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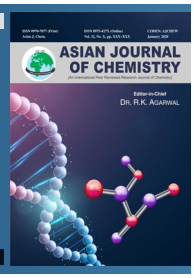

An Efficient and Facile Synthesis of Novel Triazole C-N Linked Chromone Hybrids

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A series of new C_3-N_1 directly linked chromone/1,2,3-triazole molecular hybrids synthesized by adopting low cost effective CuI catalyzed azide-alkyne 1,3-dipolar cycloaddition (Cu-AAC triazole annulation) from chromone-3-aldehyde *via* key intermediates 3-azidochromone, synthesized from another intermediate 3-hydroxychromone. These synthetic 1,2,3-triazole embedded chromones are the new addition to the click chemistry family. The structures of final products established by IR, NMR and mass spectral analysis.

Keywords: 3-Hydroxychromone, 3-Azido-chromone, Aryl/alkyl acetylenes, Click cycloaddition, Chromone, 1,2,3-Triazole.

INTRODUCTION

The chromone frame work is the core moiety in numerous flavonoid secondary metabolites such as flavones, flavonols and isoflavones [1]. Natural and synthetic compounds having chromone scaffold shows multiple biological activities, like antitumor [1], anti-hepatotoxic, antioxidant [2], anti-inflammatory [3], anti-spasmolytic, estrogenic [4] and antibacterial activities [5]. In addition 1,2,3-triazoles attracted attention in bioconjugation, medicinal chemistry, chemical biology, organic synthesis and material science [6-8], Furthermore, 1,2,3-triazoles are widely used as building block for many complex chemical compounds, such as pharmaceutical drugs like tazobactam [9].

These medicinal applications of chromone and 1,2,3-triazole pharmacophores have stimulated an organic chemist for the continuous synthesis of new chromones and their heterocyclic hybrid derivatives to evaluate biological activity. Novel hybrid heterocyclics containing two or more bioactive scaffolds are expected to possess higher biological activities than parent skeleton [10,11].

A CuI catalyzed azide-alkyne 1,3-dipolar cycloaddition click reaction is the powerful tool for the generation of regioselective 1,4 disubstituted 1,2,3-triazoles and are highly tolerant and flexible to several organic functions. In continuation of our efforts on structural modification of chromones and 1,2,3-triazole core to improve their pharmacological activity [12-14], we have designed and synthesized new C_3-N_1 directly linked chromone/1,2,3-triazole hybrid templates, adopting CuI-catalyzed click chemistry. To the best of our knowledge there is no report on *N*-heterocyclic directly linked to chromone scaffold.

EXPERIMENTAL

All chemicals and reagents were purchased from commercial source and used as such without further purification. Melting points were measured on the open capillary method and are uncorrected. IR spectra were recorded on Shimadzu-8400 FTIR spectrophotometer. ^{1}H & ^{13}C NMR spectra were measured on a Bruker Avance II 400 spectrometer, operating at 400 and 100 MHz, respectively. Molecular weights were determined with ESI Mass spectra. Reactions were monitored by thin layer chromatography (TLC) on silica gel; plates were visualized with ultraviolet light or iodine. Column chromatography was performed on silica gel 60 (0.043-0.06 mm) Merck.

Synthesis: Chromone-3-aldehyde (**2a**) and 3-hydroxychromone (**3a**) were synthesized according to the literature procedure described elsewhere [15,16].

Synthesis of 4-oxo-4*H*-chromen-3-yl trifluoromethane sulfonate (4a): To a solution of 3-hydroxychromone (**3a**) (10 mmol) in dry DCM (10 mL) triethyl amine (2.2 mmol) was added in portions under the atmosphere of N_2 maintaining at 0 ºC. After stirring the mixture at this temperature for 15 min, triflic anhydride (2 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. After completion of reaction quenched with water and extraction with DCM. The combined organic layers were washed with water and dried over conc. Na_2SO_4 under reduced pressure. The crude product

was purified by column chromatography giving the desired product 4-oxo-4*H*-chromen-3-yltrifluoromethane sulfonate (**4a**) 70-75% yield [17].

Synthesis of 3-azido-4*H*-chromen-4-one (5a): To a stirred solution of 3-((trifluoromethyl)sulfonyl)-4*H*-chromen-4-one (**4a**) (1mmol), DMF (10mL) sodium azide (1.2 mmol) was added. The reaction mixture was refluxed at 90 ºC for 3 h. After the starting materials were consumed as judged by TLC analysis, the reaction mixture was poured in to ice cold water; obtained precipitate was filtered and purified by column chromatography using ethyl acetate/pet ether (2:8) to afford 3-azido-4*H*-chromen-4-one (**5a**) in good yield. Light brown coloured solid; Yield 60%; m.f.: $C_9H_5N_3O_2$; m.p.:186-188 ºC; IR (KBr, ν_{max}, cm^{-1}): 1726 (C=O), 2123 (N=N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.42 (t, 1H, *J* = 7.5Hz, Ar-H), 7.51 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.70 (t, 1H, *J* = 7.8 Hz, Ar-H), 8.02 (s, 1H Ar-H), 8.27 (d, 1H, *J* = 8.0 Hz, Ar-H); ESI-MS: 188 $[M+H]^+$.

Synthesis of 3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-on (6a-f): To a stirred solution of 3-azido-4*H*-chromen-4-one **(5a)** (1.0 mmol) and aryl acetylenes (1.5 mmol) in DMF (8 mL) was added a saturated CuI catalyst (0.02 mmol). The reaction mixture was refluxed at 90 ºC for 2h. The completion of reaction examined by TLC. The reaction mixture poured into ice cold water and extracted with ethyl acetate. The organic layer separated and dried with Na_2SO_4 and concentrated under reduced pressure. The products purified by column chromatography to afford pure compounds (**6a-f**) (**Scheme-I**).

3-(4-(*p*-Tolyl)-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6a): Light brown colour solid; yield 80%; m.f.: $C_{18}H_{13}N_3O_2$; m.p.: 218-220 ºC. IR (KBr, ν_{max}, cm^{-1}): 1734 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.41 (s, 3H, CH_3), 7.28 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.55 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.63 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.81 (t, 3H, *J* = 7.4 Hz, Ar-H), 8.38 (d,1H, *J* = 7.8 Hz, Ar-H), 8.82 (s, 1H, triazole-H), 8.95 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.37, 114.00, 118.58, 120.90, 124.13, 125.82, 126.25, 126.42, 127.45, 128.84, 129.61, 130.94, 134.75, 138.25, 148.09, 150.31, 155.78, 170.72; ESI- MS: 304 $[M+H]^+$.

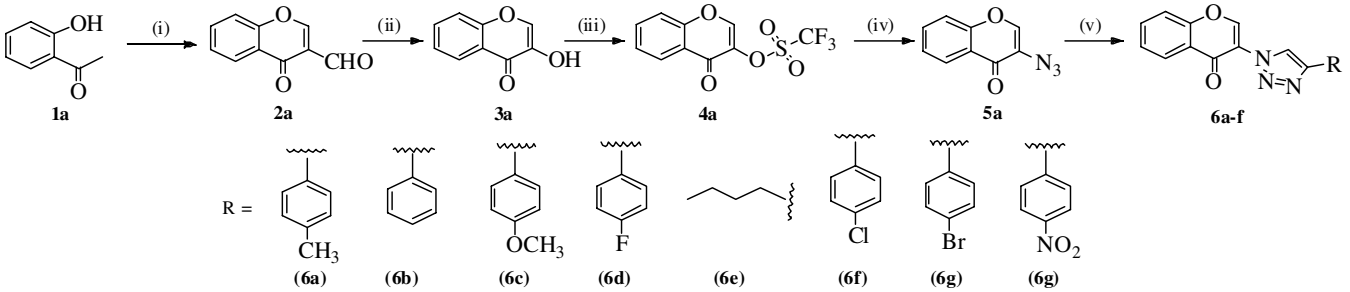
3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6b): White colour solid; yield 70%; m.f.: $C_{17}H_{11}N_3O_2$; m.p.: 226-228 ºC; 1730 (C=O), IR (KBr, ν_{max}, cm^{-1}): ^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.47 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.56 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.64 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.82 (t, 1H, *J* = 7.1 Hz, Ar-H), 7.94 (d, 2H, *J* = 7.3 Hz, Ar-H), 8.38 (d, 1H, *J* = 6.9 Hz, Ar-H), 8.87 (s, 1H, triazole-H), 8.96 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$): 114.12, 118.60, 120.92, 122.75, 125.84, 126.24, 126.47, 127.54, 129.71, 130.92, 132.54, 134.75, 138.25, 148.09, 150.31, 155.88, 170.74; ESI-MS: 290 $[M+H]^+$.

3-(4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6c): Light brown colour solid; yield 80%; m.f.: $C_{18}H_{13}N_3O_3$; m.p.: 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 1728 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.87 (s, 3H, OCH_3), 7.00 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.55 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.63 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.80 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.86 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.41-8.35 (m, 1H, Ar-H), 8.77 (s, 1H, triazole-H), 8.94 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 57.25, 114.10, 116.76, 118.58, 122.74, 123.90, 124.73, 127.82, 128.25, 129.65, 131.61, 130.94, 136.95, 143.25, 148.29, 150.31, 156.78, 161.25, 170.72; ESI- MS: 320 $[M+H]^+$.

3-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6d): Light brown colour solid; yield 80%; $C_{17}H_{10}N_3O_2F$; m.p.: 210-212 ºC. IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (t, 2H, *J* = 8.7 Hz, Ar-H), 7.56 (t, 1H, *J* = 7.9 Hz, Ar-H), 7.64 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.81 (m 1H, Ar-H), 7.91 (dd, 2H, *J* = 8.8, 5.3Hz, Ar-H), 8.38 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.83 (s, 1H, triazole-H), 8.95 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 114.11, 116.54, 116.63, 118.48, 121.92, 124.23, 126.02, 126.45, 126.42, 127.45, 132.74, 138.25, 148.09, 156.28, 164.54, 170.42; ESI- MS: 308 $[M+H]^+$.

3-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6e): Light yellow colour solid; yield 75%; m.f.: $C_{15}H_{15}N_3O_2$; m.p.: 218-220 ºC; IR (KBr, ν_{max}, cm^{-1}): 1730 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.00-0.95 (m, 3H, CH_3), 1.44 (dd, 2H, *J* = 14.9, 7.6 Hz, CH_2), 1.74 (dt, 2H, *J* = 15.4, 7.6 Hz, CH_2), 2.85-2.80 (m, 2H, CH_2), 7.56-7.50 (m, 1H, Ar-H),7.61 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.80 (dd, 1H, *J* = 8.7, 7.2, 1.7 Hz, Ar-H), 8.42–8.11 (m, 2H, Ar-H), 8.86 s (1H, triazole-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.16, 22.73, 29.73, 33.86, 114.09, 118.54, 122.46, 126.39, 128.84, 130.9, 134.66, 139.32, 148.66, 150.28, 155.62, 167.74; ESI- MS: 270 $[M+H]^+$.

3-(4-(4-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6f): White colour solid; yield 80%; m.f.: $C_{17}H_{10}N_3O_2Cl$; m.p.: 215-218 ºC; IR (KBr, ν_{max}, cm^{-1}): 1724 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.59-7.53 (m,1H, Ar-H), 7.64 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.89-7.79 (m, 3H, Ar-H), 8.38 (dd, 1H, *J* = 8.0, 1.6 Hz, Ar-H), 8.87 (s, 1H, triazole-H), 8.96 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 114.11, 118.28, 121.92, 124.23, 126.12, 132.02, 132.90, 133.12, 134.25, 134.97, 136.74, 137.35, 148.09, 150.31, 157.02, 171.12; ESI- MS: 346 $[M+Na]^+$.



Scheme-I: Synthesis of chromone-1,2,3-triazole hybrids (**6a-h**); **Reaction conditions:** (i) $POCl_3$ in DMF, room temperature, 24 h, yield 75-80%. (ii) *m*-CPBA, DCM, 40 °C reflux, 24 h, yield 70%. (iii) Trifluoro methane sulfonic anhydride, triethylamine in DCM, 0 °C, room temperature, 3 h, yield 70-75%. (iv) NaN_3, DMF, 90 °C, 3 h, yield 60%. (v) CuI, alkyl/aryl acetylenes, DMSO, 60 °C, 1 h, yield 80%

3-(4-(4-Bromophenyl)-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6g): Light white colour solid; yield 74%; m.f.: $C_{17}H_{10}N_3O_2Br$; m.p.: 208-210 ºC. IR (KBr, ν_{max}, cm^{-1}): 1728 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.48 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.55-7.52 (t, 1H, Ar-H), 7.64 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.78-7.65 (m 3H, Ar-H), 8.39 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.75 (s, 1H, triazole-H), 8.97 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 114.11, 116.53, 120.41, 123.12, 124.96, 124.23, 126.10, 128.25, 128.28, 129.15, 132.54, 134.25, 136.09, 148.13, 157.18, 171.42; ESI-MS: 369 $[M+H]^+$.

3-(4-(4-Nitrophenyl)-1*H*-1,2,3-triazol-1-yl)-4*H*-chromen-4-one (6h): White colour solid; yield 70%; m.f.: $C_{17}H_{10}N_4O_4$; m.p.: 220-221 ºC; IR (KBr, ν_{max}, cm^{-1}): 1712 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.48 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.56-7.51 (m, 1H, Ar-H), 7.67 (d, 1H, *J* = 7.2 Hz, Ar-H), 7.99-7.95 (m, 3H, Ar-H), 8.25 (dd, 1H, *J* = 8.1, Ar-H), 8.67 (s, 1H, triazole-H), 8.98 (s, 1H, C_2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 114.56, 118.42, 122.02, 124.26, 126.22, 127.12, 132.02, 128.90, 135.02, 136.25, 138.97, 148.22, 150.41, 158.02, 172.12; ESI-MS: 335 $[M+H]^+$.

RESULTS AND DISCUSSION

The synthesis of chromone-triazole hybrids involve four-step synthetic strategy. The regioselective Bayer-Villiger oxidation of chromone-3-aldehyde with *m*-CPBA (**2a**) gave corresponding 3-hydroxy-4*H*-chromen-4-one (**3a**) [15]. In order to make hydroxy group as good leaving group subsequently **3a** converted to O-triflate (**4a**) by treating with triflic anhydride (Tf_2O; 2.0 equiv). Compound **4a** on reaction with NaN_3 in DMF smoothly underwent nucleophilic substitution with azide to afford desired new key intermediate 3-azido-4*H*-chromen-4-one (**5a**) in good yield. IR spectrum of compound **5a** shows characteristic azide band appeared at 2123 cm^{-1}. Initially we tried for the generation of 3-azido chromone from 3-bromo chromone (organoazides are generally prepared by heating on alkyl/aryl halide with NaN_3 in DMF or DMSO) by treating with NaN_3 in DMF. But even after long time reaction, a low yield of azide intermediate **5a** probably due to unactivated C-3 vinyl bromo chromone. Hence, we planned for the generation of 3-azidochromone from chromone-3-O-triflate by treating with NaN_3. The key intermediate **5a** smoothly underwent CuI catalyzed 1,3-dipolar cycloaddition with variety of terminal alkynes in DMSO and gave the exclusively 1,4-regio isomeric triazole linked chromone hybrids in excellent yield with high purity.

The ^{1}H NMR of compound **6a** exhibited triazole characteristic signals at δ 8.82 (s, 1H, triazole-CH) and δ 8.95 (chromone C_2-H), Compound **6a** structure supported by ^{13}C NMR signals δ 170.72 (carbonyl carbon), 148.09 (triazole carbon) and ESI-MS: 304 (M+H). The plausible mechanism for 1,2,3-triazole formation *via* Cu(I) catalyzed azide-alkyne [1,3]dipolar cycloaddition presented in Fig. 1.

Conclusion

In conclusion, a simple and efficient synthesis of 1,4-disubstituted 1,2,3-triazole C-N linked chromone hybrids *via* key precursor azido chromone is developed using convenient and highly selective Cu(I) catalyzed click reaction.

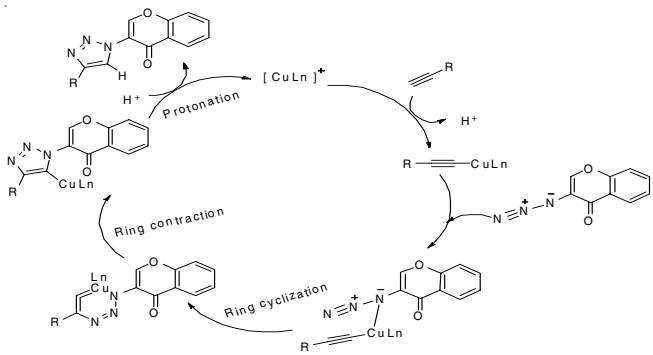


Fig. 1. Plausible mechanism of 1,3-dipolar cycloaddition of **5a** to acetylenes

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CONFLICT OF INTEREST

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

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