Synthesis and Characterisation of 5-(6-substituted phenyl -2*H*-chromen-3-yl) Oxazole Derivatives

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Abstract: Here we demonstrate the synthesis of various derivatives of 5-(6-substituted phenyl-2H-chromen-3-yl)-oxazoles **5(a-k)** by using Suzuki coupling conditions with different substituted boronic acids and obtained 23-57 % yields. We also synthesised various derivatives of the 5-(substituted 2H-chromen-3-yl)-oxazoles **3(a-j)** mediated by TOSMIC as a reagent and achieved 58-70 % yield.

Keywords: 5-(substituted 2*H*-chromen-3-yl)-oxazoles, 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazoles, suzuki coupling, TOSMIC reagent.

INTRODUCTION

The chroman structural unit is found in a large number of drugs and natural products [1]. Chroman derivatives exhibit various useful biological activities [2], such as antioxidant [3], antiestrogen [4], anticonvulsion [5], and neuroprotection [6]. Many synthetic methods for chromans have been developed [2, 7]. One of the efficient pathways is based on the transformation of 2*H*-chromenes, including oxidation [7a, 8], reduction [9] and conjugate addition [10]. Coumarins (2*H*-chromen-2-ones) are chemical compound (specifically, a benzopyrone) found in many plants or natural products, and readily recognised as the scent of newly-mown hay, and has been used in perfumes since 1882. In view of the ubiquity of this fragment in a variety of biologically active compounds, the synthesis of various 2*H*-*C*hromen-2-one analogues is important in gauging their potential as a source of chemotherapeutics. 2*H*-1-Benzopyrans, commonly known as 2*H*-benzopyrans or 2*H*-chromenes, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The 2*H*-benzopyran daurichromenic acid is known to exhibit anti-HIV properties [11], while coutareagenin possess antidiabetic activity [12]. Derivatives of 3, 4-diphenylchromans are known to have estrogenic activity [13]. Numerous derivatives of 2*H*-benzopyrans are useful for the treatment of proliferative skin disorders and microbial infections [14] and show potent antifungal activity [15]. Derivatives of 2*H*-benzopyrans, like 2,4-diphenyl-2*H*-benzopyran and 2,2, 4-triphenyl-2*H* benzopyran, have been studied for their photochromic behavior [16]. Owing to their biological and pharmaceutical importance, there has been a constant research in the development of new methodologies for the synthesis of 2*H*-chromene derivatives [17]. During the last twenty years, the study of the biological activities of chromene derivatives has been the aim of many scientists [18-27]. Fused chromenes are interesting due to their significant antibacterial [28-32] and novobiocin [33-34] activities. In addition to the above Johnson *et al.* reported [35] the structure-based design of a parallel synthetic array directed toward the discovery of irreversible inhibitors of human rhinovirus 3c protease. Mannhold *et al.* reported [36] the 6-sulfonyl chromenes as highly potent katp-channel openers. Mohamed Hegab *et al.* reported [37] the synthesis and pharmacological activities of some condensed 4-chloro-2, 2-dialkyl chromene-3-carbaldehyde derivatives. El-Saghier *et al.* reported [38] the synthesis and antibacterial activity of some new fused chromenes. Rajitha *et al.* reported [39] the synthesis and biological activity of *meso*-tetrakis (2, 10-dioxo-2*H*, 10*H*-pyrano [2, 3-*f*] chromene-9-yl) porphyrins. Synthesis of 3-substituted chromenes and its derivatives were reported by Perumal *et al.* [40], Kaye *et al.* [41], Wang *et al.* [42], Wu *et al.* [43], Brase *et al.* [44], Johnson *et al.* [35], Min Jiang and Min Shi *et al.* [45], Qian Wang and Finn M.G *et al.* reported [17c], the synthesis of 2*H*-chromenes from salicylaldehydes by a catalytic petasis reaction. Previous attempts to prepare 2*H*-chromenes chemoselectively *via* the cyclisation of 2-

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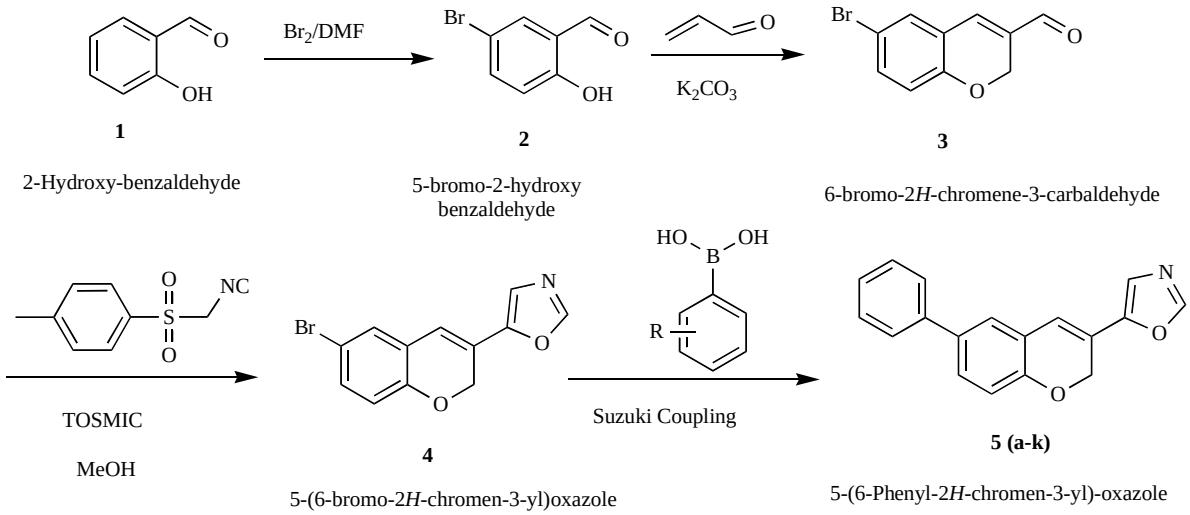


Scheme 1. Synthesis of 6-substituted (2*H*-chromen-3-yl)-oxazole derivatives (5a-k).

hydroxybenzaldehyde derived Baylis–Hillman products had proved unsuccessful affording, instead, complex mixtures of chromene and coumarin derivatives [41, 46]. Chen *et al.* reported [47] the reaction of quinoxalin-2-ones with TOSMIC reagent, and Krishna *et al.* reported [48] that the synthesis of oxazole and pyrrole 3-carbethoxy/3-arylsulfonyl D and L-2-deoxyribosides by TOSMIC addition/cyclization on D and L-2-deoxyribo-1-carboxaldehyde and unsaturated esters. Herr *et al.* [49] reported the preparation of 5-(2-methoxy-4-nitrophenyl)-oxazole, Saikachi *et al.* [50] reported the reaction with pyridine aldehydes to form oxazoles. Wildeman *et al.* reported [51] the reaction with carbon disulfide to form thiazoles. Chromene moiety is present in some of the drugs [1] which are leucoanthocy anidin, guibourtinidol, leucopelargonidin, robalzotan, catechin, nonabine, 11-*nor*-9-carboxy-THC, hyperoside, proanthocyanidin C1, brodifacoum fumarin, and difenacoum. To contribute to this area of research, here, we are interested in developing a methodology that provides facile access to 2*H*-chromene derivatives. To contribute to this area of research, we are interested in developing a methodology that provides facile access to 2*H*-chromene derivatives. However, to the best of our knowledge, there has been no report available on the synthesis of 2*H*-chromene derivatives using the present methodology in the open literature so far.

RESULTS AND DISCUSSION

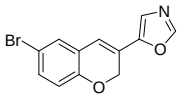
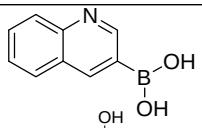
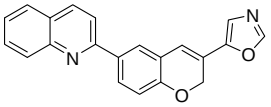
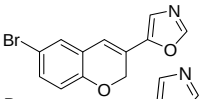
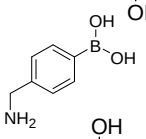
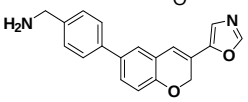
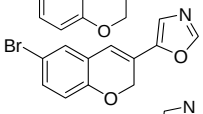
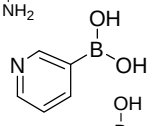
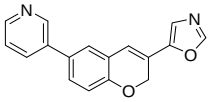
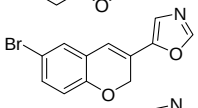
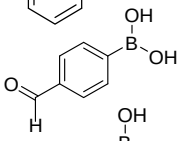
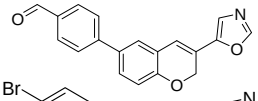
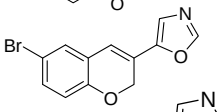
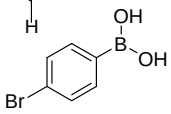
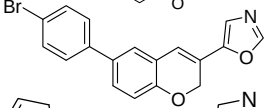
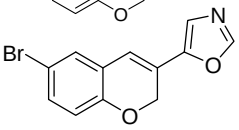
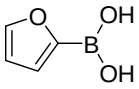
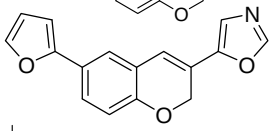
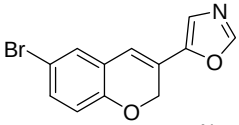
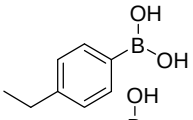
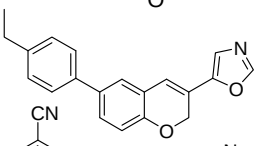
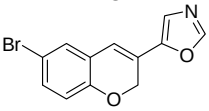
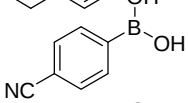
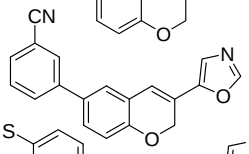
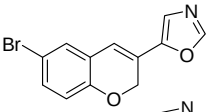
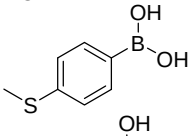
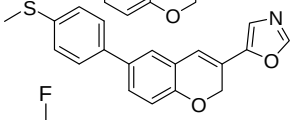
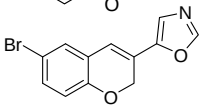
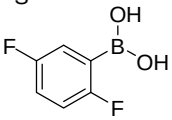
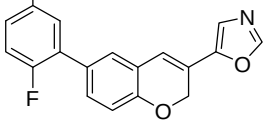
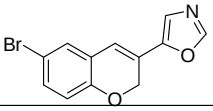
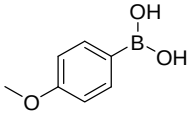
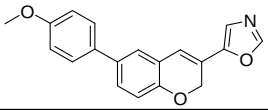
The biosynthesis of coumarin in plants is *via* hydroxylation, glycolysis and cyclisation of cinnamic acid. Coumarin can be prepared in a laboratory in a perkin reaction between salicylaldehyde and acetic anhydride. Here we prepared 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazole compounds **5(a-k)** and substituted (2*H*-chromen-3-yl)-oxazole derivatives **3(a-j)** and results are presented in Tables **1** and **2**.

Present our approach to synthesize 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazole compounds 5(a-k): 5-bromo-2-hydroxybenzaldehyde **2** (5-bromo salicilaldehyde) can be prepared by bromination of salicylaldehyde **1** (2-hydroxybenzaldehyde). By using 5-bromo-2-hydroxy -benzaldehyde **2**, we can prepare 6-bromo-2*H*-chromene-3-carbaldehyde **3** by using the acrolein. Making use of this compound, 6-bromo-2*H*-chromene-3-carbaldehyde **3** can be prepared by mixing 5-bromo-2-hydroxybenzaldehyde **2** and acrolein. Tosyl methyl isocyanide is a useful synthon for the preparation of the oxazoles. This is the key step in the present scheme. To a stirred solution of 6-bromo-2*H*-chromene-3-carbaldehyde **3** in methanol, tosylmethyl isocyanide (TOSMIC) was added at room temperature under nitrogen atmosphere and the resulting reaction mixture was refluxed for four hours. In this way we can obtain 5-(6-bromo-2*H*-chromen-3-yl) oxazole **4** as an off-white solid. By making use of the above compound 5-(6-bromo-2*H*-chromen-3-yl)-oxazole **4**, we have prepared the different derivatives of 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazole compounds **5(a-k)** by using suzuki coupling conditions with different substituted boronic acids. The resulting compounds were confirmed with the physicochemical and NMR, Mass and IR spectroscopy. Here we described the synthesis of different novel 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazole compounds using various reagents in the given below conditions (Scheme **1**).

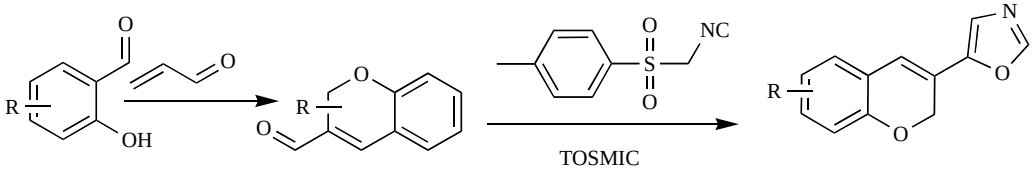
Present our approach to synthesize substituted (2*H*-chromen-3-yl)-oxazole derivatives: Tosyl methyl isocyanide (TOSMIC) is a useful synthon for the preparation of the oxazoles. To a stirred solution of substituted 2*H*-chromene-3-carbaldehyde **2(a-j)** in methanol, tosylmethyl isocyanide (TOSMIC) was added at room temperature under nitrogen atmosphere and the resulting reaction mixture was refluxed for 4 h to obtain the 5-(substituted 2*H*-chromen-3-yl) oxazole derivatives **3 (a-j)**. We can prepare the substituted 2*H*-chromene-3-carbaldehyde **2 (a-j)** by the reaction of substituted 2-hydroxybenzaldehyde **1(a-j)** with acrolein or crotanaldehyde. The reaction carried out in the given below mentioned conditions (Scheme **2**) and the resulting compounds are given in Table **2**.

By using the above substituted 2*H*-chromene-3-carbaldehyde derivatives **2(a-j)**, we have prepared the different derivatives of the 5-(substituted 2*H*-chromen-3-yl)-oxazoles **3(a-j)** mediated by TOSMIC as a reagent, which is a key step in the present scheme.

Table 1. Synthesis of 6-substituted (2H-Chromen-3-yl)-oxazole Derivatives (5a-k).

S.No.	Reagent Used	Boronic acid	Product(5a-k)[a]	Yield(%)[b]
1				34
2				57
3				33
4				23
5				24
6				28
7				39
8				37
9				28
10				34
11				36

[a]All products were characterised by IR, NMR, and mass spectroscopy. [b]Yield refers to pure products after purification by column chromatography.



1 (a-j)

Substituted 2-hydroxy benzaldehyde

2 (a-j)

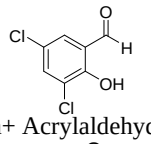
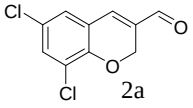
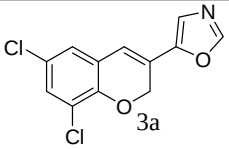
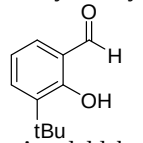
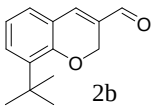
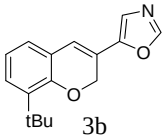
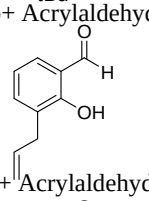
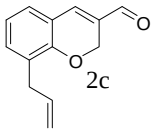
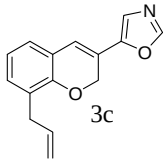
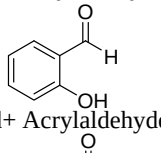
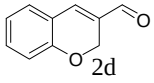
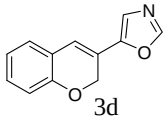
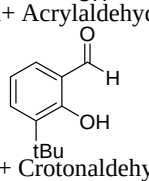
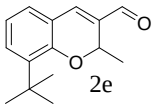
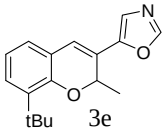
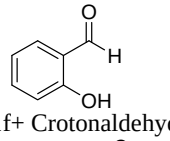
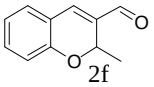
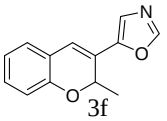
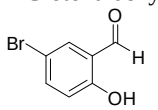
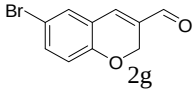
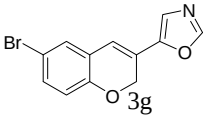
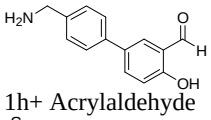
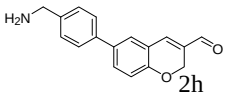
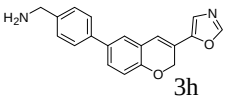
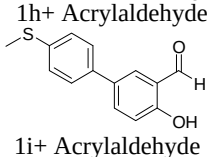
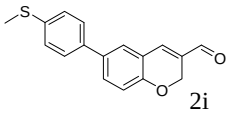
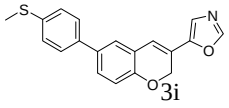
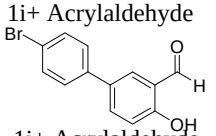
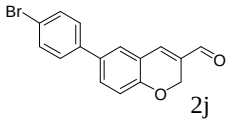
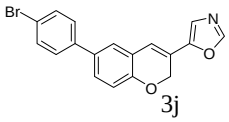
Substituted-2*H*-chromene-3-carbaldehyde

3 (a-j)

5-(Substituted 2*H*-chromen-3-yl) oxazole

Scheme 2. Synthesis of 5-(substituted 2*H*-chromen-3-yl) oxazole derivatives **3 (a-j)**.

Table 2. Synthesis of Substituted 2*H*-chromene-3-carbaldehyde Derivatives 2(a-j) and 5-(substituted 2*H*-chromen-3-yl)-oxazole Derivatives 3(a-j).

S.No.	Various Salicylaldehydes (1a-1j) + Reagent	Product(2a-2j)	Yield(%)	Time (h)	Product(3a-3j)[a]	Yield (%)[b]
1	 1a+ Acrylaldehyde	 2a	75	14.5	 3a	68
2	 1b+ Acrylaldehyde	 2b	76	14.0	 3b	64
3	 1c+ Acrylaldehyde	 2c	73	15.0	 3c	66
4	 1d+ Acrylaldehyde	 2d	76	14.5	 3d	70
5	 1e+ Crotonaldehyde	 2e	62	15.0	 3e	62
6	 1f+ Crotonaldehyde	 2f	63	15.0	 3f	68
7	 1g+ Acrylaldehyde	 2g	84	14.0	 3g	62
8	 1h+ Acrylaldehyde	 2h	60	14.5	 3h	60
9	 1i+ Acrylaldehyde	 2i	88	15.0	 3i	58
10	 1j+ Acrylaldehyde	 2j	82	15.0	 3j	62

[a]All products were characterised by IR, NMR, and mass spectroscopy. [b]Yield refers to pure products after purification by column chromatography.

In summary, we have designed and synthesised some biologically active derivatives of chromene-oxazoles by using various reagents and different conditions. We believe that this procedure is convenient, economic and a user-friendly alternative process for the synthesis of these various novel chromene-oxazole derivatives. Intially, we have prepared the 6-bromo-2*H*-chromene-3-carbaldehyde by using the acrolein and 5-bromosalicylaldehyde and used this aldehyde and tosyl methyl isocyanide (TOSMIC) which is a useful synthon for the preparation of the 5-(6-bromo-2*H*-

chromen-3-yl)-oxazole, at room temperature under nitrogen atmosphere. By making use of the above compound 5-(6-bromo-2*H*-chromen-3-yl) oxazole, we have prepared the different derivatives of 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazole compounds by using $Pd(dppf)_2Cl_2$ as catalyst, Suzuki coupling conditions with different substituted boronic acids. In addition to these compounds substituted 5-(2*H*-chromen-3-yl)-oxazole derivatives are also synthesized by using TOSMIC reagent with substituted-2*H*-chromene-3-carbaldehydes. We have prepared the substituted-2*H*-chromene-3-carbaldehydes by using the substituted salicylaldehydes on reaction with acrolein and TOSMIC is used as synthon for the preparation of the 5-(substituted 2*H*-chromen-3-yl)-oxazoles. This is the key step in the preparation of the 5-(2*H*-chromen-3-yl)-oxazole derivatives. All compounds were characterized by physico chemical and IR, NMR, Mass spectral data.

EXPERIMENTAL

All chemicals and solvents were obtained from Aldrich and Spectro Chem India Pvt. Ltd., and used without further purification. Column chromatographic separations were carried out on silica gel 60-120 mesh size. The ^{1}H NMR spectra of samples were recorded on a JEOL 400-MHz NMR spectrometer using TMS as an internal standard in DMSO-d_6. Mass spectra were recorded on a EIMS.

Synthesis of 5-bromo-2-hydroxybenzaldehyde 2 (Scheme **1):** To a stirred solution of salicylaldehyde **1** (2-hydroxybenzaldehyde) (2 g, 16.3 mmol) in chloroform (30 ml) bromine (0.945 mL, 19.65 mmol) was added at 0^{o}C and the resulting reaction mixture was stirred for 6 h at 50^{o}C. Reaction progress was monitored through TLC which was indicated that complete consumption of starting material. Then reaction mixture was diluted with water (50 ml) extracted with chloroform (3x25 ml). Combined extracts were washed with water (50 ml) followed by brine solution (50 ml), dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to obtain the compound as pale yellow solid (2.5g, 75.98% yield).

Synthesis of 6-bromo-2*H*-chromene-3-carbaldehyde 3: To a stirred solution of 5-bromo-2-hydroxybenzaldehyde (2.5 g, 10.94 mmol) in 1, 4-dioxane (25 ml), potassium carbonate (3.02 g, 21.88 mmol) was added at room temperature under nitrogen atmosphere and stirred for 15 min at room temperature, then acrolein (1.05 g, 18.65 mmol) was added and the resulting reaction mixture was refluxed for 15 h. Reaction progress was monitored by TLC, reaction mixture was cooled to room temperature, filtered through celite pad, celite pad was washed with ethylacetate (50 ml). Filtrate was washed with water (30 ml) followed by brine solution (30 ml), dried over anhydrous sodium sulfate and evaporated the solvent to obtain the crude material which was purified by silica gel (100-200 mesh) column chromatography using 0-10% EtOAc in *n*-Hexane as eluents to afford the 6-bromo-2*H*-chromene-3-carbaldehyde as yellow solid (2.5 g, 84.17% yield).

Synthesis of 5-(6-bromo-2*H*-chromen-3-yl)-oxazole 4: To a stirred solution of 6-bromo-2*H*-chromene-3-carbaldehyde (2.5 g, 10.46 mmol) in methanol (25 ml), TOSMIC (4.08 g, 20.92 mmol) was added at room temperature under nitrogen atmosphere and the resulting reaction mixture was refluxed for 4 h. TLC indicated that complete consumption of starting material. Reaction mixture was cooled to room temperature evaporated the solvent quenched with water extracted with EtOAc (3x25 ml). Combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate and solvent was evapourated to obtain5-(6-bromo-2*H*-chromen-3-yl)-oxazole as off white solid (2g, 68.8% yield).

Synthesis of 5-(6-substituted phenyl-2*H*-chromen-3-yl)-oxazole(5a-k): To a stirred solution of 5-(6-bromo-2*H*-chromen-3-yl)-oxazole (100 mg, 0.36 mmol) and boronic acid (0.431 mmol) in 1, 4-Dioxane: H_2O (4:1) mixture (5 ml), potassium carbonate (124 mg, 0.899 mmol) was added at room temperature under N_2 atm stirred for 5 min, then boronic acid (0.431 mmol) followed by $Pd(dppf)_2Cl_2$ (0.05 eq) were added at room temperature and resulting reaction mixture was degassed with argon gas for 10 min then it was kept in microwave at 100 ^{o}C for 1 h. TLC indicated that complete consumption of starting material. Reaction mixture was filtered through celite pad, celite pad was washed with EtOAc, filtrate was washed with water followed by brine solution, dried over anhydrous sodium sulphate and solvent was evapourated to obtain crude material, which was purified by silica gel (100-200 mesh) column chromatography using 0-10 % EtOAc in *n*-Hexane as eluents.

Spectral data for 5a- 5k: 3-(3-Oxazol-5-yl-2*H*-chromen-6-yl)-quinoline (5a): white solid; mp: 157-159 ^{o}C; IR (KBr): 3414.11, 1492.08, 1115.80, 820.90 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ : 4.90 (m, 4H), 6.83 (d, 2H, *J* =12.0 Hz), 6.90 (s,2H), 7.34 (s, 2H), 7.44-7.51 (m, 4H) ppm; EIMS (m/z): 327.12 (M +H)$^+$.

4-(3-Oxazol-5-yl-2*H*-chromen-6-yl)-benzylamine (5b): white solid; mp: 161-164 ^{o}C; IR (KBr): 3435.93, 1483.67, 1111.39, 814.95 cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.01-5.40 (m, 4H), 6.84 (d, 2H, *J* =8.0 Hz), 6.99 (s, 2H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.45-7.52 (m, 4H), 8.50 (s, 2H) ppm; EIMS (m/z): 304.12 (M +H)$^+$.

3-(3-Oxazol-5-yl-2*H*-chromen-6-yl)-pyridine (5c): white solid; mp: 146-148 ^{o}C; IR (KBr): 3432.40, 1476.27, 1109.61, 798.00 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.01 (s, 2H), 7.00 (d, 1H, *J* =7.0 Hz), 7.09 (s, 1H), 7.44-7.50 (m, 2H), 7.55 (m, 1H), 7.68 (s, 1H), 8.04 (d, 1H, *J* = 8.0 Hz), 8.48-8.56 (2H, m), 8.87 (1H, s) ppm; EIMS (m/z): 277.12 (M +H)$^+$.

4-(3-Oxazol-5-yl-2*H*-chromen-6-yl)-benzaldehyde (5d): white solid; mp: 135-138 ^{o}C; IR (KBr): 3434.96, 1697.08, 1171.72, 812.58 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.01 (s, 2H), 7.00 (d, 1H, *J* = 4.0 Hz), 7.10 (s, 1H), 7.49 (s, 1H), 7.63 (d, 1H, *J* = 6.0 Hz), 7.72-7.76 (m, 1H), 7.85-7.93 (m, 2H), 7.97-8.01 (m, 2H), 8.5 (s, 1H), 10.01 (s, 1H) ppm; EIMS (m/z): 304.00 (M +H)$^+$.

5-[6-(4-Bromo-phenyl)-2*H*-chromen-3-yl]-oxazole (5e): white solid; mp: 131-134 ^{o}C; IR (KBr): 3435.06, 1695.02, 1175.77, 813.57 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.01 (s, 2H), 6.80-6.86 (m,1H), 6.94-7.02 (m, 2H), 7.29-7.36 (m, 1H), 7.45-7.52 (m, 2H), 7.58-7.66 (m, 2H),

7.68-7.78 (m, 1H), 8.50 (s,1H) ppm; EIMS (m/z): 355.00 (M +H)$^+$.

5-(6-Furan-yl-2*H*-chromen-3-yl)-oxazole (5f): white solid; mp: 128-130 ^{o}C; IR (KBr): 3432.54, 1674.74, 1107.74, 815.05 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.84 (d, 3H, *J* = 7.2 Hz), 7.00 (s, 2H), 7.30-7.36 (m, 2H), 7.46-7.52 (m, 3H), 8.50 (s, 1H) ppm; EIMS (m/z): 267.00 (M +H)$^+$.

5-[6-(4-Ethyl-phenyl)-2*H*-chromen-3-yl]-oxazole (5g): white solid; mp: 128-132 ^{o}C; IR (KBr): 3430.71, 1613.76, 1238.22, 820.38 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.22 (t, 3H, *J* = 10.0 Hz), 2.63 (q, 2H, *J* = 8.0 Hz), 5.15 (s, 2H), 6.92 (d, 2H, *J* =12.0 Hz), 6.98 (s, 1H), 7.07 (s, 1H), 7.27 (s, 2H), 7.32-7.35 (m, 1H), 7.92 (d, 1H, *J* =2.0 Hz), 7.47 (d, 2H, *J* = 12.0 Hz), 7.91 (s, 1H) ppm; EIMS (m/z): 267.00 (M +H)$^+$.

4-(3-Oxazol-5-yl-2*H*-chromen-6-yl)-benzonitrile (5h): white solid; mp: 140-142 ^{o}C; IR (KBr): 3435.88, 1474.26, 1109.79, 800.05 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94-6.99 (m, 2H), 7.30-7.33 (m, 1H), 7.35-7.39 (m, 1H), 7.54 (t, 2H, *J* = 6.0 Hz), 7.61 (d, 2H, *J* = 8.0 Hz), 7.76 (d, 1H, *J* = 8.1 Hz), 7.82 (s, 1H), 7.97-8.06 (m, 2H) ppm; EIMS (m/z): 301.15 (M +H)$^+$.

5-[6-(4-Methyl sulfanyl-phenyl)-2*H*-chromen-3-yl]-oxazole (5i): white solid; mp: 151-153 ^{o}C; IR (KBr): 2922.42, 1472.90, 1018.11, 635.54 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 5.15 (s, 2H), 6.93 (d, 1H, *J* = 8.0 Hz), 6.99 (s, 1H), 7.08 (s, 1H), 7.22 (d, 1H, *J* = 8.0 Hz), 7.28-7.34 (m, 3H), 7.39 (d, 1H, *J* =12.0 Hz), 7.42 (s, 1H), 7.92 (s, 1H) ppm; EIMS (m/z): 322.15 (M +H)$^+$.

5-[6-(2,5-Difluoro-phenyl)-2*H*-chromen-3-yl]-oxazole (5j): white solid; mp: 134-136 ^{o}C; IR : (KBr): 3436.06, 1690.82, 1176.75, 814.55 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.01 (s, 2H), 6.92-7.00 (m, 3H), 7.05-7.15 (m, 3H), 7.28-7.36 (m, 2H), 7.91 (m, 1H) ppm; EIMS (m/z): 312.15 (M +H)$^+$.

5-[6-(4-Methoxy-phenyl)-2*H*-chromen-3-yl]-oxazole (5k): white solid; mp: 148-150 ^{o}C; IR (KBr): 3435.34, 1658.98, 1109.68, 825.05 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H), 5.15 (s, 2H), 6.91 (s, 1H), 6.95 (s, 1H), 6.98-6.99 (m, 1H), 7.31 (s, 1H), 7.27 (d, 1H, *J* = 3.0 Hz, 7.43-7.45 (m, 1H), 7.46-7.48 (m, 2H), 7.5 (d, 1H, *J* = 9.0 Hz), 7.91 (s, 1H); EIMS (m/z): 306.15 (M +H)$^+$.

Synthesis of substituted 2*H*-chromene-3-carbaldehyde 2(a-j): To a stirred solution of substituted 2-hydroxybenzaldehyde (10.94 mmol) in 1,4-dioxane (25 mL), K_2CO_3 (21.88 mmol) was added at room temperature under N_2 atmosphere and stirred for 15 min at room temperature, then acrolein (18.65 mmol) was added and the resulting reaction mixture was refluxed for 15 h. Reaction progress was monitored by TLC, reaction mixture was cooled to room temperature, filtered through celite pad, celite pad was washed with EtOAc (50 mL). Filtrate was washed with water (30 mL) followed by brine solution (30 mL), dried over anhydrous sodium sulfate and evaporated the solvent to obtain the crude material which was purified by silica gel (100-200 mesh) column chromatography using 0-10 % EtOAc in *n*-hexane as eluents to afford the substituted-2*H*-chromene-3-carbaldehyde (75-85 % yield).

Synthesis of 5-(substituted 2*H*-chromen-3-yl)-oxazole 3(a-j): To a stirred solution of substituted-2*H*-chromene-3-carbaldehyde (10.46 mmol) in methanol (25 mL), TOSMIC (20.92 mmol) was added at room temperature under N_2 atmosphere and the resulting reaction mixture was refluxed for 4 h. TLC indicated that complete consumption of starting material. Reaction mixture cooled to room temperature evaporated the solvent quenched with water extracted with EtOAc (3x25 mL). Combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and solvent was evaporated to obtain 5-(substituted 2*H*-chromen-3-yl)-oxazole derivatives (60- 69 % yield).

5-(6, 8-Dichloro-2*H*-chromen-3-yl)-oxazole (3a): Off white solid; mp 162–164 ^{o}C; IR (KBr): 3105.37, 1385.97, 1104.66 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.18 (s, 2H), 7.01 (s, 1H), 7.38 (d, *J* = 2.30 Hz, 1H), 7.45 (d, 1H, *J* = 2.33 Hz), 7.50 (s, 1H), 8.53 (s, 1H) ppm; EIMS (*m/z*): 268 (M +H)$^+$; *Anal. Calcd.* for $C_{12}H_7Cl_2NO_2$: C, 53.93; H, 2.62; N, 5.24. Found: C, 53.76; H, 2.60; N, 5.22.

5-(8-*tert*-Butyl-2*H*-chromen-3-yl)-oxazole (3b): Off white solid; mp 157–159 ^{o}C; IR (KBr): 3109.40, 1485.97, 1217.14 cm^{-1}; ^{1}H NMR(400 MHz, DMSO-d_6): δ 1.33 (s, 9H), 4.97(s, 2H), 6.89 (t, *J* =7.62 Hz, 1H), 6.97 (s, 1H), 7.12-7.15 (m, 1H), 7.44 (s, 1H), 8.46 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.913, 34.450, 63.611, 119.558, 119.869, 119.934, 121.902, 123.442, 123.969, 126.238, 127.139, 137.232, 137.611, 151.943, 162.659 ppm; EIMS (*m/z*): 256 (M + H)$^+$; *Anal. Calcd.* for $C_{16}H_{17}NO_2$: C, 75.29; H, 6,66; N, 5.49. Found: C, 75.26; H, 6.64; N, 5.46.

5-(8-Allyl-2*H*-chromen-3-yl)-oxazole (3c): Off-white solid; mp 149–151^{o}C; IR (KBr): 3100.37, 1480.09, 1218.12 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.49 (s, 1H), 5.01-5.05 (m, 4H), 5.99-6.00 (m, 2H), 6.89-6.90 (m, 1H), 6.98 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 8.46 (s, 1H) ppm; EIMS (*m/z*): 240 (M + H)$^+$; *Anal. Calcd.* for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.43; N, 5.85. Found: C, 75.30; H, 5.48; N, 5.83.

5-(2*H*-Chromen-3-yl)-oxazole (3d): Off-white solid; mp 154–156 ^{o}C; IR (KBr): 3105.37, 1485.97, 1217.14 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (s, 2H), 6.85(d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* =12.0 Hz, 1H), 7.15 (d, *J* =7.48, 1H), 7.36 (s, 1H), 8.16 (s, 1H) ppm; EI MS (*m/z*): 200 (M + H)$^+$; *Anal. Calcd.* for $C_{12}H_9NO_2$: C, 72.36; H, 4.52; N, 7.03. Found: C, 72.35; H, 4.50; N, 7.02.

5-(8-*tert*-Butyl-2-methyl-2*H*-chromen-3-yl)-oxazole (3e): Off-white solid; mp 165–167 ^{o}C; IR (KBr): 3105.30, 1485.91, 1217.10 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (s, 3H), 1.35 (m, 9H), 5.49-5.51 (m, 1H), 6.85-7.21 (m, 6H) ppm; EIMS (*m/z*): 270 (M$^+$ H)$^+$; *Anal. Calcd.* for $C_{17}H_{19}NO_2$: C, 75.83; H, 7.06; N, 5.20. Found: C, 75.81; H, 7.04; N, 5.19.

5-(2-Methyl-2*H*-chromen-3-yl)-oxazole (3f): White solid; mp 161–163 ^{o}C; IR (KBr): 3104.02, 1484.92, 1217.16 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (s, 3H), 5.38 (d, *J* = 6.2 Hz, 1H), 6.85 (d, *J* =6.8 Hz, 1H), 6.93-6.94 (m, 1H), 7.18-7.26 (m, 2H), 7.45 (s, 1H), 8.45 (s, 1H) ppm; EIMS (*m/z*): 214 (M + H)$^+$; *Anal. Calcd.* for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.16; N, 6.57. Found: C, 73.23; H, 5.14; N, 6.55.

5-(6-Bromo-2*H*-chromen-3-yl)-oxazole (3g): White solid; mp 168–170 ^{o}C; IR (KBr): 3421.12, 1483.79, 1112.06 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.04 (s, 2H), 6.08 (s, 1H), 6.83 (s, 1H,), 6.97 (s, 1H), 7.285 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* =2.2 Hz, 1H), 8.48 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 39.85, 64.34, 113.47, 117.63, 118.04, 121.08, 124.64, 129.94, 132.12, 147.17, 152.65, 152.99 ppm; EIMS (*m/z*): 278 $(M + H)^{+}$; *Anal. Calcd*. for $C_{12}H_8BrNO_2$: C, 51.98; H, 2.88; N, 5.05. Found: C, 51.88; H, 2.85; N, 5.04.

4-(3-Oxazol-5-yl-2*H*-chromen-6-yl)-benzylamine (3h): White solid; mp 166-168 ^{o}C; IR (KBr): 3435.93, 1483.67, 814.95 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (m, 4H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.99 (s, 2H), 7.29-7.36 (m, 2H), 7.45-7.52 (m, 4H), 8.50 (s, 2H) ppm; EIMS (m/z): 304.12 $(M + H)^{+}$; *Anal. Calcd. for* $C_{19}H_{16}N_2O_2$: C, 75.24; H, 5.28; N, 9.24. Found: C, 75.20; H, 5.26; N, 9.20.

5-[6-(4-Methylsulfanyl-phenyl)-2*H*-chromen-3-yl]-oxazole (3i): White solid; mp 164-166 ^{o}C; IR (KBr): 358.66, 1472.90, 1028.11 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.5 (s, 3H), 6.92-6.95 (d, 1H), 6.99 (s, 1H), 7.08 (s, 1H), 7.18-7.24 (m, 1H), 7.31-7.35 (m, 2H), 7.36-7.40 (m, 1H), 7.43 (s, 1H), 7.45-7.52 (m, 2H), 7.64 (s, 1H), 7.93 (s, 1H) ppm; EIMS (m/z): 322.15 $(M + H)^{+}$; *Anal. Calcd* for $C_{19}H_{15}NO_2S$: C, 71.02; H, 4.67; N, 4.36. Found: C, 71.00; H, 4.64; N, 4.34.

5-[6-(4-Bromo-phenyl)-2*H*-chromen-3-yl]-oxazole (3j): White solid; mp 162-164 ^{o}C; IR (KBr): 3436.53, 1633.93, 813.64 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (s, 2H), 6.80-6.86 (m, 1H), 6.94-7.02 (m, 2H), 7.29-7.36 (m, 1H), 7.45-7.52 (m, 2H), 7.58-7.66 (m, 2H), 7.68-7.78 (m, 1H), 8.50 (s, 1H) ppm; EIMS (m/z): 355.00 $(M + H)^{+}$; *Anal. Calcd* for $C_{18}H_{12}BrNO_2$: C, 61.01; H, 3.38; N, 3.95. Found: C, 61.00; H, 3.34; N, 3.93.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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