Tetrahedron 65 (2009) 10149–10154

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The first synthesis of 2-amino-1,4-dihydroquinolines

Guillaume Viault [a], Danielle Grée [a], Thierry Roisnel [b], Srivari Chandrasekhar [c], René Grée [a,*]

[a] Université de Rennes 1, Laboratoire CPM, CNRS UMR 6510, Avenue du Général Leclerc, 35042 Rennes Cedex, France
[b] Université de Rennes 1, Sciences Chimiques de Rennes, CNRS UMR 6226, Campus de Beaulieu, 35042 Rennes-Cedex, France
[c] Indian Institute of Chemical Technology, 500607 Hyderabad, India

ARTICLE INFO

Article history:
Received 23 July 2009
Received in revised form 2 October 2009
Accepted 6 October 2009
Available online 13 October 2009

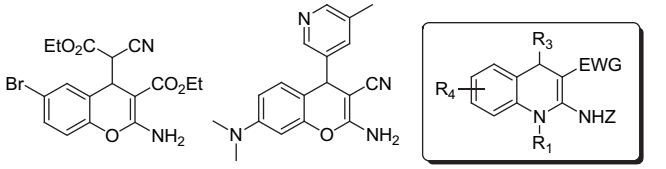
Keywords:
1,4-Dihydroquinolines
HA 14-1
Benzopyran
Anti-cancer
Bcl-2

ABSTRACT

A versatile strategy is described for the synthesis of new 2-amino-1,4-dihydroquinolines. It involved a Knoevenagel condensation of *N*-protected-2-amino-5-bromobenzaldehyde with ethylcyanoacetate, followed by a cyclization and protection of the NH group to afford the key intermediates **7** or **19**. Then various 1,4 addition reactions have been performed to introduce substituents on the upper part of the 2-amino-1,4-dihydroquinolines.

1. Introduction

The 2-amino-*4H*-chromenes belong to an important, and well studied, group of heterocyclic compounds.[1] During the last decade, molecules with this skeleton have demonstrated potent biological activity in various areas of medicinal chemistry. In particular, several derivatives such as HA 14-1 and MX58151, which are known to have proapoptotic activity, are under development as *anti*-cancer agents (Fig. 1).[2,3]



HA 14-1 MX58151 2-amino-1,4-dihydroquinolines

Figure 1. Representative 2-amino-*4H*-chromenes and general formula for targets 2-amino-1,4-dihydroquinolines.

These 2-amino-*4H*-chromenes are generally prepared by reaction of a malonic derivative with substituted salicylaldehydes. The molecular diversity around the skeleton was extensively studied either by modification of the malonic type derivative, or by introduction of halogen, aryl, or amino groups in the aromatic aldehyde part.[1–4]

As a part of our programme on new *anti*-cancer agents active through an apoptosis inducing mechanism,[5,6] we became interested in the 'aza-analogues' of these 2-amino-*4H*-chromenes, i.e, the corresponding 2-amino-1,4-dihydroquinolines (Fig. 1).

The synthesis of 1,4-dihydroquinolines has been rarely described in the literature.[7] Several 2-methyl-1,4-dihydroquinolines have been obtained by regioselective reduction of quinolinium salts with sodium dithionite in the presence of sodium carbonate. These 1,4-dihydroquinolines are inhibitors of acetylcholine esterase and therefore active against neurodegenerative diseases.[8] The same methodology was used for the synthesis of 1,2,4-trimethyl-1,4-dihydroquinolines.[9] Finally, a synthesis of *N*-substituted 1,4-dihydroquinolines, with an hydrogen on position 2, has been developed starting from Baylis–Hillman adducts.[10]

To the best of our knowledge, 2-amino-1,4-dihydroquinolines have not been reported until now in the literature. Our strategy to access such molecules was designed by analogy with the preparation of the corresponding *4H*-chromenes.[4,6] Our first target molecules (type ***A***) have been selected for Structure–Activity Relationships in comparison with HA 14-1 derivatives, and therefore, we have kept the bromo substituent in *para* position to the aromatic amine. These 1,4-dihydroquinolines could be obtained by Michael addition reactions on the key imine (***B***), which should be obtained by a Knoevenagel condensation between ethylcyanoacetate and the aldehyde (***C***). This latter derivative could be

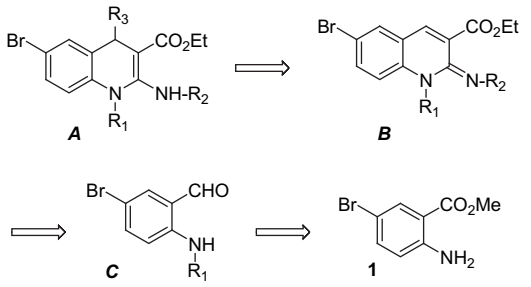
* Corresponding author. Tel.: +33 2 23 23 57 15; fax: +33 2 23 23 65 98.
E-mail address: rene.gree@univ-rennes1.fr (R. Grée).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.10.018

prepared from anilino ester **1**. In this strategy the amine function must be protected with an appropriate R_1 group. It has been established earlier that, in the case of the primary amines obtained for instance by reduction of a nitro group, the Knoevenagel condensation was followed by heterocyclization and aromatization affording 2-aminoquinolines.[11]

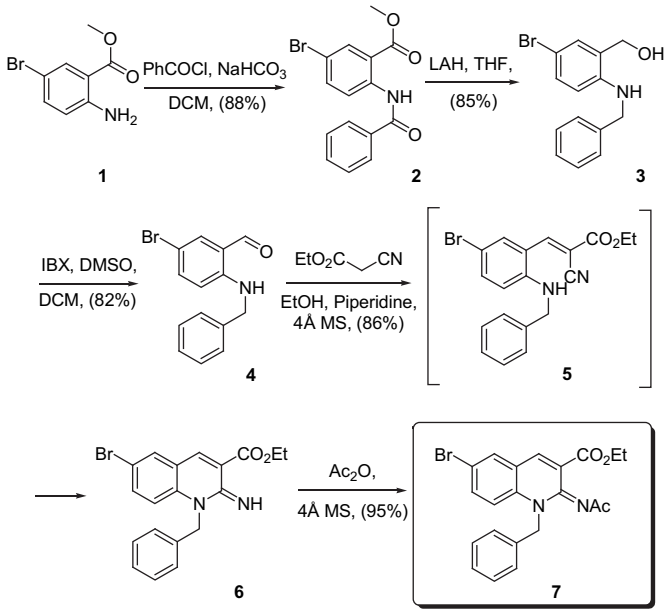
2. Results and discussion

The reaction of the commercially available methyl-2-amino-5-bromobenzoate **1** with benzoyl chloride and sodium bicarbonate in CH_2Cl_2 at 0 °C afforded **2** in 88% yield (Schemes 1 and 2). This amido ester **2** was reduced by excess lithium aluminium hydride in THF at −10 °C to give, in 85% yield, the desired amino alcohol **3** which, on further oxidation by 2-iodoxybenzoic acid (IBX) in a mixture of CH_2Cl_2/DMSO, afforded the desired aldehyde intermediate **4** in 82% yield.[12] The next step of the synthesis was the Knoevenagel condensation involving reaction of the aldehyde **4** with ethylcyanoacetate (1.1 equiv) and piperidine in ethanol. Under these conditions the imine intermediate **6** was isolated in 86% yield. This condensation gave only heterocylization on the nitrile group, in the same way as for HA 14-1 and most of the analogues.[13]



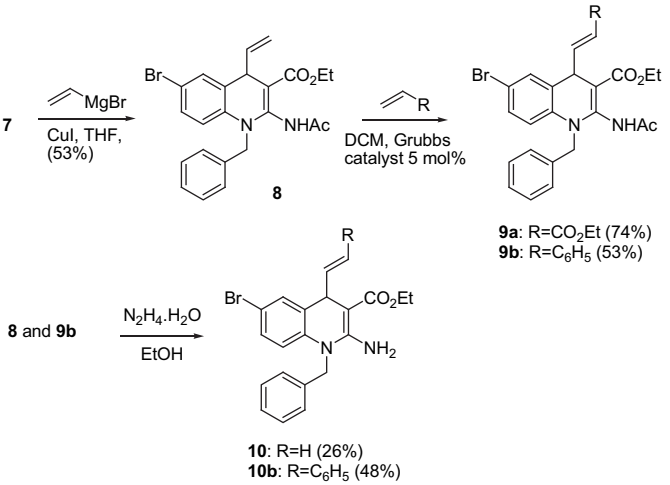
Scheme 1. Retrosynthetic analysis for the preparation of our target 1,4-dihydroquinolines.

Acetylation of the imine function was performed to give the desired intermediate **7** in 95% yield. This protection should not only stabilize imine **6** but also increase its reactivity towards the programmed Michael additions.



Scheme 2. Synthesis of the key intermediate **7**.

The access to the key intermediate **7** should allow us to synthesize a large variety of novel 2-amino-1,4-dihydroquinolines with a molecular diversity in the upper position by 1,4 additions of nucleophilic substrates. As a first example, the reaction with vinylmagnesiumbromide and copper iodide in THF at 0 °C gave the desired adduct **8** in 53% yield (Scheme 3). The structure of this compound was established by NMR and unambiguously confirmed by X-ray analysis (Fig. 2).[14]



Scheme 3. Addition of vinyl cuprate on intermediate **7**, followed by cross coupling metathesis reactions.

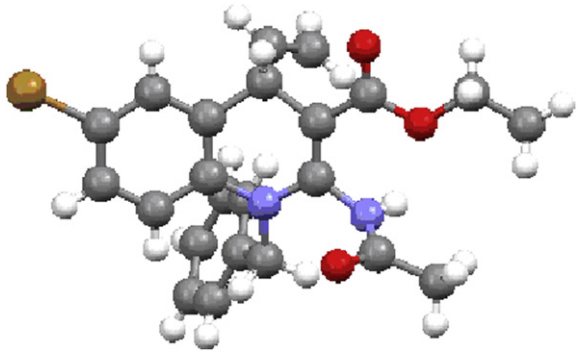
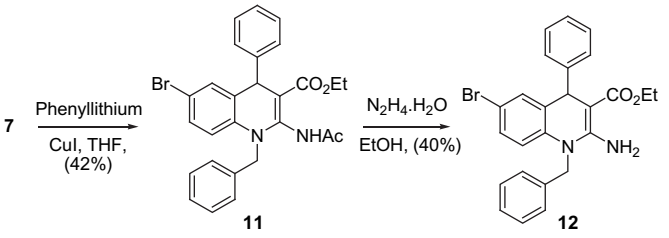


Figure 2. X-ray crystal structure of 1,4-dihydroquinoline **8**.

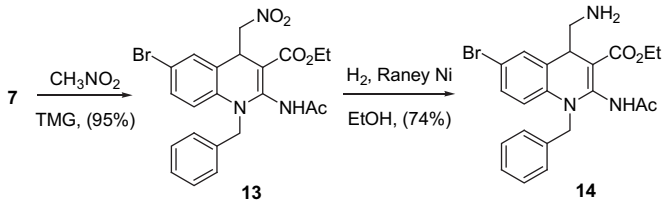
Then, cross coupling metathesis reactions of **8** with ethylacrylate or styrene in CH_2Cl_2 and in the presence of second generation Grubbs catalyst[15] at 5 mol %, gave the desired products **9a** and **9b** with 37% and 53% yields, respectively. The yield of **9a** could be increased to 74%, when taking into account the recovery of starting material. The amine function of **8** and **9b** were deprotected by reaction with hydrazine monohydrate to give the desired 2-amino-1,4-dihydroquinolines **10** and **10b** with 26% and 48% yields, respectively.

In the same way, the reaction of **7** with phenyllithium and copper iodide in THF at 0 °C gave the desired adduct **11** in 42% yield. Deprotection with hydrazine afforded the targeted amine **12** (Scheme 4).



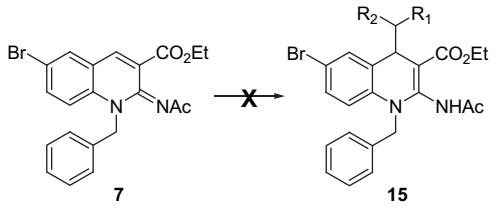
Scheme 4. Addition of phenyl cuprate on intermediate **7**.

Another series of new 2-amino-1,4-dihydroquinolines was obtained from **7** by addition of nitromethane in the presence of tetramethylguanidine to give the adduct **13** in 95% yield. The nitro group could be reduced by hydrogen with Raney Nickel, affording the desired amine **14** in 74% yield (Scheme 5).



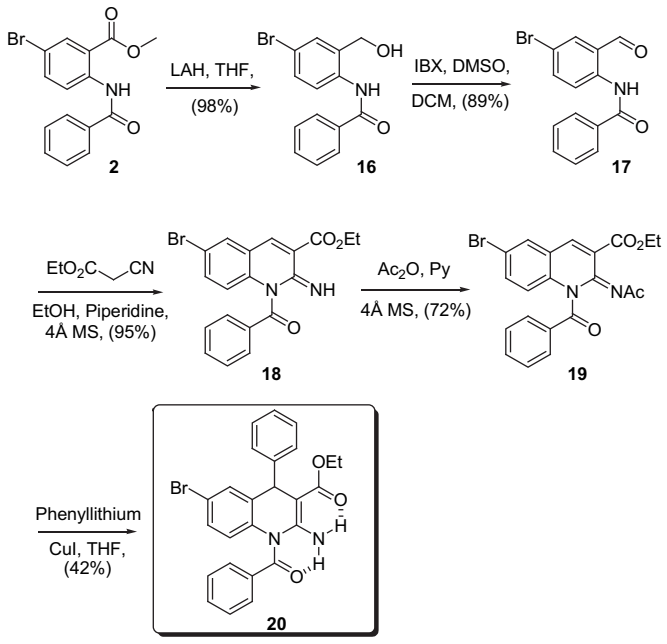
Scheme 5. Addition of nitromethane anion on intermediate **7**.

The anions of ethylcyanoacetate, diethylmalonate or malononitrile did not react in EtOH with piperidine with our intermediate **7**, affording only recovery of starting materials and/or decomposition products (Scheme 6). This unexpected result shows that **7** has a lower reactivity than its oxygen counterpart, the benzopyran-2-imine used for the synthesis of HA 14-1 and analogues.[6]



15a:R_1 = CN, R_2 = CO_2Et
15b:R_1= R_2 = CO_2Et
15c:R_1 = R_2 = CN

Scheme 6. Tentative additions of malonic derivatives on intermediate **7**.



Scheme 7. Synthesis and reaction of benzoyl protected intermediate **19**.

These series of novel 2-amino-1,4-dihydroquinolines were obtained with the benzyl group to protect the intracyclic nitrogen. In order to extend this synthesis, we changed this protecting group with a benzoyl substituent, as shown in Scheme 7. Starting from the previous intermediate **2**, the reaction with lithium aluminium hydride (1.0 equiv) reduced selectively the ester function to give the amido alcohol **16** in 98% yield. The oxidation of **16** by IBX afforded the aldehyde **17** in 89% yield. The heterocyclization was accomplished after the Knoevenagel condensation with ethylcyanoacetate in ethanol at 60 °C to give the imine **18** in 95% yield.

This compound was again activated by acetylation of the imine function with acetic anhydride and pyridine to afford the key intermediate **19** in 72% yield. This derivative appears to be less reactive than **7** as a Michael acceptor. However, the reaction of **19** with phenyllithium and copper iodide in THF at 0 °C occurred with concommittent deprotection of the amine, affording the target molecule **20** in 30% yield. The structure of this compound was established by spectral and analytical data. In particular, the ^{1}H NMR spectrum of **20** indicated two different chemical shifts at 13.29 ppm and 11.04 ppm for the protons of the amine, due to the presence of two intramolecular hydrogen bonds (Scheme 7).

3. Conclusions

We have synthesized the first series of novel 2-amino-1,4-dihydroquinolines in six to seven steps from commercial methyl-2-amino-5-bromobenzoate. The key intermediate **7**, obtained in five steps and 50% yield, allowed us to introduce various substituents in the upper position of the skeleton. Furthermore, it was also possible to modulate the protective group on the intracyclic nitrogen. Exploration of the reactivity of these Michael acceptors **7** and **19** as well as extension of these syntheses is under active study in our group. The biological activity of these new 2-amino-1,4-dihydroquinolines is under evaluation and particularly their interaction with the *anti* apoptotic family of proteins such as Bcl-2 or BcL-xL. Results of these studies will be reported in due course.

4. Experimental section

4.1. General

*4.1.1. Methyl 2-benzamido-5-bromobenzoate (**2**)*[12]. To a mixture of methyl-2-amino-5-bromobenzoate (1 g, 4.35 mmol, 1.0 equiv), $NaHCO_3$ (0.73 g, 8.70 mmol, 2.0 equiv) and anhydrous CH_2Cl_2 (8 mL), benzoyl chloride (0.56 mL, 4.80 mmol, 1.1 equiv) was added dropwise at 0 °C. The solution was stirred under argon at room temperature for 5 h. After adding water, the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 fractions were washed with water, brine, dried over $MgSO_4$, and concentrated under vacuum. The ester (**2**) was obtained after purification of the crude solid by washing with diethyl ether (1.15 g, yield 88%); mp 130–132 °C. ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 3.97 (s, 3H), 7.45–7.60 (m, 3H), 7.68 (dd, J=2.4, 9.0 Hz, 1H), 8.00–8.10 (m, 2H), 8.19 (d, J=2.4 Hz, 1H), 8.87 (d, J=9.0 Hz, 1H), 11.95 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 52.8, 115.0, 116.6, 122.1, 127.4 ($2C_{ar}$), 128.9 ($2C_{ar}$), 132.2, 133.5, 134.5, 137.5, 140.9, 165.6, 167.9. EI-HRMS: calcd for $[C_{15}H_{12}BrNO_3]$+: 333.0000, found: 332.9982.

*4.1.2. (2-(benzylamino)-5-bromophenyl)methanol (**3**)*[12]. To a suspension of $LiAlH_4$ (3,13 g, 83 mmol, 5.5 equiv) in anhydrous THF (90 mL) at −10 °C was added a solution of compound (**2**) (5 g, 15 mmol, 1.0 equiv) in anhydrous THF (40 mL) at −10 °C. The solution was stirred under argon at room temperature for 12 h. The mixture was quenched successively with a 2 M NaOH aqueous solution (4 mL) and water (4 mL). The mixture was dried over $MgSO_4$, filtered and concentrated under vacuum. The alcohol (**3**) was obtained as a colourless oil (3.7 g, yield 85%) after purification by flash column chromatography on silica gel (P/ EA: 8/2). ^{1}H NMR

δ ppm ($CDCl_3$, 300 MHz): 4.36 (s, 2H), 4.62 (s, 2H), 6.51 (d, J=8.4 Hz, 1H), 7.15–7.40 (m, 7H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 47.7, 64.1, 108.3, 112.7, 126.3, 127.3 ($3C_{ar}$), 128.7 ($2C_{ar}$), 131.4, 132.0, 138.8, 146.3.

*4.1.3. 2-(Benzylamino)-5-bromobenzaldehyde (**4**).* To a mixture of IBX (10.6 g, 38.0 mmol, 3.0 equiv), DMSO (55 mL) and CH_2Cl_2 (40 mL), a solution of compound (**3**) (3.7 g, 12.7 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added dropwise. The solution was stirred under argon at reflux for 1 h. The reaction was quenched with water (20 mL) at 0 °C and the residue of IBX was filtered on a pad of Celite. The mixture was extracted with CH_2Cl_2 and the organic layers were washed three times with water, brine, dried over $MgSO_4$, and concentrated under vacuum. The aldehyde (**4**) was obtained as a yellow solid (3.0 g, yield 82%) after purification by flash column chromatography on silica gel (P/EA): (9/1); mp 72–74 °C. ^1H NMR δ ppm ($CDCl_3$, 300 MHz): 4.47 (s, 2H), 6.55 (d, J=9.0 Hz, 1H), 7.25–7.45 (m, 6H), 7.59 (d, J=2.4 Hz, 1H), 8.75 (br s, 1H), 9.79 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 46.7, 106.3, 113.9, 119.9, 126.9 ($2C_{ar}$), 127.5, 128.8 ($2C_{ar}$), 137.7, 138.2, 138.5, 149.3, 192.9. EI-HRMS: calcd for $[C_{14}H_{12}BrNO]+$: 289.0102, found: 289.0086.

*4.1.4. Ethyl 1-benzyl-6-bromo-2-imino-1,2-dihydroquinoline-3-carboxylate (**6**).* A mixture of aldehyde (**4**) (3 g, 10.3 mmol, 1.0 equiv), molecular sieves 4 Å (3 g), absolute ethanol (55 mL), ethylcyanoacetate (1.22 mL, 11.4 mmol, 1.1 equiv) and piperidine in catalytic amount was stirred under argon at room temperature for 12 h. The solution was diluted with CH_2Cl_2 and molecular sieves were filtered on a pad of Celite. The mixture was concentrated under vacuum and the intermediate (**6**) was obtained as a yellow solid (3.8 g, yield 86%) after purification by washing with a mixture of pentane and diethyl ether (P/E: 6/4); mp 206–208 °C. ^1H NMR δ ppm ($CDCl_3$, 300 MHz,): 1.44 (t, J=7.1 Hz, 3H), 4.41 (q, J=7.1 Hz, 2H), 5.58 (br s, 2H), 6.86 (d, J=9.0 Hz, 1H), 7.20–7.40 (m, 5H), 7.45 (dd, J=2.3, 9.0 Hz, 1H), 7.58 (d, J=2.3 Hz, 1H), 8.15 (s, 1H), 9.17 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.3, 47.0, 61.6, 113.0, 115.9, 119.0, 119.9, 126.3 ($2C_{ar}$), 127.1, 128.9 ($2C_{ar}$), 132.2, 135.9, 136.1, 139.9, 141.4, 155.4, 165.1. EI-HRMS: calcd for $[C_{17}H_{12}BrN_2O_2$ ($M-C_2H_5$)]+: 355.0082, found: 355.0083.

*4.1.5. (E)-ethyl 2-(acetylimino)-1-benzyl-6-bromo-1,2-dihydroquinoline-3-carboxylate (**7**).* A mixture of compound (**6**) (2 g, 5.2 mmol, 1.0 equiv), acetic anhydride (40 mL), acetic acid (3 mL) and 4 Å molecular sieves (0.5 g) was stirred under argon and heated at 40 °C for 12 h. The solution was diluted with CH_2Cl_2 and molecular sieves were filtered on a pad of Celite. The mixture was concentrated under vacuum and coevaporated with toluene to give (7) as a yellow solid (2.1 g, yield 95%); mp 144–146 °C. ^1H NMR δ ppm ($CDCl_3$, 300 MHz): 1.43 (t, J=7.1 Hz, 3H), 2.24 (s, 3H), 4.39 (q, J=7.1 Hz, 2H), 5.70 (br s, 2H), 7.00–7.10 (m, 6H), 7.52 (dd, J=2.2, 9.1 Hz, 1H), 7.71 (d, J=2.2 Hz, 1H), 8.04 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.2, 26.8, 47.0, 62.0, 116.0, 117.5, 121.6, 123.8, 126.5 ($2C_{ar}$), 127.6, 129.0 ($2C_{ar}$), 131.9, 135.2, 135.6, 138.7, 140.1, 150.9, 165.2, 181.9. Anal. Calc for C21H19BrN2O3: C, 59.03; H, 4.48; N, 6.56. Found: C, 58.68; H, 4.43; N, 6.37. EI-HRMS: calcd for $[C_{21}H_{19}BrN_2O_3]+$: 426.0579, found: 426.0561.

*4.1.6. Ethyl 2-acetamido-1-benzyl-6-bromo-4-vinyl-1,4-dihydroquinoline-3-carboxylate (**8**).* To a suspension of copper iodide (95 mg, 0.5 mmol, 1.1 equiv) in anhydrous THF (1.5 mL), vinylmagnesiumbromide (1.0 M in THF, 1.1 mL, 1.1 mmol, 2.2 equiv) was added dropwise under argon at 0 °C. The mixture was stirred 30 min at 0 °C. The compound (**7**) (210 mg, 0.5 mmol, 1.0 equiv) in anhydrous THF (1.5 mL) solution was added to the mixture at −30 °C. The solution was warmed to room temperature and stirred for 2 h. The black mixture was quenched with a NH_4Cl saturated aqueous solution and extracted with AcOEt. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. Compound (**8**) was obtained as a white solid (120 mg, yield 53%) after purification by flash column chromatography on silica gel (P/EA: 9/1); mp 134–136 °C. ^1H NMR δ ppm ($CDCl_3$, 500 MHz): 1.35 (t, J=7.1 Hz, 3H), 2.24 (s, 3H), 4.15–4.35 (m, 2H), 4.67 (d, J=5.5 Hz, 1H), 4.74 (m, 1H), 4.84 (d, J=16.2 Hz, 1H), 4.99 (m, 1H), 5.07 (d, J=16.2 Hz, 1H), 5.76 (m, 1H), 6.88 (d, J=8.8 Hz, 1H), 7.10–7.40 (m, 7H), 10.15 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 125 MHz): 14.5, 24.7, 40.8, 50.2, 60.2, 89.5, 113.8, 116.4, 118.4 127.5, 127.6 ($2C_{ar}$), 128.5 ($2C_{ar}$), 129.3, 129.9, 131.4, 136.8, 137.4, 140.0, 147.1, 168.7, 170.7. ES-HRMS: calcd for $[C_{23}H_{23}^{79}BrN_2O_3+Na]+$: 477.0790, found: 477.0793.

*4.1.7. (E)-Ethyl 2-(acetamido)-1-benzyl-6-bromo-4-(3-ethoxy-3-oxoprop-1-enyl)-1,4-dihydroquinoline-3-carboxylate (**9a**).* A mixture of compound (**8**) (320 mg, 0.71 mmol, 1.0 equiv), anhydrous CH_2Cl_2 (5 mL), ethylacrylate (0.76 mL, 7.14 mmol, 10.0 equiv) and second generation Grubbs catalyst (30 mg, 0.035 mmol, 0.05 equiv) was stirred under argon at reflux for 48 h. The solution was concentrated under vacuum and ester (**9a**) was obtained as a brown solid (140 mg, yield 37%) after purification by flash column chromatography on silica gel (P/EA: 9/1). During this process 150 mg of starting material were also recovered. For (**9a**): ^1H NMR δ ppm ($CDCl_3$, 500 MHz): 1.20–1.40 (m, 6H), 2.24 (s, 3H), 4.10–4.30 (m, 4H), 4.75–4.90 (m, 2H), 4.99–5.05 (m, 1H), 5.33 (dd, J=1.4, 15.6 Hz, 1H), 6.80 (dd, J=5.5, 15.6 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 7.10–7.35 (m, 7H), 10.13 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 125.77 MHz): 14.3, 14.4, 24.7, 39.5, 50.4, 60.4, 60.5, 87.8, 116.8, 118.7, 120.6, 127.7 ($3C_{ar}$), 128.1, 128.6 ($2C_{ar}$), 130.3, 131.4, 136.5, 137.5, 147.47, 148.8, 166.6, 168.1, 170.6. ES-HRMS: calcd for $[C_26H_{27}^{79}BrN_2O_2+Na]+$: 549.1001, found: 549.1001.

*4.1.8. (E)-Ethyl 2-acetamido-1-benzyl-6-bromo-4-styryl-1,4-dihydroquinoline-3-carboxylate (**9b**).* A mixture of compound (**8**) (0.36 g, 0.79 mmol, 1.0 equiv), anhydrous CH_2Cl_2 (5.5 mL), styrene (0.91 mL, 7.90 mmol, 10.0 equiv) and second generation Grubbs catalyst (34 mg, 0.039 mmol, 0.05 equiv) was stirred under argon at reflux for 18 h. The solution was concentrated under vacuum and (**9b**) was obtained as a white solid (220 mg, yield 53%) after purification by flash column chromatography on silica gel (P/EA: 95/0.5); mp 84–86 °C. ^1H NMR δ ppm (C_6D_6, 500 MHz): 1.05 (t, J=7.1 Hz, 3H), 1.79 (s, 3H), 4.00–4.20 (m, 2H), 4.76 (d, J=16.4 Hz, 1H), 4.78 (d, J=5.5 Hz, 1H), 4.96 (d, J=16.4 Hz, 1H), 6.09 (dd, J=5.5, 15.9 Hz, 1H), 6.16 (d, J=15.9 Hz, 1H), 6.60 (d, J=8.8 Hz, 1H), 6.80–6.90 (m, 3H), 6.94 (dd, J=2.3, 8.8 Hz, 1H), 7.00–7.10 (m, 8H), 10.21 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.5, 24.7, 40.0, 50.4, 60.3, 89.5, 116.5, 118.4, 126.3 ($2C_{ar}$), 126.5, 127.3, 127.4, 127.6 ($2C_{ar}$), 128.4 ($2C_{ar}$), 128.6 ($2C_{ar}$), 128.8, 129.8, 130.2, 131.3, 136.7, 136.8, 137.4, 147.1, 168.1, 170.6. ES-HRMS: calcd for $[C_{29}H_{27}^{79}BrN_2O_3+Na]+$: 553.1103, found: 553.1104.

*4.1.9. Ethyl 2-amino-1-benzyl-6-bromo-4-vinyl-1,4-dihydroquinoline-3-carboxylate (**10**).* A mixture of compound (**8**) (0.20 g, 0.44 mmol, 1.0 equiv), absolute ethanol (3.0 mL), and hydrazine monohydrate (2.1 mL) was stirred at room temperature for 3 h. The solution was concentrated under vacuum and the residue was extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. Compound (**10**) was obtained as a white solid (48 mg, yield 26%) after purification by flash column chromatography on silica gel (P/EA: 8/2); mp 110–112 °C. ^1H NMR δ ppm ($CDCl_3$, 500 MHz): 1.31 (t, J=7.1 Hz, 3H), 4.15–4.25 (m, 2H), 4.58 (d, J=5.9 Hz, 1H), 4.74–4.94 (m, 3H), 5.12–5.18 (m, 1H), 5.78–5.87 (m, 1H), 6.27–6.32 (m, 2H), 6.56 (d, J=8.7 Hz, 1H), 7.10–7.40 (m, 7H). ^{13}C NMR δ ppm ($CDCl_3$, 125.77 MHz): 14.7, 39.8, 49.3, 59.0, 78.4, 112.0, 115.4, 116.0, 125.5, 127.9 ($2C_{ar}$), 129.4 ($2C_{ar}$), 129.7, 129.9, 131.5, 135.6, 138.3, 141.2, 155.2, 169.5. Anal. Calc for $C_{21}H_{21}BrN_2O_2$: C, 61.03; H, 5.12; N, 6.78.

Found: C, 60.17; H, 5.47; N, 6.33. EI-HRMS: calcd for $[C_{21}H_{21}BrN_2O_2]+$: 412.0786, found: 412.0793.

*4.1.10. (E)-Ethyl 2-amino-1-benzyl-6-bromo-4-styryl-1,4-dihydroquinoline-3-carboxylate (**10b**).* A mixture of compound (**9b**) (150 mg, 0.28 mmol, 1.0 equiv), absolute ethanol (1.5 mL), and hydrazine monohydrate (1.4 mL) was stirred at room temperature for 3 h. The solution was concentrated under vacuum and the residue was extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. Compound (**10b**) was obtained as a white solid (67 mg, yield 48%) after purification by flash column chromatography on silica gel (P/EA: 9/1); mp 156–158 °C. ^{1}H NMR δ ppm (C_6D_6, 500 MHz): 1.15 (t, J=7.1 Hz, 3H), 4.11 (d, J=18.1 Hz, 1H), 4.20–4.30 (m, 2H), 4.37 (d, J=18.1 Hz, 1H), 4.92 (d, J=5.7 Hz, 1H), 6.11 (d, J=8.7 Hz, 1H), 6.20 (br s, 2H), 6.29 (dd, J=5.7, 15.7 Hz, 1H), 6.35 (d, J=15.7 Hz, 1H), 6.69–6.71 (m, 2H), 6.92 (dd, J=2.3, 8.7 Hz, 1H), 7.00–7.14 (m, 8H), 7.27 (d, J=2.3 Hz, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.7, 39.4, 49.3, 59.1, 77.2, 115.5, 116.2, 125.6 ($2C_{ar}$), 126.3 ($2C_{ar}$), 127.0, 127.3, 128.0, 128.4 ($2C_{ar}$), 129.4 ($2C_{ar}$), 129.8, 129.9, 131.6, 131.1, 135.6, 137.4, 138.3, 155.2, 169.6. Anal. calcd for C27H25BrN2O2: C, 66.26; H, 5.15; N, 5.72. Found: C, 66.22; H, 5.36; N, 5.43. ES-HRMS: calcd for $[C_{27}H_{26}^{79}BrN_2O_2+H]+$: 489.1178, found: 489.1179.

*4.1.11. Ethyl 2-acetylimino-1-benzyl-6-bromo-4-phenyl-1,4-dihydroquinoline-3-carboxylate (**11**).* To a suspension of copper iodide (0.34 g, 1.80 mmol, 1.1 equiv) in anhydrous THF (8 mL), phenyllithium (1.9 M in butyl ether, 1.9 mL, 3.61 mmol, 2.2 equiv) was added dropwise under argon at 0 °C. The mixture was stirred 30 min at 0 °C. The compound (**6**) (0.70 g, 1.64 mmol, 1.0 equiv) in anhydrous THF (2 mL) solution was added to the mixture at −30 °C. The solution was warmed to room temperature and stirred for 2 h. The black mixture was quenched with NH_4Cl saturated aqueous solution and extracted with AcOEt. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. Compound (**11**) was obtained as a white solid (350 mg, yield 42%) after purification by flash column chromatography on silica gel (P/EA: 95/05). ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 1.38 (t, J=7.1 Hz, 3H), 2.28 (s, 3H), 4.25–4.30 (m, 2H), 4.95 (m, 2H), 5.35 (s, 1H), 6.89–7.41 (m, 13H), 10.08 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.4, 24.7, 41.5, 50.0, 60.3, 91.8, 116.5, 118.3, 126.5, 127.1 ($2C_{ar}$), 127.5, 127.7 ($2C_{ar}$), 128.3 ($2C_{ar}$), 128.5 ($2C_{ar}$), 129.8, 130.9, 131.8, 136.4, 137.5, 144.6, 147.0, 169.0, 170.9. EI-HRMS: calcd for $[C_{27}H_{25}^{81}BrN_2O_3]+$: 506.1028, found: 506.1063.

*4.1.12. Ethyl 2-amino-1-benzyl-6-bromo-4-phenyl-1,4-dihydroquinoline-3-carboxylate (**12**).* A mixture of compound (**11**) (0.14 g, 0.28 mmol, 1.0 equiv), absolute ethanol (1.5 mL), and hydrazine monohydrate (1.4 mL) was stirred at room temperature for 3 h. The solution was concentrated under vacuum and the residue was extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. Compound (**12**) was obtained as a white solid (50 mg, yield 40%) after purification by flash column chromatography on silica gel (P/EA: 9/1); mp 82–84 °C. ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 1.18 (t, J=8.0 Hz, 3H), 4.04 (q, J=8.0 Hz, 2H), 5.00 (m, 2H), 5.10 (s, 1H), 6.27 (s, 1H), 6.52 (d, 1H), 6.90–7.30 (m, 12H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.6, 41.6, 49.5, 59.3, 79.7, 115.7, 116.4, 125.5 ($2C_{ar}$), 126.1, 126.9 ($2C_{ar}$), 127.9, 128.4 ($2C_{ar}$), 129.5 ($2C_{ar}$), 129.7, 131.4, 131.8, 135.7, 138.2, 147.3, 155.1, 169.6. Anal. Calc for $C_{25}H_{23}BrN_2O_2$: C, 64.80; H, 5.00; N, 6.05. Found: C, 65.56; H, 5.19; N, 5.74. EI-HRMS: calcd for $[C_{19}H_{18}BrN_2O_2$ (M-C_6H_5)]+: 385.0552, found: 385.0574.

*4.1.13. Ethyl 2-acetamido-1-benzyl-6-bromo-4-(nitomethyl)-1,4-dihydroquinoline-3-carboxylate (**13**).* A mixture of compound (**7**) (430 mg, 1.00 mmol, 1.0 equiv), nitromethane (3 mL), and tetramethylguanidine (0.13 mL, 1.0 mmol, 1.0 equiv) was stirred under argon at room temperature for 18 h. The mixture was quenched with NH_4Cl saturated aqueous solution and extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. Compound (**13**) was obtained as a yellow solid (460 mg, yield 95%) after purification by flash column chromatography on silica gel (P/EA: 8/2); mp 78–80 °C. ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 1.24 (t, J=8.0 Hz, 3H), 2.18 (s, 3H), 3.90 (d, J=6.7 Hz, 2H), 4.11 (q, J=8.0 Hz, 2H), 4.77 (t, J=6.7 Hz, 1H), 4.78–4.97 (m, 2H), 7.00–7.30 (m, 8H), 10.09 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.2, 24.8, 37.0, 50.9, 60.7, 79.4, 89.5, 117.2, 118.9, 126.8, 127.8 ($2C_{ar}$), 128.2 ($2C_{ar}$), 128.9, 131.0, 131.1, 136.3, 137.4, 147.9, 167.8, 170.4. ES-HRMS: calcd for $[C_{22}H_{22}^{79}BrN_3O_5+Na]+$: 510.0641, found: 510.0644.

*4.1.14. Ethyl 2-acetamido-4-(aminomethyl)-1-benzyl-6-bromo-1,4-dihydroquinoline-3-carboxylate (**14**).* A mixture of compound (**13**) (0.15 g, 0.28 mmol, 1.0 equiv), absolute ethanol (1.5 mL), and a catalytic amount of Raney nickel (50% solution in water) was stirred under a hydrogen atmosphere at room temperature for 18 h. The solution was diluted with CH_2Cl_2, dried over $MgSO_4$ and filtered on a pad of Celite. The mixture was concentrated under vacuum and compound (**14**) was obtained as a white solid (0.10 g, yield 74%) after purification by flash column chromatography on silica gel (P/EA: 9/1); mp 124–126 °C. ^{1}H NMR δ ppm ($CDCl_3$, 500 MHz): 1.04 (t, J=6.8 Hz, 3H), 2.17 (s, 3H), 3.58 (m, 1H), 4.00 (m, 3H), 4.77 (t, J=6.7 Hz, 1H), 4.24 (m, 1H), 4.30 (s, 2H), 4.40 (br s, 1H), 6.50 (d, J=8.6 Hz, 1H), 7.15–7.35 (m, 7H), 10.68 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.5, 24.5, 38.8, 48.4, 51.7, 58.8, 81.2, 109.7, 112.9, 127.3, 127.4 ($2C_{ar}$), 128.7 ($2C_{ar}$), 130.1, 131.0, 131.4, 139.0, 144.4, 157.3, 168.3, 170.5. Anal. Calcd for $C_{20}H_{22}BrN_3O_2$: C, 57.70; H, 5.33; N, 10.09. Found: C, 57.61; H, 5.16; N, 8.96. ES-HRMS: calcd for $[C_{22}H_{25}^{79}BrN_3O_3+H]+$: 458.1079, found: 458.1079.

*4.1.15. N-(4-Bromo-2-(hydroxymethyl)phenyl)benzamide (**16**).* To a suspension of $LiAlH_4$ (0.57 g, 15 mmol, 1.0 equiv) in anhydrous THF (40 mL) at −10 °C was added a solution of compound (**2**) (5 g, 15 mmol, 1.0 equiv) in anhydrous THF (40 mL) at −10 °C. The solution was stirred under argon at room temperature for 2 h. The mixture was quenched successively with a 2 M NaOH aqueous solution (4 mL) and water (4 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. The amide (**16**) was obtained as a white solid (4.5 g, yield 98%) after purification by flash column chromatography on silica gel (P/EA: 8/2); mp 138–140 °C. ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 4.18 (s, 2H), 5.25 (br s, 1H), 6.87–7.03 (m, 5H), 7.43–7.45 (m, 2H), 7.64–7.67 (m, 1H), 9.70 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$+DMSO d_6, 75 MHz): 62.2, 115.5, 122.8, 126.3.0 ($2C_{ar}$), 127.8 ($2C_{ar}$), 130.0, 130.1, 131.0, 132.3, 133.6, 136.2, 164.4. EI-HRMS: calcd for $[C_{14}H_{12}BrNO_2]+$: 305.0051, found: 305.0039.

*4.1.16. N-(4-bromo-2-formylphenyl)benzamide (**17**).* To a mixture of IBX (8.2 g, 29.4 mmol, 2.0 equiv), DMSO (60 mL) and CH_2Cl_2 (45 mL), a solution of compound (**16**) (4.5 g, 14.7 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) was added dropwise. The solution was stirred under argon at reflux for 1 h. The reaction was quenched with water (20 mL) at 0 °C and the residue of IBX was filtered on a pad of Celite. The mixture was extracted with CH_2Cl_2 and the organic layers were washed three times with water, brine, dried over $MgSO_4$, and concentrated under vacuum. The amide (**17**) was obtained as a white solid (4.0 g, yield 89%) after purification by flash column chromatography on silica gel (P/EA: 8/2); mp 118–120 °C. ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 7.50–7.70 (m, 3H), 7.78 (dd, J=2.4, 9.0 Hz, 1H), 7.78 (d, J=2.4 Hz, 1H), 8.05–8.10 (m, 2H), 8.92 (d, J=9.0 Hz, 1H), 9.95 (s, 1H), 12.00 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 115.2, 121.9, 123.3, 127.5 ($2C_{ar}$), 129.0 ($2C_{ar}$), 132.5, 134.0, 138.2, 139.1,

140.2, 166.1, 194.6. EI-HRMS: calcd for [C13H10BrNO (M-C=O)]+: 274.9946, found: 274.9958.

*4.1.17. Ethyl 1-benzoyl-6-bromo-2-imino-1,2-dihydroquinoline-3-carboxylate (**18**).* A mixture of aldehyde (**17**) (4 g, 13.15 mmol, 1.0 equiv), molecular sieves 4 Å (4 g), absolute ethanol (80 mL), ethylcyanoacetate (1.68 mL, 15.8 mmol, 1.2 equiv) and piperidine in catalytic amount was stirred under argon at 60 °C for 24 h. The solution was diluted with CH_2Cl_2 and molecular sieves were filtered on a pad of Celite. The mixture was concentrated under vacuum and the compound (**18**) was obtained as a yellow solid (5.5 g, yield 95%) after purification by washing with a mixture of pentane and diethyl ether (P/E: 6/4); mp 168–170 °C. ^{1}H NMR δ ppm ($CDCl_3$, 500 MHz): 1.49 (t, J=7.2 Hz, 3H), 4.51 (q, J=7.2 Hz, 2H), 7.50–7.60 (m, 3H), 6.65 (dd, J=2.2, 9.0 Hz, 1H); 7.97 (d, J=2.2 Hz, 1H); 7.99 (d, J=9.0 Hz, 1H), 8.10–8.15 (m, 2H), 11.92 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 125 MHz): 14.2, 62.6, 113.2, 119.5, 125.2, 127.6 ($2C_{ar}$), 128.9 ($2C_{ar}$), 130.4, 130.5, 132.3, 134.7, 136.0, 141.3, 147.6, 150.0, 164.5, 166.8. EI-HRMS: calcd for $[C_{19}H_{15}BrN_2O_3]$+: 398.0266, found: 398.0265.

*4.1.18. (E)-Ethyl 2-(acetylimino)-1-benzoyl-6-bromo-1,2-dihydroquinoline-3-carboxylate (**19**).* A mixture of compound (**18**) (2.5 g, 6.3 mmol, 1.0 equiv), acetic anhydride (30 mL), pyridine (8 mL) and molecular sieves 4 Å (0.5 g) was stirred under argon and heat at 90 °C for 48 h. The solution was diluted with CH_2Cl_2 and molecular sieves were filtered on a pad of Celite. The mixture was concentrated under vacuum and coevaporated with toluene to give the compound (**19**) as a yellow solid (2 g, yield 72%); mp 108–110 °C. ^{1}H NMR δ ppm ($CDCl_3$, 300 MHz): 1.46 (t, J=7.1 Hz, 3H), 2.59 (s, 3H), 4.47 (q, J=7.1 Hz, 2H), 7.10–7.40 (m, 3H), 7.60–7.80 (m, 4H), 8.00–8.01 (m, 1H), 8.69 (s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 75 MHz): 14.2, 25.7, 62.2, 121.9, 122.8, 127.3, 128.3 ($2C_{ar}$), 128.8 ($2C_{ar}$), 130.2, 130.4, 131.9, 135.4, 135.4, 140.3, 146.3, 150.1, 164.5, 172.2, 174.4. EI-HRMS: calcd for $[C_{21}H_{17}BrN_2O_4]$+: 440.0372, found: 440.0379.

*4.1.19. Ethyl 2-amino-1-benzoyl-6-bromo-4-phenyl-1,4-dihydroquinoline-3-carboxylate (**20**).* To a solution of copper iodide (86 mg, 0.45 mmol, 1.0 equiv) and anhydrous THF (2 mL), phenyllithium (1.9 M in butyl ether, 0.48 mL, 0.90 mmol, 2.0 equiv) was added dropwise under argon at 0 °C. The mixture was stirred 30 min at 0 °C. A solution of compound (**19**) (0.20 g, 0.45 mmol, 1.0 equiv) in anhydrous THF (0.5 mL) was added to the mixture at −30 °C. The solution was warmed to room temperature and stirred for 2 h. The black mixture was quenched with a NH_4Cl saturated aqueous solution and extracted with AcOEt. The organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum. The compound (**20**) was obtained as a white solid (70 mg, yield 30%) after purification by flash column chromatography on silica gel (P/EA: 95/05). ^{1}H NMR δ ppm ($CDCl_3$, 500 MHz): 1.26 (t, J=7.0 Hz, 3H), 4.17 (q, J=7.0 Hz, 2H), 5.16 (s, 1H), 6.81 (m, 1H), 7.20–7.80 (m, 10H), 8.05 (m, 2H), 11.04 (br s, 1H), 13.29 (br s, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 125.77 MHz): 14.3, 42.2, 60.1, 82.6, 115.9, 117.5, 126.5, 127.3 ($2C_{ar}$), 127.4, 127.6, 127.9 ($2C_{ar}$), 128.5, 129.1, 130.2, 132.2, 132.8, 133.1, 133.6, 146.9, 148.1, 148.4, 168.4, 170.0. ES-HRMS: calcd for $[C_{25}H_{21}^{79}BrN_2O_3$+Na]+: 499.0633, found: 499.0636.

Acknowledgements

This research has been performed as part of the Indo-French 'Joint Laboratory for Sustainable Chemistry at Interfaces'. We thank CNRS, MESR, and CSIR as well as the 'Ligue contre le Cancer' (Comité d'Ille et Vilaine) for support of this research. We thank the 'Ligue contre le Cancer' (Comité d'Ille et Vilaine) and Région Bretagne for a fellowship to G.V. Fruitful discussions with Dr. Frederic Caijo are gratefully acknowledged.

References and notes

1. See for instance: (a) Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Il Fármaco* **2002**, *57*, 715–722; (b) Kidwai, M.; Saxena, S.; Khan, M. K. R.; Thukral, S. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4295–4298; (c) Makarem, S.; Mohammadi, A. A.; Fakhari, A. R. *Tetrahedron Lett.* **2008**, *49*, 7194–7196; (d) Elinson, M. N.; Dorofeev, A. S.; Miloserdov, F. M.; Ilovaisky, A. I.; Feducovich, S. K.; Belyakov, P. A.; Nikishin, G. I. *Adv. Synth. Catal.* **2008**, *350*, 591–601 and references cited therein.
2. (a) Wang, J.-L.; Liu, D.; Zhang, Z.-J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124–7129; (b) Skommer, J.; Wlodkowic, D.; Matto, M.; Eray, M.; Pelkonen, J. *Leuk. Res.* **2006**, *30*, 322–331; (c) Doshi, J. M.; Tian, D.; Xing, C. *J. Med. Chem.* **2006**, *49*, 7731–7739; (d) Doshi, J. M.; Tian, D.; Xing, C. *Mol. Pharm.* **2007**, *4*, 919–928 and references cited therein.
3. (a) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2004**, *47*, 6299–6310; (b) Kemnitzer, W.; Khasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labreque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745–4751; (c) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Crogan-Grundy, C.; Xu, L.; Lamothe, S.; Gourdeau, H.; Denis, R.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2007**, *50*, 2858–2864; (d) Kemnitzer, W.; Drewe, J.; Jiang, S.; Crogan-Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2008**, *51*, 417–423.
4. (a) Fujimoto, A.; Sakurai, A. *Synthesis* **1977**, 871–872; (b) Roudier, J.-F.; Foucaud, A. *Synthesis* **1984**, 159–160; (c) Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993–6996; (d) Ballini, R.; Bossica, G. B.; Conforti, M. L.; Maggi, R.; Maccazani, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395–1398; (e) Curini, M.; Epifano, F.; Chimichi, S.; Montanari, F.; Nocchetti, M.; Rosati, O. *Tetrahedron Lett.* **2005**, *46*, 3497–3499; (f) Curini, M.; Rosati, O.; Marcotullio, M. C.; Montanari, F.; Campagna, V.; Pace, V.; Cravotto, G. *Eur. J. Org. Chem.* **2006**, *3*, 746–751.
5. (a) Manero, F.; Gautier, F.; Gallenne, T.; Cauquil, N.; Grée, D.; Cartron, P.-F.; Geneste, O.; Grée, R.; Vallette, F. M.; Juin, P. *Cancer Res.* **2006**, *66*, 2757–2764; (b) Oliver, L.; Mahé, B.; Grée, R.; Vallette, F. M.; Juin, P. *Leuk. Res.* **2007**, *31*, 859–863.
6. Grée, D.; Vorin, S.; Manthati, V. L.; Caijo, F.; Viault, G.; Manero, F.; Juin, P.; Grée, R. *Tetrahedron Lett.* **2008**, *49*, 3276–3278.
7. The addition of nucleophiles to quinolinium salts is a well established method for the synthesis of substituted quinolines but it gives mainly the 1,2 dihydroderivatives. For representative examples see: (a) Mani, N. S.; Chen, P.; Jones, T. K. *J. Org. Chem.* **1999**, *64*, 6911–6914; (b) Diaba; Le Houerou, C.; Grignon-Dubois, M.; Gerval, P. *J. Org. Chem.* **2000**, *65*, 907–910 and references cited therein.
8. (a) Bohn, P.; Le Fur, N.; Hagues, G.; Costentin, J.; Torquet, N.; Papamicaël, C.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2009**, *7*, 2612–2618; (b) Marsais, F.; Bohn, P.; Levacher, V.; Le Fur, N. PCT Int. Appl., WO, 103120, 2006.
9. Mikata, Y.; Mizukami, K.; Hayashi, K.; Matsumoto, S.; Yano, S.; Yamazaki, N.; Ohno, A. *J. Org. Chem.* **2001**, *66*, 1590–1599.
10. Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341–8344.
11. (a) Zhou, L.; Zhang, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2899–2902; (b) Zhou, L.; Tu, S.; Shi, D.; Dai, G. *J. Chem. Res., Synop.* **1998**, 398–399; (c) Sharma, U.; Ahmed, S.; Boruah, R. C. *Tetrahedron Lett.* **2000**, *41*, 3493–3495; (d) Ukhin, L. Yu.; Belov, E. G. *Russ. Chem. Bull.* **2008**, *57*, 418–421.
12. For a similar sequence see: He, Y.; Mahmud, H.; Moningka, R.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2006**, *62*, 8755–8769.
13. In a few cases with some benzopyrans derivatives, cyclization occurs also on the ester affording quinolones Volmajer, J.; Toplak, R.; Bittner, S.; Leban, I.; Majcen Le Marechal, A. *Tetrahedron Lett.* **2003**, *44*, 2363–2366.
14. The crystal structure corresponding to 1,4-dihydroquinoline **8** has been deposited at the Cambridge Crystallographica Data Centre and allocated the deposition number CCDC 739472. These data can be obtained free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +441 223 336 033; email: deposit@cccdc.cam.ac.uk.
15. (a) Grubbs, R. H. *Adv. Synth. Catal.* **2007**, *349*, 34–40; (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370 and references cited therein.