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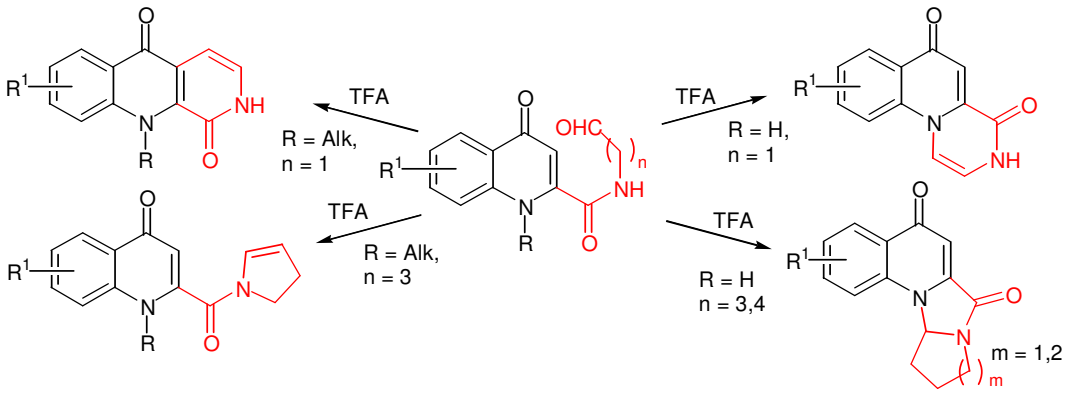

4-Quinolone fused heterocyclic ring systems by intramolecular reactions of 4-quinolone-2-carboxamides[§]

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[§]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.

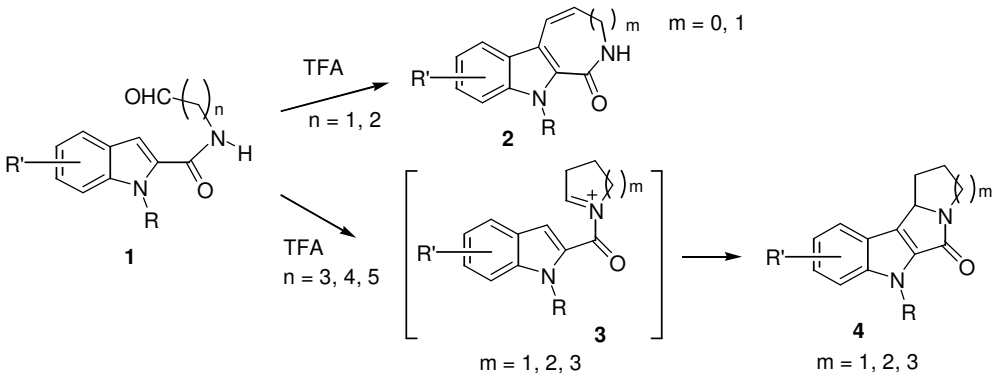
Keywords: nitrogen heterocycles, heteroannulation reaction, quinolone-2-carboxylic acid amides, quinolone-fused heterocycles, synthesis

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,[1] antimicrobial,[2] antiviral[3] and antimalarial[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 β- or γ-oxoamides (**1**) represented a simple synthesis of β-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 δ-, ε-, and ζ-oxoamides preferentially gave intermediate N-acyliminium ions, which cyclized into the novel heterocyclic rings pyrrolizino[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.

As the method could provide a route to novel heterocyclic systems, we thought to extend the study to the preparation of quinolone-fused rings.

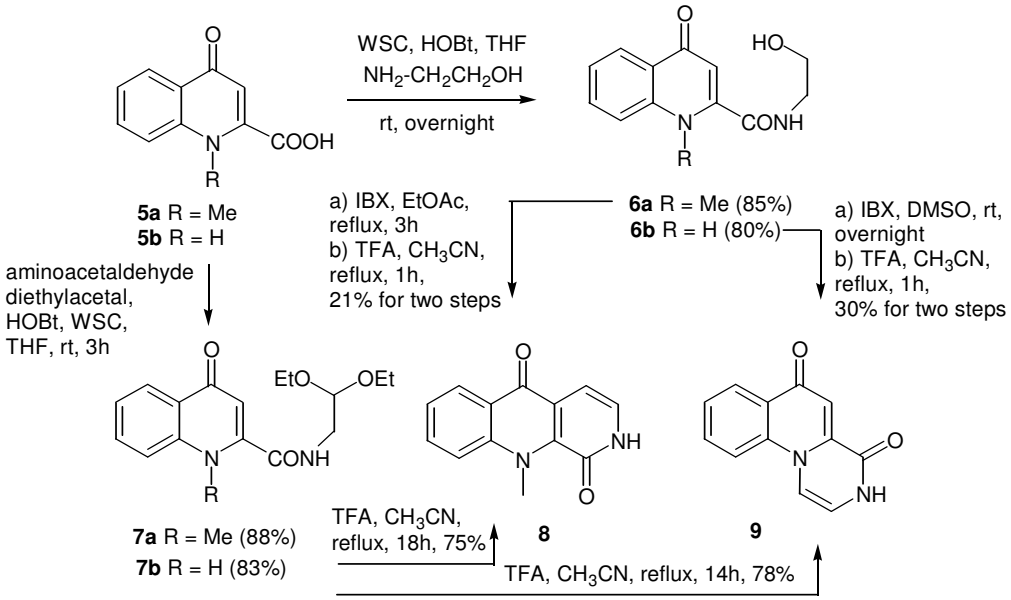
Although numerous efforts have been made to modify quinolones, there are currently few reports concerning electrophilic substitutions at C-3 of 4-quinolone rings, even though 4-quinolone is known to be in tautomeric equilibrium with its phenol form.[7] A survey of literature revealed few examples of 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, followed 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-dihydro-benzo[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]naphthyridine-6,12-diones by a Fischer type rearrangement reaction.[15] However, the versatility of this methodology was strongly limited by the need to use freshly prepared symmetric 1,2-diarylhydrazines.



Scheme 2. Synthesis of 10-methyl-2,10-dihydrobenzo[b][1,7]naphthyridine-1,5-dione and 3H-pyrazino[1,2-a]quinoline-4,6-dione

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

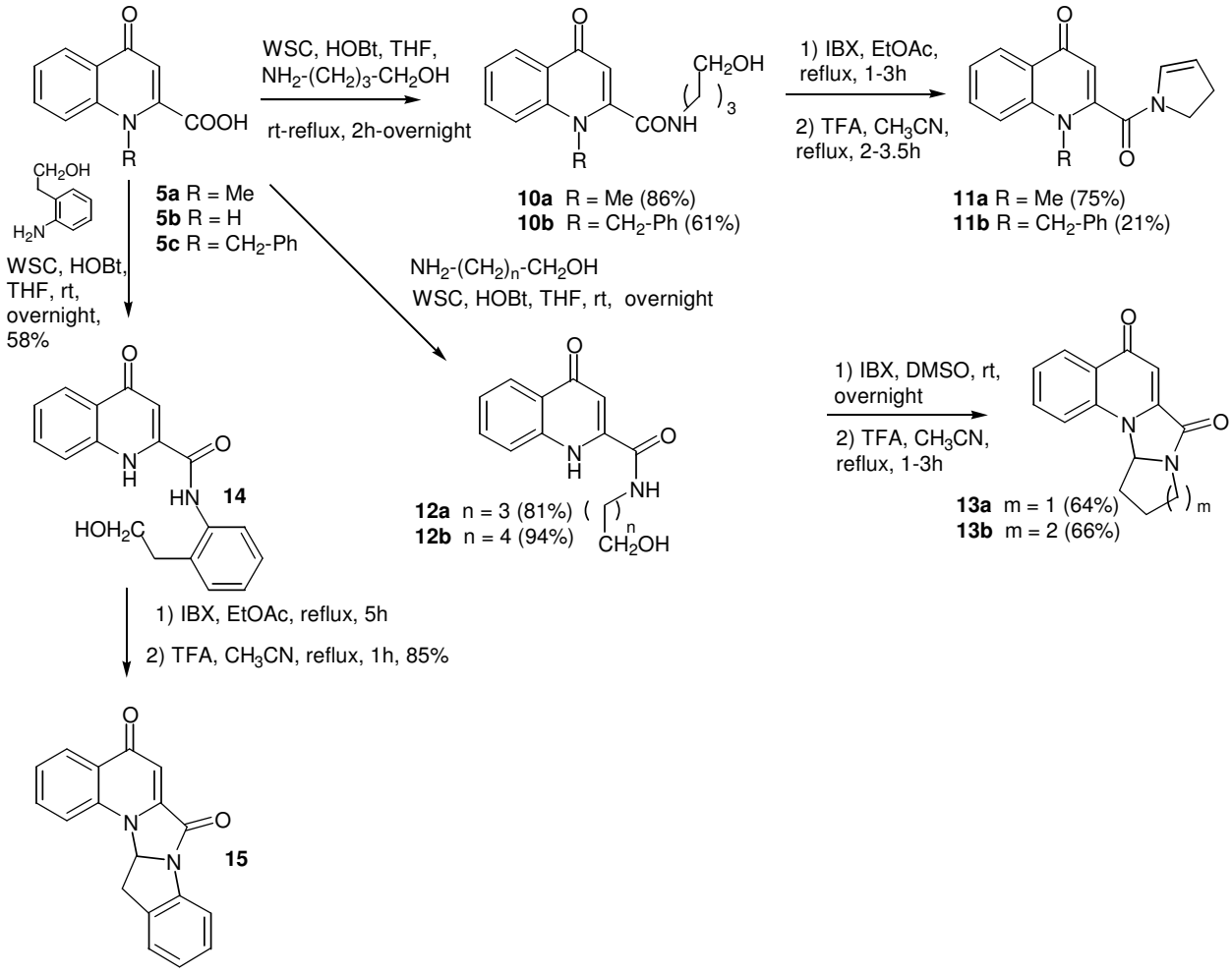
When the coupling reaction of N-methyl kynurenic acid **5a** was carried out with 4-aminobutanol, alcohol **10a** was obtained (Scheme 3). Oxidation of **10a**, followed by treatment with TFA, gave the enamide **11a**. The same result was obtained when the quinolone nitrogen was protected with a benzyl group (compound **11b**).

This confirmed that the carbonyl group underwent a nucleophilic attack by the amide nitrogen. However, unlike the case of indole,[6] 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.

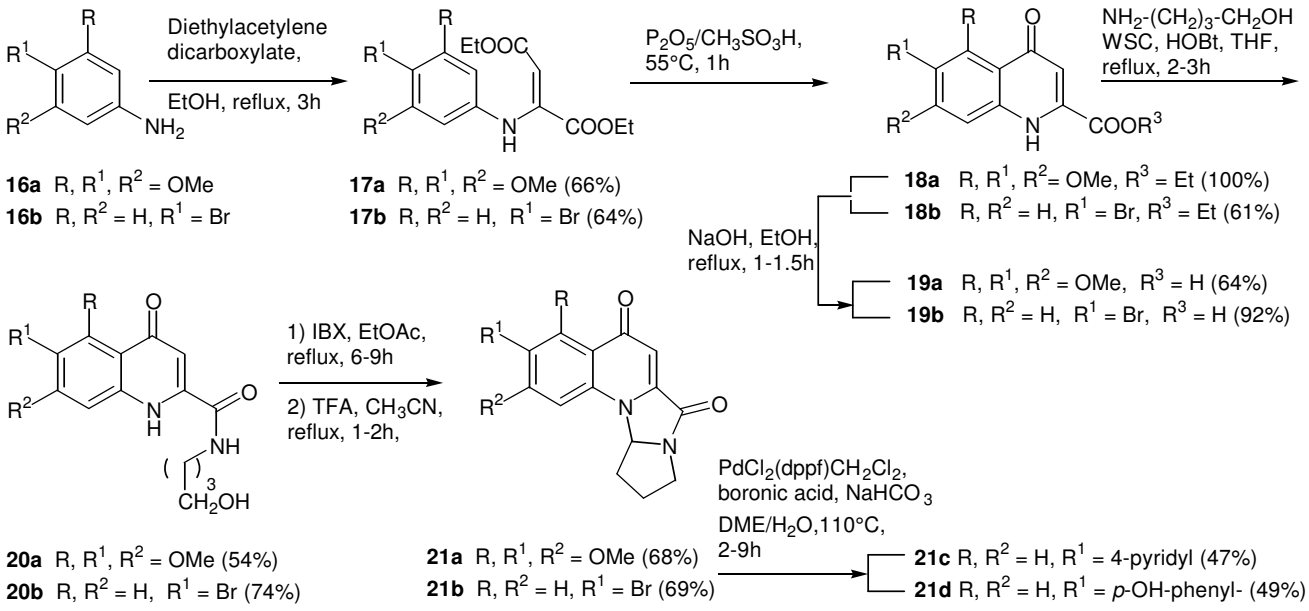
Interestingly, oxidation followed by acid treatment of compounds **12a-b**, obtained from kynurenic acid **5b**, gave the new compounds **13a-b** (Scheme 3). In this case, a tandem heteroannulation reaction - which is most likely due to a first nucleophilic attack of the amide nitrogen to the aldehyde,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

As compound **13a** showed antitumor activity (IC_{50} = 10 μM) on H460 tumor cell lines,[16] 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~~ in 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**.



Scheme 4. Synthesis of 8,9,10,10a-tetrahydro-7a,10b-diaza-pentaleno[1,2-a]naphthalene-5,7-diones

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 (Et_2O) 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 F_{254}, aluminum foil).
Compound **5b** was purchased from Sigma-Aldrich.

4.2. Methyl-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (5a)[13] To a solution of N-methylaniline (0.98 g, 9.15 mmol, 1.01 mL) in H_2O (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. (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); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40-7.08 (5H, m), 4.78 (1H, s), 3.66 (3H, s), 3.63 (3H, s), 3.20 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{15}NO_4$: 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 to ice-water, then with a solution of NH_4OH (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 (CH_2Cl_2/MeOH 195:5); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (1H, d, *J* = 8.1 Hz), 7.76 (1H, dd, *J* = 8.1 Hz, *J* =, 8.1 Hz), 7.57 (1H, d, *J* = 8.8 Hz), 7.44 (1H, dd, *J* = 8.1 Hz, *J* =, 8.8 Hz), 6.70 (1H, s), 3.86 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{11}NO_3$: 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; R_f = 0.41 (CH_2Cl_2/MeOH 19:1); ^{1}H-NMR (300 MHz, DMSO- d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 176.3, 165.7, 152.9, 140.9, 132.3, 126.2, 125.3, 125.2, 123.4, 117.1, 106.6. Anal.Calcd for $C_{11}H_9NO_3$: 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, ~~1.15 mL~~) 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; R_f : 0.10 (Hexane/EtOAc 90:10); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48-7.13 (10H, m), 4.80 (1H, s), 4.76 (2H, s), 3.72 (3H, s), 3.61 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{19}NO_4$: 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 P_2O_5/CH_3SO_3H (Eaton's reagent, 5.72 mL) and the solution was heated at 50-55 °C for 4 h under N_2. After cooling to 0-5 °C, it was dropped into a saturated cold solution of Na_2CO_3 (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 Et_2O. 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; R_f : 0.22 (CH_2Cl_2/MeOH 195:5); ^{1}H-NMR (300 MHz, $CDCl_3$) 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), 6.77 (1H, s), 5.54 (2H, s), 3.90 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{15}NO_3$: 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; R_f :

0.26 (RP-18 MeOH/H_2O 30:70); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{17}H_{13}NO_3$: 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 (CH_2Cl_2/MeOH 75:25). White solid (83 mg, 85%); mp = 62 °C; R_f: 0.29 (CH_2Cl_2/MeOH 90:10); ^{1}H-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); ^{13}C-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 $C_{13}H_{14}N_2O_3$: 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 (CH_2Cl_2/MeOH 90:10). White solid (193 mg, 80%); mp = 252 °C; R_f: 0.26 (CH_2Cl_2/MeOH 90:10); ^{1}H-NMR (300 MHz, DMSO-d_6 + 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); ^{13}C-NMR (75 MHz, DMSO-d_6 + 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 $C_{12}H_{12}N_2O_3$: 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; R_f = 0.66 (CH_2Cl_2/MeOH 90:10); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}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. Anal.Calcd for $C_{17}H_{22}N_2O_4$: 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 °C; R_f : 0.57 (CH_2Cl_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, 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); ^{13}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. Anal.Calcd for $C_{16}H_{20}N_2O_4$: 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~~ Heated at reflux for 2 h. Purified by flash column chromatography (CH_2Cl_2/MeOH 95:5). White solid (349 mg, 86%); mp = 138 °C; R_f : 0.44 (CH_2Cl_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 (~~m, 4~~H, m); ^{13}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. Anal.Calcd for $C_{15}H_{18}N_2O_3$: 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-dihydro-quinoline-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_2Cl_2/MeOH 95:5). White solid (457 mg, 61%); mp = 175 °C; R_f : 0.47 (CH_2Cl_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); ^{13}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. Anal.Calcd for $C_{21}H_{22}N_2O_3$: 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_2Cl_2/MeOH 90:10). White solid (326 mg, 81%); mp = 225-227 °C; R_f: 0.58 (CH_2Cl_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 $C_{14}H_{16}N_2O_3$: 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_2Cl_2/MeOH 75:25). Yellow solid (670 mg, 94%); mp = 233 °C; R_f: 0.40 (CH_2Cl_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), 7.36 (1H, m), 6.71 (1H, s), 4.39 (1H, s), 3.46-3.26 (4H, m, overlapped to H_2O 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 $C_{15}H_{18}N_2O_3$: 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_2Cl_2/MeOH 195:5), then crystallized from MeOH. White solid (462 mg, 58%); mp = 248 °C; R_f : 0.25 (CH_2Cl_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 $C_{19}H_{18}N_2O_3$: 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 Heated at reflux 2 h, then overnight at rt. Purified by flash chromatography (CH_2Cl_2/MeOH 95:5). White solid (149 mg, 54%); mp = 77 °C; R_f: 0.2 (CH_2Cl_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), 1.66-1.42 (4H, m); ^{13}C-NMR (75 MHz, DMSO-d_6 + 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 $C_{17}H_{22}N_2O_6$: 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 r~~R~~eflux~~ed~~ for 3 h.; White solid (460 mg, 74%); mp = 190 °C; R_f : 0.47 (CH_2Cl_2/MeOH 90:10); ^{1}H-NMR (300 MHz, DMSO-d_6 + 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); ^{13}C-NMR (75 MHz, DMSO-d_6 + 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 $C_{14}H_{15}BrN_2O_3$: 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 CH_3CN and the mixture was heated at reflux~~refluxed~~ for 18 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ solution and dried over Na_2SO_4. Purification by flash column chromatography (CH_2Cl_2/~~-~~MeOH 95:5). Yellow solid (107 mg, 75%); mp = 237 °~~-~~C; R_f : 0.30 (CH_2Cl_2/MeOH 95:5); ^{1}H-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); ^{13}C-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 $C_{13}H_{10}N_2O_2$: 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 CH_3CN and the mixture was heated at reflux~~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; R_f : 0.43 (CH_2Cl_2/MeOH 90:10); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{12}H_8N_2O_2$: 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~~refluxed~~ 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 CH_3CN and the mixture was heated at reflux~~refluxed~~ for 1-18 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ solution and dried over Na_2SO_4. 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~~refluxed~~ for 1 h with IBX to give 1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4oxobutyl)amide; R*f* : 0.24 (CH_2Cl_2/MeOH 185:15).

The above aldehyde was ~~refluxed~~ heated at reflux for 2 h with TFA. Purification by flash column chromatography (CH_2Cl_2/MeOH 195:5-190:10) afforded the title compound. White solid (113 mg, 75%); mp = 118 °C; R_f : 0.36 (CH_2Cl_2/MeOH 185:15); ^{1}H-NMR (300 MHz, DMSO-d_6). 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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, 46.6, 44.8, 37.1, 36.4, 29.5, 28.1; GC-MS (EI) m/z (%) 254 (30), 168 (78), 89 (100). Anal.Calcd for $C_{15}H_{14}N_2O_2$: 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~~refluxed~~ for 3 h with IBX to give 1-benzyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-oxobutyl)amide; light yellow solid; R_f : 0.24 (CH_2Cl_2/MeOH 185:15).

The above aldehyde was heated at reflux~~refluxed~~ for 3.5 h with TFA. Purification by flash column chromatography (CH_2Cl_2/MeOH 195:5 - 192:8) afforded the title compound. White solid (88 mg, 21%); mp = 137-139 °C; R_f : 0.52 (CH_2Cl_2/MeOH 18:2); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{21}H_{18}N_2O_2$: 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[10.8.0.0^{2,10}.0^{4,9}.0^{15,20}]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~~refluxed~~ for 7 h with IBX to give 4-oxo-1,4-dihydroquinoline-2-carboxylic acid 2-(2-oxoethyl)benzylamide; white solid; R_f : 0.46 (CH_2Cl_2/MeOH 19:1).

The above aldehyde was heated at reflux ~~refluxed~~ for 1 h with TFA to give the title compound. Purified by flash chromatography (CH_2Cl_2/MeOH 195:5). White solid (210 mg, 85%); mp = 257 °C; R_f : 0.25 (CH_2Cl_2/MeOH 19:1); ^{1}H-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); ^{13}C-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 $C_{18}H_{12}N_2O_2$: 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~~refluxed~~ 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; R_f : 0.16 (CH_2Cl_2/MeOH 195:5).

The above aldehyde was heated at reflux~~refluxed~~ for 2 h with TFA. Purified by flash chromatography (CH_2Cl_2/MeOH 95:5). Yellow solid (64 mg, 68%); mp = 108 °~~–~~C; R_f : 0.35 (DCM/MeOH 95:5); ^{1}H-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); ^{13}C-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 $C_{17}H_{18}N_2O_5$: 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 refluxrefluxed for 9 h with IBX to give 6-bromo-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-oxobutyl)amide as a yellow solid; R_f : 0.46 (CH_2Cl_2/MeOH 19:1).

The above aldehyde was heated at refluxrefluxed for 1 h with TFA**.** Purified by flash chromatography (CH_2Cl_2/MeOH 95:5). White solid (292 mg, 69%); mp = 263 °C; R_f : 0.32. (DCM/MeOH 195:5); ^{1}H-NMR (600 MHz, DMSO-d_6) 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), 3.43-3-36 (1H, m), 2.79-2.68 (1H, m), 2.36-2.19 (2H, m), 1.73-1.60 (1H, m); ^{13}C-NMR (150 MHz, DMSO-d_6) 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 $C_{14}H_{11}BrN_2O_2$: 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]naphthtalene-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. $NaHCO_3$ (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; R_f : 0.43 (CH_2Cl_2/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 CH_3CN and the mixture was heated at refluxrefluxed for 3 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ solution and dried over Na_2SO_4. Evaporation of the extract gave a crude product that was purified by crystallization from Et_2O to give the title compound as a white solid (33.8 mg, 64%). mp = 172 °C; R_f : 0.56 (CH_2Cl_2/MeOH 90:10); ^{1}H-NMR (300 MHz, DMSO- d_6) δ: 8.20 (1H, d, *J* = 8.2 Hz), 7.83 (1H, dd, *J* = 8.2, Hz, *J* = 8.2 Hz), 7.72 (1H, d, *J* = 8.2 Hz), 7.49 (1H, dd, *J* = 8.2 Hz,, 8.2 Hz), 6.33 (1H, s), 6.15-6.00 (1H, m), 3.769-3.60 (1H, m), 3.39 46-3.33 (1H, m), 2.8985-2.70 (1H, m), 2.37-2.21 (2H, m), 1.78-1.5866 (1H, m); ^{13}C-NMR (75 MHz, DMSO- d_6) 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 $C_{14}H_{12}N_2O_2$: 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-diazabenzo[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.

$NaHCO_3$ (2 mL). The solid formed was filtered and dried to give 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 CH_3CN and the mixture was heated at refluxrefluxed for 1 h. The solvent was evaporated, the residue was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ solution and dried over Na_2SO_4. 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; R_f : 0.23 (CH_2Cl_2/MeOH 195:5); ^{1}H-NMR (300 MHz, MeOD) δ: 8.33 (1H, d, *J* = 7.3 Hz), 7.94-7.75 (2H, m), 7.652-7.50 (1H, m), 6.67 (1H, s), 5.92 (1H, dd, *J* = 7.6, 3.0 Hz), 4.58-4.426 (1H, m), 3.30-3.20 (1H, m), 3.05-2.95-92 (1H, m), 2.18-2.05-00 (m, 1H), 1.98-1.79 (2H, m), 1.65-1.53-50 (1H, m), 1.45-1.31-29 (1H, m);^{13}C-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 $C_{15}H_{14}N_2O_2$: 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 refluxrefluxed 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; R_f : 0.32 (Hexane/EtOAc 80:20); ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) 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); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ: 169.5, 164.5, 153.5, 148.7, 136.5, 135.04, 98.9, 93.4, 62.0, 60.9, 59.9, 56.0, 14.3, 13.7. Anal.Calcd for $C_{17}H_{23}NO_7$: 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 (8.46 mmol, 1.47 mL) was added dropwise and the reaction was heated at refluxrefluxed for 5 h. Purified by flash chromatography (Hexane/EtOAc 195:5). Yellow oil (1.87 g, 64%); R_f : 0.63 (Hexane/EtOAc 80:20); ^{1}H-NMR (300 MHz, $CDCl_3$) 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); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.0, 163.6, 147.2, 139.2, 131.6 (××2), 122.1 (××2), 116.6, 94.6, 61.8, 59.7, 13.9, 13.3. Anal.Calcd for $C_{14}H_{16}BrNO_4$: 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 P_2O_5 in methanesulfphonic 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 Na_2CO_3 saturated solution. The precipitate was filtered under vacuum, to obtain the title compound as a white solid. (870 mg, 100%); mp = 235 °C; R_f : 0.34 (CH_2Cl_2/MeOH 19:1); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{15}H_{17}NO_6$: 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 P_2O_5 in methanesulfphonic 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 Na_2CO_3 saturated solution. The precipitate was filtered under vacuum, to obtain the title compound as a white solid. (688 mg, 61%); mp = 255-260 °C; R_f : 0.57 (CH_2Cl_2/MeOH 195:5); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{12}H_{10}BrNO_3$: 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 heated at reflux for 1 h, then EtOH was evaporated. After cooling with an ice-bath, 1N HCl was added and the white solid formed was filtered and dried (233 mg, 64%); mp = 234 °C: R_f : 0.7 (MeOH/H_2O 40:60); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.39 (1H, s), 6.49 (1H, s), 3.90 (3H, s), 3.69 (6H, s); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{13}H_{13}NO_6$: 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 heated at refluxrefluxed 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; R_f : 0.76 (RP-18 MeOH/H_2O 15:85); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 176.3, 163.5, 139.5, 139.0, 135.3, 127.1, 126.8, 122.3, 116.8, 110.2. Anal.Calcd for $C_{10}H_6BrNO_3$: 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 (38.2 mg, 0.31 mmol), $PdCl_2$(dppf) CH_2Cl_2 (5.73 mg 0.0078 mmol) and $NaHCO_3$ (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 × 10 mL), the collected organic layers were dried and the solvent evaporated. Purification by flash chromatography (CH_2Cl_2/MeOH 90:10) gave the desired compound. Yellow solid (24 mg, 47%); mp = 240 °C; R_f : 0.44. (DCM/MeOH 90:10); ^{1}H-NMR (300 MHz, DMSO-d_6) 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); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 $C_{19}H_{15}N_3O_2$: 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), $PdCl_2$(dppf) CH_2Cl_2 (5.7 mg, 0.0078 mmol) and $NaHCO_3$ (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 × 10 mL), the collected organic layers were dried and the solvent evaporated. Purification by flash chromatography (CH_2Cl_2/MeOH 19:1) gave the desired compound. Yellow sticky solid (25 mg, 49%); R_f : 0.62 (CH_2Cl_2/MeOH 18:2); ^{1}H-NMR (300 MHz, DMSO-d_6) 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), 6.10-6.05 (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); ^{13}C-NMR (150 MHz, DMSO-d_6) 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 $C_{20}H_{16}N_2O_3$: 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.

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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

1. (a) Hadjeri, M.; Peiller, E.-L.; Beney, C.; Deka, N.; Lawson, M. A.; Dumontet, C.; Boumendjel, A. *J. Med. Chem.* **2004**, *47*, 4964–4970. (b) Nakamura, S.; Kozuka, M.; Bastow, K. F.; Tokuda, H.; Nishino, H.; Suzuki, M.; Tatsuzaki, J.; Morris Natschke, S. L.; Kuo, S.-C.; Lee, K.-H. *Bioorg. Med. Chem.* **2005**, *13*, 4396–4401. (c) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hamel, E.; Brossi, A.; Lee, K.-H. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2891–2893.

2. Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559–592.

3. Cecchetti, V.; Parolin, C.; Moro, S.; Pecere, T.; Filipponi, E.; Calistri, A.; Tabarrini, O.; Gatto, B.; Palumbo, M.; Fravolini, A.; Palu, G. *J. Med. Chem.* **2000**, *43*, 3799–3802.

4. (a) Cross, R. M.; Monastyrskyi, A.; Mutka, T. S.; Burrows, J. N.; Kyle, D. E.; Manetsch, R. *J. Med. Chem.* **2010**, *53*, 7076–7094; (b) (e) Vandekerckhove, S.; Desmet, T.; Tran, H. G.; de Kock, C.; Smith, P. J.; Chibale, K.; D'hooghe, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1214-1217.

5. (a) Cincinelli, R.; Dallavalle, S.; Merlini, L. *Synlett*~~,~~ **2008**, *9*, 1309-1312; (b) Cincinelli, R.; Cassinelli, G.; Dallavalle, S.; Lanzi, C.; Merlini, L.; Botta, M.; Tuccinardi, T.; Martinelli, A.; Penco, S.; Zunino, F. *J. Med. Chem.* **2008**, *51,* 7777–7787.

6. Cincinelli, R.; Dallavalle, S.; Merlini, L.; Nannei, R; Scaglioni, L. *Tetrahedron* **2009**, *65*, 3465-3472.

7. Todorov, A. R., Nieger, M., Helaja, J. *Chem. Eur. J*. **2012**, *18*, 7269-7277.

8. (a) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron*~~,~~ **2009**, *65*, 7468-7473; (b) Alvarez, M.; Salas, M.; Rigat, L.; de Veciana, A.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 351-356.

9. Chen, J; Deady, L.W. *Tetrahedron* **1998**, *54*, 2785-2794.

10. (a) Pidathala, C.; Amewu, R.; Pacorel, B.; Nixon, G. L.; Gibbons, P.; Hong, W. D.; Leung, S. C.; Berry, N. G.; Sharma, R., Stocks, P. A.; Srivastava, A.; Shone, A. E.; Charoensutthivarakul, S.; Taylor, L.; Berger, O.; Mbekeani, A.; Hill, A.; Fisher, N. E.; Warman, A.J.; Biagini, G. A.; Ward, S. A; O'Neill, P. M. *J. Med. Chem*. **2012**, *55*, 1831-1843; (b) Onda, K.; Narazaki, F.; Ishibashi, N.; Nakanishi, K.; Sawada, Y.; Imamura, K.; Momose, K.; Furukawa, S.; Shimada, Y.; Moriguchi, N.; Yuda, M.; Kayakiri, H.; Ohta, M. *Bioorg. Med. Chem. Lett.* ~~*ers.*~~ **2011**, *21*, 6861-6866.

11. (a) Mphahlele, M. J.; Nwamadi, M. S.; Mabeta, P. *J. Heterocycl. Chem*. **2006**, *43*, 255-260. (b) Bogányi, B.; Kámán, J. *Tetrahedron*, **2013**, *69*, 9512-9519. (c) Cross, M. R.; Monastyrskyi, A.; Mutka, T. S.; Burrows, J. N.; Kyle, D. E.; Manetsch, R. *J. Med. Chem.* **2010**, *53*, 7076-7094; (d) Morris, L. C. A.; Jackson, Y. A. *Heterocycles* **2010**, *81,* 371-380.

12. (a) Venkataraman, S.; Barange, D. K.; Pal, M. *Tetrahedron Lett.* **2006**, *47*, 7317-7322; (b) Almeida, A. I. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synlett*. **2010**, *3*, 462-466; (c) Cross, R. M.; Manetsch, R. *J. Org. Chem*. **2010**, *75,* 8654-8657.

13. Baker, B. R.; Bramhall, R. R. *J. Med. Chem.* **1972**, *15*, 230-233.

14. Cairns, H.; Cox, D.; Gould, K. J.; Ingall, A. H.; Suschitzky, J. L. *J. Med. Chem.* **1985**, *28*, 1832-1842.

15. Riepl, H. M.; Kellermann, M. *Helv. Chim. Acta* **2009**, *92*, 668-676.

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_{50} is defined as the inhibitory drug concentration causing a 50% decrease of cell growth over that of untreated control.