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NOVEL SYNTHESIS OF 8, 9-DIHYDRO- 7H-BENZO 4-METHYL-2-OXO-2H-8-CHROMENYL] 5-ARYL-4, 5-DIHYDRO-4-ISOXAZOLE CARBOXYLATES

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ABSTRACT

8, 9-dihydro- 7h-benzo -4-methyl-coumarin aldehyde chlorooxime **(4)** on reaction with in the presence of polyphosperic acid reflus for 24 hours to gave 8, 9-dihydro- 7h-benzo chloro-4-methyl-2-oxo-2H-8-chromenyl]-5-phenyl-4,5-dihydro-4-isoxazole carboxylate **(5a-h)** in a good yields. The structures of all the newly synthesized molecules were assigned by elemental analysis and spectral data. The synthesized compounds were screened for their antibacterial activities strains using Cup plate method.

KEYWORDS: 7-Benzyloxy-4-methyl-coumarin aldehyde chlorooxime, triethylamine in chloroform, aldehyde chlorooxime, antibacterial activity.

INTRODUCTION

Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, chromones, flavones, isoflavones etc. Coumarins and its derivatives are ubiquitously distributed in nature and many of them exhibit diverse and useful biological activities. These compounds have numerous medicinal applications including antitumor anti-HIV therapy, central nervous system stimulation antibacterial anti-inflammatory and anti coagulant properties. In addition hydroxycoumarins are known to be powerfull chain-breaking anti-oxidants which can prevent free radical injury by scavenging reactive oxygen species. Some coumarin derivatives display cytostatic properties, while others have cytotoxic activities.

EXPERIMENTAL SECTION

Chemistry: Melting points were determined on a Buchi-510 instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument

I. General procedure for the synthesis of Synthesis of of 8,9-dihydro-7H-benzo -4-methyl-coumarin-8-aldehyde chlorooxime (4a)

To a stirred solution of 7-benzyloxy-4-methyl-coumarin aldehydeoxime **(2)** (1.2g, 3.88 mmol) in DMF (18 mL) at 0 °C, was added N-chloro succinamide **(3)** (0.62g, 4.65 mmol). Upon wanning to RT over 2 h, the reaction was quenched with H_2O/ice (90 mL), extracted with ethyl acetate (3x30 mL) and washed with brine (30 mL). The dried (Na_2SO_4 extract was concentrated and purified by column chromatography to give **(10)**. Yield = l.lg, m.p. 142-143 °C and 3-chlorinated product (**11a**). Yield = 0.2g, ^{1}HNMR: δ 2.41 (s, 4-CH_3), 5.37 (s, 7-OCH_2), 6.28 (s, H-3), 7.24-7.44 (m, Ar-H), 7.85 (d, J=8.8 Hz, H-6), 7.94 (d, J=9.2Hz, H-5), 12.43 (s, OH), 12.49 (s, OH).

II. General procedure for the synthesis of 8,9-dihydro-7H-benzo-4-methyl-2-oxo-2H-8-chromenyl]-5-phenyl-4,5-dihydro-4-isoxazole carboxylates (5a-h)

To a stirred solution of chloro oxime **(4)** (0.5g, 1.45 mmol) in chloroform (15 mL), Et_3N was added dropwise (0.22g, 2.17 mmol) continued stirring for 15-20 Min.) and added a PPA to give 8,9-dihydroxy 7H-benzo 4-methyl-2-oxo-2H-8-chromenyl]-5-phenyl-4,5-dihydro-4-isoxazole carboxylate **(5a)** as white solid. Yield = 150 mg, m.p. 130-132 °C.^{1}H NMR : δ 0.95 (t, -$COOCH_2CH_3$), 2.42 (s, 4-CH_3), 3.95 (qq, $COOCH_2CH_3$), 4.68 (d, J=8.8Hz, H-4"), 5.21 (s, 7-OCH_2), 6.11 (d, J=9.2Hz, H-5"), 6.17 (s, H-3), 6.96 (d, J=8.8 Hz, H-6), 7.33-7.39 (m, H-l"1, H-3m & H-5m, H-2' to H-6'), 7.43-7.46 (m, H-2'"& H-6m), 7.6 (d, J=8.8 Hz, H-5).^{13}C NMR: δ 13.7 (-$COOCH_2CH_3$). 18.7 (4-CH_3), 61.7 (C-4"), 63.1 (-$COOCH_2CH_3$), 71.1 (7-OCH_2), 85.6 (C-5"), 106.8 (C-8), 108.5 (C-3), 112.6 (C-4a), 114.1 (C-6), 126.6 (C-4'"), 126.9 (C-2'" & C-6'"), 127.2 (C-4'), 128.3 (C-3' & C-5'), 128.6 (C-5), 128.7 (C-2' & C-6'), 128.8 (C-5m & C-3'"), 135.4 (C-l'), 139.1 (C-l'"), 147.1 (C-4), 152.1 (C-8a), 153.1 (C-7), 159.5 (2-C=O), 159.8 (C-3"), 167.4 (ester C=O).

Employing the same exeperimental procedure mentioned above for **5a** following derivatives (**5b-h).**

8,9-dihydroxy 7H-benzo -6-chloro-4-methyl-2-oxo-2H-8-chromenyl]-5-[3-(trifluoromethyl) phenyl]-4,5-dihydro-4-isoxazole carboxylate (5b)

M.p. 146-147 °C.^{1}H NMR: δ 0.94 (t, -$COOCH_2CH_3$), 2.39 (s, 4-CH_3), 3.95 (qq, -$COOCH_2.CH_3$), 4.6 (s, J=8.4 Hz, H-4"), 5.16 (s, 7-OCH_2), 6.13 (d, J=8.8Hz, H-5"), 6.15 (s, H-3), 7.3-7.31 (m, H-2' to H-6'), 7.4-7.62 (m, H-2"', H-4 "' & H-5", H-6"'), 7.67 (d, H-5, J=8.8Hz).^{13}C NMR : δ 13.7 (-$COOCH_2CH_3$), 18.7 (4-CH_3), 62.0 (C-4"), 63.0 (-$COOCH_2.CH_3$), 71.1 (7-OCH_2), 84.6 (C-5"), 106.5 (C-8), 108.5 (C-3), 112.7 (C-4a), 122.5 (C-4"), 125.4 (C-6"'), 127.0 (C-2"), 127.1 (C-4'), 128.3 (C-5'), 128.7 (C-3'), 129.6 (C-5), 129.6 (C-6'), 130.4 (C-2'), 130.8 (C-3"'), 131.4 (C-5"'), 135.3 (C-l'), 140.2 (C-l"'), 147.3 (C-4), 152.0 (C-8a), 153.0 (C-7), 159.4 (2-C=O), 159.7 (C-3"), 167.1 (-C=O).DIPMS: m/z at 586 (M+1).

8,9-dihydro 7H-benzo -6-bromo-4-methyl-2-oxo-2H-8-chromenyl]-5-[4-(trifluoromethyl) phenyl]-4,5-dihydro-4-isoxazole carboxylate (5c)

M.p. 146-147 °C.^{1}H NMR : δ 0.95 (t, -$COOCH_2CH_3$), 2.4 (s, 4-CH_3), 3.96 (qq, -$COOCH_2CH_3$), 4.61 (d, J=8.4Hz, H-4"), 5.17 (s, 7-OCH_2), 6.14 (d, J=8.4Hz, H-5"), 6.16 (s, H-3**),** 7.31-7.32 (m, C-2' to C-6'), 7.41-7.45 (m, H-2"'), 7.57- 7.59 (m, C-6"'), 7.61-7.64 (m, C-3"' & C-5"'), 7.68 (s, H-5, J=9.2Hz).^{13}C NMR : δ 13.7 (-$COOCH_2CH_3$), 18.7 (4-CH_3), 62.0 (C-4"), 63.0 (-$COO\underline{CH_2}CH_3$), 71.1 (7-OCH_2), 84.6 (C-5"), 106.5 (C-8), 108.5 (C-3), 112.7 (C-4a), 114.1 (C-6) 122.5 (C-4‴), 123.3 (C-2"' & C-6"'), 125.5 (C-4'), 127.0 (C-3' & C-5'), 127.1 (C-5), 128.7 (C-2' & C-6'), 129.6 (C-5"' & C-3"'), 135.3 **(C-l'),** 140.2 (C-l"'), 147.3 (C-4), 152.0 (C-8a), 153.0 (C-7), 159.4 (2-C=O), 159.7 (C-3"), 167.1 (ester C=O).DIPMS: m/z = 630 (M+l).

8,9-dihydro-7H-benzo -6,4-dimethyl-2-oxo-2H-8-chromenyl]-5-(3, 5-difluorophenyl)-4,5-dihydro-4-isoxazole carboxylate (5d)

M.p. 167-168^{o}C.^{1}H NMR : δ 0.95 (t, -$COOCH_2CH_3$), 2.4 (s, 4-CH_3), 3.98 (qq, -$COOCH_2CH_3$), 4.58 (d, J=8.4Hz, H-4"), 5.17 (s, 7-OCH_2), 6.05 (d, J=8.4Hz, H-5"), 6.16 (s, H-3), 2.72 (s, 6-CH_3), 6.95-6.97 (m, H-2"', H-6"' & H-4"'), 7.31-732 (m, H-2' to H-6'), 7.6-(d, J=9.2Hz, H-5).^{13}C NMR: δ 13.7 (-$COOCH_2CH_3$), 18.7 (4-CH_3), 62.0 (C-4"), 62.9 (-$COOCH_2\_CH_3$), 71.1 (7-OCH_2), 83.9 (C-5"), 106.5 (C-8), 108.5 (C-3), 108.9 (C-4a), 109.0 (C-6), 109.1 (C-4"'), 109.2 (C-6"'), 112.7 (C-2"'), 114.1 (C-4'), 127.1 (C-3' & C-5') 128.4 (C-5), 128.7 (C-2' & C-6'), 135.2 (C-3"'), 143.1 (C-5"'), 143.2 (C-1'), 143.3 (C-1"'), 147.3 (C-4), 152.9 (C-8a), 159.7 (C-7), 161.9 (2-C=O), 164.4 (C-3.

8,9-dihydro- 7H-benzo -3-chloro-4-methyl-2-oxo-2H-8-chromenyl]-5-phenyl-4,5-dihydro-4-isoxazole carboxylate (5e)

Yield = 15 mg, m.p 118-120 °C.^{1}H NMR : δ 0.95 (t, -$COOCH_2CH_3$), 2.54 (s, 4-CH_3), 3.95 (qq, -$COOCH_2CH_3$), 4.62 (d, J=8.8Hz, H-4"), 5.21 (s, 7-OCH_2), 6.08 (d, J=8.8Hz, H-5"), 6.97 (d, J=9.2Hz, H-6), 7.31 (m, H-l'", H-3"' & H-5'", H-2' to H-6'), 7.4 (m, H-2"' & H-6'"), 7.6 (d, J=8.8Hz, H-5).^{13}C NMR : δ 13.7 (-$COOCH_2CH_3$), 18.7 (4-CH_3), 61.7 (C-4"), 63.1 (-$COOCH_2CH_3$), 71.1 (7-OCH_2), 85.6 (C-5"), 106.8 (C-8), 108.5 (C-3), 112.6 (C-4a), 114.1 (C-6), 126.6 (C-4"'), 126.9 (C-2'" & C-6"'), 127.2 (C-4'), 128.3 (C-3' & C-5'), 128.6 (C-5), 128.7 (C-2' & C-6'), 128.8 (C-5"' & C-3'"), 135.4 (C-l'), 139.1 (C-l"'), 147.1 (C-4), 152.1 (C-8a), 153.1 (C-7), 159.5 (2-C=O).

8,9-dihydro-7H-benzo 6,3-dichloro-4-methyl-2-oxo-2H-8-chromenyl] -5- [3 (trifluoro methyl) phenyl]-4,5-dihydro-4-isoxazole carboxylate (5f)

M.p. 146-147 °C.^{1}H NMR : δ 0.94 (t, -$COOCH_2CH_3$), 2.38 (s, 4-CH_3), 3.98 (qq, -$COOCH_2CH_3$), 4.61 (s, J=8.4 Hz, H-4"), 5.18 (s, 7-OCH_2), 6.14 (d, J=8.8Hz, H-5"), 7.31-7.33 (m, H-2' to H-6'), 7.42-7.62 (m, H-2"', H-4 "' & H-5"', H-6'"), 7.67 (d, H-5, J=8.8Hz).^{13}C NMR : δ 3.8 (-$COOCH_2CH_3$), 18.9 (4-CH_3), 62.2 (C-4"), 63.3 (-$COOCH_2CH_3$), 71.2 (7-OCH_2), 84.6 (C-5"), 106.6 (C-8), 108.5 (C-3), 112.9 (C-4a), 114.1 (C-6), 122.6 (C-4"'), 125.4 (C-6"'), 127.2 (C-2"'), 127.1 (C-4"), 128.3 (C-5'), 128.7 (C-3'), 129.6 (C-5), 129.8 (C-6'), 130.4 (C-2'), 130.8 (C-3'"),131.4 (C-5'"), 135.3 (C-l'), 140.2 (C-lm), 147.3 (C-4), 152.2 (C-8a), 153.6 (C-7).

8,9-dihydro-7H-benzo-6-bromo-3-chloro-4-methyl-2-oxo-2H-8-chromeny1]-5-[4-(trifluoro methyl) phenyl]-4,5-dihydro-4-isoxazole carboxylate (5g)

M.p. 125-126 °C, ^{1}H NMR: δ 0.97 (t, -$COOCH_2CH_3$). 2.4 (s, 4-CH_3), 3.96 (qq, -$COOCH_2CH_3$), 4.61 (d, J=8.4Hz, H-4"), 5.17 (s, 7-OCH_2), 6.13 (d, J=8.4Hz, H-5"), 7.29-7.31 (m, H-2' to H-6'), 7.41-7.45 (m, H-2"' &H-6"'), 7.59- 7.64 (m, H-3"' & H-5"'), 7.68 (d, J=8.8Hz, H-5).^{13}C NMR : δ 13.7 (-$COOCH_2CH_3$), 18.7 (4-CH_3), 62.0 (C-4"), 63.0 ($COOCH_2CH_3$), 71.1 (7-OCH_2), 84.6 (C-5"), 106.5 (C-8), 108.5 (C-3), 112.7 (C-4a), 114.1 (C-6), 122.5 (C-4"'), 123.3 (C-2" & C-6"'), 125.5 (C-4'), 127.0 (C-3' & C-5'), 127.16 (C-5), 128.7 (C-2' & C-6'), 129.6 (C-5"' & C-3'"), 135.3 (C-l'), 140.2 (C-l"'), 147.3 (C-4), 152.0 (C-8a), 153.0 (C-7).

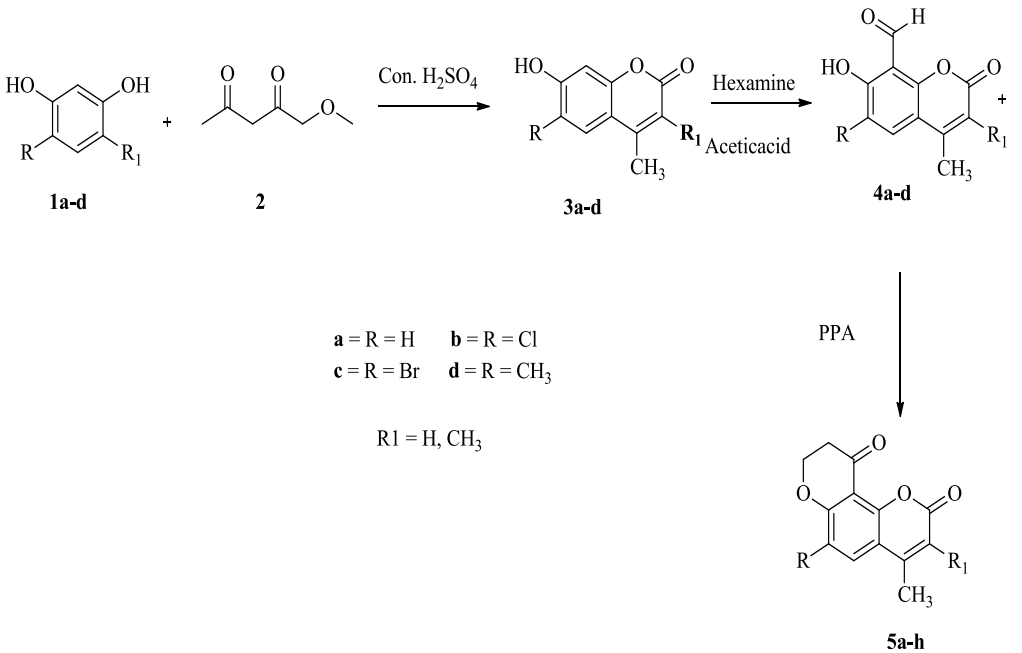
8,9-dihydro-7-H-benzo -3-chloro-6,4-dimethyl-2-oxo-2H-8-chromenyl]-5-(3,5 difluoro phenyl)-4,5-dihydro-4-isoxazole carboxylate (5h)

M.p. 142-143 °C.^{1}H NMR : δ 0.98 (t, -$COOCH_2CH_3$), 2.57 (s, 4-CH_3), 3.98 (qq, -$COOCH_2CH_3$), 4.55 (d, J=8.0Hz, H-4"), 5.17 (s, 7-OCH_2), 6.06 (d, J=8.4Hz, H-5"), 2.35 (s, 6-CH_3), 6.94-7.02 (m, H-2'", H-4'" & H-6'"), 7.27-7.34 (m, H-2' to H-6'), 7.63 (d, J=9.2Hz, H-5).^{13}C NMR : δ 13.7 (-$COOCH_2CH_3$), 18.7 (4-CH_3), 62.0 (C-4"), 62.9 (-$COOCH_2CH_3$), 71.1 (7-OCH_2), 83.9 (C-5"), 106.3 (C-8), 108.5 (C-3), 108.9 (C-4a), 109.0 (C-6), 109.1 (C-4'"), 109.2 (C-6'"), 112.7 (C-2'"), 114.1 (C-4'), 127.1 (C-3' & C-5'), 128.4 (C-5), 128.7 (C-2' & C-6'), 135.2 (C-3'"), 143.1 (C-5'"), 143.2 (C-1'"), 143.3 (C-l'"), 147.3 (C-4), 152.9 (C-8a), 159.7 (C-7), 161.9 (2- C=O), 164.4 (C-3"),

RESULTS AND DISCUSSION

I. Synthesis of 8,9-dihydroxy 7H-benzo-4-methyl-2-oxo-2H-8-chromenyl]-5-phenyl-4,5-dihydro-4-isoxazole carboxylates (5a-h).

7-Benzyloxy-4-methyl-coumarin aldehyde chlorooxime **(3)** was synthesized from the chlorination of oximein the prasance of Polyphosperic acid to give 8,9-dihydro-7h-benzo-4-methyl-coumain aldehyde chlorooxime **(5a-h)** was characterized from the ^{1}H NMR by the absence of oxime proton at δ 11.23 (s). Coumarin protons appeared at δ 2.41 (s, 4-CH_3), 5.37 (s, 7-OCH_2), 6.28 (s, H-3), 7.24-7.44 (m, Ar-H), 7.85 (d, J=8.8 Hz, H-6), 7.94 (d, J=9.2 Hz, H-5), 12.43 (s, -OH),



Scheme-1.

Antibacterial Activity

All the newly prepared compounds **(5a-h)** were screened for the antibacterial activity is done by the paper disc method. Organisms used: Escherichia coli (Gram-negitive) Staphylococcus aureus (gram-positive).

After solidification of media, petriplates inoculated with actively growing culture of Escherichia coli and Staphylococcus aureus separately as follows. Filter paper discs of 5 mm diameter were dipped in the test solution of different concentrations. After drying the disc, it was kept on Antibiotic med-3 agar in petriplates seeded with 1 ml bacterial culture of Escherichia coli and Staphylococcus aureus and incubated for 24 hrs at 37°C.

Table 1: Antibacterial activity.

***Escherichia coli (Gram-negative)* (Cone. µg/ml)**				**Staphylococcus aureus (gram-positive) (Cone. µg/ml)**		
Comp.	**200**	**100**	**50**	**200**	**100**	**50**
5a	15	11	5	17	12	5
5b	12	-	-	18	-	-
5c	23	29	24	21	19	4
5d	11	12	15	21	19	25
5e	22	11	-	18	19	21
5f	11	13	14	24	18	26
5g	28	20	24	24	29	31
5h	22	26	-	-	22	2

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