatom bonds. The azide-alkyne Huisgen 1,3-dipolar cycloaddition reaction in the presence of Cu(I) catalyst leads to substituted 1,2,3-triazoles [26]. The reaction is one pot not affected by air and water, generates negligible inoffensive byproduct, tolerant to most of the functionality highly regioselective and "spring loaded" molecules [27].

The copper-catalyzed reaction is assumed to proceed in a stepwise manner starting with the generation of copper(I) acetylide (**D**) (Fig. 1). Density functional theory calculations

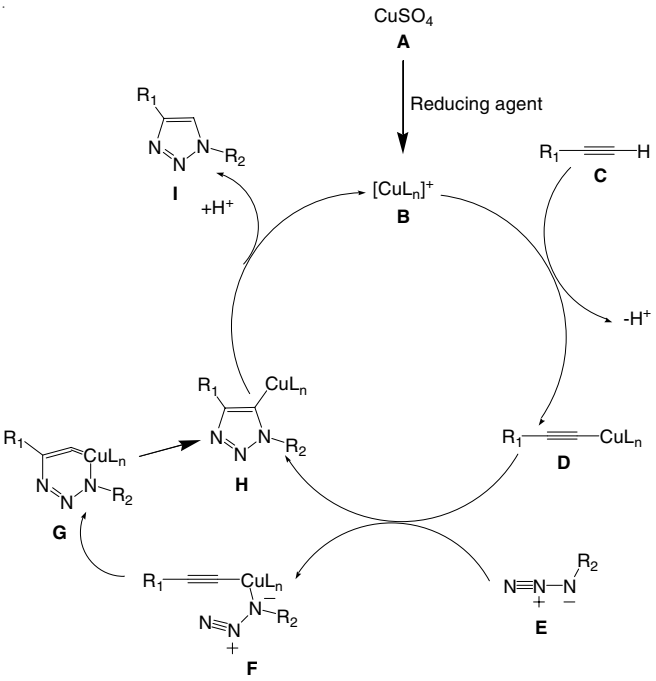


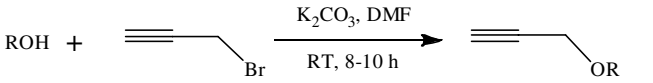
Fig. 1. Catalytic cycle for azide-alkyne coupling

show a preference for the stepwise addition (**D** → **F** → **G** → **H**) over the concerted cycloaddition (**G** → **H**) by approximately 12 to 15 kcal mol^{-1} leading to the intriguing six-membered metallocycle **G**. Further rearrangement takes place **G** → **H** → **I**, afforded triazole compound **I**.

EXPERIMENTAL

All the chemicals used in the synthesis were purchased from Sigma-Aldrich and used as such. Thin layer chromatography was used to monitor the progress of the reactions. All the compounds were purified over a silica gel column. Solvents were distilled before for purification. Melting points were determined on ERS automated melting point apparatus and are uncorrected. IR (Film) and IR (KBr) spectra were obtained using Perkin-Elmer FT-IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on Brucker Spectrospin spectrometer at 200 MHz for ^{1}H NMR and 50.32 MHz for ^{13}C NMR using TMS as an internal standard. The chemical shift values are recorded on the δ scale and the coupling constant (*J*) are in Hz. Mass spectral data were recorded on a Jeol (Japan) JMS-DX303 and micromass LCT, Mass spectrometer/ Data system.

General procedure for the synthesis of alkynes (6a-e): A solution of propargyl bromide (2 equiv.) in dry DMF was added dropwise to a stirred suspension of substituted phenol (1 equiv.) and anhydrous K_2CO_3 (6 equiv.) in dry DMF at room temperature for 8-10 h. The progress of the reaction was monitored by thin layer chromatography and after completion of the reaction; it was poured into ice-cold water (100 mL) and extracted with chloroform (3 × 60 mL). The combined organic layer was washed with water (5 × 100). The chloroform layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under reduced pressure. The crude product, thus obtained was purified over a silica gel column using EtOAc/hexane as eluent (**Scheme-I**).



5a, R = *o*-CHO-C_6H_4 **6 a,** R = *o*-CHO-C_6H_4
5b, R = *p*-CHO-C_6H_4 **6 b,** R = *p*-CHO-C_6H_4
5c, R = *o*-CH_3-Pyridine **6 c,** R = *o*-CH_3-Pyridine
5d, R = 2-Napthalene **6 d,** R = 2-Napthalene
5e, R = OTHP **6 e,** R = OTHP

Scheme-I: Synthesis of required alkynes (OTHP = oxy tetrahydropyran)

Procedure for the synthesis of 4-(bromo-alkoxy)chromen-2-one (8a-b): Solution of 4-hydroxy coumarin (**7**), (31 mmol) in 20 mL dry DMF was added dropwise (0.5 h) to a magnetically stirred suspension of 1,2-dibromoethane (111 mmol) and anhydrous K_2CO_3 (123 mmol) in dry 75 mL DMF at room temperature and progress of reaction was monitored by thin layer chromatography. Reaction took 2-3 h to complete and after completion, the reaction mixture was poured into ice-cold water and extracted with $CHCl_3$ (3 × 75 mL). Combined organic layer was washed with water (5 × 100 mL). The chloroform layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude product thus obtained was purified over silica gel column using EtOAc/hexane as an eluent to give compound (**8a-b**) in good yield.

4-(2-Bromo-ethoxy)chromen-2-one (8a): Yield: 85 %; white solid; m.p.: 148 ºC; IR (KBr, ν_{max}, cm^{-1}): 3042, 1722, 1610, 1564, 1495, 1453, 1410, 1369, 1328, 1275; ^{1}H NMR (200 MHz, $CDCl_3$): 3.70 (t, *J* = 6 Hz, 2H, CH_2CH_2Br), 4.39 (t, *J* = 6 Hz, 2H, OCH_2), 5.60 (s, 1H), 7.23-7.28 (m, 2H), 7.46-7.51 (m, 1H), 7.78-7.83 (m, 1H); ^{13}C NMR (50.32 MHz, $CDCl_3$): 27.75 (CH_2), 68.53 (CH_2), 90.90 (CH), 115.21 (Cquart), 116.69 (CH), 123.03 (CH), 123.99 (CH), 132.58 (CH), 153.23 (Cquart), 162.48 (Cquart), 164.83 (Cquart); HRMS calcd. for $C_{11}H_9O_3Br$: 269.0914, found: 269.1443 (M^+).

4-(3-Bromo-propoxy)chromen-2-one (8b): Yield: 75%; white solid; m.p.: 94 ºC; IR (KBr, ν_{max}, cm^{-1}): 3086, 1713, 1628, 1563, 1493, 1459, 1416, 1376, 1276, 1247; ^{1}H NMR (200 MHz, $CDCl_3$): 2.33-2.45 (m, 2H, $CH_2CH_2CH_2Br$), 3.56 (t, *J* = 6 Hz, 2H, CH_2CH_2Br), 4.23 (t, *J* = 6 Hz, 2H, OCH_2CH_2), 5.65 (s, 1H), 7.20-7.27 (m, 2H), 7.45-7.49 (m, 1H), 7.70-7.75 (m, 1H); ^{13}C NMR (50.32 MHz, $CDCl_3$): 28.88 (CH_2), 31.28 (CH_2), 66.65 (CH_2), 90.64 (CH), 115.37 (Cquart), 116.66 (CH), 122.72 (CH), 123.81 (CH), 132.37 (CH), 153.15 (Cquart), 162.60 (Cquart), 165.15 (Cquart); HRMS calcd. for $C_{12}H_{11}O_3Br$: 283.1179, found: 283.1256 (M^+).

Procedure for the synthesis of 4-(azido-alkoxy)chromen-2-one (9a-b): To a stirred solution of 4-(bromo-alkoxy)chromen-2-one (**8**) (5.50 mmol) in 20 mL dry DMF, NaN_3 (22.0 mmol) was added at 60 °C. Progress of the reaction was observed by a thin layer chromatography. The reaction, took 3 h to complete. After completion of reaction water (100 mL) was added to the reaction mixture. The crude product was extracted with $CHCl_3$ (3 × 50 mL) and combined organic layer was washed with water (3 × 50 mL). The chloroform layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude product (**9a-b**) thus obtained was purified over SiO_2 using EtOAc/hexane as eluent.

4-(2-Azido-ethoxy)chromen-2-one (9a): Yield: 90 %; white solid; m.p.: 175 ºC; IR (KBr, ν_{max}, cm^{-1}): 2946, 2125, 1741, 1610,

1417, 1371, 1238, 1146; ^{1}H NMR (60 MHz, $CDCl_3$): 3.90 (t, 2H, $CH_2CH_2N_3$), 4.45 (t, 2H, OCH_2), 5.80 (s, 1H), 7.40-7.60 (m, 2H), 7.70-7.90 (m, 1H), 8.01-8.15 (m, 1H); EI-MS (*m/z*): 231 (M^+).

4-(3-Azido-propoxy)chromen-2-one (9b): Yield: 87 %; white solid; m.p.: 142 ºC; IR (Film, ν_{max}, cm^{-1}): 3007, 2933, 2101, 1672, 1387, 1094; ^{1}H NMR (200 MHz, $CDCl_3$): 2.09-2.15 (m, 2H, $CH_2CH_2CH_2N_3$), 3.52 (t, *J* = 6 Hz, 2H, $CH_2CH_2N_3$), 4.16 (t, *J* = 6 Hz, 2H, OCH_2CH_2), 5.63 (s, 1H), 7.23-7.27 (m, 2H), 7.45-7.50 (m, 1H), 7.71-7.75 (m, 1H); ^{13}C NMR (50.32 MHz, $CDCl_3$): 27.86 (CH_2), 47.71 (CH_2), 65.87 (CH_2), 90.49 (CH), 115.31 (Cquart), 116.55 (CH), 122.67 (CH), 123.76 (CH), 132.3 (CH), 153.08 (Cquart), 162.50 (Cquart), 165.12 (Cquart); EI-MS (*m/z*): 245 (M^+).

General procedure for the synthesis of 1, 2, 3-triazole incorporated coumarin derivatives (10a-p): To a vigorously stirred solution of compound **9** (3.088 mmol) and respective alkyne (12.97 mmol) in 10 mL *tert*-butyl alcohol, solution of $CuSO_4 \cdot 5H_2O$ (0.67 mmol) and sodium ascorbate (1.23 mmol) in 10 mL distilled water, was added. The amount of *tert*-butyl alcohol and distilled water was kept 1:1. The deep yellow mixture was stirred vigorously at 45 ºC and the progress of reaction was monitored by thin layer chromatography. After 6 h, the reaction was completed and crude mixture was extracted with $CHCl_3$ and water. The organic layer was extracted with $CHCl_3$ (3 × 30 mL) and combined organic layer was dried over anhydrous Na_2SO_4. Excess of solvent was removed under vacuum. The crude reaction mixture was purified over SiO_2 column using MeOH:$CHCl_3$ as an eluent (**Scheme-II**).

2-{1-[2-(2-oxo-2*H*-chromen-4-yloxy)ethyl]-1*H*[1,2,3]-triazol-4-ylmethoxy}benzaldehyde (10a): IR (KBr, ν_{max}, cm^{-1}): 2916, 1727, 1684, 1624, 1565, 1456, 1421, 1380, 1278, 1241, 1186, 1156, 1113, 1042, 935, 896, 845, 753; ^{1}H NMR (300 MHz, DMSO-d_6): 4.62 (t, *J* = 6 Hz, 2H, NCH_2), 4.92 (t, *J* = 6 Hz, 2H, OCH_2), 5.36 (s, 2H, OCH_2), 5.96 (s, 1H, C*H*), 7.05-7.10 (m, 1H), 7.29-7.43 (m, 3H), 7.59-7.68 (m, 4H), 8.49 (s, 1H, C*H*), 10.31 (s, 1H, C*H*O); ^{13}C (75.5 MHz, DMSO-d_6): 48.48 (NCH_2), 62.21 (OCH_2), 67.80 (OCH_2), 91.07 (*C*H), 114.16 (*C*H), 114.87 (*C*H), 116.41 (*C*H), 121.11 (*C*H), 122.68 (*C*H), 124.13 (*C*H), 125.35 (*C*H), 127.61 (*C*H), 124.45 (Cquart), 132.82 (Cquart), 136.28 (Cquart), 142.51 (*C*H), 152.69 (Cquart), 160.32 (Cquart), 161.43 (Cquart), 164.20 (*C*O), 189.07 (*C*HO); HRMS calcd. for $C_{21}H_{17}N_3O_5$: 391.1168; found: 391.8978 (M+).

4-{1-[2-(2-Oxo-2*H*-chromen-4-yloxy)ethyl]-1*H*-[1,2,3]-triazol-4-ylmethoxy}benzaldehyde (10b): IR (KBr, ν_{max}, cm^{-1}): 3443, 2916, 1734, 1693, 1628, 1600, 1417, 1382, 1251, 1156, 1054, 986, 930, 866, 749; ^{1}H NMR (300 MHz, DMSO-d_6): 4.61 (t, *J* = 6 Hz, 2H, NCH_2), 4.92 (t, *J* = 6 Hz, 2H, OCH_2), 5.27 (s, 2H, OCH_2), 5.94 (s, 1H, C*H*), 7.17-7.38 (m, 4H), 7.60-7.83 (m, 4H), 8.44 (s, 1H), 9.82 (s, 1H, C*H*O). HRMS calcd. for $C_{21}H_{17}N_3O_5$: 391.1168; found: 391.2938 (M^+).

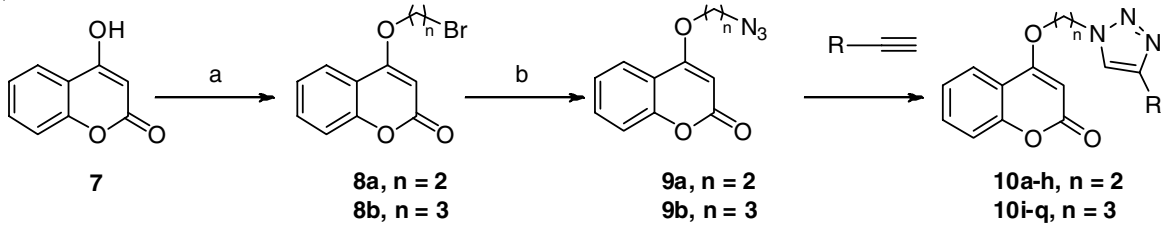
4-[2-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)ethoxy]-chromen-2-one (10c): IR (KBr, ν_{max}, cm^{-1}): 3395, 3085, 2881, 1695, 1622, 1564, 1420, 1382, 1248, 1142, 1052, 947, 851, 775; ^{1}H NMR (300 MHz, DMSO-d_6): 3.34 (brs, 1H, OH), 4.62 (t, *J* = 6 Hz, 2H, NCH_2), 4.90 (t, *J* = 6 Hz, 2H, OCH_2), 5.23 (d, *J* = 4 Hz, 2H, CH_2OH), 5.96 (s, 1H, C*H*), 7.32-7.38 (m, 2H), 7.64-7.71 (m, 2H), 8.74 (s, 1H, C*H*). Anal. calcd. (found) % for $C_{14}H_{13}N_3O_4$: C, 58.53 (58.17); H, 4.56 (4.43); N, 14.63 (14.25).

4-[2-(4-Phenyl-[1,2,3]triazol-1-yl)ethoxy]chromen-2-one (10d): IR (KBr, ν_{max}, cm^{-1}): 3085, 1729, 1625, 1566, 1421, 1380, 1244, 1184, 1110, 932, 843, 767; ^{1}H NMR (300 MHz, DMSO-d_6): 4.65 (t, *J* = 6 Hz, 2H, NCH_2), 4.94 (t, *J* = 6 Hz, 2H, OCH_2), 5.96 (s, 1H, C*H*), 7.30-7.44 (m, 5H), 7.58-7.82 (m, 4H), 8.74 (s, 1H, C*H*); Anal. calcd. (found) % for $C_{19}H_{15}N_3O_3$: C, 68.46 (68.26); H, 4.54 (4.34); N, 12.61 (12.71).

4-{2-[4-(Tetrahydropyran-2-yloxymethyl)-[1,2,3]-triazol-1-yl]ethoxy}chromen-2-one (10e): IR (KBr, ν_{max}, cm^{-1}): 2943, 2868, 1739, 1627, 1454, 1383, 1245, 1184, 1137, 1036, 935, 896, 771; ^{1}H NMR (300 MHz, DMSO-d_6): 1.41-1.62 (m, 6H), 3.73 (t, *J* = 3 Hz, 2H, OCH_2), 4.48-4.52 (m, 1H, OC*H*), 4.62-4.69 (m, 4H, 2 × OCH_2), 4.90 (s, 2H, NCH_2), 5.95 (s, 1H, C*H*), 7.34-7.39 (m, 2H), 7.62-7.73 (m, 2H), 8.28 (s, 1H, NC*H*); ^{13}C NMR (75.5 MHz, DMSO-d_6): 18.85 (CH_2), 24.90 (CH_2), 29.98 (CH_2), 48.31 (NCH_2), 59.42 (OCH_2), 61.18 (OCH_2), 67.81 (OCH_2), 91.06 (*C*H), 96.92 (O*C*H), 114.89 (*C*H), 116.39 (*C*H), 122.72 (*C*H), 124.10 (*C*H), 124.63 (*C*H), 132.81 (Cquart), 144.06 (Cquart), 152.70 (Cquart), 161.38 (Cquart), 164.20 (*C*O); Anal. calcd. (found) % for $C_{19}H_{21}N_3O_5$: C, 61.45 (61.35); H, 5.70 (5.69); N, 11.31 (11.54).

4-{2-[4-(6-Methyl-pyridin-3-yloxymethyl)-[1,2,3]-triazol-1-yl]ethoxy}chromen-2-one (10f): IR (KBr, ν_{max}, cm^{-1}): 3074, 1701, 1623, 1563, 1488, 1456, 1379, 1277, 1249, 1193, 1141, 1027, 945, 855, 826, 772, 755; ^{1}H NMR (300 MHz, DMSO-d_6): 2.35 (s, 3H, CH_3), 4.61-4.64 (m, 2H, NCH_2), 4.91-4.94 (t, *J* = 6 Hz, 2H, OCH_2), 5.19 (s, 2H, OCH_2), 5.95 (s, 1H, C*H*), 7.09-7.12 (m, 1H), 7.32 - 7.37 (m, 3H), 7.61-7.67 (m, 2H), 8.17 (s, 1H), 8.41 (s, 1H, NC*H*); HRMS calcd. for $C_{20}H_{18}N_4O_4$ 378.1328; found: 379.5938 (M^++H).

1-[3-(2-Oxo-2*H*-chromen-4-yloxy)-propyl]-1*H*-[1,2,3]-triazol-4-carboxylic acid ethyl ester (10g): IR (KBr, ν_{max}, cm^{-1}): 2927, 1726, 1625, 1566, 1421, 1384, 1275, 1246, 1176, 1142, 1030, 932, 844, 769; ^{1}H NMR (300 MHz, DMSO-d_6): 1.00 (t, *J* = 6 Hz, 3H, CH_2CH_3), 2.24 (m, 2H), 4.62 (t, *J* = 6 Hz, 2H, NCH_2), 4.91 (t, *J* = 6 Hz, 2H, OCH_2), 5.12 (m, 2H, OCH_2),



Scheme-II: (a) K_2CO_3,$Br(CH_2)_nBr$, DMF, 80 °C, 2-3 h (b) NaN_3, DMF, 60 °C, 3 h, 80 % (c) $CuSO_4$,$5H_2O$, Sodium ascorbate, *t*-butanol: H_2O (1:1), 45 °C, 6 h, 80-90 %

5.95 (s, 1H, C*H*), 7.32-7.39 (m, 2H), 7.62 - 7.72 (m, 2H), 8.32 (s, 1H, NC*H*); Anal. calcd. (found) % for $C_{17}H_{17}N_3O_5$: C, 59.47 (59.55); H, 4.99 (5.09); N, 12.24 (12.36).

4-{2-[4-(1-Hydroxy-cyclohexyl)-[1,2,3]triazol-1-yl]-ethoxy}chromen-2-one (10h): IR (KBr, ν_{max}, cm^{-1}): 3439, 2937, 2855, 1689, 1627, 1607, 1567, 1452, 1381, 1252, 1156, 948, 749; ^{1}H NMR (300 MHz, DMSO-d_6): 1.22-1.85 (m, 10H), 1.89 (brs, 1H, OH), 4.64 (t, J = 6 Hz, 2H, NCH_2), 4.88 (t, J = 6 Hz, 2H, OCH_2), 5.94 (s, 1H), 7.31-7.39 (m, 2H), 7.62-7.71 (m, 2H), 8.05 (s, 1H); HRMS calcd. for $C_{19}H_{21}N_3O_4$: 355.1532; found: 355.6414 (M^+).

4-[3-(4-Hydroxymethyl-{1,2,3}triazol-1-yl)propoxy]-chromen-2-one (10i): IR (KBr, ν_{max}, cm^{-1}): 3422, 2929, 1714, 1621, 1415, 1380, 1274, 1240, 1109, 1029, 820, 769; ^{1}H NMR (300 MHz, DMSO-d_6): 2.38-2.41 (m, 2H), 4.22 (m, 2H), 4.22 (t, 2H), 4.49-4.61 (s, 2H), 5.20 (brs, 1H), 5.87 (s, 1H), 7.33-7.77 (m, 4H), 8.06 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): 28.83 (*C*H_2), 46.42 (N*C*H_2), 55.08 (*C*H_2OH), 66.69 (O*C*H_2), 90.54 (*C*H), 115.07 (*C*H), 116.30 (*C*H), 123.01 (*C*H), 124.06 (Cquart), 132.69 (N*C*H), 152.68 (Cquart), 161.56 (Cquart), 164.74 (*C*O); Anal. calcd. (found) % for $C_{15}H_{15}N_3O_4$: C, 59.79 (59.97); H, 5.02 (5.16); N, 13.95 (13.41).

4-[3-(4-Phenyl-[1,2,3]triazol-1-yl)propoxy]chromen-2-one (10j): IR (KBr, ν_{max}, cm^{-1}): 3084, 2927, 1706, 1621, 1564, 1422, 1382, 1275, 1250, 1191, 1109, 1087, 939, 857, 764; ^{1}H NMR (300 MHz, DMSO-d_6): 2.45-2.48 (m, 2H, CH_2CH_2N), 4.29 (t, J = 6Hz, 2H, NCH_2), 4.66 (t, J = 6Hz, 2H, OCH_2), 5.89 (s, 1H), 7.18-7.46 (m, 4H), 7.59-7.83 (m, 5H), 8.67 (s, 1H, NC*H*); Anal. calcd. (found) % for $C_{20}H_{17}N_3O_3$: C, 69.15 (69.37); H, 4.93 (5.06); N, 12.10 (12.41).

4-{3-[4-(Tetrahydropyran-2-yloxymethyl)-[1,2,3]triazol-1-yl]propoxy}chromen-2-one (10k): IR (KBr, ν_{max}, cm^{-1}): 2942, 2868, 1711, 1624, 1565, 1462, 1417, 1381, 1244, 1188, 1137, 1026, 927, 856, 770, 751; ^{1}H NMR (300 MHz, DMSO-d_6): 1.44-1.62 (m, 6H), 2.40 (m, 2H, CH_2CH_2N), 3.43 (d, J = 3Hz, 2H, NCH_2), 3.76 (t, 2H, OCH_2), 4.24 (s, 2H, OCH_2), 4.47-4.67 (m, 3H, OCH_2, OC*H*), 5.86 (s, 1H, C*H*), 7.33-7.39 (m, 2H), 7.63-7.76 (m, 2H), 8.15 (s, 1H, NC*H*); HRMS calcd. for $C_{20}H_{23}N_3O_5$: 385.1638; found: 385.3630 (M^+).

1-[3-(2-Oxo-2*H*-chromen)-4-yloxypropyl]-1*H*-[1,2,3]-triazole-4-carboxylic acid ethyl ester (10l): IR (KBr, ν_{max}, cm^{-1}): 2926, 1736, 1714, 1623, 1563, 1461, 1421, 1382, 1272, 1241, 1177, 1136, 1106, 923, 845, 770; ^{1}H NMR (300 MHz, DMSO-d_6): 1.00 (t, 3H, CH_3), 2.26-2.33 (m, 2H, CH_2), 2.39 (d, J = 3 Hz, 2H, CH_2CH$_3$), 4.22 (t, J = 3 Hz, 2H, NCH_2), 4.60 (t, J = 3Hz, 2H, OCH_2), 5.09 (m, 2H, OCH_2), 5.88 (s, 1H, C*H*), 7.36-7.41 (m, 2H), 7.65-7.75 (m, 2H), 8.15 (s, 1H, C*H*); Anal. calcd. (found) % for $C_{18}H_{19}N_3O_5$: C, 60.50 (60.47); H, 5.36 (5.49); N, 11.76 (11.64).

4-{3-[4-(Napthalen-1-yloxymethyl)-[1,2,3]triazol-1-yl]-propoxy}chromen-2-one (10m): IR (KBr, ν_{max}, cm^{-1}): 2944, 1715, 1625, 1565, 1468, 1413, 1378, 1273, 1236, 1216, 1184, 1142, 1107, 1009, 922, 839, 815, 750; ^{1}H NMR (300 MHz, DMSO-d_6): 2.40 (m, 2H, NCH$_2$CH_2), 4.24 (t, J = 6 Hz, 2H, NCH_2), 4.64 (t, J = 6 Hz, 2H, OCH_2), 5.24 (s, 2H, OCH_2), 5.86 (s, 1H, C*H*), 7.32-7.45 (m, 4H, C_6H_4), 7.48-7.83 (m, 7H, $C_{10}H_7$), 8.36 (s, 1H, NC*H*); HRMS calcd. for $C_{25}H_{21}N_3O_4$: 427.1532; found: 428.7991 (M^++1).

4-{3-[4-(1-Hydroxy-cyclohexyl)-[1,2,3]triazol-1-yl]-propoxy}chromen-2-one (10 n): IR (KBr, ν_{max}, cm^{-1}): 2932, 2856, 1717, 1622, 1565, 1451, 1417, 1379, 1274, 1240, 1186, 1141, 1109, 1058, 929, 818, 751; ^{1}H NMR (300 MHz, DMSO-d_6): 1.23-1.83 (m, 10H), 2.40 (m, 2H, CH_2CH_2), 4.24 (t, J = 3 Hz, 2H, NCH_2), 4.57 (t, J = 3 Hz, 2H, OCH_2), 4.80 (brs, 1H, OH), 5.87 (s, 1H, CH), 7.36-7.40 (m, 2H), 7.64-7.82 (m, 2H), 7.95 (s, 1H, CH); HRMS calcd. for $C_{20}H_{23}N_3O_4$: 369.1689; found: 369.8452 (M^+).

4-{3-[4-(6-Methyl-pyridin-3-yloxymethyl)-[1,2,3]triazol-1-yl]propoxy}chromen-2-one (10o): IR (KBr, ν_{max}, cm^{-1}): 2928, 1718, 1622, 1567, 1493, 1381, 1272, 1239, 1185, 1141, 1109, 1029, 927, 821, 769; ^{1}H NMR (300 MHz, DMSO-d_6): 2.37 (s, 3H, CH_3), 2.39-2.45 (m, 2H, CH$_2$CH_2), 4.21-4.25 (t, J = 6 Hz, 2H, NCH_2), 4.61-4.65 (t, J = 6 Hz, 2H, OCH_2), 5.15 (s, 2H, OCH_2), 5.86 (s, 1H), 7.13-7.16 (m, 1H) 7.31-7.39 (m, 3H) 7.62 (m, 1H), 7.94 (s, 1H), 8.19 (s, 1H, CH), 8.32 (s, 1H, CH); HRMS calcd. for $C_{21}H_{20}N_4O_4$: 392.1485; found: 392.1991 (M^+).

4-[1-[3-(2-Oxo-2*H*-chromen-4-yloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethoxy}-benzaldehyde (10p): IR (KBr, ν_{max}, cm^{-1}): 2834, 1711, 1599, 1571, 1507, 1466, 1416, 1251, 1160, 1110, 992, 925, 867, 807, 774; ^{1}H NMR (300 MHz, DMSO-d_6): 2.40 (m, 2H, NCH$_2$CH_2), 4.20 (t, J = 6 Hz, 2H, NCH_2), 4.60 (t, J = 6 Hz, 2H, OCH_2), 5.21 (s, 2H, OCH_2), 5.82 (s, 1H, C*H*), 7.18-7.35 (m, 4H), 7.61-7.83 (m, 4H), 8.31 (s, 1H, NC*H*), 9.82 (s, 1H, C*H*O); HRMS calcd. for $C_{22}H_{19}N_3O_5$: 405.1325; found: 406.7173 (M^++H).

2-{1-[3-(2-Oxo-2*H*-chromen-4-yloxy)propyl]-1*H*-[1,2,3]-triazol-4-ylmethoxy}benzaldehyde (10q): IR (KBr, ν_{max}, cm^{-1}): 2926, 1730, 1689, 1628, 1600, 1488, 1458, 1387, 1291, 1250, 1191, 1107, 1053, 938, 847, 748; ^{1}H NMR (300 MHz, DMSO-d_6): 2.40 (m, 2H, CH_2), 4.22 (t, J = 6 Hz, 2H, OCH_2), 4.62 (t, J = 6 Hz, 2H, NCH_2), 5.30 (s, 2H, OCH_2), 5.84 (s, 1H, C*H*), 7.07-7.41 (m, 4H), 7.61-7.73 (m, 4H), 8.37 (s, 1H, C*H*), 10.28 (s, 1H, C*H*O); HRMS calcd. for $C_{22}H_{19}N_3O_5$: 405.1325; found: 406.6071 (M^++H).

RESULTS AND DISCUSSION

Huisgen [3+2] cycloaddition reaction occurs between a terminal alkyne and an azide to generate substituted 1,2,3-triazoles. Alkynes used in the reaction (**Scheme-II**) were prepared by treating various substituted phenols (**5a-e**) with propargyl bromide in the presence of anhydrous K_2CO_3 in dry DMF at 80 ºC for 8-10 h to yield substituted alkynes (**6a-e**) (**Scheme-I**).

The azide counterpart was synthesized by a sequence of reactions of 4-hydroxy coumarin with 1,2-dibromoethane and 1,3-dibromopropane in the presence of K_2CO_3 and dry DMF at room temperature. The corresponding 4-(2-bromo-ethoxy)- and 4-(3-bromo-propoxy)chromen-2-one on treating with sodium azide in DMF as a solvent at 60 ºC gave corresponding azide [28]. In the final click reaction, the substituted coumarins azide and above synthesized and commercially available alkynes were treated in the presence of sodium ascorbate, $CuSO_4 \cdot 5H_2O$, *t*-BuOH/H_2O (1:1) as solvent, leading to the formation of desired hybrid molecules (**10a-q**, Table-1), in good to excellent yield at 45 ºC (**Scheme-II**). All the synthesized compounds were purified over silica gel column and characterized spectroscopically.

TABLE-1
SYNTHESIZED 1,2,4-TRIAZOLE-COUMARIN DERIVATIVES WITH THEIR MELTING POINT AND YIELD

Compd.	n	R	m.p. (°C)	Yield (%)
10a	2	-$CH_2OC_6H_4CHO(o)$	178	72
10b	2	-$CH_2OC_6H_4CHO(p)$	218	68
10c	2	-CH_2OH	192	78
10d	2	-C_6H_5	158	70
10e	2	-CH_2OTHP	153-155	68
10f	2	-$CH_2OC_5H_3NCH_3(p)$	167	67
10g	2	-$CH_2OCOCH_2CH_3$	202	65
10h	2	-Cyclohexanol-1	200	69
10i	3	-CH_2OH	203	70
10j	3	-C_6H_5	161	75
10k	3	CH_2OTHP	125	68
10l	3	-$CH_2OCOCH_2CH_3$	147	68
10m	3	-$CH_2OC_{10}H_7$	168	67
10n	3	Cyclohexanol-1	178	66
10o	3	$CH_2OC_5H_3NCH_3(p)$	130	65
10p	3	-$CH_2OC_6H_4CHO(o)$	130	73
10q	3	-$C_6H_4CHO(p)$	180	75

Conclusion

In summary, a series of 17 novel 1,2,3-triazole coumarin derivatives were synthesized *via* effective alkyl-azide Cu(I) catalyzed classic click reaction. All the synthesized hybrid molecules are important biological precursors. One pot, water-mediated click reaction was found to be a useful tool for the regioselective synthesis of coumarin-triazole hybrid molecules. This simple three-step synthesis resulted in good to excellent yields of final products with high purity. The chemical structures of synthesized compounds were identified by ^{1}H NMR, IR, mass spectroscopy and elemental analysis.

CONFLICT OF INTEREST

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

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