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ORIGINAL PAPER

Heterocycles [*h*]-fused to 4-oxoquinoline-3-carboxylic acid. Part VII: synthesis of some 6-oxoimidazo[4,5-*h*]quinoline-7-carboxylic acids and esters

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Abstract A series of ethyl 2-(substituted)-9-cyclopropyl-4-fluoro-6-oxo-1*H*-imidazo[4,5-*h*]quinoline-7-carboxylates has been prepared from ethyl 7,8-diamino-1,4-dihydroquinoline-3-carboxylate via thermally induced reactions with model alkanoic acids or via microwave-assisted cyclocondensation with some arene carboxaldehydes. Acid-catalysed hydrolysis of the resulting ester derivatives furnished the corresponding imidazoquinoline-7-carboxylic acids. The structures of these new acid and ester derivatives are based on microanalytical and spectral (IR, MS, and NMR) data.

Keywords 7,8-Diaminofluoroquinolone · Alkanoic acids · Arene carboxaldehydes · Cyclocondensation · Microwave irradiation

Introduction

The benzimidazole nucleus occurs naturally as part of vitamin B12, in the form of a 5,6-dimethyl-1-(α-D-ribofuranosyl) nucleotidic entity [1–5]. The benzimidazole system, the chemistry of which has been reviewed [6, 7], is central to medicinal chemistry [8, 9] and several derivatives thereof have reached commercial use, e.g. thiabendazole **1** (Fig. 1), an antihelmintic drug [10, 11]. On the other hand, synthetic fluoroquinolones, e.g. ciprofloxacin **2** [12–15], are potent antiinfectious drugs [12–20]. It follows that various types of imidazoquinolone are known, e.g. **3**–**8** (Fig. 1) that share the features of both quinolones (rings AB) and benzimidazoles (rings BC). Linear imidazo[4,5-*g*]quinolones, e.g. **3a**, **3b** [21, 22], have been prepared utilizing the corresponding 6,7-diamino-1-ethyl-4-oxoquinoline-3-carboxylic acid.

A number of angular non-fluorinated imidazoquinoline derivatives, such as imidazo[4,5-*f*]quinolines **4** [23, 24], **5** [25–27], **6a** [28–30], and **6b**–**6d** [30], have been prepared from the corresponding 5-aminobenzimidazole under the conditions of the Gould–Jacobs reaction [31–33], but their antibacterial activity was rather low. Several 4,5-disubstituted 9-oxo-1*H*-imidazo[4,5-*f*] quinoline-8-carboxylic acids (**7a**–**7c**), directly synthesized from their 5,6-diaminoquinoline precursors [34–37], have been reported as potent antibacterial agents. The 5-fluoro derivative **7a** exhibited minimal inhibitory concentrations (MICs) of 0.025–12.5 μg/cm^3 against an assortment of bacterial strains [34, 35]. The 5-methoxy analogue **7b** showed activity equipotent to that of **7a** against *S. aureus*, but was 2–16 times less potent against *E. coli* and *P. aeruginosa* compared with **7a** [36]. In **7c**, a fluorine atom attached to C-5 was the most favourable among H, F, and Cl, whereas 4-[*N*-(azacyclyl)]-5-fluoroimidazo[4,5-*f*]quinolones showed potent and well-balanced activity against both Gram-positive and Gram-negative bacteria [37].

The isomeric 6-oxoimidazo[4,5-*h*]quinoline-7-carboxylic acid (**8**) has also been prepared from the respective

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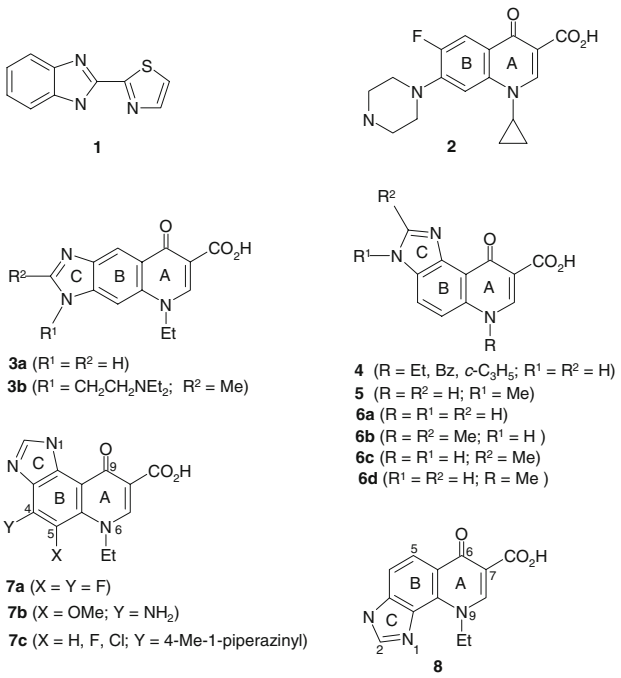


Fig. 1 Representative structures of derivatives of benzimidazole, fluoroquinolone, and isomeric imidazoquinolines

4-aminobenzimidazole [28, 29, 38, 39] under the conditions of the Gould–Jacobs reaction [31–33] .This non-fluorinated compound lacks suitable substituents at the N(9) and C(2) positions and exhibits low antibacterial activity. Accordingly, this work aims at synthesis of model 6-oxoimidazo[4,5-*h*]quinoline-7-carboxylic acids and esters having a cyclopropyl group at the N(9) locus together with alkyl/aryl appendages at carbon-2 (**11a**–**11g** and **12a**–**12g**; Scheme 1).

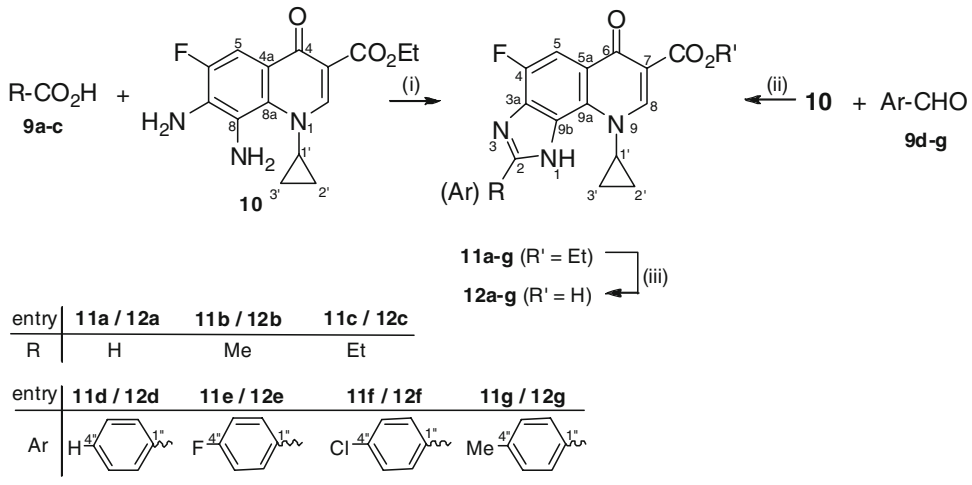
Results and discussion

The synthesis of ethyl 9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1*H*-imidazo[4,5-*h*]quinoline-7-carboxylates **(11a**–**11c)** is achieved via thermal cyclocondensation of 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**) with an excess amount (70 to 100-fold) of the appropriate alkanoic acid (**7a**–**7c**) as outlined in Scheme 1. This procedure is in line with the most widely applicable route for the preparation of 2-alkylbenzimidazoles from *o*-diaminoarenes and alkanoic acids [6, 7, 40]. Compounds **11a**–**11c** were obtained in good yield and were purified using silica gel column chromatography as detailed in the "Experimental" part.

The 2-arylimidazo[4,5-*h*]quinolines **11d**–**11g** were prepared in good yields via microwave-assisted cyclocondensation of **10** with the particular arene carboxaldehyde (**7d**–**7g**). Whilst adsorbed on silica gel in the presence of nitrobenzene as oxidizing agent the two reactants (**10** + **7**) were irradiated with a power of 350 W for 8–10 min at 140 °C. This versatile method, as applied in this study, has recently been reported for the synthesis of several 2-arylbenzimidazoles [41]. Acid-catalysed hydrolysis of the ethyl esters (**11a**–**11g**) furnished the corresponding 9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acids **(12a**–**12g)** in high yield and in the pure form.

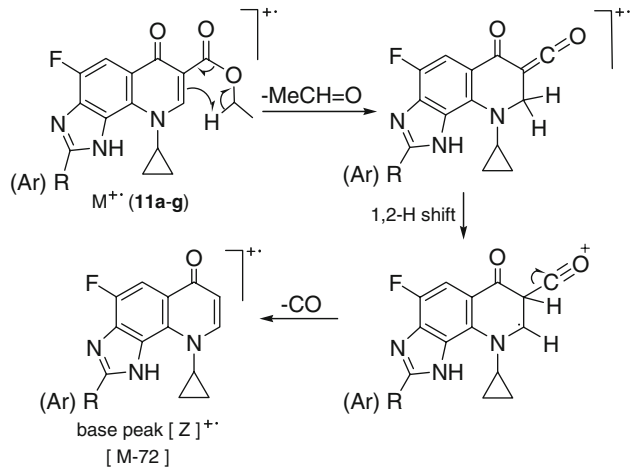
The structures of the new heterocycles **11a**–**11g** and **12a**–**12g** are supported by microanalytical and spectral (IR, MS, NMR) data; details are given in the "Experimental" part. The IR spectra showed absorption bands arising from stretching vibrations at 1,612–1,638 cm^{-1} (conjugated keto group), 1,697–1,722 cm^{-1} (carbonyl of conjugated CO_2Et/CO_2H), and 3,088–3,233 cm^{-1} (N–H). In addition,

Scheme 1

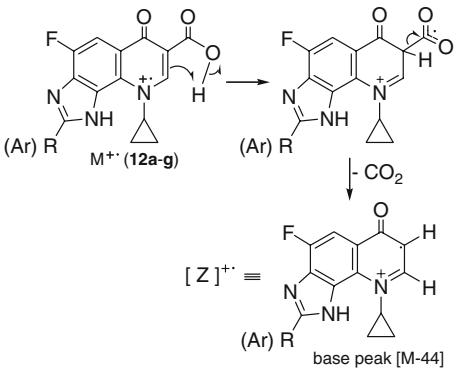


compounds **12a**–**12g** displayed strong absorption bands at 3,395–3,445 cm^{-1} (O–H). The mass spectra of **11** and **12** displayed the correct molecular ion peaks as suggested by their molecular formulas, and for which the high-resolution HRMS (ESI) data are in good agreement with the calculated values. The mass spectra of the ethyl ester derivatives **11a**–**11g** are dominated by base peaks corresponding to fragment ions $[Z]^{+\cdot}$ of $m/z = [M - 72]$ produced via successive elimination of acetaldehyde (McLafferty type) and CO from $[M]^{+\cdot}$ (Scheme 2). The corresponding acids **12a**–**12g** underwent facile decarboxylation under electron impact, with ultimate formation of similar $[Z]^{+\cdot}$ ions as the base peaks having $m/z = [M - 44]$ (Scheme 3). The latter ions undergo further fragmentation via elimination of a methyl radical or CO to produce ions $[Z - 15]^{+}$ and $[Z - 28]^{+\cdot}$, respectively (Scheme 4).

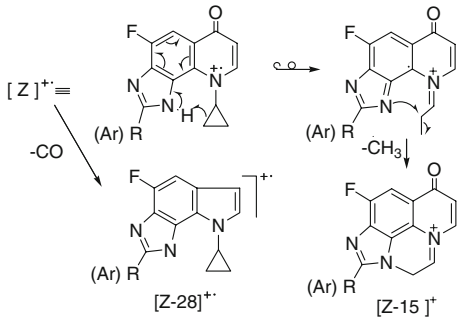
^{1}H and ^{13}C signal assignments to the different protons and carbons are based on DEPT and 2D (COSY, HMQC, HMBC) experiments which showed correlations consistent with these assignments. The skeletal carbons of the benzo-fused entity (ring B) in **11a**–**11g** and **12a**–**12g** are



Scheme 2



Scheme 3



Scheme 4

recognizable by their doublet signals (with varying *J* values) originating from scalar (through-bond) coupling with the neighboring fluorine atom at carbon-4. Likewise, the *p*-fluorophenyl carbons in **11f** and **12f** are also displayed as doublet signals arising from spin–spin coupling with the nearby *para* fluorine atom. In HMBC experiments for **11a**–**11g** and **12a**–**12g**, distinct "three-bond" (^{1}H, ^{13}C) correlations are observed between H-5 and each of C-3a, C-9a, and C-6, and between H-9 and each of C-9a, C-1′, C-6a, and CO_2H/CO_2 Et.

Experimental

Pure grade alkanoic acids, benzaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, and *p*-fluorobenzaldehyde were purchased from Acros. Microwave irradiation experiments were accomplished with a *Biotage Initiator 2.0* Microwave Synthesizer instrument. Melting points were determined on a Gallenkamp electrothermal melting-temperature apparatus. ^{1}H and ^{13}C NMR spectra were measured on a *Bruker* DPX-300 instrument. Chemical shifts are expressed in ppm with reference to *TMS* as internal standard. Electron-impact mass spectra (EIMS) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV, at an ion source temperature of 200 °C. High resolution mass spectra (HRMS) were measured in positive-ion mode by electrospray (ESI) on a *Bruker* APEX-4 (7 Tesla) instrument. IR spectra were recorded on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were preformed at the Microanalytical Laboratory of the Inorganic Chemistry Department, Tübingen University, Germany, and the results agreed with the calculated values within experimental error (±0.4%).

*Ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylate (**10**)*

This compound is prepared by reduction of ethyl 7-azido-1-cyclopropyl-6-flouro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate [42] using $SnCl_2$ and conc HCl at room temp according to a literature procedure [43, 44].

General procedure of Ethyl 2-(alkyl)-9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h] quinoline-7-carboxylates ***11a–11c***

A stirred mixture of 0.61 g **10** (2 mmol) and 10 cm^3 of the particular alkanoic acid was brought to gentle reflux for 2–3 h. The homogeneous reaction solution was then cooled and basified with 40% cold aqueous NaOH solution to pH ~7 and set aside for few minutes. The resulting white precipitate was collected by suction filtration, washed with water, and purified on preparative silica gel TLC plates using MeOH–$CHCl_3$ (1:20, *v/v*) as mobile phase.

General procedure of Ethyl 2-aryl-9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h] quinoline-7-carboxylate ***11d–11g***

To a homogeneous solution of 0.61 g **10** (2 mmol) in 10 cm^3 $CHCl_3$–MeOH (1:4, *v/v*) was added, successively, the particular aromatic aldehyde (2 mmol), 0.32 g nitrobenzene (2.6 mmol), and 3 g silica. The resulting slurry was evaporated to dryness under reduced pressure and placed in a 10-mL glass vial. The vial was sealed tightly with an aluminum–Teflon crimp top and the mixture was irradiated with an irradiation power of 250 W for 20–25 min at pre-selected temperature of 200 °C. Thereafter, the vial was cooled to 20 °C by gas-jet cooling and the reaction product was then purified by flash column chromatography, eluting at first with $CHCl_3$, followed by $CHCl_3$–MeOH (9:1, *v/v*).

General procedure of 9-Cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylic acids ***12a–12g***

A stirred solution of the particular ester **11** (2 mmol) in 30 cm^3 12% aq. HCl and 15 cm^3 ethanol was heated at 80–85 °C under reflux conditions. Progress of the ester hydrolysis was monitored by silica gel TLC and was completed within 2–3 h. Thereafter, the reaction mixture was cooled, poured on to ice-water and basified with 12% aq. sodium hydroxide solution. The resulting precipitate was collected, washed with water, and dried.

Ethyl 9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinline-7-carboxylate (**11a**, $C_{16}H_{14}FN_3O_3$)
Yield: 0.43 g (69%), mp 300–302 °C (dec); IR (KBr): $\bar{\nu}$ = 3,100, 3,021, 2,983, 2,928, 1,712, 1,612, 1,575, 1,497, 1,451, 1,374, 1,332, 1,282, 1,242, 1,178, 1,118, 878, 804 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 1.10 (m, 2H) and 1.28 (m, 2H) (H_2-2′ + H_2-3′), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 4.20 (q, *J* = 7.1 Hz, 2H, CH_2Me), 4.36 (m, 1H, H-1′), 7.73 (d, $^3J_{H\text{-}F}$ = 11 Hz, 1H, H-5), 8.45 (s, 1H, H-2), 8.47 (s, 1H, H-8) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 9.9 (C-2′ + C-3′), 14.8 (CH_3), 39.4 (C-1′), 60.4 (*C*H_2Me), 103.7 (d, $^2J_{C\text{-}F}$ = 18.9 Hz, C-5), 110.3 (C-7), 124.3 (d, $^3J_{C\text{-}F}$ = 5.6 Hz, C-5a), 130.2 (br d, $^2J_{C\text{-}F}$ = 13 Hz, C-3a), 130.4 (C-9a), 133.0 (br d, $^3J_{C\text{-}F}$ = 4 Hz, C-9b), 143.8 (C-2), 147.3 (C-8), 149.1 (d, $^1J_{C\text{-}F}$ = 250 Hz, C-4), 165.1 (*C*O_2Et), 172.5 (d, $^4J_{C\text{-}F}$ = 2.4 Hz, C-6) ppm; EIMS *m/z* (%): 315 (M^+, 21), 271 (17), 270 (14), 243 (100), 242 (51), 228 (21), 214 (15), 201 (6), 188 (5), 174 (10), 147 (7), 106 (4); HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}FN_3O_3$ $[M + H]^+$: 316.10974, found: 316.10925.

Ethyl 9-cyclopropyl-4-fluoro-2-methyl-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylate (**11b**, $C_{17}H_{16}FN_3O_3$)
Yield: 0.50 g (76%), mp 231-233 °C; IR (KBr): $\bar{\nu}$ = 3,101, 2,993, 1,716, 1,636, 1,578, 1,494, 1,456, 1,423, 1,334, 1,234, 1,178, 1,121, 1,074, 1,036, 879, 805 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 1.06 (m, 2H) and 1.27 (m, 2H) (H_2-2′ + H_2-3′), 1.25 (t, *J* = 7.1 Hz, 3H, C$H_3$$CH_2$), 2.58 (s, 3H, C(2)-$CH_3$), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2Me), 4.38 (m, 1H, H-1′), 7.63 (d, $^3J_{H\text{-}F}$ = 11 Hz, 1H, H-5), 8.43 (s, 1H, H-8) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 9.9(C-2′ + C-3′), 14.8 (*C*$H_3$$CH_2$O–), 15.3 (C(2)-*C*$H_3$), 39.3 (C-1′), 60.3 (*C*H_2Me), 103.0 (d, $^2J_{C\text{-}F}$ = 19.1 Hz, C-5), 109.7 (C-7), 123.7 (d, $^3J_{C\text{-}F}$ = 5.6 Hz, C-5a), 129.2 (C-9a), 131.1 (br d, $^2J_{C\text{-}F}$ = 12 Hz, C-3a), 133.1 (br d, $^3J_{C\text{-}F}$ = 5 Hz, C-9b), 147.1 (C-8), 148.8 (d, $^1J_{C\text{-}F}$ = 247 Hz, C-4), 153.7(C-2), 165.1(*C*O_2Et), 172.6 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, C-6) ppm; EIMS *m/z* (%): 329 (M^+, 13), 285 (30), 284 (13), 257 (100), 256 (43), 242 (29), 228 (16), 215 (8), 188 (18), 161 (7), 147 (10), 119 (7), 106(8); HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}FN_3O_3$ $[M + H]^+$: 330.12539, found: 330.12482.

Ethyl 9-cyclopropyl-2-ethyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylate (**11c**, $C_{18}H_{18}FN_3O_3$)
Yield: 0.39 g (57%), mp 211–213 °C; IR (KBr): $\bar{\nu}$ = 3,088, 2,982, 2,929, 1,722, 1,630, 1,607, 1,577, 1,537, 1,493, 1,458, 1,422, 1,331, 1,265, 1,238, 1,197, 1,174, 1,123, 1,061, 1,034, 864, 803 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 1.06 (m, 2H) and 1.25 (m, 2H, overlapped with the neighbouring triplet) (H_2-2′ + H_2-3′), 1.23 (t, *J* = 7 Hz, 3H, C$H_3$$CH_2$O–), 1.32 (t, *J* = 7.4 Hz, 3H, C$H_3$$CH_2$-C(2)), 2.92 (q, *J* = 7.4 Hz, 2H, C(2)-CH_2Me), 4.17 (q, *J* = 7 Hz, 2H, –OCH_2Me), 4.34 (m, 1H, H-1′), 7.61 (d, $^3J_{H\text{-}F}$ = 11.1 Hz, 1H, H-5), 8.41 (s, 1H, H-8) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 9.9 (C-2′ + C-3′), 12.7 (*C*$H_3$$CH_2$-C(2)), 14.7 (*C*$H_3$$CH_2$O–), 22.3 (MeC$H_2$-C(2)), 39.4 (C-1′), 60.3 (–OCH_2Me), 103.1(d, $^2J_{C\text{-}F}$ = 22.1 Hz, C-5), 109.5 (C-7), 123.7 (d, $^3J_{C\text{-}F}$ = 5.6 Hz, C-5a), 129.3 (br, C-9a), 130.5 (br d, $^2J_{C\text{-}F}$ = 12 Hz, C-3a), 133.1 (br d, $^3J_{C\text{-}F}$ = 4 Hz, C-9b),

147.3 (C-8), 148.6 (d, $^{1}J_{C\text{-}F} = 249$ Hz, C-4), 158.0 (d, $^{4}J_{C\text{-}F} = 2$ Hz, C-2), 165.0 (*C*O_2Et), 172.6 (d, $^{4}J_{C\text{-}F} = 2.3$ Hz, C-6); EIMS *m/z* (%): 343 (M^+, 13), 298 (5), 271 (100), 270 (27), 256 (28), 242 (14), 216 (4), 200 (7), 191 (17), 187 (8), 161 (5), 133 (4), 107 (5) ppm; HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}FN_3O_3$ $[M + H]^+$: 344.14104, found: 344.14051.

Ethyl 9-cyclopropyl-4-fluoro-6-oxo-2-phenyl-6, 9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylate (**11d**, $C_{22}H_{18}FN_3O_3$)

Yield: 0.63 g (80%), mp > 310 °C; IR (KBr): $\bar{\nu}$ = 3,060, 3,005, 2,978, 2,856, 2,362, 1,727, 1,696, 1,636, 1,588, 1,538, 1,486, 1,456, 1,403, 1,328, 1,265, 1,234, 1,178, 1,121, 1,069, 1,032, 944, 806, 781 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.14$ (m, 2H) and 1.32 (m, 2H) (H_2-2′ + H_2-3′), 1.26 (t, $J = 7.1$ Hz, 3H, –OCH_2CH_3), 4.20 (q, $J = 7.1$ Hz, 2H,–OCH_2Me), 4.44 (m, 1H, H-1'), 7.48 (dd, $J = 7.2$, 7.5 Hz, 2H, H-3″ + H-5″), 7.73 (d, $^{3}J_{H\text{-}F} = 10.9$ Hz, 1H, H-5), 7.91 (t, $J = 7.2$ Hz, 1H, H-4″), 8.26 (d, $J = 7.5$ Hz, 2H, H-2″ + H-6″), 8.43 (s, 1H, H-8), 12.90 (br s, 1H, N-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 10.3 (C-2′ + C-3′), 14.8 (*C*H_3CH_2O–), 40.3 (C-1′), 60.3 (–O*C*H_2Me), 104.3 (d, 19.8 Hz, C-5), 110.2 (C-7), 124.4 (d, $^{3}J_{C\text{-}F} = 4.9$ Hz, C-5a), 127.4 (C-2″ + C-6″), 128.0 (d, $^{2}J_{C\text{-}F} = 14.2$ Hz, C-3a), 130.9 (C-3″ + C-5″), 131.3 (C-9a), 133.3 (C-4″), 135.0 (C-1″), 137.4 (d, $^{3}J_{C\text{-}F} = 4$ Hz, C-9b), 147.1 (C-8), 147.2 (d, $^{1}J_{C\text{-}F} = 247$ Hz, C-4), 152.0 (C-2), 165.0 (*C*O_2Et), 172.4 (d, $^{4}J_{C\text{-}F} = 2.1$ Hz, C-6) ppm; EIMS *m/z* (%): 391 (M^+, 12), 347 (23), 333 (60), 319 (100), 304 (44), 290 (22), 264 (11), 250 (8), 223 (6), 173 (5), 146 (7), 122 (15), 105 (24); HRMS (ESI): *m/z* calcd. for $C_{22}H_{19}FN_3O_3$ $[M + H]^+$: 392.14105, found: 392.13995.

Ethyl 9-cyclopropyl-2-(4-fluororophenyl)-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h] quinoline-7-carboxylate (**11e**, $C_{22}H_{17}F_2N_3O_3$)

Yield: 0.62 g (75%), mp 265–266 °C (dec); IR (KBr): $\bar{\nu}$ = 3,096, 3,068, 2,995, 2,956, 1,720, 1,635, 1,584, 1,547, 1,391, 1,330, 1,271, 1,237, 1,137, 1,197, 1,165, 1,123, 1,036, 808, 738 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.13$ (m, 2H) and 1.31 (m, 2H) (H_2-2′ + H_2-3′), 1.26 (t, $J = 7.1$ Hz, 3H, –OCH_2CH_3), 4.19 (q, $J = 7.1$ Hz, 2H,–OCH_2Me), 4.43 (m, 1H, H-1′), 7.71 (d, $^{3}J_{H\text{-}F} = 10.8$ Hz, 1H, H-5), 7.37 (dd, $J = 8.3$, 8.8 Hz, 2H, H-3″ + H-5″), 8.29 (dd, $J = 2.6$, 8.3 Hz, 2H, H-2″ + H-6"), 8.42 (s, 1H, H-8), 13.80 (br s, 1H, N-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 10.2 (C-2′ + C-3′), 14.8 (*C*H_3CH_2O–), 40.2 (C-1′), 60.3 (-O*C*H_2Me), 104.2 (d, $^{2}J_{C\text{-}F} = 18.5$ Hz, C-5), 110.1 (C-7), 116.5 (d, $^{2}J_{C\text{-}F} = 21.9$ Hz, C-3″ + C-5″), 124.2 (d, $^{3}J_{C\text{-}F} = 5.3$ Hz, C-5a), 126.5 (d, $^{4}J_{C\text{-}F} = 2.9$ Hz, C-1″), 128.5 (d, $^{2}J_{C\text{-}F} = 14.2$ Hz, C-3a), 129.9 (d, $^{3}J_{C\text{-}F} = 8.6$ Hz, C-2″ + C-6″), 130.8 (C-9a), 137.4 (d, $^{3}J_{C\text{-}F} = 3.5$ Hz, C-9b), 147.2 (C-8), 147.5 (d, $^{1}J_{C\text{-}F} = 248$ Hz, C-4), 151.6 (C-2), 163.9 (d, $^{1}J_{C\text{-}F} = 247$ Hz, C-4″), 165.0 (*C*O_2Et), 172.4 (d, $^{4}J_{C\text{-}F} = 2.3$ Hz, C-6) ppm; EIMS *m/z* (%): 409 (M^+, 11), 365 (27), 351 (66), 337 (100), 322 (43), 308 (21), 282 (11), 241 (6), 200 (4), 123 (6). HRMS (ESI): *m/z* calcd. for $C_{22}H_{17}F_2N_3O_3Na$ $[M + Na]^+$: 432.11356, found: 432.11829.

Ethyl 9-cyclopropyl-4-fluoro-2-(4-chlorophenyl)-6-oxo-6,9-dihydro-1H-imidazo[4,5-h] quinoline-7-carboxylate (**11f**, $C_{22}H_{17}ClFN_3O_3$)

Yield: 0.67 g (79%), mp 292–294 °C (dec); IR (KBr): $\bar{\nu}$ = 3,209, 3,095, 3,051, 2,953, 2,867, 2,783, 1,745, 1,717, 1,636, 1,590, 1,484, 1,439, 1,328, 1,264, 1,232, 1,176, 1,122, 1,090, 1,068, 1,033, 844, 805 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.14$ (m, 2H) and 1.31 (m, 2H) (H_2-2′ + H_2-3′), 1.27 (t, $J = 7.1$ Hz, 3H, –OCH_2CH_3), 4.21 (q, $J = 7.1$ Hz, 2H,–OCH_2Me), 4.44 (m, 1H, H-1′), 7.74 (d, $^{3}J_{H\text{-}F} = 10.9$ Hz, 1H, H-5), 7.60 (d, $J = 8.5$ Hz, 2H, H-3″ + H-5″), 8.26 (d, $J = 8.5$ Hz, 2H, H-2″ + H-6″), 8.45 (s, 1H, H-8), 13.60 (br s, 1H, N-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 10.2 (C-2′ + C-3′), 14.8 (*C*H_3CH_2O–), 40.3 (C-1′), 60.3 (-O *C*H_2Me), 104.3 (d, $^{2}J_{C\text{-}F} = 10.3$ Hz, C-5), 110.3 (C-7), 124.2 (d, $^{3}J_{C\text{-}F} = 5.2$ Hz, C-5a), 129.1 (C-1″), 129.2 (C-3″ + C-5″), 129.5 (C-2″ + C-6″), 131.0 (d, $^{4}J_{C\text{-}F} = 1.3$ Hz, C-9a), 131.5 (C-4″), 135.5 (d, $^{3}J_{C\text{-}F} = 4.0$ Hz, C-9b), 129.7 (d, $^{2}J_{C\text{-}F} = 14.2$ Hz, C-3a), 147.0 (C-8), 148.8 (d, $^{1}J_{C\text{-}F} = 244$ Hz, C-4), 151.6 (C-2), 165.1 (*C*O_2Et), 172.4 (C-6) ppm; EIMS *m/z* (%): 425 (M^+, 11), 381 (40), 367 (52), 353 (100), 338 (38), 324 (19), 298 (11), 284 (10), 248 (6), 215 (6), 189 (6), 132 (6). HRMS (ESI): *m/z* calcd. for $C_{22}H_{18}ClFN_3O_3$ $[M + H]^+$: 426.10207, found: 426.10194.

Ethyl 9-cyclopropyl-4-fluoro-2-(4-methylphenyl)-6-oxo-6,9-dihydro-1H-imidazo [4,5-h] quinoline-7-carboxylate (**11g**, $C_{23}H_{20}FN_3O_3$)

Yield: 0.61 g (74%), mp 301–302 °C (dec); IR (KBr): $\bar{\nu}$ = 3,092, 3,048, 2,919, 2,866, 1,711, 1,634, 1,586, 1,546, 1,495, 1,393, 1,330, 1,301, 1,270, 1,235, 1,191, 1,069, 1,036, 833, 808 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.12$ (m, 2H) and 1.29 (m, 2H) (H_2-2′ + H_2-3′), 1.26 (t, $J = 7.1$ Hz, 3H, CH_3CH_2O–), 2.31 (s, 3H, C(4″)-CH_3), 4.19 (q, $J = 7.1$ Hz, 2H, –OCH_2Me), 4.43 (m, 1H, H-1′), 7.31 (d, $J = 8.0$ Hz, 2H, H-3″ + H-5″), 7.68 (d, $^{3}J_{H\text{-}F} = 10.9$ Hz, 1H, H-5), 8.13 (d, $J = 8.0$ Hz, 2H, H-2″ + H-6″), 8.41 (s, 1H, H-8), 13.82 (br s, 1H, N-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 10.2 (C-2′ + C-3′), 14.8 (*C*H_3CH_2O–), 40.2 (C-1′), 60.3 (–O*C*H_2Me), 103.8 (d, $^{2}J_{C\text{-}F} = 18.5$ Hz, C-5), 109.9 (C-7), 124.1 (d, $^{3}J_{C\text{-}F} = 5$ Hz, C-5a), 127.1 (C-1″), 127.4 (C-2″ + C-6″), 129.7 (d, $^{2}J_{C\text{-}F} = 14.5$ Hz, C-3a), 129.9 (C-3″ + C-5″), 130.6 (C-9a), 137.5 (d, $^{3}J_{C\text{-}F} = 4.2$ Hz, C-9b), 140.6 (C-4″),

147.2 (C-8), 147.5 (d, $^{1}J_{C\text{-}F} = 247$ Hz, C-4), 152.6 (C-2), 165.0 (CO_2Et), 172.5 (d, $^{4}J_{C\text{-}F} = 2$ Hz, C-6) ppm; EIMS *m/z* (%): 405 (M^+, 14), 390 (6), 361 (15), 347 (56), 333 (100), 318 (41), 304 (15), 278 (7), 265 (6), 119 (19), 91 (15); HRMS (ESI): *m/z* calcd. for $C_{23}H_{21}FN_3O_3$ $[M + H]^+$: 406.15670, found: 406.15675.

9-Cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylic acid
(**12a**, $C_{14}H_{10}FN_3O_3$)
Yield: 0.53 g (93%), mp > 310 °C; IR (KBr): $\bar{\nu} = 3{,}435$, 3,092, 2,843, 2,793, 1,685, 1,631, 1,589, 1,546, 1,459, 1,315, 1,096, 923, 810 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.18$ (m, 2H) and 1.34 (m, 2H) (H_2-2′ + H_2-3′), 4.49 (m, 1H, H-1′), 7.74 (d, $^{3}J_{H\text{-}F} = 10.4$ Hz, 1H, H-5), 8.55 (s, 1H, H-2), 8.67 (s, 1H, H-8), 12.80 (br s, 1H, N-H), 15.24 (br, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 9.9$ (C-2′ + C-3′), 40.7 (C-1′), 103.0 (d, $^{2}J_{C\text{-}F} =$ 19.2 Hz, C-5), 107.7 (C-7), 121.5 (d, $^{3}J_{C\text{-}F} = 6.7$ Hz, C-5a), 130.3 (br d, $^{2}J_{C\text{-}F} = 12$ Hz, C-3a), 131.4 (C-9a), 133.6 (br d, $^{3}J_{C\text{-}F} = 3.5$ Hz, C-9b), 144.1 (C-2), 147.0 (C-8), 149.5 (d, $^{1}J_{C\text{-}F} = 251$ Hz, C-4), 166.4 (CO_2H), 177.2 (d, $^{4}J_{C\text{-}F} = 2.9$ Hz, C-6) ppm; EIMS *m/z* (%): 287 (M^+, 4), 243 (100), 242 (30), 228 (21), 214 (8), 188 (5), 174 (12), 160 (5), 147 (12), 119 (5), 106 (9); HRMS (ESI): *m/z* calcd. for $C_{14}H_{11}FN_3O_3$ $[M + H]^+$: 288.07844, found: 288.07795.

9-Cyclopropyl-4-fluoro-2-methyl-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylic acid
(**12b**, $C_{15}H_{12}FN_3O_3$)
Yield: 0.55 g (92%), mp > 310 °C; IR (KBr): $\bar{\nu} = 3{,}445$, 3,119, 2,922, 2,856, 1,709, 1,634, 1,595, 1,543, 1,473, 1,318, 1,230, 1,131, 1,037, 1,010, 806 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.21$ (m, 2H) and 1.32 (m, 2H)(H_2-2′ + H_2-3′), 2.62 (s, 3H, C(2)-CH_3), 4.52 (m, 1H, H-1′), 7.75 (d, $^{3}J_{H\text{-}F} = 10.3$ Hz, 1H, H-5), 8.67 (s, 1H, H-8), 13.34 (br s, 1H, N-H), 15.30 (s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 10.0$ (C-2′ + C-3′), 15.2 (C(2)-CH_3), 38.6 (C-1′), 102.5 (d, $^{2}J_{C\text{-}F} = 19.1$ Hz, C-5), 107.5 (C-7), 121.1(d, $^{3}J_{C\text{-}F} = 6.7$ Hz, C-5a), 129.1 (C-9a), 130.4 (br d, $^{2}J_{C\text{-}F} = 11.8$ Hz, C-3a), 132.0 (br d, $^{3}J_{C\text{-}F} =$ 4.6 Hz, C-9b), 146.9 (C-8), 152.6 (d, $^{1}J_{C\text{-}F} = 247$ Hz, C-4), 153.4 (C-2), 166.4 (CO_2H), 177.3 (d, $^{4}J_{C\text{-}F} = 2.8$ Hz, C-6) ppm; EIMS *m/z* (%): 301 (M^+, 14), 282 (3), 257 (100), 256 (31), 242 (35), 228 (10), 201 (6), 188 (11), 161 (7), 121 (4), 106 (3); HRMS (ESI): *m/z* calcd. for $C_{15}H_{13}FN_3O_3$ $[M + H]^+$: 302.09409, found: 302.09354.

9-Cyclopropyl-2-ethyl-4-fluoro-6-oxo-6,9-dihydro-1H-imidazo[4,5-h]quinoline-7-carboxylic acid
(**12c**, $C_{16}H_{14}FN_3O_3$)
Yield: 0. 58 g (92%), mp > 310 °C; IR (KBr): $\bar{\nu} = 3{,}423$, 3,122, 2,923, 2,850, 1,707, 1,635, 1,593, 1,541, 1,473, 1,318, 1,217, 1,139, 1,030, 959, 807 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.20$ (m, 2H) and 1.25 (m, 2H, overlapped with the neighboring triplet) (H_2-2′ + H_2-3′), 1.37 (t, $J = 7.4$ Hz, 3H, CH_3CH_2-C(2)), 2.96 (q, $J = 7.4$ Hz, 2H, C(2)-CH_2Me), 4.56 (m, 1H, H-1′), 7.79 (d, $^{3}J_{H\text{-}F} = 8.2$ Hz, 1H, H-5), 8.70 (s, 1H, H-8), 13.40 (br, 1H, N-H), 15.38 (s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 10.1$ (C-2′ + C-3′), 12.6 (CH_3CH_2-C(2)), 22.4 (MeCH_2-C(2)), 39.3 (C-1′), 102.6 (d, $^{2}J_{C\text{-}F} =$ 19.7 Hz, C-5), 107.5 (C-7), 121.1 (d, $^{3}J_{C\text{-}F} = 5.5$ Hz, C-5a), 129.3 (br, C-9a), 131.3 (br d, $^{2}J_{C\text{-}F} = 15$ Hz, C-3a), 132.0 (br d, $^{3}J_{C\text{-}F} = 3.5$ Hz, C-9b), 147.0 (C-8), 148.5 (d, $^{1}J_{C\text{-}F} = 249$ Hz, C-4), 158.0 (d, $^{4}J_{C\text{-}F} = 2$ Hz, C-2), 166.5 (CO_2H), 177.4 (d, $^{4}J_{C\text{-}F} = 2$ Hz, C-6) ppm; EIMS *m/z* (%): 315 (M^+, 9), 271 (100), 256 (39), 242 (15), 215 (8), 188 (6); HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}FN_3O_3$ $[M + H]^+$: 316.10974, found: 316.10926.

9-Cyclopropyl-4-fluoro-6-oxo-2-phenyl-6,9-dihydro-1H-imidazo[4,5-h] quinoline-7-carboxylic acid
(**12d**, $C_{20}H_{14}FN_3O_3$)
Yield: 0.66 g (91%), mp > 310 °C; IR (KBr): $\bar{\nu} = 3{,}460$, 3,121, 3,079, 2,883, 2,846, 2,669, 1,706, 1,630, 1,588, 1,536, 1,481, 1,365, 1,316, 1,247, 1,132, 1,069, 1,031, 948, 889, 862 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.16$ (m, 2H) and 1.33 (m, 2H) (H_2-2′ + H_2-3′), 4.45 (m, 1H, H-1′), 7.50 (m, 3H, H-4″ + H-3″ + H-5″), 7.66 (d, $^{3}J_{H\text{-}F} = 10.4$ Hz, 1H, H-5), 8.17 (m, 2H, H-2″ + H-6″), 8.50 (s, 1H, H-8), 13.91 (br s, 1H, N-H), 15.20 (s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 10.2$ (C-2′ + C-3′), 41.6 (C-1′), 103.4 (d, $^{2}J_{C\text{-}F} = 19.1$ Hz, C-5), 107.8 (C-7), 121.5 (d, $^{3}J_{C\text{-}F} = 6.2$ Hz, C-5a), 127.5 (C-2″ + C-6″), 128.8 (d, $^{2}J_{C\text{-}F} = 14.5$ Hz, C-3a), 129.4 (C-1″), 129.5 (C-3″ + C-5″), 132.0 (C-9a), 131.2 (C-4″), 137.3 (d, $^{3}J_{C\text{-}F} = 4$ Hz, C-9b), 146.8 (C-8), 147.8 (d, $^{1}J_{C\text{-}F} = 249$ Hz, C-4), 152.5 (C-2), 166.3 (CO_2H), 177.1 (d, $^{4}J_{C\text{-}F} = 2.7$ Hz, C-6) ppm; EIMS *m/z* (%): 363 (M^+, 11), 319 (100), 304 (66), 290 (18), 271 (14), 250 (11), 223 (8),159 (6), 147 (10), 131 (6); HRMS (ESI): *m/z* calcd. for $C_{20}H_{15}FN_3O_3$ $[M + H]^+$: 364.10974, found: 364.10917.

9-Cyclopropyl-2-(4-fluorophenyl)-4-fluoro-6-oxo-6, 9-dihydro-1H-imidazo [4,5-h]quinoline-7-carboxylic acid (**12e**, $C_{20}H_{13}F_2N_3O_3$)
Yield: 0.69 g (91%), mp > 310 °C; IR (KBr): $\bar{\nu} = 3{,}438$, 3,169, 3,098, 2,925, 1,712, 1,634, 1,586, 1,527, 1,493, 1,441, 1,318, 1,220, 1,159, 1,131, 1,065, 1,000, 946, 881, 841, 809 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.22$ (m, 2H) and 1.37 (m, 2H) (H_2-2′ + H_2-3′), 4.52 (m, 1H, H-1′), 7.35 (dd, $J = 8.1$, 8.7 Hz, 2H, H-3″ + H-5″), 7.74 (d, $^{3}J_{H\text{-}F} = 10.3$ Hz, 1H, H-5), 8.26 (dd, $J = 8.1$, 2.3 Hz, 2H, H-2″ + H-6″), 8.60 (s, 1H, H-8), 14.02 (s, 1H, N-H), 15.28 (br s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 10.2$ (C-2′ + C-3′), 41.6 (C-1′), 103.5 (d, $^{2}J_{C\text{-}F} =$ 19.0 Hz, C-5), 107.8 (C-7), 116.6 (d, $^{2}J_{C\text{-}F} = 21.6$ Hz,

C-3″ + C-5″), 121.6 (d, $^{3}J_{C\text{-}F}$ = 4.8 Hz, C-5a), 125.9 (d, $^{4}J_{C\text{-}F}$ = 2.1 Hz, C-1″), 129.0 (d, $^{2}J_{C\text{-}F}$ = 14 Hz, C-3a), 130.0 (d, $^{3}J_{C\text{-}F}$ = 7.0 Hz, C-2″ + C-6″), 132.0 (C-9a), 137.4 (d, $^{3}J_{C\text{-}F}$ = 4.5 Hz, C-9b), 146.8 (C-8), 147.8 (d, $^{1}J_{C\text{-}F}$ = 249 Hz, C-4), 151.6 (C-2), 164.1 (d, $^{1}J_{C\text{-}F}$ = 246 Hz, C-4″), 166.3 (CO_2H), 177.2 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz, C-6) ppm; EIMS *m/z* (%): 381 (M^+, 8), 337 (100), 322 (47), 308 (15), 268 (11), 241 (9), 215 (5), 169 (4), 155 (7), 134 (6); HRMS (ESI): *m/z* calcd. for $C_{20}H_{14}F_2N_3O_3$ $[M + H]^+$: 382.10032, found: 382.09979.

2-(4-Chlorophenyl)-9-cyclopropyl-4-fluoro-6-oxo-6, 9-dihydro-1H-imidazo [4,5-h] quinoline-7-carboxylic acid (**12f**, $C_{20}H_{13}ClFN_3O_3$)

Yield: 0.74 g (93%), mp > 310 °C; IR (KBr): $\bar{\nu}$ = 3,427, 3,165, 3,098, 3,975, 2,877, 1,709, 1,632, 1,590, 1,518, 1,483, 1,317, 1,132, 1,102, 1,065, 1,003, 946, 879, 834, 809 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 1.21 (m, 2H) and 1.36 (m, 2H) (H_2-2′ + H_2-3′), 4.49 (m, 1H, H-1′), 7.57 (d, *J* = 8.1 Hz, 2H, H-3″ + H-5″), 7.74 (d, $^{3}J_{H\text{-}F}$ = 10.3 Hz, 1H, H-5), 8.19 (d, *J* = 8.1 Hz, 2H, H-2″ + H-6″), 8.61 (s, 1H, H-8), 14.10 (s, 1H, N-H), 15.30 (br s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 10.2 (C-2′ + C-3′), 41.6 (C-1′), 103.6 (d, $^{2}J_{C\text{-}F}$ = 19.0 Hz, C-5), 107.7 (C-7), 121.5 (d, $^{3}J_{C\text{-}F}$ = 6.3 Hz, C-5a), 128.1 (C-1″), 128.8 (d, $^{2}J_{C\text{-}F}$ = 15.1 Hz, C-3a), 129.1 (C-3″ + C-5″), 129.6 (C-2″ + C-6″), 132.0 (C-9a), 135.9 (C-4″), 137.2 (d, $^{2}J_{C\text{-}F}$ = 4.2 Hz, C-9b), 146.8 (C-8), 147.8 (d, $^{1}J_{C\text{-}F}$ = 250 Hz, C-4), 151.3 (C-2), 166.3 (CO_2H), 177.1 (d, $^{4}J_{C\text{-}F}$ = 2.6 Hz, C-6) ppm; EIMS *m/z* (%): 397 (M^+, 6), 353 (100), 338 (48), 324 (14), 248 (9), 257 (6), 199 (4), 176 (7), 132 (6); HRMS (ESI): *m/z* calcd. for $C_{20}H_{14}ClFN_3O_3$ $[M + H]^+$: 398.07077, found: 398.07017.

9-Cyclopropyl-4-fluoro-2-(4-methylphenyl)-6-oxo-6, 9-dihydro-1H-imidazo[4,5-h] quinoline-7-carboxylic acid (**12g**, $C_{21}H_{16}FN_3O_3$)

Yield: 0.68 g (90%), mp > 310 °C; IR (KBr): $\bar{\nu}$ = 3,435, 3,139, 3,018, 2,924, 2,855, 1,693, 1,632, 1,591, 1,528, 1,491, 1,317, 1,187, 1,118, 1,066, 1,030, 946, 832, 810 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 1.18 (m, 2H) and 1.36 (m, 2H) (H_2-2′ + H_2-3′), 2.47 (s, 3H, C(4″)-CH_3), 4.52 (m, 1H, H-1′), 7.31 (d, *J* = 7.8, 2H, H-3″ + H-5″), 7.83 (d, $^{3}J_{H\text{-}F}$ = 9.5 Hz, 1H, H-5), 8.08 (d, *J* = 7.8, 2H, H-2″ + H-6″), 8.58 (s, 1H, H-8), 14.01 (br s, 1H, N-H), 15.33 (s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 10.3 (C-2′ + C-3′), 41.6 (C-1′), 21.5 (C-(4″) + CH_3), 103.4 (d, $^{2}J_{C\text{-}F}$ = 15.8 Hz, C-5), 107.8 (C-7), 121.6 (d, $^{3}J_{C\text{-}F}$ = 4.3 Hz, C-5a), 126.7 (C-1″), 127.4 (C-2″ + C-6″), 128.9 (d, $^{2}J_{C\text{-}F}$ = 14 Hz, C-3a), 130.1 (C-3″ + C-5″), 132.1 (C-9a), 137.5 (d, $^{3}J_{C\text{-}F}$ = 4.2 Hz, C-9b), 141.1 (C-4″), 146.9 (C-8), 150.2 (d, $^{1}J_{C\text{-}F}$ = 238 Hz, C-4), 152.8 (C-2), 166.4 (CO_2H), 177.3 (d, $^{4}J_{C\text{-}F}$ = 2 Hz, C-6) ppm; EIMS *m/z* (%): 377 (M^+, 6), 333 (100), 318 (91), 304 (20), 278 (9), 264 (14), 249 (6), 215 (5), 167 (6), 147 (5); HRMS (ESI): *m/z* calcd. for $C_{21}H_{17}FN_3O_3$ $[M + H]^+$: 378.12539, found: 378.12484.

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