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One Pot Multicomponent Synthesis of Anti-inflammatory Active Tetrahydrofuro[3,2-*c*]pyridinone-2-carboxylate Derivatives

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A novel, one-pot method has been developed for the synthesis of tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate derivatives *via* cascade four-component condensation of 6-methyl, 4-hydroxy pyranone, aryl amines, aromatic aldehydes and pyridinium ylide, in presence of triethylamine as a catalyst under ethanol reflux conditions. It affords the corresponding product in high yield (78-92 %) with short reaction time (15-25 min).The anti-inflammatory activity of these compounds was determined. Out of the 17 synthesized compounds, compounds **5j**, **5k**, **5l**, **5m** and **5n** were excellent inhibitors of TNF-α and IL-6, COX-2, β-glucuronidase.

Keywords: 6-Methyl, 4-hydroxy pyranone, Pyridinium ylied, Multicomponent, Furopyridinone.

INTRODUCTION

The search for biologically active substances led to the investigation of condensed oxygen and nitrogen containing heterocycles. Furopyridines are very similar to such skeletons as quinoline and isoquinoline which are present in many compounds exhibiting biological activity [1]. Furo[3,2-c]pyridinone alkaloids are widespread among the *Rutaceae* family of plants and display important biological activities. In general furopyridone derivatives like citridone A, acridone alkaloid, dictamine, γ-fagarine, kimmianine, rutacridone-epoxide, hydroxyl rutacridone-epoxide shows good antibacterial activity (Fig. 1) [2-8].

Although a few synthetic approaches for the construction of this kind of heterocycle have been reported. Most of them may suffer from tedious steps, low yields and poor region and stereoselectivity [9-17]. Recently we have developed two new methodologies for the synthesis of C3-dihydrofuran substituted coumarins, dihydrofuro pyrazole by employing one pot multicomponent synthesis with pyridinium ylide. As part of our continued interest in the synthesis of diverse heterocyclic compounds of biological significance [18-25], we contemplated to synthesize novel tetrahydrofuro[3,2-*c*]pyridinone-2-carboxylate (**5**) by the one-pot four-component reaction of 6-methyl, 4-hydroxy pyran, aryl amine, aromatic aldehyde and pyridinium ylide to study their biological activity. Our previously developed methodology has been taken as a reference for developing furopyridone derivatives due to its slight structural similarity.

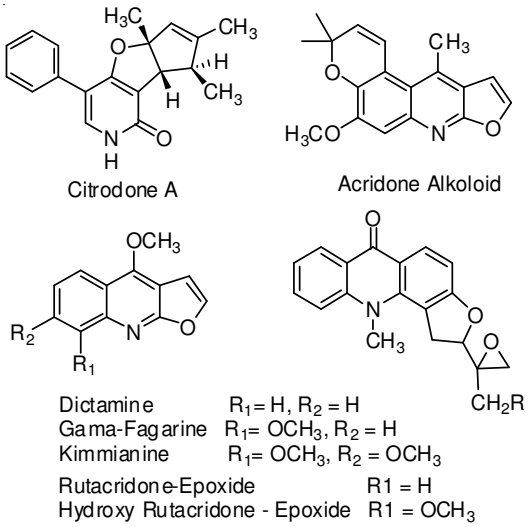


Fig. 1. Biologically active furopyridene derivatives

Our present work has provided not only an efficient route to the structurally interesting and biologically significant furo[3,2-*c*]pyridinone skeleton from readily available starting materials in a single step involves a tandem Michael addition fallowed by cyclization.

EXPERIMENTAL

Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. The progression of all

the reactions was monitored by TLC using a mixture of hexanes (60-80 °C boiling mixture) and ethyl acetate. Column chromatography was performed on silica gel (100-200 mesh, SRL Chemicals) using increasing percentage of ethyl acetate in hexanes. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded for $CDCl_3$ + CCl_4 (2:1) solutions on a Bruker-400 spectrometer with tetramethylsilane (TMS) as internal standard; *J* values are given in Hz. IR spectra were recorded as KBr solid solution on a Nicolet-6700 spectrometer. High resolution mass spectra were recorded on a Waters Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use. Melting points were measured in open capillary tubes and are uncorrected. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

General procedure for synthesis of (2*R*,3*R*)-ethyl 5-benzyl-6-methyl-4-oxo-3-phenyl-2,3,4,5-tetrahydrofuro[3,2-*c*]-pyridine-2-carboxylate (5a): A mixture of 4-hydroxy-6-methyl-2*H*-pyran-2-one (100 mg, 0.786 mmol), benzyl amine (84 mg, 0.786 mmol) in EtOH (5 mL), was stirred at room temperature for 5 min. Then benzaldehyde (83 mg, 0.147 mmol), pyridinium ylide (193 mg, 0.786 mmol), triethylamine (8 mg, 0.786 mmol) added sequentially to the mixture and it was refluxed at 80 °C for 20 min till the completion of the reaction (monitored by TLC). After completion of reaction ethanol was distilled out and in the product crushed ice (25 g) was added. To this 0.5 M HCl (1 mL) was added and the resulting aqueous with suspended solids was extracted with dichloromethane (2 × 10 mL) and concentrated. Crude product was purified through column chromatography by eluting with hexanes and EtOAc mixtures (TLC, 45 % EtOAc in hexanes; R_f = 0.34). After recrystallization from EtOH, product obtained as light yellow colour crystalline solid; Yield 86 % (264 mg), m.p.: 154.3 °C, IR (KBr, ν_{max}, cm^{-1}): 3015, 3002, 2995, 1789, 1680, 1622, 1502, 1208, 1180, 1073, 963, 870, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.29 -7.23 (m, 6H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.1, 140.6, 136.5, 128.6, 128.4, 127.9, 126.8, 126.5, 100.7, 100.4, 79.3, 61.6, 48.8, 40.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 412.1519 calcd. for $C_{24}H_{23}NO_4$ (M+Na) found: 412.1515. Analysis calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60; Found C, 74.01; H, 5.93; N, 3.58.

(2*R*,3*R*)-Ethyl 5-benzyl-3-(4-fluorophenyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5b): Yellow colour solid, Yield 89 % (286 mg), m.p.: 157.5 °C, IR (KBr, ν_{max}, cm^{-1}): 3011, 3000, 2981, 1781, 1676, 1618, 1500, 1233, 1191, 1081, 968, 877, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 9H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H),2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 167.3, 160.1, 157.6, 150.2, 136.5, 136.2, 129.3, 128.5, 126.9, 126.7, 115.4, 100.7, 100.4, 79.4, 61.6, 48.7, 40.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 430.1425 calcd. for $C_{24}H_{22}FNO_4$ (M+Na) found: 430.1422. Analysis calcd. for $C_{24}H_{22}FNO_4$: C, 70.75; H, 5.44; N, 3.44; Found C, 70.73; H, 5.42; N, 3.41.

(2*R*,3*R*)-Ethyl 5-benzyl-3-(4-chlorophenyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5c) Yellow colour solid, Yield 92 % (308 mg), m.p.: 157.9 °C, IR (KBr, ν_{max}, cm^{-1}): 3015, 3002, 2995, 1789, 1680, 1622, 1502, 1208, 1180, 1073, 963, 870, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 3H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.97 (s, 2H), 4.43 (d, *J* = 4.6 Hz, 1H), 4.22 (q, *J* = 6.6 Hz, 2H), 2.25 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.2, 157.6, 150.2, 140.6, 138.7, 136.7, 131.6, 128.9, 128.5, 126.9, 126.7, 100.7, 100.4, 79.3, 61.6, 48.6, 40.8, 20.4, 14.1 ppm; HRMS (ESI, *m/z*) : 423.1237 calcd. for $C_{24}H_{22}NO_4Cl$ (M+Na) found: 423.1235. Analysis calcd. for $C_{24}H_{22}NO_4Cl$: C, 68.00; H, 5.23; N, 3.30; Found C, 67.98; H, 5.21; N, 3.27.

(2*R*,3*R*)-Ethyl 5-benzyl-3-(4-bromophenyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5d): Yellow colour solid, Yield 91 % (337 mg), m.p.: 158.9 °C, IR (KBr, ν_{max}, cm^{-1}): 3021, 3012, 3003, 1784, 1691, 1622, 1610, 1502, 1203, 1198, 1081, 955, 862, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.97 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.20 (q, *J* = 6.6 Hz, 2H), 2.27 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.1, 139.8, 136.5, 131.5, 129.9, 128.5, 126.9, 126.7, 120.5,100.7, 100.4, 79.3, 61.6, 48.7, 40.8, 20.4, 14.1 ppm; HRMS (ESI, *m/z*) : 490.0630 calcd. for $C_{24}H_{22}NO_4Br$ (M+Na) found: 490.0626. Analysis calcd. for $C_{24}H_{22}NO_4Br$: C, 61.55; H, 4.73; N, 2.99; Found C, 61.53; H, 4.71; N, 2.98.

(2*R*,3*R*)-Ethyl 5-benzyl-6-methyl-4-oxo-3-*p*-tolyl-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5e): Yellow colour solid, Yield 90 % (287 mg), m.p.: 158.3 °C, IR (KBr, ν_{max}, cm^{-1}): 3021, 3008, 3002, 2998, 1791, 1682, 1620, 1508, 1218, 1181, 1069, 952, 853, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.4, 2H), 7.23 (t, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 7.4 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.22 (q, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 2.16 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.1, 137.6, 136.5, 135.6, 128.9, 128.5, 127.6, 126.7, 100.7, 100.4, 79.3, 61.6, 48.5, 40.6, 21.3, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 426.1681 calcd. for $C_{25}H_{25}NO_4$ (M+Na) found: 426.1679. Analysis calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47; Found C, 74.40; H, 6.22; N, 3.44.

(2*R*,3*R*)-Ethyl 5-benzyl-3-(4-methoxyphenyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5f): Yellow colour solid, Yield 90 % (332 mg), m.p.: 159.1°C, IR (KBr, ν_{max}, cm^{-1}): 3023, 3015, 2995, 1798, 1675, 1614, 1500, 1204, 1172, 1062, 957, 865, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 2H), 6.94 (d, *J* = 6.8 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 2.18 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.2, 157.8, 157.6, 150.1, 136.5, 132.9,

128.9, 128.9, 128.7, 128.5, 126.9, 126.7, 114.2, 100.4, 79.3, 61.6, 55.9, 48.6, 40.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 442.1630 calcd. for $C_{25}H_{25}NO_5$ (M+Na) found: 442.1628. Analysis calcd. for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34; Found C, C, 71.55; H, 6.00; N, 3.32.

(2*R*,3*R*)-Ethyl 5-benzyl-3-(4-hydroxyphenyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5g): Yellow colour solid, Yield 92 % (295 mg), m.p.: 157.6°C, IR (KBr, ν_{max}, cm^{-1}): 3125, 3081, 3009, 3001, 2981, 1764, 1691, 1618, 1521, 1321, 1202, 1178, 1054, 961, 875, 762 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 2H), 6.70 (d, *J* = 6.8 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 5.23 (br s, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 155.7, 150.1, 136.5, 133.2, 129.1, 128.5, 126.9, 126.7, 115.8, 100.7, 100.4, 79.3, 61.6, 48.6, 40.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 428.1474 calcd. for $C_{24}H_{23}NO_5$ (M+Na) found: 428.1471. Analysis calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45; Found C, 71.07; H, 5.70; N, 3.42.

(2*R*,3*R*)-Ethyl 5-benzyl-6-methyl-3-(4-nitrophenyl)-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5h): Yellow colour solid, Yield 81 % (278 mg), m.p.: 161.4 °C, IR (KBr, ν_{max}, cm^{-1}): 3034, 3016, 3005, 2981, 1776, 1689, 1614, 1502, 1384, 1208, 1180, 1079, 971, 888, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.33 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.5, 147.2, 145.2, 136.5, 128.6, 128.5, 126.9, 126.8, 123.8, 100.7, 100.4, 79.4, 61.5, 48.7, 40.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 457.1370 calcd. for $C_{24}H_{22}N_2O_6$ (M+Na) found: 457.1368. Analysis calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45; Found C, 66.32; H, 5.08; N, 6.43.

(2*R*,3*S*)-Ethyl 5-benzyl-3-(2,4-dichlorophenyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5i): Yellow colour solid, Yield 83 % (301 mg), m.p.: 166.7°C, IR (KBr, ν_{max}, cm^{-1}): 3031, 3022, 3011, 2987, 1774, 1698, 1643, 1621, 1513, 1209, 1181, 1079, 974, 878, 758 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.33 (d, *J* = 6.8 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.28 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 1H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 3H), 2.76 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.1, 136.3, 134.4, 132.9, 130.5, 130.3, 128.5, 126.8, 126.7, 100.7, 100.4, 78.8, 61.6, 48.7, 35.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 480.0740 calcd. for $C_{24}H_{21}NO_4Cl_2$ (M+Na) found: 480.0738. Analysis calcd. for $C_{24}H_{21}NO_4Cl_2$: C, 62.89; H, 4.62; N, 3.06; Found C, 62.86; H, 4.60; N, 3.04.

(2*R*,3*R*)-Ethyl 5-benzyl-6-methyl-4-oxo-3-(2,4,5-trimethoxyphenyl)-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5j): Yellow colour solid, Yield 84 % (373 mg), m.p.: 172.1°C, IR (KBr, ν_{max}, cm^{-1}): 3098, 3065, 3010, 2982, 1764, 1692, 1644, 1615, 1534, 1423, 1221, 1175, 1066, 951, 853, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 5H), 6.85 (s, 1H), 6.42 (s, 1H), 5.55 (s, 1H), 5.41 (d, *J* =4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 9H), 2.96 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.1, 148.8, 144.5, 136.5, 128.5, 126.9, 126.7, 119.5, 111.1, 100.7, 100.4, 100.1, 79.6, 61.6, 56.13, 56.12, 56.11, 48.7, 35.2, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 502.1842 calcd. for $C_{27}H_{29}NO_7$ (M+Na) found: 502.1840. Analysis calcd. for $C_{27}H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92; Found C, 67.63; H, 6.10; N, 2.92.

(2*R*,3*R*)-Ethyl 5-(4-methoxybenzyl)-6-methyl-4-oxo-3-(2,4,5-trimethoxyphenyl)-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5k): Yellow colour solid, Yield 85 % (342 mg), m.p.: 175.4 °C, IR (KBr, ν_{max}, cm^{-1}): 3025, 3014, 3004, 2985, 1763, 1674, 1618, 1501, 1211, 1158, 1154,1073, 963, 870, 842, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.57 (s, 1H), 7.25 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 6.8 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.5, 158.7, 157.6, 150.1, 138.4, 130.5, 128.8, 128.5, 128.3, 126.8, 124.4, 124.3, 123.0, 122.3, 114.1, 100.7, 100.4, 79.6, 61.6, 55.8, 48.7, 38.3, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 532.1942 calcd. for $C_{28}H_{31}NO_8$ (M+Na) found: 532.1941. Analysis calcd. for $C_{28}H_{31}NO_8$: C, 66.00; H, 6.13; N, 2.75; Found C, 65.98; H, 6.10; N, 2.72.

(2*R*,3*R*)-Ethyl 3-[2,4-bis(trifluoromethyl)phenyl]-5-(4-methoxybenzyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro-[3,2-*c*]pyridine-2-carboxylate (5l): Yellow colour solid, Yield 79 % (304 mg), m.p.: 175.5°C, IR (KBr, ν_{max}, cm^{-1}): 3112, 3023, 3004, 2991, 1765, 1684, 1620, 1543, 1226, 1180, 1115, 1064, 961, 864, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 6.8 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.5, 158.8, 157.6, 150.1, 143.9, 130.5, 128.8, 128.2, 128.0, 125.0, 124.1, 114.1, 100.7, 100.4, 79.3, 61.6, 55.8, 48.7, 40.8, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 510.1499 calcd. for $C_{26}H_{24}NO_5F_3$ (M+Na) found: 510.1494. Analysis calcd. for $C_{26}H_{24}NO_5F_3$: C, 64.06; H, 4.96; N, 2.87; Found C, 64.04; H, 4.95; N, 2.83.

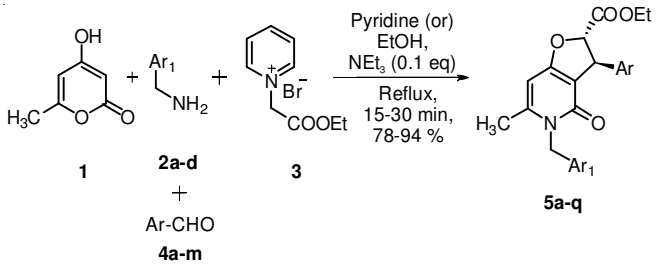
(2*R*, 3*R*)-Ethyl 3-(2,4-bis(trifluoromethyl)phenyl)-5-(4-methoxybenzyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro-[3,2-*c*]pyridine-2-carboxylate (5m): Yellow colour solid, Yield 78 % (343 mg), m.p.: 176.5°C, IR (KBr, ν_{max}, cm^{-1}): 3042, 3014, 2987, 1792, 1692, 1618, 1523, 1218, 1184, 1082, 942, 854, 763 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 6.8 Hz, 2H), 5.55 (s, 1H), 5.41 (d, *J* = 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.5, 158.8, 157.6, 150.1, 143.9, 130.5, 128.8, 128.2, 128.0, 125.0, 124.1, 114.1, 100.7, 100.4, 79.3, 61.6, 55.8, 48.7, 40.8, 20.3 ppm; HRMS (ESI, *m/z*) : 578.1373 calcd. for $C_{27}H_{23}NO_5F_6$ (M+Na) found: 578.1370. Analysis calcd. for $C_{27}H_{23}NO_5F_6$: C, 58.38; H, 4.17; N, 2.52; Found C, 58.35; H, 4.14; N, 2.51.

(2*R*,3*R*)-Ethyl 3-[2,4-*bis*(trifluoromethyl)phenyl]-5-(3,4-dimethoxybenzyl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5n): Yellow colour solid, Yield 83 % (384 mg), m.p.: 177.3°C, IR (KBr, ν_{max}, cm^{-1}): 3124, 3016, 3011, 2985, 1795, 1692, 1634, 1532, 1202, 1171, 1063, 958, 854, 745 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7. 46 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 1H)7.15 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 6.8 Hz, 1H), 5.55 (s, 1H), 5.41 (d, *J* = 1H), 4.98 (s, 2H), 4.44 (d, *J* = 1H), 4.21 (q, *J* = 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.76 (s, 3H), 1.29 (t, *J* = 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 158.6, 157.6, 150.1, 138.4, 130.5, 128.8, 128.5, 128.3, 126.8, 124.4, 124.3, 123.0, 122.3, 114.1, 100.7, 100.4, 78.9, 61.7, 55.8, 48.7, 38.3, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 608.1478 calcd. for $C_{28}H_{25}NO_6F_6$ (M+Na) found: 608.1475. Analysis calcd. for $C_{28}H_{25}NO_6F_6$: C, 57.44; H, 4.30; N, 2.39; Found C, 57.42; H, 4.28; N, 2.36.

(2*R*,3*R*)-Ethyl 5-benzyl-3-(furan-2-yl)-6-methyl-4-oxo-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5o): Yellow colour solid, Yield 88 % (264 mg), m.p.: 168.8°C, IR (KBr, ν_{max}, cm^{-1}): 3114, 3015, 1774, 1684, 1638, 1622, 1604, 1521, 1432, 1217, 1179, 1087, 968, 864, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.6 Hz, 1H), 7.33 (m, 2H), 7.27 - 7.23 (m, 3H), 6.40 (t, *J* = 8.4 Hz, 1H), 6.08 (d, *J* = 8.4 Hz, 1H), 5.55 (s, 1H), 5.41 (d, *J* = 1H), 4.98 (s, 2H), 4.67 (d, *J* = 1H), 4.21 (q, *J* = 2H), 2.26 (s, 3H), 1.29 (t, *J* = 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 151.6, 150.1, 141.5, 136.5, 128.7, 126.9, 126.7, 110.0, 105.9, 100.7, 100.4, 77.5, 61.6, 48.7, 40.5, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 379.1420 calcd. for $C_{30}H_{22}N_2O_6F_6$ (M+Na) found: 379.1416. Analysis calcd. for $C_{30}H_{22}N_2O_6F_6$: C, 69.64; H, 5.58; N, 3.69; Found C, 69.62; H, 5.55; N, 3.65.

(2*R*,3*R*)-Ethyl 5-benzyl-6-methyl-4-oxo-3-(thiophen-2-yl)-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5p): Yellow colour solid, Yield 87 % (272 mg), m.p.: 169.2°C, IR (KBr, ν_{max}, cm^{-1}): 3076, 3056, 3012, 1799, 1696, 1646, 1612, 1546, 1317, 1208, 1178, 1089, 989, 888, 779 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 1H), 7.33 (t, *J* =7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.93 (t, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 1H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 157.6, 150.1, 139.4, 136.5, 128.5, 127.1, 127.0, 126.7, 126.6, 125.5, 100.7, 100.4, 80.0, 61.6, 48.7, 40.0, 20.3, 14.1 ppm; HRMS (ESI, *m/z*) : 395.1191 calcd. for $C_{22}H_{21}NO_4S$ (M+Na) found: 395.1189. Analysis calcd. for $C_{22}H_{21}NO_4S$: C, 66.82; H, 5.35; N, 3.54; S, 8.11; Found C, 66.80; H, 5.33; N, 3.52; S, 8.10.

(2*R*,3*R*)-Ethyl 5-benzyl-6-methyl-4-oxo-3-(pyridin-3-yl)-2,3,4,5-tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate (5q): Yellow colour solid, Yield 91 % (281 mg), m.p.: 168.5°C, IR (KBr, ν_{max}, cm^{-1}): 3078, 3012, 3001, 1765, 1675, 1646, 1602, 1497, 1232, 1196, 1077, 954, 881, 767 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.33-7.28 (m, 6H), 5.55 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 2H), 4.44 (d, *J* = 4.6 Hz, 1H), 4.21 (q, *J* = 6.6 Hz, 2H), 2.26 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.4, 157.8, 150.7,148.4, 146.9, 139.1, 136.5, 133.5, 128.6, 126.9, 126.7, 123.6, 100.7, 100.4, 79.3, 61.8, 48.9, 40.9, 20.5, 14.5 ppm; HRMS (ESI, *m/z*): 413.1477 calcd. for $C_{23}H_{22}N_2O_4$ (M+Na) found: 413.1473. Analysis calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17; Found C, 70.73; H, 5.65; N, 7.16.



Scheme-I: Synthesis of tetrahydrofuro[3,2-*c*]pyridinone-2-carboxylate derivatives (**5a-q**)

RESULTS AND DISCUSSION

Initially, the condensation of with 6-methyl, 4-hydroxy pyran (**1**), aromatic aldehyde (**2**) pyridinium ylide (**3**) and aryl amine (**4**), was chosen as a model reaction and the influence of various solvents and catalysts was examined to find the optimal conditions for the reaction. In the first instance the reaction was investigated in the absence of catalyst (Table-1, entry 1) under solvent free microwave mediated conditions, but no product was formed. Then we decided to perform the reaction in suitable solvents under conventional heating methods. When the reaction was carried out in the presence of catalytic amount of NEt_3 under ethanol solvent conditions, the reaction was occurred within 15 min. Moreover, the nature of a base also has a pronounced impact on the reaction, NEt_3 appears to be better than morpholine, L-proline, piperidene, K_2CO_3. On further modification of the reaction conditions, we were delighted to find that the usage of stoichiometric quantity of NEt_3 was not necessary, only catalytic amount (0.1 eq.) was sufficient to effect this transformation efficiently. Next, we examined the effect of different solvents, which included MeOH, water, CH_2Cl_2, THF, CH_3CN, DMF, toluene, $CHCl_3$ under same reaction conditions (entries 12-21, Table-1). Among various solvents tested, EtOH was found to be the best solvent for the reaction, in terms of rapid transformation and quantified yields.

The structure of the compound was characterized by ^{1}H and ^{13}C NMR, MS and IR spectra and elemental analysis. In the ^{1}H NMR spectra, the two protons at 2,3-position of dihydrofuran ring display two doublets at 5.41 and 4.44 ppm with the vicinal coupling constant *J* = 4.6 and 4.6 Hz, respectively. It has been documented that in *cis*-2,3-dihydrofuran the vicinal coupling constant of the two methine protons *J* = 7-10 Hz, while in *trans*-2,3-dihydrofuran vicinal coupling constant *J* = 4-7 Hz (Fig. 2). It is concluded that thermodynamically stable *trans* isomer of 2, 3-dihydrofuran derivatives were formed on pyridone moiety [26]. Stereochemical disposition of *trans* H's were confirmed by 2D NMR *vis* HSQC and HMBC. As anticipated all the 19 signals are appeared in ^{13}C NMR spectrum. HRMS spectra shows molecular ion (M+ Na) peak at 412.1515.

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS

Entry	Base[a]	Solvent	Time (min)	Yield (%)[b]
1	No	No	10 min	0
2	Piperizene	No	20 min	28
3	Mapholine	No	30 min	37
4	DBU	No	30 min	16
5	K_2CO_3	No	25 min	39
6	Piperidene	No	20 min	42
7	Piperidene	water	25 min	57
8	Piperidene	Ethanol	25 min	61
8	$NHEt_2$	No	20 min	57
9	NEt_3	No	15 min	75
10	NEt_3	EtOH	30 min	86
11	NEt_3	Water	35min	65
12	NEt_3	DD Water	40 min	72
12	NEt_3	DMF	70 min	60
13	NEt_3	MeCN	60 min	56
14	NEt_3	THF	3.5 h	Trace
15	NEt_3	CH_2Cl_2	2.5 h	Trace
16	NEt_3	Toluene	2.0 h	Trace
17	NEt_3	$CHCl_3$	2.0 h	Trace

[a] Catalyst (0.1 eq); [b]Yields for isolated pure products.

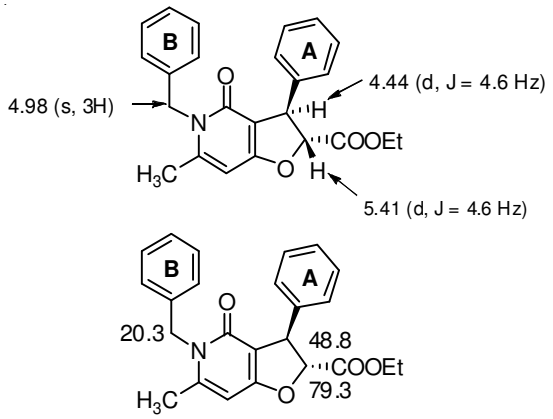


Fig. 2. Structure of tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate

By using the above the optimized reaction conditions, we subjected a series of aromatic aldehyde derivatives, benzylamine derivatives for this protocol to explore the generality of substrate scope of the process and the results are summarized in Table-2. In almost all cases, the furo pyridone derivatives formation was quick and in good yields. Substitution of various ring substituted aromatic aldehyde derivatives, benzylamine derivatives with hydrazine and pyridinium ylide afforded pyrazole spiro chromanones **5a-q** in 78-94 % (Table-2, entries 1-17). Spectroscopic data of the products matched well with those of the parent compound **5a**.

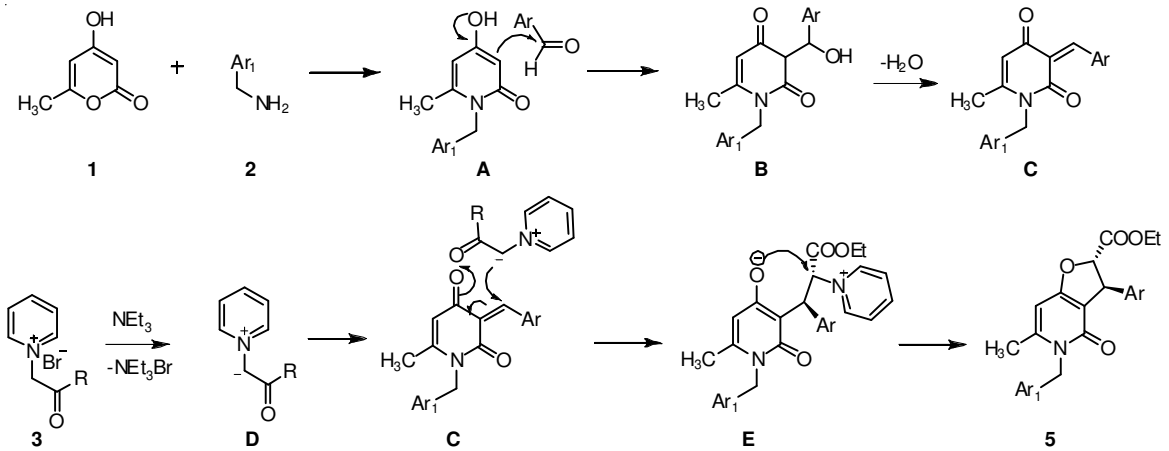
TABLE-2
SYNTHESIS OF TETRAHYDROFURO[3,2-*c*]-PYRIDINONE-2-CARBOXYLATE (**5a-q**)

Entry	Compd.	Ar	Ar_1	Yield (%)[c]
1	**5a**	C_6H_5	C_6H_5	86
2	**5b**	C_6H_4Cl	C_6H_5	89
3	**5c**	C_6H_4Br	C_6H_5	92
4	**5d**	C_6H_4F	C_6H_5	91
5	**5e**	*p*-CH_3-C_6H_4	C_6H_5	90
6	**5f**	*p*-OCH_3-C_6H_4	C_6H_5	90
7	**5g**	*p*-OH-C_6H_4	C_6H_5	92
8	**5h**	*p*-$NO_2C_6H_4$	C_6H_5	81
9	**5i**	2,4-di Cl-C_6H_3	C_6H_5	83
10	**5j**	2,4,5-tri $OMeC_6H_2$	C_6H_5	84
11	**5k**	2,4,5-tri $OMeC_6H_2$	*p*-(OMe)-C_6H_4	85
12	**5l**	*p*-CF_3-C_6H_4	*p*-(OMe)-C_6H_4	79
13	**5m**	2,4-di CF_3-C_6H_3	*p*-(OMe)-C_6H_4	78
14	**5n**	2,4-di CF_3-C_6H_3	3,4-di(OMe)-C_6H_4	83
15	**5o**	2-Furyl	C_6H_5	88
16	**5p**	2-Thiophenyl	C_6H_5	87
17	**5q**	3-Pyridyl	C_6H_5	91

[a]Yields for isolated pure products

As shown in Table-2, this protocol can be excellently applied on aromatic aldehydes with both electron-withdrawing groups and electron-donating groups and it is well amenable for aromatic aldehydes only (Table-2, entries 1-17). The reactions were completed within 15-25 min and the pure products were isolated in high yields. The synthetic route is facile, convergent and allows easy placement of a variety of substituents on aromatic ring A and B (Fig. 3). In the reaction protocol equimolar amounts of 6-methyl, 4-hydroxy pyranone, aryl amines, aromatic aldehydes and pyridinium ylide were reacted in the presence of 0.1 equivalents of NEt_3 in ethanol solvent under reflux conditions afforded **5a** in good yield. The expected product was formed in good yield in absence of any other stereomeric impurities.

A probable mechanism for the formation of product is depicted in **Scheme-II**, which is similar to that of mechanism



Scheme-II: Plausible mechanism for synthesis of tetrahydrofuro[3,2-*c*]pyridinone-2-carboxylate derivatives

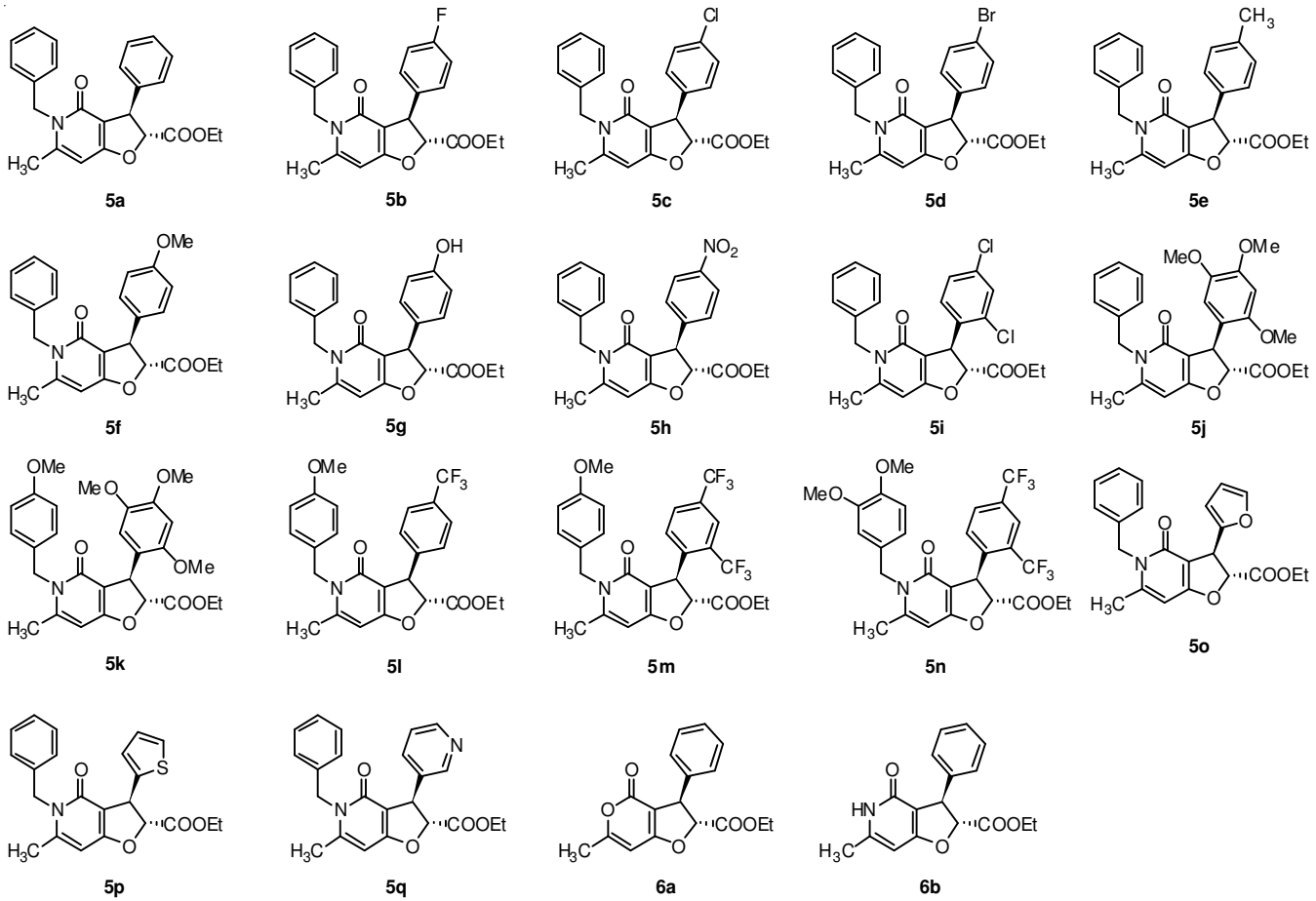


Fig. 3. Synthesis of SAR directed a combinatorial library of tetrahydrofuro[3,2-*c*]pyridinone-2-carboxylate derivatives

of dihydrofuropyrazole synthesis. Further the reaction occurs *via* an initial Knoevenagel condensation between 6-methy, 4-hydroxy pyranone **A** and aromatic aldehyde **3** to give the intermediate **C**. On the other hand, the pyridinium ylide **4**, which forms from the reaction of *N*-phenacyl pyridinium bromide **3** with triethyl amine undergoes Michael addition with an intermediate **D** to afford the enolate intermediate **E**. The enolate **E** eliminates pyridine and cyclizes instantly to give dihydrofuro-[1,2-*b*]pyrazole **5**.

Anti-inflammatory activity: All the synthesized compounds were evaluated for anti-inflammatory (TNF-α, IL-6, COX-1 and COX-2, β-glucuronidase and trypsin activity). TNF-α, IL-6, COX-1 and -2, β-glucuronidase and trypsin inhibition assays are prepared according to the literature procedure [27-29]. Anti-inflammatory activity against TNF-α and IL-6 and results are summarized in Table-3. Results revealed that almost all the synthesized compounds **5a** to **5q** have shown significant activity against of TNF-α (68-38 %) as compared with standard dexamethasone (72 %). Overall, compounds **5j**, **5k**, **5l**, **5m** and **5n** are the most active among the series against TNF-α and have least cytotoxicity against CCK-8 cell line. The structure activity relationship study in these compounds revealed that compounds containing electron-withdrawing substituent on aromatic ring **A** have higher TNF-α inhibition than their counterpart containing electron-donating substituent on aromatic ring **B**. Bioisosteric replacement of aromatic ring by furan, thiophene, pyridine there is slight decrease in TNF-α inhibition. When we compared these results with its siblings, the newly synthesized pyridone derivatives shows promising activity against of all TNF-α and IL-6, COX-2, β-glucuronidase enzymes than **6a** and **6b** compounds.

TABLE-3
ANTI-INFLAMMATORY ACTIVITY AGAINST TNF-α AND IL-6

Compounds	Inhibition (%) at 10 μM		
	TNF-α	IL-6	Toxicity
5a	44	52	53
5b	48	50	52
5c	42	48	56
5d	38	56	46
5e	39	57	48
5f	41	58	43
5g	37	61	44
5h	38	41	53
5i	31	43	56
5j	51	78	25
5k	56	81	22
5l	68	83	24
5m	54	76	30
5n	58	70	38
5o	39	47	47
5p	38	48	41
5q	41	47	43
Dexamethasone (1 μM)	72	94	00

The results summarized are the mean values of n = 2

The synthesized compounds screened for IL-6 inhibition and results are summarized in Table-3. Results showed that synthesized compounds are found to be active against IL-6. Compounds **5a** to **5q** have shown significant inhibition against of IL-6 (98-95 %) as compared with standard dexamethasone (94 %). Overall, compounds **5j**, **5k**, **5l**, **5m**, **5n** are most active and have lowest cytotoxicity against CCK-8 cell line. Compounds with fluorine and trifluoromethyl substitution have highest activity than the compounds containing chloro and bromo substitution on aromatic ring **A**.

The synthesized compounds are subjected to COX inhibition study and results are shown in Table-4. Compounds **5j**, **5l**, **5m**, **5n** and **5n** have shown potent (89.25-83.28 %) COX-2 inhibition. COX-2 is expressed during inflammation and COX-1 is constitutive, which is involved in physiological functions. Therefore, compounds selectively inhibit the COX-2 have good account of anti-inflammatory activity. Compounds under investigation have inhibited COX-2 preferentially and are more selective towards COX-2 rather than COX-1. Structure-activity relationship study with respect to cyclooxygenase inhibition revealed that compounds containing OMe and CF_3 groups shows better activity.

TABLE-4
ANTI-INFLAMMATORY ACTIVITY OF NOVEL DERIVATIVES AT 1 μM CONCENTRATION

Compd.	COX-1 (%)	COX-2 (%)	Trypsin (%)	β-Glucuronidase (%)
5a	38.41	60.37	50.85	44.32
5b	43.43	76.54	56.33	63.46
5c	37.14	59.46	48.13	43.87
5d	36.14	57.11	48.38	40.87
5e	37.22	58.34	47.45	41.25
5f	40.13	62.47	52.76	43.53
5g	39.18	60.55	51.23	42.78
5h	42.69	74.32	59.83	62.15
5i	40.25	54.78	46.72	40.43
5j	44.25	79.84	64.43	71.65
5k	46.86	82.37	68.56	73.58
5l	53.32	83.89	69.08	74.24
5m	57.68	85.15	69.86	75.03
5n	59.63	86.78	71.34	75.82
5o	38.12	50.76	49.47	42.93
5p	37.78	51.39	48.64	40.15
5q	39.13	49.38	50.18	43.19
5r	10.43	11.64	09.11	06.05
5s	12.75	13.54	11.90	09.47
ASA	–	36.93	–	–
SC 560	36.71	–	–	–
SA	–	–	84.99	24.77

The results are summarized are the mean values of n = 2
ASA = Acetyl salicylic acid, SC 560 = a standard COX-1

Trypsin is a member of the serine proteases family. These proteases are involved in initiation of inflammation; moreover, serine protease inhibition has been considered as one of the target for design of anti-inflammatory drugs [30]. From Table-4, compounds **5j** (64.43 %), **5k** (68.56 %), **5l** (69.08 %), **5m** (69.86 %), **5n** (71.84 %) have shown good trypsin inhibition as compared with standard salicylic acid (84.99 %). The enzyme β-glucuronidase has been considered as one of the targets in the design of anti-inflammatory agents as it play the role in the initiation of inflammation. The lysosomes of the polymorphonuclear neutrophils are rich in β-glucuronidase. This enzyme is attributed as one of the mediators for initiating the process of inflammation. Compounds **5j**, **5k**, **5l**, **5m** and **5n** have shown excellent inhibition of β-glucuronidase (75.82-71.65 %) as compared with standard salicylic acid (24.77 %).

Conclusion

In conclusion we have developed a facile, ecofriendly methodology for synthesis of tetrahydrofuro[3,2-*c*]pyridine-2-carboxylate derivatives by one pot multi-component condensation of 6-methyl, 4-hydroxy pyranone, aryl amines, aromatic aldehydes and pyridenium ylied, in presence of triethylamine as a catalyst under ethanol reflux conditions. Anti-inflammatory activity study of newly synthesized compounds shows that compounds **5j**, **5k**, **5l**, **5m** and **5n** were excellent inhibitors of TNF-α, IL-6, COX-2, trypsin and β-glucuronidase.

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