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An Expeditious and Metal-Free Synthetic Route towards Quinolones, Naphthyridones and Benzonaphthyridones

Napoleon John Victor[a] and Kannoth Manheri Muraleedharan[a,*]

[a] Department of Chemistry, Indian Institute of Technology Madras, – Chennai 600 036, India
Fax: (+91)-44-2257-4202; phone: (+91)-44-2257-4233; e-mail: mkm@iitm.ac.in

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Abstract: An efficient, two-step synthetic strategy has been developed to access the quinolone, naphthyridone and benzonaphthyridone classes of chemotherapeutic agents from Baylis–Hillman adducts. The method involves tandem aza-Michael addition, S_NAr cyclisation followed by oxidation of the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline or 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative using IBX, and works well with substrates having a wide variety of substitution pattern.

Keywords: Baylis–Hillman reaction; benzonaphthyridones; naphthyridones; oxidation; quinolones

Introduction

Quinolones and naphthyridones constitute one of the most important classes of antibacterial agents in clinical use today.[1] Ciprofloxacin, levofloxacin and gemifloxacin are well known examples from this group and are special because of their effect on both Gram-positive and Gram-negative organisms. Whilst most of the earlier literature deals with their antibacterial properties, there is growing interest to develop them against other diseases as well.[2] Such a broad-spectrum anti-infective property is certainly encouraging but the emergence of bacterial resistance against the existing drugs is a matter of great concern.[3] Concerted efforts are being put to identify new drug candidates from this series, of which, 6-nitro- and 6-aminoquinolone derivatives have come up as the most promising (*vide infra*).

Antibacterial effects from quinolones have been linked to their inhibitory effect on bacterial DNA topoisomerase IV and gyrase, and structural details of their complexes with DNA and relevant domains of these enzymes are currently available.[4] Interestingly, substitution around the core can alter their target specificity and make them useful against other diseases as well. For example, most of the quinolones with antibacterial,[5] anticancer,[6] anti-HIV[7] and antituberculosis[8] activities have a free carboxyl group at the C-3 position. At the same time, a number of quinolone-3-carboxylate esters with suitable substitution on the aromatic ring have shown antimalarial activity, likely through the inhibition of *P. falciparum bc1*.[9] Similarly, quinolone-3-carboxamide derivatives are known to act as CB2 receptor modulators,[10] calpain I inhibitors[11] and trypanosomicidal agents.[12] As mentioned above, there are a number of reports highlighting promising biological activities of 6-nitro- and 6-aminoquinolones; compounds **I–III** (Figure 1) are some selected examples from this group.[13] Like quinolones, naphthyridones are also promising, and voreloxin (compound **IV**) from this series has undergone phase II clinical trials against acute myeloid leukemia and ovarian cancer.[14] Similarly, gemifloxacin (**V**) is a broad spectrum antibacterial agent and has promising *in vitro* and *in vivo* activities against *S. pneumoniae* and *H. influenzae*.[15] Benzonaphthyridones, with a tricyclic nature, constitute a closely related family of compounds and are also getting significant attention as promising chemotherapeutic agents. The compound RP60556A (**VI**), for example, is active against multidrug resistant Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA) and is potent *in vivo*.[16]

Success in identifying second-line drug candidates relies primarily on our ability to access a large number of structurally diverse quinolones, naphthyridones and benzonaphthyridones for structure-activity relationship studies. Gould–Jacobs cyclisation and Grohe–Heitzer reaction are two well-known routes to 4-quinolones.[17] The former starts with the reaction between a substituted aniline and diethyl 2-(ethoxymethylene)malonate at elevated temperature to fur-

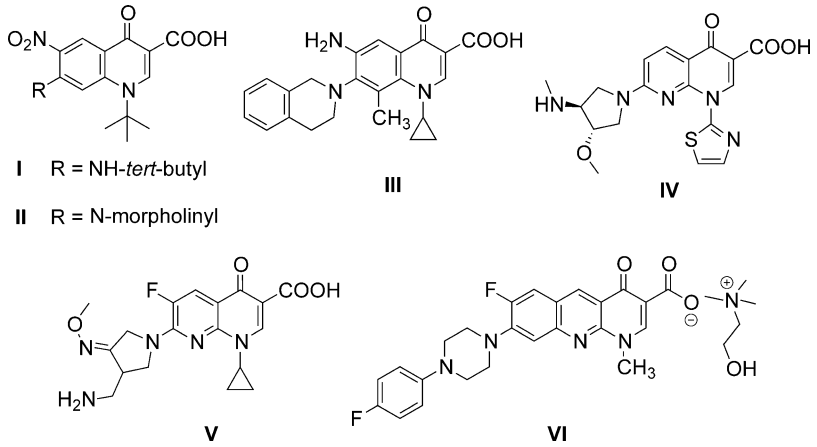


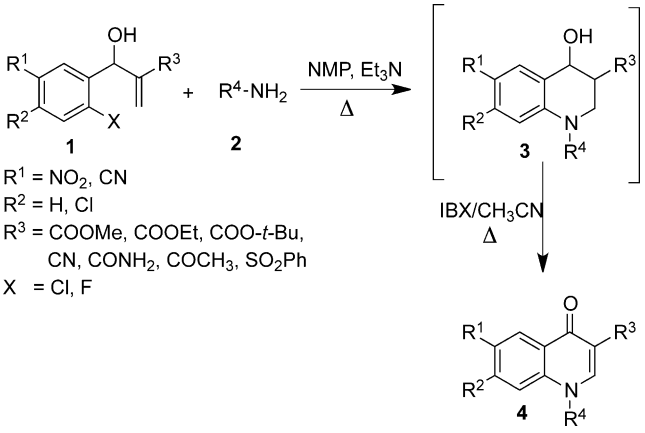
Figure 1. Examples of quinolone-, naphthyridone- and benzonaphthyridone-based chemotherapeutic agents.

nish a 4-hydroxyquinoline-3-carboxylate derivative which is subjected to N-alkylation in the next step. In the latter approach, ethyl 3-(2-halophenyl)-3-oxopropanoate is first synthesised from *ortho*-haloaroyl halide and diethyl malonate and then condensed with triethyl orthoformate to form an enol ether intermediate. This on treatment with the amine of interest gives the corresponding N-substituted quinolone through an addition–elimination–cyclisation sequence. One-step formation of 4-quinolones through reaction of isatoic anhydride with sodio-ethyl formylacetate,[18] a one-pot strategy towards 2-substituted 4-quinolones through Pd-catalysed amidation of *o*-halo acetophenone and base-mediated cyclisation,[19] preparation of 2-substitued quinolones through Pd-catalysed cyclisation of *ortho*-haloaryl acetylenic ketones,[20] quinolone formation through TFA-catalysed cyclisation of *ortho*-nitrobenzaldehyde-derived Baylis–Hillman adducts and reduction of the resulting 4-hydroxyquinoline *N*-oxide,[21] use of 2-[hydroxy(2-halophenyl)methyl]-3-iodoacrylate, accessible from Baylis–Hillman-type reaction of arylaldehydes with methyl propiolate in the presence of $ZrCl_4/Bu_4NI$ system as a key precursor for 4-quinolones,[22] formation of 4- and 2-quinolones from Baylis–Hillman acetates and amines through a dihydroquinoline intermediate under photosensitised oxidation condition,[23] one-pot preparation of 2-substituted 3-carboxyquinolones by base-promoted condensation of *o*-halo-3-oxo-3-arylpropanoate with *in situ* generated imidoyl chloride and subsequent S_NAr cyclisation,[24] are other notable developments in this area. Lots of attention is also being given to develop new methods toward naphthyridones and benzonaphthyridones as well. For instance, Iaroshenko et al. have recently reported the syntheses of these skeletons using *ortho*-chloroheteroaryl acetylenic ketones and primary amines as starting materials under Pd catalysis.[25]

Of various reports on quinolone synthesis mentioned above, the photosensitised oxidation method reported by us,[23] although two-step, leads to a mixture of 4- and 2-quinolones. While suitable for making libraries of both compounds, the lack of selectivity in this case prompted us to look for an efficient alternate route that can give the most important 4-quinolones exclusively. Ready availability of starting materials, lesser number of reaction/purification steps, high efficiency, substituent compatibility and generalisability to other related skeletons were considered important. The success we have in our efforts towards such a unified approach is delineated in this report.[26]

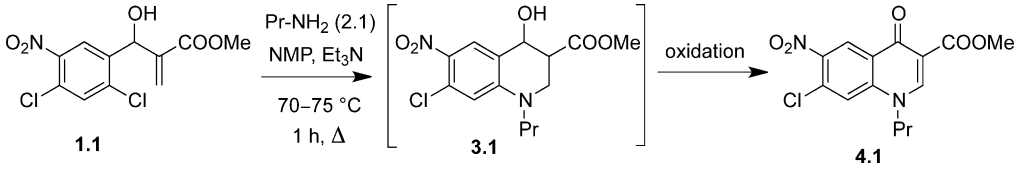
Results and Discussion

The 4-hydroxy-1,2,3,4-tetrahydroquinoline (THQ) derivative **3**, accessible by Michael addition and S_NAr cyclisation of the Baylis–Hillman adduct **1** was identified as a suitable starting material (Scheme 1). Such '5+1' strategies involving amines and suitably substituted five-carbon frameworks are highly useful in the syntheses of nitrogen heterocycles, especially pyridine



Scheme 1. Synthesis of quinolones from Baylis–Hillman adducts.

Table 1. Optimisation of the oxidation step.



Entry[a]	Reagent	Solvent	Temp [°C]	Time [h]	Overall yield [%][b]
1	IBX (2.2 equiv.)	DMSO	80	48	65
2	IBX (2.2 equiv.)	EtOAc	70–75	48	57
3	IBX (2.2 equiv.)	CH_3CN	70–75	12	80
4	IBX (1.1 equiv.)	CH_3CN	70–75	12	40
5	IBX:NMO	DMSO	r.t.	240	39
6	cat. IBX/Oxone®	CH_3CN-H_2O	70–75	48	trace
7	cat. IBA/Oxone®	CH_3CN-H_2O	70–75	48	trace
8	$PhI(OAc)_2$-TEMPO	CH_2Cl_2	r.t.	120	20
9	DMP	$CHCl_3$	r.t.	52	45

[a] All reactions were carried out using THQ derivative **3.1** derived from 100 mg (0.33 mmol) of Baylis–Hillman adduct **1.1** and propylamine (0.66 mmol).
[b] The overall yield from the Baylis–Hillman adduct is reported.

derivatives and fused pyridines.[20,25a,27] Benzylic oxidation of intermediate **3** followed by dehydrogenation across the C-2–C-3 bond was expected to give 4-quinolones of our interest. While looking for reagents capable of bringing about this transformation, hypervalent iodine compounds, especially 2-iodoxybenzoic acid (IBX), studied well by Nicolaou and co-workers,[28] appeared most suitable. To test the feasibility of this approach, the THQ intermediate **3.1** (Table 1) was synthesised and reacted with IBX in DMSO at 80 °C for 48 h, which led to the formation of the expected product **4.1** in 65% yield. While there was no yield improvement on carrying out the reaction in ethyl acetate, use of acetonitrile improved the yield to 80% (entries 2 and 3). Use of 1.1 equiv. of IBX (entry 4) led to 40% of quinolone (**4.1**) along with unreacted starting materials, indicating the higher enolisation and reactivity of the expected keto ester intermediate. Efforts to carry out the reaction at room temperature by using IBX in combination with NMO,[29] or to decrease the amount of hypervalent iodine species by using IBX(cat)/Oxone®,[30] and IBA(cat)/Oxone® also ended in vain (entries 5, 6 and 7, Table 1). Reagents such as $PhI(OAc)_2$-TEMPO,[31] and Dess–Martin periodinane (DMP) were also found inefficient as shown (entries 8 and 9).

An advantage of the present strategy is that purification of the THQ intermediate is not necessary, and after an aqueous work-up, the crude product can be dissolved in acetonitrile and heated in the presence of 2.2 equiv. of IBX at 70–75 °C to afford the products in good yields. After identifying the optimum conditions, the method was applied to THQ intermediates generated from a variety of Baylis–Hillman adducts and amines. Baylis–Hillman adducts used in this study were synthesised from the corresponding aldehydes and activated olefins according to reported procedures.[32] These starting materials were selected so as to demonstrate the suitability of this method to access structurally diverse sets of quinolones. As evident from Table 2, a range of functionalities like ester, cyano, amide, keto and sulphone groups were found to be well tolerated at C-3. Alkyl (cyclic as well as acyclic), arylalkyl, allyl and heteroarylalkyl groups at N-1 were compatible to the reaction conditions showing the high substrate scope of this route and the suitability to generate large chemical libraries by simple permutation and combination of starting materials. A requirement, however, is the presence of electron-withdrawing substituent(s) such as NO_2 and CN on the aromatic ring for making the S_NAr step feasible. Table 2 also show that an S_NAr reaction through *ortho*-activation can be achieved efficiently and used for preparing quinolones **4.24** and **4.25** with CN and NO_2 groups at the 8 position. When sulphonyl, carboxylate ester, trifluoromethyl or fluoro groups were present on the aromatic ring, the expected intermediate **3** was not formed, likely due to a lower S_NAr activation and competing side reactions.[33] As evident from Table 2, yields in all cases were high and ranged between 60–90%. Only in the case of quinolones **4.8** and **4.19** with $COCH_3$ and SO_2Ph groups, respectively, at C-3, the yields were 50%. Benzylic oxidation of Baylis–Hillman adducts with IBX to 1,3-dicarbonyl compounds is known, and use of such intermediates for aza-Michael–S_NAr steps could be an alternative approach to improve the yields of **4.8** and **4.19**.[34] To have an aldehyde group at the C-3 position, the THQ intermediate (e.g., **3.1**) can be first reduced using $NaBH_4$ and then subjected to oxidation using IBX.

Table 2. Quinolones synthesised from Baylis–Hillman adducts (**1**) and amines.[a]

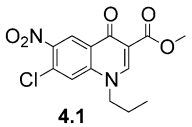
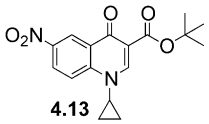
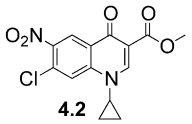
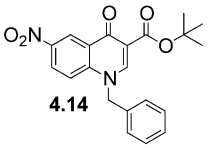
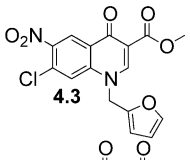
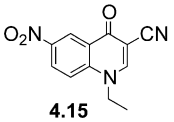
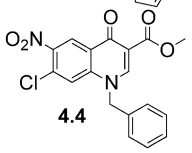
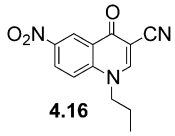
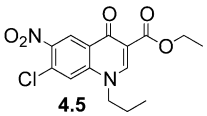
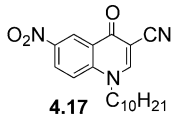
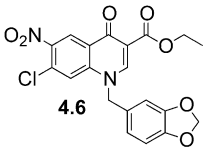
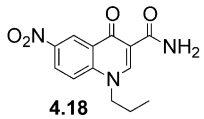
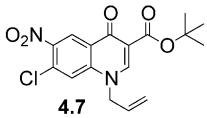
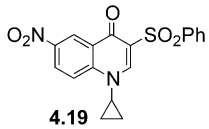
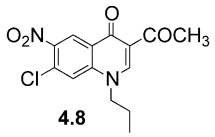
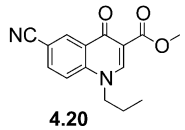
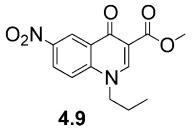
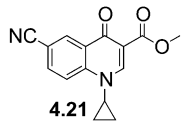
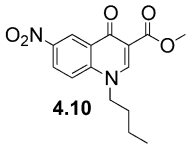
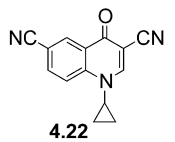
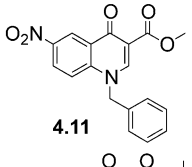
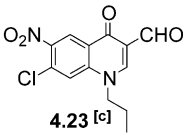
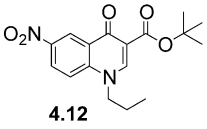
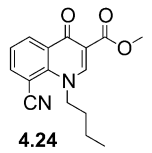
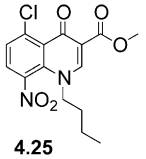
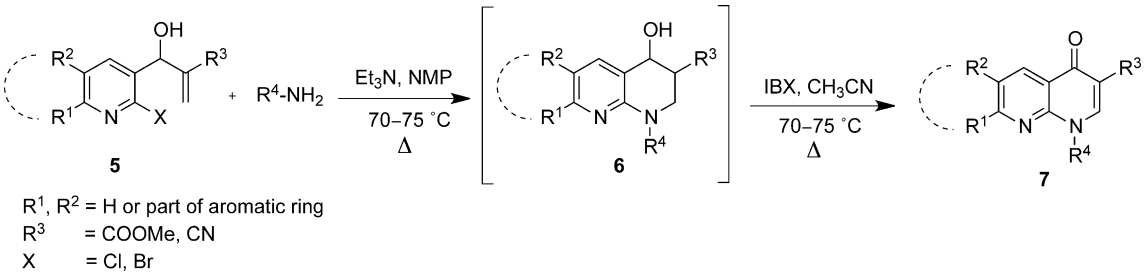
Compound	Time [b] [h]	Yield [%]	Compound	Time [b] [h]	Yield [%]
 **4.1**	1+12	80	 **4.13**	12+12	87
 **4.2**	7+20	74	 **4.14**	8+24	81
 **4.3**	4+10	87	 **4.15**	10+20	73
 **4.4**	4+24	77	 **4.16**	10+12	70
 **4.5**	2+12	81	 **4.17**	5+24	71
 **4.6**	5+12	80	 **4.18**	14+20	65
 **4.7**	12+12	76	 **4.19**	8+8	50
 **4.8**	1+12	50	 **4.20**	12+15	72
 **4.9**	8+12	86	 **4.21**	12+12	90
 **4.10**	2+12	83	 **4.22**	10+11	71
 **4.11**	5+20	70	 **4.23** [c]	1+2+12	60
 **4.12**	4+10	90			

Table 2. (Continued)

Compound	Time [b] [h]	Yield [%]	Compound	Time [b] [h]	Yield [%]
 **4.24**	12+20	60	 **4.25**	5+24	63

[a] All reactions were carried out using IBX (2.2 equiv.) and **3** derived from Baylis–Hillman adduct (1 equiv.) and amine (2 equiv.).
[b] Reaction time needed for the cyclisation and oxidation steps.
[c] THQ intermediate **3.1** was first reduced using $NaBH_4$ and then subjected to oxidation using IBX.



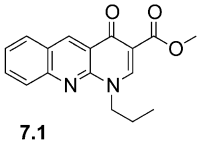
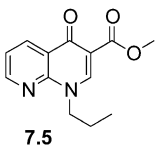
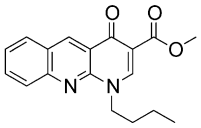
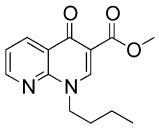
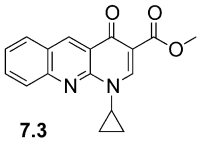
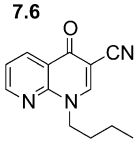
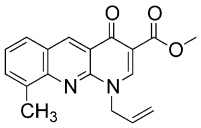
Scheme 2. Synthesis of naphthyridones and benzonaphthyridones.

Following this route, we have prepared the quinolone **4.23** in an overall yield of 60% by executing all the five steps without purification of any of the intermediates. Interestingly, cleavage of 1,3-diols to 1,2-dicarbonyl compounds was not observed here.[35] Presented in Table 2 are the overall yields from Baylis–Hillman adducts which makes this strategy superior over most of the existing methods. Due to the low solubility of the by-product iodosobenzoic acid (IBA) in acetonitrile, simple filtration was sufficient to recover it at the end of the reaction. TLC analysis of the filtrate in most of the cases indicated only the product which made the chromatographic purification easy. In the case of **4.1**, we have scaled up the reaction to get a gram of this product and the yield was found consistent (80%). Since metal-mediated N-arylation of the Michael addition product can also lead to the key intermediate **3**, we have conducted a number of experiments involving CuI/phenanthroline/base, CuI/proline/base, Cu_2O, $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2$ to increase the substrate scope in unactivated systems.[36] These efforts, however, did not give fruitful results.

Since naphthyridones and benzonaphthyridones are as important as quinolones, we continued our studies involving Baylis–Hillman adducts (**5**) from 2-halopyridine and 2-haloquinoline-3-carboxaldehyde with different Michael acceptors (Scheme 2).[37] As expected, they underwent smooth tandem Michael addition–S_NAr cyclisation to give the corresponding tetrahydronaphthyridine intermediates (**6**) in short reaction times. Subsequent oxidative transformation to naphthyridones and benzonaphthyridones was also efficient without any side reactions. As shown in Table 3, the entire sequence starting from Baylis–Hillman products was completed in less than 16 h with the overall yields ranging from 63–90%. Since Baylis–Hillman adducts of pyridine/quinolinecarboxaldehyde with methyl acrylate can be prepared quantitatively under 'neat' condition,[37] it is possible to execute all the steps sequentially without purification of intermediates. This was verified by carrying out the sequence from 2-bromopyridine-3-carboxaldehyde, which afforded the naphthyridone **7.6** in an overall yield of 65% (for 5 steps). We were able to get X-ray quality crystals of compounds **4.1** and **7.5** by slow evaporation of their solutions in methanol and the ORTEP diagrams are presented in Figure 2.

Most of the quinolone-based drugs possess substitution at the C-7 position of the aromatic ring. To demonstrate the possibility of accessing such compounds, we have reacted **4.1** with piperidine in DMF at 80 °C which resulted in the formation of **8** in 95% yields (Scheme 3). This product was further subjected to reduction using Lindlar's catalyst under hydrogen atmosphere to get the amino quinolone **9** in 96% yields. Since the amino group can be substituted by fluorine

Table 3. Naphthyridones and benzonaphthyridones synthesised from Baylis–Hillman adduct **5** and various amines.[a]

Compound	Time[b] [h]	Yield [%]	Compound	Time[b] [h]	Yield [%]
 **7.1**	5+8	90	 **7.5**	5+5	80
 **7.2**	3+10	80	 **7.6**	5+7	71
 **7.3**	3+6	74	 **7.7**	4+8	73
 **7.4**	5+10	63			

[a] All reactions were carried out using IBX (2.2 equiv.) and intermediate **6** derived from Baylis–Hillman adduct **5** (1 equiv.) and amine (2 equiv.).
[b] Reaction time needed for cyclisation and oxidation steps.

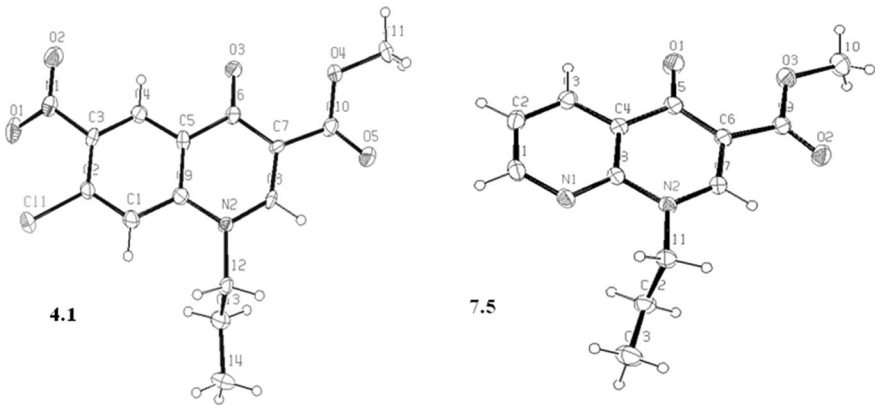
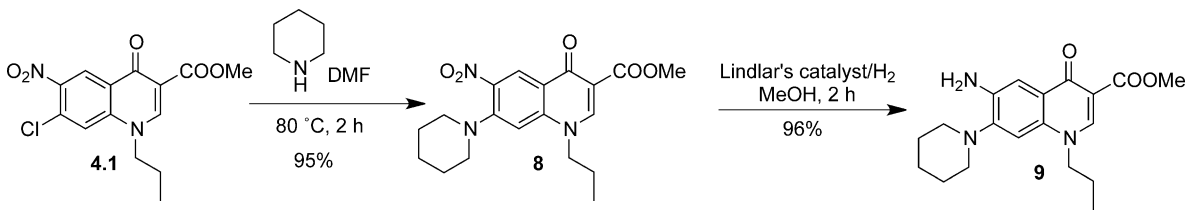


Figure 2. ORTEP diagrams of quinolone **4.1**, and naphthyridone **7.5**.[38]



Scheme 3. Synthesis of 6-aminoquinolones.

through diazotisation and treatment with HBF_4, the nitro derivatives in hand can be considered as precursors of the fluoroquinolone class of antibiotics as well.[13c] Increased efficiency, metal-free and mild reaction conditions, and easy purification of products are some of the advantages of the synthetic route presented here. Chromatographic purification of the THQ intermediate is in fact not necessary, and the entire sequence takes only 9–34 h to complete, making it suitable for library synthesis in a combinatorial fashion.

The by-product iodosobenzoic acid can be recycled quantitatively to IBX by oxidation with Oxone® if desired. Apart from giving direct access to quinolones, naphthyridones and benzonaphthyridones, the examples presented here clearly show that a broad substitution pattern can be introduced around these cores by the proper choice of starting materials. This therefore provides a strong synthetic platform to initiate the drug discovery process against diseases such as bacterial infections, cancer and AIDS.

Conclusions

A short and efficient synthetic route towards quinolones, naphthyridones and benzonaphthyridones is presented. The strategy makes use of easily accessible Baylis–Hillman adducts as starting materials and involves Michael addition, S_NAr cyclisation and IBX-mediated oxidation as the key steps. Separation of the THQ intermediate is not necessary and the extract after water wash can be directly taken forward for oxidation to get the products. The entire sequence takes only 9–34 h to complete and is suitable to create large libraries of therapeutically important compounds in a short span of time.

Experimental Section

General Experimental Information

All reactions were carried out under nitrogen atmosphere using dry solvents under anhydrous conditions, unless otherwise mentioned. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (60 F254 grade) from Merck, and were analysed using a 254 nm UV light. The chromatographic separation was carried out on 100–200 mesh silica gel. Melting points were obtained on an electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz and 500 MHz instruments, and the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, with *J* values in Hertz. The splitting patterns in ^{1}H NMR spectra are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; ddd = doublet of doublet of doublet; dddd = doublet of doublet of doublet of doublet; bs = broad singlet; dt = doublet of triplet; app = apparant; m = multiplet. ^{13}C NMR spectral data were reported with the solvent peak ($CDCl_3$ = 77.16) as the internal standard. ^{1}H NMR peak assignments were made based on DEPT-135, COSY, HSQC and HMBC experimental data. High-resolution mass spectra (HR-MS) were recorded on a Waters Q-Tof *micro*™ spectrometer with lock spray source. The intensity data collection during X-ray crystallographic analysis was carried out on a diffractometer equipped with graphite monochromated Mo (K_α) radiation. Infrared spectra were recorded using a Nicolet 6700 FT-IR spectrophotometer.

General Procedure for the Preparation of Quinolones, Naphthyridones and Benzonaphthyridones

To a stirred solution containing a mixture of Baylis–Hillman adduct (1 mmol) and triethylamine (2 mmol) in *N*-methyl-2-pyrrolidinone (NMP; 3 mL) in a reaction vessel was added the appropriate amine (2 mmol), and mixture was heated at 70–75 °C until the starting materials were consumed. It was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (3 × 20 mL) followed by brine (10 mL). After drying the organic layer with sodium sulphate, it was filtered and evaporated under reduced pressure to get a residue which was re-dissolved in acetonitrile (20 mL), and 2-iodoxybenzoic acid (IBX; 2.2 mmol) was added to it. The mixture was then heated at 70–75 °C for 5–24 h. After complete consumption of starting materials, the by-product was removed by filtration, diluted with ethyl acetate (20 mL) and washed with 10% aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried using sodium sulphate, filtered and evaporated under reduced pressure to get a residue which was chromatographed on silica gel using an ethyl acetate-hexanes mixture in a gradient mode to get the product. The spectral and analytical data of these compounds are presented below.

Methyl 7-Chloro-6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4.1)

Methyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (1 g, 3.28 mmol) and propylamine (0.39 g, 0.54 mL, 6.56 mmol) in NMP (10 mL) were reacted in the presence of triethylamine (0.9 mL, 6.56 mmol) at 75 °C for 1 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative in acetonitrile (50 mL) was oxidised by heating the mixture with IBX (2 g, 7.14 mmol) for 12 h according to the general procedure discussed above to get **4.1** as a pale yellow crystalline solid; yield: 850 mg (80%). R_f (70% EtOAc/hexanes) = 0.17; mp 175–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.02 (s, 1H, C-2-H), 8.51 (s, 1H, ArH), 7.57 (s, 1H, ArH), 4.15 (t, 2H, N-CH_2, J = 7.5 Hz), 3.95 (s, 3H, -OCH_3), 1.96 (sextet, 2H, N-CH_2-CH_2-CH_3, J = 7.5 Hz), 1.08 (t, 3H, CH_2-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 165.2, 150.7, 144.3, 141.2, 131.4, 127.7, 126.3, 119.4, 112.4, 56.1, 52.6, 22.2, 11.1; IR (KBr): ν = 2967, 1693, 1638, 1613, 1602, 1523, 1478, 1337, 1251, 1231, 1212, 1132, 1005, 870 cm^{-1}; HR-MS (ESI): m/z = 325.0588, exact mass calcd. for $C_{14}H_{14}N_2O_5Cl$ $[M+H]^+$ 325.0591.

Methyl 7-Chloro-1-cyclopropyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.2)

Methyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.66 mmol) and cyclopropylamine (0.075 g, 0.091 mL, 1.32 mmol) in NMP (2 mL) were reacted in presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 7 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative in acetonitrile (20 mL) was oxidised by heating the mixture with IBX (407 mg, 1.45 mmol) for 20 h according to the general procedure discussed above to get **4.2** as a pale yellow crystalline solid;[20b] yield: 156 mg (74%). R_f (70% EtOAc/hexanes) = 0.47; mp 254–256 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.86 (s, 1H, C-2-H), 8.59 (s, 1H, ArH), 8.07 (s, 1H, ArH), 3.90 (s, 3H, OCH_3), 3.54–3.47 [m, 1H, N-C*H*$(CH_2)_2$], 1.46–1.40 (m, 2H, 2cyclopropyl CH_aH$_b$), 1.25–1.19 (m, 2H, 2cyclopropyl CH_aH$_b$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 165.1, 150.3, 144.6, 142.8, 131.2, 127.0, 125.8, 120.2, 112.5, 52.6, 35.0, 8.6 (2C); IR (KBr): ν = 3105, 2952, 1736, 1635, 1605, 1519, 1462, 1431, 1375, 1330, 1307, 1253, 1208, 1192, 1129, 1104, 1011 cm^{-1}; HR-MS (ESI): *m/z* = 323.0450, exact mass calcd. for $C_{14}H_{12}N_2O_5Cl$ $[M+H]^+$: 323.0435.

Methyl 7-Chloro-1-(furan-3-ylmethyl)-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.3)

Methyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.66 mmol) and furfurylamine (0.128 g, 0.117 mL, 1.32 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (407 mg, 1.45 mmol) by heating the mixture for 10 h according to the general procedure discussed above to afford **4.3** as a pale yellow crystalline solid; yield: 206 mg (87%). R_f (70% EtOAc/hexanes) = 0.67; mp 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1H, C-2-H), 8.57 (s, 1H, ArH), 7.80 (s, 1H, ArH), 7.44 (d, 1H, furfuryl-H, J = 1.2 Hz), 6.54 (d, 1H, furfuryl-H, J = 3.2 Hz), 6.42 (dd, 1H, furfuryl-H, J = 3.2, 2.0 Hz), 5.33 (s, 2H, N-CH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 165.2, 150.5, 145.9, 144.6, 144.4, 141.3, 131.4, 127.6, 126.2, 119.6, 113.1, 111.3, 111.2, 52.7, 50.6; IR (KBr): ν = 3036, 1702, 1636, 1603, 1540, 1474, 1377, 1230, 1185, 1143, 1007, 745 cm^{-1}; HR-MS (ESI); *m/z* = 363.0366, exact mass calcd. for $C_{16}H_{12}N_2O_6Cl$ $[M+H]^+$: 363.0384.

Methyl 1-Benzyl-7-chloro-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.4)

Methyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.66 mmol) and benzylamine (0.141 g, 0.144 mL, 1.32 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (407 mg, 1.45 mmol) by heating the mixture for 24 h according to the general procedure discussed above to afford **4.4** as a pale yellow crystalline solid; yield: 188 mg (77%). R_f (70% EtOAc/hexanes) = 0.35; mp 199–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1H, C-2-H), 8.62 (s, 1H, ArH), 7.49 (s, 1H, ArH), 7.44–7.38 (m, 3H, ArH), 7.19–7.17 (m, 2H, ArH), 5.40 (s, 2H, N-CH_2), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 165.2, 151.2, 144.5 141.4, 132.8, 131.4, 129.9 (2C), 129.4, 127.7, 126.2 (2C), 126.1, 120.2, 112.7, 57.9, 52.6; IR (KBr): ν = 2969, 1691, 1648, 1561, 1484, 1463, 1435, 1369, 1249, 1232, 1142, 1000 cm^{-1}; HR-MS (ESI): *m/z* = 373.0575, exact mass calcd. for $C_{18}H_{14}N_2O_5Cl$ $[M+H]^+$: 373.0591.

Ethyl 7-Chloro-6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4.5)

Ethyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.63 mmol) and propylamine (0.07 g, 0.1 mL, 1.23 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.17 mL, 1.23 mmol) at 75 °C for 2 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (388 mg, 1.39 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.5** as a pale yellow crystalline solid; yield: 171 mg (81%). R_f (70% EtOAc/hexanes) = 0.33; mp 147–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.98 (s, 1H, C-2-H), 8.46 (s, 1H, ArH), 7.57 (s, 1H, ArH), 4.39 (q, 2H, O-C*H*$_2$-CH_3, J = 7.5 Hz), 4.15 (t, 2H, N-C*H*$_2$-CH_2, J = 7.5 Hz), 1.96 (sextet, 2H, CH_2-C*H*$_2$-CH_3, J = 7.5 Hz), 1.41 (t, 3H, O-CH_2-C*H*$_3$, J = 7.5 Hz), 1.08 (t, 3H, N-CH_2-C*H*$_3$, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 164.7, 150.4, 144.3, 141.2, 131.4, 127.7, 126.4, 119.3, 112.9, 61.6, 56.0, 22.2, 14.5, 11.1; IR (KBr): ν = 2973, 1724, 1635, 1600, 1561, 1545, 1481, 1386, 1346, 1321, 1250, 1208, 1197, 825, 806 cm^{-1}; HR-MS (ESI): *m/z* = 339.0733, exact mass calcd. for $C_{15}H_{16}N_2O_5Cl$ $[M+H]^+$: 339.0748.

Ethyl 1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-7-chloro-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.6)

Ethyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.63 mmol) and 3,4-(methylenedioxy)benzylamine (0.19 g, 0.16 mL, 1.26 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.17 mL, 1.26 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (484 mg, 1.73 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.6** as a pale yellow crystalline solid; yield: 217 mg (80%). R_f (50% EtOAc/hexanes) = 0.2; mp 217–219 °C; ^{1}H NMR (500 MHz, $CDCl_3$); δ = 8.94 (s, 1H, C-2-H), 8.54 (s, 1H, ArH), 7.52 (s, 1H, ArH), 6.82 (d, 1H, ArH, J = 8.0 Hz), 6.70–6.66 (bd, 1H, ArH), 6.63 (d, 1H, ArH, J = 1.5 Hz), 6.0 (s, 2H, O-CH_2-O), 5.28 (s, 2H, N-CH_2), 4.39 (q, 2H, O-C*H*$_2$-CH_3, J = 7.0 Hz), 1.40 (t, 3H, CH_2-C*H*$_3$, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 164.6, 150.6, 149.1, 148.6, 144.5, 141.4, 131.3, 127.7, 126.4, 126.1, 120.2, 120.1, 113.1, 109.3, 106.7, 101.9, 61.6, 57.8, 14.5; IR (KBr): ν = 2980, 1681, 1655, 1604, 1563, 1529, 1482, 1465, 1444, 1370, 1355, 1252, 1237, 1205, 1147, 1040 cm^{-1}; HR-MS (ESI): *m/z* = 431.0631, exact mass calcd. for $C_{20}H_{16}N_2O_7Cl$ $[M+H]^+$: 431.0646.

tert-Butyl 1-Allyl-7-chloro-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.7)

tert-Butyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.58 mmol) and allylamine (0.066 g, 0.087 mL, 1.16 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.16 mL, 1.16 mmol) at 75 °C for 12 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline

derivative was oxidised using IBX (357 mg, 1.28 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.7** as a pale yellow crystalline solid; yield: 159 mg (76%). R_f (50% EtOAc/hexanes) = 0.42; mp 165–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.00 (s, 1H, C-2-H), 8.39 (s, 1H, ArH), 7.52 (s, 1H, ArH), 6.01 (dt, 1H, C*H*=CH_2, J = 17.0, 10.5, 5.0 Hz), 5.46 (d, 1H, CH=CH_aH$_b$, J = 10.0 Hz), 5.23 (app d, 1H, CH=CH$_a$$H_b$, J = 17.5 Hz), 4.81–4.76 (m, 2H, N-CH_2), 1.60 [s, 9H, C(CH_3)$_3$]; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 163.4, 149.9, 144.2, 141.4, 131.2, 129.6, 127.5, 126.2, 120.4, 119.8, 114.6, 82.3, 56.2, 28.4 (3C); IR (KBr): ν = 2974, 2933, 1716, 1633, 1601, 1562, 1522, 1474, 1370, 1340, 1253, 1164, 1136, 997, 922 cm^{-1}; HR-MS (ESI): m/z = 365.0893, exact mass calcd. for $C_{17}H_{18}N_2O_5Cl$ [M+H]$^+$: 365.0904.

3-Acetyl-7-chloro-6-nitro-1-propylquinolin-4(1*H*)-one (4.8)

3-[(2,4-Dichloro-5-nitrophenyl)(hydroxy)methyl]but-3-en-2-one (0.2 g, 0.69 mmol) and propylamine (0.08 g, 0.11 mL, 1.38 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.19 mL, 1.38 mmol) at 75 °C for 1 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (425 mg, 1.52 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.8** as a pale yellow crystalline solid; yield: 106 mg (50%). R_f (EtOAc) = 0.73; mp 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (s, 1H,C-2-H), 8.48 (s, 1H, ArH), 7.59 (s, 1H, ArH), 4.17 (t, 2H, N-CH_2, J = 7.6 Hz), 2.75 (s, 3H, CO-CH_3), 1.95 (sextet, 2H, CH_2-CH_2-CH_3, J = 7.6 Hz), 1.06 (t, 3H, CH_2-CH_2-CH_3, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 174.0, 149.8, 144.3, 141.3, 131.5, 128.3, 126.4, 119.7, 119.4, 56.1, 31.6, 22.3, 11.1; IR (KBr): ν = 2963, 1670, 1637, 1591, 1518, 1475, 1376, 1327, 1309, 1228, 1194, 1126, 987, 977 cm^{-1}; HR-MS (ESI): m/z = 309.0645, exact mass calcd. for $C_{14}H_{14}N_2O_4Cl$ [M+H]$^+$: 309.0642.

Methyl 6-Nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4.9)

Methyl 2-[(2-chloro-5-nitrophenyl)(hydroxy)methyl]acrylate (0.2 g, 0.74 mmol) and propylamine (0.087 g, 0.12 mL, 1.48 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 8 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (456 mg, 1.63 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.9** as a pale yellow crystalline solid; yield: 184 mg (86%). R_f (EtOAc) = 0.36; mp 189–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.25 (d, 1H, ArH, J = 2.5 Hz), 8.50 (s, 1H, C-2-H), 8.44 (dd, 1H, ArH, J = 9.0, 2.5 Hz), 7.58 (d, 1H, ArH, J = 9.5 Hz), 4.21 (t, 2H, N-CH_2-CH_2, J = 7. 5 Hz), 3.92 (s, 3H, OCH_3), 1.96 (sextet, 2H, -CH_2-CH_2-CH_3, J = 7.5 Hz), 1.06 (t, 3H, -CH_2-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 165.5, 150.4, 144.5, 142.6, 129.2, 126.9, 124.4, 117.4, 112.2, 56.2, 52.5, 22.3, 11.1; IR (KBr): ν = 3058, 2974, 2942, 1736, 1644, 1615, 1560, 1520, 1489, 1342, 1321, 1235, 1203, 1122, 1068 cm^{-1}; HR-MS (ESI): m/z = 291.0969, exact mass calcd. for $C_{14}H_{15}N_2O_5$ [M+H]$^+$: 291.0981.

Methyl 1-Butyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.10)

Methyl 2-[(2-chloro-5-nitrophenyl)(hydroxy)methyl]acrylate (0.2 g, 0.74 mmol) and butylamine (0.108 g, 0.146 mL, 1.48 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.48 mmol) at 75 °C for 2 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (456 mg, 1.63 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.10** as a pale yellow crystalline solid; yield: 186 mg (83%). R_f (70% EtOAc/hexanes) = 0.21; mp 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.35 (d, 1H, ArH, J = 3.0 Hz), 8.53 (s, 1H, C-2-H), 8.50 (dd, 1H, ArH, J = 9.0, 3.0 Hz), 7.58 (d, 1H, ArH, J = 9.5 Hz), 4.23 (t, 2H, N-CH_2-CH_2, J = 7.5 Hz), 3.96 (s, 3H, OCH_3), 1.90 (pentet, 2H, CH_2-CH_2-CH_2, J = 7.5 Hz), 1.47 (sextet, 2H, CH_2-CH_2-CH_3, J = 7.5 Hz), 1.02 (t, 3H, CH_2-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 165.7, 150.4, 144.5, 142.6, 129.3, 127.0, 124.6, 117.3, 112.4, 54.5, 52.6, 30.9, 20.0, 13.7; IR (KBr): ν = 2962, 1690, 1648, 1613, 1556, 1515, 1485, 1334, 1231, 1200, 1157, 1125, 1065, 837 cm^{-1}; HR-MS (ESI); m/z = 305.1133, exact mass calcd. for $C_{15}H_{17}N_2O_5$ [M+H]$^+$: 305.1137.

Methyl 1-Benzyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.11)

Methyl 2-[(2-chloro-5-nitrophenyl)(hydroxy)methyl]acrylate (0.2 g, 0.74 mmol) and benzylamine (0.159 g, 0.162 mL, 1.48 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.48 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (456 mg, 1.63 mmol) by heating the mixture for 20 h according to the general procedure discussed above to afford **4.11** as a pale yellow crystalline solid; yield: 174 mg (70%). R_f (EtOAc) = 0.63; mp 233–234 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (d, 1H, ArH, J = 2.8 Hz), 8.66 (s, 1H, C-2-H), 8.33 (dd, 1H, ArH, J = 9.2, 2.8 Hz), 7.46 (d, 1H, ArH, J = 9.2 Hz), 7.42–7.33 (m, 3H, ArH), 7.20–7.15 (m, 2H, ArH), 5.46 (s, 2H, N-CH_2), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 165.5, 151.0, 144.7, 142.9, 133.3, 129.8 (2C), 129.3 (2C), 127.0, 126.1 (2C), 124.4, 118.2, 112.7, 58.1, 52.6; IR (KBr): ν = 3073, 1738, 1633, 1614, 1557, 1522, 1483, 1341, 1310, 1236, 1185, 1163, 1117, 1065 cm^{-1}; HR-MS (ESI): m/z = 339.0992, exact mass calcd. for $C_{18}H_{15}N_2O_5$ [M+H]$^+$: 339.0981.

tert-Butyl 6-Nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4.12)

tert-Butyl 2-[(2-chloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.64 mmol) and propylamine (0.076 g, 0.106 mL, 1.28 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (393 mg, 1.41 mmol) by heating the mixture for 10 h according to the general procedure discussed above to afford **4.12** as a pale yellow crystalline solid; yield: 190 mg (90%). R_f (70% EtOAc/hexanes) = 0.57; mp 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (d, 1H, ArH, J = 2.8 Hz), 8.42 (dd, 1H, ArH, J = 9.2, 2.8 Hz), 8.37 (s, 1H, C-2-H) 7.55 (d, 1H, ArH, J = 9.6 Hz),

4.18 (t, 2H, N-CH_2-CH$_2$, J=7.6 Hz), 1.95 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J=7.6 Hz), 1.59 [s, 9H, C(CH$_3$)$_3$], 1.05 (t, 3H, CH$_2$-CH_3, J=7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ= 173.3, 163.7, 149.7, 144.2, 142.6, 129.1, 126.8, 124.4, 117.3, 113.9, 82.0, 56.0, 28.4 (3C), 22.2, 11.1; IR (KBr): ν=3046, 2978, 2967, 1724, 1712, 1632, 1615, 1605, 1523, 1487, 1394, 1337, 1248, 1169, 1156, 1126, 1066, 970 cm^{-1}; HR-MS (ESI): m/z=333.1467, exact mass calcd. for $C_{17}H_{21}N_2O_5$ [M+H]$^+$: 333.1450.

tert-Butyl 1-Cyclopropyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.13)

tert-Butyl 2-[(2-chloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.64 mmol) and cyclopropylamine (0.073 g, 0.089 mL, 1.28 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 12 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (393 mg, 1.41 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.13** as a pale yellow crystalline solid; yield; 183 mg (87%). R_f (70% EtOAc/hexanes)= 0.47; mp 228–230 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=9.24 (d, 1H, ArH, J=2.5 Hz), 8.53 (s, 1H, C-2-H), 8.46 (dd, 1H, ArH, J=9.0, 2.5 Hz), 8.04 (d, 1H, ArH, J=9.5 Hz), 3.54–3.49 [m, 1H, N-CH(CH$_2$)$_2$], 1.60 [s, 9H, C(CH$_3$)$_3$], 1.43–1.38 (m, 2H, 2cyclopropyl CH_aH$_b$), 1.20–1.15 (m, 2H, 2cyclopropyl CH$_a$$H_b$); ^{13}C NMR (125 MHz, CDCl$_3$): δ=173.3, 163.8, 149.2, 144.7, 144.3, 128.6, 126.7, 124.1, 118.0, 114.1, 82.1, 35.0, 28.4 (3C), 8.6 (2C); IR (KBr): ν=2979, 2927, 1697, 1641, 1616, 1563, 1480, 1348, 1334, 1255, 1167 cm^{-1}; HR-MS (ESI); m/z=331.1285, exact mass calcd. for $C_{17}H_{19}N_2O_5$ [M+H]$^+$: 331.1294.

tert-Butyl 1-Benzyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.14)

tert-Butyl 2-[(2-chloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.64 mmol) and benzylamine (0.137 g, 0.14 mL, 1.28 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 8 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (393 mg, 1.41 mmol) by heating the mixture for 24 h according to the general procedure discussed above to afford **4.14** as a pale yellow crystalline solid; yield: 197 mg (81%). R_f (EtOAc)=0.77; mp 173–176 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=9.32 (d, 1H, ArH, J=2.5 Hz), 8.53 (s, 1H, C-2-H), 8.32 (dd, 1H, J=9.5, 2.5 Hz), 7.43 (d, 1H, ArH, J=9.5 Hz), 7.42–7.37 (m, 3H, ArH), 7.20–7.10 (m, 2H, ArH), 5.43 (s, 2H, -NCH$_2$-), 1.61 [s, 9H, C(CH$_3$)$_3$]; ^{13}C NMR (125 MHz, CDCl$_3$): δ=173.5, 163.7, 150.2, 144.5, 142.9, 133.4, 129.8 (2C), 129.3, 129.2, 126.9, 126.3 (2C), 124.4, 118.1, 114.4, 82.2, 58.0, 28.4 (3C); IR (KBr): ν=3091, 2974, 1733, 1636, 1561, 1521, 1489, 1335, 1248, 1156, 1119, 1064, 966 cm^{-1}; HR-MS (ESI): m/z= 381.1455, exact mass calcd. for $C_{21}H_{21}N_2O_5$ [M+H]$^+$: 381.1450.

1-Ethyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carbonitrile (4.15)

2-[(2-Chloro-5-nitrophenyl)(hydroxy)methyl]acrylonitrile (0.2 g, 0.84 mmol) and 70% ethylamine (0.108 g, 0.09 mL, 1.68 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.24 mL, 1.68 mmol) at 75 °C for 10 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (518 mg, 1.85 mmol) by heating the mixture for 20 h according to the general procedure discussed above to afford **4.15** as a pale yellow crystalline solid; yield: 148 mg (73%). R_f (EtOAc)=0.5; mp 305–308 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.02 (s, 1H, C-2-H), 8.89 (brs, 1H, ArH), 8.58 (d, 1H, ArH, J=9.6 Hz), 8.14 (d, 1H, ArH, J=9.2 Hz), 4.43 (q, 2H, N-CH_2-CH$_3$, J= 7.2 Hz), 1.40 (t, 3H, N-CH$_2$-CH_3, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ=172.7, 151.7, 143.5, 142.0, 126.8, 125.3, 121.2, 119.4, 115.0, 94.8, 48.5, 13.6; IR (KBr): ν= 3045, 2227, 1632, 1607, 1561, 1529, 1488, 1338, 1174, 1078 cm^{-1}; HR-MS (ESI): m/z=282.0293, exact mass calcd. for $C_{12}H_9N_3O_3K$ [M+K]$^+$: 282.0281.

6-Nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carbonitrile (4.16)

2-[(2-Chloro-5-nitrophenyl)(hydroxy)methyl]acrylonitrile (0.2 g, 0.84 mmol) and propylamine (0.099 g, 0.138 mL, 1.68 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.24 mL, 1.68 mmol) at 75 °C for 10 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (518 mg, 1.85 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.16** as a pale yellow crystalline solid; yield: 151 mg (70%). R_f (EtOAc)=0.67; mp 250–252 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=9.01 (s, 1H, C-2-H), 8.86 (d, 1H, ArH, J=2.5 Hz), 8.54 (dd, 1H, ArH, J= 9.5, 3.0 Hz), 8.14 (d, 1H, ArH, J=9.5 Hz), 4.35 (t, 2H, N-CH_2-CH$_3$, J=7.5 Hz), 1.81 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J= 7.5 Hz), 0.93 (t, 3H, CH$_2$-CH_3, J=7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ=172.7, 152.0, 143.6, 142.2, 126.8, 125.3, 121.2, 119.6, 115.0, 94.7, 54.5, 21.1, 10.0; IR (KBr): ν= 3055, 2970, 2229, 1647, 1617, 1563, 1513, 1488, 1342, 1231, 1177, 1076 cm^{-1}; HR-MS (ESI): m/z=296.0437, exact mass calcd. for $C_{13}H_{11}N_3O_3K$ [M+K]$^+$: 296.0437.

1-Decyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carbonitrile (4.17)

2-[(2-Chloro-5-nitrophenyl)(hydroxy)methyl]acrylonitrile (0.2 g, 0.84 mmol) and decylamine (0.264 g, 0.34 mL, 1.68 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.24 mL, 1.68 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (518 mg, 1.85 mmol) by heating the mixture for 24 h according to the general procedure discussed above to afford **4.17** as a pale yellow crystalline solid; yield: 189 mg (71%). R_f (70% EtOAc/hexanes)=0.69; mp 120–122 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=9.20 (d, 1H, ArH, J=3.0 Hz), 8.54 (dd, 1H, ArH, J=9.5, 3.0 Hz), 8.17 (s, 1H, C-2-H), 7.66 (d, 1H, ArH, J=9.5 Hz), 4.28 (t, 2H, N-CH_2-CH$_2$, J=7.5 Hz), 1.93 (pentet, 2H, decyl-H, J= 7.5 Hz), 1.50–1.34 (m, 4H, decyl-H), 1.33–1.20 (m, 10H, decyl-H), 0.86 (t, 3H, CH$_2$-CH_3, J=7.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$): δ=173.4, 150.0, 144.8, 142.6, 127.8, 127.0, 123.9, 118.0, 114.6, 97.8, 55.3, 31.9, 29.5 (2C), 29.3, 29.2, 29.0, 26.7, 22.8, 14.2; IR (KBr): ν=2926, 2853, 2225, 1635, 1619, 1561, 1519, 1485, 1346, 1228, 1079 cm^{-1}; HR-MS

(ESI): $m/z = 356.1968$, exact mass calcd. for $C_{20}H_{26}N_3O_3$ $[M+H]^+$: 356.1974.

6-Nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide (4.18)

2-[(2-Chloro-5-nitrophenyl)(hydroxy)methyl]acrylamide (0.2 g, 0.78 mmol) and propylamine (0.09 g, 0.13 mL, 1.56 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.21 mL, 1.56 mmol) at 75 °C for 14 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (480 mg, 1.72 mmol) by heating the mixture for 20 h according to the general procedure discussed above to afford **4.18** as a pale yellow crystalline solid; yield: 139 mg (65%). R_f (EtOAc) = 0.38; mp 238–240 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 9.01$ (brs, 2H, NH_2), 8.94 (s, 1H, C-2-H), 8.52 (dd, 1H, ArH, $J = 9.5$, 3.0 Hz), 8.14 (d, 1H, ArH, $J = 9.0$ Hz), 7.66 (d, 1H, ArH, $J = 3.5$ Hz), 4.48 (t, 2H, N-CH_2, $J = 7.5$ Hz), 1.80 (sextet, 2H, CH_2-CH_2-CH_3, $J = 7.5$ Hz), 0.92 (t, 3H, CH_2-CH_2-CH_3, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 174.4$, 164.2, 149.7, 143.2, 142.2, 126.5, 126.1, 121.8, 119.1, 112.2, 54.3, 21.4, 10.0; IR (KBr): $\nu = 3380$, 3352, 3307, 2974, 1678, 1661, 1614, 1558, 1526, 1493, 1343, 1232, 1069 cm^{-1}; HR-MS (ESI): $m/z = 276.0977$, exact mass calcd. for $C_{13}H_{14}N_3O_4$ $[M+H]^+$: 276.0984.

1-Cyclopropyl-6-nitro-3-(phenylsulphonyl)quinolin-4(1*H*)-one (4.19)

1-(2-Chloro-5-nitrophenyl)-2-(phenylsulphonyl)prop-2-en-1-ol (0.2 g, 0.56 mmol) and cyclopropylamine (0.06 g, 0.08 mL, 1.13 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.16 mL, 1.13 mmol) at 75 °C for 8 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (348 mg, 1.24 mmol) by heating the mixture for 8 h according to the general procedure discussed above to afford **4.19** as a pale yellow crystalline solid; yield: 106 mg (50%). R_f (50% EtOAc/hexanes) = 0.17; mp 199–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.21$ (d, 1H, ArH, $J = 2.5$ Hz), 8.79 (s, 1H, C-2-H), 8.53 (dd, 1H, ArH, $J = 9.5$, 2.5 Hz), 8.19–8.17 (m, 2H, ArH), 8.11 (d, 1H, ArH, $J = 9.5$ Hz), 7.62–7.58 (m, 1H, ArH), 7.55–7.52 (m, 2H ArH), 3.63–3.57 [m, 1H, N-C*H*$(CH_2)_2$], 1.50–1.44 (m, 2H, 2cyclopropyl CH_aH_b), 1.26–1.20 (m, 2H, 2cyclopropyl CH$_a$H$_b$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.1$, 147.3, 145.0, 144.8, 140.1, 133.8, 128.9 (3C), 128.1, 127.4 (2C), 123.6, 122.4, 118.6, 35.6, 8.9 (2C); IR (KBr): $\nu = 3223$, 1647, 1614, 1521, 1470, 1337, 1296, 1153, 1072, 830 cm^{-1}; HR-MS (ESI): $m/z = 371.0694$, exact mass calcd. for $C_{18}H_{15}N_2O_5S$ $[M+H]^+$: 371.0702.

Methyl 6-Cyano-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4.20)

Methyl 2-[(5-cyano-2-fluorophenyl)(hydroxy)methyl]acrylate (0.1 g, 0.43 mmol) and propylamine (0.05 g, 0.07 mL, 0.86 mmol) in NMP (1 mL) were reacted in the presence of triethylamine (0.12 mL, 0.86 mmol) at 75 °C for 12 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (262 mg, 0.95 mmol) by heating the mixture for 15 h according to the general procedure discussed above to afford **4.20** as a colourless crystalline solid; yield: 84 mg (72%). R_f (EtOAc) = 0.33; mp 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.84$ (s, 1H, ArH), 8.53 (s, 1H, C-2-H), 7.89 (d, 1H, ArH, $J = 8.4$ Hz), 7.54 (d, 1H, ArH, $J = 8.8$ Hz), 4.17 (t, 2H, N-CH_2-CH_2, $J = 7.2$ Hz), 3.95 (s, 3H, OCH_3), 1.95 (sextet, 2H, CH_2-CH_2-CH_3, $J = 7.2$ Hz), 1.06 (t, 3H, CH_2-CH_2-CH_3, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.7$, 165.7, 150.3, 141.4, 134.8, 133.6, 129.3, 118.0, 117.2, 112.3, 108.9, 55.9, 52.5, 22.3, 11.1; IR (KBr): $\nu = 2971$, 2228, 1728, 1632, 1593, 1561, 1494, 1480, 1389, 1314, 1243, 1207, 1088 cm^{-1}; HR-MS (ESI): $m/z = 271.1084$, exact mass calcd. for $C_{15}H_{15}N_2O_3$ $[M+H]^+$: 271.1083.

Methyl 6-Cyano-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.21)

Methyl 2-[(5-cyano-2-fluorophenyl)(hydroxy)methyl]acrylate (0.1 g, 0.43 mmol) and cyclopropylamine (0.05 g, 0.06 mL, 0.86 mmol) in NMP (1 mL) were reacted in the presence of triethylamine (0.12 mL, 0.86 mmol) at 75 °C for 12 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (262 mg, 0.95 mmol) by heating the mixture for 12 h according to the general procedure discussed above to afford **4.21** as a colourless crystalline solid; yield: 104 mg (90%). R_f (EtOAc) = 0.33; mp 247–249 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.79$ (d, 1H, ArH, $J = 2.0$ Hz), 8.66 (s, 1H, C-2-H), 8.03 (d, 1H, ArH, $J = 8.5$ Hz), 7.91 (dd, 1H, ArH, $J = 8.5$, 2.0 Hz), 3.94 (s, 3H, OCH_3), 3.52–3.47 [m, 1H, N-C*H*$(CH_2)_2$], 1.43–1.37 (m, 2H, 2cyclopropyl CH_aH_b), 1.19–1.14 (m, 2H, 2cyclopropyl CH$_a$H$_b$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.8$, 165.6, 149.9, 143.0, 134.7, 133.1, 128.7, 118.0 (2C), 112.5, 109.1, 52.5, 34.9, 8.6 (2C); IR (KBr): $\nu = 3234$, 2953, 2918, 2229, 1729, 1633, 1618, 1597, 1559, 1545, 1486, 1347, 1321, 1251, 1213, 1091, 825 cm^{-1}; HR-MS (ESI): $m/z = 269.0935$, exact mass calcd. for $C_{15}H_{13}N_2O_3$ $[M+H]^+$: 269.0926.

1-Cyclopropyl-4-oxo-1,4-dihydroquinoline-3,6-dicarbonitrile (4.22)

3-(2-Cyano-1-hydroxyallyl)-4-fluorobenzonitrile (0.1 g, 0.49 mmol) and cyclopropylamine (0.056 g, 0.07 mL, 0.99 mmol) in NMP (1 mL) were reacted in the presence of triethylamine (0.14 mL, 0.99 mmol) at 75 °C for 10 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidised using IBX (305 mg, 1.09 mmol) by heating the mixture for 11 h according to the general procedure discussed above to afford **4.22** as a colourless crystalline solid; yield: 82 mg (71%). R_f (EtOAc) = 0.53; mp 286–288 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.89$ (s, 1H, C-2-H), 8.52 (d, 1H, ArH, $J = 1.0$ Hz), 8.28–8.27 (m, 2H, ArH), 3.71–3.67 [m, 1H, N-C*H*$(CH_2)_2$], 1.25–1.22 (m, 2H, 2cyclopropyl CH_aH_b), 1.20–1.18 (m, 2H, 2cyclopropyl CH_aH_b); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 172.9$, 151.9, 143.2, 135.5, 130.8, 125.5, 119.8, 117.9, 115.6, 108.2, 95.2, 35.3, 7.7 (2C); IR (KBr): $\nu = 3042$, 2228, 1656, 1630, 1563, 1479, 1421, 1317, 1195, 830 cm^{-1}; HR-MS (ESI): $m/z = 236.0817$, exact mass calcd. for $C_{14}H_{10}N_3O$ $[M+H]^+$: 236.0824.

7-Chloro-6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carbaldehyde (4.23)

Methyl 2-[(2,4-dichloro-5-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.66 mmol) and propylamine (0.078 g, 0.11 mL,

1.31 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.18 mL, 1.31 mmol) at 75 °C for 1 h. The mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), washed with water (3×20 mL) and brine (10 mL). The organic layer was dried with sodium sulphate, filtered and evaporated under reduced pressure to get a residue. To the methanol solution of this residue, $NaBH_4$ (100 mg, 2.64 mmol) was added and stirred at room temperature for 2 h. After complete consumption of starting materials, solvents were removed under reduced pressure and diluted with ethyl acetate (20 mL) and water (30 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated to get the 1,3-diol which was re-dissolved in acetonitrile (10 mL) and 2-iodoxybenzoic acid (647 mg, 2.31 mmol) was added to it. The mixture was then heated at 75 °C for 12 h according to the general procedure discussed above to afford **4.23** as a pale yellow crystalline solid; yield: 116 mg (60%). R_f (EtOAc) = 0.77; mp 194–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.36 (s, 1H, CHO), 9.02 (s, 1H, C-2-H), 8.30 (s, 1H, ArH), 7.63 (s, 1H, ArH), 4.18 (t, 2H, N-CH_2-CH$_2$, J = 7.5 Hz), 1.98 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J = 7.5 Hz), 1.08 (t, 3H, CH$_2$-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.5, 175.0, 147.6, 141.6, 133.3, 132.0, 128.3, 125.8, 119.9, 118.2, 56.3, 22.2, 11.1; IR (KBr): ν = 2958, 1684, 1635, 1601, 1561, 1520, 1484, 1448, 1368, 1346, 1293, 1224 cm^{-1}; HR-MS (ESI): m/z = 295.0489, exact mass calcd. for $C_{13}H_{12}N_2O_4Cl$ $[M+H]^+$: 295.0486.

Methyl 1-Butyl-8-cyano-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.24)

Methyl 2-[(2-bromo-3-cyanophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.67 mmol) and butylamine (0.075 g, 0.1 mL, 1.35 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 12 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative in acetonitrile (15 mL) was oxidised by heating the mixture with IBX (416 mg, 1.48 mmol) for 20 h according to the general procedure discussed above to afford **4.24** as a colourless crystalline solid; yield: 115 mg (60%). R_f (50% EtOAc/hexanes) = 0.37; mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.83 (d, 1H, ArH, J = 7.5 Hz), 8.47 (s, 1H, C-2-H), 8.06 (d, 1H, ArH, J = 7.0 Hz), 7.51 (t, 1H, ArH, J = 7.5 Hz), 4.65 (t, 2H, N-CH$_2$, J = 7.5 Hz), 3.94 (s, 3H, OCH$_3$), 1.96 (pentet, 2H, CH$_2$-CH_2-CH$_2$, J = 7.5 Hz), 1.50 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J = 7.5 Hz), 1.01 (t, 3H, CH$_2$-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 165.7, 151.7, 141.4, 139.2, 134.3, 130.9, 124.8, 118.3, 112.3, 100.6, 56.4, 52.6, 32.8, 19.2, 13.8; IR (KBr): ν = 2953, 2228, 1678, 1641, 1559, 1428, 1326, 1248, 787 cm^{-1}; HR-MS (ESI): m/z = 285.3228, exact mass calcd. for $C_{16}H_{17}N_2O_3$ $[M+H]^+$: 285.3237.

Methyl 1-Butyl-5-chloro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4.25)

Methyl 2-[(2,6-dichloro-3-nitrophenyl)(hydroxy)methyl]-acrylate (0.2 g, 0.65 mmol) and butylamine (0.075 g, 0.1 mL, 1.35 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.2 mL, 1.47 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative in acetonitrile (15 mL) was oxidised by heating the mixture with IBX (416 mg, 1.48 mmol) for 24 h according to the general procedure discussed above to afford **4.25** as a semisolid; yield: 139 mg (63%). R_f (50% EtOAc/hexanes) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1H, C-2-H), 7.85 (d, 1H, ArH, J = 8.8 Hz), 7.46 (d, 1H, ArH, J = 8.4 Hz), 3.93 (s, 3H, OCH$_3$), 3.83 (t, 2H, N-CH$_2$, J = 7.6 Hz), 1.64 (pentet, 2H, CH$_2$-CH_2-CH$_3$, J = 7.6 Hz), 1.15 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J = 7.6 Hz), 0.85 (t, 3H, CH$_2$-CH_3, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 165.2, 149.8, 141.0, 140.4, 136.0, 128.2, 128.1, 127.7, 114.9, 56.9, 52.6, 32.2, 19.7, 13.4; IR (KBr): ν = 2958, 2938, 1733, 1646, 1613, 1585, 1530, 1466, 1314, 1199, 1124 cm^{-1}; HR-MS (ESI): m/z = 339.7560, exact mass calcd. for $C_{15}H_{16}N_2O_5Cl$ $[M+H]^+$: 339.7561.

Methyl 4-Oxo-1-propyl-1,4-dihydrobenzo[*b*][1,8]-naphthyridine-3-carboxylate (7.1)

Methyl 2-[(2-chloroquinolin-3-yl)(hydroxy)methyl]acrylate (0.1 g, 0.36 mmol) and propylamine (0.042 g, 0.060 mL, 0.72 mmol) in NMP (1 mL) were reacted in the presence of triethylamine (0.1 mL, 0.72 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydrobenzo[*b*][1,8]naphthyridine derivative was oxidised using IBX (222 mg, 0.79 mmol) by heating the mixture for 8 h according to the general procedure discussed above to afford **7.1** as a colourless crystalline solid; yield: 96 mg (90%). R_f (50% EtOAc/hexanes) = 0.28; mp 179–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.32 (s, 1H, C-2-H), 8.78 (s, 1H, ArH), 8.07 (brs, 1H, ArH), 8.05 (brs, 1H, ArH), 7.85 (ddd, 1H, J = 7.0, 5.5, 1.5 Hz, ArH), 7.58 (app t, 1H, ArH), 4.51 (t, 2H, N-CH$_2$, J = 7.5 Hz), 3.96 (s, 3H, OCH$_3$), 2.01 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J = 7.5 Hz), 1.04 (t, 3H, CH$_2$-CH$_2$-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7, 166.3, 151.8, 149.0, 147.9, 139.1, 132.8, 129.6, 128.4, 126.5, 126.1, 122.4, 109.3, 53.4, 52.3, 22.9, 11.3; IR (KBr): ν = 2954, 1679, 1652, 1600, 1486, 1428, 1319, 1215, 1142, 1091, 809, 757 cm^{-1}; HR-MS (ESI): m/z = 297.1224, exact mass calcd. for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1239.

Methyl 1-Butyl-4-oxo-1,4-dihydrobenzo[*b*][1,8]naphthyridine-3-carboxylate (7.2)

Methyl 2-[(2-chloroquinolin-3-yl)(hydroxy)methyl]acrylate (0.1 g, 0.36 mmol) and butylamine (0.052 g, 0.07 mL, 0.72 mmol) in NMP (1.5 mL) were reacted in the presence of triethylamine (0.1 mL, 0.72 mmol) at 75 °C for 3 h and the resulting 4-hydroxy-1,2,3,4-tetrahydrobenzo[*b*][1,8]-naphthyridine derivative was oxidised using IBX (222 mg, 0.79 mmol) by heating the mixture for 10 h according to the general procedure discussed above to afford **7.2** as a colourless crystalline solid; yield: 89 mg (80%). R_f (50% EtOAc/hexanes) = 0.33; mp 186–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (s, 1H, C-2-H), 8.79 (s, 1H, ArH), 8.09–8.06 (m, 2H, ArH), 7.86 (ddd, 1H, ArH, J = 8.5, 7.0, 1.5 Hz), 7.60 (ddd, 1H, ArH, J = 8.0, 7.0, 1.5 Hz), 4.56 (t, 2H, N-CH_2-CH$_2$-, J = 7.5 Hz), 3.96 (s, 3H, OCH$_3$), 1.96 (pentet, 2H, CH$_2$-CH_2-CH$_2$, J = 7.5 Hz), 1.47 (sextet, 2H, CH$_2$-CH_2-CH$_3$, J = 7.5 Hz), 1.02 (t, 3H, CH$_2$-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7, 166.3, 151.7, 148.9, 147.9, 139.0, 132.7, 129.6, 128.4, 126.5, 126.1, 122.4, 109.3, 52.3, 51.5, 31.7, 20.1, 13.8; IR (KBr): ν = 3056, 2954, 1678, 1653, 1617, 1600, 1559, 1484, 1430, 1412, 1337, 1321, 1215, 1093,

810 cm^{-1}; HR-MS (ESI): $m/z = 311.1396$, exact mass calcd. for $C_{18}H_{19}N_2O_3$ $[M+H]^+$: 311.1396.

Methyl 1-Cyclopropyl-4-oxo-1,4-dihydrobenzo[*b*]-[1,8]naphthyridine-3-carboxylate (7.3)

Methyl 2-[(2-chloroquinolin-3-yl)(hydroxy)methyl]acrylate (0.1 g, 0.36 mmol) and cyclopropylamine (0.04 g, 0.05 mL, 0.72 mmol) in NMP (1 mL) were reacted in the presence of triethylamine (0.1 mL, 0.72 mmol) at 75 °C for 3 h and the resulting 4-hydroxy-1,2,3,4-tetrahydrobenzo[b][1,8]naphthyridine derivative was oxidised using IBX (222 mg, 0.79 mmol) by heating the mixture for 6 h according to the general procedure discussed above to afford **7.3** as a colourless crystalline solid; yield: 78 mg (74%). R_f (70% EtOAc/hexanes) = 0.31; mp 186–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.27$ (s, 1H, C-2-H), 8.82 (s, 1H, ArH), 8.11 (d, 1H, ArH, $J = 8.5$ Hz), 8.04 (d, 1H, ArH, $J = 8.5$ Hz), 7.85 (ddd, 1H, ArH, $J = 8.0$, 6.5, 1.5 Hz), 7.58 (ddd, 1H, ArH, $J = 8.0$, 6.5, 1.5 Hz), 3.94 (s, 3H, OCH_3), 3.85–3.80 [m, 1H, N-C*H*$(CH_2)_2$], 1.38–1.32 (m, 2H, 2cyclopropyl C*H*$_a$H$_b$), 1.12–1.08 (m, 2H, 2cyclopropyl CH$_a$*H*$_b$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.7$, 166.1, 151.3, 149.3, 149.1, 138.8, 132.7, 129.6, 128.7, 126.6, 126.2, 122.0, 109.4, 52.3, 34.4, 7.9 (2C); IR (KBr): $\nu = 3050$, 1730, 1631, 1618, 1602, 1580, 1476, 1435, 1421, 1360, 1330, 1319, 1086, 1036, 811 cm^{-1}; HR-MS (ESI): $m/z = 295.1070$, exact mass calcd. for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: 295.1083.

Methyl 1-Allyl-9-methyl-4-oxo-1,4-dihydrobenzo[*b*]-[1,8]naphthyridine-3-carboxylate (7.4)

Methyl 2-[(2-chloro-8-methylquinolin-3-yl)(hydroxy)methyl]acrylate (0.16 g, 0.58 mmol) and allylamine (0.066 g, 0.09 mL, 1.16 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.16 mL, 1.16 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydrobenzo[*b*][1,8]naphthyridine derivative was oxidised using IBX (357 mg, 1.28 mmol) by heating the mixture for 10 h according to the general procedure discussed above to afford **7.4** as a pale yellow crystalline solid; yield: 113 mg (63%). R_f (50% EtOAc/hexanes) = 0.27; mp 199–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.27$ (s, 1H, C-2-H), 8.79 (s, 1H, ArH), 7.89 (d, 1H, ArH, $J = 8.0$ Hz), 7.69 (dd, 1H, ArH, $J = 6.0$, 1.0 Hz), 7.47 (dd, 1H, ArH, $J = 8.5$, 7.0 Hz), 6.14 (dddd, 1H, C*H*=CH$_2$, $J = 17.2$, 10.0, 6.0, 6.0 Hz), 5.39 (app dd, 1H, CH=C*H*$_a$H$_b$, $J = 17.5$, 1.0 Hz), 5.34 (app dd, 1H, CH=CH$_a$*H*$_b$, $J = 10.5$, 1.5 Hz), 5.17 (ddd, 2H, N-CH$_2$, $J = 6.0$, 1.5, 1.5 Hz), 3.95 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.8$, 166.2, 151.2, 148.0, 146.7, 139.2, 136.3, 132.6, 131.9, 127.5, 126.4, 126.1, 121.9, 119.9, 109.8, 53.3, 52.3, 18.1; IR (KBr): $\nu = 3352$, 3239, 1693, 1639, 1560, 1481, 1429, 1329, 1219, 1117 cm^{-1}; HR-MS (ESI): $m/z = 331.1063$, exact mass calcd. for $C_{18}H_{16}N_2O_3Na$ $[M+Na]^+$: 331.1059.

Methyl 4-Oxo-1-propyl-1,4-dihydro-1,8-naphthyridine-3-carboxylate (7.5)

Methyl 2-[(2-bromopyridin-3-yl)(hydroxy)methyl]acrylate (0.125 g, 0.46 mmol) and propylamine (0.054 g, 0.08 mL, 0.92 mmol) in NMP (1 mL) were reacted in the presence of triethylamine (0.13 mL, 0.92 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative was oxidised using IBX (283 mg, 1.01 mmol) by heating the mixture for 5 h according to the general procedure discussed above to afford **7.5** as a colourless crystalline solid; yield: 90 mg (80%). R_f (EtOAc) = 0.36; mp 117–119 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.78$ (dd, 1H, ArH, $J = 8.0$, 2.0 Hz), 8.73 (dd, 1H, ArH, $J = 4.5$, 2.0 Hz), 8.66 (s, 1H, C-2-H), 7.40 (dd, 1H, ArH, $J = 8.0$, 5.0 Hz), 4.39 (t, 2H, N-C*H*$_2$-CH$_2$, $J = 7.5$ Hz), 3.93 (s, 3H, OCH_3), 1.92 (sextet, 2H, CH$_2$-C*H*$_2$-CH$_3$, $J = 7.5$ Hz), 1.00 (t, 3H, CH$_2$-C*H*$_3$, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.8$, 166.3, 152.5, 149.9, 149.4, 137.1, 124.0, 121.2, 111.6, 53.4, 52.3, 23.1, 11.2; IR (KBr): $\nu = 3235$, 2966, 1722, 1678, 1636, 1618, 1564, 1490, 1438, 1413, 1335, 1236, 1137 cm^{-1}; HR-MS (ESI): $m/z = 247.1082$, exact mass calcd. for $C_{13}H_{15}N_2O_3$ $[M+H]^+$: 247.1083.

Methyl 1-Butyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (7.6)

Methyl 2-[(2-bromopyridin-3-yl)(hydroxy)methyl]acrylate (0.1 g, 0.37 mmol) and butylamine (0.054 g, 0.07 mL, 0.74 mmol) in NMP (2 mL) were reacted in the presence of triethylamine (0.1 mL, 0.74 mmol) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative was oxidised using IBX (227 mg, 0.81 mmol) by heating the mixture for 7 h according to the general procedure discussed above to afford **7.6** as a colourless crystalline solid; yield: 68 mg (71%). R_f (EtOAc) = 0.55; gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.76$ (d, 1H, ArH, $J = 7.6$ Hz), 8.72 (d, 1H, ArH, $J = 4.0$ Hz), 8.65 (s, 1H, C-2-H), 7.39 (dd, 1H, ArH, $J = 8.0$, 4.8 Hz), 4.41 (t, 2H, N-C*H*$_2$-CH$_2$, $J = 7.2$ Hz), 3.91 (s, 3H, OCH_3), 1.84 (pentet, 2H, CH$_2$-C*H*$_2$-CH$_2$, $J = 7.2$ Hz), 1.39 (sextet, 2H, CH$_2$-C*H*$_2$-CH$_3$, $J = 7.2$ Hz), 0.95 (t, 3H, -CH$_2$-C*H*$_3$, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.9$, 166.1, 152.5, 149.9, 149.3, 137.0, 123.9, 121.2, 111.5, 52.3, 51.6, 31.8, 20.0, 13.8; IR (neat): $\nu = 3055$, 2959, 2928, 1730, 1699, 1628, 1611, 1552, 1492, 1438, 1412, 1381, 1332, 1265, 1229, 1208, 1101, 1094 cm^{-1}; HR-MS (ESI): $m/z = 261.1233$, exact mass calcd. for $C_{14}H_{17}N_2O_3$ $[M+H]^+$: 261.1239.

1-Butyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbonitrile (7.7)

2-[(2-Bromopyridin-3-yl)(hydroxy)methyl]acrylonitrile (0.1 g, 0.42 mmol) and butylamine (0.06 g, 0.08 mL, 0.84 mmol) in NMP (1.5 mL) were reacted in the presence of triethylamine (0.12 mL, 0.84 mmol) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative was oxidised using IBX (259 mg, 0.92 mmol) by heating the mixture for 8 h according to the general procedure discussed above to afford **7.7** as a colourless crystalline solid; yield: 70 mg (73%). R_f (EtOAc) = 0.83; mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.80$ (dd, 1H, ArH, $J = 4.5$, 2.0 Hz), 8.73 (dd, 1H, ArH, $J = 8.0$, 2.0 Hz), 8.20 (s, 1H, C-2-H), 7.46 (dd, 1H, ArH, $J = 8.0$, 4.5 Hz), 4.44 (t, 2H, N-C*H*$_2$-CH$_2$, $J = 7.5$ Hz), 1.86 (pentet, 2H, CH$_2$-C*H*$_2$-CH$_2$, $J = 7.5$ Hz), 1.42 (sextet, 2H, CH$_2$-C*H*$_2$-CH$_3$, $J = 7.5$ Hz), 0.99 (t, 3H, -CH$_2$-C*H*$_3$, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.1$, 153.4, 149.3, 149.1, 136.6, 122.1, 121.8, 115.2, 97.0, 52.0, 31.8, 20.0, 13.8; IR (KBr): $\nu = 3047$, 2957, 2869, 2222,

1635, 1553, 1493, 1421, 1367, 786 cm^{-1}; HR-MS (ESI): m/z = 228.1134, exact mass calcd. for $C_{13}H_{14}N_3O$ $[M+H]^+$: 228.1137.

6-Nitro-4-oxo-7-(piperidin-1-yl)-1-propyl-1,4-dihydroquinoline-3-carboxylate (8)

To a stirred solution of **4.1** (0.2 g, 0.62 mmol) in DMF (2 mL), was added piperidine (0.21 mg, 0.24 mL, 2.48 mmol) and the mixture was heated at 80 °C for 2 h. It was allowed to cool to room temperature, diluted with ethyl acetate (10 mL), washed with water (3×10 mL) and brine (10 mL). The organic portion was dried (Na_2SO_4), filtered and the solvents were evaporated to get a residue which was purified by silicagel column chromatography to afford the product **8** as a yellow crystalline solid; yield: 219 mg (95%). R_f (EtOAc) = 0.58; mp 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1H, ArH), 8.41 (s, 1H, C-2-H), 6.75 (s, 1H, ArH), 4.09 (t, 2H, N-CH_2, J = 7.2 Hz), 3.92 (s, 3H, OCH_3), 3.20–3.10 (m, 4H, piperidinyl-*H*a & *H*a′), 1.94 (sextet, 2H, CH_2-CH_2-CH_3, J = 7.2 Hz), 1.80–1.70 (m, 4H, piperidinyl-*H*b & *H*b′), 1.70–1.50 (m, 2H, piperidinyl-Hc), 1.05 (t, 3H, CH_2-CH_3, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 165.8, 150.3, 149.1, 142.1, 139.6, 127.2, 121.0, 110.9, 104.5, 55.7, 52.4 (2C), 52.2, 25.6 (2C), 23.8, 21.9, 11.2; IR (KBr): ν = 2970, 2939, 1731, 1613, 1583, 1566, 1471, 1378, 1335, 1313, 1248, 1110, 1074 cm^{-1}; HR-MS (ESI): m/z = 374.1715, exact mass calcd. for $C_{19}H_{24}N_3O_5$ $[M+H]^+$: 374.1716.

Methyl 6-Amino-4-oxo-7-(piperidin-1-yl)-1-propyl-1,4-dihydroquinoline-3-carboxylate (9)

To the methanol solution of compound **8** (0.1 g, 0.27 mmol), Lindlar's catalyst (20 mg) was added and it was stirred under hydrogen atmosphere (balloon) at room temperature for 2 h. After completion, the reaction mixture was passed through a celite bed and the filtrate was evaporated to get the product in almost pure form. Small amounts of residual impurities present were subsequently removed by silica gel column chromatography to afford the aminoquinolone **9** as a yellowish white solid; yield: 88 mg (96%). R_f (100% EtOAc) = 0.17; mp 233–235 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1H, C-2-H), 7.77 (s, 1H, ArH), 6.87 (s, 1H, ArH), 4.13 (brs, 2H, NH_2), 4.08 (t, 2H, N-CH_2-CH_2, J = 7.5 Hz), 3.90 (s, 3H, OCH_3), 3.10–2.90 (m, 4H, piperidinyl-*H*a & *H*a′), 1.91 (sextet, 2H, CH_2-CH_2-CH_3, J = 7.5 Hz), 1.78–1.72 (m, 4H, piperidinyl-*H*b & *H*b′), 1.63 (m, 2H, piperidinyl-Hc), 1.00 (t, 3H, -CH_2-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 167.4, 147.4, 146.3, 140.0, 132.4, 126.2, 110.8, 108.7, 105.7, 55.7, 52.2 (2C), 52.1, 26.6 (2C), 24.3, 22.3, 11.3; IR (KBr): ν = 3233, 2929, 1723, 1636, 1618, 1561, 1501, 1320, 1097 cm^{-1}; HR-MS (ESI): m/z = 344.1984, exact mass calcd. for $C_{19}H_{26}N_3O_3$ $[M+H]^+$: 344.1974.

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[38] CCDC 926961 and CCDC 926960 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

