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REGULAR ARTICLE

A novel synthesis of chromone based unnatural α-amino acid derivatives†

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Abstract. An efficient method for the preparation of chromone based α-amino acid derivatives by alkylation of glycinate schiff base with 3-bromomethyl chromone as well as 2-bromomethyl chromone has been described. Using this method, 2-amino-3-(4-oxo-2-chromenyl)propanoic acid and 2-amino-3-(4-oxo-3-chromenyl)propanoic acid, two novel chromone-amino acid conjugates have been prepared. Furthermore, the separation of chromone amino acid enantiomers by chiral column chromatography was accomplished.

Keywords. Chromone; unnatural aminoacids; isoflavones; alkylation; hybrid molecules; glycine derivatives.

1. Introduction

Chemically, chromones (4H-chromene-4-ones) are heterocyclic compounds with the benzo-γ-pyrone framework. Molecules containing the chromone or benzopyrone ring have a wide range of biological activities.[1] They have been shown to be tyrosine and protein kinase inhibitors,[2,3] as well as anti-inflammatory,[4] antiviral,[5] antioxidant[6] and antihypertensive agents.[5] Chromone derivatives are also active as benzodiazepine receptors,[7] on lipooxygenase and cyclooxygenase.[8] In addition to this, they have shown to be anticancer agents.[9] Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator.[10] The vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure.[11] The main objectives of the chromone synthesis are not only for the development of more diverse and complex molecules for biological activities but also for other applications such as preparation of fluorescent probes due to the photochemical properties of chromones.[12]

Unnatural amino acids, the non-proteinogenic α-amino acids that either occurs naturally or chemically synthesized have been used widely as chiral building blocks. They have also been used as molecular scaffolds in constructing combinatorial libraries.[13] In recent years, both pharmaceutical companies and academics became interested in the design and synthesis of peptidomimetics and peptide analogues as new therapeutic drugs.[14–16] The progress of Medicinal Chemistry in these fields was probably inspired by the biochemical advancements in the recognition of new naturally occurring peptides possessing useful biological activities and in the elucidation of their physiological functions.[17] However, peptides assembled with natural amino acids present several drawbacks related to metabolic instability, deficiency in selective interactions and reduced oral absorption that prevent their use in therapy.[18] On the other hand, peptidomimetics offer the advantages of nearly countless manipulations in order to control the biological functions, stability, potency, and ADME parameters.[19] In particular, the inclusion of the amino acid framework in a cyclic or bicyclic structure con-

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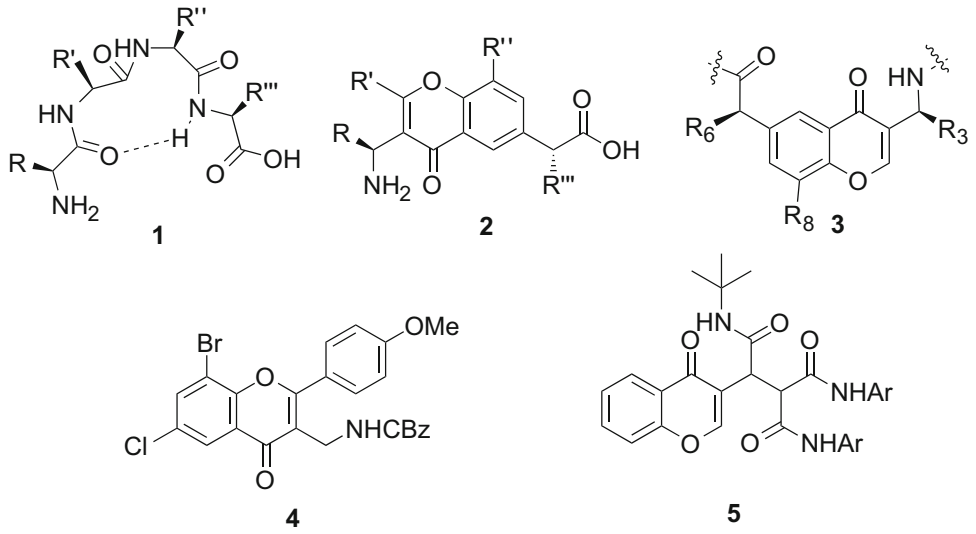


Figure 1. Chromone derivatives as β-turn peptidomimetcis.

fers specific features to the synthesized molecules: well-defined secondary structure, structural rigidity, enhanced binding activity and selectivity.[20,21] The seminal work on synthesis of unnatural amino acids has been done by O'Donnell[22] and Maruoka[23] independently which accelerated the application of this amino acid for practical application.

β-turn peptidomimetics (**1,** Figure 1) has attracted the attention of many researchers in the design of structures[24,25] due to the importance of this fragment in protein folding and in the protein-receptor interaction process.[26,27] Luthman *et al*., has proposed chromones with different functionalized substituents as mimetics of short peptides.[28,29] The reason for their proposal is that the conformation of a β-turn of a peptide (**1,** Figure 1) corresponds well with 2,3,6,8-tetrasubstituted chromone (**2,** Figure 1). The same group has also prepared the chromone derivative **3** as a potential β-turn peptidomimetics with the incorporation of an amino group in the 3-position and a carboxy functionality in the 6-position (**3**, Figure 1).[30] Also, the chromone derivatives **4** and **5** were prepared using different synthetic methodology as β-turn peptidomimetics.[28,31]

Synthesis of hybrid natural products has gained momentum in recent years.[32,33] It is expected that combining features of more than one biologically active natural segment in a single molecule may result in pronounced pharmacological activity while retaining high diversity and biological relevance.[34] Taking into consideration these two biologically significant structures (chromone and α-amino acid), we plan to develop a general method for the synthesis of chromone-amino acid hybrids. There is a report describing the preparation of chromone based amino acid in the literature.[35] However, the method suffers from several disadvantages such as low yield, formation of side products, use of concentrated acid and isolation of polar compounds in each step was cumbersome. In our continuation of endeavour to prepare novel hybrid molecules consisting a variety of natural products,[36] we developed an interest in the synthesis of chromone-based amino acid hybrid and herein we report our results.

2. Experimental

2.1 *Materials and characterization*

Compound **6a** (95% purity) was purchased from Spectrochem, India. Dry solvents were purchased from chemical suppliers and used without further purification. All melting points were taken in open capillaries and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on commercially available Merck TLC Silica gel 60 F_{254}. Silica gel column chromatography was performed on silica gel 60 (spherical 100–200 μm). FTIR spectra were recorded on Perkin-Elmer FT/IR-4000 spectrophotometer and only the characteristic peaks are reported. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. ^{1}H NMR spectra were recorded on Varian-400 (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane. ^{13}C NMR spectra were recorded on Varian-400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR spectra were reported to relative to $CDCl_3$ (77.0). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; br, broad.

2.2 *Experimental procedure for the preparation of 4-oxo-4H-chromene-3-carbaldehyde (**7a**):*

To a solution of compound **6a** (20 g, 147.12 mmol) in DMF (57 mL, 735.02 mmol) was added $(COCl)_2$ (62.5 mL, 735.01 mmol) in a dropwise manner at 0°C under argon atmosphere; then was added 50 mL of DMF and stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After completion of the reaction, the reaction mixture was quenched with water; brown solids were formed. Filtered the solids and washed with water to give the compound **7a** (20 g, 80% yield) as a brown solid. (Melting Range) M.R: 149–153°C; FT-IR: (KBr, cm^{-1}): 3059, 2867, 1647, 1460, 1307, 1145, 1105, 847, 765. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (s, 1H, CHO), 8.5 (s, 1H, Ar-H), 8.3 (dd, J = 8.4, 1.6 Hz, 1H, Ar-H), 7.76 (t, 1H, Ar-H), 7.53 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 (C-11), 175.9 (C-4), 160.6 (C-2), 156.1(C-9), 134.8 (C-7), 126.6 (C-5), 126.1 (C-6), 125.2 (C-10), 120.2 (C-3), 118.5 (C-8); MS: (EI): m/z 175 (M + 1, 100); HRMS: (ESI): Calcd. for $C_{10}H_6O_3$ [M+H]: 175.0392; Found: 175.0395.

2.2a *6-methyl-4-oxo-4H-chromene-3-carbaldehyde (**7b**)*: The compound was prepared according to the procedure similar to compound **7a**. M.R: 166–170°C; FT-IR: (KBr, cm^{-1}): 3427, 3076, 2920, 2852, 1652, 1477, 1329, 1190, 946, 887, 769, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.39 (s, 1H, CHO), 8.53 (s, 1H, Ar-H), 8.08 (d, J = 1.2 Hz, 1H, Ar-H), 7.55 (dd, J = 8.4 Hz, 1H, Ar-H), 7.44 (d, J = 1.2 Hz, 1H, Ar-H), 2.49 (s, 3H, Ar-CH3); MS: (EI): m/z 189 (M + 1, 100).

2.3 *Experimental procedure for the preparation of 3-(hydroxymethyl)-4H-chromen-4-one (**8a**):*

To a solution of compound **7a** (8 g, 45.90 mmol) in THF (80 mL) was added dropwise to 1 M BH_3 in THF (92 mL, 91.90 mmol) under argon atmosphere at 0°C. Then slowly warmed the reaction mixture to RT and stirred for 16 h. The progress of the reaction was monitored by TLC analysis (30% EtOAc/pet ether). After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (3×100 mL). The organic layers were combined, washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gives the compound **8a** (7.0 g, 87% yield) as a pale yellow solid. M.R: 104–108°C; FT-IR: (KBr, cm^{-1}): 3363, 3067, 2293, 1637, 1604, 1466, 1350, 1162, 1026; ^{1}H NMR (400 MHz, DMSO): δ 8.3 (s, 1H, Ar-H), 8.15, (dd, J = 10, 2 Hz,1H, Ar-H), 7.8 (t, 1H, Ar-H), 7.65 (d, J = 11.2 Hz, 1H, Ar-H), 7.55 (t, 1H, Ar-H), 5.2 (t,1H, OH), 4.45 (d, J = 7.6 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO) δ 175.9, 155.9, 153.5, 134.0, 125.2, 124.8, 124.0, 123.1, 118.4, 55.3, MS: (EI): m/z 177 (M+1, 100).HRMS: (ESI): Calcd. for $C_{10}H_8O_3$ [M+H] :177.0542; Found:177.0552

2.3a *3-(hydroxymethyl)-6-methyl-4H-chromen-4-one (**8b**)*: The compound was prepared according to the procedure similar to compound **8a**. M.R: 136–140°C; FT-IR: (KBr, cm^{-1}): 3417, 3065, 2923, 1636, 1481, 1330, 1202, 1020, 814, 693. ^{1}H NMR (400 MHz, CDCl3): δ 8.0 (s, 1H, Ar-H), 7.91, (s, 1H, Ar-H), 7.49 (d, J =2 Hz, 1H, Ar-H), 7.38 (d, J =8.8 Hz, 1H, Ar-H), 4.58 (d, J =6 Hz, 2H, CH_2), 2.97 (t, 1H, OH), 2.47 (s, 3H, Ar-CH_3); MS: (EI): m/z 191 (M+1, 100).

2.4 *Experimental procedure for the preparation of 3-(bromomethyl)-4H-chromen-4-one (**9a**):*

To a solution of compound **8a** (7 g, 39.70 mmol) in CH_2Cl_2 (70 mL) was added PBr_3 (12.88 g, 47.70 mmol) at 0°C and stirred the reaction mixture at RT for 1 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After the reaction was completed, the reaction mixture was quenched with ice and extracted with EtOAc (3×100 mL). Combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the compound **9a** (8 g, 84% yield) as a light yellow solid. M.R: 143–147°C; FT-IR: (KBr, cm^{-1}): 2925, 2853, 1645, 1617, 1569, 1465, 1172, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3 (dd, J = 8.0 Hz, 1H, Ar-H), 8.15 (s, 1H, Ar-H), 7.7 (t, 1H, Ar-H), 7.45 (m, 2H, Ar-H), 4.45(s, 2H, CH_2); ^{13}CNMR (100 MHz, $CDCl_3$); δ 175.7, 156.9, 154.6, 133.9, 126.0, 125.5, 121.8, 123.7, 118.1,23.6; MS:(ESI):m/z 238 (M + 2,100). HRMS (ESI): Calcd. for $C_{10}H_7BrO_2$ [M + H]: 238.9714; Found: 238.9708.

2.4a *3-(bromomethyl)-6-methyl-4H-chromen-4-one (**9b**)*: The compound was prepared according to the procedure similar to compound **9a**. M.R: 150–154°C; FT-IR: (KBr, cm^{-1}): 3299, 3065, 2938, 1733, 1647, 1546, 1483, 1309, 1246, 1024, 816.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H, Ar-H), 8.04 (d, J = 4 Hz, 1H, Ar-H), 7.37 (s, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 4.40 (s, 2H, CH_2), 2.46 (s, 3H, Ar-CH_3); MS:(ESI):m/z 255 (M + 2,100).

2.5 *Experimental procedure for the preparation of methyl 2-(diphenylmethyleneamino)-3-(4-oxo-4H-chromen-3-yl)propanoate(**11a**):*

To a solution of compound **9a** (0.5 g, 2.09 mmol) in CH_3CN (10 mL) was added methyl 2-(diphenylmethyleneamino) acetate (**10**) (0.52 g, 2.09 mmol) and K_2CO_3 (0.86 g, 6.27 mmol) and stirred for 24 h at reflux temp. The progress of the reaction was monitored by TLC analysis (30% EtOAc/pet ether). After the reaction was completed, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc. Organic layer was separated and washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product which was purified by silica gel column chromatography (20% EtOAc/Pet ether) to give the pure compound **11a** (0.7 g, 81% yield) as an off white solid. M.R: 118–122°C; FT-IR: (KBr, cm^{-1}): 3059,

2950, 2927, 2852, 1737, 1644, 1613, 1465, 782, 761; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.0 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.6 (m, 3H, Ar-H), 7.35 (m, 7H, Ar-H), 7.2 (t, 2H, Ar-H), 6.85 (d, J = 7.2 Hz, 2H, Ar-H), 4.5 (m, 1H, CH), 3.72 (s, 3H, OCH_3), 3.32 (dd, J = 14.4 Hz, 1H, CH_2), 2.85 (dd, J = 13.6, 8.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 172.1, 171.5, 156.2, 153.6, 139.3, 139.3, 135.6, 133.2, 133.2, 130.4, 130.0, 130.0, 130.0, 128.8, 128.7, 128.6, 128.6, 128.0, 128.0, 123.8, 120.4, 118.0, 62.8, 52.1, 29.6; MS (EI): m/z 412 (M+1, 100). HRMS: (ESI): Calcd. for $C_{26}H_{21}NO_4$ [M + H]:412.1522; Found: 412.1549.

2.5a *Methyl 2-(diphenylmethyleneamino)-3-(6-methyl -4-oxo-4H-chromen-3-yl)propanoate (**11b**)*: The compound was prepared according to the procedure similar to compound **11a**. M.R: 102–106°C; FT-IR: (KBr, cm^{-1}): 3441, 2927,1736, 1640, 1481, 1437, 1280, 1164, 783, 694.; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.854 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.58 (dd, J = 1.2 Hz, 2H, Ar-H), 7.44 (d, J=1.6 Hz, 1H, Ar-H), 7.42 (d, J = 1.6 Hz, 1H, Ar-H), 7.37 (m, 4H, Ar-H), 7.20 (t, J=12.4 Hz, 2H, Ar-H), 6.88 (d, J = 5.6 Hz, 2H, Ar-H), 4.47 (m, 1H, CH), 3.72 (s, 3H, OCH_3), 3.30 (dd, J = 10.8 Hz, 1H, CH_2), 2.81 (dd, J = 11.2 Hz, 1H, CH_2), 2.44 (s,2H, Ar-CH_3); MS (EI): m/z 426 (M + 1, 100).

2.6 *Experimental procedure for the preparation of methyl 2-amino-3-(4-oxo-4H-chromen-3-yl) propanoate hydrochloride (**12**):*

To a solution of compound **11a** (0.2 g, 0.486 mmol) in Et_2O (10 mL) was added 1N HCl (1 mL) at 0°C. The reaction mixture was stirred at RT for 2 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether) which indicated completion of the reaction. After completion of the reaction, ether layer was separated. Lyophilization of aqueous layer gave the compound **12 (**off-white solid) as HCl salt (0.110 g, 80% yield). M.R: 207–210°C; FT-IR: (KBr, cm^{-1}): 2988, 2957, 2924, 2852, 1741, 1644, 1463, 1347, 1246, 114; ^{1}H NMR (400 MHz, D_2O): δ 8.25 (s, 1H, Ar-H), 8.1 (d, J = 8 Hz, 1H, Ar-H), 7.85 (t, 1H, Ar-H), 7.69 (d, J = 8.4 Hz, 1H, Ar-H), 7.5 (t, 1H, Ar-H), 4.3 (t, 1H, CH), 3.7 (s, 3H, OCH_3) 3.06 (dd, J = 14.4 Hz, 1H, CH_2), 2.87 (dd, J = 14.4 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO) δ 176.7, 169.2, 155.9, 155.8, 134.2, 125.4, 124.9, 123.1, 118.3, 117.0, 52.8, 50.4, 26.6; MS: (EI): m/z 248 (M + 1,100). HRMS: (ESI): Calcd. for $C_{13}H_{13}NO_4$ [M + H]: 248.0931; Found: 248.0923.

2.6a *Methyl 2-amino-3-(6-methyl-4-oxo-4H-chromen-3-yl)propanoate hydrochloride (**16**)*: The compound was prepared according to the procedure similar to compound **12**. M.R: 212–216°C; FT-IR: (KBr, cm^{-1}): 3427, 2022, 1750, 1640, 1484, 1237, 1125, 1046, 814, 700.: ^{1}H NMR (400 MHz, DMSO): δ 8.43 (bs, 3H, NH2.HCl), 8.25 (s, 1H, Ar-H), 7.85 (d, J = 1.2 Hz, 1H, Ar-H), 7.66 (t, J = 8 Hz, 1H, Ar-H), 7.58 (d, J = 8 Hz, 1H, Ar-H), 4.28 (s, 1H, CH), 3.74 (s, 1H, OCH_3), 2.99 (dd, J = 14.4 Hz, 1H, CH_2) 2.87 (dd, J = 14.4 Hz, 1H, CH_2), 2.49 (s, 3H, CH3); MS: (EI): m/z 262 (M + 1,100).

2.7 *Experimental procedure for the preparation of methyl 2-(tert-butoxycarbonylamino)-3-(4-oxo-4H-chromen-3-yl)propanoate(**13**):*

To a solution of compound **12** (0.2 g, 0.81 mmol) in dioxaneb(10 mL) was added Et_3N (0.24 g, 2.43 mmol) followed by Boc_2O (0.358 g, 1.618 mmol) at 0°C and the reaction mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After completion of the reaction, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc. The combined organic layers was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum to give the crude product which was purified by silica gel column chromatography (15 % EtOAc/Pet ether) to give the pure compound **13** (0.210 g, 75% yield) as an off-white solid. M.R: 123–127°C. FT-IR: (KBr, cm^{-1}):. 3306, 2979, 2927, 1751, 1717, 1630, 1600,1522, 1363, 1164, 1058, 1015; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 6.4 Hz, 1H, Ar-H), 7.8 (s, 1H, Ar-H), 7.675–7.655 (m, 1H, Ar-H), 7.45–7.39 (m, 2H, Ar-H), 5.73 (bs,1H, NH), 4.51 (bs, 1H, CH), 3.75 (s, 3H, OCH_3), 3.02–2.89 (m, 2H, CH_2),1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO) δ 178.0, 172.1, 156.4, 155.3, 153.8, 133.7, 126.0, 125.1, 123.6, 119.9, 118.0, 79.7, 53.5, 52.3, 28.4, 28.2, 28.2, 28.2: MS: (EI): m/z 348 (M^+1, 100). HRMS: (ESI): Calcd. for $C_{18}H_{21}NO_6$ [M + H]:348.1424; Found: 348.1447

2.7a *Methyl 2-(tert-butoxycarbonylamino)-3-(6-methyl-4-oxo-4H-chromen-3-yl)propanoate (**17**)*: The compound was prepared according to the procedure similar to compound **13**. M.R: 116–120°C. FT-IR: (KBr, cm^{-1}): 3323, 2970, 2923, 1754, 1716, 1637, 1531, 1164, 1045, 807; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8 Hz, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.48 (dd, J = 8.8 Hz, 1H, Ar-H), 7.34 (d, J = 8.8 Hz, 1H, Ar-H), 5.76 (bs,1H, NH), 4.49 (bs, 1H, CH), 3.74 (s, 3H, OCH_3), 3.02 (d, J = 4.8 Hz, 2H, CH_2), 2.45 (s, 3H, Ar-CH_3), 1.39 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO) δ 178.1, 172.1, 155.4, 154.7, 153.7, 135.1, 135.0,125.2, 123.3, 119.7, 117.7, 79.7, 53.6, 52.3, 29.6, 28.4,28.3,28.2, 20.9.: MS: (EI): m/z 362 (M^+1, 100).

2.8 *Experimental procedure for the preparation of methyl 3-(4-oxo-4H-chromen-3-yl)-2-pivalamidopropanoate (**14**)***:**

To a solution of compound **12** (0.2 g, 0.809mmol) in dioxane (10 mL) was added Et_3N (0.245 g, 2.43 mmol) followed by pivolyl chloride (0.194 g, 1.618 mmol) at 0°C and then the reaction mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After completion of the reaction, water was added to

the reaction mixture and extracted with EtOAc. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum to give the crude product which was purified by silica gel column chromatography (15 % EtOAc/Pet ether) to give the pure compound **14** (0.205 g, 77% yield) as an off-white solid. M.R: 118–122°C. FT-IR (KBr, cm^{-1}): 3334, 2974, 1738, 1636, 1533, 1467, 1248, 1147, 1008; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 8 Hz 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.71–7.67 (m, 1H, Ar-H), 7.47–7.41 (m, 3H, Ar-H), 4.62 (t, 1H, CH), 3.72 (s, 3H, OCH_3), 2.99 (m, 2H, CH_2),1.18 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO): δ 178.8, 171.6, 156.4, 154.2, 154.2, 133.9, 125.8, 125.4, 123.5, 120.3, 118.1, 53.6, 52.2, 38.4, 27.7, 27.3, 27.3, 27.3; MS: (EI): m/z 332 (M^+1, 100); HRMS: (ESI): Calcd. for $C_{18}H_{21}NO_5$ [M + H] :332.1554; Found: 332.1498.

2.8a *Methyl 3-(6-methyl-4-oxo-4H-chromen-3-yl)-2-pivalamidopropanoate (**18**)*: The compound was prepared according to the procedure similar to compound **14**. M.R: 99–104°C. FT-IR (KBr, cm^{-1}): 3364, 2963, 2924, 1745, 1641, 1523, 1481, 1268, 753.; ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.01 (s, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.51 (dd, J = 4.8 Hz 2H, Ar-H), 7.36 (s, 1H, NH), 4.61 (t, J = 6.4 Hz, 1H, CH), 3.72 (s, 3H, OCH_3), 2.98 (t, J=7.2 Hz, 2H, CH_2), 2.46 (s, 3H, Ar-CH_3), 1.24 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO): δ 178.9,178.9, 171.6, 154.7, 154.1, 135.4, 135.3, 125.0, 123.2, 120.1, 117.8, 53.7, 52.2, 38.47, 27.8,27.8, 27.8, 27.3,20.9. MS: (EI): m/z 346 (M^+1, 100);

2.9 *Experimental procedure for the preparation of methyl 2-acetamido-3-(4-oxo-4H-chromen-3-yl) propanoate (**15**)*:

To a solution of compound **12** (0.25 g, 1.01 mmol) in THF (10 mL) was added Et_3N (0.306 g, 3.03 mmol) fallowed by acetyl chloride (0.157 g, 2.02 mmol) at 0°C. Then the reaction mixture was stirred at RT for 24 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/ pet ether). After completion of the reaction, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc. The combined organic layers was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum to give the crude product which was purified by silica gel column chromatography to give pure compound **15** (0.230 g, 79% yield) as an off-white solid. M.R: 130–134°C, FT-IR: (KBr, cm^{-1}): 3328, 3059, 2943, 1741, 1644, 1534, 1462, 1356, 1284, 1043; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 8 Hz 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.72–7.68 (m, 1H, Ar-H), 7.41–7.52 (m, 2H, Ar-H), 7.26 (bs, 1H, Ar-H), 4.69 (m, 1H, CH), 3.73 (s, 3H, OCH-$_3$), 2.98 (d, 2H, CH_2), 2.0 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3): δ 178.9, 171.6, 170.3, 156.5, 154.3, 134.1, 126.0, 125.5, 123.6, 120.2, 118.2, 53.5, 52.4, 28.2, 23.1; MS: (EI): m/z 290 (M^+1, 100); HRMS: (ESI): Calcd. for $C_{15}H_{16}NO_5$ [M+H] :290.1039; Found: 290.1028. The racemic compound **15** was purified by chiral HPLC using Chiralcel OX-H, Hexane/EtOH (70:30) as eluent.

2.9a *Methyl 2-acetamido-3-(4-oxo-4H-chromen-3-yl) propanoate **15i (-)***: M.R: 152–156°C, FT-IR: (KBr, cm^{-1}): 3295, 3063, 2925, 1729, 1647, 1538, 1465, 1315, 1254,1021; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 8 Hz 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.72–7.68 (m, 1H, Ar-H), 7.41–7.52 (m, 2H, Ar-H), 7.26 (bs, 1H, Ar-H), 4.69 (m, 1H, CH), 3.73 (s, 3H, OCH_3), 2.98 (d, 2H, CH_2),2.0 (s, 3H, CH_3); ^{13}C NMR(100 MHz, CDCl3): δ 178.9, 171.6, 170.3, 156.5, 154.3, 134.1, 126.0, 125.5, 123.6, 120.2, 118.2, 53.5, 52.4, 28.2, 23.1; MS (EI): m/z 290 (M^+1, 100); HRMS: (ESI): Calcd. for $C_{15}H_{16}NO_5$ [M+H]: 290.1021; Found: 290.1028; Specific Rotation: $[\alpha]^{25}_{(C=0.25\%,CHCl3)} = -7.024$

2.9b *Methyl 2-acetamido-3-(4-oxo-4H-chromen-3-yl) propanoate **15i (+)***: M.R:149–153°C, FT-IR: (KBr, cm^{-1}): 3295, 3063, 2954, 1730, 1647, 1539, 1465, 1314, 1275,1020; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 8 Hz 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.72–7.68 (m, 1H, Ar-H), 7.41–7.52 (m, 2H, Ar-H), 7.26 (bs, 1H, Ar-H), 4.69 (m, 1H, CH), 3.73 (s, 3H, OCH_3), 2.98 (d, 2H, CH_2), 2.0 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3): δ 178.9, 171.6, 170.3, 156.5, 154.3, 134.1, 126.0, 125.5, 123.6, 120.2, 118.2, 53.5, 52.4, 28.2, 23.1; MS: (EI): m/z 290 (M^+1, 100).HRMS (ESI): Calcd. for $C_{15}H_{16}NO_5$ [M+H]: 290.1022; Found: 290.1028; Specific Rotation:$[\alpha]^{25}_{(C=0.25\%,\ CHCl3)} = +7.76$

2.9c *Methyl 2-acetamido-3-(6-methyl-4-oxo-4H-chromen-3-yl)propanoate (**19**)*: The compound was prepared according to the procedure similar to compound **15.** M.R: 159–163°C, FT-IR: (KBr, cm^{-1}): 3433, 3298, 3065, 2924, 1735, 1636, 1478, 1329, 814, 697, 595; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, J = 8 Hz 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.51 (dd, J = 8.8 Hz 2H, Ar-H), 7.37 (bs, 1H, NH), 4.68 (d, J = 6.4 Hz, 1H, CH), 3.72 (s, 3H, OCH-$_3$), 2.96 (d, J = 6 Hz, 2H, CH_2), 2.46 (s, 3H, -Ac), 2.01 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, CDCl3): δ 178.9, 171.5, 170.2, 154.7, 154.2, 135.4, 135.3, 125.1, 123.2, 119.8, 117.8, 53.5, 52.3, 28.1, 23.0, 20.9,; MS: (EI): m/z 304 (M^+1, 100).

2.10 *Experimental procedure for the preparation of ethyl 4-oxo-4H-chromene-2-carboxylate (**20a**):*

To a solution of compound **6a** (5 g, 36.71 mmol) in THF (50 mL) was added 21% NaOEt in EtOH (25 mL) at 0°C in drop wise manner under argon atmosphere. Then diethyl oxalate was added in drop wise manner and stirred at 60°C for 3 h. Then cooled the reaction mixture to 0°C and slowly added 20 mL of 36% HCl and stirred at 60°C. The progress of the reaction was monitored by TLC analysis (10% EtOAc/pet ether). After completion of the reaction, solvent was distilled off and quenched with water. Solid was formed, filtered the solid and washed with water to give the pure compound **20a** (7 g, 87% yield) as a brown solid. M.R: 71–75°C; FT-IR: (KBr, cm^{-1}): 3073, 2924, 1738, 1627, 1584, 1465, 1304, 1245, 750;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, J = 8.0 Hz, 1H, Ar-H), 7.8 (t, 1H, Ar-H), 7.63 (d, J = 8 Hz, 1H, Ar-H), 7.4 (t, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 4.5 (m, 2H, CH_2), 1.45 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 160.5, 155.9, 152.8, 134.2, 125.4, 125.7, 124.4, 118.3, 114.7, 62.8, 14.4;. MS: (EI): m/z 219 (M+1, 100); HRMS: (ESI): Calcd. for $C_{12}H_{10}O_4$ [M+H]: 219.0666; Found: 219.0657

2.10a *Ethyl 6-methyl-4-oxo-4H-chromene-2-carboxylate (**20b**)*: The compound was prepared according to the procedure similar to compound **20a**. M.R: 108–112°C; FT-IR: (KBr, cm^{-1}): 3043, 2917, 1749, 1653, 1481, 1242, 1096, 1019, 949, 832. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 7.11 (s, 1H, Ar-H), 4.47 (q, 2H, OCH_2), 2.47 (s, 3H, Ar-CH_3), 1.43 (t, J = 5.6 Hz, 3H, CH_3); MS: (EI): m/z 233 (M+1, 100)

2.11 *Experimental procedure for the preparation of 2-(hydroxymethyl)-4H-chromen-4-one (**21a**):*

To a solution of compound **20a** (3 g, 13.70 mmol) in MeOH (60 mL) was added $NaBH_4$ (0.99 g, 27.5 mmol) under argon atmosphere at 0°C and stirred the reaction mixture at RT for 16 h. The progress of the reaction was monitored by TLC analysis (30% EtOAc/pet ether). After completion of the reaction, the reaction mixture was quenched with 1N HCl (20 mL) and extracted with EtOAc (3×100 mL). Combined organic layers was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the pure compound **21a** (2.0 g, 82% yield) as an off-white solid. M.R: 162–166°C; FT-IR: (KBr-cm^{-1}): 3858, 3359, 3077, 2930, 2449, 1639, 1598, 1570, 1464, 1402, 1354, 1225, 1118, 1089, 756; ^{1}H NMR (400 MHz, DMSO): δ 8.04 (dd, J = 7.6 Hz, 1H, Ar-H), 7.8 (t, 1H, Ar-H), 7.62 (d, J = 8 Hz, 1H, Ar-H), 7.55 (t, 1H, Ar-H), 6.35 (s, 1H, Ar-H), 5.8 (t, 1H, OH), 4.45 (d, J = 6.4 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO) δ 176.7, 169.6, 155.6, 134.0, 125.2, 124.8, 123.3, 118.1, 107.2, 59.7.; MS: (EI): m/z 177 (M+1,100); HRMS: (ESI): Calcd. for $C_{10}H_8O_3$ [M+H] :177.0541; Found:177.0552.

2.11a *2-(hydroxymethyl)-6-methyl-4H-chromen-4-one (**21b**)*: The compound was prepared according to the procedure similar to compound **21a.** M.R: 154–158°C; FT-IR: (KBr-cm^{-1}): 3360, 2831, 1736, 1649, 1607, 1479, 1363, 1225, 1091, 960, 812.; ^{1}H NMR (400 MHz, CDCl3): δ 7.98 (d, J = 7.2 Hz, 1H, Ar-H), 7.48 (dd, J = 8.8 Hz, 1H, Ar-H), 7.32 (d, J = 8.4 Hz, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 4.6 (s, 2H, CH_2), 2.45 (s, 3H, Ar-CH_3); MS: (EI): m/z 191 (M+1,100).

2.12 *Experimental procedure for the preparation of 2-(bromomethyl)-4H-chromen-4-one (**22a**):*

To a solution of compound **21a** (1g, 5.6 mmol) in CH_2Cl_2 (20 mL) was added PBr_3 (1 mL, 11.36 mmol) at 0°C and stirred at RT for 1 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After completion of the reaction, the reaction mixture was quenched with ice and extracted with EtOAc (3×100mL). Organic layers were combined and washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuum gave the pure compound **22** (1.1 g, 82% yield) as light yellow solid. M.R: 122 − 126°C; FT-IR (KBr,cm^1): 3348, 3066, 3037, 2975, 1667, 1631, 1463, 1386, 1220, 1117; ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8 Hz,1H, Ar-H), 7.8 (t, 1H, Ar-H), 7.50 (d, J = 9.6 Hz, 1H, Ar-H), 7.43 (t,1H, Ar-H),6.45(s,1H, Ar-H),4.3(s,2H, CH_2);^{13}CNMR:(100 MHz,$CDCl_3$); δ=178.0, 162.5, 156.3, 134.1, 125.6, 125.4, 118.0, 117.8, 111.2, 27.3; MS (EI): m/z 239(M, 100); HRMS (ESI): Calcd. for $C_{10}H_7BrO_2$ [M+H] :238.9708; Found: 238.9708.

2.12a *2-(bromomethyl)-6-methyl-4H-chromen-4-one (**22b**)*:: The compound was prepared according to the procedure similar to compound **22a**. M.R : 124 − 128°C; FT-IR (KBr,cm^1): 3045, 1636, 1621, 1479, 1431, 1372, 1283, 1216, 1122, 968, 874, 811.; ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 1.2 Hz, 1H, Ar-H), 7.51 (dd, J = 9.2 Hz 1H, Ar-H), 7.39 (d, J = 8.8 Hz, 1H, Ar-H), 6.38 (s,1H, Ar-H), 4.25 (s,2H, CH_2), 2.45 (s, 3H, Ar-CH_3); MS (EI): m/z 255(M+2, 100).

2.13 *Experimental procedure for the preparation of methyl 2-(diphenylmethyleneamino)-3-(4-oxo-4H-chromen-2-yl)propanoate (**23a**):*

To a solution of compound **22a** (0.5 g, 2.09 mmol) in CH_3CN (10 mL) was added methyl 2-(diphenylmethyleneamino) acetate **10** (0.52 g, 2.09 mmol) and K_2CO_3 (0.865 g, 6.27 mmol) at RT and the reaction mixture was stirred for 24 h at reflux temp. The progress of the reaction was monitored by TLC analysis (30% EtOAc/pet ether). After completion of the reaction, water was added to the reaction mixture and extracted with EtOAc. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product which was purified by silica gel column chromatography to give compound **23a** (0.6 g, 70% yield) as an off-white solid. M.R: 116–120°C; FT-IR: (KBr, cm^{-1}): 3057, 2950, 1982, 1741, 1659, 1618, 1468, 1381, 1276, 1166; ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 7.6, 1.6 Hz, 1H, Ar-H), 7.6 (m, 3H, Ar-H), 7.35 (m, 5H, Ar-H), 7.3 (m, 2H, Ar-H), 7.12 (d, J = 8.4 Hz, 1H, Ar-H), 6.89 (d, J = 6.8 Hz, 2H, Ar-H), 6.2 (s,1H, Ar-H), 4.65 (dd, J = 9.6, 4 Hz, 1H, CH), 3.8 (s, 3H, OCH_3), 3.30 (dd, J = 14.0, 3.6 Hz, 1H, CH_2), 3.21(dd, J = 14.0, 9.6 Hz,1H, CH_2); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 177.8, 172.3, 171.1, 165.3, 156.1, 138.8, 138.8, 135.4, 133.3, 133.3, 130.7, 130.7, 128.8, 128.7, 128.3, 128.3, 128.0, 128.0, 125.6, 124.9, 123.5, 117.8, 112.0, 62.7, 52.6, 38.4; MS (EI): m/z 412 (M+1, 100). HRMS (ESI): Calcd. for $C_{26}H_{21}NO_4$ [M+H]: 412.1528; Found: 412.1549.

2.13a *Methyl 2-(diphenylmethyleneamino)-3-(6-methyl-4-oxo-4H-chromen-2-yl)propanoate (**23b**)*: The compound was prepared according to the procedure similar to compound **23a**. M.R: 138–142°C; FT-IR: (KBr, cm^{-1}): 3054, 1735, 1645, 1434, 1370, 1278, 1217, 1072, 954, 820, 694.; ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 7.92 (s, 1H, Ar-H), 7.53 (dd, J= 6 Hz, 2H, Ar-H), 7.41-7.39 (m, 3H, Ar-H), 7.38-7.35 (m, 2H, Ar-H), 7.29-7.27 (m, 2H, Ar-H), 7.03 (dd, J = 6.8 Hz, 1H, Ar-H), 6.87 (s, 2H, Ar-H), 6.17 (s, 1H, Ar-H), 4.62 (m,1H, CH), 3.79 (s, 3H, OCH_3), 3.29-3.16 (m, 2H, CH_2), 2.43 (s,3H, Ar-CH_3); MS (EI): m/z 426 (M+1, 100).

2.14 *Experimental procedure for the preparation of methyl 2-amino-3-(4-oxo-4H-chromen-2-yl) propanoate hydrochloride (**24**):*

To a solution of compound **23a** (0.2 g, 0.486 mmol) in Et_2O (10 mL) was added 1N HCl (1 mL) at 0°C. Then, the reaction mixture was stirred at RT for 2 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After completion of the reaction, ether layer was separated. Lyophilisation of aqueous layer gave compound **24** as HCl salt (0.1 g, 73% yield) as an off-white solid. M.R: 148–152°C; FT-IR: (KBr, cm^{-1}): 3729, 3625, 2326, 2899, 2690, 1752, 1495, 1331,1281, 1181; ^{1}H NMR: (400 MHz, D_2O): δ 8.13 (d, J = 10.8 Hz, 1H, Ar-H), 7.9 (t, 1H, Ar-H), 7.65 (m, 2H, Ar-H), 6.5 (s, 1H, Ar-H), 4.8 (m, 1H, CH), 3.9 (s,3H, OCH_3), 3.51 (d, J = 8.8 Hz, 2H, CH_2); ^{13}C NMR: (100 MHz, DMSO) δ 180.9, 169.1, 164.8, 156.4, 136.2, 126.6, 126.2, 124.7, 118.7, 112.2, 53.9, 50.9, 34.5; MS: (EI): m/z 248 (M^+1, 100); HRMS (ESI): Calcd. for $C_{13}H_{13}NO_4$ [M+H] : 248.0921; Found: 248.0923.

2.14a *Methyl 2-amino-3-(6-methyl-4-oxo-4H-chromen -2-yl)propanoate hydrochloride (**28**)*: The compound was prepared according to the procedure similar to compound **24.** M.R: 185–189°C; FT-IR: (KBr, cm^{-1}):. 3406, 2925, 2102, 1739, 1645, 1437, 1222, 1065, 956, 755.; ^{1}H NMR: (400 MHz, D_2O): δ 7.80 (s, 1H, Ar-H), 7.66 (d, J = 8.8Hz, 1H, Ar-H), 7.45 (d, J = 8.4 Hz, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 4.71 (m, 1H, CH), 3.89 (s,3H, OCH_3), 3.45 (d, J = 3.6 Hz, 2H, CH_2), 2.44 (s, 3H, Ar-CH3),; ^{13}C NMR: (100 MHz, DMSO) δ 176.8, 169.6, 168.7, 162.8, 154.2, 124.06, 122.9, 118.0, 112.1, 111.9, 53.0, 49.7, 34.1, 20.4.; MS: (EI): m/z 262 (M^+1, 100);

2.15 *Experimental procedure for the preparation of methyl 2-(tert-butoxycarbonylamino)-3-(4-oxo-4H-chromen-2-yl)propanoate(**25**):*

To a solution of compound **24** (0.2 g, 0.809 mmol) in dioxane (10 mL) was added Et_3N (0.245 g, 2.43 mmol) at 0°C; then added Boc_2O (0.358 g, 1.618 mmol). Then the reaction mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After the reaction was completed, water was added to the reaction and extracted with EtOAc. The organic layers were combined, washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product which was purified by silica gel column chromatography to give compound **25** (0.198 g, 70% yield) as an off-white solid. M.R.: 111–115°C; FT-IR: (KBr, cm^{-1}):. 3286, 3044, 2932, 1756, 1646, 1536, 1463, 1394, 1168, 967; ^{1}H NMR (400 MHz, CDCl3): δ 8.18 (d, J = 6.0 Hz 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.39 (t, 2H, Ar-H), 6.17 (s, 1H, Ar-H), 5.22 (bs,1H, NH), 4.75 (bs,1H, CH), 3.81 (s, 3H, OCH_3), 3.21 (dd,J=12.0 Hz 1H, CH_2),3.10 (dd, J = 11.2 Hz 1H, CH_2),1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR(100 MHz, DMSO): δ 177.5, 171.2, 164.0, 156.3, 154.8, 133.7, 125.7, 125.2, 123.6, 117.7, 112.1, 80.4, 52.7, 51.5, 37.3, 28.1, 28.1, 28.1;MS:(EI): m/z 348 (M^+1, 100).HRMS: (ESI): Calcd. for $C_{18}H_{21}NO_6$ [M+H] :348.1448; Found: 348.1447.

2.15a *Methyl 2-(tert-butoxycarbonylamino)-3-(6-methyl-4-oxo-4H-chromen-2-yl)propanoate (**29**)*: The compound was prepared according to the procedure similar to compound **25**. FT-IR: (KBr, cm^{-1}): 3331, 2978, 1713, 1649, 1487, 1369, 1268, 1165, 1055, 822, 756.; ^{1}H NMR (400 MHz, CDCl3): δ 7.95 (s, 1H, Ar-H), 7.95 (dd, J = 6.4 Hz, 1H, Ar-H), 7.28 (d, J = 6.8 Hz, 1H, Ar-H), 6.15 (s, 1H, Ar-H), 5.20 (bs, 1H, NH), 4.73 (bs, 1H, CH), 3.79 (s, 3H, OCH_3), 3.18 (dd, J = 11.6 Hz 1H, CH_2),3.09 (dd, J = 11.2 Hz 1H, CH_2), 2.44 (s, 3H), 1.56 (s, 9H, $C(CH_3)_3$); ^{13}C NMR(100 MHz,DMSO): δ 178.0, 171.2, 163.9, 154.8, 154.5, 135.1, 134.9, 125.0, 123.2, 117.5, 111.9, 80.4, 52.7, 51.5, 37.3, 28.1, 28.1, 28.1, 20.8; MS:(EI): m/z 362 (M^+1, 100).

2.16 *Experimental procedure for the preparation of methyl 3-(4-oxo-4H-chromen-2-yl)-2-pivalamidopropanoate (**26**):*

To a solution of compound **24** (0.2 g, 0.809 mmol) in dioxane (10 mL) was added Et_3N (0.245 g, 2.43 mmol) at 0°C and pivaloyl chloride (0.194 g, 1.618 mmol) Then, the reaction mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis (20% ethyl acetate/pet ether). After the reaction was complete, water was added to the reaction mixture and extracted with EtOAc. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product which was purified by silica gel column chromatography to give the compound **26** (0.217 g, 81% yield) as an off-white solid. M.R: 114–116°C; FT-IR: (KBr, cm^{-1}): 3358, 2958, 1736, 1650, 1523, 1465, 1388, 1220, 1121, 759; ^{1}H NMR (400 MHz, CDCl3): δ 8.18 (dd, J = 6.4 Hz, 1H, Ar-H), 7.67–7.64 (t, 1H, Ar-H), 7.42–7.35 (m, 2H, Ar-H), 6.39 (bs,1H, NH), 6.12 (s,1H, Ar-H), 4.98 (dd, J = 10.0 Hz, 1H, CH), 3.83 (s, 3H, OCH_3), 3.28 (dd, J = 11.6 Hz, 1H, CH_2), 3.15 (dd, J = 11.6 Hz, 1H, CH_2), 1.25 (s, 9H, $C(CH_3)_3$); ^{13}C NMR:(100 MHz, DMSO) δ 178.2, 177.7, 171.3, 164.1, 156.2, 133.8, 125.8, 125.2, 123.5, 117.6, 112.1, 52.8, 50.3, 38.7, 36.7, 27.3, 27.3, 27.3.; MS: (EI): m/z 332 (M^+1,100); HRMS: (ESI): Calcd. for $C_{18}H_{21}NO_5$ [M+H]:332.1496; Found: 332.1498.

2.16a *Methyl 3-(6-methyl-4-oxo-4H-chromen-2-yl)-2-pivalamidopropanoate (**30**)*: The compound was prepared according to the procedure similar to compound **26**. M.R: 139–143°C; FT-IR: (KBr, cm^{-1}): 3340, 2959, 1754, 1647, 1530, 1433, 1339, 1211, 1033, 972, 830.; ^{1}H NMR (400 MHz, CDCl3): δ 7.95 (d, J = 1.2 Hz, 1H, Ar-H), 7.47 (dd, J = 8.4 Hz, 1H, Ar-H), 7.24 (s, 1H, Ar-H), 6.36 (bs,1H, NH), 6.09 (s, 1H, Ar-H), 4.96 (dd, J = 12.8 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 3.25 (dd, J = 14.4 Hz, 1H, CH_2), 3.13 (dd, J = 14.4 Hz, 1H, CH_2), 2.44 (s, 3H, Ar-CH_3), 1.17 (s, 9H, $C(CH_3)_3$); ^{13}C NMR:(100 MHz, DMSO) δ 178.2, 177.9, 171.3, 163.9, 154.5, 135.3, 135.0, 125.1, 123.2, 117.4, 112.0, 52.8, 50.4, 38.7, 36.7, 27.4,27.4, 27.4, 20.9..; MS: (EI): m/z 346 (M^+1,100).

2.17 *Experimental procedure for the preparation of methyl 2-acetamido-3-(4-oxo-4H-chromen-2-yl) propanoate (**27**):*

To a solution of compound **24** (0.25 g, 1.01mmol) in THF (10 ml) was added Et_3N (0.306 g, 3.03 mmol) followed by acetyl chloride (0.157 g, 2.02 mmol) at 0°C. Then, the reaction mixture was stirred at RT for 24 h. The progress of the reaction was monitored by TLC analysis (20% EtOAc/pet ether). After the reaction was completed, water was added to the reaction mixture and extracted with EtOAc. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product which was purified by silica gel column chromatography to give compound 27 (0.220 g, 75% yield) as an off-white solid. M.R: 144–148°C; FT-IR: (KBr, cm^{-1}) : 3307, 3073, 2948, 2848, 1734, 1657, 1545, 1459, 1381, 1117, 1022; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.18 (dd, J = 8 Hz, 1H, Ar-H), 7.64–7.68 (m, 1H, Ar-H), 7.35–7.42 (m, 2H, Ar-H), 6.19 (bs, 1H, NH),6.15 (s, 1H, Ar-H),5.01 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 3.11–3.26 (m, 2H, CH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 177.9, 171.2, 169.9, 164.1, 156.3, 133.9, 125.8, 125.3, 123.6, 117.7, 112.1, 52.9, 50.4, 36.9, 23.0.; MS: (EI): m/z 290 (M^+1, 100); HRMS(ESI): Calcd. for $C_{15}H_{16}NO_5$ [M+H]:290.1069; Found:290.1028. The racemic compound **27** was purified by chiral HPLC using, Chiralcel OX-H, Hexane/EtOH (70:30) as eluent.

2.17a *Methyl 2-acetamido-3-(4-oxo-4H-chromen-2-yl) propanoate (**27i (-)**)*: M.R.: 129–133°C; FT-IR: (KBr, cm^{-1}): 3301, 3071, 2954, 1730, 1659, 1538, 1428, 1380, 1275,1022; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.18 (dd, J = 8 Hz 1H, Ar-H), 7.64–7.68 (m, 1H, Ar-H), 7.35–7.42 (m, 2H, Ar-H), 6.19 (bs, 1H, Ar-H),6.15 (s, 1H, NH),5.01 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 3.11–3.26 (m, 2H, CH_2), 2.01 (s, 3H, CH_3); ^{13}CNMR:(100 MHz, DMSO) δ 177.9, 171.2, 169.9,164.1, 156.3, 133.9, 125.8, 125.3, 123.6, 117.7, 112.1, 52.9, 50.4, 36.9, 23.0;MS (EI): m/z 290 (M^+1, 100).HRMS: (ESI): Calcd. for $C_{15}H_{16}NO_5$ [M+H]: 290.1069; Found: 290.1028; Specific Rotation: $[\alpha]^{25}_{(C=0.25\%,CHCl3)}$= -108.064.

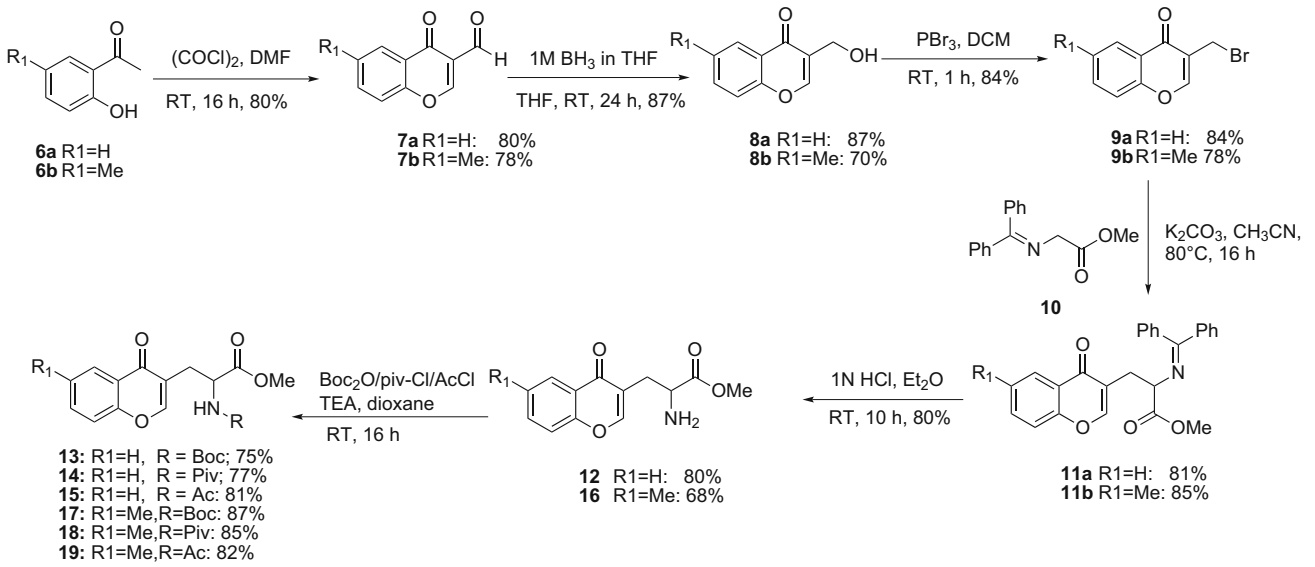
2.17b *Methyl 2-acetamido-3-(4-oxo-4H-chromen-2-yl) propanoate (**27i (+)**)*: M.R.:128–132°C FT-IR (KBr, cm^{-1}): 3301, 3071, 2954, 1731, 1659, 1538, 1459, 1380, 1277, 1023; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.18 (dd, J = 8 Hz 1H, Ar-H), 7.64–7.68 (m, 1H, Ar-H), 7.35–7.42 (m, 2H, Ar-H), 6.19 (bs, 1H, Ar-H),6.15 (s, 1H, NH),5.01 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 3.11-3.26 (m, 2H, CH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR: (100 MHz, DMSO): δ 177.9, 171.2, 169.9, 164.1, 156.3, 133.9, 125.8, 125.3, 123.6, 117.7, 112.1, 52.9, 50.4, 36.9, 23.0.; MS (EI): m/z 290 (M^+1, 100); HRMS (ESI): Calcd. for $C_{15}H_{16}NO_5$ [M+H] :290.1029; Found: 290.1028; Specific Rotation: $[\alpha]^{25}_{(C=0.25\%,CHCl3)}$= +107.024

2.17c *Methyl 2-acetamido-3-(6-methyl-4-oxo-4H -chromen-2-yl)propanoate (**31**)*: The compound was prepared according to the procedure similar to compound **27**. M.R: 132–136°C.: FT-IR (KBr, cm^{-1}): 3374, 3052, 2930, 1747, 1652, 1540, 1436, 1370, 1281, 1182, 966, 825, 749.: ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8 Hz 1H, Ar-H), 7.49 (dd, J = 8.8 Hz, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 6.23 (bs, 1H, NH), 6.14 (s, 1H, Ar-H), 5.02 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 3.25 (dd, J = 14.4 Hz, 1H, CH_2), 3.16 (dd, J = 14.4 Hz,1H, CH_2) 2.46 (s, 3H, Ac), 2.26 (s, 3H, Ar-CH_3); ^{13}C NMR: (100 MHz, CDCl3): δ 177.9, 171.1, 169.7, 163.7, 154.5, 135.3, 135.0, 125.1, 123.2, 117.4, 111.9, 52.9, 50.4, 36.8, 23.0, 20.8..; MS (EI): m/z 304 (M^+1, 100);

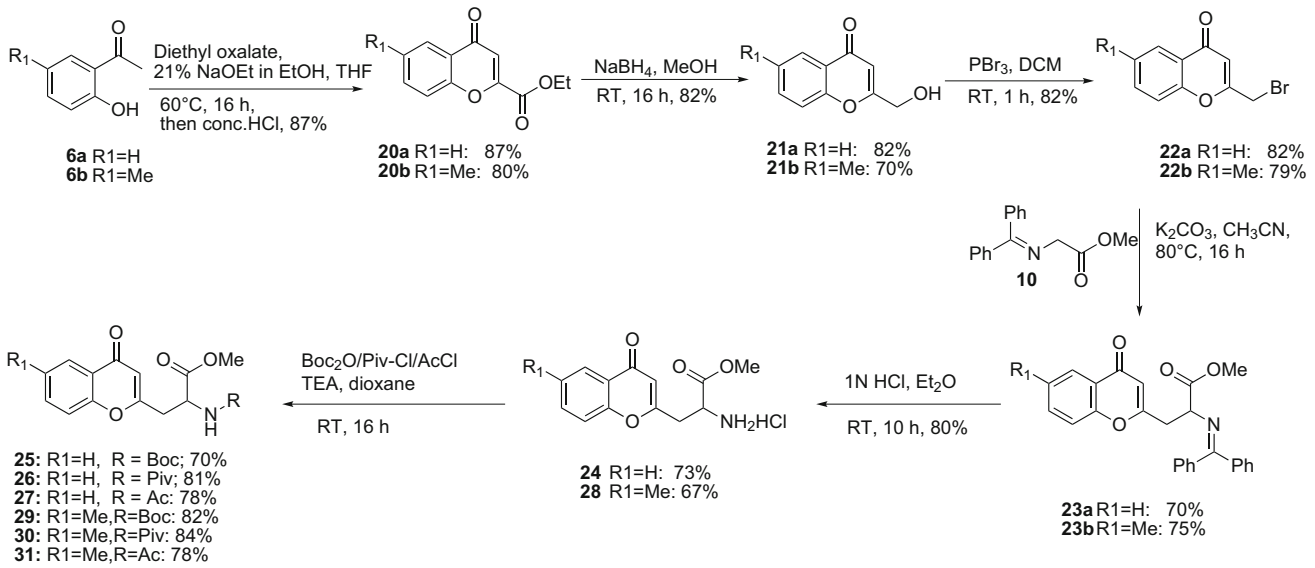
3. Results and Discussion

3.1 *Synthesis*

Our synthesis started from commercially available 2-hydroxy acetophenone **6a** (Scheme 1). Thus, compound **6a** was treated with oxalyl chloride in DMF at RT according to literature procedure to prepare the 3-formyl chromone **7a**.[37] The reduction reaction of formyl group was tried using $NaBH_4$ in THF which was not successful. We have tried a couple of reduction reaction conditions *viz.* $NaCNBH_3$, $LiBH_4$, etc. without much success. Finally, using BH_3 in THF conditions, we were able to prepare the methyl alcohol **8a** in good yields. The conversion of 3-hydroxymethyl chromone **8a** to bromo derivative **9a** was achieved using PBr_3 in DCM condition. The key alkylation reaction was performed by reaction of bromomethyl chromone **9a** with N-(diphenylmethylene) glycine methyl ester **10** in K_2CO_3/CH_3CN reflux condition to give the compound **11a** in very good yield. The compound **11a** was well characterized by ^{1}H NMR, ^{13}C-NMR and MS data. The appearance of signals at δ 3.33 (dd, 1H) and 2.83 (dd, 1H) corresponding to the CH_2 protons attached to the chromone ring and peak at δ 4.49 (m, 1H) corresponding to α-proton of amino acid peak at δ 6.86 (s, 1H) corresponding to chromone olefinic proton in ^{1}H-NMR



Scheme 1. Synthesis of 3-substituted chromone based α-amino acid.

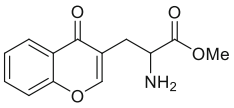
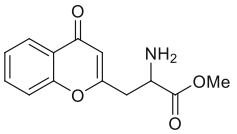
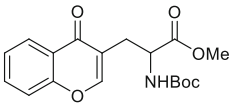
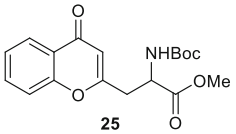
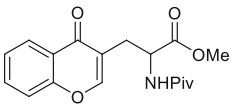
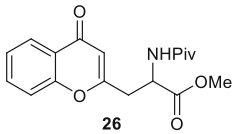
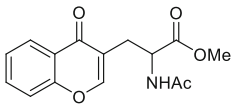
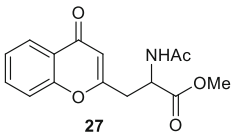
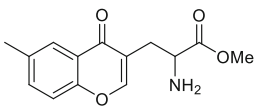
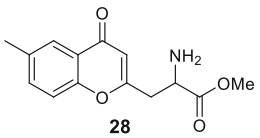
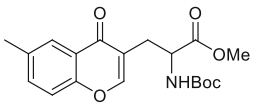
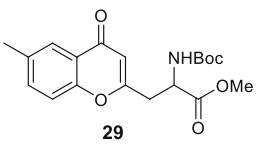
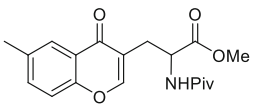
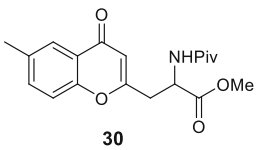
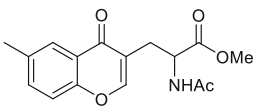
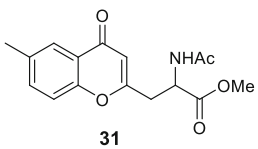


Scheme 2. Synthesis of 2-substituted chromone based α-amino acid.

spectrum confirmed the formation of the compound **11a**. Then, the compound **11a** was treated with 1N aqueous HCl at RT and the reaction mixture was freeze dried to give the designed chromone based hybrid amino acid **12** as its HCl salt. The compound **16** was prepared following the similar procedure as **12** starting from procedure 2-hydroxy-5-methy-acetophenone **6b** in a five step synthetic sequence. Various N-protected chromo based amino acid derivatives (**13**–**19**) were prepared using the standard protecting group procedure.[38] The N-acetyl protected amino acid **15** was subjected to chiral HPLC separation using Chiralcel OX-H column and hexane/EtOH (70:30) as the mobile phase (Figure 2). The chiral purity of the obtained pure enantiomer **15i** and **15ii** was analysed by chiral HPLC and specific rotation. The relative configuration of the enantiomer **15i** and **15ii** was assigned with reference to the configuration of alanine based on the specific rotation.

The success of synthetic route for the preparation of compound **12** and **16** encouraged us to focus on the preparation of 2-substitued chromone hybrid amino acid **24** and **28**. Thus, the reaction of 2-hydroxy acetopheone **6a** with diethyl oxalate in presence of NaOEt at 60°C gave the ethyl 4-oxo-4H-chromene-2-carboxylate **20a** (Scheme 2). The reduction reaction of ester moiety was achieved using $NaBH_4$ in MeOH conditions to obtain the methyl alcohol **21a** in good yields. The conversion of 3-hydroxymethyl chromone to bromo derivative **22a** was achieved using PBr_3 in DCM condition. The key alkylation reaction was performed by reaction bro-

Table 1. The yields and purity of the novel chromone based α-amino acids derivatives.

S.No	3-(3-Chromonyl-alanine) derivative	Yield(%)	Purity[a]	S.No	3-(2-Chromonyl-alanine) derivative	Yield(%)	Purity[a]
1	 **12**	84	96	9	 **24**	73	97
2	 **13**	75	98	10	 **25**	70	95
3	 **14**	77	98	11	 **26**	81	95
4	 **15**	81	97	12	 **27**	78	98
5	 **16**	82	96	13	 **28**	85	90
6	 **17**	87	99	14	 **29**	82	99
7	 **18**	85	99	15	 **30**	84	98
8	 **19**	82	93	16	 **31**	75	93

[a]The purity of the compounds were determined by LC-MS analysis

momethyl chromone **22a** with N-(diphenylmethylene) glycine methyl ester **10** in K_2CO_3/CH_3CN reflux condition to give the compound **24a** in very good yield. The compound **24a** was thoroughly characterized by ^{1}H NMR, ^{13}C-NMR and MS data. ^{1}H-NMR of compound **24a** shows peaks at δ 3.31 (dd, 1H) and 3.21 (dd, 1H) corresponding to the CH_2 protons attached to the chromone ring and peak at δ 4.63 (dd, 1H) corresponding to 1H) corresponding to α-proton of amino acid. Also, the peak at δ 6.19 (s, 1H) corresponding to chromone olefinic proton in ^{1}H-NMR confirmed the and also the formation of the compound **24a**. Then the compound **24a** was treated with 1N aqueous HCl at RT and the reaction mixture was freeze dried to give the designed chromone based hybrid amino acid **24** as its HCl salt in good yields. The compound **28** was prepared following the similar procedure as **24** starting from procedure 2-hydroxy-5-methy-acetophenone **6b** in a five step synthetic sequence. Various N-protected chromo based amino acid derivatives (**25**–**31**) were prepared

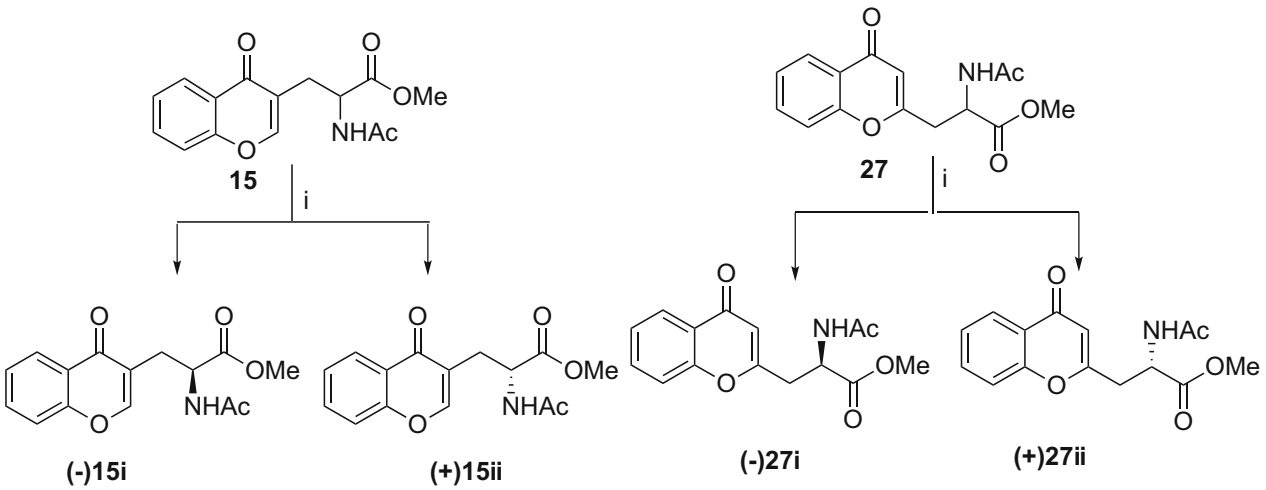


Figure 2. The racemic compound **15 & 27** was purified by chiral HPLC.

using standard conditions.[38] The N-acetyl protected amino acid **27** was subjected to chiral HPLC separation using Chiralcel OX-H column and hexane/EtOH (70:30) as the mobile phase (Figure 2). The chiral purity of the obtained pure enantiomer **27i** and **27ii** was analysed by chiral HPLC and specific rotation (See Supplementary Information). The relative configuration of the enantiomer **27i** and **27ii** was assigned with reference to the configuration of alanine based on the specific rotation.

It is noteworthy to mention here that previously inaccessible 2-chromone amino acid conjugates (**25-31**) were synthesized in good yields as indicated in Table 1. The 3-chromone amino acid conjugates (**13-19**) were prepared in five easy synthetic steps in good yield. All these compounds were well characterized by ^{1}H-NMR, ^{13}C-NMR, LC-MS and HRMS analysis.

4. Conclusions

We have developed an efficient and accessible route to synthesize chromone based amino acid hybrid which can act as β-turn peptidomimetics. Further application of these chromone-amino acid conjugates to peptides is underway in our laboratory.

Supplementary Information (SI)

The spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR and HRMS) of the synthesized compounds are presented in the Supplementary Information which is available at www.ias.ac.in/chemsci.

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