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Cu(I)-catalyzed alkyne–azide 'click' cycloaddition (CuAAC): a clean, efficient, and mild synthesis of new 1,4-disubstituted 1*H*-1,2,3-triazole-linked 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile–crystal structure

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Abstract

Cu(I)-catalyzed alkyne–azide 'click' cycloaddition (CuAAC) is an important ''click chemistry'' reaction that is widely known in materials science, chemical biology, and pharmaceutical chemistry. The CuAAC reaction of terminal alkynes affords an efficient and mild production of triazolic 1,4-disubstituted compounds. In this work, a green and valuable method was introduced for the synthesis of the category of different new 1,4-disubstituted 1,2,3-triazole swapped with a 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-cyano moiety. These triazolic derivatives were produced by treatment of various 2-amino-6-(azidomethyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles with phenylacetylene in the presence of CuI as a catalyst with excellent yields (because CuAAC is selective to 1,4-disubstituted triazole derivatives) in a green solvent (ethanol/water). All structures were evaluated by ^{13}C, ^{1}H NMR, and FT-IR spectroscopy and a compound was analyzed by crystallography (X-ray) technique.

Keywords 4*H*-pyrans · 2-Amino-6-(azidomethyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile · Azide-alkyne 1,3-dipolar cycloaddition · Click reaction · Copper catalysis · 1,2,3-Triazoles · Dimeric form · Co-crystal

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Introduction

In the past decades, the synthesis of different heterocyclic structures owing to their wide applicability has been a subject of great interest. Heterocyclic compounds are necessary to life and found very widely in nature. 1,2,3-Triazoles, important five-membered nitrogen heterocycles, occupy a singular dwelling in heterocyclic chemistry. The triazole ring as a slice of the structure of many compounds has various biological, chemical and technical characteristics. The 1*H*-1,2,3-triazole derivatives category has displayed various industrial applications such as dyes, corrosion inhibitors, optical brighteners, and agrochemicals [1–7]. In addition, many of the 1,2,3-triazole compounds indicate a wide spectra of biological applications such as antifungal [8], anticancer [9], antibacterial [10], anti-HIV [11], antiallergic [12], antitubercular [13], hypotensive medications, pesticides, neuroleptics and anti-inflammatory [7, 14].

4*H*-pyrans heterocyclic scaffolds are one of the very interesting and biologically important structures that formed key motifs of the numerous natural compounds [15–24]. Among the many frameworks, 4*H*-pyrans and their derivatives are receiving great attention owing to their medicinal activities such as anticancer, analgesic, etc. [25–30]. Also, 4*H*-pyrans are convenient intermediates in the production of different compounds [31–33]. Furthermore, 4*H*-pyrans represent structure blocks of categories of natural compounds [34, 35]. In addition, a number of 2-amino-4*H*-pyrans exemplify a significant series of compounds. They are employed as photoactive materials [36], pigments [37], cosmetics and potential biodegradable agrochemicals [25, 36]. 2-Amino-4*H*-pyrans, in particular 2-amino-3-cyano-4*H*-pyrans, also possess noteworthy photochemical features [36] and have interested synthetic organic chemists as these show biological properties such as anticancer [38–46], antifungal, antibacterial [25, 43, 47, 48], antirheumatic [49], anti-oxidant, antimicrobial, fungicidal, antiviral, herbicidal, and antitumor [50–52]. These are key precursors for the preparation of compounds with medicinally activities such as imidoesters 1,4-dihydropyridines, pyridones, lactones, pyranopyrazoles, and aminopyrimidines [25, 53]. The most general and useful method used thus far for the synthesis of 1,2,3-triazoles relies on the Huisgen thermal 1,3-dipolar cycloaddition of azides with alkynes [54]. The disadvantages of this method include a high temperature requirement, the formation of two isomeric products (non-selectivity), and long reaction time. In recent decades, the copper (I)-catalyzed modification reaction introduction has allowed the 1,3-dipolar reaction to be carried out at low temperatures (RT, etc.) leading to the selecte formation of 1,4-disubstituted triazolic products with the shortest purification steps [55].

Recently, we have reported a new category of hybrid molecules of 1*H*-1,2,3-triazole coupled to kojic acid (KA) and which we have evaluated for antioxidant activity [56]. In the light of the above-mentioned facts, our research has been dedicated to the improvement of a new category of heterocyclic systems which incorporate the various pharmacophoric groups of biological relevance such as 1,2,3-triazole and 2-amino-3-cyano-4*H*-pyrans moieties into a single molecule,

with the hope that they may be biologically active and pave a way to drug discovery. Therefore, in this study, we present a clean, efficient, and safe method for the construction of new 1,2,3-triazole derivatives from various 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile with phenylacetylene in ethanol:water (2:1) as a green solvent.

Experimental

Materials

All utilized material was purchased from Fluka or Merck. Melting points were measured with an electrothermal digital melting point apparatus and were uncorrected. FT-IR spectra were measured on a NEXUS 670 FT-IR spectrometer in the region 4000–400 cm^{-1} by preparing KBr pills (Urmia University, Urmia, Iran). The ^{1}H and ^{13}C NMR spectra at 300 and 75 MHz on a Bruker 300 FT NMR (Urmia University) were recorded. TLC (silica gel-coated plates) was used to control all the reactions.

General procedure for the preparation of the variety of 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles

Various Knoevenagel adducts (1 mmol) and azido-KA (1 mmol) in ethanol (5 mL) were solved and, following the addition of ammonium chloride (30 mol%), were refluxed for 12–24 h. After the achievement of the reaction, the mixture was evaporated and the resultant precipitate was recrystallized from acetonitrile:methanol (1:1) for purification [57].

General procedure for the synthesis of variety 2-amino-4-(phenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4a–4m)

Copper (I) iodide (10 mol%) and phenylacetylene (2 mmol) were added to a stirred solution of azide (0.5 mmol) in ethanol:water (2:1) solvent (6.0 mL). The reaction mixture was then heated to 80 °C and monitored by TLC. After completion of the reaction, the mixture solvent was removed. The resulting crude product was purified by recrystallization from methanol:acetonitrile (1:1) to afford the desired substituted 1,2,3-triazole.

Spectral data

2-Amino-8-oxo-4-phenyl-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4a, $C_{24}H_{17}N_5O_3$)

Cream solid: yield 0.2 g (94%); m.p.: 205–207 °C; FT-IR (KBr): $\nu = 3369$, and 3309 (–NH_2), 3192, 3052, 2855, 2197 (–CN), 1645 (pyrone-CO), 1596, 1441, 1408, 1365,

1254, 1206, 1074, 1014, 856, 768 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.77$ (s, 1H, –CH-chiral), 5.53–5.70 (dd, 2H, –CH_2N–), 6.54 (s, 1H, pyrone-H) and 7.08 (m, 1H, H-Ph), 7.16 (m, 4H, NH_2, H-Ph), 7.26 (m, 2H, H-Ph), 7.33–7.38 (m, 1H, H-Ph), 7.44–7.49 (m, 2H, H-Ph), 7.78–7.80 (m, 2H, H-Ph), 8.40 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.2$ (C-chiral), 55.4 (–CH_2N–), 114.7, 115.8, 119.6, 121.2, 123.5, 124.6, 126.8, 127.1, 128.2, 128.5, 128.9, 129.2, 130.0, 130.8, 136.8, 140.4, 147.1, 150.1, 159.8, 160.7, 162.3, 169.8 (pyrone-CO) ppm.

2-Amino-4-(3-nitrophenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4b**, $C_{24}H_{16}N_6O_5$)

Brown solid: yield 0.24 g (98%); m.p.: 217–219 °C; FT-IR (KBr): $\nu = 3404$, and 3329 (–NH_2), 3149, 3071, 2859, 2195 (–CN), 1651 (pyrone-CO), 1591, 1528, 1437, 1347, 1219, 1077, 1011, 908, 764 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 5.08$ (s, 1H, –CH-chiral), 5.48–5.62 (dd, 2H, –CH_2N–), 6.58 (s, 1H, pyrone-H), 7.35–7.45 (m, 6H, NH_2, H-Ph), 7.62–7.64 (m, 1H, H-Ph), 7.68–7.71 (m, 2H, H-Ph), 7.82–7.85 (m, 1H, H-Ph), 8.04 (s, 1H, H-Ph), 8.30 (s, 1H, triazole-H) ppm; ^1H NMR (300 MHz, DMSO-d_6 + D_2O): $\delta = 5.01$ (s, 1H, –CH-chiral), 5.42–5.56 (dd, 2H, –CH_2N–), 6.56 (s, 1H, pyrone-H), 7.34–7.39 (m, 4H, NH_2, H-Ph), 7.53–7.61 (m, 3H, H-Ph), 7.71–7.73 (m, 1H, H-Ph), 7.93 (s, 1H, H-Ph), 8.19 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.1$ (C-chiral), 54.7 (–CH_2N–), 114.3, 116.7, 119.3, 120.9, 122.0, 123.3, 124.4, 126.6, 128.4, 130.6, 137.1, 142.5, 147.0, 148.2, 148.7, 148.79, 149.1, 159.8, 160.6, 162.4, 169.8 (pyrone-CO) ppm.

2-Amino-4-(2,4-dichlorophenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4c**, $C_{24}H_{15}Cl_2N_5O_3$)

Cream solid: yield 0.24 g (98%); m.p.: 248–250 °C; FT-IR (KBr): $\nu = 3377$, and 3320 (–NH_2), 3203, 3078, 3005, 2952, 2192 (–CN), 1640 (pyrone-CO), 1592, 1431, 1368, 1211, 1092, 1014, 865, 741 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 5.22$ (s, 1H, –CH-chiral), 5.51–5.63 (dd, 2H, –CH_2N–), 6.57 (s, 1H, pyrone-H), 7.26–7.38 (m, 6H, NH_2, H-Ph), 7.44–7.49 (m, 2H, H-Ph), 7.76–7.78 (m, 2H, H-Ph), 8.35 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.0$ (C-chiral), 54.4 (–CH_2N–), 114.1, 116.3, 119.1, 123.5, 124.4, 126.7, 127.4, 128.4, 129.4, 130.7, 131.6, 133.8, 136.4, 137.3, 146.9, 148.5, 159.8, 160.7, 163.1, 169.7 (pyrone-CO) ppm.

2-Amino-4-(4-nitrophenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4d**, $C_{24}H_{16}N_6O_5$)

Dark brown; yield 0.24 g (98%); m.p.: 185–187 °C; FT-IR (KBr): $\nu = 3458$, and 3285 (–NH_2), 3154, 3070, 2924, 2193 (–CN), 1668 (pyrone-CO), 1590, 1519, 1439, 1346, 1221, 1023, 861, 765 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 5.01$ (s, 1H, –CH-chiral), 5.50–5.62 (dd, 2H, –CH_2N–), 6.59 (s, 1H, pyrone-H), 7.35–7.45 (m, 7H, NH_2, H-Ph), 7.68–7.70 (m, 2H, H-Ph), 7.97–7.99 (m, 2H, H-Ph), 8.34 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 49.8$ (C-chiral), 54.6

(–CH_2N–), 114.3, 119.2, 123.0, 124.2, 125.3, 126.5, 127.5, 128.5, 129.4, 130.5, 131.7, 137.1, 138.8, 147.6, 148.6, 159.7, 160.7, 169.7 (pyrone-CO) ppm.

2-Amino-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-4-(3,4,5-trimethoxyphenyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4e**, $C_{27}H_{23}N_5O_6$)

Cream solid: yield 0.24 g (93%); m.p.: 108–110 °C; FT-IR (KBr): $\nu = 3120$ and 3098 (–NH_2), 2933, 2838, 2188 (–CN), 1649 (pyrone-CO), 1598, 1504, 1421, 1325, 1214, 1125, 1094, 1005, 847, 769 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.71$ (s, 3H, –OMe), 2.77 (s, 3H, –OMe), 3.48 (s, 2H, –CH_2N–) 3.67 (s, 3H, –OMe), 4.71 (s, 1H, –CH-chiral), 5.58 (s, 1H, pyrone-H), 6.51 (s, 2H, NH_2), 7.22 (s, 1H, H-Ph), 7.32–7.33 (m, 1H, H-Ph), 7.40–7.44 (m, 2H, H-Ph), 7.75–7.77 (m, 2H, H-Ph), 7.95–7.96 (m, 1H, H-Ph), 8.45 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.9$ (C-chiral), 52.3 (–OMe), 54.5 (–OMe), 55.6 (–CH_2N–), 114.1, 119.6, 120.9, 121.0, 123.4, 124.51, 124.58, 126.7, 128.2, 128.4, 129.4, 130.7, 136.1, 136.9, 137.4, 147.0, 149.8, 153.4, 159.7, 160.7, 169.8 (pyrone-CO) ppm.

2-Amino-4-(2-methoxyphenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4f**, $C_{25}H_{19}N_5O_4$)

Cream solid: yield 0.21 g (93%); m.p.: 180–182 °C; FT-IR (KBr): $\nu = 3143$, and 3045 (–NH_2), 2839, 2192 (–CN), 1643 (pyrone-CO), 1596, 1489, 1440, 1405, 1248, 1210, 1110, 1077, 1022, 861, 761 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.63$ (s, 3H, –OMe), 4.97 (s, 1H, –CH-chiral), 5.48–5.59 (dd, 2H, –CH_2N–), 6.49 (s, 1H, pyrone-H), 6.81–6.83 (m, 2H, H-Ph), 7.06–7.11 (m, 4H, NH_2, H-Ph), 7.35–7.37 (m, 1H, H-Ph), 7.43–7.47 (m, 2H, H-Ph), 7.73–7.75 (m, 2H, H-Ph), 8.30 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 36.2$ (–OMe), 50.2 (C-chiral), 55.3 (–CH_2N–), 113.4, 121.0, 123.2, 123.6, 124.6, 126.8, 127.5, 128.1, 128.5, 128.8, 128.9, 129.4, 130.4, 130.7, 137.3, 147.1, 150.6, 157.3, 160.0, 160.5, 169.7 (pyrone-CO) ppm.

2-Amino-4-(4-hydroxyphenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4g**, $C_{24}H_{17}N_5O_4$)

Yellow solid: yield 0.2 g (91%); m.p.: 237–239 °C; FT-IR (KBr): $\nu = 3404$ and 3301 (–NH_2, OH), 3203, 3186, 2925, 2855, 2195 (–CN), 1641 (pyrone-CO), 1598, 1511, 1444, 1413, 1356, 1271, 1206, 1103, 1034, 838, 761 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.63$ (s, 1H, –CH-chiral), 5.54–5.63 (m, 2H, –CH_2N_3), 6.47 (s, 1H, pyrone-H), 6.63–6.66 (m, 2H, H-Ph), 6.98–7.01 (m, 2H, H-Ph), 7.19 (s, 2H, NH_2), 7.35–7.37 (m, 1H, H-Ph), 7.44–7.49 (m, 2H, H-Ph), 7.80–7.82 (m, 2H, H-Ph), 8.44 (s, 1H, triazole-H) and 9.41 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.2$ (C-chiral), 55.9 (–CH_2N–), 114.8, 119.7, 121.2, 123.7, 124.6, 126.8, 128.3, 128.5, 130.2, 130.9, 136.5, 147.1, 150.7, 157.5, 159.7, 160.7, 169.8 (pyrone-CO) ppm.

2-Amino-4-(3-hydroxyphenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4h, $C_{24}H_{17}N_5O_4$)

Dark brown solid: yield 0.2 g (91%); m.p.: 176–178 °C; FT-IR (KBr): $\nu = 3379$, 3317 and 3196 (–NH_2, OH), 2963, 2852, 2199 (–CN), 1645 (pyrone-CO), 1596, 1443, 1410, 1361, 1260, 1211, 1078, 1011, 869, 763 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.65$ (s, 1H, –CH-chiral), 5.55–5.61 (m, 2H, –CH_2N–), 6.49 (s, 1H, pyrone-H), 6.54–6.62 (m, 3H, H-Ph), 6.93–6.99 (m, 1H, H-Ph), 7.25 (s, 2H, NH_2), 7.35–7.37 (m, 1H, H-Ph), 7.44–7.59 (m, 2H, H-Ph), 7.78–7.81 (m, 2H, H-Ph), 8.43 (s, 1H, triazole-H), 9.49 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.3$ (C-chiral), 55.7 (–CH_2N–), 114.6, 119.6, 121.1, 124.64, 124.67, 126.9, 128.4, 128.5, 130.4, 130.5, 130.7, 132.3, 136.8, 142.1, 147.2, 150.3, 158.2, 159.7, 160.8, 169.7 (pyrone-CO) ppm.

2-Amino-8-oxo-6-((4-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)methyl)-4-(p-tolyl)-4, 8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4i, $C_{25}H_{21}N_5O_3$)

Orange solid: yield 0.21 g (96%); m.p.: 214–216 °C; FT-IR (KBr): $\nu = 3372$, and 3325 (–NH_2), 3205, 3091, 2923, 2859, 2197 (–CN), 1651 (pyrone-CO), 1598, 1511, 1420, 1360, 1208, 1074, 1012, 823, 765 cm-1; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.98$ (s, 3H, –Me), 4.69 (s, 1H, –CH-chiral), 5.51–5.63 (m, 2H, –CH_2N–), 6.54 (s, 1H, pyrone-H), 6.912–6.914 (m, 2H, H-Ph), 6.93–6.99 (m, 2H, H-Ph), 7.22 (s, 2H, NH_2), 7.35–7.36 (m, 1H, H-Ph), 7.44–7.46 (m, 2H, H-Ph), 7.77–7.80 (m, 2H, H-Ph), 8.38 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.3$ (–Me), 50.5 (C-chiral), 55.4 (–CH_2N–), 115.0, 119.6, 123.4, 124.4, 124.5, 126.8, 128.3, 129.2, 130.1, 130.7, 136.5, 137.3, 147.0, 150.2, 159.7, 160.5, 169.7 (pyrone-CO) ppm.

2-Amino-4-(4-fluorophenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4j, $C_{24}H_{16}FN_5O_3$)

Yellow solid: yield 0.22 g (99%); m.p.: 187–189 °C; FT-IR (KBr): $\nu = 3302$, and 3189 (–NH_2), 3072, 3048, 2929, 2860, 2195 (–CN), 1663 (pyrone-CO), 1594, 1506, 1408, 1365, 1218, 1074, 1018, 838, 761 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.79$ (s, 1H, –CH-chiral), 5.52–5.62 (m, 2H, –CH_2N–), 6.53 (s, 1H, pyrone-H), 6.93–6.94 (m, 2H, –NH_2), 7.18–7.19 (m, 2H, H-Ph), 7.25 (s, 2H, NH_2), 7.34–7.36 (m, 1H, H-Ph), 7.42–7.44 (m, 2H, H-Ph), 7.76–7.78 (m, 2H, H-Ph), 8.38 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.2$ (C-chiral), 55.4 (–CH_2N–), 114.6, 119.5, 121.1, 123.5, 124.5, 126.7, 128.4, 128.5, 131.0, 133.4, 136.7, 139.1, 143.0, 147.1, 149.7, 159.7, 160.6, 169.7 (pyrone-CO) ppm.

2-Amino-4-(4-methoxyphenyl)-8-oxo-6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (4k, $C_{25}H_{19}N_5O_4$)

Cream solid: yield 0.21 g (93%); m.p.: 206–208 °C; FT-IR (KBr): $\nu = 3431$ (–NH_2), 3065, 2925, 2853, 2196 (–CN), 1647 (pyrone-CO), 1600, 1511, 1439, 1364, 1255,

1211, 1075, 1026, 835, 764 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.49$ (s, 3H, –OMe), 4.70 (s, 1H, –CH-chiral), 5.52–5.64 (s, 2H, $–CH_2N–$), 6.53 (s, 1H, pyrone-H), 6.69–6.71 (m, 2H, H-Ph), 7.05–7.08 (m, 2H, H-Ph), 7.22 (s, 2H, $–NH_2$), 7.35–7.37 (m, 1H, H-Ph), 7.44–7.48 (m, 2H, H-Ph), 7.80–7.82 (m, 2H, H-Ph), 8.43 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 35.4$ (–OMe), 50.2 (C-chiral), 55.5 ($–CH_2N–$), 115.6, 119.6, 121.1, 123.6, 124.5, 126.8, 128.3, 128.4, 130.2, 130.8, 132.3, 134.1, 136.5, 147.1, 150.3, 159.7, 160.5, 169.8 (pyrone-CO) ppm.

2-Amino-4-(4-chlorophenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4l**, $C_{24}H_{16}ClN_5O_3$)

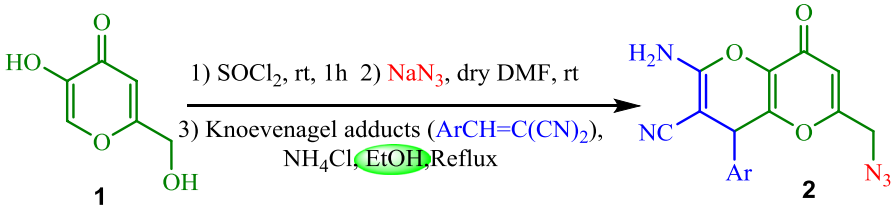
Cream solid: yield 0.22 g (96%); m.p.: 221–223 °C; FT-IR (KBr): $\nu = 3334$ and 3189 ($–NH_2$), 3089, 2926, 2856, 2195 (–CN), 1650 (pyrone-CO), 1597, 1487, 1413, 1360, 1212, 1081, 1015, 828, 765 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.81$ (s, 1H, –CH-chiral), 5.52–5.61 (m, 2H, $–CH_2N–$), 6.54 (s, 1H, pyrone-H), 7.19 (m, 4H, $–NH_2$, H-Ph), 7.29–7.37 (m, 3H, H-Ph), 7.43–7.48 (m, 2H, H-Ph), 7.78–7.80 (m, 2H, H-Ph), 8.42 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 35.4$ (–OMe), 51.1 (C-chiral), 55.0 ($–CH_2N–$), 114.4, 119.4, 121.1, 122.8, 124.5, 126.7, 127.1, 128.4, 129.0, 130.2, 130.8, 132.8, 136.8, 139.3, 149.5, 159.8, 160.6, 169.7 (pyrone-CO) ppm.

2-Amino-4-(2-chlorophenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (**4m**, $C_{24}H_{16}ClN_5O_3$)

Cream solid: yield 0.22 g (96%); m.p.: 142–146 °C; FT-IR (KBr): $\nu = 3362$ ($–NH_2$), 3182, 3067, 2191 (–CN), 1651 (pyrone-CO), 1593, 1440, 1366, 1263, 1214, 1077, 1018, 862, 764 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 5.21$ (s, 1H, –CH-chiral), 5.49–5.60 (m, 2H, $–CH_2N–$), 6.54 (s, 1H, pyrone-H), 7.04–7.09 (m, 1H, H-Ph), 7.17–7.28 (m, 5H, NH_2, H-Ph), 7.36–7.38 (m, 1H, H-Ph), 7.44–7.49 (m, 2H, H-Ph), 7.73–7.75 (m, 2H, H-Ph), 8.29 (s, 1H, triazole-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.1$ (C-chiral), 54.7 ($–CH_2N–$), 115.5, 119.2, 121.0, 123.4, 124.0, 126.8, 127.3, 128.4, 129.2, 130.1, 130.8, 131.1, 132.1, 137.3, 146.9, 149.1, 153.3, 159.8, 160.7, 169.7 (pyrone-CO) ppm.

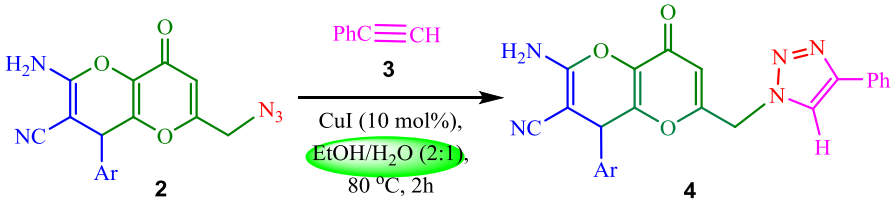
Results and discussion

In association with our attention to the synthesis of heterocyclic derivatives [56–58] and the wide-ranging uses of 2-amino-4*H* pyran-3-cyano and 1,2,3-triazoles as biologically active compounds, we became concerned in the synthesis of 2-amino-4-(phenyl)-8-oxo-6-((4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile from different 2-amino-6-(azidomethyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile with phenylacetylene. To pursue our objective, the reaction of KA (**1**) with $SOCl_2$ (thionyl chloride) at room temperature formed chloro kojic acid (2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one)



Ar = Ph (**a**), 3-NO_2-Ph (**b**), 2,4-di-Cl-Ph (**c**), 4-NO_2-Ph (**d**), 3,4,5-tri-MeO-Ph (**e**), 2-MeO-Ph (**f**), 4-OH-Ph (**g**), 3-OH-Ph (**h**), 4-Me-Ph (**i**), 4-F-Ph (**j**), 4-OMe-Ph (**k**), 4-Cl-Ph (**l**), 2-Cl-Ph (**m**)

Scheme 1 The reaction of azido-KA with Knoevenagel adduct to prepare 2 [57]



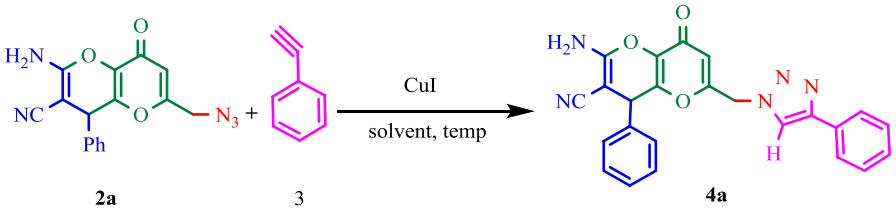
Ar = Ph (**a**), 3-NO_2-Ph (**b**), 2,4-di-Cl-Ph (**c**), 4-NO_2-Ph (**d**), 3,4,5-tri-MeO-Ph (**e**), 2-MeO-Ph (**f**), 4-OH-Ph (**g**), 3-OH-Ph (**h**), 4-Me-Ph (**i**), 4-F-Ph (**j**), 4-OMe-Ph (**k**), 4-Cl-Ph (**l**), 2-Cl-Ph (**m**)

Scheme 2 The regio-selective reaction of **2** with phenylacetylene **3** obtained **4**

[59], followed by 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one in the reaction with sodium azide (NaN_3) in dry DMF [60]. The reaction of azido-KA with Knoevenagel adducts afforded 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*] pyran-3-carbonitrile (**2**) (Scheme 1) [57]. Then, we subjected phenylacetylene (**3**) to reaction with **2** in the presence of copper iodide (Scheme 2). Continuing this work, the effect of temperature, mol% of CuI, and a screening of solvents in the synthesis of **4a** as representative was undertaken (Table 1).

The reaction was performed in various solvents such as H_2O, EtOH, MeOH, MeCN, acetone, and THF in the presence of 10 mol% of CuI under the reflux conditions for 24 h. However, this resulted in a trace amount of the wanted 1,4-disubstituted 1,2,3-triazole compound to be synthesized (**4a**) (Table 1, entries), such as THF, MeCN, MeOH, and acetone were screened at 60, 80, 60, and 50 °C, respectively. A good result was found in MeOH/H_2O, THF/H_2O, and acetone/H_2O (2:1) media (Table 1, entries 11–14). Finally, this reaction was conducted in the presence of different amounts of CuI as a catalyst and at various temperatures (RT and 80 °C) in a green solvent [EtOH/H_2O (2:1)]. The best

Table 1 The effect of several factors (mol% of catalysts, temperatures, and various solvents) on the synthesis of **4a**



2a 3 **4a**

Entry[a]	Cat. (%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	10	H_2O	Reflux	24	Trace
2	10	EtOH	Reflux	24	Trace
3	10	MeOH	Reflux	24	Trace
4	10	CH_3CN	Reflux	24	Trace
5	10	Acetone	Reflux	24	Trace
6	10	THF	Reflux	24	Trace
7	10	EG	100	24	60
8	10	DMF	100	24	40
9	10	1,4-dioxane	100	24	20
10	10	DMSO	100	24	70
11	10	CH_3CN/H_2O	80	24	Trace
12	**10**	**Acetone/H_2O**	**50**	**6**	**94**
13	**10**	**THF/H_2O**	**60**	**4**	**96**
14	**10**	**MeOH/H_2O**	**60**	**3**	**95**
15	10	EtOH/H_2O	rt	24	40
16	5	EtOH/H_2O	80	2	96
17	**10**	**EtOH/H_2O**	**80**	**2**	**98**
18	15	EtOH/H_2O	80	2	95

Bold indicates the best results

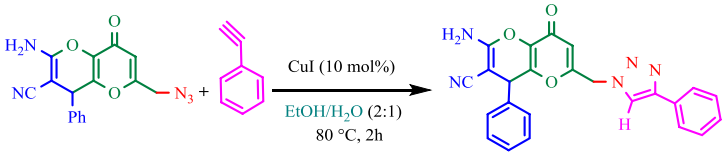
[a]Reaction conditions: azide (0.5 mmol), phenylacetylene (2.0 mmol)

[b]Isolated yields

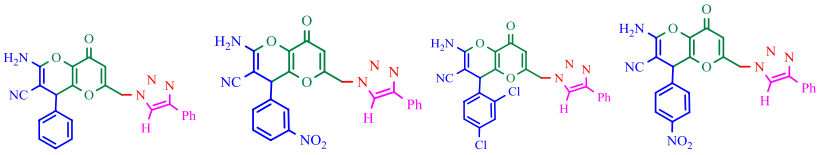
results were obtained with 2-amino-6-(azidomethyl)-4,8-dihydropyrano[3,2-*b*] pyran-3-carbonitrile (0.5 mmol) and phenylacetylene (2.0 mmol) in the presence of CuI (10 mol%) and EtOH/H_2O (2:1) (6 mL) as clean solvents at 80 °C (Table 1, entries 15–18).

After obtaining reaction optimal conditions, various azides and phenylacetylene were utilized for evaluation of the scope of the reaction. For this purpose, we first examined the reaction with different azides and the results are given in Table 2, in which it is shown that in general a wide range of azides could react

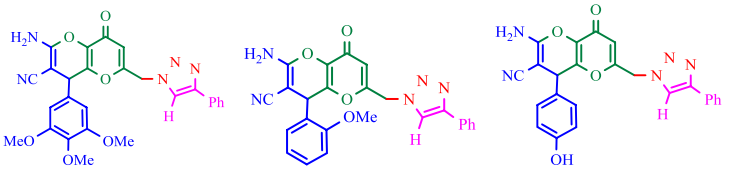
Table 2 Scope of the reaction with a variety of azides and phenylacetylene



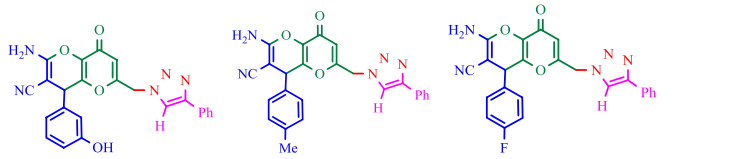
2a-m **3** **4a-m**



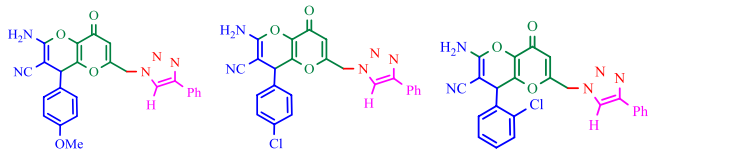
4a (94%) **4b (98%)** **4c (98%)** **4d (98%)**



4e (93%) **4f (93%)** **4g (91%)**



4h (91%) **4i (96%)** **4j (99%)**



4k (93%) **4l (96%)** **4m (96%)**

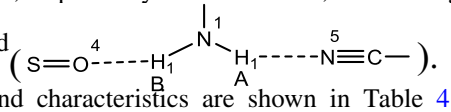
smoothly with phenylacetylene and gives compounds **4a**–**m** in good to excellent yields.

X-ray diffraction analysis of 4j

To determine the crystal structure, single-crystal of compound **4j** was measured by a Rigaku R-AXIS RAPID-S diffractometer (a four-circle instrument equipped with a two-dimensional area IP detector) for data collection. Also, the oscillation scans technique with $\Delta w = 5°$ and graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) for one image were utilized. The lattice parameters were determined

by the least-squares procedure based on all reflections with $F^2 > 2\sigma(F^2)$. Correction for polarization and Lorentz effects, cell refinement, and integration of the intensities that had been received outdoors was by way of Crystal Clear software (Rigaku/MSC, 2005) [61]. The frameworks were solved using direct methods by SHELXS-97 [62], which allowed a place for most of the heaviest atoms, with the rem residual non-hydrogen atoms being located from various Fourier-calculated maps from consecutive perfect-matrix least-squares refinement circles on F^2 by SHELXL-97 [62]. All atoms except hydrogen were refined by anisotropic replacement parameters. The location of hydrogen bonded to carbon was determined at their geometric place in SHELXL by suitable HFIX instructions.

The end difference Fourier maps displayed no peaks regarding chemical importance. Crystal data for **4j** were: $C_{24}H_{16}FN_5O_3$, C_2H_6OS, crystal system, space group: triclinic, P-1; (no:2); unit cell dimensions: $a = 10.0128$ (12), $b = 11.5310$ (11), $c = 11.5802$ (14) Å, $\alpha = 98.943$ (5), $\beta = 94.587$ (6), $\gamma = 103.174$ (5)º; volume: 1276.7 (3) Å^3; $Z = 2$; calculated density: 1.352 g/cm^3; absorption coefficient: 0.176 mm^{-1}; $F(000) = 540$; θ-range for data collection 2.2–26.6º; refinement method: full matrix least-square on F^2; data/parameters: 3214/336; goodness-of-fit on F^2: 1.199; final R-indices $[I > 2\sigma(I)]$: $R_1 = 0.085$, $wR_2 = 0.191$; largest diff. peak and hole: 0.741 and −0.605 e Å^{-3} (See supporting information and crystal structure data section for more information). Crystallographic data for the structure of **4j** presented in this study have been preserved with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-1858846. Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; FAX: (+44) 1223 336033, or online via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk.

X-ray analysis of the molecule 2-amino-4-(4-fluorophenyl)-8-oxo-6-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile dimethyl sulfoxide solvate (**4j**.DMSO) were performed to confirm the structure. The crystal structure of the molecule with the atom labeling is shown in Fig. 1a, and dimeric *H*-bonding geometry is indicated in Fig. 1b. Compound **4j** was crystallized with two molecules in the unit cell ($Z = 2$). In the triclinic P-1 space group, the structure contains an asymmetric carbon atom (C4) and has a (*S*) configuration stereogenic center. The crystal structure indicated that the molecule of **4j** formed a dimeric form with two intermolecular hydrogen bonds ($d_{N1}\cdots_{N5} = 3.059$ Å, $d_{N5}\cdots_{H1H} = 2.222$ Å) and a 12-membered centrosymmetric C_i form. One of the interesting phenomena is the sticking of a dimethyl sulfoxide molecule to the **4j** with an intermolecular hydrogen bond between the O4 atom of dimethyl sulfoxide with the amino group ($d_{N1}\cdots_{O4} = 2.927$ Å, $d_{H1B}\cdots_{O4} = 2.136$ Å). The selected bond length, angles and torsion angles for **4j** are shown in Table 3. The two hydrogen atoms of the amino group (H1A and H1B) displayed intermolecular H-bonds with N5 of the nitrile and O4 of the sulfoxide groups, respectively. In other words, the amino group showed a di-hydrogen bridge H-bond  .

All intermolecular hydrogen bond characteristics are shown in Table 4. The fluorine atom on the phenyl ring does not interfere with the formation of the

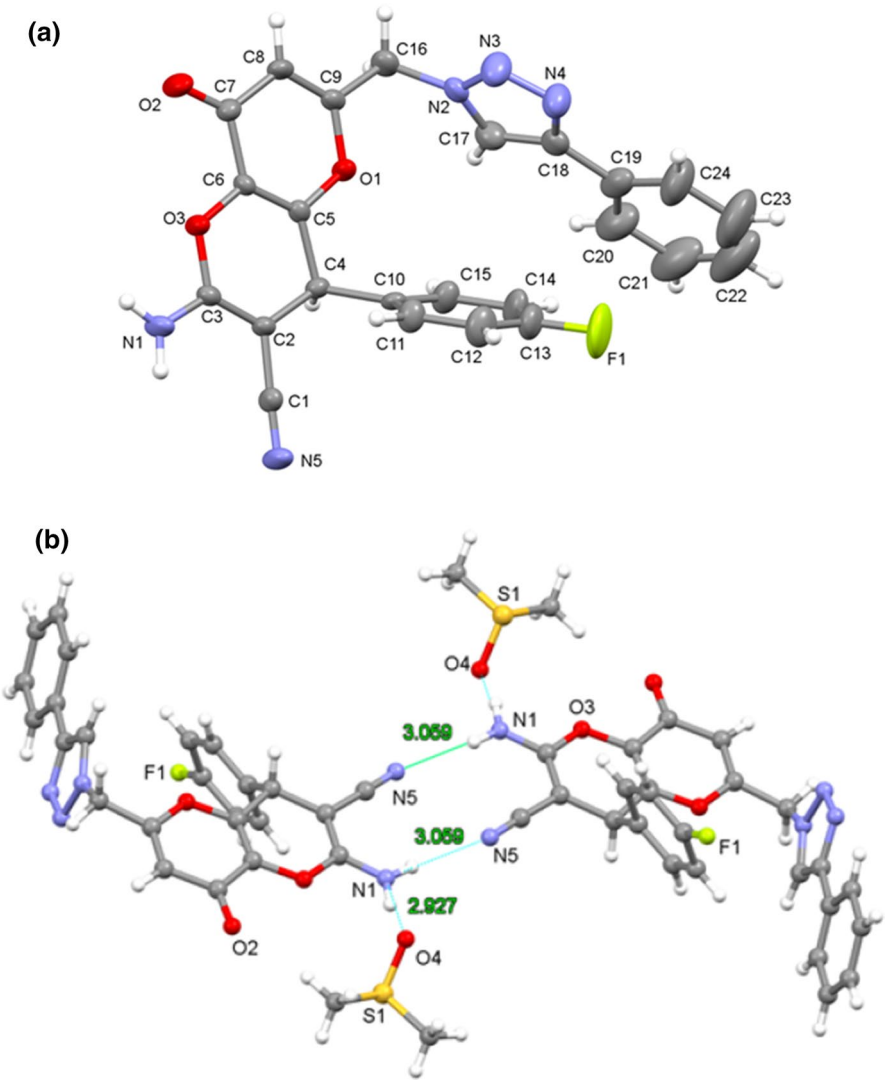


Fig. 1 **a** Molecular structure of the molecule **4j**. Thermal *ellipsoids* are drawn at the 40% probability level. **b** Dimeric structure with the H-bonding geometry. Hydrogen bonds are drawn as *dashed lines*

intermolecular hydrogen bond. The fused pyrano[3,2-*b*]pyran-4(8*H*)-one ring has a planar form. Also, two aromatic rings of triazole and phenyl that are linked together by a covalent bond have a nearly planar form (Table 3, entries 11 and 13, respectively).

Representatively, the FT-IR spectrum of **4b** displayed broad peaks at the frequencies of 3404 and 3329 cm^{-1} corresponded to the NH_2 functional group, and a sharp peak at 2195 cm^{-1} corresponded to the nitrile group. A sharp peak at 1651 cm^{-1} is assigned to the pyrone carbonyl group. The ^1H NMR spectrum of this compound

Table 3 Selected bond length (*d,* Å), bond angles (*θ,* °) and torsion angles (*φ,* °) for **4j**

Entry	Atom	*d* (Å), *θ* (°), *φ* (°)	Entry	Atom	*d* (Å), *θ* (°), *φ* (°)
1	N2–N3	1.337(3)	8	O4–S1–C25	106.5 (5)
2	N3–N4	1.310(3)	9	O4–S1–C26	109.2 (4)
3	C18–N4	1.347(3)	10	C26–S1–C25	98.2 (5)
4	C1–N5	1.134(3)	11	O3–C6–C7–C8	178.9 (4)
5	C7–O2	1.222(3)	12	N4–C18–C19–C20	−176.4 (7)
6	O1–C9	1.357(3)	13	C11–C10–C4–C2	−29.8 (7)
7	F1–C13	1.363(3)	14	O1–C9–C16–N2	−42.5 (7)

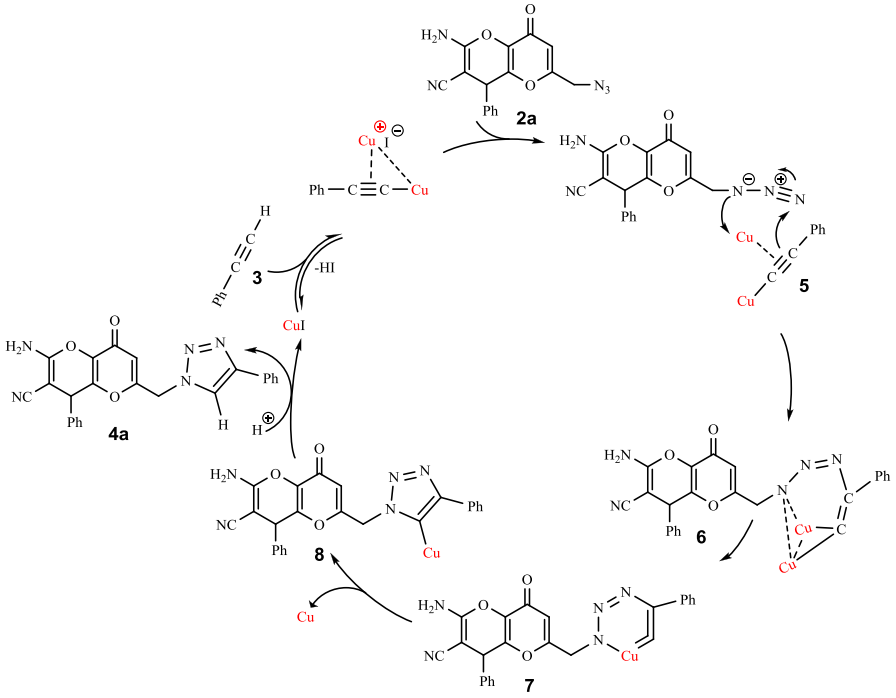
Table 4 Hydrogen bond geometry (Å, °) for **4j**

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N1–H1*A*···N5^{i}	0.86	2.222	3.058 (6)	164
N1–H1*B*···O4^{ii}	0.86	2.136	2.927	153
N1–H1*B*···S1^{iii}	0.86	2.888	3.736 (5)	169
C16–H16*A*···N5^{iv}	0.97	2.698	3.333 (8)	123
C16–H16*B*···N3^{v}	0.97	2.561	3.389 (8)	144

Symmetry codes: (v) $-x+2, -y+1, -z+1$; (iv) $x+1, y, z$; (iii) $x, y-1, z$; (ii) $x, y+1, z$; (i) $-x, -y, -z+1$

indicated a singlet at $\delta = 5.08$ ppm corresponding to a benzylic methine proton in the chiral center. The doublet of doublet peaks at $\delta = 5.48$–5.62 ppm are assigned to diastereotopic methylene protons connected to the azide substituent. The peak of amino protons is overlapped in the aromatic peaks region which was confirmed by the ^{1}H NMR spectrum of **4b** in D_2O examination. The singlet peak at $\delta = 8.30$ ppm is connected to the proton on the carbon atom of the 1,2,3-triazole ring. Other proton peaks had good agreement with the assigned structure. The ^{13}C NMR spectrum of **4b** showed 23 distinct peaks that confirmed the proposed structure. Two peaks at $\delta = 54.763$ and 50.198 ppm corresponded to methylene and methine carbon atoms, respectively. The peak at $\delta = 169.822$ ppm connected to cthe arbonyl carbon atom. (See "Experimental" and supporting information). Representatively, a possible mechanism for the production of **4a** is shown in (Scheme 3).

The reaction of phenylacetylene **3** with the CuI catalyst forms Cu (I)-acetylide (**5**) that coordinates with the azide (**2a**) to obtain a dicuprate complex (**6**). Then, the C–N bond is formed between the end nitrogen of the coordinated azide and the *β*-carbon of Cu (I)-acetylide generating intermediate **7**, followed by reductive elimination from **7** leading to the 5-cuprated triazolic intermediate **8**. Eventually, the final product (**4a**) is obtained with protonolysis and reforms the Cu (I) catalyst [63–65].



Scheme 3 A plausible mechanism for the reaction of Cu-catalyzed 2-amino-6-(azidomethyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile **2a** cycloaddition with phenylacetylene **3**

Conclusions

In the current research, we have successfully developed a clean, mild, and efficient process for the synthesis of a different array of 1,4-disubstituted 1,2,3-triazole-linked 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles by the use of different azides with phenylacetylene in the presence of the catalytic amount of CuI in excellent yields.

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