4-Quinolone fused heterocyclic ring systems by intramolecular reactions of 4-quinolone-2-carboxamides

Raffaella Cincinelli, Loana Musso, Giangiacomo Beretta, Sabrina Dallavalle*
4-Quinolone fused heterocyclic ring systems by intramolecular reactions of 4-quinolone-2-carboxamides

Raffaella Cincinelli\textsuperscript{a}, Loana Musso\textsuperscript{a}, Giangiacomo Beretta\textsuperscript{b}, Sabrina Dallavalle\textsuperscript{a}*

\textsuperscript{a}Department of Food, Environmental and Nutritional Sciences, Division of Chemistry and Molecular Biology, University of Milan, via Celoria 2, 20133 Milan, Italy.

\textsuperscript{b}Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Milan, via Mangiagalli 25, 20133, Milan, Italy

Corresponding author e-mail: sabrina.dallavalle@unimi.it

\textsuperscript{§}Dedicated to Professor Lucio Merlini on the occasion of his 80th birthday.

Abstract.

A versatile synthetic route to new 4-quinolone-based polycyclic systems is described. TFA-catalyzed intramolecular reaction of N-unsubstituted quinolone-2-carboxylic acid amides gives structurally diverse compounds, depending on the length of the chain. Acid treatment of β-oxoamides furnishes 3H-pyrazino[1,2-a]quinoline-4,6-diones, due to the nucleophilic attack of N-1 to the carbonyl group, whereas TFA treatment of δ- and ε-oxoamides leads to the formation of tetracyclic compounds by a tandem heteroannulation reaction.

Keywords: nitrogen heterocycles, heteroannulation reaction, quinolone-2-carboxylic acid amides, quinolone-fused heterocycles, synthesis

1. Introduction

The quinolone moiety is an important structural unit in medicinal chemistry and many compounds with this scaffold have shown a broad range of biological properties including anticancer\textsuperscript{1}, antimicrobial\textsuperscript{2}, antiviral\textsuperscript{3} and antimalarial\textsuperscript{4} activity.
In pursuance of our research on the development of new antitumor compounds, we became interested in accessing structurally diverse heterocyclic rings containing the quinolone moiety. In recent papers\(^5\) we reported that the TFA-catalyzed intramolecular Friedel-Crafts cyclization of indole-2-carboxylic acid \(\beta\)- or \(\gamma\)-oxoamides (1) represented a simple synthesis of \(\beta\)-carbolin-1-ones (2, \(m = 0\)) or dihydro-2H-azepino[3,4-b]indol-1-ones (2, \(m = 1\)) (Scheme 1). Conversely, acid treatment of \(\delta\)-, \(\epsilon\)-, and \(\zeta\)-oxoamides preferentially gave intermediate N-acyliminium ions, which cyclized into the novel heterocyclic rings pyrrolo[2,1-b]indole (4, \(m = 1\)), indolizino[2,1-b]indole (4, \(m = 2\)), and 9a,11-diaza-indeno[1,2-a]azulene (4, \(m = 3\)).\(^6\)

![Scheme 1. TFA-catalyzed intramolecular Friedel-Crafts cyclization of indole-2-carboxylic acid oxoamides.](image)

As the method could provide a route to novel heterocyclic systems, we thought to extend the study to the preparation of quinolone-fused rings. Although numerous efforts have been made to modify quinolones, there are currently few reports concerning electrophilic substitutions at C-3 of 4-quinolone rings, even though 4-quinolone is known to be in tautomeric equilibrium with its phenol form.\(^7\) A survey of literature revealed few examples of Friedel-Crafts alkylation\(^8\) and acylation of 4-quinolones.\(^9\) Chlorination,\(^10\) bromination\(^11\) and iodination\(^12\) reactions of 4-oxo-1,4-dihydro-quinoline-2-carboxylic acid derivatives are reported as well. These findings motivated us to apply the synthetic sequence to 4-quinolone-2-carboxamides. We herein describe the outcome of these reactions.

2. Results and discussion

The investigation began with N-methyl kynurenic acid 5a,\(^{13}\) which was obtained by treatment of N-methylaniline with DMAD, followed by cyclization with PPA and basic hydrolysis.\(^{14}\)
The coupling of 5a with 2-aminoethanol, through WSC and HOBt, gave the alcohol 6a. Oxidation of 6a, followed by treatment with TFA afforded the expected tricyclic compound 8, although in poor yield (21% overall) (Scheme 2). The yield was increased by coupling 5a with commercially available aminoacetaldehyde diethylacetal to obtain the amide 7a in 88% yield. Treatment of 7a with TFA gave the cyclization product in 75% yield. When the sequence was performed on the free-NH quinolone 5b, the reaction proceeded smoothly to give compound 9, derived from the attack of N-1 to the carbonyl group of the intermediate aldehyde, followd by elimination. Compound 9 was also obtained from the intermediate acetal 7b, whereas the product of cyclization at C-3 was not isolated at all. There are currently no reports on the synthesis of 2,10-dihydrobenzo[b][1,7]naphthyridine-1,5-diones (8) or 3H-pyrazino[1,2-a]quinoline-4,6-diones (9). Riepl et al. reported the preparation of 5,7-dihydrodibenzo[b,f][1,7]naphtyridine-6,12-diones by a Fischer type rearrangement reaction. However, the versatility of this methodology was strongly limited by the need to use freshly prepared symmetric 1,2-diarylhydrazines.

To evaluate the influence of the chain length on the cyclization, the reactivity of δ- and ε-oxamides was investigated as well.

When the coupling reaction of N-methyl kynurenic acid 5a was carried out with 4-aminobutanol, alcohol 10a was obtained (Scheme 3). Oxidation of 10a, followed by treatment with TFA, gave the enamide 11a. The same result was obtained when the quinolone nitrogen was protected with a benzyl group (compound 11b).
This confirmed that the carbonyl group underwent a nucleophilic attack by the amide nitrogen. However, unlike the case of indole, the lower reactivity of the quinolone ring towards the electrophilic substitution prevented the acid-catalyzed intramolecular cyclization and gave rise to compounds 11a-b by an elimination reaction.

Interestingly, oxidation followed by acid treatment of compounds 12a-b, obtained from kynurenic acid 5b, gave the new compounds 13a-b (Scheme 3). In this case, a tandem heteroannulation reaction - which is most likely due to a first nucleophilic attack of the amide nitrogen to the aldehyde, followed by the N-1 attack on the pentaatomic intermediate ring - furnishes a tetracyclic fused system.

As compound 13a showed antitumor activity (IC50 = 10 μM) on H460 tumor cell lines, the scope of the reaction was explored by preparing differently substituted analogues. Accordingly, treatment of kynurenic acid 5b with 2-(2-aminophenyl)-ethanol gave the alcohol 14, which was oxidized to the corresponding aldehyde, on its turn converted into the pentacyclic derivative 15 by the usual treatment with TFA (Scheme 3).

Scheme 3. Synthesis of 4-quinolone fused heterocyclic ring systems 13a-b and 15.
Compounds 21a-d, bearing substituents on ring A were obtained from the suitable anilines 16a-b (Scheme 4). Further elaboration of the bromoderivative 21b via Suzuki-Miyaura palladium-catalyzed cross-coupling reactions generated compounds 21c and 21d.

3. Conclusions

In conclusion, we have devised a reliable synthetic route to 4-quinolone-based fused systems starting from 4-quinolone-2-carboxylic acid oxoamides. The acid-catalyzed intramolecular reaction of N-unsubstituted quinolones gives structurally diverse compounds, depending on the length of the chain. Acid treatment of β-oxoamides furnishes 3H-pyrazino[1,2-a]quinoline-4,6-diones, due to the nucleophilic attack of N-1 to the carbonyl group, whereas acid treatment of δ- and ε-oxoamides leads to the formation of tetracyclic compounds by a tandem heteroannulation reaction.

To the best of our knowledge, no examples of such heterocyclic structures have been reported in the literature so far. Therefore, our sequence represents a versatile approach to new biologically relevant scaffolds and specifically provides a method for the rapid preparation of differently substituted derivatives.
4. Experimental section

4.1. General method. All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries and are uncorrected. NMR spectra were recorded at 300 MHz. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et₂O) were obtained by distillation from sodium-benzophenone ketyl; dry methylene chloride was obtained by distillation from phosphorus pentoxide. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow, and all glassware were oven dried and/or flame dried. Isolation and purification of the compounds were performed by flash column chromatography on silica gel 60 (230-400 mesh). Analytical thin-layer chromatography (TLC) was conducted on Fluka TLC plates (silica gel 60 F₂₅₄, aluminum foil). Compound 5b was purchased from Sigma-Aldrich.

4.2. Methyl-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (5a)\textsuperscript{13} To a solution of N-methylaniline (0.98 g, 9.15 mmol, 1.01 mL) in H₂O (30 mL), DMAD (1.08 g, 7.62 mmol, 0.96 mL) was added dropwise and the reaction was stirred for 2 h at room temperature, then the aqueous phase was extracted with EtOAc (3 × 30 mL) and the collected organic layers were dried, filtered and evaporated. The crude was purified by flash chromatography.\textsuperscript{1} (Hexane/EtOAc from 90:10 to 85:15) to give 2-(methylphenylamino)but-2-enedioic acid dimethyl ester. Yield 71%; white solid; mp = 74 °C; R_f : 0.16 (AcOEt/Hexane 10:90); \textsuperscript{1}H-NMR (300 MHz, CDCl₃) δ: 7.40-7.08 (5H, m), 4.78 (1H, s), 3.66 (3H, s), 3.63 (3H, s), 3.20 (3H, s); \textsuperscript{13}C-NMR (75 MHz, CDCl₃) δ: 167.4, 164.9, 153.8, 144.1, 129.0 (× 2), 127.0, 126.1 (× 2), 87.7, 52.2, 50.5, 40.4. Anal.Calcd for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.88; H, 6.04; N, 5.66.

A solution of 2-(methylphenylamino)-but-2-enedioic acid dimethyl ester (1.16 g, 4.65 mmol) in PPA (2.40 g, 70.40 mmol) was heated at 80 °C for 1.5 h. The mixture was added with ice-water, then a solution of NH₄OH (33%) was added. The aqueous phase was extracted with EtOAc (3 × 50 mL). The collected organic layers were washed with water, dried filtered and evaporated to obtain 877 mg of 1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester as a white solid. Yield 87%; mp = 140 °C; R_f : 0.25 (CH₂Cl₂/Methanol 195:5); \textsuperscript{1}H-NMR (300 MHz, CDCl₃) δ: 8.44 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 8.1 - 8.1 Hz), 7.57 (1H, d, J = 8.8 Hz), 7.44 (1H, dd, J = 8.1 Hz - 8.8 Hz), 6.70 (1H, s), 3.86 (3H, s); \textsuperscript{13}C-NMR (75 MHz, CDCl₃) δ: 177.6, 163.7, 143.3, 141.5, 132.7, 126.7, 126.2, 123.8, 115.6, 112.0, 53.1, 36.9. Anal.Calcd for C₁₂H₁₁NO₃: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.58; H, 5.13; N, 6.41.
To a suspension of 1-methyl-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid methyl ester (857 mg, 3.94 mmol) in MeOH (13 mL), 1N NaOH (13 mL) was added. The resulting mixture was refluxed heated at reflux for 1 h, then MeOH was evaporated. After cooling with an ice-bath, 1N HCl was added and the white solid 5a formed was filtered and dried. Yield 95%; mp > 300 °C; Rf = 0.41 (CH2Cl2/MeOH 19:1); 1H-NMR (300 MHz, DMSO-d6) δ: 8.13 (1H, d, J = 7.3 Hz), 7.75–7.64 (2H, m), 7.35 (1H, m), 5.83 (1H, s), 3.75 (3H, s); 13C-NMR (75 MHz, DMSO-d6) δ: 176.3, 165.7, 152.9, 140.9, 132.3, 126.2, 125.3, 125.2, 123.4; 1H-NMR (300 MHz, CDCl3) δ: 8.13 (1H, d, J = 7.3 Hz), 7.75–7.64 (2H, m), 7.35 (1H, m), 5.83 (1H, s), 3.75 (3H, s); 13C-NMR (75 MHz, CDCl3) δ: 176.3, 165.7, 152.9, 140.9, 132.3, 126.2, 125.3, 125.2, 123.4; Anal.Calcd for C11H9NO3: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.33; H, 4.43; N, 6.85.

4.3. 1-Benzyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (5c). To a solution of N-benzylaniline (1.50 g, 8.19 mmol) in MeOH (36 mL), DMAD (1.15 mL, 9.14 mmol) was added dropwise and the reaction was refluxed heated at reflux for 6 h. The solvent was evaporated and the crude product was purified by flash chromatography (Hexane/EtOAc 19:1, then 85:15) to give 2-(benzylphenylamino)but-2-enedioic acid dimethyl ester (22) as a white solid (1.89 g, 85%); mp = 113 °C; Rf : 0.10 (Hexane/EtOAc 90:10); 1H-NMR (300 MHz, CDCl3) δ: 7.48-7.13 (10H, m), 4.80 (1H, s), 4.76 (2H, s), 3.72 (3H, s), 3.61 (3H, s); 13C-NMR (75 MHz, CDCl3) δ: 167.4, 165.0, 153.5, 142.9, 135.3, 129.0 (2C), 128.3 (2C), 127.2 (2C), 127.1 (2C), 126.9 (2C), 88.7, 56.9, 52.3, 50.5. Anal.Calcd for C19H19NO4: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.38; H, 5.84; N, 4.34.

2-(Benzylphenylamino)but-2-enedioic acid dimethyl ester (1.65 g; 5.40 mmol) was dissolved in P2O5/CH3SO3H (Eaton’s reagent, 5.72 mL) and the solution was heated at 50-55 °C for 4 h under N2. After cooling to 0-5 °C, it was dropped into a saturated cold solution of Na2CO3 (40 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the collected organic layers were dried, filtered and evaporated to obtain a crude product that was recrystallized from Et2O. 1-Benzyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester (23) was obtained as a yellow solid (1.30 g, 82%); mp = 133 °C; Rf : 0.22 (CH2Cl2/MethOH 195:5); 1H-NMR (300 MHz, CDCl3) δ: 8.45 (1H, d, J = 7.3 Hz), 7.58 (1H, dd, J = 7.3, 8.2 Hz), 7.47-7.28 (5H, m), 7.15 (2H, d, J = 7.3 Hz), 7.07 (1H, d, J = 7.3 Hz), 5.54 (2H, s), 3.90 (3H, s); 13C-NMR (75 MHz, CDCl3) δ: 177.7, 163.7, 143.5, 141.0, 135.5, 132.7, 128.6, 127.4, 127.0, 126.3, 125.4, 123.9, 116.7, 112.5, 53.1, 52.3. Anal.Calcd for C18H15NO3: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.56; H, 5.12; N, 4.81.

The above compound (1.30 g, 4.00 mmol) was suspended in MeOH (13.2 mL). After addition of 1N NaOH (13.2 mL) the mixture was refluxed heated at reflux for 1h. Methanol was evaporated and the solution was cooled with an ice-bath. 2N HCl was added to pH 1-2 and the precipitate was filtered to obtain 1.19 g of the title compound as a white solid (1.12 g, 100%); mp = 201 °C; Rf :
0.26 (RP-18 MeOH/H₂O 30:70); ¹H-NMR (300 MHz, DMSO-d₆) δ: 8.18 (1H, d, J = 7.9 Hz), 7.71-7.56 (2H, m), 7.43-7.12 (6H, m), 6.43 (1H, s); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 176.4, 164.9, 147.1, 140.5, 136.6, 133.0, 128.7 (×2), 127.4, 126.8, 126.2, 125.6 (×2), 124.1, 118.1, 109.7, 51.8.

Anal. Calcd for C₁₇H₁₃NO₃: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.28; H, 4.63; N, 5.07.

4.4. General procedure A: synthesis of amides 6, 7, 10, 12, 14, 20.

To a suspension of the appropriate quinolonecarboxylic acid (1 mmol) in 6 mL of dry THF at 25 °C, HOBt (1.5 mmol), WSC (1.5 mmol) and the appropriate aminoalcohol (1.5 mmol) were added sequentially. The mixture was stirred at room temperature under nitrogen, then the solvent was evaporated, water was added and the solid formed filtered. The crude product was purified by flash chromatography.

4.4.1.1-Methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (2-hydroxyethyl)amide (6a). Synthesized from 5a (80 mg, 0.39 mmol) and 2-aminoethanol. Stirred overnight at room temperature. Purified by flash chromatography (CH₂Cl₂/MeOH 75:25). White solid (83 mg, 85%); mp = 62 °C; Rf: 0.29 (CH₂Cl₂/MeOH 90:10); ¹H-NMR (300 MHz, MeOD) δ: 8.28 (1H, d, J = 7.9 Hz), 7.84-7.75 (2H, m), 7.47 (1H, m), 6.35 (1H, s), 3.83 (3H, s), 3.73 (2H, t, J = 5.8 Hz), 3.52 (2H, t, J = 5.8 Hz); ¹³C-NMR (75 MHz, MeOD) δ: 176.7, 162.8, 148.3, 139.4, 131.3, 124.1, 123.4, 122.4, 114.7, 105.9, 57.8, 40.0, 34.3. Anal. Calcd for C₁₃H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.50; H, 5.77; N, 11.34.

4.4.2. 4-Oxo-1,4-dihydroquinoline-2-carboxylic acid (2-hydroxyethyl)amide (6b). Synthesized from kynurenic acid (200 mg, 1.04 mmol) and aminoethanol. Stirred overnight at room temperature. Purified by flash chromatography (CH₂Cl₂/MeOH 90:10). White solid (193 mg, 80%); mp = 252 °C; Rf: 0.26 (CH₂Cl₂/MeOH 90:10); ¹H-NMR (300 MHz, DMSO-d₆ + TFA) δ: 9.03 (1H, t, J = 6.1 Hz), 8.10 (1H, d, J = 8.2 Hz), 7.99 (1H, d, J = 8.2 Hz), 7.72 (1H, dd, J = 8.2, 8.2 Hz), 7.41 (1H, dd, J = 8.2, 8.2 Hz), 6.92 (1H, s), 3.55 (2H, t, J = 6.1 Hz), 3.38 (2H, q, J = 6.1 Hz); ¹³C-NMR (75 MHz, DMSO-d₆ + TFA) δ: 175.1, 162.1, 143.3, 140.8, 132.3, 124.4, 124.2, 120.8, 105.9, 59.3, 42.4. Anal. Calcd for C₁₂H₁₂N₂O₃: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.21; H, 5.27; N, 12.03.

4.4.3.1-Methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (2,2-diethoxyethyl)amide (7a). Synthesized from 5a (250 mg, 1.23 mmol) and aminoacetaldehyde diethylacetal. Stirred 3 h at room temperature. Purified by crystallization from diethyl ether. White solid (346 mg, 88%); mp = 136 °C; Rf: 0.66 (CH₂Cl₂/MeOH 90:10); ¹H-NMR (300 MHz, DMSO-d₆) δ: 9.09 (1H, t, J = 5.2 Hz),
8.18 (1H, d, J = 8.5 Hz), 7.85-7.76 (2H, m), 7.45 (1H, m), 6.03 (1H, s), 4.67 (1H, t, J = 5.2 Hz), 3.72 (3H, s), 3.69-3.30 (6H, m), 1.15 (6H, t, J = 7.0 Hz); $^1$C-NMR (75 MHz, DMSO-$d_6$) δ: 176.2, 163.6, 149.6, 141.0, 132.8, 126.3, 125.4, 123.8, 117.2, 107.9, 99.6, 61.4, 41.5, 36.5, 15.3.

Analyzed Calcd for C$_{17}$H$_{22}$N$_2$O$_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 63.89; H, 6.95; N, 8.78.

4.4.4. 4-Oxo-1,4-dihydroquinoline-2-carboxylic acid (2,2-diethoxyethyl)amide (7b). Synthesized from kynurenic acid (260 mg, 1.35 mmol) and aminoacetaldehyde diethylacetal. Stirred 3 h at room temperature. White solid (343 mg, 83%); mp = 226 $^\circ$C; R$_f$: 0.57 (CH$_2$Cl$_2$/MeOH 90:10); $^1$H-NMR (300 MHz, DMSO-$d_6$ + TFA) δ: 9.11 (1H, t, J = 5.5 Hz), 8.10 (1H, d, J = 8.2 Hz), 7.98 (1H, d, J = 8.2 Hz), 7.72 (1H, dd, J = 8.2 Hz, J = 8.2 Hz), 7.41 (1H, dd, J = 8.2 Hz, J = 8.2 Hz), 6.91 (1H, s), 4.65 (1H, t, J = 5.5 Hz), 3.65 (2H, m), 3.50 (2H, m), 3.40 (2H, t, J = 5.5 Hz), 1.15 (6H, t, J = 7.0 Hz); $^1$C-NMR (75 MHz, DMSO-$d_6$ + TFA) δ: 174.8, 162.3, 143.2, 141.0, 132.3, 124.5, 124.4, 124.1, 121.0, 105.9, 99.8, 61.3, 42.3, 15.3. Analyzed Calcd for C$_{16}$H$_{20}$N$_2$O$_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.34; H, 6.59; N, 9.23.

4.4.5. 1-Methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-hydroxybutyl)amide (10a). Synthesized from 5a (300 mg, 1.48 mmol) and 4-aminobutanol. Refluxed at reflux for 2 h. Purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 95:5). White solid (349 mg, 86%); mp = 138 $^\circ$C; R$_f$: 0.44 (CH$_2$Cl$_2$/MeOH 80:20); $^1$H-NMR (300 MHz, DMSO-$d_6$) δ: 9.02 (1H, t, J = 5.5 Hz), 8.18 (1H, d, J = 7.9 Hz), 7.83-7.75 (2H, m), 7.44 (1H, m), 6.06 (1H, s), 4.47 (1H, t, J = 5.5 Hz), 3.70 (3H, s), 3.49-3.39 (2H, m, 2H), 3.32-3.29 (2H, m, 2H), 1.63-1.44 (4H, m, 4H, m); $^1$C-NMR (75 MHz, DMSO-$d_6$) δ: 176.3, 163.3, 149.8, 141.1, 132.8, 126.4, 125.4, 123.8, 117.2, 108.0, 60.4, 1C overlapped to the solvent signal, 36.5, 29.9, 25.4. Analyzed Calcd for C$_{15}$H$_{20}$N$_2$O$_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.44; H, 6.63; N, 10.23.

4.4.6. 1-Benzyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-hydroxy-butyl)-amide (10b). Synthesized from 5c (600 mg, 2.15 mmol) and 4-aminobutanol. Stirred overnight at room temperature. Purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 95:5). White solid (457 mg, 61%); mp = 175 $^\circ$C; R$_f$: 0.47 (CH$_2$Cl$_2$/MeOH 16:4); $^1$H-NMR (300 MHz, DMSO-$d_6$) δ: 9.15 (1H, t, J = 5.8 Hz), 8.18 (1H, d, J = 7.9 Hz), 7.55-7.70 (2H, m), 7.41-7.17 (6H, m), 6.18 (1H, s), 5.52 (2H, s), 4.40 (1H, t, J = 5.2 Hz), 3.40-3.28 (2H, m), 3.26-3.14 (2H, m), 1.54-1.30 (4H, m); $^1$C-NMR (75 MHz, DMSO-$d_6$) δ: 176.4, 163.4, 150.0, 140.3, 136.5, 132.7, 128.6 (×2), 127.4, 126.7 (×2), 126.4, 125.6, 123.9, 118.0, 108.7, 60.3, 51.1, 29.8, 25.3. Analyzed Calcd for C$_{21}$H$_{22}$N$_2$O$_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.13; H, 6.30; N, 8.01.
4.4.7. 4-Oxo-1,4-dihydroquinoline-2-carboxylic acid (4-hydroxybutyl)amide (12a).

Synthesized from kynurenic acid 5b (300 mg, 1.55 mmol) and 4-aminobutanol. Stirred overnight at room temperature. Purified by flash chromatography (CH$_2$Cl$_2$/MeOH 90:10). White solid (326 mg, 81%); mp = 225-227 °C; R$_f$: 0.58 (CH$_2$Cl$_2$/MeOH 90:10); $^1$H-NMR (300 MHz, DMSO-$_d_6$ + TFA) δ: 9.14 (1H, t, J = 6.1 Hz), 8.14 (1H, d, J = 8.5 Hz), 8.04 (1H, d, J = 8.5 Hz), 7.77 (1H, dd, J = 8.5, 8.5 Hz), 7.47 (1H, dd, J = 8.5, 8.5 Hz), 6.96 (1H, s), 3.45 (2H, t, J = 6.4 Hz), 3.33 (2H, m), 1.58 (2H, m), 1.49 (2H, m); $^{13}$C-NMR (75 MHz, DMSO-$_d_6$ + TFA) δ: 174.9, 161.3, 143.7, 140.3, 132.9, 125.0, 124.1, 123.9, 120.6, 105.6, 60.4, 29.9, 25.5. Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.53; H, 6.23; N, 10.74.

4.4.8. 4-Oxo-1,4-dihydroquinoline-2-carboxylic acid (5-hydroxypentyl)amide (12b).

Synthesized from kynurenic acid 5b (500 mg, 2.59 mmol) and 5-aminopentanol. Stirred overnight at room temperature. Purified by flash chromatography (CH$_2$Cl$_2$/MeOH 75:25). Yellow solid (670 mg, 94%); mp = 233 °C; R$_f$: 0.40 (CH$_2$Cl$_2$/MeOH 90:10); $^1$H-NMR (300 MHz, DMSO-$_d_6$) δ: 11.83 (1H, s), 9.02 (1H, s), 8.07 (1H, m), 7.96 (1H, m), 7.71 (1H, m), 6.71 (1H, s), 4.39 (1H, s), 3.46-3.26 (4H, m, overlapped to H$_2$O signal), 1.65-1.25 (6H, m); $^{13}$C-NMR (75 MHz, DMSO-$_d_6$ + TFA) δ: 175.4, 161.6, 143.4, 140.5, 132.6, 124.6, 124.3, 124.2, 120.5, 105.9, 60.6, (1 signal overlapped to the solvent signal), 32.2, 28.6, 23.0. Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.44; H, 6.63; N, 10.19.

4.4.9. 4-Oxo-1,4-dihydroquinoline-2-carboxylic acid [2-(2-hydroxyethyl)phenyl]amide (14).

Synthesized from kynurenic acid 5b (500 mg, 2.59 mmol) and 2-aminophenyl alcohol. Stirred overnight at room temperature. Purified by flash chromatography (CH$_2$Cl$_2$/MeOH 75:25), then crystallized from MeOH. White solid (462 mg, 58%); mp = 248 °C; R$_f$: 0.25 (CH$_2$Cl$_2$/MeOH 90:10); $^1$H-NMR (300 MHz, DMSO-$_d_6$ + TFA) δ: 8.16 (1H, d, J = 8.2 Hz), 8.05 (1H, d, J = 8.2 Hz), 7.76 (1H, m), 7.67 (1H, d, J = 7.9 Hz), 7.47 (1H, m), 7.37-7.16 (3H, m), 7.13 (1H, s), 3.70 (2H, t, J = 6.4 Hz), 2.83 (2H, t, J = 6.4 Hz); $^{13}$C-NMR (75 MHz, DMSO-$_d_6$ + TFA) δ: 173.9, 161.2, 144.7, 142.1, 135.8, 134.3, 132.1, 130.5, 126.7, 126.0, 125.0, 124.1, 123.9, 122.4, 105.4, 62.0, 34.8. Anal. Calcd for C$_{19}$H$_{18}$N$_2$O$_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.88; H, 5.60; N, 8.66.

4.4.10. 5,6,7-Trimethoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-hydroxybutyl)amide (20a).

Synthesized from 19a (220 mg, 0.79 mmol) and 4-aminobutanol. Refluxed at reflux 2 h, then overnight at rt. Purified by flash chromatography (CH$_2$Cl$_2$/MeOH 95:5). White solid (149 mg, 54%); mp = 77 °C; R$_f$: 0.2 (CH$_2$Cl$_2$/MeOH 95:5); $^1$H-NMR (300 MHz, DMSO-$_d_6$ + TFA) δ:
9.23 (1H, t, J = 6.1 Hz), 7.56 (1H, s), 7.15 (1H, s), 3.94 (3H, s), 3.86 (3H, s), 3.82 (3H, s), 3.43 (2H, t, J = 6.1 Hz), 3.33 (2H, q, J = 6.1 Hz); 13C-NMR (75 MHz, DMSO-d6 + TFA) δ: 171.2, 160.4, 158.4, 149.8, 143.6, 141.5, 139.8, 112.3, 104.6, 97.5, 62.1, 61.1, 60.3, 56.3, 1 signal overlapped to the solvent signal, 29.8, 25.4.

Anal.Calcd for C17H22N2O6: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.45; H, 6.30; N, 7.97.

4.4.11. 6-Bromo-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-hydroxybutyl)-amide (20b). Synthesized according to the general procedure A from 19b (497 mg, 1.83 mmol) and 4-aminobutanol. Heated at refluxed for 3 h.; White solid (460 mg, 74%); mp = 190 °C; Rf: 0.47 (CH2Cl2/MeOH 90:10); 1H-NMR (300 MHz, DMSO-d6 + TFA) δ: 9.02 (1H, t, J = 5.5 Hz), 8.16 (1H, d, J = 1.5 Hz), 7.96-7.80 (2H, m), 6.85 (1H, s), 3.42 (2H, t, J = 5.5 Hz), 3.31 (2H, q, J = 5.5 Hz), 1.65-1.40 (4H, m); 13C-NMR (75 MHz, DMSO-d6 + TFA) δ: 174.7, 161.7, 143.2, 139.6, 134.9, 126.6, 126.3, 123.1, 116.9, 106.6, 60.4, 1 signal overlapped to the solvent signal, 29.9, 25.5. Anal.Calcd for C14H15BrN2O3: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.74; H, 4.44; N, 8.29.

4.5. 10-Methyl-2,10-dihydrobenzo[b][1,7]naphthyridine-1,5-dione (8). Trifluoroacetic acid (297 μL, 1.26 mmol) was added to a suspension of 7a (200 mg, 0.63 mmol) in 12 mL of CH3CN and the mixture was heated at refluxed for 18 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. NaHCO3 solution and dried over Na2SO4. Purification by flash column chromatography (CH2Cl2/MeOH 95:5). Yellow solid (107 mg, 75%); mp = 237 °C; Rf: 0.30 (CH2Cl2/MeOH 95:5); 1H-NMR (300 MHz, MeOD) δ: 8.35 (1H, d, J = 9.1 Hz), 7.95-7.79 (3H, m), 7.41 (1H, t, J = 6.4 Hz), 7.18-7.04 (2H, m), 4.36 (3H, s); 13C-NMR (150 MHz, MeOD) δ: 178.5, 161.2, 145.5, 136.7, 135.6, 128.2, 127.3, 126.8, 124.8, 124.5, 118.3, 102.7, 38.8. Anal.Calcd for C13H10N2O2: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.30; H, 4.49; N, 12.36.

4.6. 3H-Pyrazino[1,2-a]quinoline-4,6-dione (9). Trifluoroacetic acid (600 μL) was added to a suspension of 7b (400 mg, 1.31 mmol) in 24 mL of CH3CN and the mixture was heated at refluxed for 14 h. The resulting solution was allowed to cool to room temperature and the solid formed was filtered, washed with cold ether and dried to give the desired product. Yellow solid (217 mg, 78%); mp = 254-255 °C; Rf: 0.43 (CH2Cl2/MeOH 90:10); 1H-NMR (300 MHz, DMSO-d6) δ: 11.64 (1H, brs), 8.43 (1H, d, J = 8.8 Hz), 8.32 (1H, d, J = 7.9 Hz), 7.99-7.87 (2H, m), 7.65 (1H, m), 7.10 (1H, s), 6.90 (1H, t, J = 5.5 Hz); 13C-NMR (75 MHz, DMSO-d6) δ: 173.8, 156.1, 139.9, 137.1, 133.4, 126.6, 126.4, 125.5, 117.3, 114.6, 106.4, 106.2. Anal.Calcd for C12H8N2O2: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.64; H, 3.83; N, 13.18.
4.7. General procedure B: oxidation of compounds 10, 14, 20 with IBX in EtOAc followed by TFA-catalyzed cyclization to give compounds 11, 15, 21

To a suspension of the appropriate alcohol (1 mmol) in EtOAc (30 mL), IBX (3 mmol) was added. The mixture was heated at reflux for 1-10 h. IBX in excess was filtered through a medium glass frit and the filter cake was washed with hot EtOAc (2 × 30 ml). The combined filtrates were concentrated to give a crude product that was used without further purification.

Trifluoroacetic acid (470 μL) was added to a suspension of the carbonyl compound (1 mmol) in 19 mL of CH₃CN and the mixture was heated at reflux for 1-18 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. NaHCO₃ solution and dried over Na₂SO₄. Evaporation of the extract gave a crude product that was purified by flash column chromatography.

4.7.1. 2-(2,3-Dihydropyrrole-1-carbonyl)-1-methyl-1H-quinolin-4-one (11a). Compound 10a (342 mg, 1.25 mmol) was heated at reflux for 1 h with IBX to give 1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4oxobutyl)amide; Rf: 0.24 (CH₂Cl₂/MeOH 185:15).

The above aldehyde was heated at reflux for 2 h with TFA. Purification by flash column chromatography (CH₂Cl₂/MeOH 195:5-190:10) afforded the title compound. White solid (113 mg, 75%); mp = 118 °C; Rf : 0.36 (CH₂Cl₂/MeOH 185:15); ¹H-NMR (300 MHz, DMSO-d₆). 2 rotamers (ratio 1:0.2) First rotamer δ: 8.19 (1H, d, J = 7.9 Hz), 7.83-7.73 (2H, m), 7.45 (1H, m), 6.54 (1H, m), 6.02 (1H, s), 5.39 (1H, m), 3.96 (2H, t, J = 8.8 Hz), 3.65 (3H, s), 2.69 (2H, m). Second rotamer δ: 8.19 (1H, d, J = 7.9 Hz), 7.83-7.73 (2H, m), 7.45 (1H, m), 6.99 (1H, m), 6.16 (1H, s), 5.61 (1H, m), 3.77 (2H, t, J = 8.8 Hz), 3.70 (3H, s), 2.69 (2H, m); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 176.1, 159.0, 148.3, 141.1, 132.7, 129.1, 127.7, 126.5, 126.4, 125.4, 123.9, 117.3, 115.7, 115.2, 114.5, 107.6, 106.8, 44.6, 44.8, 37.1, 36.4, 29.5, 28.1; GC-MS (EI) m/z (%) 254 (30), 168 (78), 89 (100). Anal.Calcd for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.99; H, 5.57; N, 11.00.

4.7.2. 1-Benzyl-2-(2,3-dihydropyrrole-1-carbonyl)-1H-quinolin-4-one (11b). Compound 10b (447 mg, 1.27 mmol) was heated at reflux for 3 h with IBX to give 1-benzyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-oxobutyl)amide; light yellow solid; Rf : 0.24 (CH₂Cl₂/MeOH 185:15).

The above aldehyde was heated at reflux for 3.5 h with TFA. Purification by flash column chromatography (CH₂Cl₂/MeOH 195:5 - 192:8) afforded the title compound. White solid (88 mg, 21%); mp = 137-139 °C; Rf : 0.52 (CH₂Cl₂/MeOH 18:2); ¹H-NMR (300 MHz, DMSO-d₆) 2
rotamers (ratio 1:0.3) First rotamer: δ: 8.20 (1H, dd, J = 8.2, 1.8 Hz), 7.71-7.55 (2H, m), 7.44-7.15 (6H, m), 6.55 (1H, m), 6.13 (1H, s), 5.57-5.26 (3H, m), 3.82 (2H, m), 2.61 (2H, m); Second rotamer: δ: 8.20 (1H, dd, J = 8.2, 1.8 Hz), 7.71-7.55 (2H, m), 7.44-7.15 (6H, m), 6.91 (1H, m), 6.28 (1H, s), 5.57-5.26 (3H, m), 3.82 (2H, m), 2.61 (2H, m); 13C-NMR (75 MHz, DMSO-d6) δ: 176.2, 176.1, 158.8, 158.5, 148.5, 148.4, 140.5, 140.4, 136.2, 136.0, 132.8, 132.7, 132.6, 129.13, 129.1, 128.7, 127.7, 127.6, 127.5, 126.9, 126.4, 125.7, 125.6, 124.0, 123.9, 118.0, 116.1, 115.6, 114.4, 108.3, 108.2, 107.7, 51.5, 51.3, 46.8, 44.8, 29.5, 28.0; GC-MS (EI) m/z (%) 330 (10), 234 (35), 91 (100). Anal.Calcd for C21H18N2O2: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.12; H, 5.44; N, 8.45.

4.7.3. 1,10-Diazapentacyclo[10.8.0.02,10.04,9.015,20]icosa-4,6,8,12,15(20),16,18-heptaene-11,14-dione (15). Compound 14 (265 mg, 0.86 mmol) was heated at reflux for 7 h with IBX to give 4-oxo-1,4-dihydroquinoline-2-carboxylic acid 2-(2-oxoethyl)benzylamide; white solid; Rf: 0.46 (CH2Cl2/MeOH 19:1).

The above aldehyde was heated at reflux for 1 h with TFA to give the title compound. Purified by flash chromatography (CH2Cl2/MeOH 195:5). White solid (210 mg, 85%); mp = 257 °C; Rf: 0.25 (CH2Cl2/MeOH 19:1); 1H-NMR (300 MHz, MeOD) δ: 8.36 (1H, d, J = 7.9 Hz), 7.91 (1H, m), 7.75 (1H, d, J = 8.5 Hz), 7.67-7.52 (2H, m), 7.45-7.31 (2H, m), 7.25 (1H, m), 6.80 (1H, m), 6.72 (1H, s), 4.05 (1H, m), 3.48 (1H, m); 13C-NMR (75 MHz, DMSO) δ: 177.5, 161.3, 142.9, 137.8, 136.9, 133.7, 133.2, 128.1, 126.5, 126.3, 126.2, 126.18, 124.9, 116.3, 116.0, 103.9, 78.8, 34.7. Anal.Calcd for C18H12N2O2: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.75; H, 4.22; N, 9.76.

4.7.4. 2,3,4-Trimethoxy-8,9,10,10a-tetrahydro-7a,10b-diazapentaleno[1,2-a]naphthalene-5,7-dione (21a). Compound 20a (107 mg, 0.31 mmol) was heated at reflux for 6 h with IBX to give 5,6,7-trimethoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (3-oxopropyl)amide as a yellow solid; Rf: 0.16 (CH2Cl2/MeOH 195:5).

The above aldehyde was heated at reflux for 2 h with TFA. Purified by flash chromatography (CH2Cl2/MeOH 95:5). Yellow solid (64 mg, 68%); mp = 108 °C; Rf: 0.35 (DCM/MeOH 95:5); 1H-NMR (300 MHz, MeOD) δ: 6.85 (1H, s), 6.61 (1H, s), 6.12 (1H, m), 4.08 (3H, s), 3.93 (3H, s), 3.89 (3H, s), 3.84 (1H, m), 3.50 (1H, m), 2.88 (1H, m), 2.52-2.39 (2H, m), 1.70 (1H, m); 13C-NMR (75 MHz, MeOD) δ: 178.8, 164.6, 160.6, 154.4, 143.4, 142.6, 137.5, 115.8, 104.9, 94.6, 80.1, 62.8, 61.9, 57.3, 42.9, 30.8, 26.9. Anal.Calcd for C17H18N2O5: C, 61.81; H, 5.49; N, 8.48. Found: C, 62.04; H, 5.47; N, 8.46.

4.7.5. 3-Bromo-8,9,10,10a-tetrahydro-7a,10b-diazapentaleno[1,2-a]naphthalene-5,7-dione (21b).
Compound 20b (453 mg, 1.33 mmol) was heated at reflux for 9 h with IBX to give 6-bromo-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-oxobutyl)amide as a yellow solid; Rf: 0.46 (CH₂Cl₂/MeOH 19:1).

The above aldehyde was heated at reflux for 1 h with TFA. Purified by flash chromatography (CH₂Cl₂/MeOH 95:5). White solid (292 mg, 69%); mp = 263 °C; Rf: 0.32 (DCM/MeOH 195:5); ¹H-NMR (600 MHz, DMSO-d₆) δ: 8.27 (1H, d, J = 2.3 Hz), 7.98 (1H, dd, J = 2.3, 8.9 Hz), 7.72 (1H, d, J = 8.9 Hz), 6.37 (1H, s), 6.09-6.02 (1H, m), 3.73-3.63 (1H, m), 2.79-2.68 (1H, m), 2.36-2.19 (2H, m), 1.73 -1.60 (1H, m); ¹³C-NMR (150 MHz, DMSO-d₆) δ: 175.5, 162.6, 142.7, 135.4, 135.1, 127.7, 127.1, 118.4, 117.0, 102.7, 77.1, 41.1, 28.7, 25.0. Anal. Calcd for C₁₄H₁₁BrN₂O₂: C, 52.69; H, 3.47; N, 8.78. Found: C, 52.55; H, 3.45; N, 8.76.

4.7.5. 8,9,10,10a-Tetrahydro-7a,10b-diaza-pentaleno[1,2-a]naphthalene-5,7-dione (13a). To a solution of IBX (135 mg, 0.50 mmol) in DMSO (0.68 mL) compound 12a (65 mg, 0.25 mmol) was added and the mixture was stirred overnight at rt under nitrogen. The mixture was diluted with sat. aq. NaHCO₃ (2 mL). The solid formed was filtered and dried to give 4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-oxobutyl)amide as a white solid; Rf: 0.43 (CH₂Cl₂/MeOH 90:10). The compound was used without further purification.

Trifluoroacetic acid (177 μL) was added to a suspension of the above aldehyde (100 mg, 0.39 mmol) in 7 mL of CH₃CN and the mixture was heated at reflux for 3 h. The solvent was evaporated, the residue was dissolved in EtOAc, was hed with sat. aq. NaHCO₃ solution and dried over Na₂SO₄. Evaporation of the extract gave a crude product that was purified by crystallization from Et₂O to give the title compound as a white solid (33.8 mg, 64%). mp = 172 °C; Rf: 0.56 (CH₂Cl₂/MeOH 90:10); ¹H-NMR (300 MHz, DMSO-d₆) δ: 8.20 (1H, d, J = 8.2 Hz), 7.83 (1H, dd, J = 8.2 Hz), 7.72 (1H, d, J = 8.2 Hz), 7.49 (1H, dd, J = 8.2 Hz), 6.33 (1H, s), 6.15-6.00 (1H, m), 3.76-3.60 (1H, m), 3.39-3.33 (1H, m), 2.89-2.70 (1H, m), 2.37-2.21 (2H, m), 1.78-1.5866 (1H, m); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 177.7, 163.8, 143.2, 137.4, 133.4, 126.7, 126.5, 125.0, 116.6, 103.3, 77.9, 42.0, 29.9, 26.0; GC-MS (EI) m/z (%) 240 (52), 143 (100), 88 (28). Anal. Calcd for C₁₄H₁₂N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.11; H, 5.06; N, 11.62.

4.7.6. 9,10,11,11a-Tetrahydro-8H-7a,11b-diaza-benzo[c]fluorene-5,7-dione (13b). To a solution of IBX (394 mg, 1.46 mmol) in DMSO (2 mL) compound 12b (200 mg, 0.73 mmol) was added and the mixture was stirred overnight at rt under nitrogen. The mixture was diluted with sat. aq.
NaHCO₃ (2 mL). The solid formed was filtered and dried to give 4-oxo-1,4-dihydroquinoline-2-carboxylic acid (5-oxopentyl)amide as a white solid; mp = 190°C.

Trifluoroacetic acid (175 μL) was added to a suspension of the above aldehyde (100 mg, 0.37 mmol) in 7 mL of CH₃CN and the mixture was heated at reflux for 1 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. NaHCO₃ solution and dried over Na₂SO₄. Evaporation of the extract gave a crude product that was purified by flash column chromatography. (CH₂Cl₂/MeOH 19:1). White solid (62 mg, 66%); mp = 181°C; Rf: 0.23 (CH₂Cl₂/MeOH 19:1); ¹H-NMR (300 MHz, MeOD) δ: 8.33 (1H, d, J = 7.3 Hz), 7.94-7.75 (2H, m), 7.65-7.50 (1H, m), 6.67 (1H, s), 5.92 (1H, dd, J = 7.6, 3.0 Hz), 4.58-4.42 (1H, m), 3.30-3.26 (1H, m), 3.05-2.95-2.80 (1H, m), 2.18-2.05 (m, 1H), 1.98-1.79 (2H, m), 1.65-1.53-1.42 (1H, m), 1.45-1.34-1.29 (1H, m); 13C-NMR (75 MHz, MeOD) δ: 177.6, 156.6, 139.9, 134.8, 131.2, 124.4, 123.0, 122.6, 113.8, 101.1, 71.1, 38.3, 31.0, 22.8, 19.5. Anal.Calcd for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.98; H, 5.52; N, 11.05.

4.7.7. 2-(3,4,5-Trimethoxyphenylamino)but-2-enedioic acid diethyl ester (17a). To a solution of 3,4,5-trimethoxyaniline (1.5 g, 8.02 mmol) in EtOH (27 mL), DEAD (diethylacetylene dicarboxylate) (8.03 mmol, 1.35 mL) was added dropwise and the reaction was heated at reflux for 3 h. The solvent was evaporated and the crude product was purified by flash chromatography (Hexane/EtOAc 80:20). Yellow solid (1.88 g, 66%); mp = 64-66°C; Rf : 0.32 (Hexane/EtOAc 80:20); ¹H-NMR (300 MHz, DMSO-d₆) δ: 9.59 (1H, s), 6.18 (2H, s), 5.33 (1H, s), 4.22-4.12 (4H, m), 3.81 (9H, s), 1.30 (3H, t, J = 7.3 Hz), 1.13 (3H, t, J = 7.3 Hz); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 169.5, 164.5, 153.5, 148.7, 136.5, 135.0, 98.9, 93.4, 62.0, 60.9, 59.9, 56.0, 14.3, 13.7. Anal.Calcd for C₁₇H₂₃NO₇: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.95; H, 6.51; N, 3.92.

4.7.8. 2-(4-Bromophenylamino)but-2-enedioic acid diethyl ester (17b). To a solution of 4-bromoaniline (1.5 g, 8.46 mmol) in EtOH (27 mL), DEAD (diethylacetylene dicarboxylate) (8.46 mmol, 1.47 mL) was added dropwise and the reaction was heated at reflux for 5 h. Purified by flash chromatography (Hexane/EtOAc 195:5). Yellow oil (1.87 g, 64%); Rf : 0.63 (Hexane/EtOAc 80:20); ¹H-NMR (300 MHz, CDCl₃) δ: 9.61 (1H, brs), 7.38 (2H, d, J = 8.8 Hz), 6.79 (2H, d, J = 8.8 Hz), 5.45 (1H, s), 4.25-4.13 (4H, m), 1.31 (3H, t, J = 7.0 Hz), 1.15 (3H, t, J = 7.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ: 169.0, 163.6, 147.2, 139.2, 131.6 (xx 2), 122.1 (xx 2), 116.6, 94.6, 61.8, 59.7, 13.9, 13.3. Anal.Calcd for C₁₄H₁₆BrNO₄: C, 49.14; H, 4.71; N, 4.09. Found: C, 49.37; H, 4.73; N, 4.11.
4.7.9. 5,6,7-Trimethoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid ethyl ester (18a). To a 7.7% solution of P₂O₅ in methanesulfonic acid (3 mL, Eaton Reagent), compound 17a (1g, 2.83 mmol) was added and the resulting mixture was heated at 55°C for 1 h. After cooling, the solution was dropped into a cold Na₂CO₃ saturated solution. The precipitate was filtered under vacuum, to obtain the title compound as a white solid. (870 mg, 100%); mp = 235°C; Rf : 0.34 (CH₂Cl₂/MeOH 19:1); ¹H-NMR (300 MHz, DMSO-d₆) δ: 7.17 (1H, s), 6.62 (1H, s), 4.32 (2H, q, J = 7.3 Hz), 3.86 (3H, s), 3.77 (3H, s), 3.75 (3H, s), 1.31 (3H, t, J = 7.3 Hz); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 173.9, 164.8, 155.3, 150.8, 144.3, 142.0, 139.0, 116.1, 109.5, 101.0, 61.8, 61.3, 60.9, 55.7, 14.1. Anal.Calcd for C₁₅H₁₇NO₆: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.97; H, 5.54; N, 4.53.

4.7.10. 6-Bromo-4-oxo-1,4-dihydroquinoline-2-carboxylic acid ethyl ester (18b). To a 7.7% solution of P₂O₅ in methanesulfonic acid (4 mL, Eaton Reagent), compound 17b (1.3 g, 3.79 mmol) was added and the resulting mixture was heated at 55°C for 1 h. After cooling, the solution was dropped into a cold Na₂CO₃ saturated solution. The precipitate was filtered under vacuum, to obtain the title compound as a white solid. (688 mg, 61%); mp = 255-260°C; Rf : 0.57 (CH₂Cl₂/MeOH 195:5); ¹H-NMR (300 MHz, DMSO-d₆) δ: 12.2 (1H, brs), 8.13 (1H, s), 7.94-7.79 (2H, m), 6.68 (1H, s), 4.40 (2H, q, J = 6.8 Hz), 1.34 (3H, t, J = 6.8 Hz); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 175.7, 162.1, 139.3, 138.8, 135.2, 127.1, 126.7, 122.6, 117.0, 110.1, 62.7, 13.9. Anal.Calcd for C₁₂H₁₀BrNO₃: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.41; H, 3.38; N, 4.70.

4.7.11. 5,6,7-Trimethoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (19a). To a suspension of 18a (400 mg, 1.30 mmol) in EtOH (4.29 mL), 1N NaOH (4.29 mL) was added. The resulting mixture was refluxed for 1 h, then EtOH was evaporated. After cooling with an ice-bath, 1N HCl was added and the white solid formed was filtered, to obtain the product as a white solid. (233 mg, 64%); mp = 234°C; Rf : 0.7 (MeOH/H₂O 40:60); ¹H-NMR (300 MHz, DMSO-d₆) δ: 7.39 (1H, s), 6.49 (1H, s), 3.90 (3H, s), 3.69 (6H, s); ¹³C-NMR (75 MHz, DMSO-d₆) δ: 175.7, 163.7, 156.7, 151.5, 139.5, 139.2, 137.7, 115.1, 110.7, 97.0, 61.8, 61.0, 55.8. Anal.Calcd for C₁₃H₁₃NO₆: C, 55.91; H, 4.69; N, 5.02. Found: C, 55.79; H, 4.63; N, 5.06.

4.7.12. 6-Bromo-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (19b). To a suspension of 18b (628 mg, 2.12 mmol) in EtOH (7.0 mL), 1N NaOH (7.0 mL) was added. The resulting mixture was refluxed for 1.5 h, then EtOH was evaporated. After cooling with an ice-bath, 1N
HCl was added and the white solid formed was filtered and dried (525 mg, 92%); mp >300 °C; Rf: 0.76 (RP-18 MeOH/H2O 15:85); 1H-NMR (300 MHz, DMSO-d6) δ: 12.2 (1H, brs), 8.15 (1H, d, J = 2.1 Hz), 7.91 (1H, dd, J = 8.8 Hz), 7.85 (1H, dd, J = 2.1 Hz, 8.8 Hz); 13C-NMR (75 MHz, DMSO-d6) δ: 176.3, 163.5, 139.5, 139.0, 135.3, 127.1, 126.8, 122.3, 116.8, 110.2. Anal. Calcd for C10H6BrNO3: C, 44.81; H, 2.26; N, 5.23. Found: C, 44.66; H, 2.23; N, 5.26.

4.7.13. 3-Pyridin-4-yl-8,9,10,10a-tetrahydro-7a,10b-diazapentaleno[1,2-a]naphthalene-5,7-dione (21c). To a degassed 3.5:1 mixture of dimethoxyethane and water (0.62 mL), compound 21b (50 mg, 0.16 mmol), the appropriate boronic acid (38.15-2 mg, 0.31 mmol), PdCl2(dppe)_CH2Cl2 (5.73 mg 0.0078 mmol) and NaHCO3 (39.50 mg, 0.47 mmol) were added under nitrogen. The mixture was heated at reflux for 9 h. Water was added (5 mL) and after extraction with EtOAc (2 x 10 mL), the collected organic layers were dried and the solvent evaporated. Purification by flash chromatography (CH2Cl2/MeOH 90:10) gave the desired compound. Yellow solid (24 mg, 47%); mp = 240 °C; Rf: 0.44. (DCM/MeOH 90:10); 1H-NMR (300 MHz, DMSO-d6) δ: 8.68 (2H, m), 8.55 (1H, s), 8.27 (1H, d, J = 9.2 Hz), 7.92-7.78 (3H, m), 6.40 (1H, s), 6.12 (1H, m), 3.70 (1H, m), 2.80 (1H, m), 2.40-2.18 (2H, m), 1.71 (1H, m); 13C-NMR (150 MHz, DMSO-d6) δ: 177.2, 163.2, 150.4 (× 2), 145.7, 143.0, 137.4, 133.3, 131.4, 126.5, 124.1, 121.2 (× 2), 117.4, 103.3, 77.6, 41.7, 29.4, 25.6. Anal. Calcd for C19H15N3O2: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.96; H, 4.77; N, 13.22.

4.7.14. 3-(4-Hydroxyphenyl)-8,9,10,10a-tetrahydro-7a,10b-diazapentaleno[1,2-a]naphthalene-5,7-dione (21d). To a degassed 3.5:1 mixture of dimethoxyethane and water (0.62 mL), compound 21b (50 mg, 0.16 mmol), 4-hydroxyphenylboronic acid (43 mg, 0.31 mmol), PdCl2(dppe)_CH2Cl2 (5.7 mg 0.0078 mmol) and NaHCO3 (40 mg, 0.47 mmol) were added under nitrogen. The mixture was heated at reflux for 2 h. Water was added (5 mL) and after extraction with EtOAc (2 x 10 mL), the collected organic layers were dried and the solvent evaporated. Purification by flash chromatography (CH2Cl2/MeOH 19:1) gave the desired compound. Yellow sticky solid (25 mg, 49%); Rf: 0.62 (CH2Cl2/MeOH 18:2); 1H-NMR (300 MHz, DMSO-d6) δ: 9.66 (1H, s), 8.33 (1H, d, J = 1.8 Hz), 8.07 (1H, dd, J = 1.8, 8.5 Hz), 7.76 (1H, d, J = 8.5 Hz), 7.65-7.55 (2H, m), 6.94-6.83 (2H, m), 6.34 (1H, s), 6.40-15.6-05 (1H, m), 3.78-3.65-60 (1H, m), 3.54-3.42-40 (1H, m), 2.78-85-2.70 (1H, m), 2.38-2.21 (2H, m), 1.69 (1H, m); 13C-NMR (150 MHz, DMSO-d6) δ: 174.6, 165.4, 159.4, 144.4, 138.5, 137.5, 132.9, 131.4, 129.8, 128.5, 124.1, 118.8, 117.9, 104.5, 79.4, 43.5, 30.9, 24.3. Anal. Calcd for C20H16N2O3: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.55; H, 4.87; N, 8.40.
Acknowledgments

We are grateful to Dr. Franco Zunino for cytotoxic activity evaluation.

Supplementary data

$^1$H NMR and $^{13}$C spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at

References and notes


16. Human non-small cell lung cancer NCI-H460 cells were cultured in RPMI 1640 containing 10% fetal calf serum. Cytotoxicity was assessed by growth inhibition assay after 1 h drug exposure. Cells in the logarithmic phase of growth were harvested and seeded in duplicates into 6-well plates. Twenty-four hours after seeding, cells were exposed to the drug, harvested 72 h, and counted with a Coulter counter. IC<sub>50</sub> is defined as the inhibitory drug concentration causing a 50% decrease of cell growth over that of untreated control.