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FIRST SYNTHESIS OF 2-TROPOLONYLQUINOLINE-4-CARBOXYLIC ACID DERIVATIVES *VIA* PFITZINGER REACTION IN WATER

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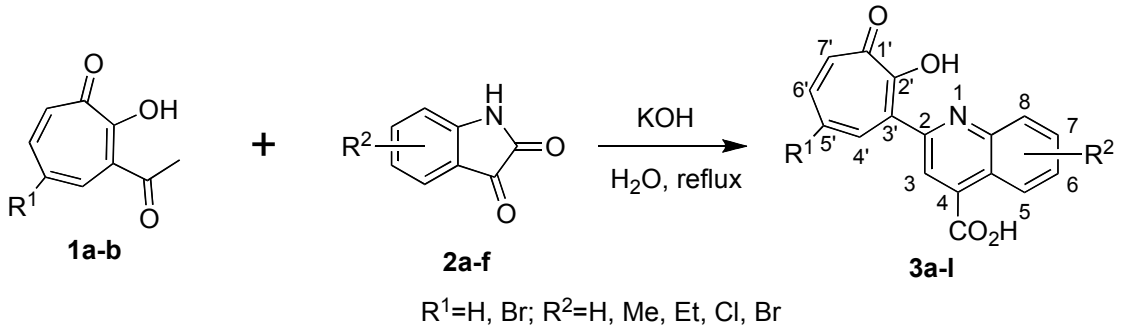
Abstract – A facile and clean synthesis of novel 2-tropolonyl substituted quinoline-4-carboxylic acids *via* Pfitzinger reaction of 3-acetyltropolone or 3-acetyl-5-bromotropolone with different isatins in water was described. It was the first time that the Pfitzinger reaction was applied to the troponoid field. The structures of all the synthesized compounds were characterized by elemental analysis and spectral data.

Quinoline-4-carboxylic acids are of great synthetic interest due to their wide variety of medicinal applications, or as the key intermediates for synthesis of drugs.[1,2] Especially, some 2-substituted quinoline-4-carboxylic acids have been reported to have potent antibacterial, antifungal activities, and selective inhibition of aminoacyl-tRNA synthetases (aaRSs) and cyclooxygenase-2 (COX-2).[3-6] For example, compound 2-(4-bromophenyl)quinoline-4-carboxylic acid inhibits *C. albicans* poly-tRNA synthetase (IC_{50}=0.5 μM) with high selectivity over the human enzyme (IC_{50}>100 μM).[4] Consequently, currently there is considerable interest in the development of novel 2-substituted-quinoline-4-carboxylic acid derivatives.[7-10]

Although 2-substituted quinoline-4-carboxylic acids are among the most extensively studied heterocyclic compounds in recent years, to the best of our knowledge, the synthesis of tropolonyl-substituted quinoline-4-carbocylic acids is very few.[11] It is noteworthy to mention that numerous tropolone natural products and several synthetic tropolone compounds have shown a range of potent biological activities due to its unique molecular structure.[12-16] In addition, the tropolone moiety also plays an important role in molecular assemblies for a faster and efficient lead generation towards the new drug discovery. But tropolone derivatives are scarce in nature,[17] occurring only in lower plants and fungi[18] and very limited information is available on these compounds.

In light of these findings and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and efficient lead generation towards the new drug discovery,[19] we felt that there is a real need for the synthesis of new prototypes by introducing tropolone moiety to quinoline-4-carboxylic acid moiety at 2-position, which might be important for pharmacological studies or create new medicinal properties since their properly substituted 2-aryl analogous are biologically active and exist in the structures of various antitumor agents.[20] Meanwhile, considering the green process, it is of importance to perform this reaction in water since water is environmentally benign and potential advantages of using water as a solvent are its low cost, safety, and ease of use. Therefore, herein, we would like to report the synthesis of a series of hybrid molecules 2-tropolonyl-substituted quinoline-4-carboxylic acid derivatives *via* the Pfitzinger reaction of 3-acetyltropolone or 3-acetyl-5-bromotropolone with various isatins in aqueous media.

In continuation of our studies on the synthesis of novel and interesting tropolone and heterocyclic compounds,[21-25] in this paper we wish to describe the synthesis of 2-tropolonylquinoline-4-carboxylic acid derivatives (**3a-l**) as outlined in Scheme 1, involving the Pfitzinger reactions of tropolones (**1a-b**) with substituted isatins (**2a-f**) in water followed by the acidification.



Scheme 1. Synthetic route of the title compounds **3a-l**

According to the literature, ethanol and water are both popular solvents used for Pfitzinger type reactions. For comparison, at the outset we studied the reaction of 3-acetyltropolone (**1a**) with isatin (**2a**) in water and ethanol, and found that the corresponding 2-(tropolon-3-yl)quinoline-4-carboxylic acid (**3a**) was obtained in a low yield of 21% when the reaction was carried out in ethanol based on the method of Buu-Hoii [33% KOH (aq.) in ethanol].[26] Through an effort to optimize the reaction conditions, we found that the best results could be achieved when the reaction was conducted in water using 18% KOH as the base. As a reaction solvent, water also offers many practical and economic advantages including low cost, safe handling and environmental compatibility. Thus, under the same reaction conditions, a series of target compounds **3b-l** were synthesized and the yields are listed in Table 1.

Table 1. Synthesis of 2-(tropolon-3-yl)quinoline-4-carboxylic acid derivatives **3a-l**

Entry	Product	R^1	R^2	Yield (%)[a]
1	**3a**	H	6-H	51
2	**3b**	H	6-Me	45
3	**3c**	H	6-Et	44
4	**3d**	H	6-Cl	74
5	**3e**	H	6-Br	69
6	**3f**	H	8-Et	42
7	**3g**	Br	6-H	49
8	**3h**	Br	6-Me	44
9	**3i**	Br	6-Et	41
10	**3j**	Br	6-Cl	64
11	**3k**	Br	6-Br	59
12	**3l**	Br	8-Et	37

[a]Isolated yield.

As shown in Table 1, some trends in the reactions of isatins with acetyltropolones were noted, that is, the yields were slightly affected by the substituents of the investigated isatins. Those having electron-withdrawing halo substituents (e.g. Cl, Br) were efficiently reacted to give the corresponding quinoline-4-carboxylic acids in good yields (entries 4, 5, 10, and 11), whereas those having slightly electron-donating groups (e.g. Me, Et) lower the yields under the same reaction conditions (entries 2, 3, 6, 8, 9, and 12). The condensation of unsubstituted isatin with tropolones **1a** or **1b** afforded the corresponding products in average yields of 51% and 49%, respectively (entries 1 and 7). This observation is consistent with the proposed mechanism which involves a base induced ring opening of isatins to render salts of the corresponding isatic acids and subsequent condensation with acetyltropolones.

The spectral data gave satisfactory results consistent with the suggested molecular structures. For example, the 400 MHz ^{1}H NMR spectra of all the synthesized compounds **3a-l** showed two downfield signal peaks at δ 10.75-11.09 and 13.78-14.11 attributable to OH of tropolone ring and COOH attached to quinoline ring, respectively. The resonance of C_3 proton is a distinct singlet at the region of δ 8.35-8.50, which is a clear evidence for the 2,4-disubstituted quinoline structure, in addition to the peaks of other protons of quinoline structure synthesized and tropolone nucleus exactly matching their structures in the range of aromatic region.

EXPERIMENTAL

The melting points were measured on WRS-1B digital melting points apparatus and are uncorrected. The progress of the reaction was monitored by (TLC). Infrared spectra were recorded on KBr pellets on an FT/IR-430 spectrophotometer. ^{1}H NMR spectra were determined on a Brucker AVANCE 400 NMR spectrometer at 400 MHz in DMSO-d_6 using TMS as internal standard. Elemental analysis were estimated on an Elementar Vario EL-III element analyzer. The Mass spectra were determined using a MSD VL ESI1 spectrometer. The following materials were prepared according to literature methods: 3-acetyltropolone,[27] 3-acetyl-5-bromotropolone.[28]

General procedure for the synthesis of 3-(4-carboxylquinolin-2-yl)tropolones (3a-l). The mixture of 3-acetyltropolone (**1a**) or 3-acetyl-5-bromotropolone (**1b**) (1 mmol), isatin **2** (3.4 mmol) and potassium hydroxide (2.2 g) in water (10 mL) was stirred at reflux temperature for 5-30 h (Table 1). Then the mixture was cooled to room temperature and acidified with 3 mol/L hydrochloric acid to pH 4-5. The precipitate was filtered out, washed with water, and recrystalized to afford the pure product **3a-l**.

2-(Tropolon-3-yl)quinoline-4-carboxylic acid (3a). This compound was obtained as red crystals from MeOH, mp 213-214 ^{o}C (lit.[11] 213-214 ^{o}C). IR (KBr) ν/cm^{-1}: 3158 (OH), 1611 (carboxy C=O), 1594 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.10-7.12 (1H, m, tropolone-H), 7.41-7.44 (m, 1H, tropolone-H), 7.70-7.83 (m, 3H, ArH), 8.09-8.11 (m, 1H, H_7), 8.21-8.29 (m, 2H, ArH), 8.31-8.34 (m, 1H, ArH), 8.50 (s, 1H, H_3), 10.91 (s, 1H, 2'-OH), 13.83 (s, 1H, 4-COOH); ESI-MS *m/z*: 294 $(M+1)^+$. Anal. Calcd for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78. Found: C, 69.48; H, 3.92; N, 4.91.

6-Methyl-2-(tropolon-3-yl)quinoline-4-carboxylic acid (3b). This compound was obtained as yellow crystals from EtOH, mp 267-269 ^{o}C. IR (KBr) ν/cm^{-1}: 3197 (OH), 1706 (carboxy C=O), 1602 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.60 (s, 3H, CH_3), 7.21-7.25 (m, 1H, tropolone-H), 7.38-7.40 (m, 1H, tropolone-H), 7.48-7.51 (m, 1H, tropolone-H), 7.62 (d, 1H, J = 6.5 Hz, tropolone-H), 8.04 (d, 1H, J = 8.2 Hz, H_7), 8.16 (d, 1H, J = 7.9 Hz, H_8), 8.44 (d, 1H, s, H_3), 8.61 (s, 1H, H_5), 10.83 (s, 1H, 2'-OH), 13.91 (s, 1H, 4-COOH); ESI-MS *m/z*: 308 $(M+1)^+$. Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H,

4.26; N, 4.56. Found: C, 70.29; H, 4.37; N, 4.69.

6-Ethyl-2-(tropolon-3-yl)quinoline-4-carboxylic acid (3c). This compound was obtained as orange crystal from acetic acid, mp 289-291 ^{o}C. IR (KBr) ν/cm^{-1}: 3423 (OH), 1720 (carboxy C=O), 1610 (tropolone C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.29 (t, 3H, J = 6.0 Hz, CH_3), 2.84 (q, 2H, J = 5.9 Hz, CH_2), 6.78-6.81 (m, 1H, tropolone-H), 6.96 (d, 1H, J = 8.3 Hz, $H_{4'}$), 7.32-7.36 (m, 1H, tropolone-H), 7.66 (d, 1H, J = 6.5 Hz, tropolone), 7.88 (d, 1H, J= 10.6 Hz, H_7), 8.02 (d, 1H, J = 11.0 Hz, H_8), 8.35 (s, 1H, H_3), 8.49 (s, 1H, H_5), 10.79 (s, 1H, 2'-OH), 13.87 (s, 1H, 4-COOH); ESI-MS *m/z*: 322 $(M+1)^+$. Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.86; H, 4.98; N, 4.44.

6-Chloro-2-(tropolon-3-yl)quinoline-4-carboxylic acid (3d). This compound was obtained as yellow crystals from acetic acid, mp 296-297 ^{o}C. IR (KBr) ν/cm^{-1}: 3197 (tropolone OH), 1711 (carboxy C=O), 1604 (tropolone C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.23-7.27 (m, 1H, tropolone-H), 7.38 (d, 1H, J = 6.3 Hz, tropolone-H), 7.53-7.57 (m, 1H, tropolone-H), 7.87 (d, 1H, J = 6.3 Hz, tropolone-H), 8.09 (d, 1H, J = 7.6 Hz, H_7), 8.18 (d, 1H, J= 8.8 Hz, H_8), 8.45 (s, 1H, H_3), 8.87 (s, 1H, H_5), 10.82 (s, 1H, 2'-OH), 13.88 (s, 1H, 4-COOH); ESI-MS *m/z*: 328 $(M+1)^+$. Anal. Calcd for $C_{17}H_{10}ClNO_4$: C, 62.30; H, 3.08; N, 4.27. Found: C, 62.17; H, 3.12; N, 4.36.

6-Bromo-2-(tropolon-3-yl)quinoline-4-carboxylic acid (3e). This compound was obtained as yellow crystals from acetic acid, mp >300 ^{o}C. IR (KBr) ν/cm^{-1}: 3161 (tropolone OH), 1712 (carboxy C=O), 1601 cm (tropolone C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.25 (t, 1H, J =7.8 Hz, tropolone-H), 7.38-7.44 (m, 1H, tropolone-H), 7.53-7.57 (m, 1H, tropolone-H), 7.66 (m, 1H, tropolone-H), 7.98 (d, 1H, J= 8.2 Hz, H_7), 8.11 (d, 1H, J= 8.4 Hz, H_8), 8.45 (s, 1H, H_3), 9.03 (s, 1H, H_5), 10.75 (s, 1H, 2'-OH), 14.00 (s, 1H, 4-COOH); ESI-MS *m/z*: 373 $(M+1)^+$. Anal. Calcd for $C_{17}H_{10}BrNO_4$: C, 54.86; H, 2.71; N, 3.76. Found: C, 54.78; H, 2.83; N, 3.64.

8-Ethyl-2-(tropolon-3-yl)quinoline-4-carboxylic acid (3f). This compound was obtained as yellow crystals from acetic acid, mp >300 ^{o}C. IR (KBr) ν/cm^{-1}: 3428 (tropolone OH), 1707 (carboxy C=O), 1595 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.31 (t, 3H, J = 7.2 Hz, CH_3), 2.71 (q, 2H, J = 7.2 Hz, CH_2), 7.14-7.17 (m, 1H, tropolone-H), 7.32-7.36 (m, 2H, ArH), 7.65-767 (m, 1H, ArH), 8.05 (d, 1H, J = 8.2 Hz, ArH), 8.12-8.15 (m, 1H, ArH), 8.36-8.38 (d, 1H, J = 7.6 Hz, ArH), 8.47 (s, 1H, H_3), 11.02 (s, 1H, 2'-OH), 13.93 (s, 1H, 4-COOH); ESI-MS *m/z*: 322 $(M+1)^+$. Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.11; H, 4.82; N, 4.27.

2-(5-Bromotropolon-3-yl)quinoline-4-carboxylic acid (3g). This compound was obtained as yellow crystals from acetic acid, mp 265-267 ^{o}C. IR (KBr) ν/cm^{-1}: 3210 (tropolone OH), 1698 (carboxy C=O), 1552 (tropolone C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.16-7.18 (d, 1H, J = 10.8 Hz, tropolone-H), 7.68-7.86 (m, 3H, ArH), 8.17 (d, 1H, J = 7.2 Hz, H_8), 8.26 (s, 1H, $H_{4'}$), 8.44 (s, 1H, H_3), 8.56 (d, 1H, J = 8.4 Hz, H_5), 10.91 (s, 1H, 2'-OH), 13.78 (s, 1H, 4-COOH); ESI-MS *m/z*: 373 $(M+1)^+$.

Anal. Calcd for $C_{17}H_{10}BrNO_4$: C, 54.86; H, 2.71; N, 3.76. Found: C, 54.97; H, 2.76; N, 3.89.

2-(5-Bromotropolon-3-yl)-6-methylquinoline-4-carboxylic acid (3h). This compound was obtained as green crystals from acetic acid, mp 293-294 °C. IR (KBr) ν/cm^{-1}: 3422 (tropolone OH), 1662 (carboxy C=O), 1606 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.54 (s, 3H, CH_3), 7.09 (d, 1H, J =10.6 Hz, $H_{6'}$), 7.67 (d, 1H, J =11.0 Hz, $H_{7'}$), 8.00 (d, 1H, J = 8.8 Hz, H_7), 8.12 (d, 1H, J = 8.1 Hz, H_8), 8.25 (s, 1H, $H_{4'}$), 8.42 (s, 1H, H_3), 8.54 (s, 1H, H_5), 10.98 (s, 1H, 2'-OH), 14.02 (s, 1H, 4-COOH) ; ESI-MS *m/z*: 387 $(M+1)^+$. Anal. Calcd for $C_{18}H_{12}BrNO_4$: C, 55.98; H, 3.13; N, 3.63. Found: C, 56.12; H, 3.29; N, 3.74.

2-(5-Bromotropolon-3-yl)-6-ethylquinoline-4-carboxylic acid (3i). This compound was obtained as yellow crystals from ethanol, mp >300 °C. IR (KBr) ν/cm^{-1}: 3420 (tropolone OH), 1653 (carboxy C=O), 1592 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.26 (t, 3H, J = 6.0 Hz, CH_3), 2.54 (q, 2H, J = 6.0 Hz, CH_2), 7.10 (d, 1H, J =11.0 Hz, $H_{6'}$), 7.71 (d, 1H, J =11.2 Hz, $H_{7'}$), 8.06 (d, 1H, J = 8.0 Hz, H_7), 8.17 (d, 1H, J = 8.8 Hz, H_8), 8.29 (s, 1H, $H_{4'}$), 8.41 (s, 1H, H_3), 8.51 (s, 1H, H_5), 11.01 (s, 1H, 2'-OH), 13.97 (s, 1H, 4-COOH); ESI-MS *m/z*: 401 $(M+1)^+$. Anal. Calcd for $C_{19}H_{14}BrNO_4$: C, 57.02; H, 3.53; N, 3.50. Found: C, 57.13; H, 3.68; N, 3.43.

2-(5-Bromotropolon-3-yl)-6-chloroquinoline-4-carboxylic acid (3j). This compound was obtained as green crystals from acetic acid, mp 291-293 °C. IR (KBr) ν/cm^{-1}: 3200 (tropolone OH), 1698 (carboxy C=O), 1604 (tropolone C=O); ^{1}H NMR(DMSO-d_6, 400 MHz) δ (ppm): 7.16 (d, 1H, J =10.8 Hz, $H_{6'}$), 7.89 (d, 1H, J = 11.2 Hz, $H_{7'}$), 8.08 (d, 1H, J =8.4 Hz, H_7), 8.16 (d, 1H, J =8.7 Hz, H_8), 8.33 (s, 1H, $H_{4'}$), 8.43 (s, 1H, H_3), 8.89 (s, 1H, H_5), 11.09 (s, 1H, 2'-OH), 13.85 (s, 1H, 4-COOH); ESI-MS *m/z*: 407 $(M+1)^+$. Anal. Calcd for $C_{17}H_9BrClNO_4$: C, 50.22; H, 2.23; N, 3.44. Found: C, 50.37; H, 2.33; N, 3.58.

2-(5-Bromotropolon-3-yl)-6-bromoquinoline-4-carboxylic acid (3k). This compound was obtained as yellow crystals from acetic acid, mp >300 °C. IR (KBr) ν/cm^{-1}: 3192 (tropolone OH), 1699 (carboxy C=O), 1653 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.14 (d, 1H, J =11.2 Hz, $H_{6'}$), 7.85 (d, 1H, J = 11.4 Hz, $H_{7'}$), 8.00 (d, 1H, J =8.8 Hz, H_7), 8.15 (d, 1H, J = 9.2 Hz, H_8), 8.25 (s, 1H, $H_{4'}$), 8.42 (s, 1H, H_3), 9.03 (s, 1H, H_5), 11.07 (s, 1H, 2'-OH), 14.11 (s, 1H, 4-COOH); ESI-MS *m/z*: 452 $(M+1)^+$. Anal. Calcd for $C_{17}H_9Br_2NO_4$: C, 45.27; H, 2.01; N, 3.11. Found: C, 45.33; H, 2.15; N, 3.09.

2-(5-Bromotropolon-3-yl)-8-ethylquinoline-4-carboxylic acid (3l). This compound was obtained as yellow crystals from acetic acid, mp >300 °C. IR (KBr) ν/cm^{-1}: 3080 (tropolone OH), 1695 (carboxy C=O), 1589 (tropolone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.32 (t, 3H, J = 7.2 Hz, CH_3), 2.73 (q, 2H, J = 7.2 Hz, CH_2), 7.15 (d, 1H, J =11.0 Hz, $H_{6'}$), 7.59 (d, 1H, J = 6.3 Hz, ArH), 7.71-7.83 (m, 2H, ArH), 8.06 (m, 1H, ArH), 8.36 (s, 1H, $H_{4'}$), 8.49 (s, 1H, H_3), 10.78 (s, 1H, 2'-OH), 13.86 (s, 1H, 4-COOH); ESI-MS *m/z*: 401 $(M+1)^+$. Anal. Calcd for $C_{19}H_{14}BrNO_4$: C, 57.02; H, 3.53; N, 3.50. Found: C, 56.89; H, 3.70; N, 3.64.

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