

A FACILE SYNTHESIS OF 3-[4'-(2',6'-DIMETHYL-3',5'DICARBETHOXY-1',4'-DIHYDROPYRIDYL)]CHROMENES

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Abstract: 2H-3-Chromenecarbaldehydes (**3a-h**) on reaction with ethyl 3-aminocrotonate (**4**) in the presence of acetic acid gave 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromenes (**5a-h**) in good yields.

Introduction

Several chromanones and substituted chromenes show a variety of biological activities such as dopamine agonist,¹ antihypertensive,² ATP sensitive potassium channel opener,³ coronary vasodilator⁴ and adrenergic agent.⁵ Chromones such as nedocromil sodium and khellin have vasodilator action and are used to treat asthma.⁶⁻⁸ Nifedipine, nicorpidine and nimopidine which are substituted dihydropyridines obtained by Hantzsch synthesis, are used to treat *angina pectoris* and for lowering blood pressure.⁹ Hantzsch 1,4-dihydro-pyridine synthesis involves the reaction of an aldehyde with ethyl or methyl acetoacetate and ammonia or by the reaction of aldehyde with ethyl or methyl aminocrotonate.¹⁰⁻¹⁸ Earlier, substituted chromone and flavone aldehydes by a Hantzsch synthesis gave 1,4-dihydropyridyl, 1,2-dihydropyridyl and pyridine fused derivatives.¹⁹⁻²⁰ We have earlier reported the synthesis of dimethyl 2,6-dimethyl-4-(4-oxo-4H-3-chromenyl)-1,4-dihydro-3,5-pyridinedicarboxylate, ethyl 2-methyl-5H-chromeno[3,4-c]pyridine-1-carboxylates starting from 3-formylchromones,²¹ 3-formyl-4-chlorochromenes²² and 3-formyl-4-chloro-2-arylchromenes.²³

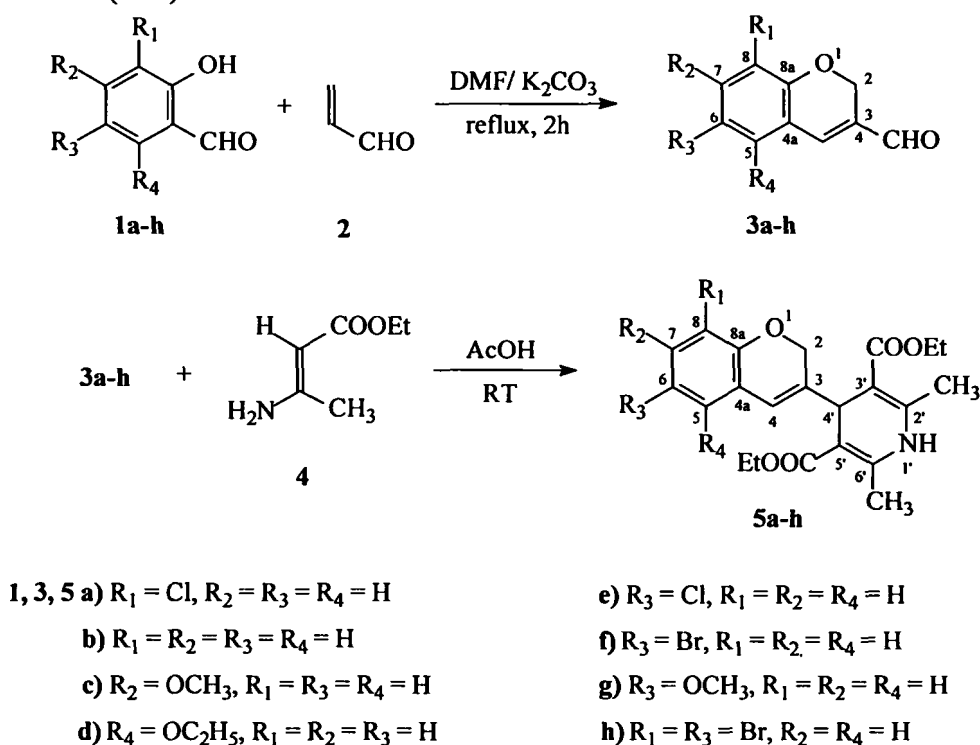
Results and discussion

In this view of our interest in dihydropyridyl substituted chromenes, we now studied the reaction of 2H-3-chromenecarbaldehydes (**3a-h**) with ethyl 3-aminocrotonate (**4**). 2H-3-Chromenecarbaldehydes (**3a-h**) were synthesized by the reaction of salicylaldehydes with acrolein in DMF/K₂CO₃ medium.^{24,25} IR spectrum of **3a** showed peak due to aldehyde C=O at 1667 cm⁻¹. The UV spectrum showed absorption bands at 248 nm (log ε 4.7), 308 nm (log ε 4.7), 360 nm (log ε 3.8). In the ¹H NMR of **3a**, the aldehyde proton resonated at δ 9.62 as a singlet, the OCH₂ protons appeared as a singlet at δ 5.15 and the H-4 appeared as a singlet at δ 7.22. H-5 appeared as double doublet at δ 7.35 (J=10.0, 2.0 Hz), H-6 appeared as double doublet at δ 6.90 (J=10.0, 10.0 Hz) and H-7 as double doublet at δ 7.15 (J=10.0, 2.0 Hz). In its ¹³C NMR of **3a**, the aldehyde carbon resonated at δ 189.0 and the OCH₂ at δ 63.0, C-4 at δ 132.6 and C-3 at δ 139.6. The aromatic carbon signal assignments are δ 119.6 (C-4a), 127.6 (C-5), 124.2 (C-6), 127.8 (C-7), 121.8 (C-8) and 130.0 (C-8a). The mass spectrum of **3a** showed the molecular ion peak at m/z 194 (M⁺). The base peak appeared at m/z 166 due to the loss of CO from molecular ion.

2H-3-Chromenecarbaldehydes (**3a-h**), ethyl 3-aminocrotonate (**4**) in acetic acid were stirred at room temperature for 24 h. The acetic acid was distilled off under reduced pressure and the crude product purified by using column chromatography to give 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromenes (**5a-h**). In the IR spectrum of **5a**, the peak at 3447 cm⁻¹ is due to NH and the peak at 1728 cm⁻¹ is assignable to the ester carbonyl. The

UV spectrum showed absorption maxima at 252 nm ($\log \epsilon$ 4.2), 279 nm ($\log \epsilon$ 3.8) and 360 nm ($\log \epsilon$ 3.6). In the ^1H NMR spectrum of **5a**, the H-4 of chromene appeared as a singlet at δ 6.10 indicating that the new heterocyclic moiety is pendent at C-3 of the chromene ring. The signals due to the 1,4-dihydropyridyl moiety are as follows: NH appeared as a broad D_2O exchangeable singlet at δ 5.62. H-4' appeared as singlet at δ 4.50. The two methyl groups at 2' and 6' position appeared as singlet at δ 2.34. The methyl protons of the two COOEt groups at 3' and 5' appeared at δ 1.30 as triplet with $J=7.0\text{Hz}$, while the OCH_2 protons appeared at δ 4.15 as overlapping multiplet. These chemical shifts also indicate that the two COOEt groups are located in symmetrical environment. The other signals in ^1H NMR spectrum are due to the chromene moiety. The methylene protons at 2 position appeared as a singlet at δ 4.88. The aromatic protons H-6 and H-7 appeared as a multiplet at δ 6.72 and H-5 appeared as a double doublet at δ 7.05 ($J=10.0, 2.0\text{ Hz}$).

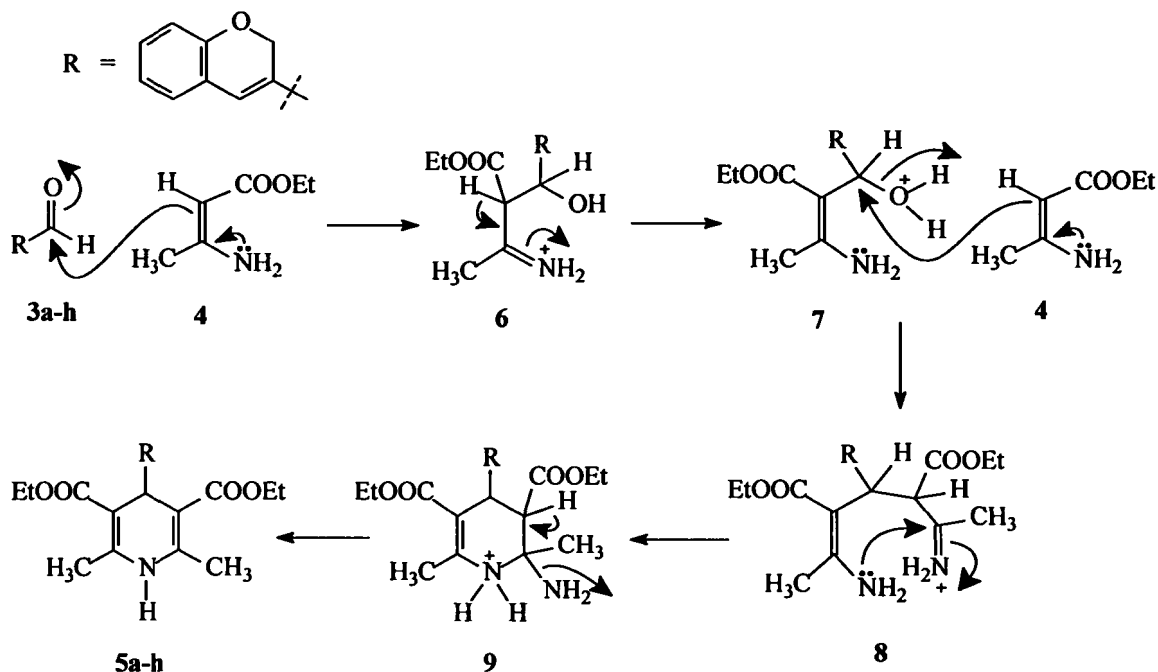
The ^{13}C NMR (CDCl_3) of **5a** showed the signals due to dihydropyridyl moiety as follows: δ 178.0 (C=O), 60.0 (OCH_2), 37.4 (C-4'), 14.2 (CH_2CH_3), 19.8 (CH_3 -2',6'), 144.8 (C-2',6') and 100.2 (C-3',5'). The carbon signal assignments due to chromene moiety are as follows: 68.0 (C-2), 128.8 (C-3), 139.8 (C-4), 120.2 (C-4a), 121.8 (C-6), 125.0 (C-5,7), 118.4 (C-8) and 148.6 (C-8a).



Scheme-1: Synthesis of 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromenes (**5a-h**)

In **5a** MS showed the M^+ at m/z 417 (19%). The base peak appeared at m/z 252 which arises from the dihydropyridyl moiety. The ions at m/z 224 and 196 are due to the successive loss of C_2H_5 from the m/z 252 and the ion m/z 388 arises due to the loss of ethyl group from M^+ , while the ion at m/z 344 arise due to the loss of COOC_2H_5 from M^+ . The ions m/z 224 and 196 are due to further fragmentation of dihydropyridyl group.

The formation of 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromenes (**5a-h**) (Scheme-2) involve the addition of ethyl 3-amino-crotonate (**4**) to the aldehyde group of (**3a-h**) leading to the intermediate **6**. This is tautomerises to **7** and reacts with a second molecule of ethyl 3-aminocrotonate (**4**) to give an intermediate **8**. The nitrogen attacks the electron deficient carbon to give intermediate **9**, which on elimination of ammonia gives rise to 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromenes (**5a-h**).



Scheme-2: Mechanism of the formation of 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromenes (**5a-h**)

Thus the oxygen heterocyclic analogs **5a-h** of nifedipine, nicorpidine and nimopidine are easily synthesized in this reaction.

EXPERIMENTAL SECTION

Melting points were determined in sulphuric acid bath and are uncorrected. IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrophotometer and ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) on a Varian Gemini 200 spectrometer using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on a VG micro mass 70-70H instrument. Elemental analyses were performed on a PE-2400 elemental analyzer.

2H-3-Chromenecarbaldehydes (**3a-h**) were synthesized by literature method.^{24,25}

General Procedure for the synthesis of 3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)] chromenes (**5a-h**):

To a solution of 2H-3-chromenecarbaldehydes (**3a-h**) (20 mmol), ethyl 3-amino crotonate (**4**) (40 mmol) is added drop wise at RT. The stirring is continued for 24hrs. After completion of the reaction, excess acetic acid is removed by distillation under reduced pressure and the residue was treated with crushed ice (50g). The solid obtained was filtered and subjected to column chromatography over silica gel (60-120 mesh, ACME). Elution with petroleum ether: ethylacetate (8: 2) gave 3-[4'-(2',6'-dimethyl-3',5' dicarbethoxy-1',4'-dihydropyridyl)] chromenes (**5a-h**) (55-65 % yield).

8-Chloro-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5a): mp 155 °C. IR (KBr): 3447 cm^{-1} (N-H), 1728 cm^{-1} (C=O, ester); UV (MeOH): λ_{max} 252 nm (log ϵ 4.2), λ_{max} 279 nm (log ϵ 3.8) and λ_{max} 360 nm (log ϵ 3.6); ^1H NMR (CDCl_3): δ 1.30 (t, $J=7.0\text{Hz}$, 2 x CH_3), 2.34 (s, 2 x CH_3), 4.15 (m, OCH_2 x 2), 4.50 (s, H-4'), 4.88 (s, OCH_2 -2), 5.62 (bs, NH), 6.10 (s, H-4), 6.72 (m, H-6, 7) and 7.05 (dd, $J=10.0, 2.5\text{Hz}$, H-5); ^{13}C NMR (CDCl_3): δ 14.2 (CH_3 -3',5'), 19.8 (CH_3 -2',6'), 37.4 (C-4'), 60.0 (OCH_2 -3',5'), 68.0 (OCH_2 -2), 100.2 (CH_2 -3',5'), 118.4 (C-8), 120.2 (C-

4a), 121.8 (C-6), 125.0 (C-5,7), 128.8 (C-3), 139.8 (C-4), 144.8 (C-2',6'), 148.6 (C-8a) and 178.0 (C=O) MS : m/z 417 (M^+) (19), 388 (9), 344 (26), 252 (100), 224 (6) and 196 (13); Anal. Cald. For $C_{22}H_{24}ClNO_5$: C, 63.23, H, 5.79, N, 3.35. Found C, 63.19, H, 5.82, N, 3.38%.

3-[4'-(2',6'-Dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5b): mp 136 °C; IR (KBr): 3446 cm^{-1} (N-H), 1724 cm^{-1} (C=O, ester); UV (MeOH): λ_{max} 248 nm (log ϵ 4.90), λ_{max} 282 nm (log ϵ 3.23) and λ_{max} 365 nm (log ϵ 3.02). 1H NMR ($CDCl_3$): δ 1.28(t, J=7Hz, CH_3 -3',5'), 2.60 (s, CH_3 -2',6'), 4.32 (m, OCH_2), 4.68 (s, H-4'), 4.82 (d, J=1Hz, OCH_2 -2), 5.49 (bs, NH), 6.32 (s, H-4), 6.90 (m, H-6, 8), 7.15 (m, H-5, 7); ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_2 - CH_3), 23.6 (CH_3 -2', 6'), 35.8 (C-4'), 62.0 (OCH_2 -pyridyl), 68.0 (OCH_2 -2), 102.8 (C-3', 5'), 119.8 (C-4a), 116.0 (C-8), 122.0 (C-4), 125.0 (C-6), 127.8 (C-5), 130.0 (C-7), 150.4 (C-8a), 153.8 (C-3), 156.0 (C-2',6') and 167.8 (C=O); MS: m/z 383 (M^+) (19), 354 (9), 310 (26), 218 (100), 190 (6) and 162 (13); Anal. Cald. For $C_{22}H_{25}NO_5$: C, 68.91, H, 6.57, N, 3.65. Found C, 68.89, H, 6.54, N, 3.61%.

7-Methoxy-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5c): mp 157 °C. IR (KBr): 3362 (N-H), 1732 (C=O, ester); UV(MeOH): λ_{max} 244 nm (log ϵ 4.65), λ_{max} 284 nm (log ϵ 4.57) and λ_{max} 320 nm (log ϵ 4.65); 1H NMR ($CDCl_3$): δ 1.29 (t, J=7 Hz, CH_3 -3',5'), 2.35 (s, CH_3 -2',6'), 3.72(s, OCH_3), 4.18 (m, OCH_2 x 2), 4.48 (s, H-4'), 4.69 (d, J=1Hz, OCH_2), 5.58 (bs, NH), 6.04 (s, H-4), 6.45 (d, J=10.0 Hz, H-8), 6.58 (d, J=2.5 Hz, H-5), 6.66 (dd, J=10.0, 2.5 Hz, H-7); ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_2 - CH_3), 23.6 (C-4'), 25.8 (CH_3 -2',6'), 55.8 (OCH_3), 61.8 (OCH_2 -pyridyl), 68.0 (OCH_2 -2), 101.8 (C-3',5'), 108.0 (C-4a), 123.4 (C-8), 124.8 (C-4), 127.2 (C-5), 128.2 (C-7), 141.4 (C-3), 162.8 (C-2', 6'), 166.4 (C-8a), 168.0 (C=O); MS: m/z 413 (M^+) (19), 384 (9), 340 (26), 248 (100), 220 (6) and 192 (13); Anal. Cald. For $C_{23}H_{27}NO_6$: C, 66.81, H, 6.58, N, 3.39. Found C, 66.77, H, 6.56, N, 3.34%.

5-Ethoxy-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5d): mp 151 °C. IR (KBr): 3568 cm^{-1} (N-H), 1718 cm^{-1} C=O, ester); UV (MeOH): λ_{max} 248 nm (log ϵ 4.5), λ_{max} 272 nm (log ϵ 4.4) and λ_{max} 312 nm (log ϵ 4.5); 1H NMR ($CDCl_3$): δ 1.30 (t, J=7Hz, CH_3 -3',5'), 1.45 (t, J=7Hz, OCH_2CH_3), 2.60 (s, CH_3 -2',6'), 4.12 (m, OCH_2), 4.30 (m, OCH_2), 4.90 (d, J=1Hz, OCH_2 -2), 5.87 (s, NH), 6.30 (s, H-4), 6.60-6.80 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3 -3',5'), 14.8 (OCH_2CH_3), 19.6 (CH_3 -2', 6'), 37.8 (C-4'), 60.0 (OCH_2 -pyridyl), 64.8 (OCH_2 -2), 100.8 (C-3', 5'), 113.2 (C-8), 119.2 (C-6), 119.4 (C-7), 124.2 (C-4a), 139.0 (C-3), 145.8 (C-2', 6'), 147.0 (C-5), 148.0 (C-8a), 168.2 (C=O); MS: m/z 427 (M^+) (19), 398 (9), 354 (26), 262 (100), 234 (6) and 206 (13); Anal. Cald. For $C_{24}H_{29}NO_6$: C, 67.43, H, 6.84, N, 3.28. Found C, 67.46, H, 6.82, N, 3.25%.

6-Chloro-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5e): mp 135 °C. IR (KBr): 3420 cm^{-1} (N-H), 1728 cm^{-1} (C=O, ester); UV (MeOH): λ_{max} 236 nm (log ϵ 4.31), λ_{max} 285 nm (log ϵ 4.42) and λ_{max} 324 nm (log ϵ 4.6); 1H NMR ($CDCl_3$): δ 1.30 (t, J=7Hz, CH_3 -3',5'), 2.32 (s, CH_3 -2',6'), 4.07 (m, OCH_2), 4.43 (s, H-4'), 4.75 (s, OCH_2 -2), 5.85 (bs, NH), 6.00 (s, H-4), 6.60 (d, J=10.0, 8.0 Hz, H-8), 6.85 (d, J=2.5Hz, H-5), 6.91 (dd, J=10.0, 2.5Hz, H-7); ^{13}C NMR($CDCl_3$): δ 14.2 (CH_3 -3',5'), 19.6 (CH_3 -2', 6'), 37.6 (C-4'), 60.0 (OCH_2 -pyridyl), 67.8 (OCH_2 -2), 101.0 (C-3', 5'), 112.8 (C-4a), 116.2 (C-8), 118.6 (C-4), 125.8 (C-5), 127.8 (C-7), 141.0 (C-3), 145.6 (C-2', 6'), 151.6 (C-8a), 167.4 (CO₂); MS: m/z 417 (M^+) (19), 388 (9.21), 344 (26.3), 252 (100), 224 (6.5) and 196 (13.15); Anal. Cald. For $C_{22}H_{24}ClNO_5$: C, 63.23, H, 5.79, N, 3.35. Found C, 63.21, H, 5.76, N, 3.31%.

6-Bromo-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5f): mp 162 °C. IR (KBr): 3321 cm^{-1} (N-H), 2980 cm^{-1} (C-H), 1720 cm^{-1} (C=O, ester); UV (MeOH): λ_{max} 241 nm (log ϵ 4.3), λ_{max} 284 nm (log ϵ 3.6) and λ_{max} 331 nm (log ϵ 3.9). 1H NMR ($CDCl_3$): δ 1.30 (t, J=7.0 Hz, CH_3 -3', 5'), 2.35 (s, CH_3 -2', 6'), 4.18 (m, OCH_2 x2), 4.47 (s, H-4'), 4.78 (d, J=1.0 Hz, OCH_2 -2), 5.60 (bs, NH), 6.00 (s, H-4), 6.58 (d, J=10.0, Hz, H-8), 7.00 (d, J=2.5 Hz, H-5), 7.10 (dd, J=10.0, 2.5Hz, H-7); ^{13}C NMR ($CDCl_3$): δ 14.6 (CH_3 -3',5'), 19.8 (CH_3 -2', 6'), 37.8 (C-4'), 60.0 (OCH_2 -pyridyl), 68.0 (OCH_2 -2), 101.8 (C-3', 5'), 113.6 (C-4a), 117.6 (C-8), 119.0 (C-4), 125.8 (C-6), 129.2 (C-5), 131.2 (C-7), 141.4 (C-3), 145.6 (C-2', 6'), 152.4 (C-8a), 167.6 (C=O); MS: m/z 461 (M^+)(19), 432(9), 388(26), 296(100), 268(6) and 240(13). Anal. Cald. For $C_{22}H_{24}BrNO_5$: C, 57.15, H, 5.23, N, 3.03. Found C, 57.18, H, 5.21, N, 3.07%.

6-Methoxy-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5g): mp 163 °C. IR (KBr): 3334 cm^{-1} (N-H), 1720 cm^{-1} (C=O), 2941 cm^{-1} (C-H); UV (MeOH): λ_{max} 246 nm (log ϵ 4.7), λ_{max} 272 nm (log ϵ 4.6)

and λ_{max} 316 nm (log ϵ 4.7); ^1H NMR (CDCl_3): δ 1.30 (t, $J=7$ Hz, $\text{CH}_3\text{-3',5'}$), 2.35 (s, $\text{CH}_3\text{-2',6'}$), 3.72 (s, 3H, OCH_3), 4.18 (m, $\text{OCH}_2\text{x2}$), 4.48 (s, H-4'), 4.69 (d, $J=1.0$ Hz, OCH_2), 5.58 (bs, NH), 6.04 (s, H-4), 6.45 (d, $J=10.0$ Hz, H-8), 6.58 (d, $J=2.5$ Hz, H-5), 6.66 (dd, $J=10.0$, 2.5 Hz, H-7); ^{13}C NMR (CDCl_3): δ 14.8 ($\text{CH}_3\text{-3',5'}$), 18.4 ($\text{CH}_3\text{-2',6'}$), 39.0 (C-4'), 55.0 (OCH_3), 59.0 ($\text{OCH}_2\text{-pyridyl}$), 68.0 ($\text{OCH}_2\text{-2}$), 100.4 (C-3', 5'), 111.0 (C-4a), 115.2 (C-8), 118.4 (C-4), 126.2 (C-6), 129.4 (C-5), 132.2 (C-7), 143.2 (C-3), 146.2 (C-2', 6'), 154.2 (C-8a), 168.2 (C=O); MS: m/z 413 (M^+) (19), 384 (9), 340 (26), 248 (100), 220 (6) and 192 (13); Anal. Cald. For $\text{C}_{23}\text{H}_{27}\text{NO}_6$: C, 66.81, H, 6.58, N, 3.39. Found C, 66.78, H, 6.55, N, 3.37%.

6,8-Dibromo-3-[4'-(2',6'-dimethyl-3',5'-dicarbethoxy-1',4'-dihydropyridyl)]chromene (5h): mp 137 °C. IR (KBr): 3336 cm^{-1} (N-H), 1685 cm^{-1} (C=O); UV (MeOH): λ_{max} 241 nm (log ϵ 4.3), λ_{max} 282 nm (log ϵ 4.4) and λ_{max} 326 nm (log ϵ 4.7); ^1H NMR (CDCl_3): δ 1.30 (t, $J=7.0$ Hz, $\text{CH}_3\text{-3',5'}$), 2.30 (s, $\text{CH}_3\text{-2',6'}$), 4.15 (m, $\text{OCH}_2\text{x2}$), 4.48 (s, H-4'), 4.87 (s, $\text{OCH}_2\text{-2}$), 5.58 (bs, NH), 5.95 (s, H-4), 6.90 (d, $J=2.0$ Hz, H-7), 7.32 (d, $J=2.0$ Hz, H-5). ^{13}C NMR (CDCl_3): δ 14.6 ($\text{CH}_3\text{-3',5'}$), 19.8 ($\text{CH}_3\text{-2',6'}$), 37.8 (C-4'), 60.0 ($\text{OCH}_2\text{-pyridyl}$), 68.4 ($\text{OCH}_2\text{-2}$), 100.6 (C-3', 5'), 110.0 (C-8), 113.0 (C-6), 118.0 (C-4), 126.0 (C-4a), 128.0 (C-5), 133.8 (C-7), 138.0 (C-8a), 141.6 (C-3), 145.6 (C-2', 6'), 167.6 (CO); MS: m/z 541 (M^+) (19), 539 (9), 468 (26); Anal. Cald. For $\text{C}_{22}\text{H}_{23}\text{Br}_2\text{NO}_5$: C, 48.82, H, 4.28, N, 2.59. Found C, 48.8, H, 4.26, N, 2.61%.

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References

1. H. A. DeWald, T. G. Heffner, J. C. Jaen, D. M. Lustgarten, A. T. McPhail, L. T. Meltzer, T. A. Pugsley, L. D. Wise, *J. Med. Chem.* **33**, 445-450 (1990).
2. R. Bergmann, R. Gericke, *J. Med. Chem.* **33**, 492-504 (1990).
3. K. S. Atwal, G. J. Grover, S. Z. Ahmed, F. N. Ferrara, T. W. Harper, K. S. Kim, P. G. Sleph, S. Dzwonczyk, A. D. Russell, S. Moreland, J. R. McCullough, D. E. Normandin, *J. Med. Chem.* **36**, 3971-3974 (1993).
4. P. Da Re, L. Sagramora, V. Mancini, P. Valenti, L. Cima, *J. Med. Chem.* **13**, 527-531 (1970).
5. B. Macchia, A. Balsamo, C. M. Breschi, A. Lapucci, A. Lucacchini, F. Macchia, C. Manera, A. Martinelli, C. Martini, E. Martinotti, S. Nencetti, *J. Med. Chem.* **35**, 1009-1018 (1992).
6. G. P. Ellis, D. Shaw, *J. Med. Chem.* **15**, 865-867 (1972); *J. Chem. Soc., Perkin Transactions*, **1**, 779-783 (1972).
7. G. Atassi, P. Brit, J. J. Berthalen, T. Collenges, *Eur. J. Med. Chem.* **1985**, **20**, 393-402 (1985); *Chem Abstr*, **104**, 122574 (1986).
8. N. P. Buu-Hoi, N. D. Xuong, M. Sy, *Bull. Soc. Chem.* 1646-1650 (1956).
9. Z. S. Ariyan, H. Suschitzky, *J. Chem. Soc.* 2242-2244 (1961).
10. A. Hantzsch, *Just. Leib. Ann. De. Chem.* **215**, 1-82 (1882).
11. A. Hantzsch, *Berichte*, **19**, 289-293 (1886).
12. F. Bossert, W. Vater, *Med. Res. Rev.* **9**, 291-324 (1989).
13. B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi, E. Macko, *J. Med. Chem.* **19**, 956-965 (1974).
14. R. Alajarin, J. J. Vaquero, J. L. García Navío, J. Alvarez-Builla, *Synlett.* 297-299 (1992).
15. B. Loev, K. M. Snader, *J. Org. Chem.* **30**, 1914-1916 (1965).
16. Y. Watanabe, K. Shiota, T. Hoshiko, S. Ozaki, *Synthesis* 761-762 (1983).
17. J. S. Yadav, B. V. S. Reddy, P. T. Reddy, *Syn. Commun.* **31**, 425-430 (2001).
18. G. Haas, J. L. Stanton, A. V. Sprecher, P. Wenk, *J. Heterocyclic Chem.* **18**, 607-612 (1981).

19. K. Gorlitzer, K. Michels, *Arch. Pharm.* **321**, 567-568 (1988).
20. L. Amedeo, P. Renzo, C. Pietro, N. Dante, *Eur. Pat. Appl. EP*, 223744; *Chem. Abstr.* **107**, 175780j (1987).
21. M. S. N. Reddy, G. L. David Krupadanam, G. Srimannarayana, *Indian J. Chem.* **29B**, 978-979 (1990).
22. S. Ramadas, G. L. David Krupadanam, *Syn. Commun.* **30**, 1103-1114 (2000).
23. M. Venkati, G. L. David Krupadanam, *Syn. Commun.* **31**, 2589-2598 (2001).
24. F. Loiodice, A. Longo, P. Bianco, V. Tortorella, *Tetrahedron Asymmetry* **6**, 1001-1011 (1995).
25. Y. Satoh, J. L. Stanton, A. J. Hutchison, A. H. Libby, T. J. Kowalski, W. H. Lee, D. H. White, E. F. Kimble, *J. Med. Chem.* **36**, 3580-3594 (1993).

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