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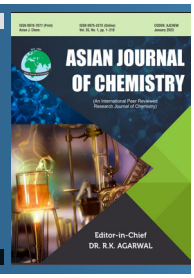

Synthesis of Novel Isoxazoline/Isoxzolyl Pyrano Heterocyclic Annulated Flavones

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The synthesis of new isoxazoline/isoxazole pyrano fused flavone derivatives from 6-hydroxy 5-formyl flavone *via in situ* generation of nitrile oxide from aldoxime using ceric ammonium nitrate (CAN) as an oxidant followed by intramolecular cycloaddition reaction at olefin/alkyne functions is reported in high yields. The reaction involves regio selective annulation at C_5/C_6 position in preference to the C_6/C_7 position of flavones. All the synthesized compounds were successfully characterized by IR, ^{1}H NMR, ^{13}C NMR and ESI-MS.

Keywords: 1,3-Dipolar cycloaddition, Flavone aldoximes, Flavone-isoxazoline/isoxazole, Ceric ammonium nitrate.

INTRODUCTION

Flavonoids are a class of secondary metabolites found in almost all the plant species [1,2]. They fulfill many functions of plants including flower pigmentation and protection against plant microorganisms and arthropods [3]. These compounds are commonly found in human diet especially in fruits, vegetables, tea, red wine and juices and also posses numerous biological activities [4,5]. Flavones are the sub-group of flavonoids, known to exhibit wide range of biological properties such as antioxidant [6], antitumor [7], estrogenic [8], antibacterial [9], anti-inflammatory [10,11], antimicrobial [12], ion transport effects [13], cardiovascular disease protection [14], *etc*.

Besides, isoxazoline/isoxazoles are important family of five-membered nitrogen and oxygen heterocyclic compounds, which are widely used as precursors for the development of drugs [15]. Isoxazoline/isoxazole skeletons exhibited diverse pharmacological activities such as antiviral [16,17], antioxidant [18,19], antitumor [20,21], anti-inflammatory [22,23], antimicrobial [24,25], *etc.* These heterocycles were also applied as dyes, electric insulating oils and high temperature lubricants [26,27] and also synthetic precursor of bioactive natural products [28]. Some bioactive flavones and isoxazoline/isoxazoles are shown in Fig. 1.

Due to the vast range of biological activities displayed by flavone isoxazoline/isoxazoles, novel pyrano-isoxazoline/isoxazole annulated flavone derivatives have been the subject of much research and development using *in situ* generation of nitrile oxides from aldoximes involving intramolecular 1,3-dipolar cycloaddition reaction at alkene and alkyne functions. Our approach for synthesizing useful compounds has many benefits, including excellent yields, simple work up and low cost of ceric ammonium nitrate (CAN) reagent.

EXPERIMENTAL

All the commercially available reagents starting materials and solvents were of reagent grade and used as such. Preparative column chromatography was performed using silica gel 60-120 mesh. Analytical TLC was carried out employing silica gel 60 F_{254} plates (Merck). IR spectra were recorded on Shimadzu-8400 FT-IR spectrophotometer. The NMR spectra were recorded on a Bruker-400 (^{1}H NMR 400 MHz; ^{13}C at 101 MHz) spectrometer using TMS as an internal reference. Molecular weights were determined with ESI Mass spectra. Melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected.

Synthesis of 6-hydroxy-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde (2a-b): 6-Hydroxy-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde (**2a-b**) was synthesized according to Duff reaction. A solution of 6-hydroxy flavone (**1a-b**, 1.0 mmol) and hexamethylene tetramine (HMTA, 4.0 mmol) were refluxed in glacial acetic acid (20 mL) and then the resulting solution was stirred at 100 ºC for 12 h. The resulting imminium complex was hydrolyzed by the addition of 0.1 N aq. HCl and continued

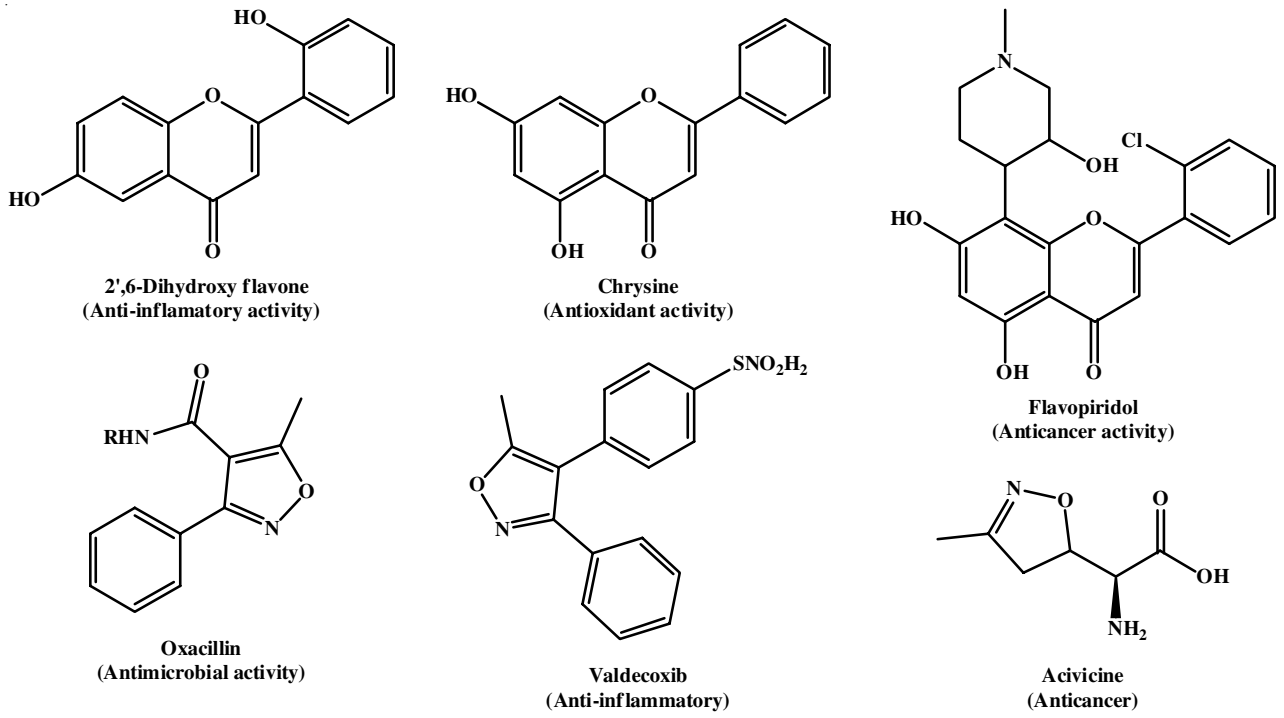


Fig. 1. Pharmacological important flavone and isoxazoline/isoxazole derivatives

heating for 1 h, then diluted with cold water and left for overnight in a refrigerator. Product (**2a-b**) was filtered, dried and purified by column chromatography in ethyl acetate and *n*-hexane (9:1).

Synthesis of (*E*)-6-(allyloxy)-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde oxime (3a-d): Substituted allyl bromide (1.2 mmol) was added to a stirred solution of compound **2a-b** (1.0 mmol) and K_2CO_3 (1.8 mmol) in DMF (10 mL) and the reaction mixture was stirred at 80 ºC for 2 h. After the completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature followed by the addition of CH_3COONa (1.0 mmol) and hydroxylamine hydrochloride (1.0 mmol) to the reaction mixture and stirred for 3 h at room temperature. After the completion of reaction, a pale yellow colour solid was poured in to water (30 mL) and collected by filtration, dried and purified by column chromatography in ethyl acetate and *n*-hexane (8:2) afforded **3a-d** with good yield.

Synthesis of (*E*)-4-oxo-2-phenyl-6-(prop-2-yn-1-yloxy)-4*H*-chromene-5-carbaldehyde oxime (5a-d): Substituted propargyl bromide (1.1 mmol) was mixed to a stirred solution of compound **2a-b** (1.0 mmol) and K_2CO_3 (1.5 mmol) in DMF (10 mL) and the reaction mixture was stirred at 80 ºC for 4 h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature then added the sodium acetate (1.0 mmol) and hydroxylamine hydrochloride (1.0 mmol) to the reaction mixture and stirred for 6 h at room temperature, after completion of reaction pale yellow colour solid was poured in to water (20 mL), a solid precipitate was collected by filtration, dried and purified by column chromatography using ethyl acetate and *n*-hexane (8:2) afforded **5a-d** as white coloured solid with 70% yield.

6-Hydroxy-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde (2a): White solid; yield: 60%; m.p.: 227-229 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 1730 (CH=O), 1700 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 13.15 (s, 1H), 11.66 (s, 1H), 7.83 (d, *J* = 9.03 Hz, 2H), 7.61 (m, 2H), 7.50-7.54 (m, 2H), 7.37 (d, *J* = 9.03 Hz, 1H), 6.81 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 195.90, 178.59, 161.88, 152.47, 151.19, 137.72, 131.09, 129.72, 129.05, 126.24, 122.53, 121.36, 119.90, 107.37. ESI-MS: *m/z* 266 $[M+H]^+$.

2-(4-Chlorophenyl)-6-hydroxy-4-oxo-4*H*-chromene-5-carbaldehyde (2b): White solid; yield: 55%; m.p.: 222-226 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 1732 (CH=O), 1702 (C=O); ^{1}H NMR (400 MHz, DMSO) δ ppm: 10.09 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 8.4 Hz, 3H), 7.28 (d, *J* = 8.9 Hz, 1H), 6.99 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 194.92, 177.95, 163.65, 156.42, 151.84, 131.80, 131.60, 129.14, 126.34, 124.72, 123.51, 123.20, 120.26, 106.74. ESI- MS: *m/z* 319 $[M+H]^+$.

(*E*)-6-(Allyloxy)-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde oxime (3a): Off-white solid; yield: 75%; m.p.: 292-296 ºC. IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.71 (s, 1H), 7.95-7.89 (m, 2H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.60-7.50 (m, 3H), 7.38 (d, 2H), 6.79 (s, 1H), 6.02 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H), 5.43 (ddd, *J* = 17.3, 3.0, 1.5 Hz, 1H), 5.31 (dd, *J* = 10.6, 1.3 Hz, 1H), 4.65 (dt, *J* = 5.0, 1.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 178.63, 163.63, 152.74, 150.41, 132.27, 131.90, 131.30, 129.14, 126.72, 126.36, 123.65, 121.23, 120.78, 118.29, 106.97, 70.89. ESI-MS: *m/z* 322 $[M+H]^+$.

(*E*)-6-(((*E*)-But-2-en-1-yl)oxy)-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde oxime (3b): Off-white solid; yield: 80%; m.p.: 294-298 ºC. IR (KBr, ν_{max}, cm^{-1}): 1739 (C=O); ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.16 (d, *J* = 6.9 Hz, 2H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.77 (d, *J* = 9.4 Hz, 1H), 7.68-7.58 (m, 4H), 6.80 (s, 1H), 6.48 (d, *J* = 11.5 Hz, 1H), 6.12-5.91 (m, 1H), 5.01 (d, *J* = 2.1 Hz, 2H), 2.55–2.49 (m, 3H); ^{13}C NMR (101

MHz, $CDCl_3$) δ ppm: 178.23, 163.32, 155.59, 151.36, 143.76, 139.12, 130.31, 129.08, 126.19, 124.54, 124.03, 121.24, 120.59, 119.82, 106.90, 62.00, 20.96. ESI-MS: *m/z* 335 $[M+H]^+$.

(*E*)-6-(Cinnamyloxy)-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde oxime (3c): Off-white solid; yield: 85%; m.p.: 299-303 ºC. IR (KBr, ν_{max}, cm^{-1}): 1740 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.24 (d, *J* = 8.6 Hz, 1H), 7.95-7.90 (m, 2H), 7.69 (m, 3H), 7.57-7.50 (m, 5H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 9.1, 3.0 Hz, 2H), 6.82 (s, 1H), 6.12 (m, *J* = 10.5 Hz, 1H), 5.31 (d, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 178.23, 163.01, 155.45, 151.39, 148.00, 141.5, 131.66, 129.10, 128.67, 127.29, 126.30, 124.57, 124.40, 124.02, 123.18, 121.64, 121.04, 119.84, 106.38, 62.01. ESI-MS: *m/z* 398 $[M+H]^+$.

(*E*)-6-(Allyloxy)-2-(4-chlorophenyl)-4-oxo-4*H*-chromene-5-carbaldehyde oxime (3d): Off-white solid; yield: 80%; m.p.: 285-290 ºC. IR (KBr, ν_{max}, cm^{-1}): 1736 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.94 (s, 1H), 7.94-7.89 (m, 2H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.54-7.52 (m, 2H), 7.38 (d, *J* = 9.3 Hz, 1H), 6.76 (s, 1H), 6.04 (ddd, *J* = 22.2, 10.3, 5.0 Hz, 1H), 5.48-5.39 (m, 1H), 5.30 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.67 (dd, *J* = 3.5, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 179.14, 162.36, 153.86, 151.50, 147.52, 132.71, 131.62, 131.44, 131.00, 129.05, 126.24, 123.24, 120.66, 120.02, 117.99, 107.91, 71.06. ESI- MS: *m/z* 355 $[M+H]^+$.

(*E*)-4-Oxo-2-phenyl-6-(prop-2-yn-1-yloxy)-4*H*-chromene-5-carbaldehyde oxime) (5a): Off-white solid; yield: 80%; m.p.: 252-254 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 1739 (C=O); ^{1}H NMR (400 MHz, DMSO) δ ppm: 10.50 (s, 1H), 8.16 (d, *J* = 3.7 Hz, 1H), 7.89 (s, 1H), 7.77 (d, *J* = 9.4 Hz, 1H), 7.68-7.57 (m, 5H), 6.89 (s, 1H), 5.01 (d, *J* = 2.1 Hz, 2H), 3.09 (dd, *J* = 14.4, 10.0 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 178.18, 166.47, 161.19, 152.47, 150.51, 144.78, 137.72, 131.09, 129.72, 129.05, 128.66, 120.24, 106.98, 74.91, 73.94, 57.22. ESI- MS: *m/z* 319 $[M+H]^+$.

(*E*)-6-(But-2-yn-1-yloxy)-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde oxime (5b): Off-white solid; yield: 80%; m.p.: 250-255 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.89 (s, 1H), 7.93 (m, 2H), 7.54 (m, 5H), 6.77 (s, 1H), 4.76 (s, 2H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 177.20, 161.43, 152.52, 150.96, 144.74, 130.88, 130.79, 129.11, 126.28, 122.55, 119.98, 106.98, 84.07, 74.48, 57.56, 3.17. ESI- MS: *m/z* 333 $[M+H]^+$.

(*E*)-4-Oxo-6-(pent-2-yn-1-yloxy)-2-phenyl-4*H*-chromene-5-carbaldehyde oxime (5c): Off-white solid; yield: 65%; m.p.: 251-255 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 1739 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.94 (s, 1H), 7.94-7.90 (m, 2H), 7.60 (d, *J* = 10.3 Hz, 2H), 7.57-7.52 (m, 5H), 6.94 (s, 1H), 4.79 (s, 2H), 2.24-2.17 (m, 2H), 1.12 (dd, *J* = 9.8, 5.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 178.60, 166.45, 161.51, 152.16, 150.81, 144.48, 137.75, 131.09, 129.64, 128.66, 126.24, 122.54, 120.36, 106.98, 89.29, 74.92, 57.51, 13.39, 11.42. ESI- MS: *m/z* 347 $[M+H]^+$.

(*E*)-2-(4-Chlorophenyl)-4-oxo-6-(prop-2-yn-1-yloxy)-4*H*-chromene-5-carbaldehyde oxime (5d): Off-white solid; yield: 68%; m.p.: 248-253 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 1737 (C=O); ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.16 (d, *J* = 6.9 Hz, 2H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.77 (d, *J* = 9.4 Hz, 1H), 7.66-7.58 (m, 3H), 7.17 (s, 1H), 5.01 (d, *J* = 2.1 Hz, 2H), 3.66 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 178.43, 163.65, 154.63, 151.76, 149.57, 132.03, 129.14, 126.34, 123.51, 120.26, 119.89, 118.94, 106.74, 76.24, 74.86, 59.01. ESI- MS: *m/z* 353 $[M+]^+$.

Synthesis of 9-phenyl-3a,4-dihydro-3*H*,11*H*-pyrano-[3′,2′:5,6]chromeno[4,3-*c*]isoxazol-11-one (4a-d): Compounds **3a-d** (1 mmol) dissolved in acetonitrile (10 mL) was added to a CAN solution (2 mmol) at 0-5 ºC and continued to stirring for 2-4 h. The progress of the reaction monitored by TLC, after completion of the reaction, 20 mL of water was added to reaction mixture to obtain a solid precipitate. It was collected by filtration, the crude material was purified by column chromatography in ethyl acetate and *n*-hexane (7:3) afforded **4a-d** (**Scheme-I**) in good yields.

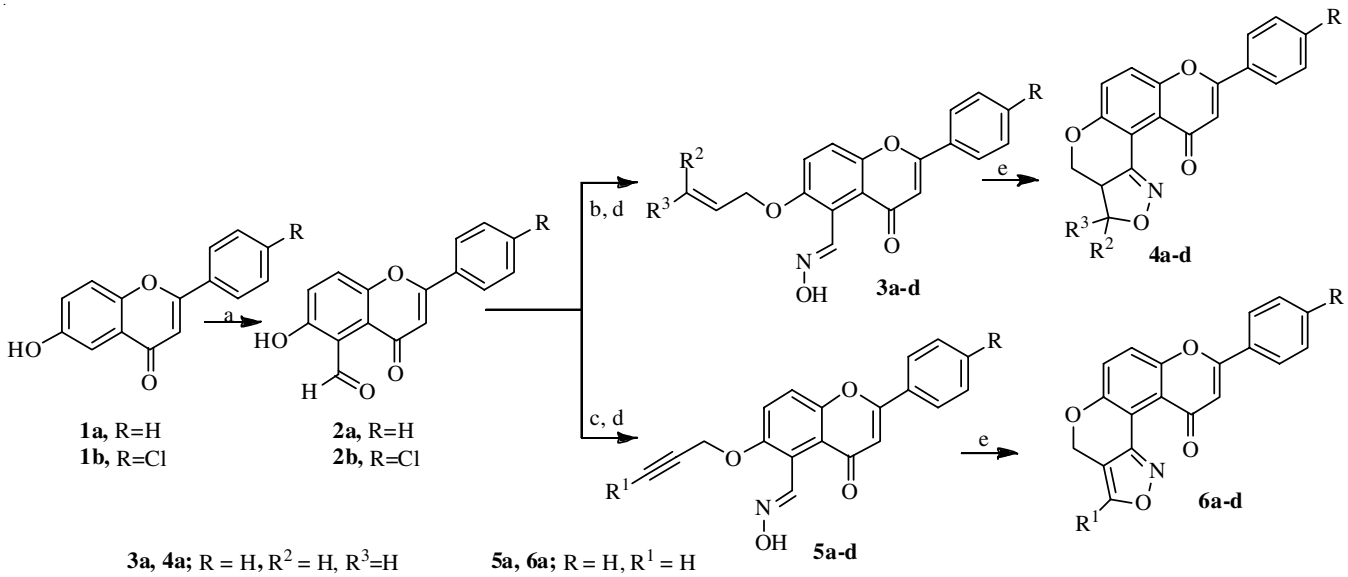
Synthesis of 9-phenyl-4*H*,11*H*-pyrano[3′,2′:5,6]chromeno[4,3-*c*]isoxazol-11-one (6a-d): To a stirred solution of compounds **5a-d** (1 mmol) dissolved in acetonitrile (10 mL) was added to CAN reagent (3 mmol) at 0-5 ºC and then the resulting reaction mixture was stirred for 4-6 h. After completion of the reaction monitored by TLC, 30 mL of water was added to reaction mixture to get solid precipitate. The crude material was purified by column chromatography in ethyl acetate and *n*-hexane (7:3) afforded compound **6a-d** white coloured solid with good yields (**Scheme-I**).

9-Phenyl-3a,4-dihydro-3*H*,11*H*-pyrano[3′,2′:5,6]-chromeno[4,3-*c*]isoxazol-11-one (4a): Off-white solid; yield: 70%; m.p.: 300-302 ºC. IR (KBr, ν_{max}, cm^{-1}): 1740 (C=O); ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.10 (d, *J* = 6.0 Hz, 2H), 7.81 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 6.5 Hz, 3H), 7.42 (d, *J* = 9.2 Hz, 1H), 7.01 (s, 1H), 4.73 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.60-4.52 (m, 1H), 4.10 (dd, *J* = 14.8, 7.1 Hz, 2H), 3.98 (dt, *J* = 18.6, 9.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 175.86, 160.47, 153.19, 151.74, 149.25, 131.72, 130.64, 129.15, 126.13, 123.97, 122.07, 120.00, 109.05, 107.64, 70.57, 70.03, 43.54. ESI- MS: *m/z* 319 $[M+H]^+$.

3-Methyl-9-phenyl-3a,4-dihydro-3*H*,11*H*-pyrano-[3′,2′:5,6]chromeno[4,3-*c*]isoxazol-11-one (4b): Off-white solid; yield: 75%; m.p.: 295-297 ºC. IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O); ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.11 (d, *J* = 5.0 Hz, 2H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.60 (m, 3H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.01 (s, 1H), 4.85–4.65 (m, 1H), 4.51 (t, *J* = 19.4 Hz, 1H), 4.26-4.03 (m, 1H), 3.57 (m, 1H), 1.45 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 176.09, 160.58, 153.30, 151.80, 131.76, 131.41, 130.49, 126.08, 124.07, 122.02, 109.21, 107.51, 78.91, 70.00, 49.68, 19.79. ESI- MS: *m/z* 333 $[M+H]^+$.

3,9-Diphenyl-3a,4-dihydro-3*H*,11*H*-pyrano[3′,2′:5,6]-chromeno[4,3-*c*]isoxazol-11-one (4c): Off-white solid; yield: 70%; m.p.: 294-296 ºC. IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.95-7.90 (m, 3H), 7.60-7.51 (m, 6H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.26 (d, 2H), 6.89 (s, 1H), 5.48-5.28 (m, 1H), 5.07 (d, 2H), 2.46 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 179.83, 163.72, 161.05, 156.25, 155.72, 145.08, 133.55, 133.13, 132.26, 131.12, 125.89, 124.80, 124.44, 121.26, 120.62,109.55, 105.83, 79.40, 63.04, 30.99. ESI- MS: *m/z* 395 $[M+H]^+$.

9-(4-Chlorophenyl)-3a,4-dihydro-3*H*,11*H*-pyrano-[3′,2′:5,6]chromeno[4,3-*c*]isoxazol-11-one (4d): White solid;



Scheme-I: Synthesis of pyrano isoxazoline/isoxazole annulated flavones (**4a-d, 6a-d**); **Reaction conditions:** (a) Hexamethylenetetramine (HMTA), glacial acetic acid, 100 °C for 6 h; (b,c) Substituted allyl, propargyl bromides, K_2CO_3, DMF, 80 °C, 2-4 h; (d) CH_3COONa, $NH_2OH{\cdot}HCl$, rt, 3-6 h; (e) CAN (20 mol%), acetonitrile, 0-5 °C, 2-6 h

yield: 60%; m.p.: 290-295 ºC. IR (KBr, ν_{max}, cm^{-1}): 1735 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.93-7.90 (m, 2H), 7.52 (d, 3H), 7.45-7.39 (m, 1H), 7.09-7.08 (m, 1H), 6.71 (d, 1H), 4.20 (d, *J* = 5.0 Hz, 1H), 4.12 (dd, *J* = 6.6 Hz, 1H), 4.04 (d, *J* = 11.4, 6.2 Hz, 1H), 3.94 (d, *J* = 5.1 Hz, 1H), 2.52 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 178.41, 168.23, 156.33, 146.32, 138.96, 134.59, 133.96, 131.16, 127.55, 126.43, 125.00, 111.75, 111.33, 102.14, 77.46, 69.90, 34.19. ESI- MS: *m/z* 353 $[M+H]^+$ and 354 $[M+2+H]^+$.

9-Phenyl-4*H*,11*H*-pyrano[3′,2′:5,6]chromeno[4,3-*c*]-isoxazol-11-one (6a): Off-white solid; yield: 80%; m.p.: 296-298 ºC. IR (KBr, ν_{max}, cm^{-1}): 1740 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.34 (s, 1H), 7.96-7.90 (m, 2H), 7.59 (dd, *J* = 10.6, 5.9 Hz, 1H), 7.57-7.51 (m, 3H), 7.40 (d, *J* = 9.2 Hz, 1H), 6.90 (s, 1H), 5.19 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 177.16, 161.44, 154.10, 153.14, 152.85, 150.56, 131.52, 131.33, 129.05, 126.17, 124.56, 122.27, 121.39, 112.41, 110.65, 108.68, 61.33. ESI- MS: *m/z* 318 $[M+H]^+$.

3-Methyl-9-phenyl-4*H*,11*H*-pyrano[3′,2′:5,6]chromeno-[4,3-*c*]isoxazol-11-one (6b): Off-white solid; yield: 75%; m.p.: 300-304 ºC. IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.94-7.91 (m, 2H), 7.58 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 2H), 7.53-7.51 (m, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 6.94 (s, 1H), 5.07 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 177.23, 169.62, 161.10, 153.81, 153.12, 133.24, 131.47, 129.05, 126.19, 124.46, 121.94, 121.43, 109.26, 108.60, 108.01, 61.76, 11.17. ESI- MS: *m/z* 331 $[M+H]^+$.

3-Ethyl-9-phenyl-4*H*,11*H*-pyrano[3′,2′:5,6]chromeno-[4,3-*c*]isoxazol-11-one (6c): Off-white solid; yield: 75%; m.p.: 302-305 ºC. IR (KBr, ν_{max}, cm^{-1}): 1737(C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.94-7.91 (m, 2H), 7.57 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 2H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 9.1 Hz, 1H), 6.89 (s, 1H), 5.10 (s, 2H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 177.23, 165.84, 161.29, 153.98, 153.54, 153.11, 131.46, 129.05, 126.18, 124.41, 121.25, 121.43, 111.37, 109.26, 108.78, 61.76, 19.55, 11.87. ESI-MS: *m/z* 345 $[M+H]^+$.

9-(4-Chlorophenyl)-4*H*,11*H*-pyrano[3′,2′:5,6]chromeno[4,3-*c*]isoxazol-11-one (6d): Off-white solid; yield: 65%; m.p.: 298-304 ºC. IR (KBr, ν_{max}, cm^{-1}): 1740 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.10 (s, 1H), 7.77 (d, *J* = 3.1 Hz, 1H), 7.67 (d, *J* = 2.1 Hz, 3H), 7.55 (d, *J* = 2.1 Hz, 2H), 6.84 (s, 1H), 5.39 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 177.90, 163.45, 154.80, 151.83, 135.06, 131.70, 129.10, 129.05, 128.80, 127.28, 126.30, 124.60, 124.15, 120.11, 107.00, 106.35, 61.52. ESI-MS: *m/z* 352 $[M+H]^+$, 353 $[M+2+H]^+$.

RESULTS AND DISCUSSION

6-Hydroxy flavone (**1a-b**) on Duff reaction [29-31] with glacial acetic acid and hexamethylenetetramine (HMTA) for 12 h at 100 ºC underwent selective formylation at C_5 position in preference to competitive C_7 position to give 6-hydroxy-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde (**2a-b**). The alkene appended flavone-5-aldoximes (**3a-d**) derivatives were synthesized in one pot synthesis by reacting 6-hydroxy-4-oxo-2-phenyl-4*H*-chromene-5-carbaldehyde (**2a-b**) with substituted allyl bromide in the presence of DMF/K_2CO_3 at 80 ºC for 4 h subsequently the reaction mixture was cooled to room temperature. The alkylation and hydroxylamine hydrochloride condensation with aldehyde underwent at one time in single step to furnish intermediates **3a-d** in good yields.

The alkene tethered intermediates **3a-d** were then subjected to intramolecular cyclization using oxidant ceric ammonium nitrate (CAN) in acetonitrile at 0-5 ºC *via in situ* generation of

nitrile oxide from the aldoxime to afford pyrano-isoxazoline annulated flavone derivatives **4a-d** (**Scheme-I**) in good yields. All the products **4a-d** were characterized by spectral analysis. In ^{1}H NMR spectrum of compound **4a** newly formed dihydropyrano isoxazoline signals appeared at δ 4.73 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.60-4.52 (m, 1H), 4.10 (dd, *J* = 14.8, 7.1 Hz, 2H, -OCH_2) and 3.98 (dt, *J* = 18.6, 9.5 Hz, 1H). In ^{13}C NMR, compound **4a** of isoxazoline carbons resonated at δ 70.50, 70.03, 43.54 ppm, whereas the ESI-MS of **4a** showed quasi-molecular ion $[M+H]^+$ peak at *m/z* 319 (**Scheme-I**).

With this success as motivation, we set out to synthesize a wide variety of pyrano-isoxazole fused flavone derivatives. Similar to the synthesis of compounds **4a-d**, 6-propargyloxy flavone-5-aldoximes (**5a-d**) were synthesized in one pot by treating 6-hydroxy-5-formyl flavone with substituted propargyl bromide and sodium acetate/hydroxylamine hydrochloride in DMF. The intermediates **5a-d** were then subjected to nitrile oxide 1,3-dipolar cycloaddition at alkyne using oxidant CAN in acetonitrile solvent to afford pyrano isoxazole fused flavone derivatives **6a-d** in good yields. The structures of all the compounds **6a-d** were confirmed by spectral analysis. Dihydropyrano-isoxazole **6a** proton signal appeared at δ 8.34 (s, 1H), -OCH_2 protons appeared at δ 5.19 ppm (s, 2H). The ^{13}C NMR spectrum of isoxazole carbons resonated at δ 154.10, 153.14, 108.68, 61.33 ppm whereas ESI-MS of **6a** molecular ion $[M+H]^+$ peak was observed at *m/z* 318.

Conclusion

In summary, a new series of novel pyrano-isoxazoline/isoxazole fused flavone derivatives was synthesized *via* nitrile oxide intramolecular 1,3-dipolar cycloaddtion reaction at alkene and alkyne using oxidant ceric ammonium nitrate (CAN). In this synthetic method, regioselective intramolecular 1,3-dipolar cycloaddition and one-pot synthesis of allyloxy and propargyloxy flavone aldoxime derivatives are the key steps. The isoxazoline/isoxazole fused flavone potential bioactive molecules could be used as precursors for the development of new drugs with more efficacy.

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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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