Bismuth Triflate–L(−)-Proline Catalyzed Synthesis of Chiral 2,5-Diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones

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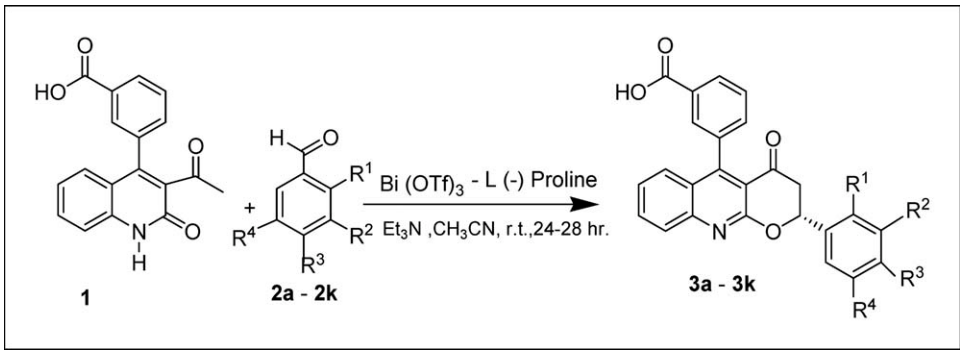

The synthesis of chiral (2*R*) 2,5-diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones, was achieved, at ambient temperature, by the reaction of 3-acetyl-4-aryl-carbostyril and an aldehyde, in the presence of bismuth triflate–L(−)-proline complex, formed *in situ*. The products were obtained in 62–78% yield with high enantioselectivity (72–96% ee).

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INTRODUCTION

Pyranoquinoline nucleus constitutes the core moiety of a small group of naturally occurring bioactive alkaloids [1], mostly found in the plants belonging to family *Rutaceae* [2]. These alkaloids display a wide array of biological activity [3], such as antimicrobial [4], antiasthmatic [5], anti-inflammatory [6], psychotropic [7], immunemodulating [8], protein glysomal GAPDH enzyme inhibiting [9], and insect antifeedant [10] activity. They are believed to be useful in the treatment of rheumatoid arthritis, cirrhosis, fibrosis, prevention of graft rejection, and diabetic complications [11]. Additionally, these compounds may also find use in the photochemical applications [12]. With all these potential pharmacological properties, the synthesis of pyranoquinoline derivatives continues to receive significant attention.

Several synthetic protocols, involving cycloaddition reactions, such as Diel's–Alder reaction [13] and 1,3-dipolar addition of nitrile amines, nitrones, and nitrile oxides [14], for the preparation of pyranoquinoline derivatives are known. These compounds have also been prepared by the oxidative cyclization with DDQ [15], Provost reaction [16], $FeCl_3$-NaI reductive cyclization [17], organolithiation of dihyropyrans and furans [18], cyclization with PPA [19], and ring cleavage of cyclopentanone carboxamides [20]. Despite their attractiveness, most of the known synthetic methodologies are complicated by one or other drawback, such as multistage processes and operational difficulty, harsh reaction conditions, low to moderate yield, difficult availability of substrates, and difficult stereochemical control. Therefore, there is ample scope for the development of efficient synthetic methodologies for the preparation of these biologically important compounds.

2-Arylpyrano[2,3-b]quinolin-4-ones are the structural analogues of the privileged naturally occurring flavones [21]. Therefore, these compounds are expected to exhibit interesting biological properties. Normally, an enantioselective synthesis of pyranone derivatives possessing C-2 chiral centre is a difficult process. A few strategies known for the asymmetric synthesis of chiral pyranone derivatives include resolution of the related alcohols [22], substitution reactions [23] and addition reactions of 2-chromenes [24], using Cu (I) and Et_2Zn. During our studies on the exploration of the catalyst potential and limitations of the nontoxic and readily available bismuth salts, in the preparation of heterocyclic compounds, we got interested in the development of a suitable methodology for the preparation of chiral pyranoquinoline derivatives. We opined that asymmetrical catalysis would be an ideal approach for the preparation of optically active pyranoquinolines. In this article, we report a simple and efficient two-step synthesis of 2,5-diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones, from carbostyril derivatives, under ambient reaction conditions, using a chiral Bi^{3+}-L(−)

Table 1

Percent yield of 3a–3k.

Compounds	R^1	R^2	R^3	R^4	% Yield	M.P (°C)	$[\alpha]_D$	Time (h)	ee (%)[a]
3a	H	H	H	H	70	205	+55°	25	90
3b	H	H	OCH_3	H	76	195	+58°	28	89
3c	H	H	Cl	H	72	176	+52°	24	91
3d	H	H	F	H	68	165	+50°	25	96
3e	H	H	Br	H	70	215	+51°	24	91
3f	Cl	H	Cl	H	64	188	+52°	26	88
3g	H	H	—O—CH_2—O—		67	199	+54°	24	72
3h	H	H	OCH_3	OCH_3	78	173	+54°	24	90
3i	H	H	CH_3	H	69	218 (dec.)	+53°	28	92
3j	H	H	NO_2	H	62	225 (dec.)	+45°	38	87
3k	Br	H	H	H	74	210	+52°	26	89

[a] The ee were determined by HPLC, using Diacel OD-H column; solvent: hexane-isoPrOH.

proline complex. It is pertinent to mention here that only few examples of the enantioselective reactions involving a chiral bismuth catalyst [25] are known.

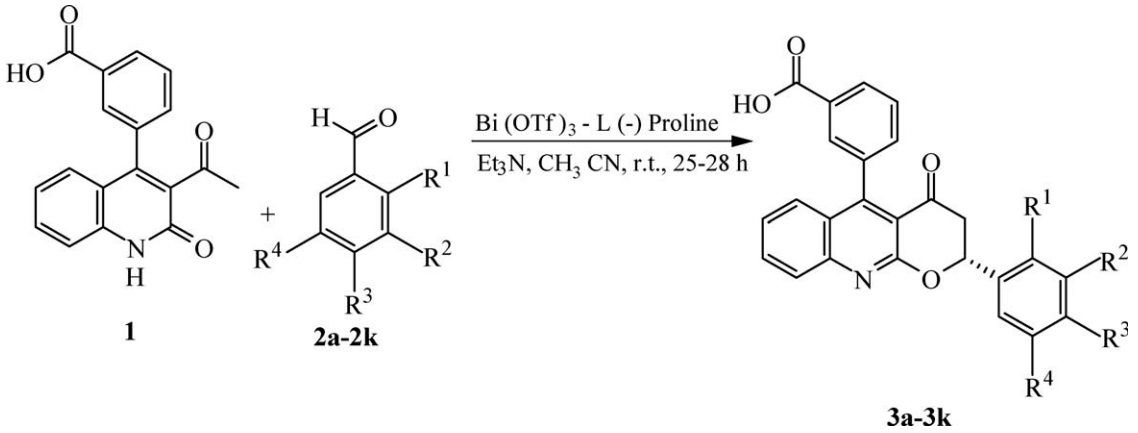
RESULTS AND DISCUSSION

Our strategy for the preparation of optically active 2,5-diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones, from carbostyril derivatives, involved the introduction of an unsaturated carbonyl side chain, adjacent to the imido carbonyl, of the compound. This side chain may provide the basic site for interaction with a chiral Bi^{3+} catalyst and permit intramolecular carbon–oxygen bond formation, *via* enolization of the carbostyril imido carbonyl group. Accordingly, our protocol consisted of 3-acetyl-4-arylcarbostyril, an aldehyde, and a suitable Bi^{3+} ion-based chiral catalyst. 3-Acetyl-4-(3-carboxyphenyl)carbostyril **1**, was used as a model substrate for the present reaction.

For the asymmetric synthesis of the desired pyranoquinolines, we surveyed bismuth salts, which could be used in the presence of L(−) proline to provide a suitable catalyst for the one-pot condensation-intramolecular conjugate addition reaction of 3-acetyl-4-(3-carboxyphenyl) carbostyril **1** and an aldehyde. After a few experiments, we observed that bismuth triflate–L(−)-proline was the catalyst of choice and dry acetonitrile was the appropriate solvent for the preparation of 2-phenyl-5-(3-carboxyphenyl)-2,3-dihydropyrano[2,3-b]quinolin-4-one at room temperature. However, the yield of the products was not encouraging. This could be attributed to the possible coordination of carbostyril nitrogen to the catalyst, under the reaction conditions, and the difficulty in the enolization of the amido carbonyl. We assumed that this difficulty may be surmounted by modifying the reaction conditions such that the abstraction of hydrogen from the amido nitrogen of the carbostyril is facilitated. In fact, bismuth triflate–L(−)-proline and Et_3N in a single catalyst provided the desired pyrano[2,3-b]quinolones, **3a**, in good yield (Table 1). Optimization of the catalyst composition revealed that, for the maximum yield of **3a**, the ideal composition of the catalyst was 10 mol % of bismuth triflate, 15 mol % of L(−)-proline and 15 mol % of Et_3N. We also observed that the presence of moisture was detrimental to intramolecular conjugate addition.

With optimized conditions in hand, we prepared compounds **3a**–**3k** (Scheme 1) by stirring compound **1**, aldehyde **2a**–**2k** (1:1.4 mol), and the catalyst mixture at room temperature. The reactions were monitored by TLC. On completion of the reaction (24–28 h) and usual work up, the products **3a**–**3k** were obtained in 62–78% yield (Table 1); the lowest yield was obtained when 4-nitrobenzaldehyde was used in the reaction. The products were purified by column chromatography on silica gel, followed by crystallization, and analyzed by spectral methods (IR, ^{1}H NMR, ^{13}C NMR, DEPT 135°, and HRMS) and elemental analysis. In their ^{1}H NMR spectra (See Experimental section), compounds **3a**–**3k** displayed a typical ABX pattern with resonance signals near δ 2.80 (1H, dd, J = 16.5, 13.2 Hz), 3.08 (1H, dd, J = 16.5, 3.2 Hz) and 5.06 (1H, dd, J = 13.2, 3.2 Hz), besides the expected aromatic proton signals and carboxylic proton signal, δ 11.2. The ^{13}C NMR coupled with DEPT 135° placed the C-3 CH_2 near δ_C 44.5. In addition to the expected aromatic carbon signals, the ^{13}C NMR displayed resonance signals near δ_C 78.3–80.1 (C-2), 198.1 (C-4), and 167.5 (COOH). The mass fragmentation agreed with the assigned structures. The compounds showed optical rotation $[\alpha]_D$ (20°C) = +45° to +58° (c. 0.5, EtOH; Table 1). The enentioselective excess (Table 1) was determined by HPLC, using Diacel OD-H column and hexane-isoPrOH as eluent. The stereochemistry at C-2 was fixed on the basis of the comparison of the multiplicity and coupling constant of the carbinylic proton (H-2) with the reported data for 2-aryl chromanans[26c].

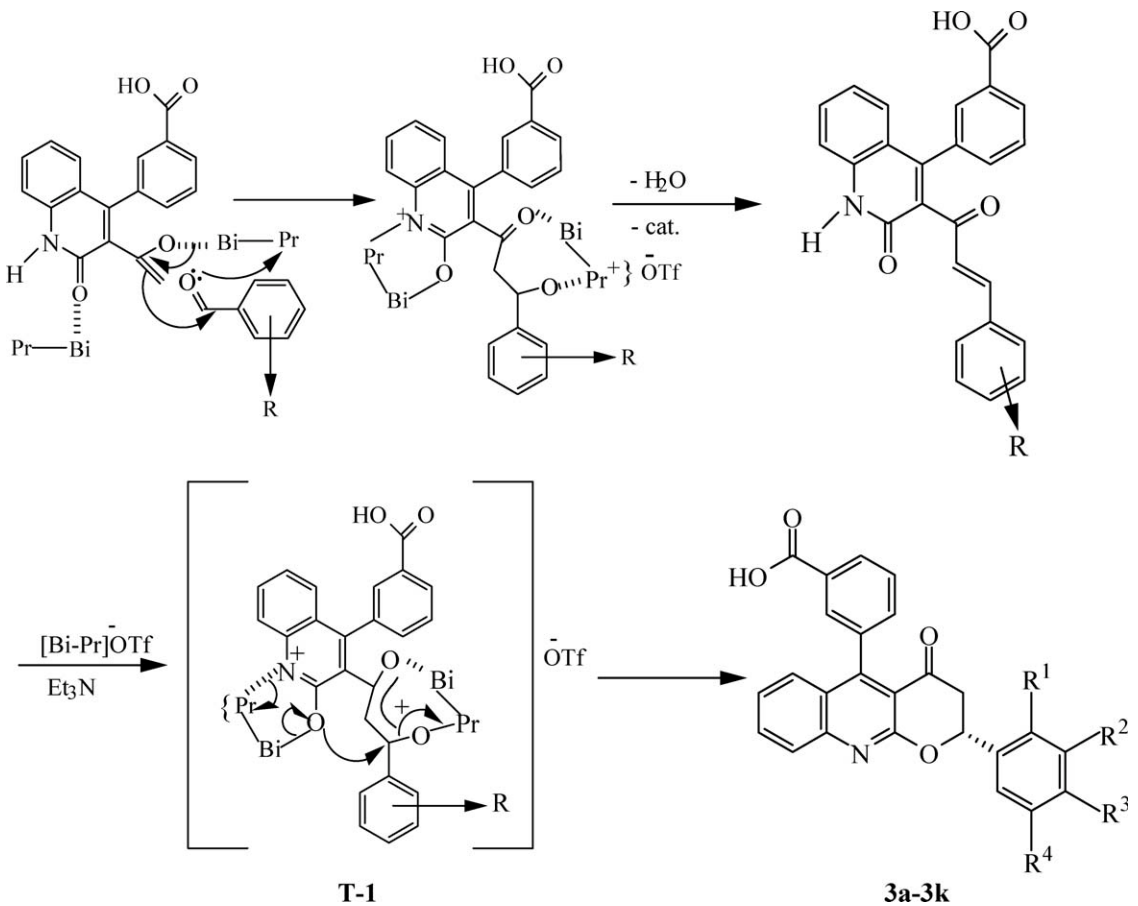
Scheme 1. Preparation of 2,5-diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones.



The most plausible mechanism (Scheme 2) for the reaction may involve the Lewis acid-catalyzed Claisen–Schmidt condensation [27] of 3-acetyl-4-aryl-carbostyril, such as compound **1**, with an arylaldehyde, to generate a α,β-unsaturated ketone. Subsequent enolization of the activated carbonyl as also the carbostyril amido group, in the presence of the catalyst Bi^{3+}-L(−) proline complex, formed *in situ*, may bring about asymmetric intramolecular oxa-Micheal addition [27], probably *via* the formation of a transition state **T-1** with the catalyst [27a], to form chiral 2,5-diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones. Triethylamine may be facilitating the enolization of the carbostyril amido group by the facile removal of proton from the ring nitrogen.

In conclusion, we have developed an efficient and simple catalytic asymmetric method for the preparation

Scheme 2. Probable mechanism for the formation of (2*R*) 2,5-diaryl-2,3-dihydropyrano [2,3-b]quinolin-4-ones.



of optically active (2*R*) 2-phenyl-5-(3-carboxyphenyl)-2,3-dihydropyrano[2,3-b]quinolin-4-ones, from easily accessible 3-acetyl-4-arylcarbostyrils, using chiral Bi^{3+}-L(−) proline complex, formed *in situ*, as catalyst. Current research efforts are directed toward the scope of this process in the synthesis of other optically active nitrogen heterocyclic compounds.

EXPERIMENTAL

Melting points are uncorrected and were determined on Perfit melting point apparatus. IR spectra were recorded on Brucker 4800 IR spectrometer. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded in $CDCl_3$, using a Brucker AcDPX-200 spectrometer; some spectra were recorded on Varian Gemini 300 MHz instrument, using TMS as standard. HRMS were recorded at 70 eV on JEOL D-300 mass spectrometer; CHN analysis was done on Fison Model EA 1108 elemental analyzer. $[\alpha]_D$ was measured on Perkin-Elmer 241 polarimeter. TLC was performed on 0.5-mm thick plates, using silica gel-G (BDH) adsorbent. Column chromatography was performed on silica gel (mesh size 60–120 BDH). The enantiomeric excess (ee) of the products were determined by HPLC, using Diacel OD-H column and solvent system *n*-hexane-isoPrOH as eluant; retention times are given with the spectral data of individual compounds. The calculated mass values are based on the values obtained by Chem 4-D Draw (Chemical Innovation) software.

General method for the preparation of 2,5-diaryl-2,3-dihydropyrano[2,3-b]quinolin-4-ones. To a mixture of 3-acetyl-4-(3-carboxy)phenylcarbostyril, compound **1** (1×10^{-3} mol) and aldehyde **2a–2k** (1.4×10^{-3} mol) in dry acetonitrile (10 mL) were added with a mixture of bismuth triflate (10 mol %) and L(−)-proline (15 mol %) in dry acetonitrile (5 mL), stirred separately at ice-salt bath temperature for 1 h. The reaction mixture was stirred further for 1.5 h, under similar conditions, and Et_3N (15 mol %) was added. After stirring for another 3 h, at the same temperature, the reaction mixture was brought to room temperature and stirred further for 20–23 h. The reaction was monitored by TLC on silica gel G plates using $CHCl_3$-EtOAc (9:1 v/v). On completion of the reaction, the solvent was removed under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and water, dried over anhydrous Na_2SO_4, filtered, concentrated, and subjected to column chromatography over silica gel, using graded solvent system of CH_2Cl_2-EtOAc (9:1, 7:3, 1:1 v/v). The compounds **3a–3k** were obtained with CH_2Cl_2-EtOAc (1:1 v/v). The compounds were further purified by crystallization from hot methanol.

5-(3-Carboxyphenyl)-2-phenyl-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3a). IR: υ_{max} cm^{-1} 3125, 1710, 1685, 1597, 1460, 1440, 1410, 1360, 1282, 1262, 1210, 1158, 1040, 930. ^{1}H NMR: δ 2.83 (1H, dd, J = 16.8, 2.7 Hz), 3.06 (1H, dd, J = 16.8, 13.4 Hz), 5.27 (1H, dd, J = 13.4, 2.7 Hz), 7.28–7.30 (5H, m), 7.33 (1H, dd, J = 8.2, 2.0 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.66 (1H, dd, J = 7.8, 2.1 Hz), 7.80 (1H, dd, J = 8.1, 2.0 Hz), 8.01 (1H, dd, J = 8.1, 2.1 Hz), 8.23 (1H, dd, J = 7.8, 2.1 Hz), 8.28 (1H, d, J = 2.1 Hz), 11.23 (1H, s br, CO_2H). ^{13}C NMR ($CDCl_3$): δ_C 44.5, 79.2, 119.5, 123.4, 124.8, 126.0 (2C), 127.9, 128.0, 128.2, 128.5, 128.9, 129.0 (2C), 129.5, 131.5, 132.2, 132.5, 138.3, 140.1, 148.2, 151.5, 168.6, 179.9, 194.6. HRMS: *m*/*z* (rel.int.) 395.1166 (M^+) (48) (Calc. for $C_{25}H_{17}NO_4$, 395.1158), 394 (62), 351 (100), 350 (78), 248 (62), 220 (48), 154 (43), 116 (65), 91 (66), 77 (80). Anal.: CHN (%): Found; C, 75.90; H, 4.38; N, 3.59; Calc.; C, 75.94; H, 4.33; N, 3.54. HPLC: solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 8.58 min; t_r (major), 10.65 min.

5-(3-Carboxyphenyl)-2-(4-methoxyphenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3b). IR: υ_{max} cm^{-1} 3150, 1713, 1685, 1595, 1460, 1440, 1410, 1360, 1280, 1255, 1215, 976, 930. ^{1}H NMR($CDCl_3$): δ 2.81 (1H, dd, J = 16.8, 2.7 Hz), 3.04 (1H, dd, J = 16.7, 13.3 Hz), 3.73 (3H, s), 5.20 (1H, dd, J = 13.3, 2.7 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.16 (2H, d, J = 8.8 Hz), 7.28 (1H, m), 7.32 (1H, dd, J = 8.2, 2.6 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.66 (1H, dd, J = 7.8, 2.1 Hz), 8.02 (1H, dd, J = 8.1, 2.1 Hz), 8.20 (1H, dd, J = 7.8, 2.1 Hz), 8.36 (1H, d, J = 2.1 Hz), 11.23 (1H, s br exch. D_2O). ^{13}C NMR ($CDCl_3$): δ_C 44.8, 56.1, 78.9, 107.5, 113.8 (2C), 123.7, 126.4, 126.6, 126.7, 127.6 (2C), 127.7, 128.4, 128.5, 129.6, 130.5, 132.5, 135.3, 136.7, 146.3, 148.5, 158.5, 168.1, 178.4, 194.7. HRMS: *m*/*z* at (rel.int.) 425.1272 (M^+) (45), (Calc. for $C_{26}H_{19}NO_5$, 425.1263), 424 (60), 381 (83), 380 (100), 248 (71), 220 (53), 154 (36), 132 (76), 118 (53), 107 (61), 93 (88). Anal.: CHN (%): Found; C, 73.46; H, 4.58; N, 3.22; Calc.; C, 73.40; H, 4.50; N, 3.29. HPLC: solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 6.85 min; t_r (major), 7.49 min.

5-(3-Carboxyphenyl)-2-(4-chlorophenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3c). IR: υ_{max} cm^{-1} 3154, 1716, 1686, 1595, 1460, 1440, 1410, 1360, 1280, 1255, 1215, 976, 930. ^{1}H NMR: δ 2.84 (1H, dd, J = 16.8, 2.6 Hz), 3.06 (1H, dd, J = 16.8, 13.4 Hz), 5.18 (1H, dd, J = 13.4, 2.6 Hz), 7.23 (2H, d, J = 8.5 Hz), 7.28 (1H, d, J = 7.6 Hz), 7.33 (1H, dd, J = 8.2, 2.0 Hz), 7.38 (2H, d, J = 8.5 Hz), 7.52 (1H, dd, J = 8.1, 2.0 Hz), 7.65 (1H, dd, J = 7.6, 2.1 Hz), 7.80 (1H, m), 8.01 (1H, dd, J = 8.1, 2.1 Hz), 8.20 (1H, dd, J = 7.8, 2.1 Hz), 8.34 (1H, d, J = 2.1 Hz), 11.23 (1H, s br exch. D_2O, CO_2H). ^{13}C NMR ($CDCl_3$): δ_C 44.7, 78.6, 107.4, 123.7, 126.4, 126.7, 127.7 (2C), 128.1, 128.3, 128.5, 128.7, 129.1 (2C), 129.5, 130.5, 132.7, 133.1, 135.1, 139.1, 147.9, 148.8, 167.9, 178.5, 194.5. HRMS: *m*/*z* at 431.0776, 429.0775 (Calc. for $C_{25}H_{16}ClNO_4$, 429.0768, 431.0768) (M^+) (35), 387 (48), 385 (52), 384 (86), 384 (100), 248 (62), 220 (49), 154 (62), 136 (49), 113 (64), 111 (61), 107 (64). Anal.: CHN (%): Found; C, 69.89; H, 3.78; N, 3.21; Calc.; C, 69.85; H, 3.75; N, 3.26. HPLC: solvent, *n*-hexane-isoPrOH (7.5:2.5 v/v); t_r (minor), 8.45 min; t_r (major), 9.69 min.

5-(3-Carboxyphenyl)-2-(4-fluorophenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3d). IR: υ_{max} cm^{-1} 3150, 1710, 1680, 1599, 1460, 1440, 1410, 1360, 1282, 1262, 1206, 936. ^{1}H NMR: δ 2.84 (1H, dd, J = 16.8, 2.8 Hz), 3.10 (1H, dd, J = 16.8, 13.4 Hz), 5.20 (1H, dd, J = 13.4, 2.8 Hz), 6.80 (2H, d, J = 7.5 Hz), 7.18 (2H, d, J = 7.5 Hz), 7.33 (1H, dd, J = 8.1, 2.3 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.53 (2H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 7.8, 1.9 Hz), 8.01 (1H, dd, J = 8.1, 2.3 Hz), 8.22 (1H, dd, J = 7.8, 2.1 Hz), 8.3 (1H, d, J = 2.1 Hz), 11.18 (1H, s br, CO_2H). ^{13}C NMR ($CDCl_3$): δ_C 48.8, 72.9, 115.2 (2C), 119.9, 123.4, 124.8, 128.2, 128.3, 128.5, 128.7, 128.9, 130.6 (2C), 131.1, 132.0, 132.5, 136.5, 138.0, 148.2,

151.5, 162.9, 172.0, 179.9, 197.6. HRMS: *m/z* (rel. int.) at 413.1072, (M^+) (46) (Calc. for $C_{25}H_{16}FNO_4$, 413.1063), 412 (59), 369 (100) (M^+-CO_2), 248 (65), 220 (54), 154 (48), 120 (35), 105 (59), 93 (72). Anal.: CHN (%): Found; C, 72.65; H, 3.85; N, 3.36; Calc.; C, 72.63; H, 3.90; N, 3.39. HPLC solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 9.48 min; t_r (major), 11.46 min.

5-(3-Carboxyphenyl)-2-(4-bromophenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3e). IR: υ_{max} cm^{-1} 3158, 1713, 1680, 1595, 1460, 1442, 1412, 1360, 1280, 1242, 1210, 1050, 980. ^{1}H NMR: δ 2.79 (1H, dd, J = 16.8, 2.6 Hz), 3.00 (1H, dd, J = 16.8, 13.4 Hz), 5.30 (1H, dd, J = 13.4, 2.6 Hz), 7.18 (2H, d, J = 8.5 Hz), 7.26 (2H, d, J = 8.5 Hz), 7.28 (1H, m), 7.33 (1H, dd, J = 8.1, 2.3 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.53 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 7.8, 1.9 Hz), 8.01 (1H, dd, J = 8.1, 2.3 Hz), 8.22 (1H, dd, J = 7.8, 2.1 Hz), 8.3 (1H, d, J = 2.1 Hz), 11.18 (1H, s br, CO_2H). ^{13}C NMR ($CDCl_3$): δ_C 44.9, 78.9, 107.3, 123.5, 126.5, 126.7, 127.6, 128.2 (2C), 128.5, 128.7, 128.9 (2C), 129.5, 129.8 (2C), 130.5, 132.5, 135.5, 136.9, 146.7, 148.7, 167.8, 177.9, 194.6. HRMS: *m/z* at 475.0270, (44), 473.0270 (M^+) (46) (Calc. for $C_{25}H_{16}BrNO_4$, 473.0263, 475.0263), 431 (55), 429 (52), 428 (61), 248 (68), 220 (50), 180 (54), 155 (66), 154 (63), 74 (62). Anal.: CHN (%): Found; C, 63.39; H, 3.44; N, 2.98; Calc.; C, 63.31; H, 3.40; N, 2.95 . HPLC: solvent, *n*-hexane-isoPrOH (7.5:2.5 v/v); t_r (minor), 9.29 min; t_r (major), 12.06 min.

5-(3-Carboxyphenyl)-2-(2,4-dichlorophenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3f). IR: υ_{max} cm^{-1} 3155, 1715, 1685, 1595, 1460, 1440, 1420, 1410, 1370, 1360, 1280, 1265, 1255, 1215, 976. ^{1}H NMR: δ 2.80 (1H, dd, J = 16.8, 2.7 Hz), 3.06 (1H, dd, J = 16.8, 13.4 Hz), 5.54 (1H, dd, J = 13.4, 2.7 Hz), 7.27 (1H, d, J = 8.2 Hz), 7.33 (1H, dd, J = 8.2, 2.0 Hz), 7.37 (1H, d, J = 7.6 Hz), 7.40 (1H, dd, J = 8.4, 1.6 Hz), 7.53 (1H, d, J = 8.2 Hz), 7.56 (1H, d, J = 1.6 Hz), 7.66 (1H, dd, J = 7.6, 2.1 Hz), 7.80 (1H, m), 8.10 (1H, d, J = 8.1 Hz), 8.22 (1H, dd, J = 7.5, 2.1 Hz), 8.36 (1H, s), 11.23 (1H, s br, exch. D_2O). ^{13}C NMR ($CDCl_3$): δ_C 46.3, 68.8, 119.9, 124.0, 126.6, 127.8, 128.1, 128.3 (2C), 128.5, 129.4, 129.6, 130.4, 130.7, 131.8, 132.6, 134.1, 134.3, 135.3, 139.4, 146.2, 151.2, 168.4, 180.1, 197.6. HRMS: *m/z* at 467.0378, (34), 463.0376 (33) (M^+) (Calc. for $C_{25}H_{15}Cl_2NO_4$, 463.0378, 467.0378), 466 (20), 462 (23), 422 (90), 418 (100), 248 (66), 220 (48), 174 (60), 170 (68), 145 (33), 154 (38), 91 (42). Anal.: CHN (%): Found; C, 64.63; H, 3.21; N, 3.11; Calc.; C, 64.67; H, 3.26; N, 3.16. HPLC: solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 10.25 min; t_r (major), 13.20 min.

5-(3-Carboxyphenyl)-2-(benzo[d][1,3]dioxol-6-yl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3g). IR: υ_{max} cm^{-1} 3165, 1710, 1680, 1590, 1460, 1450, 1440, 1355, 1270, 1240, 1210, 1205, 1040, 980, 785. ^{1}H NMR: δ 2.81 (1H, dd, J = 16.7, 2.7 Hz), 3.04 (1H, dd, J = 16.7, 13.4 Hz), 5.10 (1H, dd, J = 13.4, 2.7 Hz), 6.01 (2H, s), 6.79 (2H, s), 6.94 (1H, d, J = 2.1 Hz), 7.26 (1H, m), 7.32 (1H, dd, J = 8.2, 2.6 Hz), 7.36 (1H, dd, J = 7.6, 2.1 Hz), 7.54 (1H, d, J = 8.2 Hz), 7.66 (1H, dd, J = 7.6, 2.1 Hz), 8.08 (1H, dd, J = 8.1, 2.2 Hz), 8.22 (1H, dd, J = 7.6, 2.1 Hz), 8.32 (1H, d, J = 2.1 Hz), 11.23 (1H, s br, exch. D_2O). ^{13}C NMR ($CDCl_3$): δ_C 44.9, 76.8, 100.7, 107.6, 115.3, 123.6, 123.9, 126.5 (2C), 126.9, 127.4, 127.6, 128.3, 128.5, 129.6, 130.5, 132.4, 134.2, 136.7, 146.2, 148.3, 149.5, 149.8, 176.8, 167.6, 194.6. HRMS: *m/z* at 439.1064, (100), (M^+) (Calc. for $C_{26}H_{17}NO_6$, 439.1056), 438 (54), 409 (45), 381 (32), 337 (38), 317 (54), 273 (65), 245 (23), 243 (62), 215 (41), 179 (48), 102 (53). Anal.: CHN (%): Found; C, 71.01; H, 3.12; N, 3.27; Calc.; C, 71.07; H, 3.90; N, 3.19. HPLC: solvent, *n*-hexane-isoPrOH (7.5:2.5 v/v); t_r (minor), 9.25 min; t_r (major), 11.35 min.

5-(3-Carboxyphenyl)-2-(3,4-dimethoxyphenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3h). IR: υ_{max} cm^{-1} 3155, 1715, 1685, 1597, 1460, 1440, 1360, 1282, 1260, 1240, 1210, 930. ^{1}H NMR: δ 2.81 (1H, dd, J = 16.7, 2.7 Hz), 3.08 (1H, dd, J = 16.7, 13.4 Hz), 3.75 (3H, s), 3.77 (3H, s), 5.19 (1H, dd, J = 13.4, 2.7 Hz), 6.38 (1H, d, J = 2.0 Hz), 6.59 (1H, d, J = 8.1 Hz), 6.64 (1H, dd, J = 8.1, 2.0 Hz), 7.32 (1H, dd, J = 8.2, 2.1 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.66 (1H, dd, J = 7.6, 2.1 Hz), 7.78 (1H, m), 8.12 (1H, dd, J = 8.1, 2.1 Hz), 8.20 (1H, dd, J = 7.8, 2.1 Hz), 8.36 (1H, s), 11.30 (1H, s br). ^{13}C NMR ($CDCl_3$) : δ_C 46.8, 55.7, 55.9, 73.5, 107.5, 115.3, 115.5, 123.7, 126.4, 126.6, 126.8, 127.3, 127.6, 128.3, 128.5, 129.6, 130.5, 132.3, 134.2, 136.7, 146.2, 148.3, 158.2, 158.5, 168.0, 177.9, 194.6. HRMS: *m/z* at 455.1362 (M^+) (36) (Calc. for $C_{27}H_{21}NO_6$, 455.1369), 454 (32), 410 (100), 248 (69), 220 (58), 162 (48), 148 (68), 134 (36), 123 (58), 77 (71). Anal.: CHN (%): Found; C, 71.29; H, 4.61; N, 3.03; Calc.; C, 71.20; H, 4.65; N, 3.08. HPLC: solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 7.56 min; t_r (major), 10.53 min.

5-(3-Carboxyphenyl)-2-(4-methylphenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3i). IR: υ_{max} cm^{-1} 3155, 1710, 1683, 1597, 1460, 1440, 1410, 1360, 1280, 1250, 1210, 970, 930. ^{1}H NMR: δ 2.35 (3H, s), 2.80 (1H, dd, J = 16.8, 2.7 Hz), 3.11 (1H, dd, J = 16.8, 13.4 Hz), 5.20 (1H, dd, J = 13.4, 2.7 Hz), 6.99 (2H, d, J = 8.5 Hz), 7.17 (2H, d, J = 8.5 Hz), 7.33 (1H, dd, J = 8.5, 2.1 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 8.5 Hz), 7.66 (1H, dd, J = 7.6, 2.1 Hz), 7.80 (1H, dd, J = 8.5, 2.0 Hz), 8.10 (1H, dd, J = 8.1, 2.1 Hz), 8.23 (1H, dd, J = 7.8, 2.1 Hz), 8.36 (1H, d, J = 2.1 Hz), 11.22 (1H, s br, exch D_2O). ^{13}C NMR ($CDCl_3$): δ_C 20.9, 44.6, 78.3, 107.5, 123.9, 126.4, 126.5, 126.6, 127.2 (2C), 127.8, 128.1, 128.5, 129.4 (2C), 129.7, 130.4, 132.5, 135.2, 136.6, 137.9, 146.2, 148.7, 168.5, 178.3, 195.0. HRMS: *m/z* at 409.1322, (100), (Calc. for $C_{26}H_{19}NO_4$, 409.1314), (56), 408 (M^+) (67), 365 (100), 364 (82), 248 (66), 220 (53), 154 (45), 116 (76), 91 (63), 77 (88). Anal.: CHN (%): Found; C, 76.22; H, 4.65; N, 3.48; Calc.; C, 76.27; H, 4.68; N, 3.42. HPLC: solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 6.55 min; t_r (major), 9.46 min.

5-(3-Carboxyphenyl)-2-(4-nitrophenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3j). IR: υ_{max} cm^{-1} 3158, 1712, 1687, 1598, 1465, 1440, 1365, 1286, 1262, 1210, 1205, 930. ^{1}H NMR: δ 2.83 (1H, dd, J = 16.7, 2.8 Hz), 3.10 (1H, dd, J = 16.7, 13.2 Hz), 5.48 (1H, dd, J = 13.2, 2.8 Hz), 7.32 (1H, dd, J = 8.1, 2.7 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.60 (2H, d, J = 8.2 Hz), 7.62 (1H, dd, J = 7.6, 2.1 Hz), 7.78 (1H, m), 8.0 (1H, dd, J = 8.1, 2.0 Hz), 8.18 (2H, d, J = 8.2 Hz), 8.24 (1H, dd, J = 7.8, 2.1 Hz), 8.32 (1H, d, J = 2.1 Hz), 11.20 (1H, s br, exch D_2O). ^{13}C NMR ($CDCl_3$): δ_C 48.8, 71.9, 108.0, 122.4, 122.8, 123.6 (2C), 126.1, 126.5, 127.8, 128.3 (2C), 128.7, 129.4, 130.6, 132.4, 133.8 (2C), 136.9, 141.3, 146.3, 148.4, 167.8, 178.6, 195.3. HRMS: *m/z* (rel. int.) at 440.4053, (M^+) (36) (Calc. for $C_{25}H_{16}N_2O_6$, 440.1008), 439 (42), 396 (55), 395 (48), 273 (49), 272 (58), 247 (62), 245 (33), 219 (38), 191 (62), 77 (67). Anal.: CHN (%): Found; C, 68.11; H, 3.63; N, 6.39; Calc.; C, 68.18; H, 3.66; N, 6.36. HPLC: solvent, *n*-hexane-isoPrOH (6:4 v/v); t_r (minor), 14.45 min; t_r (major), 15.46 min.

5-(3-Carboxyphenyl)-2-(2-bromophenyl)-2H-pyrano[2,3-b]quinolin-4(3H)-one, (3k). IR: υ_{max} cm^{-1} 3158, 1715, 1680, 1595, 1460, 1440, 1410, 1360, 1280, 1240, 1210, 1050, 980. ^1H NMR: δ 2.80 (1H, dd, J = 16.7, 2.6 Hz), 3.11 (1H, dd, J = 16.8, 13.4 Hz), 5.30 (1H, dd, J = 13.4, 2.6 Hz), 7.18 (2H, dd, J = 8.5, 1.8 Hz), 7.32 (1H, d, J = 8.5 Hz), 7.33 (1H, dd, J = 8.2, 2.0 Hz), 7.38 (2H, ddd, J = 7.8, 8.5, 1.8 Hz), 7.50 (1H, d, J = 8.1 Hz), 7.66 (1H, d, J = 7.6, 2.1 Hz), 7.80 (1H, m), 8.11 (1H, dd, J = 8.1, 2.1 Hz), 8.22 (1H, dd, J = 7.6, 2.1 Hz), 8.35 (1H, s), 11.23 (1H, s br, exch D_2O). ^{13}C NMR ($CDCl_3$): δ_C 46.3, 70.2, 119.9, 122.3, 126.4, 126.8, 127.6, 128.0, 128.2, 128.4, 128.5, 128.7 (2C), 128.9, 129.4, 129.7, 130.1, 132.1, 132.6, 135.0, 146.7, 148.6, 167.9, 178.1, 195.6. HRMS: m/z at 475.0268, (42), 473.0669 (45) (M^+) (Calc. for $C_{25}H_{16}BrNO_4$, 473.0263, 475.0263), 431 (59), 429 (60), 428 (65), 248 (66), 220 (50), 180 (59), 155 (63), 154 (60), 74 (68). Anal.: CHN (%): Found; C, 68.38; H, 3.46; N, 2.91; Calc.; C, 68.31; H, 3.40; N, 2.95. HPLC: solvent, *n*-hexane-isoPrOH (8:2 v/v); t_r (minor), 9.29 min; t_r (major),12.46 min.

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