



CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Catalyst Free Synthesis of Some Novel Trimethoxy-Quinoline-4-Carboxylic Acid Derivatives

Krunalkumar Mehariya, Dilip Detroja, Rajesh Kakadiya, Anamik Shah*

National Facility for Drug Discovery Centre, Department of Chemistry, Saurashtra University, Rajkot-360005, Gujarat (India)

E-mail: krunal.mehariya@gmail.com, anamik_shah@hotmail.com*

Received 7 April 2015; Accepted 25 April 2015

Abstract: A novel series of trimethoxy quinoline-4-carboxylic acid derivatives is synthesized by doebner multi-component reaction of 3,4,5-trimethoxy aniline, pyruvic acid and aromatic aldehyde in alcohol under catalyst free conditions. Under the established reaction protocol, quinoline-4-carboxylic derivatives were isolated in high yield without any purification in short reaction time. This method can be useful for the synthesis of substituted quinoline with carboxylic acid group at 4C. All the synthesized compounds are characterized by IR, NMR and mass spectroscopy and confirmed by X-ray crystallographic studies.

Keywords: Doebner reaction, Quinoline-4-carboxylic acid

Introduction

Over the last century, quinoline-4-carboxylic acid derivatives have been largely used as precursor for the synthesis of biologically active quinoline¹. Quinoline-4-Carboxylic acid and their analogous are active ingredients of a large number of natural products, drugs and prodrugs i.e. (angiotensin II receptor², neurokinin receptors³, antitumor⁴, antiviral⁵, NK-3 receptors⁶, antimalarial⁷, Phospholipase A₂ inhibitors⁸, Hedgehog signaling inhibitors⁹, antimicrobial agents¹⁰). Carboxylic acid group at 4C of quinoline skeleton can be directly

introduced by means of doebner reaction¹¹⁻¹² and pfitzinger reaction¹³⁻¹⁴. These methods require large amount of harsh organic solvent (e.g. benzene, chloroform, dichloromethane) and long reaction time¹⁵.

Doebner reaction was originally reported by Doebner in 1887. It explains the synthesis of quinoline-4-carboxylic acid (e.g. Cinchoninic Acid) derivatives from the three component reaction of substituted aniline, aromatic aldehydes and pyruvic acid. This reaction involves an aldol condensation between the

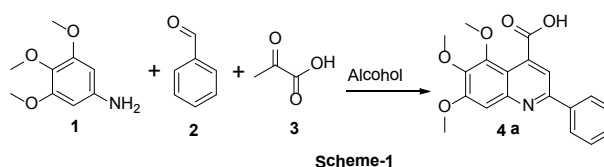
aldehyde and pyruvic acid to afford a β , γ -unsaturated α -keto acid which then undergoes the Michael addition with aniline. Alternatively, this reaction might undergo via the formation of a Schiff base between aromatic aniline and aldehyde, which then combines with pyruvic acid and form quinoline-4-carboxylic acids. However, the Doebner reaction is reported as failed in some cases of aromatic and heterocyclic amines such as 2-chloro-5-aminopyridine¹⁶ and 3-aminopyridine¹⁶ and 2-aminopyridine¹⁷.

There are several synthetic approaches reported in literature for the synthesis of quinoline-4-carboxylic acid derivatives under various conditions such as, microwaves¹⁸, ytterbium perfluorooctanoate catalyzed¹⁹, and base catalyzed²⁰. All these reactions proceeded in presence of catalyst and required large amount of organic solvent, long reaction time and extensive workup procedure. In the present work, we have synthesized various quinoline-4-carboxylic acid using tri-substituted aniline, substituted aromatic aldehyde and pyruvic acid in ethanol. The established method proceeded well without the use of any catalyst and large amount of solvent in short time providing desired product in high yield. In addition, product was isolated by simple filtration with high purity.

Result and Discussion

In order to examine the effect of different alcohol as solvent, Doebner reaction of 3,4,5-trimethoxy aniline **1**, pyruvic acid **2** and benzaldehyde **3** is selected as model reaction for condition optimization. The results are summarized in **Table 1**. Subsequently, ethanol serves as most effective solvent among alcohols used providing product in 90% yield (entry a2) within 3 h of reaction time.

Table 1 Yield optimization with the help of different alcoholic solvent



Entry ^a	Solvent	Time (h)	Yield ^b %
a1	Methanol	5	70
a2	Ethanol	3	87
a3	<i>iso</i> -ropanol	5	65
a4	n-butanol	6	60
a5	tert-butanol	7	58

^aAll reactions were carried out under refluxing.

^bIsolated yield using simple filtration.

Synthesis of various quinoline-4-carboxylic acid using structurally diverse aromatic aldehydes, 3,4,5-trimethoxy aniline and pyruvic acid under the optimized reaction conditions was then performed to establish the substitution effect relationships. The outcomes are summarized in the table 2. We found that the use of the aromatic aldehyde having electron donating groups is favorable for the transformation (Entry **4b–4e**). The introduction of nitro function in methoxy containing aldehyde resulted in slightly decrease in yield (Entry **4f**). The best results was found, when indole-3-carboxaldehyde was used as aldehyde (Entry **4g**). However, the presence of methyl or electron withdrawing substituent such as halogens and nitro on the aldehydes resulted in poor yield (entry **4h** and **4k**).

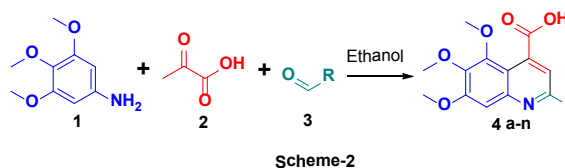


Table-2 Synthesis of quinolinecarboxylic acids by doebner reactions^a

Entry	Compound	R	M.F.	mp °C	Yield % ^b
1	4a	Ph-	C ₁₉ H ₁₇ NO ₅	229-231	87
2	4b	3-OCH ₃ Ph-	C ₂₀ H ₁₉ NO ₆	210-212	88
3	4c	2,4,5-OCH ₃ Ph-	C ₂₂ H ₂₃ NO ₈	236-238	89
4	4d	2,6- OCH ₃ Ph-	C ₂₁ H ₂₁ NO ₇	230-232	91
5	4e	3,4- OCH ₃ Ph-	C ₂₁ H ₂₁ NO ₇	228-230	90
6	4f	3-NO ₂ 4,5- OCH ₃ Ph-	C ₂₁ H ₂₀ N ₂ O ₉	270-272	83
7	4g	3-Indole	C ₂₁ H ₁₈ N ₂ O ₅	250-252	92
8	4h	4-Br Ph-	C ₁₉ H ₁₆ BrNO ₅	222-224	82
9	4i	2-F Ph-	C ₁₉ H ₁₆ FNO ₅	262-264	75
10	4j	3,4-CH ₃ Ph-	C ₂₁ H ₂₁ NO ₅	248-250	80
11	4k	2,5-Br Ph-	C ₁₉ H ₁₅ Br ₂ NO ₅	260-262	75
12	4l	3-F 4-Cl Ph-	C ₁₉ H ₁₅ ClFNO ₅	256-258	81
13	4m	4-CF ₃ Ph-	C ₂₀ H ₁₆ F ₃ NO ₅	268-270	75
14	4n	4-NO ₂ Ph-	C ₁₉ H ₁₆ N ₂ O ₇	264-266	80

^aAll reactions were carried out in ethanol at reflux for 3 h^bIsolated yields

Crystal Structure Determination and Refinements

The crystallographic data analysis reveals that the 2-(1H-indol-3-yl)-5,6,7-trimethoxy quinoline-4-carboxylic acid (**4g**), a yellow chunk crystal of C₂₁H₁₈N₂O₅ having approximate dimensions of 0.400 × 0.370 × 0.330 mm was mounted on a glass fiber. All measurements were made on a Rigaku SCX mini diffractometer using graphite monochromated Mo-K α radiation. The crystal-to-detector distance was 52.00 mm and 2 θ max is 55.0°. Data Reduction of the 8984 reflections that were collected, 4069 were unique ($R_{\text{int}} = 0.0512$); equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). The linear absorption coefficient, μ , for Mo-K α radiation is 1.016 cm⁻¹. An empirical absorption correction was applied which resulted in transmission factors ranging

from 0.764 to 0.967. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods²¹ and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F² was based on 4069 observed reflections and 253 variable parameters and converged. The standard deviation of an observation of unit weight was 1.04. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.38 and -0.26 e/Å³, respectively. The absolute structure was deduced based on Flack parameter, -0.5(18), using 2013 Friedel pairs²². Neutral atom scattering factors were taken from Cromer and Waber²³. Anomalous dispersion effects were included in F_{calc}²⁴; the values for “ Δf ” and “ $\Delta f'$ ” were those of Creagh and McAuley²⁵. The

Table 3 Bond Lengths (Å)

Atom	Atom	Distance
O4	C20	1.401(7)
O1	C18	1.246(6)
N1	C1	1.351(5)
N2	C10	1.352(6)
C2	H2	0.930
O2	H2B	0.820
C20	H20A	0.960

Atom	Atom	Distance
O5	C21	1.440(6)
O2	C18	1.224(5)
N1	C9	1.381(5)
N2	C17	1.370(6)
N2	H2A	0.860
C19	H19A	0.960
C21	H21A	0.960

Table 4 Bond angles (°)

Atom	Atom	Atom	Angle
C1	N1	C9	122.8(3)
N2	C10	C11	109.8(4)
O1	C18	C3	111.6(4)

Atom	Atom	Atom	Angle
C10	N2	C17	109.0(4)
O1	C18	O2	128.2(4)
O2	C18	C3	120.1(4)

values for the mass attenuation coefficients are those of Creagh and Hubbell²⁶. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97²⁷ and Goodness of Fit of crystal is 1.042. Fig. 1 and Fig. 2 are represents the ORTEP²⁸.

Table 2 and Table 3 give the list of Bond Lengths and Bond Angles of non-hydrogen atoms respectively. The bond lengths and bond angles are in excellent conformity with the standard values. The X-ray crystal structure determination shows that the interatomic distances 1.436(7)Å for O3-C19, 1.401(7)Å for O4-C20 and 1.440(6)Å for O5-C21 is near to that of a typical alkyl O-C ether linker (OCH₃) bond (1.40 Å). The bond length of 1.246(6)Å for O1-C18 and 1.224(5)Å for O2-C18 is near to that of a typical C=O and C-O bond (carboxylic acid).

The bond angle of 122.8(3)° for C1-N1-C9 is near to that of a typical Aromatic C-N-C bond angle(120°, sp² hybridized atoms). The bond angle of 109.0(4)° for C10-N2-C17 is near to that of a typical Aromatic C-N-C bond angle(109°, sp³ hybridized atoms).

Fig. 1 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

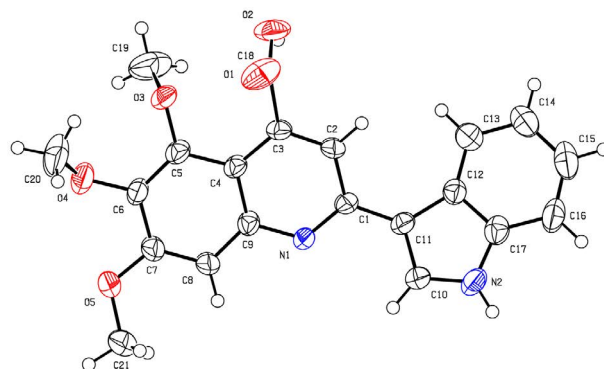


Fig. 2 Packing diagram of the molecules when viewed down the a* axis. The dashed lines represent the hydrogen bonds

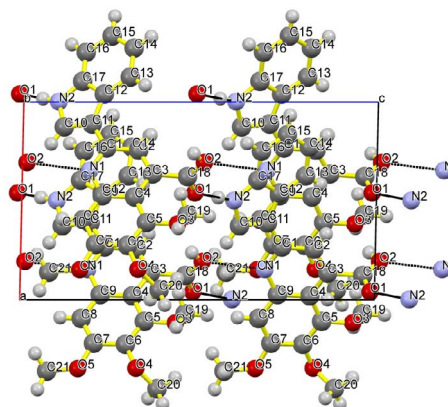


Table 4 Possible hydrogen bonds

Donor	H	Acceptor	D...A	D-H	H...A	D-H...A
N2	H2A	O11	2.681(5)	0.86	1.86	158.95

Symmetry Operators:

(1) X+1/2-1, -Y+1/2, Z+1/2-1

*The D-H and H-A distances are essentially standard values and are not derived from the experiment. However, intermolecular hydrogen bonds N2-H2A-O11 this order is likely the cause of the apparent short H...H contacts involving the indole and quinoline-4-carboxylic acid skeleton.

Table 5 Torsion Angles (°)

(Those having bond angles > 160 or < 20 degrees are excluded)

Atom ¹	Atom ²	Atom ³	Atom ⁴	Angle	Atom ¹	Atom ²	Atom ³	Atom ⁴	Angle
C9	N1	C1	C2	-2.3(5)	C17	N2	C10	C11	-0.9(5)
N1	C1	C11	C10	-26.1(6)	N2	C10	C11	C1	-172.9(3)

A study of the torsion angles, asymmetric parameters and least-squares plane calculations reveals that the six membered ring of quinoline [C9/N1/C1/C2] is -2.3(5) and [C17/N2/C10/C11] is -0.9(5) are showing that the two groups are staggered in six membered ring. The torsion angle between the quinoline ring with nitrogen with carbon atoms and indole ring with nitrogen with carbon atoms [N1/C1/C11/C10] is -26.1(6) and [N2/C10/C11/C1] is -172.9(3) this shows that the quinoline ring with indole ring is not coplanar.

Table 6 Intermolecular contacts less than 3.60 Å

Atom	Atom	Distance	Atom	Atom	Distance
O1	N2 ¹	2.681(5)	N2	O1 ⁶	2.681(5)
C15	O4 ¹¹	3.326(6)	O4	C15 ³	3.326(6)

Symmetry Operators:

(1) X+1/2, -Y+1/2, Z+1/2

(3) X+1/2+1, Y+1/2-1, Z

(5) X, -Y, Z+1/2-1

(7) X+1/2-1, Y+1/2, Z

(9) X+1, Y, Z

(11) X+1/2-2, Y+1/2, Z

(2) X, -Y, Z+1/2

(4) X+1/2, Y+1/2-1, Z

(6) X+1/2-1, -Y+1/2, Z+1/2-1

(8) X-1, -Y, Z+1/2-1

(10) X-1, Y, Z

(12) X+1, -Y, Z+1/2

Further analysis showed that each molecule is linked to other molecules by weak N-H...N, N-H...O and C-H...O interactions. These intermolecular contacts are explained in terms of the substructure shown in figure ?? The N2 atom in indole ring at (X+1/2-1, -Y+1/2, Z+1/2-1) acts as hydrogen bond donor to quinoline-4-carboxylic acid ring of O1 atom at (X+1/2, -Y+1/2, Z+1/2). Growth of the crystal is reinforced by the weak interaction O4-C15...H in which the C15 atom of the indole ring at (X+1/2+1, Y+1/2-1, Z) acts as hydrogen-bond donor to atom O4 in the molecule at (X+1/2-2, Y+1/2, Z).

Conclusion

In conclusion, a series of trimethoxy substituted quinoline-4-carboxylic acid derivatives were synthesized by doebner reaction under catalytic free condition. The established procedure afforded the desired compounds in high yield without tedious workup of the reaction. The merit of the synthetic procedure is high yield, chromatography free purification, simple work-up and high number of functional group compatibility.

Experimental

All chemicals were of analytical grade and used as received. The progress of the reaction was monitored by TLC. Melting points of all the synthesized compounds were recorded by open capillary method. Reactions were monitored by thin layer chromatography technique using silica gel-G plates of 0.5 mm thickness and spots were observed using iodine and UV. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^1H NMR spectra were determined in $\text{DMSO}-d_6$ solution by a Bruker Ac 400 MHz spectrometer.

General procedure for the synthesis of Quinolinecarboxylic Acids (4a-n) by Doebner reaction

A mixture of 3,4,5-trimethoxy aniline (1.0 mmol) (**1**), pyruvic acid (1.0 mmol) (**3**), aromatic aldehyde (1.0 mmol) (**2**) in 5 ml of ethanol was well stirred and reflux for 3 h. When the reaction was completed as monitored by TLC ($\text{EtOAc}/\text{Hexane}$, 1/9 mL), the reaction mixture was cooled at room temperature. The precipitated solid was collected by filtration recrystallized from ethanol to afford pure product.

6,7,8-trimethoxy-2-phenylquinoline-4-carboxylic acid (4a): White solid; yield: 87%; mp 229-231°C; MS: m/z 338; ^1H NMR (400

MHz, $\text{DMSO}-d_6$): δ 13.39 (s, 1H, exchangeable COOH), 8.29 – 8.27 (d, 2H, $J = 7.16$ Hz, ArH), 7.91 (s, 1H, ArH), 7.54 – 7.52 (d, 3H, $J = 7.56$ Hz, $3 \times \text{ArH}$), 7.38 (s, 1H, ArH), 4.01 (s, 3H, OCH_3), 3.90 – 3.89 (d, 6H, $J = 5.88$ Hz, $2 \times \text{OCH}_3$); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 55.8, 60.4, 61.4, 104.4, 112.3, 114.0, 126.7, 128.7, 129.0, 139.0, 140.7, 146.0, 148.0, 154.8, 155.2, 172.5; IR (KBr): $\nu = 3456, 3310, 3021, 1655, 1600, 1487, 1370 \text{ cm}^{-1}$

5,6,7-trimethoxy-2-(3-methoxyphenyl)quinoline-4-carboxylic acid (4b): White solid; yield: 88%; mp 210-212°C; MS: m/z 369; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 8.13 - 8.12$ (d, 2H, $J = 5.04$ Hz, $2 \times \text{ArH}$), 7.69 – 7.67 (d, 1H, $J = 5.2$ Hz, $3 \times \text{ArH}$), 7.28 (s, 1H, ArH), 3.97 (s, 3H, $3 \times \text{OCH}_3$), 3.85 – 3.84 (d, 6H, $J = 4.64$ Hz, $2 \times \text{OCH}_3$), 2.42 (s, 3H, OCH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 55.3, 60.0, 61.1, 104.1, 117.5, 121.4, 128.5, 131.0, 137.3, 140.2, 141.1, 145.4, 146.8, 154.2, 156.1, 159.0; IR (KBr): $\nu = 3399, 3210, 3125, 1599, 1442, 1387, 1370 \text{ cm}^{-1}$

6,7,8-trimethoxy-2-(2,4,5-trimethoxyphenyl)quinoline-4-carboxylic acid (4c): White solid; yield: 89%; mp 236-238°C; MS: m/z 429; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 13.39$ (s, 1H, exchangeable COOH), 7.73 (s, 1H, ArH), 7.57 (s, 1H, ArH), 7.34 (s, 1H, ArH), 3.99 (d, 3H, $J = 3.96$ Hz, OCH_3), 3.89 (m, 12H, $J = 5.2$ Hz, $4 \times \text{OCH}_3$), 3.79 (s, 3H, OCH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 56.1, 56.4, 56.6, 56.8, 61.6, 61.5, 98.8, 105.0, 112.6, 114.6, 117.8, 119.0, 141.1, 143.3, 151.3, 152.6, 154.8, 156.2, 170.5; IR (KBr): $\nu = 3357, 3200, 3156, 1600, 1553, 1386, 1289 \text{ cm}^{-1}$

2-(2,6-dimethoxyphenyl)-6,7,8-trimethoxyquinoline-4-carboxylic acid (4d): White solid; yield: 91%; mp 230-232°C; MS: m/z 399; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 13.99$ (s, 1H, exchangeable COOH), 7.71 (s, 1H, ArH), 7.41 – 7.39 (t, 1H, $J = 2.06$ Hz, $2 \times \text{ArH}$), 7.15 – 7.14 (d, 1H, $J = 7.20$ Hz, ArH),

7.09 – 7.05 (m, 1H, ArH), 4.01 (s, 3H, OCH₃), 3.91 – 3.89 (d, 6H, J = 4.64 Hz, 2 × OCH₃), 3.80 – 3.78 (d, 6H, J = 7.64 Hz, 2 × OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 40.0, 55.6, 56.2, 56.3, 60.8, 61.2, 103.9, 112.9, 113.5, 115.9, 116.2, 117.7, 138.9, 141.3, 144.7, 146.3, 151.2, 153.3, 154.3, 156.4, 169.7; IR (KBr): ν = 3368, 3200, 3100, 1564, 1489, 1380, 1344, 1289 cm⁻¹

2-(3,4-dimethoxyphenyl)-5,6,7-trimethoxyquinoline-4-carboxylic acid (4e): White solid; yield: 90%; mp 228-230°C; MS: *m/z* 400; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 13.80 (s, 1H, exchangeable COOH), 7.82 (s, 1H, ArH), 7.61 (d, 1H, J = 2.06 Hz, 2 × ArH), 7.32 (s, 1H, ArH), 7.10 (s, 1H, ArH), 4.05 (s, 3H, OCH₃), 3.85 (d, 6H, J = 4.89 Hz, 2 × OCH₃), 3.80 (d, 6H, J = 7.80 Hz, 2 × OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 41.0, 55.8, 56.1, 56.4, 60.1, 61.0, 102.9, 113.1, 113.4, 115.5, 116.1, 117.8, 138.1, 142.1, 144.6, 148.1, 150.2, 153.5, 154.9, 155.4, 167.7; IR (KBr): ν = 3361, 3210, 3105, 1589, 1458, 1372, 1349, 1260 cm⁻¹

2-(3,4-dimethoxy-5-nitrophenyl)-5,6,7-trimethoxyquinoline-4-carboxylic acid (4f): White solid; yield: 83%; mp 270-272°C; MS: *m/z* 444; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.66 – 7.59 (d, 2H, J = 29.08 Hz, 2 × ArH), 7.25 – 7.22 (d, 2H, J = 14.08 Hz, 2 × ArH), 3.98 (m, 15H, 5 × OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 56.4, 56.5, 56.7, 61.0, 61.5, 104.7, 108.3, 113.2, 113.5, 116.1, 128.7, 139.7, 141.6, 141.7, 145.5, 146.7, 148.9, 152.2, 155.1, 156.6, 170.0; IR (KBr): ν = 3359, 3250, 3100, 1789, 1658, 1582, 1459, 1350, 1280 cm⁻¹

2-(1H-indol-3-yl)-5,6,7-trimethoxyquinoline-4-carboxylic acid (4g): White solid; yield: 92%; mp 250-252°C; MS: *m/z* 376; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.66 (s, 1H, exchangeable NH), 8.88 – 8.86 (t, 1H, J = 3.96 Hz, ArH), 8.42 – 8.41 (s, 1H, J = 2.28 Hz, ArH), 7.82 (s, 1H, ArH), 7.46 – 7.44 (m, 1H, ArH), 7.35 (s, 1H, ArH), 7.21 – 7.19 (t, 2H, J = 3.12 Hz, 2 × ArH), 4.03 (d, 3H, J = 4.28 Hz, 3 × OCH₃), 3.90 (t, 6H,

J = 4.12 Hz, 2 × OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 40.1, 56.1, 60.6, 61.1, 104.5, 111.1, 111.7, 113.7, 115.0, 120.3, 122.1, 122.7, 125.5, 128.0, 137.1, 138.4, 139.9, 145.8, 146.6, 154.7, 155.7, 170.2; IR (KBr): ν = 3396, 3310, 3200, 3105, 1689, 1558, 1472, 1369, 1250, 1196 cm⁻¹

2-(4-bromophenyl)-6,7,8-trimethoxyquinoline-4-carboxylic acid (4h): White-Yellow solid; yield: 82%; mp 222-224°C; MS: *m/z* 417; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.25 – 8.23 (d, 2H, J = 6.84 Hz, 2 × ArH), 7.92 (s, 1H, ArH), 7.73 – 7.71 (d, 2H, J = 6.84 Hz, 2 × ArH), 7.37 (s, 1H, ArH), 4.0 (s, 3H, 3XOCH₃), 4.01 (s, 3H, OCH₃), 3.90 – 3.89 (d, 6H, J = 15.4 Hz, 2X OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 56.4, 61.0, 61.6, 105.1, 113.5, 123.7, 129.6, 132.0, 137.4, 140.3, 141.6, 145.9, 146.7, 154.1, 156.7, 170.1; IR (KBr): ν = 3389, 3300, 3100, 1666, 1596, 1450, 1386, 690 cm⁻¹

2-(2-fluorophenyl)-5,6,7-trimethoxyquinoline-4-carboxylic acid (4i): White solid; yield: 75%; mp 262-262°C; MS: *m/z* 359; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.03-7.97 (t, 1H, J = 15.2 Hz, ArH), 7.70 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.51 (s, 1H, ArH), 7.43 – 7.38 (t, 2H, J = 17 Hz, 2 × ArH), 4.00 (s, 3H, OCH₃), 3.92- 3.90 (d, 6H, 2 × OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 56.7, 61.1, 61.7, 90.6, 103.6, 113.7, 116.6, 116.8, 117.2, 125.2, 131.6, 132.5, 140.9, 142.1, 144.6, 146.7, 151.6, 157.4, 161.4, 169.5; IR (KBr): ν = 3356, 3320, 3250, 1756, 1696, 1550, 1476, 1378, 600 cm⁻¹

2-(3,4-dimethylphenyl)-5,6,7-trimethoxyquinoline-4-carboxylic acid (4j): White solid; yield: 80%; mp 248-250°C; M.W.: 367.3951, MS: *m/z* 367; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.97 (t, 1H, ArH), 7.87 – 7.85 (d, 1H, J = 6 Hz, ArH), 7.51 (s, 1H, ArH), 7.26 – 7.21 (t, 2H, J = 16.68 Hz, 2 × ArH), 4.00 (s, 3H, OCH₃), 3.92- 3.90 (d, 6H, 2 × OCH₃); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 56.7, 61.1, 61.7, 90.6, 103.6, 113.7, 116.6, 116.8, 117.2, 125.2,

131.6, 132.5, 140.9, 142.1, 144.6, 146.7, 151.6, 157.4, 161.4, 169.5; IR (KBr): ν = 3360, 3200, 3155, 1680, 1588, 1470, 1479, 1350, 1211 cm^{-1}

2-(2,5-dibromophenyl)-6,7,8-trimethoxyquinoline-4-carboxylic acid (4k):

White solid; yield: 75%; mp 260-262°C; MS: m/z 499; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 13.89 (br, 1H, exchangeable COOH), 7.97 (s, 1H, ArH), 7.87 - 7.85 (d, 1H, J = 6.8 Hz, ArH), 7.51 (s, 1H, ArH), 7.26 - 7.21 (t, 2H, J = 16.68 Hz, 2 $\times$ ArH), 4.02 (s, 3H, OCH_3), 3.87 - 3.83 (d, 6H, J = 16.64 Hz, 2 $\times$ OCH_3), 2.29 - 2.26 (d, 6H, J = 11.28 Hz, 2 $\times$ OCH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 19.5, 19.8, 56.1, 60.7, 61.7, 104.7, 112.7, 114.0, 124.5, 128.0, 130.1, 136.7, 137.8, 140.9, 146.3, 147.7, 148.1, 155.2, 155.6, 164.9; IR (KBr): ν = 3369, 3310, 3250, 1606, 1576, 1560, 1476, 680, 660 cm^{-1}

2-(4-chloro-3-fluorophenyl)-5,6,7-trimethoxyquinoline-4-carboxylic acid (4l):

White solid; yield: 81%; mp 268-270°C; MS: m/z 391; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.15 - 8.12 (d, 1H, J = 10.14 Hz, ArH), 8.01 - 7.99 (d, 1H, J = 7.84 Hz, ArH), 7.64 - 7.51 (m, 2H, 2 $\times$ ArH), 7.26 (s, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 56.2, 60.7, 61.8, 104.7, 112.7, 114.6, 114.8, 115.0, 123.9, 131.1, 140.4, 141.4, 146.2, 148.2, 152.5, 155.8, 172.7; IR (KBr): ν = 3323, 3300, 3240, 1706, 1676, 1620, 1566, 780, 689, 650 cm^{-1}

5,6,7-trimethoxy-2-(4-(trifluoromethyl)phenyl)quinoline-4-carboxylic acid (4m):

White solid; yield: 75%; mp 256-258°C; MS: m/z 408; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.38 (s, 1H, ArH), 8.26 (s, 1H, ArH), 8.05 (s, 1H, ArH), 7.55 (s, 2H, 2 $\times$ ArH), 7.42 (s, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.91 - 3.90 (d, 6H, J = 3.84 Hz, 2 $\times$ OCH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 56.5, 61.0, 61.5, 105.2, 108.1, 113.7, 125.9, 126.9, 129.7, 131.0, 140.3, 146.6, 153.7, 156.7, 170.0; IR (KBr): ν = 3310, 3250, 3230, 1756, 1666, 1610, 1576, 770, 669, 640 cm^{-1}

5,6,7-trimethoxy-2-(4-nitrophenyl)quinoline-4-carboxylic acid (4n):

White solid; yield: 80%; mp 264-266°C; MS: m/z 385; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.38 - 8.34 (d, 2H, J = 8.00 Hz, 2 $\times$ ArH), 7.81 - 7.79 (d, 2H, J = 8.00 Hz, 2 $\times$ ArH), 7.59 (s, 1H, ArH), 7.28 (s, 1H, ArH), 3.98 (s, 3H, OCH_3), 3.87 (s, 6H, 2 $\times$ OCH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 56.2, 60.7, 61.8, 104.8, 112.9, 114.8, 125.8, 127.7, 141.4, 146.4, 148.3, 150.1, 155.8, 171.0; IR (KBr): ν = 3349, 3200, 3140, 1799, 1708, 1602, 1509, 1399, 1390, 1200 cm^{-1}

References:

1. "Quinoline", Encyclopedia Britannica, **1911**
2. D. E. Ryono, J. Lloyd, Bioorganic & Medicinal Chemistry Letter, **1994**, 4, 201-206
3. R. E. Lutz, J. Med. Chem., **1999**, 42, 1053-1065
4. G. J. Atwell, B. C. Baguley, J. Med. Chem. **1989**, 32, 396-401
5. J. K. De Brabander, J. Med. Chem. Letter, **2013**, 4, 517-521
6. G. A. M. Giardian, H. M. Sarau, C. Farina, A. D. Medhurst, M. Grugni, L. F. Raveglia, D. B. Schmidt, R. Rigolio, M. Luttmann, V. Vecchiotti, D. W. P. Hay, J. Med. Chem. **1997**, 40, 1794-1807
7. P. M. S. Chauhan, Chemistry & Biology Interface, **2014**, 4, 268-280
8. Y. Wua, Z. Chen, Y. Liu, L. Yu, L. Zhou, S. Yang, L. Lai, Bio. & Med. Chem., **2011**, 19, 3361-3366
9. T. Ohashi, Y. Oguro, T. Tanaka, Z. Shiokawa, S. Shibata, Y. Sato, H. Yamakawa, H. Hattori, Y. Yamamoto, S. Kondo, M. Miyamoto, H. Tojo, A. Baba, S. Sasaki, Bio. Med. Chem., **2012**, 20, 5496-5506
10. K. A. Metwally, L. M. Abdel-Aziz, El-S Lashine, M. I. Hussein, R. H. Badawy, Bio. Med. Chem., **2006**, 14, 8675-8682
11. O. Doebner, Ann., **1887**, 242-265
12. O. Doebner, Ber., **1887**, 20, 277
13. W. Pfitzinger, J. Prakt. Chem., **1886**, 33, 100
14. W. Pfitzinger, J. Prakt. Chem., **1888**, 38, 582
15. A. Gopalsamy and P. V. Pallai, Tetrahedron Lett., **1997**, 6, 907-910
16. M. J. Weiss, C. R. Hauser, J. Am. Chem. Soc., **1946**, 68, 722
17. (a) C. F. H. Allen, F. W. Spangler and E. R., J. Webster, Org. Chem., **1951**, 16, 17; (b) G. R. Lappin, Q. R. Petersen, and C. E., J. Wheeler, Org. Chem., **1950**, 15, 377; (c) G. R. Lappin, J. Am. Chem. Soc., **1948**, 70, 3348-3350
18. M. C. Lasne, Org. Biomol. Chem., **2005**, 3, 3794-3804

19. L. M. Wang, Journal of Fluorine Chemistry, **2009**, 130, 406-409
20. Milburn, Michael PCT Int. Appl., **2006**, WO 2006094237
21. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, J. Appl. Cryst., **1994**, 27, 435
22. H. D. Flack, Acta Cryst., **1983**, A39, 876-881
23. D. T. Cromer, J. T. Waber, International Tables for X-ray Crystallography, The Kynoch Press, **1974**
24. J. A. Ibers, W. C. Hamilton, Acta Crystallogr., **1964**, 17, 781
25. D. C. Creagh, W.J. McAuley, International Tables for Crystallography, Kluwer Academic Publishers, **1992**, 219-222
26. D. C. Creagh, W.J. McAuley, International Tables for Crystallography, Kluwer Academic Publishers, **1992**, 200-206
27. G.M. Sheldrick, Acta Crystallogr., **2008**, A64, 112-122
28. C.K. Johnson, ORTEP-II, Oak Ridge National Laboratory, **1976**