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Synthesis Of Chromeno Oxadiazole Derivatives

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ABSTRACT

2H-3-chromene cyanides react with $NH_2OH.HCl$ in presence of triethyl amine in ethanol yields 2H-chromene-3-amidoximes, which on reaction with chloroacetyl chloride in presence of DIPEA gave 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2H-chromenes. These on reaction with morpholine, piperidine and pyrrolidine afforded 3-[5-(morpholinomethyl/ piperidinomethyl/pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2H-chromenes in good yields.

Keywords: 2*H*-chromene-3-cyanides, 2*H*-chromene-3-amidoximes, DIPEA, cyclic secondary amines, chromeno oxadiazole.

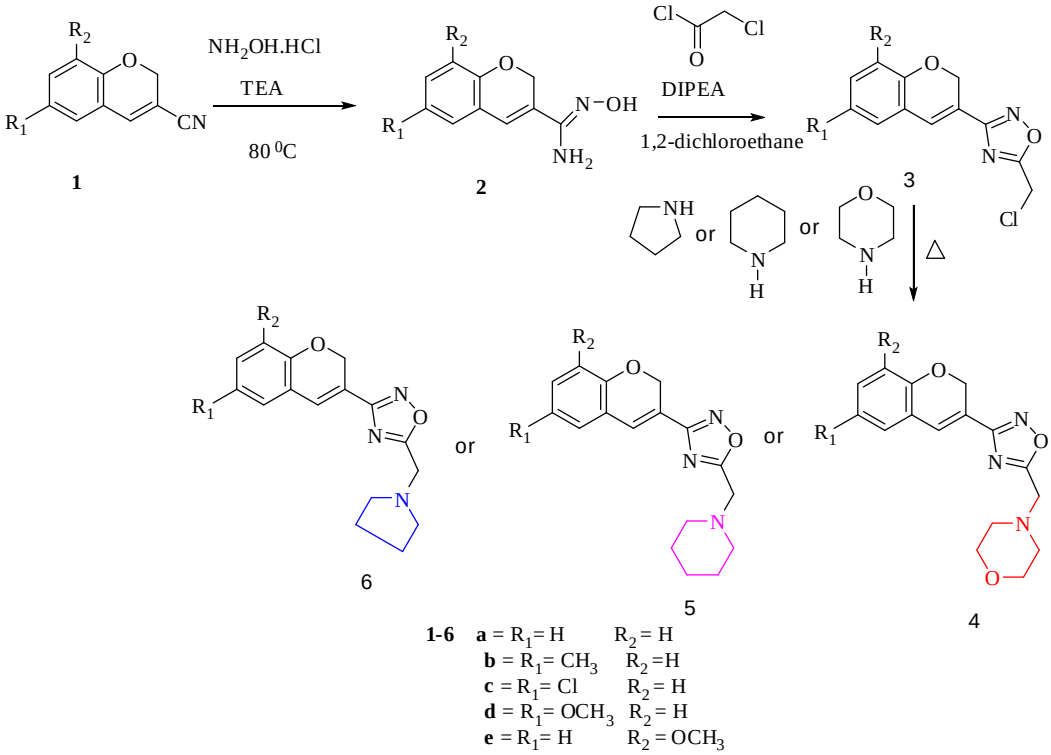
INTRODUCTION

The oxadiazole is a five-membered nitrogen and oxygen containing heterocycle which has been commonly used as a privileged scaffold to produce various novel therapeutic molecules. 3,5-Disubstituted-1,2,4-oxadiazoles exhibit various biological activities[1], oxolamine **(a)** is an anti-inflammatory and antitussive agent[2], proxazole **(b)** exhibits antispasmodic activity[3], imolamine **(c)** is an antianginal agent[4], prenoxdiazine or libexin **(d)** is a cough suppressant[5], butalamine **(e)** is a peripheral vasodilator[6] and (-)-2-(1,2,4-Oxadiazol-5-methyl)-3-phenyltropane **(f)** is a phenyltropane derivative acts as a potent monoamine reuptake inhibitor and stimulant drug[7] as shown in fig 1.

In other hand Chromene and its derivatives are biologically interesting compounds known for their antimicrobial and antifungal[8], antioxidant[9], antileishmanial[10], antitumor[11] Hypotensive[12] antiproliferation[13] localanesthetic[14] antiallergenic[15,16], centralnervoussystem(CNS) activities and effects[17], as well as treatment of Alzheimer's disease[18] and Schizophrenia disorder[19]. Fused chromene ring systems have platelet antiaggregating, localanesthetic[20-22] and antihistaminic activities[23]. They also exhibit antidepressant effects[24], inhibitory effect on influenza virus sialidases[25,26], DNA breaking activities and mutagenicity[27] antiviral activities[28] and act as sex pheromone homologes[29].

In view of the several biological activities of 1,2,4-oxadiazoles and Chromene derivatives we planned to synthesize new chromeno oxadiazole derivatives 3-[5-(morpholinomethyl/ piperidinomethyl/pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl)] 2*H*-chromenes **(4-6)** as shown in scheme-1.

Fig 1. Biologically active 3,5-Disubstituted-1,2,4-oxadiazoles



1-6 **a** = R_1= H R_2 = H
b = R_1= CH_3 R_2 =H
c = R_1= Cl R_2 = H
d = R_1= OCH_3 R_2 = H
e = R_1= H R_2 = OCH_3

Scheme1. Synthesis of 3-oxadiazole substituted chromenes **(4-6)**.

MATERIALS AND METHODS

General methods

Reagents were purchased from commercial sources and were used as received. ^{1}H NMR spectra were obtained on a Bruker AVANCE 400 spectrometer at 400 MHz or Bruker AVANCE 300 spectrometer at 300 MHz with tetramethylsilane used as an internal reference. ^{13}C NMR spectra were obtained on a Bruker AVANCE 300 spectrometer at 100 MHz with the solvent peak used as the reference. Thin-layer chromatography (TLC) was performed using Whatman No. 4500-101 (Diamond No. MK6F silica-gel 60 Å) plates. Visualization of TLC plates was performed using UV light (254 nm). Mass spectra record on mass spectrometer.

General procedure for synthesis of 2*H*-chromene-3-amidoximes (2): A mixture of 2*H*-chromene-3-cyanide **(1)** (25.4 mmol), hydroxylamine hydrochloride (33.4 mmol) and 10 mL of triethylamine in 50 mL of ethanol was refluxed for 2 h. The ethanol and excess of triethylamine was removed under reduced pressure. A light yellow solid was obtained to which water (20 mL) was added. The solid precipitate was collected by filtration and washed with water and dried at 50 ^{o}C to furnish amidoxime (**2**) in good yields.

2*H*-chromene-3-amidoxime (2a): Colorless amorphous solid (4. 2 g, 87% yield). mp 201 ^{o}C. IR (KBr): 3400 cm^{-1} (OH), 3340 cm^{-1} (NH_2). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.76 (s, OH), 7.06 (m, H-7, H-4), 6.83 (m, H-6, H-5), 6.74 (d, *J* = 8.20 Hz, H-8), 5.19 (s, NH_2), 4.97 (s, OCH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.7 (C=N), 148.9 (C-8a), 129.2 (C-7), 127.1 (C-5), 125.2 (C-3), 121.9 (C-4a), 121.3 (C-6), 120.5 (C-4), 115.2 (C-8), 63.8 (C-2). DIPMS: m/z 191 [M+H].

6-Methyl- 2*H*-chromene-3-amidoxime (2b): White solid, mp 220 ^{o}C. Yield: 90%. IR (KBr): 3510 cm^{-1} (OH), 3355 cm^{-1}(NH_2).^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.79 (s, OH), 6.80-6.92 (m, H-7, H-5, H-4), 6.62 (d, *J* = 8.14 Hz, H-8), 5.30 (bs, NH_2), 4.86 (s, OCH_2), 2.25 (s, 6-CH_3).^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.2 (C=N), 148.5 (C-8a), 129.7 (C-6), 129.2 (C-7), 127.0 (C-3), 124.8 (C-4a), 121.3 (C-5), 120.2 (C-4), 114.5 (C-8), 63.3 (C-2), 19.5 (6-CH_3). DIPMS: m/z 205 [M+H].

6-Chloro-2*H*-chromene-3-amidoxime (2c): White solid. mp 230 ^{o}C. Yield: 90%. IR (KBr): 3530 cm^{-1}(OH), 3315 cm^{-1}(NH_2). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.94 (s, OH), 6.98-7.08 (m, H-7, H-4), 6.82 (d, *J* = 2.4 Hz, H-5), 6.72 (d, *J* = 8.2 Hz, H-8), 5.24 (s, NH_2), 4.94 (d, *J* = 1.2 Hz, OCH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.0 (C=N-OH), 148.3 (C-8a), 128.2 (C-7), 126.2 (C-3), 125.8 (C-5), 124.6 (C-4a), 123.2 (C-6), 119.0 (C-4), 116.4 (C-8). ESIMS: m/z 225[M+H], 227[M+H+2].

6-Methoxy- 2*H*-chromene-3-amidoxime (2d): White solid. mp 202 ^{o}C. Yield: 88 %. IR (KBr): 3480 cm^{-1}(OH), 3360 cm^{-1}(NH_2). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.94 (s, OH), 6.96 (s, H-4), 6.69-6.76 (m, H-8, H-7, H-5), 5.59 (s, NH2), 4.79 (s, OCH2), 3.69 (s, 6-OCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.8 (C=N-OH), 148.8 (C-6), 147.5 (C-8a), 126.0 (C-3), 122.5 (C-4a), 120.5 (C-4), 115.6 (C-7), 114.6 (C-5), 112.1 (C-8), 63.7 (C-2), 55.3 (6-OCH_3). ESIMS: m/z 221 [M+H], 259[M+K].

8-Methoxy- 2*H*-chromene-3-amidoxime (2e): White solid. mp 160 ^{o}C. Yield: 92 %. IR (KBr): 3470 cm^{-1} (OH), 3350 cm^{-1} (NH_2). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.90 (s, OH), 6.68-6.80 (m, H-7, H-6, H-5, H-4), 5.10 (s, NH_2), 4.99 (d, *J* = 1.2 Hz, OCH_2), 3.85 (s, OCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 148.3 (C=N-OH), 147.0 (C-8), 142.4 (C-8a), 124.7 (C-3), 122.2 (C-4), 120.4 (C-6), 120.0 (C-4a), 118.8 (C-7), 113.2 (C-5), 64.6 (C-2), 57.2 (8-OCH_3). DIPMS: m/z 221 [M+H].

General procedure for synthesis of 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes (4): A mixture of 2*H*-chromene-3-amidoxime **(2)** (15.8 mmol) and DIPEA (5.0 mL) were taken in 50 mL of 1,2-dichloroethane. The reaction mixture was cooled to 10^{o}C. A solution of chloroacetylchloride (18.8 mmol) in 10mL of 1,2-dichloroethane was added dropwise. After completion of the addition the resulting reaction mixture was refluxed for 2h. A brownish solution obtained was poured into ice cold water and extracted with $CHCl_3$(2x50 mL) and the organic layer was washed with $NaHCO_3$ solution (2x20mL), water (2x20mL) and dried over Na_2SO_4. The crude product was purified by column chromatography to afford **3**.

3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromene(3a): White amorphous solid**,**(1.6g,41% yield), mp108°C.^{1}HNMR($CDCl_3$,400MHz):δ7.47(s,H-4),7.22(ddd,J=8.0Hz,J=7.2Hz,J=1.2Hz,H-7),7.15(d,J=7.6Hz,J=1.6,H-5),6.93(dd,J=7.2Hz,J=7.6Hz,J=1.2Hz,H-6),6.87(d,J=8.0Hz,H-8),5.18(s,OCH_2),4.69(s,CH_2-Cl).^{13}CNMR($CDCl_3$,100MHz):δ173.8(C-3'),166.2(C-5'),154.8(C-8a),131.2(C-7),128.8(C-4),128.2(C-5),121.7(C-6),121.1(C-3),118.6(C-4a),116.0(C-8),64.3(C-2),33.1 (CH_2-Cl). DIPMS: m/z249[M+H], 251[M+H+2].

6-Methyl-3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromene(3b):.mp128^{o}C.Yield:40%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (s, H-4), 6.99 (d, *J* = 8.16 Hz, H-8), 6.92 (d, *J* = 1.48 Hz, H-5), 6.73 (d, *J* = 8.l6 Hz, H-8), 5.12 (s, OCH_2), 4.68 (s, CH_2-Cl), 2.28 (s, 6-CH_3). ^{13}CNMR ($CDCl_3$, 100 MHz): δ 173.7 (C-3'), 166.3 (C-5'), 152.7 (C-8a), 131.6 (C-6), 131.0 (C-4), 129.0 (C-7), 128.5 (C-4a), 121.0 (C-5), l18.6 (C-3), 115.7 (C-8), 64.3 (C-2), 33.1 (CH_2-Cl), 20.2 (6-CH_3).ESIMS: m/z 263 [M+H], 265 [M+H+2].

6-Chloro-3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromene(3c): White solid. mp149^{o}C. ^{1}HNMR($CDCl_3$,400 MHz): δ7.39(s,H-4),7.10-7.18 (m, H-5, H-7), 6.80 (d, J=8.2Hz, H-8),5.18(s,OCH_2),4.69(s,CH_2-Cl). ^{13}CNMR($CDCl_3$+DMSO-d_6,100MHz):δ 173.5(C-3'), 165.0 (C-5'), 152.4 (C-8a), 129.8 (C-7), 126.7 (C-4), 126.6 (C-5), 125.7 (C-3), 121.6 (C-4a), 119.2 (C-6), 116.5 (C-8), 63.6 (C-2), 32.4 (CH_2-Cl). ESIMS: m/z 283[M+H], 285[M+H+2].

6-Methoxy-3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (3d):Yellow solid. mp 120^{o}C. Yield: 38 %;^{1}H NMR ($CDCl_3$, 400 MHz): 7.42 (s, H-4), 6.78-6.84 (H-7, H-5, m), 6.72 (d, *J* = 8.1 Hz, H-8), 5.14 (s, OCH_2), 4.71 (s, CH_2-Cl), 3.78 (s, 6-OCH_3).^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.9 (C-3'), 116.1 (C-5'), 154.4(C-6), 148.6 (C-8a), 129.0(C-4), 121.7 (C-4a), 119.4 (C-3), 116.7 (C-7), 116.7 (C-5), 112.8 (C-8), 64.2 (C-2), 55.7 (6-OCH_3), 33.2 (CH_2-Cl). ESIMS: m/z 279 [M+H], 281[M+H+2].

8-Methoxy- 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (3e):White solid. mp 144 ^{o}C. Yield: 44 %.^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (s, H-4), 6.88-6.91 (m, H-7, H-5), 6.81 (m, H-6), 5.26 (s, OCH_2), 4.70 (s, CH_2-Cl), 3.80 (s, 8-OCH_3).^{13}C NMR ($CDCl_3$, 100 MHz) : δ 173.8 (C-3'), 166.1 (C-5'), 148.1 (C-8), 144.0(C-8a), 128.8 (C-4), 122.0 (C-3), 121.4 (C-4a), 120.6 (C-6), 118.7 (C-7), 114.9 (C-5), 64.5 (C-2), 56.0 (8-OCH_3), 33.1 (CH_2-Cl). ESI MS: m/z 279[M+H], 281 [M+H+2].

General procedure for synthesis of 3-[5-(morpholinomethyl/piperidinomethyl/pyrrolidine methyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes (4-6). A mixture of 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene **(3)** (1,2 mmol) in corresponding amine 6 mL of morpholine or 5 mL of piperidine or 5 mL of pyrrolidine was heated at 60 ^{o}C for 1 h. After completion of the reaction the mixture was poured into ice cold water. A light yellow precipitate was collected by filtration and purified by column chromatography to afford **(4-6)** in good yields.

3-[5-(morpholinomethyl)-1,2,4-oxadiazo-3-yl] 2*H*-chromene (4a):White solid (0.18 g, 50 % yield), mp 98^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, H-4),7.22 (ddd, *J* = 8.4 Hz, *J* = 7.6 Hz, *J* = 1.2 Hz, H-7), 7.20 (dd, *J* = 7.2 Hz, *J* = 1.2 Hz, H-5), 6.86 (ddd, *J* = 7.6 Hz, *J* = 7.2 Hz, *J* = 0.8 Hz, H-6), 6.82 (d, *J* = 8.4 Hz, H-8), 5.20 (s, OCH_2), 3-86 (s, N-CH_2), 3.76 (t, *J* = 5.2 Hz, 3'', 5''-2xCH_2), 2.64 (t, *J* = 5.2 Hz, 2'',6''-2 x CH_2).^{13}C NMR ($CDCl_3$, 100 MHz) : δ 175.2 (C-3'), 165.4 (C-5'), 154.3 (C-8a), 130.8 (C-7), 128.2 (C-4), 128.0 (C-5), 121.5 (C-6), 115.8 (C-8), 120.9 (C-3), 118.7 (C-4a), 66.4 (C-2), 64.1 (C-3''), (C-5''), 52.9 (N-CH_2), (C-2''), (C-6''). ESIMS: m/z 300 [M+H], 338[M+K].

6-Methyl-3-[5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (4b):White solid. mp 110^{o}C. Yield 60 %.^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.40 (s, H-4), 6.98 (d, *J* = 8.1 Hz, H-7), 6.92 (d, *J* = 1.5 Hz, H-5), 6.73 (d, *J* = 8.l Hz, H-8), 5.12 (s, OCH_2), 3.84 (s, N-CH_2), 3.73 (t, *J* = 4.8 Hz, 3'', 5''-2xCH_2), 2.62 (t, *J* = 4.8 Hz, 2'',6''- 2xCH_2), 2.28 (s, 6-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 175.2 (C-3'), 165.5 (C-5'), 152.3

(C-8a), 131.4 (C-6), 130.9 (C-4), 128.5 (C-7),128.4 (C-4a), 120.9 (C-5), 118.8 (C-3), 115.6 (C-8), 66.5 (C-2), 64.2 (C-3"), (C-5"), 53.0 (N-CH_2), (C-2"),(C-6"), 20.3 (6-CH_3). ESIMS: m/z 314[M+H].

6-Chloro-3-[5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (4c):White solid. mp 130 ^oC. Yield: 52 %.^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, H-4), 7.16 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, H-7), 7.12 (d, *J* = 2.4 Hz, H-5), 6.82 (d, *J* = 8.4 Hz, H-8), 5.19 (s, OCH_2), 3.88 (s, N-CH_2), 3.77 (t, *J* = 5.2 Hz, 3", 5"-2 x CH_2), 2.65 (t, *J* = 5.2 Hz, 2",6"- 2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 175.5 (C-3'), 165.3 (C-5'), 152.9 (C-8a), 130.5 (C-7), 127.4 (C-4), 127.2 (C-5), 126.4 (C-3), 122.3 (C-4a), 120.1 (C-6), 117.3 (C-8), 66.6 (C-2), 64.4 (C-3"), (C-5"), 53.1 (N-CH_2), (C-2"), (C-6"). ESIMS: m/z 334[M+H], and 336[M+H+2].

6-Methoxy-3-[5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (3d):White solid. mp 128 ^oC. Yield: 62 %. ^1H NMR ($CDCl_3$, 400 MHz) : δ 7.41 (s, H-4), 6.70-6.82 (m, H-5, H-7), 6.68 (d, *J* = 8.2 Hz, H-8), 5.12 (s, OCH_2), 3.80 (s, N-CH_2), 3.74 (t, *J* = 5.0 Hz, 3", 5"-2xCH_2), 3.69 (s, 6-OCH_3), 2.62 (t, *J* = 5.0 Hz, 2", 6"-2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 175.3 (C-3"), 165.4 (C-5"), 154.1 (C-6), 148.3 (C-8a), 128.3 (C-4), 121.7 (C-4a), 119.6 (C-3), 116.4 (C-7), 116.2 (C-5), 112.5 (C-8), 66.5 (C-2), 64.1 (C-2") , (C-6"), 55.5 (N-CH_2), (C-3"), (C-5"), 53.0 (6-OCH_3).ESIMS: m/z 330[M+H], 352[M+Na].

8-Methoxy-3-[5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (3e):White solid. mp 131 ^oC. Yield: 54 %.^1H NMR ($CDCl_3$, 400 MHz) : δ 7.20 (m, H-5), 6.90-6.94 (m, H-4, H-7), 6.72 (m, H-6), 4.88 (s, OCH_2), 3.88 (8-OCH_3) 3.78 (s, N-CH_2), 3.72 (t, *J* = 4.8 Hz, 3", 5" - 2xCH_2), 2.64 (t, *J* = 4.8 Hz, 2", 6" - 2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 175.3 (C-3'), 165.4 (C-5'), 147.6 (C-8), 143.2 (C-8a), 128.3 (C-4), 121.7 (C-3), 121.3 (C-4a), 120.2 (C-6), 118.8 (C-7), 113.5 (C-5), 66.5 (C-2), 64.5 (C-3"), (C-5"), 55.9 (C-N-CH_2), (C-2"), (C-6"), 53.0 (8-OCH_3).ESIMS: m/z 330 [M+H].

3-[5-(piperidinonomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (5a):White solid (0.13 g, 55% yield), mp 80 ^oC.^1H NMR ($CDCl_3$, 400 MHz): δ 7.45 (s, H-4), 7.18 (ddd, *J* = 8.3 Hz, *J* = 7.6 Hz, *J* = l .2 Hz, H-7), 7.12 (dd, *J* = 7.2 Hz, *J* = 1.6 Hz, H-5), 6.90 (ddd, *J* = 7.6 Hz, *J* = 7 .2 Hz, *J* = 1.2 Hz, H-6), 6.84 (d, *J* = 8.4 Hz, H-8), 5.18 (s, OCH_2), 3.86 (s, N-CH_2), 2.52 (t, *J* = 5.4 Hz, 2", 6"- 2xCH_2), 1.65 (m, 3",5"-2xCH_2), 1.41 (m, 4"-CH_2).^{13}C NMR ($CDC1_3$, 100 MHz) : δ δ 176.0 (C-3'), 165.5 (C-5'), 154.5 (C-8a), 130.8 (C-7) 128.2 (C-4), 128.1 (C-5), 121.7 (C-6), 121.0 (C-3), 119.0(C-4a), 116.0 (C-8), 64.3 (C-2), 54.1 (C-2"), (C-6"), 53.6 (N-CH_2), 25.5 (C-3"), (C-5"), 23.6 (C-4").ESIMS: m/z 298 [M+H].

6-Methyl-3-[5-(piperidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (5b):White solid. mp 92 ^oC. Yield: 60 %.^1H NMR ($CDCl_3$, 400 MHz) : δ 7.42 (s, H-4), 6.98 (d, *J* = 8.1 Hz, H-7), 6.92 (d, *J* = 1.4 Hz, H-5), 6.73 (d, *J* = 8.1 Hz, H-8), 5.12 (s, OCH_2), 3.82 (s, N-CH_2), 2.56 (t, *J* = 5.3 Hz, 2",6"-2xCH_2), 2.29 (s, 6-CH_3),1.65 (m, 3", 5"-2xCH_2), 1.45 (m, 4"-CH_2).^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.0 (C-3'), 165.5 (C-5'), 152.3 (C-8a), 131.3 (C-6) 130.9 (C-4), 128.4 (C-7), 128.3 (C-4a), 121.0 (C-5), 119.0 (C-3), 115.6 (C-8), 64.3 (C-2), 54.1 (C-2"), (C-6"), 53.6 (N-CH_2), 25.6 (C-3"), (C-5"), 23.6 (C-4"), 20.3 (6-CH_3).ESIMS: m/z 312 [M+H].

6-Chloro- 3-[5-(piperidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (5c):White solid, mp140 ^oC, yield 57 %. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (s, H-4), 7.16 (m, H-7), 7.11 (d, *J* = 2.3 Hz, H-5), 6.78 (d, *J* = 8.3 Hz, H-8), 5.17(s, OCH_2), 3.82 (s, N-CH_2), 2.57 (t, *J* = 5.3 Hz, 2", 6"-2xCH_2), 1.66 (m, 3", 5"-2xCH_2), 1.45 (m, 4"-CH_2).^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.2 (C-3'), 165.1 (C-5'), 152.9 (C-8a), 130.3 (C-7) 127.3 (C-4), 126.9 (C-5), 126.3 (C-3), 122.4 (C-4a), 120.2 (C-6), 117.2 (C-8), 64.4 (C-2), 54.1 (C-2"), (C-6"), 53.5 (N-CH_2), 25.6 (C-3"), (C-5"), 23.5 (C-4"). ESIMS: m/z 332[M+H], 334[M+H+2].

6-Methoxy- 3-[5-(piperidinomelhyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (5d):White solid, mp 72 ^oC.^1H NMR ($CDCl_3$, 400 MHz) : δ 7.42 (s, H-4), 6.70-6.81 (m, H-5, H-7), 6.67 (d, *J* = 8.1 Hz, H-8), 5.12 (s, OCH_2), 3.82 (s, N-CH_2), 3.72 (s, 6-OCH_3), 2.55 (t, *J* = 5.2Hz, 2", 6"-2xCH_2), 1.62 (m, 3", 5"-2xCH_2), 1.44 (m, 4"-CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.0 (C-3'), 165.5 (C-5'), 154.2 (C-6), 148.4 (C-8a), 128.3

(C-4), 121.8 (C-4a), 119.9 (C-3), 116.5 (C-7), 116.2 (C-5), 112.6 (C-8), 64.3 (C-2), 55.6 (6-OCH_3), 54.1 (C-2"), (C-6"), 53.5 (N-CH_2), 25.6 (C-3"), (C-5"), 23.5 (C-4").ESIMS: m/z 328 [M+H].

8-Methoxy-3-[5-(piperidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (5e): Yellow solid, mp 98 ^oC. Yield: 50 %.^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (m, H-5), 6.89 (m, H-4, H-7), 6.80 (m, H-6), 5.26 (s, OCH_2), 3.90 (s, 8-OCH_3), 3.84 (s, N-CH_2), 2.56 (t, *J* = 5.3 Hz, 2", 6"-2xCH_2), 1.63 (m, 3", 5" -2xCH_2), 1.45(m, 4"-CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.1 (C-3'), 165.4 (C-5'), 147.7 (C-8), 143.3 (C-8a), 128.1 (C-4), 121.8 (C-3), 121.3 (C-4a), 120.2 (C-6), 119.1 (C-7), 113.6 (C-5), 64.6 (C-2), 55.9 (8-OCH_3), 54.1 (C-2"), (C-6"), 50.0 (N-CH_2), 25.6 (C-3"), (C-5"), 23.5 (C-4").ESIMS: m/z 328[M+H], 350[M+Na].

3-[5-(pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (6a):White solid, (0.16 g, 47 % yield), mp 76^oC. ^1H NMR ($CDCl_3$, 400 MHz) : δ 7.48 (s, H-4), 7.18 (dd, *J* = 7.8 Hz, *J* = 8.4 Hz, H-7), 7.12 (d, *J* = 7.6 Hz, H-5), 6.90 (dd, *J* = 7.8 Hz, 7.6 Hz, H-6), 6.83 (d, *J* = 8.4 Hz, H-8), 5.19 (s, OCH_2), 3.98 (s, N-CH_2), 2.71 (t, *J* = 5.2 Hz, 2", 5"-2xCH_2), 1.87 (t, *J* = 5.2 Hz, 3", 4"-2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.0 (C-3'), 165.5 (C-5'), 154.4 (C-8a), 130.8 (C-7) 128.2 (C-4), 128.1 (C-5), 121.6 (C-6), 115.8 (C-8), 121.1 (C-3), 118.8 (C-4a), 64.2 (C-2), 53.8 (C-2"), (C-5") 49.8 (N-CH_2), 23.5 (C-3"),(C-4"). ESIMS: m/z 284[M+H].

6-Methyl- 3-[5-(pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (6b):White solid. mp 82 ^oC. Yield: 64 %.^1H NMR ($CDCl_3$, 400 MHz): δ 7.41 (s, H-4), 6.98 (d, *J* = 8.1 Hz, H-7), 6.91 (d, *J* = 1.5 Hz, H-5), 6.72 (d, *J* = 8.1 Hz, H-8), 5.12 (s, OCH_2), 3.94 (s, N-CH_2), 2.70 (t, *J* = 5.0 Hz, 2", 5"-2xCH_2), 2.26 (s, 6-CH_3), 1.84 (t, *J* = 5.0 Hz, 3", 4"-2xCH_2). ^{13}C NMR ($CDCl_3$,100 MHz) : δ 176.3 (C-3'), 165.4 (C-5'), 154.2 (C-8a), 131.3 (C-6), 130.8 (C-4), 128.3 (C-7), (C-5), 120.9 (C-4a), 118.8 (C-3), 115.5 (C-8), 64.1 (C-2), 53.8 (C-2"), (C-5"), 50.0 (N-CH_2), 23.5 (C-3"), (C-4"), 20.3 (6-CH_3). ESIMS: m/z 298 [M+H]

6-Chloro-3-[5-(pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (6c):Light brownish solid, mp 96 ^oC, yield 55 %. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (s, H-4), 7.18 (dd, *J* = 8.3 Hz, 2.4 Hz, H-7), 7.13 (d, *J* = 2.3 Hz, H-5), 6.83 (d, *J* = 8.3 Hz, H-8), 5.21 (s, OCH_2), 4.0 (s, N-CH_2), 2.74 (t, *J* = 5.4 Hz, 2", 5" -2xCH_2, 1.91 (t, J = 5.4 Hz, 3",4"-2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.7 (C-3'), 165.2 (C-5'), 152.9 (C-8a), 130.3 (C-7), 127.4 (C-4), 127.0 (C-5), 126.4 (C-3), 122.4 (C-4a), 120.2 (C-6), 117.2 (C-8), 64.4 (C-2), 53.9 (C-2"), (C-5"), 50.1 (N-CH_2), 23.6 (C-3"), (C-4").ESIMS: m/z 318[M+H], 320[M+H+2].

6-Methoxy-3-[5-(pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene (6d):White solid, mp 78 ^oC, yield 60 %.^1H NMR ($CDCl_3$, 400 MHz): δ 7.45 (s, H-4), 6.76 (m, H-8, H-5), 6.68 (d, *J* = 8.14 Hz, H-8), 5.12 (s, OCH_2), 3.98 (s, N-CH_2), 3.80 (s, 6-OCH_3), 2.75 (t, *J* = 5.2 Hz, 2",5"-2xCH_2), l .90 (t, *J* = 5.2 Hz ,3",4"-2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.5 (C-3'), 165.5 (C-5'), 154.2 (C-6), 148.4 (C-8a), 128.3 (C-4), 121.8 (C-4a), 119.9 (C-3), 116.5 (C-7), 116.3 (C-5), 112.7 (C-8), 64.3 (C-2), 55.6 (6-OCH_3), 53.9 (C-2"), (C-5"), 50.1 (N-CH_2), 23.6 (C-3"), (C-4").ESIMS: m/z 314 [M+H].

8-Methoxy-3-[5-(pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromene(6e):White solid, mp83^oC, yield 52 %. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.47 (m, H-5), 6.83 (m, H-7, H-4), 6.76 (m, H-6), 5.22 (s, OCH_2), 3.94 (s, N-CH_2), 3.89 (s, 8-OCH_3), 2.70 (t, *J* = 5.1 Hz, 2", 5"-2xCH_2), 1.84 (t, *J* = 5.1 Hz, 3",4"-2xCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 176.4 (C-3'), 165.3 (C-5'), 147.6 (C-8), 143.2 (C-8a), 128.0 (C-4), 121.7 (C-3), 121.2 (C-4a), 120.1 (C-6), 118.9(C-7), 113.5 (C-5), 64.5 (C-2), 55.8 (8-OCH_3), 53.8 (C-2"), (C-5"), 50,0 (N-CH_2), 23.5 (C-3"), (C-4"). ESIMS: m/z 314 [M+H].

RESULTS AND DISCUSSION

The synthesis some new heterocyclics several substituted 2*H*-chromene-3-amidoximes **(2)** were synthesized by the reaction of 2*H*-chromene-3-cyanides **(1)** with $NH_2OH.HCl$ in alkaline medium, which on reaction with chloroacetyl chloride in presence of DIPEA leads to 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes**(3)**. These oxadiazole substituted chromenes **(3)** on reaction with different cyclic secondary amines gave new 3-[5-(morpholinomethyl / piperidinomethyl/pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes **(4-6)**.

Synthesis of 2*H*-chromene-3-amidoximes (2a-e):2*H*-chromene-3-amidoximes **(2)** were synthesized by the reaction 2H-chromene-3-cyanides **(1)** with $NH_2OH.HCl$ in presence of triethylamine in ethanol (Scheme-1). These were purified by recrystallisation in ethanol and characterized from their spectra. In the IR spectrum of 2*H*-chromene-3-amidoxime **2a**, the peaks at 3400 cm^{-1} and 3340 cm^{-1} are due to OH and NH_2. In the ^1H NMR (DMSO-d_6, 400 MHz) spectrum of **2a** the *N*-OH appeared at δ 9.76 (s) and the NH_2 at δ 5.19 as broad singlet. In the ^{13}C NMR (DMSO-d_6, 100 MHz) of **2a** the amidoxime carbon resonated at δ 153.7. The DIPMS of **2a** showed the quasi molecular ion peaks at m/z 191(M+H).

Synthesis of 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes (3a-e): 3-[5-(Chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes**(3)** were synthesized by the reaction of 2*H*-chromene-3-amidoximes **(2)** with chloroacetylchloride in the presence of DIPEA in 1,2-dichloroethane at 70^oC (Scheme-1). These were purified by column chromatography and characterized by their spectral data. 3-[5-(Chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromene **(3a)** characterized from its spectral data. In its ^1H NMR ($CDCl_3$, 400 MHz) spectrum, **3a** the CH_2-Cl appeared at δ 4.69 (s). In the ^{13}C NMR ($CDCl_3$, 100 MHz) of **3a** the signals due to oxadiazole ring carbons are at δ 173.8 (C-3'), 166.2 (C-5'), and the CH_2-Cl at δ33.1. The DIPMS of **3a** showed the quasi molecular ion peaks are at m/z 249 (M+H) and 251 (M+H+2).

Synthesis of 3-[5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes (4a-e) : 3-[5-(Morpholinomethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes **(4)** were synthesized by the reaction of 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes **(3)** with morpholine (Scheme-1). These were purified by column chromatography and characterized from their spectral data. 3-[5-(Morpholinomethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromene **(4a)** is characterized from its spectral data. In its ^1H NMR spectrum ($CDCl_3$, 400MHz) the 3", 5"-$(CH_2)_2$ appeared at δ 3.76 (t, J = 5.2 Hz) the 2", 6"-$(CH_2)_2$ at δ 2.64 (t, J = 5.2 Hz), and the N-CH_2 at δ 3.86 (s). In the ^{13}C NMR ($CDCl_3$, 100 MHz) the morpholine and oxadiazole carbons appeared at δ 64.1 (C-3", C-5"), δ 52.9 (C-2", C-6", N-CH_2), δ 175.2 (C-3') and 165.4 (C-5'). The DIPMS of **4a** showed the quasi molecular ion peaks are at m/z 300 (M+H).

Synthesis of 3-[5-(piperidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes (5a-e) : 3-[5-(Piperidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes **(5)** were synthesized by the reaction of 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes **(3)** with piperidine (Scheme-1). These were purified by column chromatography and characterized from their spectral data. 3-[5-(Piperidinomethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromene **5a** is characterized from its spectral . In its ^1H NMR spectrum ($CDCl_3$, 400 MHz), the piperidine 4"-CH_2 appeared at δ 1.41 (m), the 3", 5"-$(CH_2)_2$ at δ 1.65 (m), 2", 6"-$(CH_2)_2$ at δ 2.52 (t, J = 4.7 Hz). 5'-NCH_2 at δ 3.86 (s). In the ^{13}C NMR ($CDCl_3$, 100 MHz) of **5a** the piperidine - oxadiazole carbons appeared at δ 54.1(C-2", C-6"), δ 53.6 (N-CH_2), δ 25.5 (C-3", C-5"), δ 23.6 (C-4"), δ 176.0 (C-3'), and 165.5 (C-5'). The DIP mass spectrum of **5a** showed the quasimolecular ion peak at m/z 298 (M+H).

Synthesis of 3-[5-(pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes (6a-e) : 3-[5-(Pyrrolidinomethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes **(6a-e)** were synthesized by the reaction of 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]2*H*-chromenes **(5)** with pyrrolidine (Scheme-1). These were purified by column chromatography and characterized from their spectral data. 3-[5-(Pyrrolidinomethyl)-1, 2,4-oxadiazol-3-yl]-2*H*-chromene **5a** is characterized from its spectral data. In its ^1H NMR spectrum ($CDCl_3$, 400 MHz), the 2", 5"-$(CH_2)_2$ appeared at δ 2.71 (t, J = 5.2 Hz), the 3",4"-$(CH_2)_2$ appeared at δ 1.87 (t, J =

5.2 Hz), and N-CH_2 at δ 3.98 (s). In the ^{13}C NMR ($CDCl_3$, 100 MHz) of **5a** the pyrrolidine-oxadiazole carbons appeared at δ 53.8 (C-2", C-5"), δ 23.5 (C-3", C-4"), and δ 49.8 (N-$\underline{C}H_2$), δ 176.0 (C-3'), 165.5 (C-5'). The DIPMS of **5a** showed the quasi molecular ion peaks are at m/z 284 (M+H).

APPLICATIONS

The synthesized Chromene and its derivatives are biologically interesting compounds known for their antimicrobial and antifungal, antioxidant, antileishmanial, antitumor etc,

CONCLUSIONS

In conclusion we have developed new heterocyclic systems pendent at 3 positions of 2*H*-3-chromene ring, 2*H*-3-chromene cyanides were synthesized by the Baylis-Hillman reaction. These on reaction with $NH_2OH.HCl$ in presence of triethyl amine in ethanol furnish 2*H*-chromene-3-amidoximes, which on reaction with chloroacetyl chloride in presence of DIPEA gave 3-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes. These on reaction with morpholine, piperidine and pyrrolidine afforded 3-[5-(morpholinomethyl/piperidinomethyl/pyrrolidino methyl)-1,2,4-oxadiazol-3-yl] 2*H*-chromenes.

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